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Aims & Scope

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The aims of the journal are to: (1) publish cutting-edge, innovative and topical research that addresses screening, diagnosis, management, and care in women's health; (2) deliver evidence-based information; (3) promote the sharing of clinical experience; and (4) address women-related health promotion.

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Editorial

Unlock the future of minimally invasive therapy after six decades

Minimally invasive therapy helps women with diseases to bravely accept treatments and avoid unnecessary incisions. This treatment not only will improve patients' quality of life, but also increase survival rates for cancer patients. Specially with the assistance of artificial intelligence, minimally invasive surgery has greater potential for development [1–6].

Looking back at the history of surgical procedures in gynecology and obstetrics, Dr. Ephraim McDowell began performing ovarian and fallopian tube surgery in 1809. After almost 50 years, Dr. Ellis Burnham conducted hysterectomy in 1853. However, until the endotracheal anesthesia showed up in 1920, surgical techniques began gradually improved. As you can imaging, before the minimally invasive therapy showed up in 1989, the procedure of laparotomy remains the same in 12 decades long. Showing that the progress of surgical techniques was quite slow.

In 1989, the field of minimally invasive gynecologic surgery experienced a significant breakthrough with Dr. Harry Reich's performance of laparoscopic hysterectomy. In 1993, the first radical hysterectomy for cervical cancer was performed by Dr. Camran Nezhat from the United States, Dr. Denis Querleu from Europe, and Prof. Chyi-Long Lee and Dr. Kuan-Gen Huang from the Asia Region, marking the beginning of a thriving era for minimally invasive surgery in cancer treatment [7,8]. As of today in 2024, minimally invasive treatment has reached a milestone of 60 years.

Sixty years later, it's crucial to evaluate our progress. Reflecting on milestones like the Wright brothers' first flight in 1903 and Neil Armstrong's moon landing in 1969, we witnessed remarkable advancements in aviation from something to something. Conversely, the field of minimally invasive gynecologic surgery appears to have plateaued after six decades. Despite the success of minimally invasive endometrial cancer surgery, there's still people who are doubting in using laparoscopy for treatment like radical hysterectomy for cervical cancer or ovarian cancer surgery.

In 2010, our study published in the American Journal of Obstetrics and Gynecology (AJOG) reported high survival rates for minimally invasive cervical cancer treatment, exceeding traditional surgery. However, a 2018 study in The New England Journal of Medicine [9] discovered higher survival rates with laparotomy compared to minimally invasive surgery, causing a significant concern in the medical community.

In 2020, the European Society of Gynecologic Oncology reported a sharp decline in minimally invasive surgery usage for cervical cancer treatment in Europe, from 48.9% to 18.2%. However, The Asia–Pacific Association for Gynecologic Endoscopy in Minimally Invasive Therapy (APAGE) discovered contradictory evidence which is by Prof. Chyi-Long Lee and Assoc. Prof. Kuan-Gen Huang in Taiwan. The study tracked 69 cases over five years from 2009 to 2014, revealing a 100% survival rate with no instances of recurrence or death, which indicates there may have biases in previous LACC studies.

Additionally, a Danish study comparing outcomes of minimally invasive and open surgery for cervical cancer from 2005 to 2017 discovered that minimally invasive surgery is safe for cervical cancer treatment. Consequently, they incorporated minimally invasive surgery into standard surgery for all radical hysterectomy procedures.

Regarding treatments for early ovarian cancer, a study published in the Journal of Minimally Invasive Gynecology (JMIG) [10] showed from 2010 to 2015 analyzed 8850 cases in the US cancer registry, with about 29.4% using minimally invasive therapy, rising from 19.8% in 2010 to 34.9% in 2015. The study also discovered that for non-ruptured tumors, survival rates were 91.5% for minimally invasive surgery and 90.5% for laparotomy. As for ruptured tumors, rates were 88.9% and 86.8% respectively. Moreover, our research from 2002 to 2014 showed a 95.9% survival rate in minimally invasive surgery patients, which indicate a significant improvement in ovarian cancer survival rates. Our data also showed the similar survival outcomes [11].

Although laparoscopy has made a significant technical progress, from the perspective of the conservative medical community, the application of endoscopic surgery is still in its infancy, especially in cancer treatments that require precision operations. There are three reasons. First, the accreditation of minimally invasive treatment is not widely known; secondly, the training and assessment system has not widely established; lastly, when doctors treating diseases, they usually refer to use traditional treatment methods. This is so-called “path dependence”, which means that it is difficult for most people to accept new changes [12–14].

We should not be bound by the past but should focus on the future. Through continuous research and efforts to reduce these limitations, along with improving physician training, we can provide better treatment for patients. Only then can minimally invasive treatment and medicine continue to progress. Let's work together for another sixty years, conducting surgeries like conducting an orchestra, waving the baton to create a moving symphony.

Conflicts of interest

All authors declare no conflict of interest.

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Editorial

Early removal of urinary catheter is an essential component of the enhanced recovery after surgery (ERAS) programs

Similar to early diet intake and adequate pain control, early removal of urinary catheter or other drainage tubes is one of the essential strategies to conduct the enhanced recovery after surgery (ERAS) program, which has steadily gained in attention and considered an advanced key step in modern clinical care to achieve a better quality of medical care which is cooperated by buying-in from care team partners, such as the patient and family participants and the professional team (physicians, nurses, pharmacologists, technicians, and others), who are involved in every phase of care and cover the entire medical care beginning the preoperative period (nil per os [NPO] time for liquid, selection of mechanical or oral antibiotic bowel preparation, and preoperative nonopioid analgesia pain prophylaxis), passing through intraoperative period (local and regional anesthesia, tight fluid balance, adequate oxygen administration and minimized alternation of body temperatures for the purpose to minimize the variation of organ function and maintain the stable homeostasis), and ending the postoperative period (shortening time to oral intake, ambulation, indwelling urethra catheter and nasogastric tube use, adequate prophylaxis for deep vein thrombosis, routine multiclass antiemetic and painkiller prescriptions for painless recovery) [1–5].

Additionally, many advanced improvement of surgical techniques, such as minimally invasive approach and more reliable instruments for homeostasis and better understandings of pathophysiologic changes during and after the surgery, ERAS has become one of the standard of care for surgical patients based on its high cost-effectiveness without compromising the therapeutic effects [5–8], although there are many barriers, such as the providers' perceptions and routine practice behaviors which are the leading cause to impede the success to perform ERAS programs [5]. Foley catheter may be one of the most well-known factors reflective of this debated issue, which includes the need of placement of catheter during the operation as well as the appropriate timing of removal of Foley catheter after surgery, particularly for those patients treated with vaginal surgery and/or major surgery, such as radical hysterectomy if Foley catheter is applied during the operation [5]. Prolonged deposition of Foley catheter after vaginal surgery is believed a good clinical and routine practice; however, evidence is weak, suggesting this issue is worthy of investigation. We are happy to introduce the recent systemic review and meta-analysis conducted by Dr. Fang's to explore the effect of the timing of Foley catheter removal after vaginal surgery [9].

Dr. Fang enrolled eight studies to perform this analysis. Although all eight studies had investigated the outcomes between early catheter removal and late catheter removal in women after vaginal surgery, the heterogeneity is dramatically high, including the significant difference of the cut of value to distinguish the early (3 h or 24 h after operation) and late (24 h or 72 h after operation) removal or to compare the outcome between the early and late removal (24 h vs. 48 h; 3 h vs. 24 h; 24 h vs. 72 h; 48 h vs. 120 h; and 24 h vs. 96 h), contributing to many forest plots available [9]. In term of incidence of urinary tract infection (UTI), the authors found there is no difference between 3 h and 24 h (odds ratio [OR] 0.86, 95% confidence interval [95% CI] 0.51–1.46); however, the proportion trend became much apparent favoring the early-removal of Foley catheter in reducing the incidence of UTI with OR 0.22 (95% CI 0.10–0.51) in comparison between 24 h vs. 48 h and over, and OR 0.09 (95% CI 0.03–0.24) in comparison between 48 h vs. 120 h [9]. If the agreement of benefits, such as a reduction of incidence of UTI in patients with early removal of Foley catheter after vaginal surgery is made, the incidence of urinary retention after removing Foley catheter should not be increased. However, this part may be relatively conflicted. According to the authors' report, there was no statistically significant difference of Foley removal between 3 h versus 24 h or more (OR 2.54, 95% CI 0.87–7.41) as well as 24 h versus 48 h or more (OR 1.82, 0.71–4.64), but significant difference between 48 h versus 120 h or more (OR 6.88, 95% CI 2.44–19.40), suggesting that removal of Foley catheter within postoperative 48 h seemed to be associated with the similar risk of urinary retention at any time (3 h, 24 h, and 48 h) and only maintenance of Foley catheter more than 120 h (five days) may decrease the incidence of urinary retention in patients after vaginal surgery. Moreover, average of length of hospital stay was dramatically and significantly decreased in the early removal of Foley catheter group compared to the late removal of Foley catheter group. All suggest that early removal of Foley catheter may be a better recommendation for patients after vaginal surgery. Additionally, the authors concluded that the use of prolonged deposition of Foley catheter strategy, although may prevent urinary retention, will increase the incidence of UTI, bother the patients, limit the activity of patients, prolong the stay of hospital and of the most importance, increase the medical costs [9]. The current meta-analysis and systemic review is a really interesting topic to refresh our long-term thought about the appropriate timing of Foley catheter removal

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for women after vaginal surgery favoring the trend to remove Foley catheter earlier. However, there is no doubt that the deposition of Foley catheter more than 120 h may be associated with the decreased incidence of urinary retention.

Based on the aforementioned findings, there is still absent of consensus about the recommended timing to remove Foley catheter in women after vaginal surgery. In fact, surgery about pelvic floor dysfunction is relatively complicated. As shown by authors, the study population included anterior colporrhaphy and vaginal hysterectomy with or without pelvic floor reconstruction. Additionally, the preoperatively accompanied symptoms or signs about pelvic floor disorder diseases (PFDD) and the severity of PFDD have not been included for the current analysis. Moreover, no data addressing the additional accessary material, such as mesh applied to vaginal surgery have been found. Finally, some of the authors' mentioned surgeries, such as anterior colporrhaphy have been rarely performed by urogynecologists, since stress urinary incontinence was often corrected by recently developed technology, such as minimally invasive pectopexy with concomitant I-stop-mini sling, midurethral slings and many others [10–13]. All may impede the findings reported by authors and subsequently result in inconsistent conclusion.

Finally, the time interval used to determine the phase "early" after vaginal surgery may be not precise or accurate. As shown by authors, 3 h, 24 h and 48 h were all grouped as "early removal of Foley catheter". Additionally, it is well known that operation time for vaginal surgery for PFDD may vary greatly, such as supposed shortening operative time for anterior colporrhaphy and needing a relatively longer operative time for vaginal hysterectomy with pelvic floor reconstruction, and is largely dependent on the complexity of the surgery and/or seniority of the surgeons. However, the recent trend to remove Foley catheter as soon as possible after surgery is apparent. Based on the well-accepted concept about ERAS, the appropriate time to remove Foley catheter after specific type of vaginal surgeries should be evaluated in more precise and more specific patterns, which not only provides a better patient's care but also offers a clear guide for the health-providers to reach "win-win" and cost-effective state of both patients and health-providers.

Conflicts of interest

Dr. Peng-Hui Wang, Dr. Szu-Ting Yang and Dr. Chia-Hao Liu, editorial board members at Taiwanese Journal of Obstetrics and Gynecology, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Editorial

Besides the front-line maintenance therapy, is any positive impact of poly (ADP-ribose) polymerase (PARP) inhibitors on recurrent high-grade ovarian cancer?

High-grade epithelial ovarian cancer (HG-EOC) is still one of the most lethal gynecologic-organ cancers, partly because of its obscure clinical presentation with apparently delayed diagnosis and partly because of its high recurrence without an effective rescue treatment protocol [1–5]. The standard of care therapy for HG-EOC includes the combination of complete and thorough cytoreductive surgery mediated by either primary cytoreductive surgery or neoadjuvant chemotherapy-based interval cytoreductive surgery and platinum-paclitaxel based multi-agent chemotherapy [1,2]. After the completion of platinum-paclitaxel multiagent chemotherapy (CT), many patients can reach the complete clinical remission [1–3]. However, although the initial therapeutic effect is good, up to three-quarters of the patients will recur, contributing the biggest challenge for these HG-EOC patients. With better understandings of pathophysiology of HG-EOC and far-advanced technology to improve the outcome, more and more patients can have the satisfactory disease control and obtain the longer progression-free survival (PFS) or even overall survival (OS). Among these, poly (ADP-ribose) polymerase (PARP) inhibitors (PARP-i) may be one of the most successful product to revolutionize the landscape of HG-ECO treatment and become the one of the therapeutic choices for HG-EOC patients, particularly for those with BRCA1 or BRCA2 mutations [4]. In this editorial comment, we are happy to introduce Dr. Adrianto's work addressing the topic entitled “Efficacy and safety of rucaparib in patients with recurrent high-grade ovarian carcinoma: A systematic review and meta-analysis” [6].

The authors found that objective response rate (ORR) was apparently better in patients treated with rucaparib compared to control group (hazard ratio [HR] 0.33, 95% confident interval [95% CI] 0.22–0.45) [6]. The favorable or superior ORR in patients treated with rucaparib was also apparent and significant in terms of evaluation of PFS in patients treated with rucaparib than the control group with HR of 0.36 (10.8 months vs. 5.4 months) and 0.67 (7.4 months vs. 5.7 months), respectively (95% CI 0.30–0.45, and 0.52–0.86, respectively) [6]. Both superiorities (ORR and PFS) of rucaparib treatment was also reflective by prolonged OS, particularly for those patients with BRCA mutation (BRCAmut) with 22.7 months compared to 14.7 months or 13.3 months in patients without BRCAmut, respectively [6]. Additionally, the authors found that the significant enhancement in PFS was present in all corners, including platinum-partial sensitive, platinum-resistant, and platinum-sensitive subpopulation compared to the CT cohort, suggesting that rucaparib could offer therapeutic benefits to patients with recurrent HG-EOC, regardless of their platinum sensitivity status [6].

However, the aforementioned survival benefits were conflicted by high percentage of adverse events (AEs), particularly severe AEs (grade 3 or above) with 58.6%~60% in the rucaparib group compared to 16%~38% in the control group [6]. This extensive and high incidence of treatment-emergent AEs (TEAEs) in patients treated with rucaparib may underscore the treatment's potential risks [6], suggesting the recommendation of using rucaparib in the management of patients with recurrent HG-EOC is still controversial. The NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Ovarian Cancer/Fallopian Tube cancer/Primary peritoneal Cancer (NCCN Guidelines®) Version 3.2024–July 15, 2024, acceptable recurrence therapies for platinum-sensitive EOC/Fallopian tube/primary peritoneal cancer treatment include carboplatin/gemcitabine, or liposomal doxorubicin or paclitaxel with/without adding bevacizumab as preferred regimen [7]. By contrast, little evidence supports the use targeted therapy as other recommended regimens, including niraparib, olaparib, pazopanib, and rucaparib (category 2 B or 3) [7]. For recurrent therapy to platinum-resistant HG EOC, targeted therapy using single agent, such as niraparib, Olaparib, pazopanib and rucaparib is all classified as category 2 b or 3, meaning no recommendation [7]. The possible useful indication is only limited to patients with deleterious germline and/or somatic BRCAmut (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of CT [7]. All suggest that the role of PARP-I in recent HG-EOC patients is uncertain, and this treatment is still un-recommended in the current clinical practice. The possible valuable situation is only limited to these HG-EOC patients having heavy CT therapy (two lines or above) and BRCAmut.

In the current review by Dr. Lin addressing the topic about the treatment paradigms for platinum-resistant EOC also showed monotherapy with PARP-i is generally not recommended for patients with BRCA wild-type platinum-resistant disease in clinical practice, although they highlighted the possibility of using combination of PARP-i and immune checkpoint inhibitors (ICIs) for treatment of platinum-resistant EOC patients, based on PARP-i modulating the tumor microenvironment, promoting an immune-supportive milieu, increasing the expression of programmed cell death protein ligand 1 (PD-L1) on cancer cells, damaging cancer cell DNA leading to release of tumor-associated antigens, promoting an inflamed tumor microenvironment, favoring efficacy of ICIs [4]. In fact, the evolutionary development of ICIs antibodies (Abs) targeting cytotoxic programmed cell death protein 1 (anti-PD-1, including pembrolizumab,

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dostarlimab, etc.) and/or anti-PD-L1 (including avelumab, durvalumab, nivolumab, etc.) has advanced in the brand-new field of cancer treatment and many of them have been proved by the U.S. Food and Drug Administration (FDA) for the treatment of various advanced solid or hematologic malignancies by blocking the PD-1 or PD-L1 immune checkpoint [8]. In gynecologic cancers, ICIs may be more active in the management of cervical cancer and endometrial cancer [8–10]. However, with combination of other agents, such as PARP-I, the potential therapeutic efficacy to HG-EOC has been tried [11], although the evidence is still lacking [12].

Since the outcome of patients with HG-EOC is still poor, we welcome more and more studies focusing on this topic.

Conflicts of interest

Dr. Peng-Hui Wang, editorial board members at Taiwanese Journal of Obstetrics and Gynecology, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Review Article

Efficacy and safety of rucaparib in patients with recurrent high-grade ovarian carcinoma: A systematic review and meta-analysis

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ABSTRACT

Ovarian cancer stands as the third most prevalent gynecological malignancy. The advent of PARP inhibitors, particularly rucaparib, has revolutionized the landscape of advanced ovarian cancer treatment, demonstrating notable efficacy with minimal toxicity, especially in patients not previously exposed to PARP inhibitors. Rucaparib's precision-driven approach, targeting specific genetic mutations, disrupts DNA repair mechanisms, resulting in cytotoxic effects on neoplastic cells. This comprehensive review delves into the clinical efficacy and safety profile of rucaparib in recurrent ovarian cancer, showcasing its promising therapeutic approach. A systematic search of studies reporting rucaparib efficacy and safety, up to September 2023, was conducted across various reputable databases and sources. The meta-analysis of seven articles revealed a pooled objective response rate (ORR) of 0.331 (95% CI, 0.221–0.449; I2 = 92.4%), underscoring rucaparib's efficacy, particularly evident in the BRCA-mutated cohort. Rucaparib consistently outperformed controls in progression-free survival (PFS) and overall survival (OS). Safety evaluations indicated that 98.7% of patients experienced treatment-emergent adverse events (TEAEs), with 61% being grade ≥3. Notable TEAEs included nausea (69.0%), fatigue (66.8%), vomiting (37.3%), and constipation (32.1%). Hematological concerns comprised anemia (47.9%), thrombocytopenia, elevated AST/ALT (37.3%), and serum creatinine levels (19.7%). Despite favourable outcomes, the rucaparib group recorded higher event rates across various metrics than controls. The findings underscore the need for meticulous monitoring and dose adjustments to optimize therapeutic outcomes and mitigate the increased risks associated with adverse events. International Prospective Register of Systematic Review Identifier: CRD42023459646.

Introduction

Ovarian cancer ranks as the third most prevalent gynecological malignancy. It represents a significant cause of mortality among women, with an age-standardized rate of 4.2 [1]. Most diagnosed epithelial ovarian cancer cases do not exhibit associations with genetic mutations. Nonetheless, 18 percent of these cases can be attributed to hereditary mutations in BRCA1 and 2 genes [2]. Despite the best treatments, about 80–85% of patients will experience cancer recurrence or resistance. The risk of recurrence is higher for patients with more advanced cancer at diagnosis [3,4]. Current treatments focus on maintenance therapy with anti-angiogenic drugs and PARP inhibitors [5,6]. Poly (ADP-ribose) polymerase (PARP) inhibitors have revolutionized the treatment of advanced ovarian cancer. These drugs are effective and well-tolerated and have become a treatment mainstay, especially for patients without previous exposure to PARP inhibitors, maintenance of PARP inhibition improves progression-free survival. Rucaparib, a potent PARP inhibitor, selectively impedes the enzymatic activity of poly(ADP-ribose) polymerase (PARP). The primary function of PARP is to mediate the repair of DNA lesions. Therefore, the inhibition of PARP by rucaparib promotes cytotoxicity in neoplastic cells harbouring DNA aberrations, chiefly through the entrapment of PARP1 and the subsequent obstruction of the DNA single-strand break repair pathway [7,8]. Rucaparib, as a targeted therapeutic agent, influences the susceptibilities inherent in

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specific genetic mutations present within tumor cells. This promotes a precision-driven strategy in combating these malignant cells and accomplishes it with reduced systemic toxicity [9]. Such advancements present a promising avenue for numerous patients. This review seeks to illuminate the clinical effectiveness and safety profile of rucaparib in treating recurrent ovarian cancer.

Material and methods

Literature search

Literature searches were performed on PubMed, ScienceDirect, Cochrane Library, EBSCOHost, ProQuest, and gray literature databases (Google Scholar, OpenGrey, WorldCat) for articles published from 01 July 2013 to 01 September 2023. Due to the limited language resources, this review excluded articles in languages other than English. The keywords applied were ("Rucaparib") AND ("Ovarian Cancer" OR "Ovarian Malignancy" OR "Ovarian Tumor" OR "Ovary Neoplasm" OR "Ovary Cancer" OR "Ovary Tumor") and their respective Medical Subject Headings (MeSH) terms, if applicable.

Selection criteria

In our literature search, we focused on English-language clinical studies. Inclusion criteria required participants to be $\geq$ 18 years old, with histologically confirmed diagnoses of high-grade ovarian, fallopian tube, or primary peritoneal cancer. Eligible studies had patients with radiologically confirmed relapsed or recurrent disease prior to enrollment, and those in the intervention group were administered rucaparib, contrasting other treatments or placebo in the control group. Essential data included overall survival (OS), progression-free survival (PFS), objective response rate (ORR) based on RECIST v1.1, and adverse events (AEs). We excluded studies involving prior PARPis recipients, animal research, single case reports/series, editorials, commentaries, letters, and non-full texts.

Data extraction

Three authors (NA, GM, EJT) independently conducted the search, screened articles using specified keywords, and removed duplicates. Articles were then shortlisted based on title/abstract. Full-texts meeting eligibility were thoroughly reviewed for data synthesis, with exclusion reasons noted. Discrepancies were settled by a fourth party (CNRS). All abstracts were independently evaluated by three authors, with conflicts resolved by CNRS. If multiple studies shared participants and outcomes, excluding others, the most detailed study was chosen to avoid redundancy. NA, GM, and EJT assessed the articles' quality independently. Our research followed PRISMA, Cochrane ROB-2, and ROBINS-I guidelines [10–12].

Statistical analyses

Meta-analysis of proportions was used to combine all the data; logit transformations were conducted before meta-analysis, and the reported pooled proportions of depression were calculated using a random-effects model. All meta-analyses were performed using MedCalc, version 19.5.1 [13]. The P-value for the overall effect, $P < 0.05$ with two-tailed, was considered statistically significant. I2 was used to assess the heterogeneity of all the detailed studies. When it was lower than 50%, studies with acceptable heterogeneity were considered, and the fixed-effects model was used; otherwise, a random-effects model with the DerSimonian and Laird method was adopted.

Egger's linear regression test assessed Publication bias for each pooled study group. Begg's rank correlation was also applied to assess potential publication bias; when P was >0.05, there was no publication bias in the study. This systematic review and meta-analysis was registered in PROSPERO on September 13, 2023, with registration number CRD42023459646.

Results

The initial electronic search identified 3739 potential articles. After title and abstract screening, eleven articles were evaluated for in-depth evaluation, of which seven met the criteria for inclusion in meta-analysis [14–21] Fig. 1 illustrates the search and selection process. Among the selected, six were RCTs, and one was a retrospective study, totaling 1038 patients from various countries and centers. Participants aged 35–91 typically received 600 mg of rucaparib orally twice daily over 21 or 28-day cycles, with a significant subset being BRCA mutants (n = 574). The characteristics of included studies are summarized in Table 1. Most of the studies showed some bias concerns due to the randomization process [16–19]. One study was judged to have a severe risk of bias as it did not account for confounding factors (Fig. 2) [20].

Overall survival

Two studies provided median OS data for 276 participants, ranging from 5.5 to 28.6 months. Swisher et al. performed a subgroup analysis based on BRCA status. The results demonstrated that the BRCAmut subgroup (n = 84) showed a superior OS of 22.7 months (95% CI 16.7–28.6) in comparison to the BRCAwt/LOH-high subgroup (n = 73) which had an OS of 14.7 months (95% CI 10.8–19.8) and the BRCAwt/LOH-low subgroup (n = 107) which demonstrated an OS of 13.3 months (95% CI 9.1–16.0).

Progression-free survival

Median PFS data was sourced from six distinct studies (n = 1166), demonstrating a range of 1.8–22.9 months. Of particular note, Coleman et al. and Kristeleit et al. detailed that the ITT population receiving rucaparib treatment had higher PFS than the control group. Specifically, Coleman et al. recorded a PFS of 10.8 (8.3–11.4) in contrast to the control group's 5.4 (5.3–5.5) (HR 0.36, 95% CI 0.30–0.45). Kristeleit et al. observed a PFS of 7.4 (6.7–7.9) compared to 5.7 (5.5–6.7) months in their respective control group (HR 0.67, 95% CI 0.52–0.86).

Objective response rate

A meta-analysis examined data from seven studies that included 957 patients, focusing on the objective response rate (ORR) based on RECIST criteria (Fig. 3, Table 2). The combined ORR was 0.331 (95% CI, 0.221–0.449). Significant heterogeneity was detected among these studies ($Q = 79.9349$, $P < 0.001$, $I2 = 92.4\%$). Among five studies that covered 489 patients and reported both complete and partial responses, the rates were 62.4% (0.624, 95% CI, 0.361–0.951) for complete response and 30.7% (0.307, 95% CI, 0.161–0.475) for partial response. While there was significant heterogeneity in the studies about the partial response ($Q = 1.826$, $P < 0.001$, $I2 = 92.2\%$), the complete response data was relatively consistent ($Q = 6.3380$, $P = 0.1753$, $I2 = 87.0\%$). 32.6% of patients exhibited stable disease (SD) as their best response to rucaparib, while 14.1% showed progressive disease (PD). The heterogeneity tests for these responses indicated I2 values of 91.56% and 81.54%, respectively. No publication bias was found regarding ORR ($p = 0.3807$), CR ($p = 0.8702$), PR ($p = 0.737$), SD ($p = 0.185$), and PD ($p = 0.793$).

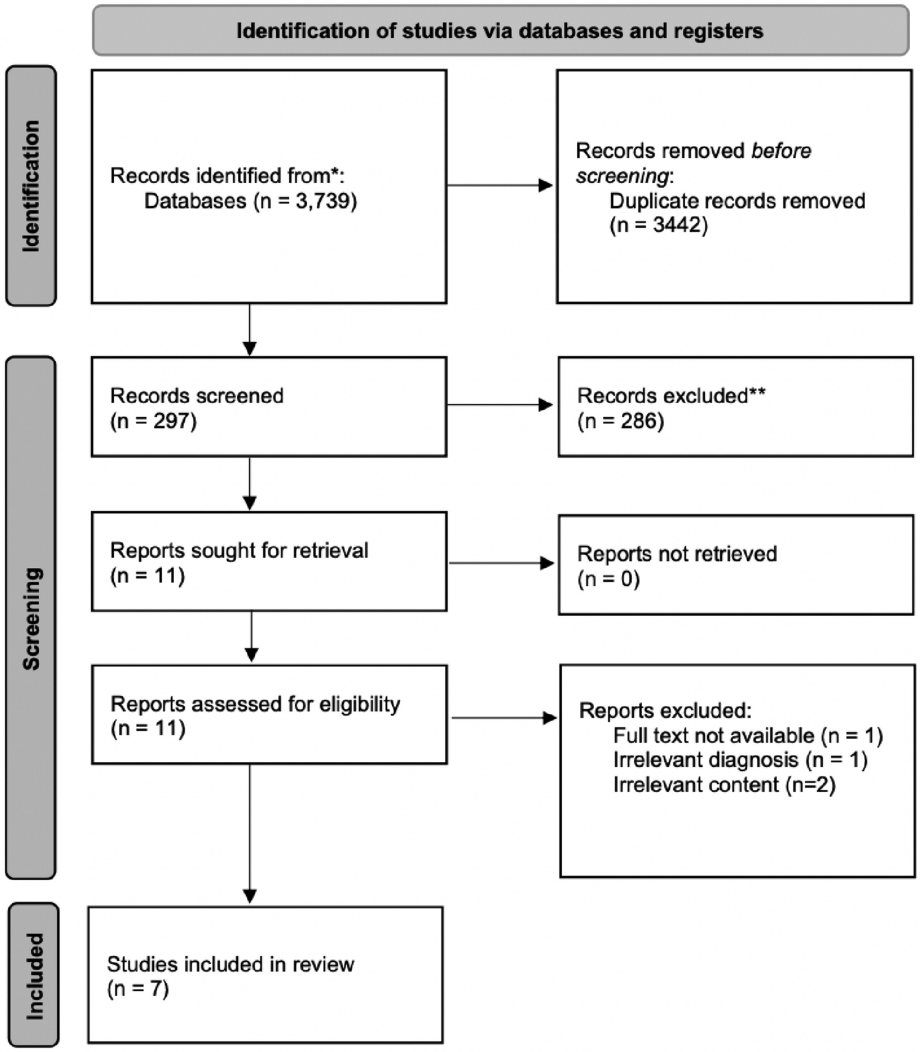

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. The diagram summarizes the search strategy and selection process to include articles eligible for this meta-analysis [10].

Table 1
Characteristics of the studies incorporated into this meta-analysis (n = 7).

No	Author	Study Design	Location	Intervention	Age (Years)	BRCA status				ECOG
						BRCA mutant (%)		BRCA wild-type (%)	Unknown	
						BRCA 1 (%)	BRCA2 (%)			
1	Coleman et al, 2017 [14]	Randomized, double-blind, placebo-controlled phase 3 trial (ARIEL3)	Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, UK, and USA	Oral rucaparib 600 mg twice daily (n=375)	61.0 (53.0-67.0)	80 (21)	50 (13)	245 (65)	-	0–1
				Placebo (n=189)	62.0 (53.0-68.0)	37 (20)	29 (15)	123 (65)	-	0–1
2	Kristeleit et al, 2023 [15]	Open-Label, Phase 1/2 Trial (Study10)	UK, Spain, Israel, Canada	Oral Rucaparib 600 mg twice daily (21 days) (n=54)	57 (42.0-84.0)	39 (72.2)	15 (27.8)	-	-	0–1
3	Kristeleit et al, 2022 [16]	International, open-label, randomized, phase 3 trial (ARIEL4) NCT02855944	Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA	Oral Rucaparib 600 mg twice daily (28 days) (n= 233)	58 (50-63)	181 (78)	52 (22)	-	-	0–1
				Chemotherapy (n = 116)	59 (52-64)	79 (68)	36 (31)	1 (non-BRCA)	-	0–1
4	Swisher E M et al, 2017 [18]	An international, multicentre, open-label, phase 2 trial (ARIEL2 part 1) NCT01891344	Multicenter, International	Oral Rucaparib 600 mg twice daily (28 days) (n = 204)	64.5 (31.0-86.0)	40 (19.6)		164 (80.4)	-	0–2
5	Swisher E M et al, 2021 [17]	Open-Label, Phase 2 Trial (ARIEL2 part 2) NCT01891344	Multicenter, International	Oral Rucaparib 600 mg twice daily (28 days) (n = 287)	63 (35.0-91.0)	84 (29)		203 (71)	-	0–2
6	Kristeleit R et al, 2017 [19]	A Phase I–II Study NCT01482715	-	Oral Rucaparib 600 mg twice daily (21 days) (n = 42)	57 (42.0-84.0)	30 (71.4)	12 (28.6)	-	-	0–1
7	Yubero A et al, 2022 [20]	Retrospective study (GEICO Study)	Spain	Oral Rucaparib 600 mg twice daily (n = 51)	63 (36-86)	31		16	4	0–2

ECOG, Eastern Cooperative Oncology Group performance status.

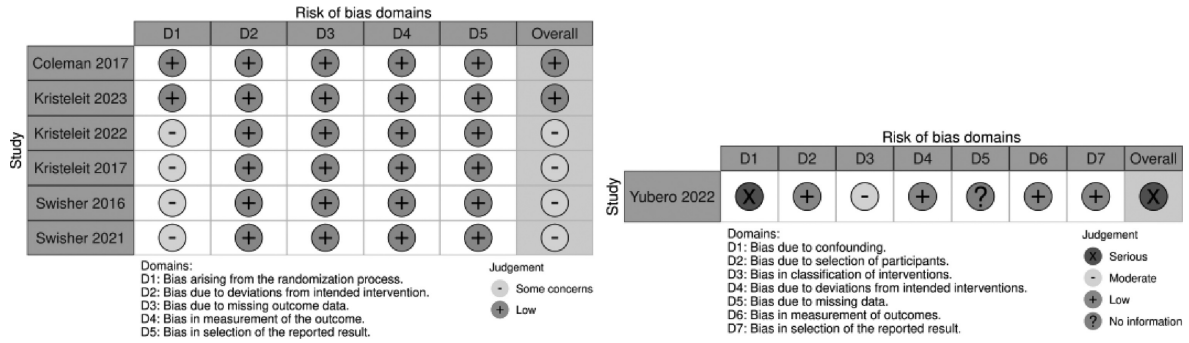

Fig. 2. Risk of Bias Assessment using Cochrane ROB-2 (left) and ROBINS-I (right) Tool [11,12].

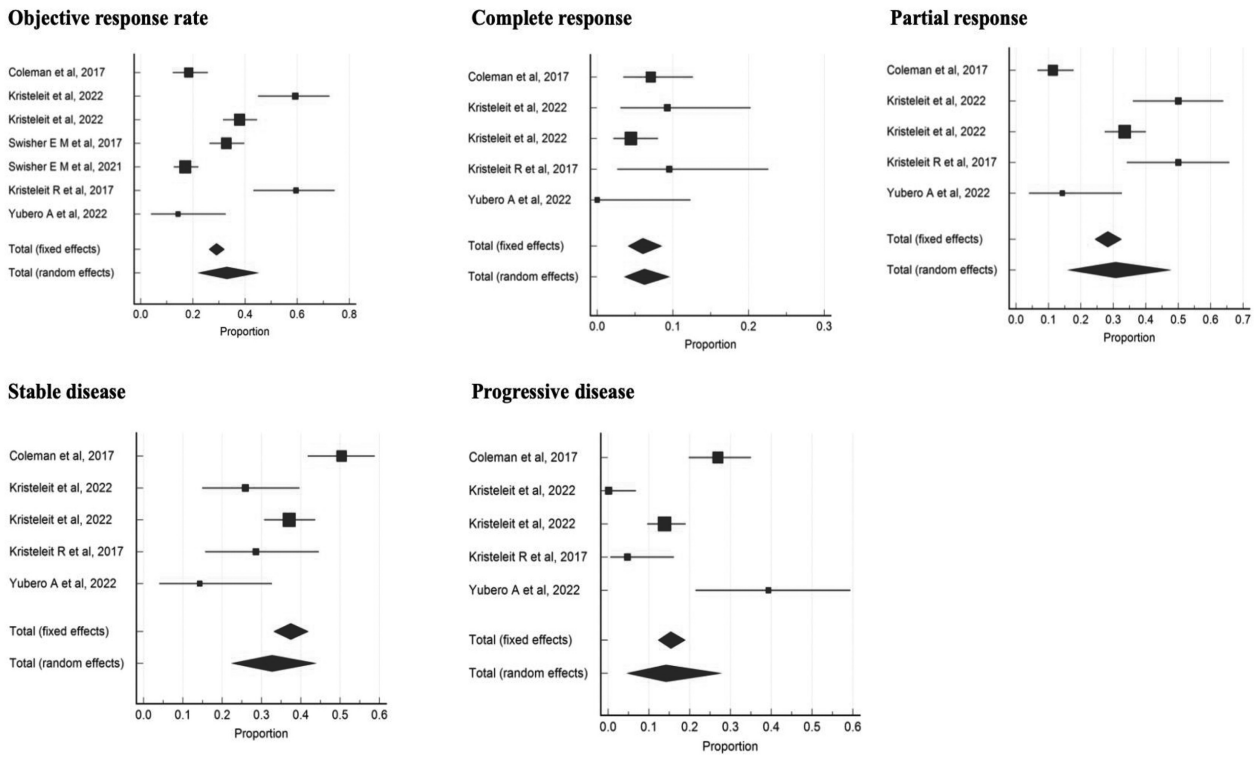

Fig. 3. Forrest plot of six studies assessing the prevalence of ORR.

Safety

Seven articles, encompassing a population of 1,242, were evaluated for safety. The incidence data for treatment-emergent adverse events (TEAEs) showed that 98.7% (with a 95% confidence interval (CI) ranging from 96.2% to 99.9%) of participants encountered TEAEs. Of these, 637/1038 (62%) were deemed to be of grade 3 or higher severity, with a 95% CI ranging from 55.0% to 68.8%. In two studies by Ledermann JA et al. and Kristeleit et al., the incidence of TEAEs in the rucaparib group was observed to be greater than that in the control group, with rates of 100% vs. 96% and 95.6% vs. 94%, respectively. Regarding grade 3 or 4 adverse events, the rucaparib group, at 58.6%–60%, exhibited a higher incidence than 16%–38% in the control cohort.

Frequent TEAE manifestations, observed in a minimum of one-third of the participants, encompassed nausea (present in 881 individuals or 69.1%), fatigue (noted in 842 individuals or 67.0%), vomiting (documented in 482 individuals or 37.4%), and constipation (observed in 409 individuals or 32.3%). The prevalence of these predominant symptoms in the rucaparib cohort consistently exceeded that in the control cohort, as corroborated by the findings from two studies: Ledermann JA et al. (2020) and Kristeleit et al. (2022).

On hematological parameters, the incidences of anemia, thrombocytopenia, and neutropenia were documented at 48.2% (95% CI, 39.5%–56.8%), 25.5% (95% CI, 20.4%–31.0%), and 17.8% (95% CI, 13.0%–23.1%), in sequence. The frequencies of anemia, thrombocytopenia, and neutropenia were discernibly elevated in the rucaparib cohort as opposed to the control group. The prevalence of hepatotoxicity, characterized by an escalation in serum AST/ALT, was recorded at 37.5% (95% CI, 31.8%–43.4%). This prevalence was accentuated in the rucaparib cohort compared to the control cohort (34%–34.4% vs. 4%–12%). Furthermore, nephrotoxicity, outlined by an augmentation in serum creatinine concentrations, exhibited a rate of 19.9% (95% CI, 14.9%–25.5%), again predominantly in the rucaparib cohort (14.2%–16% vs 2%–8%). Nonetheless, a noticeable heterogeneity was manifested across studies for all safety endpoints. This meta-analysis found no evidence of publication bias, as

Table 2
Efficacy of included studies (n = 7).

No	Author	PFS (median, months)		HR	OS (median, months)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)	DOR (median, months)
1	Coleman et al., 2017 [14]	Rucaparib (n = 375)	ITT 10.8 (8.3–11.4) BRCAmut (n = 130) 16.6 (13.4–22.9)	ITT 0.36 (0.30–0.45)	Data not mature	26/141 (18.4, 12.4–25.8)	10/141 (7.1)	16/141 (11.3)	71/141 (50.4)	38 (27.0)	–
		Placebo (n = 189)	ITT 5.4 (5.3–5.5) BRCAmut (n = 66) 5.4 (3.4–6.7)	BRCAmut 0.23 (0.16–0.34)		5/66 (8, 2–17)	1/66 (1.5)	4/66 (6.1)	29/66 (43.9)	32/66 (48.5)	
2	Kristeleit et al., 2023 [15]	8.5 (6.7–11.7)		–	(n = 12) 25.1 (5.5-not reached)	32/54 (59.3, 45.0–72.4)	5/54 (9.3)	27/54 (50.0)	14/54 (25.9)	4/54 (7.4)	8.9 (6.6–12.9)
3	Kristeleit et al., 2022 [16]	Rucaparib (n = 233	ITT 7.4 (6.7–7.9) BRCA 1 (n = 173) 7.4 (7.2–9.1) BRCA2 (n = 78) 8.3 (6.5–16.3)	ITT 0.67 (0.52–0.86) BRCA1 0.68 (0.49–0.92) BRCA2	Data not mature	85/224 (38, 32–45)	10/224 (4.0)	75/224 (33.0)	83/224 (37)	31/224 (14)	9.4 (7.5–11.1)
		Placebo (n = 111)	ITT 5.7 (5.5–6.7) BRCA 1 (n = 74) 5.7 (4.7–7.4) BRCA2 (n = 31) 5.6 (4.1–7.9)	0.51 (0.29–0.89)		32/116 (30, 22–40)	2/116 (2)	30/116 (28)	43/116 (41)	19/116 (18)	7.2 (3.9–9.4)
4	Swisher E M et al., 2017 [18]	BRCAmut (n = 40) 12.8 (9–14.7) BRCAwt/LOH-high (n = 82) 5.7 (5.3–7.6) BRCAwt/LOH-low (n = 70) 5.2 (3.6–5.5)		BRCAmut vs BRCA wild-type and LOH low 0.27 (0.16–0.44) BRCA wild-type and LOH high vs BRCA wild-type and LOH low 0.62 (0.42–0.90)	–	BRCAmut (n = 40) 32/40 (80,64–91) BRCAwt/LOH-high (n = 82) 24/82 (29, 20–40) BRCAwt/LOH-low (n = 70) 7/70 (10, 4–20) BRCA wild-type and LOH not classified (n = 12) 4/12 (33, 10–65)	–	–	–	–	BRCAmut (n = 40) 9.2 (6.4–12.9) BRCAwt/LOH-high (n = 82) 10.8 (5.7-NR) BRCAwt/LOH-low (n = 70) 5.6 (4.6–8.5)
5	Swisher E M et al., 2021 [17]	BRCAmut (n = 84) 7.3 (6.2–9.0) BRCAwt/LOH-high (n = 73) 1.9 (1.8–3.7) BRCAwt/LOH-low (n = 107) 3.7 (2.1–5.4)		BRCAmut vs BRCAwt/LOH-low 0.58 (0.43–0.78) BRCAwt/LOH-high vs BRCAwt/LOH-low 1.06 (0.78–1.45)	BRCAmut (n = 84) 22.7 (16.7–28.6) BRCAwt/LOH-high (n = 73) 14.7 (10.8–19.8) BRCAwt/LOH-low (n = 107) 13.3 (9.1–16.0)	BRCAmut (n = 84) 31% (21.3–42.0) BRCAwt/LOH-high (n = 73) 6.8% (2.3–15.3) BRCAwt/LOH-low (n = 107) 5.6% (2.1–11.8)	–	–	–	–	BRCAmut (n = 84) 5.8 (5.6–10.3) BRCAwt/LOH-high (n = 73) 9.3 (3.6-NR) BRCAwt/LOH-low (n = 107) 10.3 (5.6-NR)
6	Kristeleit R et al., 2017 [19]	–		–	–	25/42 (52.4, 36.4–68)	4/42 (9.5)	21/42 (50)	12/42 (28.6)	2/42 (4.8)	7.8 (5.6–10.5)
7	Yubero A et al., 2022 [20] –	Maintenance 9.1 (4.2–11.6) Treatment Pt-S = 10.6 (2.5-NA) Pt-R = 2.2 (1.1–3.2)		–	–	4/28 (14)	0 (0)	4/28 (14)	4/28 (14)	11/28 (39)	–

PFS, Progression-free survival; HR, Hazard ratio; ITT, Intention-to-treat; OS, Overall survival; ORR, Objective response rate; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; DOR, Duration of response; LOH, loss of heterozygosity; BRCAmut, BRCA mutation, BRCAwt, BRCA wild type. Pt-S, Platinum sensitive; Pt-R, Platinum resistant.

Table 3
Safety of included studies (n = 7).

No	Adverse Effect	Ledermann JA et al., 2020 [21]		Kristeleit et al., 2023 [15] (n = 54)	Kristeleit et al., 2022 [16] (n = 232)		Swisher E M et al., 2017 [18] (n = 204)	Swisher E M et al., 2021 [17] (n = 287)	Kristeleit R et al., 2017 [19] (n = 42)	Yubero A et al., 2022 [20] (n = 51)
		Rucaparib (n = 372)	Placebo (n = 189)		Rucaparib (n = 232)	Placebo (n = 113)				
1	TEAE (%)	372 (100)	182 (96)	54 (100)	222 (95.6)	106 (94)	204 (100)	287 (100)	42 (100)	44 (86.2)
2	TEAE ≥3 (%)	222 (60)	30 (16)	41 (75.9)	136 (58.6)	43 (38)	–	186 (64.8)	32 (76.2)	20 (39)
3	Treatment Interruption (%)	243 (65)	19 (10)	36 (66.7)	115 (50)	50 (44)	–	172 (59.9)	27 (64.3)	30 (60)
4	Dose Reduction (%)	206 (55)	8 (4)	34 (63)	115 (50)	50 (44)	–	134 (46.7)	29 (69)	25 (49)
5	Discontinuation (%)	57 (15)	3 (2)	8 (14.8)	19 (8)	14 (12)	–	69 (24)	26 (61.9)	46 (90)
6	Death (%)	6 (2)	2 (1)	1 (1.9)	10 (4)	1 (1)	–	18 (6.2)	3 (7)	–
General Disorder										
7	Fatigue/Asthenia (%)	263 (71)	84 (45)	42 (78)	115 (50)	50 (44)	159 (78)	212 (73.9)	36 (85.7)	15 (29)
8	Peripheral edema (%)	41 (11)	14 (7)	–	–	–	22 (11)	38 (13.2)	–	–
9	Pyrexia (%)	45 (12)	9 (5)	–	23 (9)	7 (6)	25 (12)	34 (11.8)	–	–
Gastrointestinal										
10	Nausea (%)	282 (76)	69 (37)	46 (85.2)	124 (53.4)	36 (32)	163 (79)	219 (76.3)	35 (83.3)	12 (23.2)
11	Abdominal pain (%)	112 (30)	49 (26)	25 (46.3)	54 (23.2)	18 (16)	61 (29)	93 (32.4)	18 (42.9)	4 (7.8)
12	Abdominal distension (%)	42 (11)	24 (13)	–	–	–	43 (21)	32 (11.1)	10 (23.8)	–
13	Constipation (%)	141 (38)	46 (24)	29 (53.7)	37 (16)	19 (17)	94 (46)	84 (29.3)	22 (52.4)	2 (3.9)
14	Diarrhea (%)	121 (33)	41 (22)	20 (37)	47 (20.2)	24 (21)	68 (33)	84 (29.3)	16 (38.1)	4 (7.8)
15	Vomiting (%)	138 (37)	29 (15)	22 (61.1)	79 (34)	19 (17)	89 (44)	126 (43.9)	23 (54.8)	5 (9.8)
16	Dyspepsia (%)	54 (15)	9 (5)	–	–	–	–	–	–	–
Hematology										
17	Decreased hemoglobin (Anemia) (%)	145 (39)	10 (6)	38 (70.4)	125 (53.8)	36 (33)	74 (36)	127 (44.3)	30 (71.4)	15 (29)
18	Decreased platelet count (Thrombocytopenia) (%)	109 (29)	5 (3)	19 (35.2)	54 (23.2)	13 (12)	30 (14)	78 (27.2)	15 (35.7)	10 (19.6)
19	Decreased neutrophil count (Neutropenia) (%)	72 (20)	9 (6)	14 (25.9)	52 (22.4)	32 (28)	26 (12)	30 (10.5)	13 (31)	5 (9.8)
Investigation										
20	Increased AST/ALT (%)	129 (34)	8 (4)	26 (48.1)	80 (34.4)	13 (12)	86 (42)	101 (35.2)	24 (57.1)	9 (17.6)
21	Increased Creatinine (%)	61 (16)	3 (2)	21 (38.9)	33 (14.2)	9 (8)	34 (17)	65 (22.6)	14 (33.3)	4 (7.8)
22	Increased ALP (%)	–	–	11 (20.4)	–	–	–		10 (23.8)	5 (9.8)
Nervous System Disorder										
23	Dizziness (%)	57 (15)	15 (8)	–	–	–	38 (18)	35 (21.2)	9 (21.4)	–
24	Dysgeusia (%)	148 (40)	13 (7)	19 (35.2)	39 (17)	8 (7)	87 (43)	93 (32.4)	17 (40.5)	2 (3.9)
25	Headache (%)	71 (19)	31 (17)	22 (40.7)	–	–	34 (17)	35 (11.8)	19 (45.2)	–
Musculoskeletal										
26	Arthralgia (%)	59 (16)	24 (13)	12 (22.2)	–	–	–	–	–	–
27	Myalgia/Backpain (%)	50 (13)	28 (15)	–	–	–	16 (7)	–	–	–
Infection										
28	Upper respiratory infection (%)	44 (12)	6 (3)	14 (25.9)	–	–	21 (10)	–	10 (23.8)	–
29	Urinary Tract Infection (%)	–	–	11 (20.4)	–	–	37 (18)	36 (12.5)	–	–
30	Pneumonia (%)	–	–	–	10 (4)	0 (0)	2 (1)	–	–	–
Respiratory										
31	Cough (%)	55 (15)	25 (13)	12 (22.2)	–	–	33 (16)	30 (10.5)	9 (21.4)	–
32	Dyspnea (%)	53 (14)	14 (7)	12 (22.2)	10 (4)	9 (8)	–	68 (23.7)	–	–
Metabolism and Nutrition Disorder										
33	Decrease appetite (%)	88 (24)	26 (14)	15 (27.8)	44 (19)	20 (18)	84 (41)	–	–	–
34	Hypomagnesemia (%)	43 (11)	11 (6)	–	–	–	–	29 (10.1)	–	–

TEAE, Treatment-emergent adverse event; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase.

substantiated by Begg's and Egger's statistical assays. Summary is elucidated in Table 3 and Fig. 4.

Discussion

Ovarian cancer (OC) is a leading gynecological malignancy, responsible for roughly 207,000 global deaths annually [1]. Around 70% of OC patients are diagnosed at advanced stages, leading to poor prognosis [22]. The primary treatment for advanced OC involves cytoreductive surgery followed by mainly platinum-based chemotherapy. However, about 90% of patients might face disease progression or recurrence post-treatment [23]. Prior studies confirm the efficacy of PARPis, especially olaparib, for BRCA-mutated OC patients. Our results concur with prior findings on PARPis [24–28].

This study examines rucaparib's efficacy and safety for advanced ovarian cancer (OC). The data reveals rucaparib's superior efficacy in extending progression-free survival (PFS) and overall survival (OS) against controls. The derived hazard ratio underscores a significant reduction in disease progression risk with rucaparib [14,16]. Notably. In contrast, rucaparib consistently improves PFS, and benefits vary across clinical subgroups. Despite the observed significant enhancement in PFS solely within the subset displaying partial sensitivity to platinum, elevated PFS rates were also evident across both platinum-resistant and platinum-sensitive subpopulations in contrast to the chemotherapy cohort. These findings suggest that Rucaparib could offer therapeutic benefits to patients experiencing relapsed ovarian cancer, regardless of their platinum sensitivity status [16]. Rucaparib is a potent therapeutic option, particularly in enhancing PFS in BRCA1/2-mutated, relapsed OC patients compared to standard treatments. We echo other findings and show longer PFS in BRCA-mutated patients than in BRCA wild types [29,30]. PARPis, pivotal in addressing single-strand and double-strand DNA breaks, are now approved as first-line and maintenance therapies to augment PFS post-platinum-based chemotherapy in OC [31]. Given their target on cancers associated

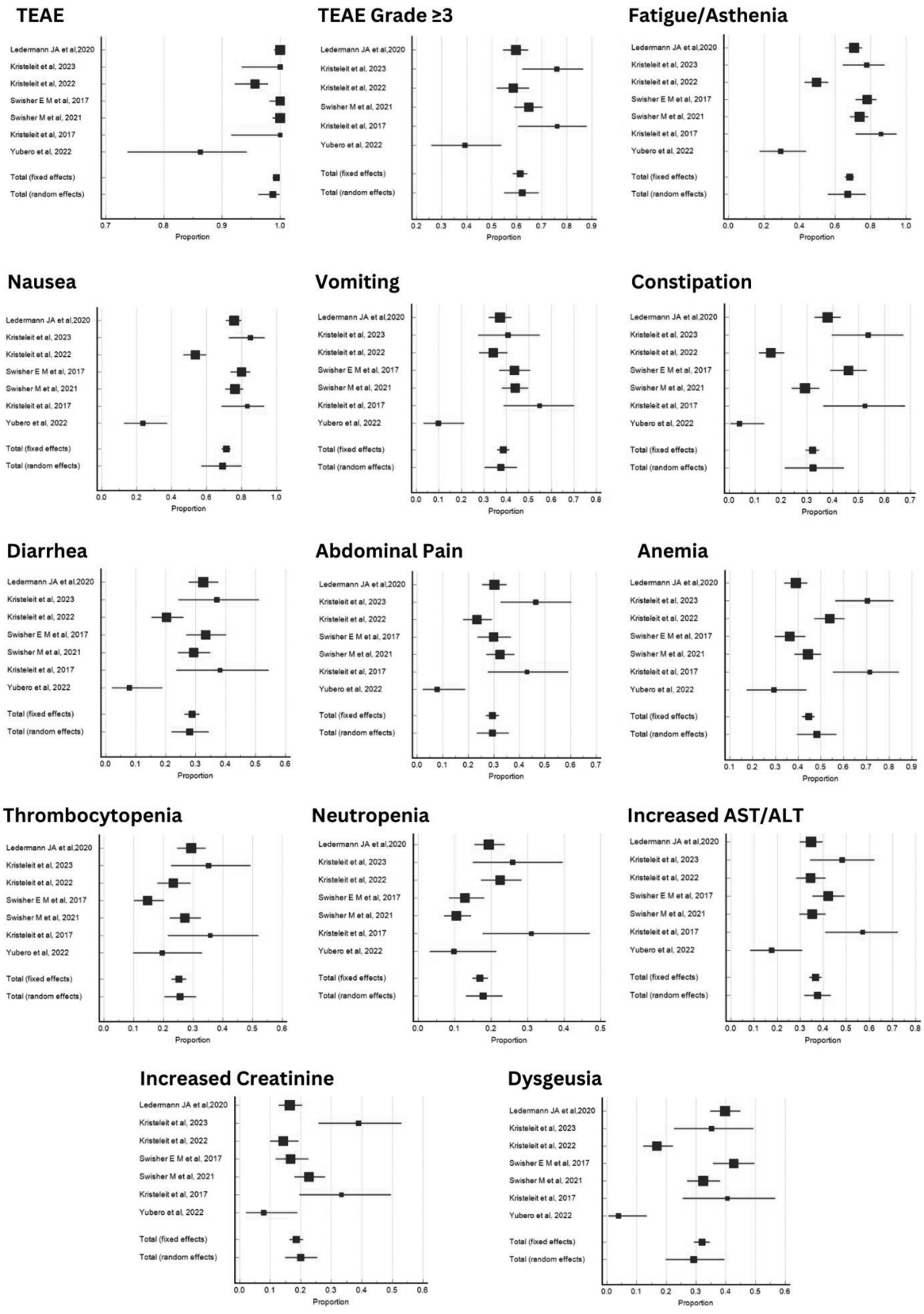

Fig. 4. Forest plot of six studies assessing the prevalence of TEAE.

with BRCA1/2 mutations essential for homologous recombination (HR) DNA repair, their therapeutic significance is evident [32]. Outcome discrepancies arise from participant differences and different therapy durations.

The combined ORR highlights rucaparib's therapeutic promise and reveals a higher ORR than the control group. The result further revealed complete and partial response rates, respectively. While there was heterogeneity in the data, the complete response (CR) trended consistently, suggesting sustained benefits from rucaparib for certain patients. A higher CR percentage was evident in the rucaparib cohort compared to controls, highlighting rucaparib's potential for durable positive outcomes [14,16]. Nevertheless, one-third of the patients receiving rucaparib in this investigation demonstrated stable disease, while a subset experienced disease progression. High heterogeneity in these findings points to possible variances in patient demographics, dosages, co-medications, or study methodologies. This outcome aligns with findings from other studies on PARPis, wherein PARPis consistently demonstrated a superior ORR compared to the control group [33].

Regarding safety, our study revealed an extensive incidence of treatment-emergent adverse events (TEAEs) in patients on rucaparib. This high TEAE frequency underscores the treatment's potential risks. Alarmingly, nearly two-thirds of these TEAEs were of grade 3 or higher, necessitating close monitoring. Comparative analysis from Coleman et al. and Kristeleit et al. affirmed a higher TEAE rate, especially grade$\geq$3 events, in the rucaparib group. Another study associated olaparib treatment with increased fatigue and anemia, aligning with our meta-analysis findings [34,35]. The analysis highlights prevalent treatment-emergent adverse events (TEAEs) like nausea, fatigue, vomiting, and constipation, consistent with other research on PARPis, especially olaparib, linked to increased severe nausea and vomiting. These findings align with other PARPis, in which AE was significantly higher in the PARPis group than the control group [30,33].

Although no markers identify high-risk patients, ongoing monitoring and timely supportive care are crucial [31]. Through strategic dosage modifications, adverse effects were managed, ensuring sustained PFS [36]. Hematological assessments highlighted significant incidences of anemia, thrombocytopenia, and neutropenia. The prevalence of anemia, a recurrent adverse event linked with PARP inhibitors, can be ascribed to the reduced functionality of PARP-2, associated with a decreased longevity of erythrocytes and the compromised maturation of erythroid progenitor cells. Furthermore, discernible rates of nephrotoxicity were recorded. Rucaparib has been documented to inhibit the actions of MATE1 and MATE2-K transporters, pivotal in renal creatinine secretion. A distinct AE, infrequently seen with other PARP inhibitors, was hepatotoxicity, characterized by elevated alanine aminotransferase levels or aspartate aminotransferase. However, these alterations typically exhibited a transient nature, were self-limiting, and did not coincide with other signs of liver damage [7,15]. Systematic monitoring and management of side effects are vital to ensure patients tolerate the therapy, enabling optimal dosing for maximal therapeutic benefit and minimal complications. This meta-analysis reveals considerable heterogeneity across studies, potentially due to varying study designs, patient demographics, or other factors.

In our meta-analysis, several limitations should be noted. Firstly, the level of evidence presented could be more optimal due to the inclusion of only two phase III clinical trials thus, only these two studies offer a comparator to rucaparib. Secondly, a mere one-third of the incorporated studies present data on overall survival. There is also a variation in therapy duration across the studies. Notably, the studies observed significant heterogeneity in both efficacy and safety outcomes. This variability may be ascribed to differences in therapy durations and the diverse number of chemotherapy regimens received.

Conclusion

Based on the accumulated evidence, rucaparib is a prominent therapeutic choice, illustrating a commendable safety record for patients facing relapsed high-grade ovarian carcinoma. This meta-analysis's consolidated objective response rate robustly highlights rucaparib's therapeutic efficacy. The marked complete response rate, especially in the BRCA-mutated cohort, further supports its therapeutic value. While rucaparib substantially prolongs progression-free and overall survival, variations are discernible among distinct clinical subgroups. Considering the observed uptick in adverse event frequency, meticulous surveillance, judicious clinical measures, and dose modulations become paramount to amplify therapeutic gains and attenuate potential risks. For a more robust validation of these conclusions, future endeavors should focus on conducting expansive, multi-center randomized studies, determining the optimal duration and commencement of treatment, and exploring synergies with other therapeutic modalities.

Statement of ethics

This study has not been done on human or animal subjects.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Review Article

Is there an association between vaginal microbiome community state types and diversity and preterm birth: A non-systematic literature review

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ABSTRACT

Worldwide, preterm birth (PTB) is a significant cause of neonatal mortality and morbidity. Surprisingly, the rate of PTB in the United States is among the top 10 nations in the world, comparable to those of the Democratic Republic of the Congo, Bangladesh, India, and Nigeria. However, there is no predictive biomarker or understanding of the mechanisms of PTB. Recent evidence suggests that the vaginal microbiome can be clustered into Community State Types (CST) and is altered in various obstetrical syndromes. The review aimed to summarize multiple studies on the vaginal microbiome and PTB and identify a particular microbe or CST associated with PTB. We hypothesized that there exists a specific microorganism that, when dominant within the vaginal microbiome, is protective against PTB. We hypothesized that the absence of a particular microbe or CST is a risk factor for PTB. To answer this question, we reviewed the current literature aiming to identify such a microorganism or a group of microorganisms. Our results indicate that no particular microbe or CST can be implicated in PTB. However, the review suggests that an increase in alpha and beta diversity of the vaginal microbiome can be predictive and involved in the pathogenesis of PTB.

Introduction

Worldwide, sequelae of preterm birth (PTB) are the leading cause of death among children less than five years of age [1], with over 15 million instances of PTB in 2019 [1]. In the United States, 10.5% of deliveries are complicated by PTB(2), with a disproportionate effect on non-Hispanic black women [2] and at a cost to the United States healthcare system of over $26.2 billion annually [3]. This rate of PTB in the United States is among the top 10 nations in the world, comparable to those of the Democratic Republic of the Congo, Bangladesh, India, and Nigeria [4]. Despite the public health significance of PTB and its associated morbidity and mortality, the mechanistic causes of PTB remain poorly understood [5]. Inflammation is commonly cited as a potential cause of PTB, with genetic variants in women thought to be a predisposing factor [6,7]. Vaginal infections, and seemingly unrelated periodontal infections, are also associated with PTB [8]. More recently, a connection between the vaginal microbiome and PTB has been postulated as a contributing factor [9].

Advancements in microbial sequencing technology have led to an increase in our understanding of how human microbiomes contribute to human disease. Recent studies have clustered the vaginal microbiome into five Community State Types (CST I–V) [10]. The four groups (CST I, II, III, and V) are dominated by *Lactobacillus crispatus*, *Lactobacillus gasseri*, *L.* iners, and *Lactobacillus jensenii*, respectively. The CST IV had lower proportions of lactic acid bacteria and higher proportions of strictly anaerobic organisms (Table 1) [10]. Other than CST, another important characteristic of the vaginal microbiome is the microbial diversity, described as alpha and beta diversity. Alpha diversity reflects the diversity of microbial species in a single sample, whereas beta diversity reflects the similarity or dissimilarity of microbial species between samples [11]. Importantly, an increase in the diversity of the species that are present in the vagina has been associated with increased rates of human papillomavirus infection and cervical intraepithelial neoplasia [12–14]. An increased vaginal microbiome species diversity has also been associated with preeclampsia [15], adenomyosis [16], chronic endometritis [17], increased rates of HIV viral shedding [18], and decreased pregnancy rates among women using assisted reproductive technology [19].

The association between healthy pregnancy and differences in the composition of the vaginal microbiome has become an

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Table 1
The proportion of each of the five Community State Type (CST) clusters containing major vaginal bacteria species.

CST	I	II	III	IV	V
L. crispatus	100.0	36.0	53.3	51.9	57.1
L. gasseri	49.5	100.0	38.5	26.9	52.4
L. iners	76.2	60.0	100.0	78.7	66.7
Prevotella	53.3	72.0	56.3	99.1	61.9
L. jensenii	69.5	28.0	51.1	18.5	100.0
Lactobacillales_6	99.1	0.0	8.2	6.5	0.0
Lactobacillales_5	71.4	36.0	97.0	18.5	95.2
Anaerococcus	41.9	84.0	36.3	80.6	42.9
Lactobacillales_2	32.4	4.0	97.8	29.6	28.6
Peptoniphilus	31.4	76.0	34.1	88.9	42.9
Dialister	24.8	68.0	40.0	93.5	38.1
Atopobium	21.0	52.0	25.2	79.6	19.0
Megasphaera	20.0	16.0	20.7	76.9	14.3
Gardnerella	8.6	44.0	14.8	78.7	28.6
Lactobacillales_1	8.6	84.0	15.6	3.7	4.8

important area of focus for researchers investigating the causes of PTB. We hypothesized that there exists a specific microorganism that, when dominant within the vaginal microbiome, is protective against PTB. Likewise, we hypothesize the absence of this species is a risk factor for PTB. To answer this question, we reviewed the current literature with the aim that such a microorganism can be identified.

In this study, we reviewed prior studies investigating the link between vaginal microbiome composition and risk of PTB and guide potential areas of future research. In multiple studies, we observed increased species diversity (alpha diversity) and less stability in species composition (beta diversity) correlate with increased PTB rates. Still, there is limited evidence supporting a specific microorganism or vaginal CST that consistently relates to PTB. In fact, different studies are conflicting regarding the impact of a specific microorganism or CSTs on PTB rates. While the correlations between species diversity and PTB rates are high, a causative mechanism linking the two has yet to be established. Below, we summarize these findings to assist others interested in studying this growing public health concern.

Materials and methods

We conducted a nonsystematic literature review to identify, evaluate, and summarize articles that report on associations between alterations in the vaginal microbiome and their effect on term and preterm labor.

Eligibility criteria, information sources, and search

Our initial search was conducted in September of 2023 and updated monthly. The literature search was designed to identify studies of the vaginal microbiome and its relation to the onset of labor and the rate of term and preterm birth. Our review included animal and human studies with no language or publication date limit. We queried two databases, PubMed and Scopus, to identify studies on vaginal microbiome and PTB. The search terms used were ((vaginal[Title])AND (microbiome[Title])) AND (labor) or ((vaginal[Title]) AND (microbiome[Title])) AND (preterm).

Study selection

The initial search results from both databases were abstracted and imported into Endnote 21. The majority of duplicates were automatically removed using the software, followed by a manual removal of any remaining duplicates. Each remaining title and abstract was reviewed, and those that were outside of the review topic were excluded. Case reports, case series, and review articles were excluded from this review.

Results and discussion

Our initial search identified 472 articles across both databases; after duplicates were removed duplicates were removed, 253 articles remained. Of these, based on a review of the titles and abstracts, 198 articles were excluded due to inconsistency with the topic of interest. After removing case reports and case series, 41 articles were fully reviewed. These articles include 40 human studies and one animal study. An additional 24 articles were removed after a full-text review as they were irrelevant to our study question. One additional article was included after reviewing the reference sections of the articles that underwent full-text review, resulting in 18 included articles.

Most studies utilized 16S ribosomal RNA (rRNA) sequencing to identify which microbial species were present in the collected samples, though the hypervariable region chosen was variable, with two choosing V1-3 [9,20], three choosing V4 [21–23], and three choosing V3-4 [24–26]. Three other studies used 16S rRNA sequencing, but the region sequenced was not specified [27–29]. Some studies used other techniques, including metagenome-assembled genomes (MAGs) [30], shotgun metagenomic sequencing [31] and direct on-swab desorption electrospray ionization mass spectrometry (DESI-MS) [32].

Vaginal community state types and preterm birth

The study aimed to identify a particular vaginal microbe, CST, or other related parameter which may be predictive or associated with PTB. The studies reviewed show contradicting evidence concerning dominant species and CSTs and how well they predict PTB. In one study directly comparing the vaginal CSTs of pregnant women delivering at term versus preterm, Dunlop et al. found an increased risk of spontaneous PTB with CST III (*Lactobacillus iners* dominant) and CST IV (diverse species) with adjusted odds ratios (aOR) of 4.0 [1.1-infinity] and 7.7 [1.8-infinity], respectively(24). Tabatabaei et al. found that CST IV was associated with PTB prior to 34 weeks (OR 4.22 [1.23–24.85] but not PTB between 34 and 36 weeks (OR 1.63 [0.68–5.04](23). In another study from 2019, pregnant patients with a vaginal microbiome dominated by *L. crispatus* had a significantly higher chance of reaching term ($p = 0.014$) (9), whereas another study suggests that a greater relative abundance of *L. gasseri* decreases the risk of PTB ($p = 0.01$); however, the relative abundance of *Lactobacillus* species, in general, was greater in patients delivering preterm versus those delivering at term [26].

In contrast, Ng et al. found that when comparing vaginal CSTs between women delivering at term versus preterm, CST I (*L. crispatus* dominant) was the most common CST in both sample groups ($p = 0.57$). Surprisingly, CST IV was in a higher proportion of samples in the term delivery group(22). One potential confounder in these results is the race of the studied subjects, which may at least partially explain these findings. In a study comparing vaginal microbiome composition in patients delivering preterm versus term, stratified by race (black vs white), *L. crispatus* was associated with decreased rates of PTB ($p = 0.013$), but such microbiome composition was more common in white patients compared with black patients. Notably, when comparing rates of PTB between black and white women of the same vaginal CST, no significant difference was found [20].

Vaginal microbiota species diversity and preterm birth

While there does not appear to be a consistent species or CST associated with PTB, multiple studies suggest that increased

species diversity is a risk factor for PTB. One such study examined the vaginal microbiome longitudinally throughout pregnancy [33]. It directly compared both the alpha diversity and beta diversity of vaginal microbiome samples in subjects eventually delivering preterm versus term. In this study, the microbial diversity across longitudinal samples from a given subject (beta diversity) was increased in PTB compared to term birth (0.7 vs 0.3, $p < 0.001$), suggesting that subjects who develop increased species diversity over the course of pregnancy are at greater risk of preterm delivery [33]. Likewise, Pruski et al. found that both microbiome diversity (alpha diversity) and instability (beta diversity) were associated with higher rates of PTB ($p = 0.04$) [32]. Both studies also corroborate the findings of Hocevar et al. who found that women who experienced PTB had higher alpha diversity than women with term deliveries ($p = <0.001$) [25]. A recent meta-analysis performed by Kulshreshtha et al. investigated the variations of species composition and diversity between races, ethnicities, and geographic locations. In this study, the authors conducted a statistical analysis of samples collected from PTB patients and stratified these results by race, ethnicity, and geographic location. Among their findings, black patients who experienced PTB had the greatest alpha diversity while whites had the lowest. Non-Hispanics exhibited higher alpha diversity than those who did not indicate their ethnicity, and subjects from India had the highest alpha diversity. Subjects from Europe had the lowest alpha diversity. In addition, Hispanics showed the most distinct microbial composition based on race, non-Hispanics based on ethnicity, and subjects from India based on geographical location [33]. This study revealed differences within a group of patients who experienced PTB, potentially, in part, explaining the increased risk of PTB in black patients compared to white seen in other studies; black patients may have a baseline higher vaginal microbial species diversity. These studies collectively suggest increased alpha diversity in early pregnancy and increased beta diversity throughout pregnancy might be associated with PTB.

Conclusion and discussion

Our review shows that PTB is common in different geographic locations, and a single microbiome or CST is not predictive or causative of PTB. However, both increased alpha diversity and beta diversity are associated with an increased incidence of PTB, which indicates a more diverse microbiome or microbiome instability over the course of pregnancy may be risk factors for PTB. However, further investigation is required to understand if increased alpha or beta diversity is the result or cause of the mechanisms leading to PTB. Also, the review indicates that alpha or beta diversity may be used as a potentially predictive marker for PTB and is an opportunity for future study. Other areas for future research would be to conduct studies comparing vaginal microbiome composition with preterm premature rupture of membranes (PPROM) or with short cervix, as lower amounts of bacterial abundance have been observed in patients with short cervical length compared to normal cervical length [34] and greater bacterial diversity has been described in patients with PPROM compared to non-ruptured patients in preterm labor [29].

This review is limited by its focus on the bacteriome of the vagina and did not include possible contributions of the vaginal virome or mycobiome to the risk of PTB. Our review also included studies using variable microbial genetic sequencing techniques, which may introduce variation that could bias our conclusions. As there are limited studies investigating the results of vaginal microbiome alterations with PTB, we decided to include all relevant studies, regardless of the specific sequencing technique used. As more work is done with vaginal microbiome sequencing, direct comparisons between bacterial species diversity and PTB reported by studies using different sequencing methods could be an area of future research. For example, one article that was ultimately excluded from the review highlighted a discrepancy between metagenomic sequencing and 16S rRNA sequencing in the V1-3 region [35]. In this study, sequencing in the V1-3 hypervariable region appears to underrepresent the relative abundance of *Gardnerella vaginalis*. However, no clinically significant difference in the reported rate of PTB using these two methods was observed.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

The first time devastating food poisoning happened in Taiwan – Bongkrekic acid poisoning

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ABSTRACT

Bongkrekic acid (BKA), a rarely happened foodborne toxin by *Burkholderia gladioli pathovar cocovenenans* (*Burkholderia cocovenenans*) might leads to devastating life-threatening condition after eating meal contaminated BKA. Unbelievable event from March 19, 2024, to March 24, 2024, there was an outbreak of BAP in a luxury shopping area of eastern Taipei, Taiwan. Most of the victims are young to middle-aged people who made a tour over there and ate the cooked wet rice noodles. Of them, 13 males and 20 females, aged 40.9 ± 14.7 years old visited or were sent by ambulances to the emergency department presenting with watery diarrhea, and vomiting. Some progressed to severe hepatic and renal failure, altered mental status, disseminated intravascular coagulation, and fatalities within several hours within 2 days. The primary health workers especially emergency physicians need to keep in mind of BKA poisoning is quite different in presentations from other infectious colitis commonly seen before. Knowing the toxic-kinetic and toxic-dynamic mechanisms is important to farseeing the presentation of these BAP patients. Throughout this outbreak, we gathered abundant experiences in mitigating and managing these debilitated patients. Aggressively supportive care and early liver transplantation if there is no concurrent inflammatory process and the patient's condition is tolerable to surgical intervention saves lives. For food safety education, it is crucial to enhance our understanding of inhibiting BKA production and promote proper food preservation methods and a suitable environment to ensure food safety.

Introduction

Bongkrekic acid (BKA), a rarely happened foodborne contamination by *Burkholderia gladioli* pathovar *cocovenenans (Burkholderia cocovenenans)*, a gram-negative, aerobic, rod shaped bacteria [1]. Among more than 60 species of *Burkholderia bacteria*, only *B. gladioli* cocovenenans produces BKA (highly toxic) and toxoflavin [2–6]. In special circumstances of environmental settings, such as warm (22–30 °C), low NaCl concentration (less than 2%), and a suitable fatty acid composition (rich in oleic acid, such as coconut and corn) via wet rice noodles and *Auricularia auricula* releasing life-threatening toxin [2,7,8]. BKA is an unsaturated tricarboxylic fatty acid, which is soluble in various organic solvents and stable for heat, fat-soluble substance with optimal toxin-production temperature between 26 and 28 °C [3].

According to a 10-year statistical analysis from China, Bongkrekic acid poisoning (BAP) happened more commonly at home (79%), and in restaurants (21.0%). Unbelievable event from March 19, 2024, to March 24, 2024, there was an outbreak of BAP in a luxury shopping area of eastern Taipei, Taiwan. Most of the victims are young to middle-aged people who made a tour over there and ate the cooked wet rice noodles. Of them, 13 males and 20 females, aged 40.9 ± 14.7 years old visited or were sent by ambulances to the emergency department presenting with watery diarrhea, and vomiting [6]. Some progressed to severe hepatic and renal failure, altered mental status, disseminated intravascular coagulation, and fatalities within several hours within 2 days.

First-time outbreak in Taiwan

The first fatal BAP case consumed wet rice noodles on 19 March 2024 and sought medical help from a local medical doctor initially. Progressively debilitated status and he visited our emergency department (ED) on 21 March 2024. The clinical course was

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fulminant with the presentation of out-of-hospital cardiac arrest (OHCA) and expired in the medical intensive care unit, despite aggressive resuscitation after recovery of spontaneous circulation (ROSC) at ED. He died in the medical intensive care unit (ICU) 6 h later. The second severe BAP patient presented on 24 March 2024 and she also consumed wet rice noodles in the same luxury eastern Taipei shopping mall's restaurant. Dramatic shock with consciousness alertness after intubation with mechanical ventilator support was applied and she was admitted to the medical ICU, too. After the Critical Care Department, Dr. Wang consulted the director of the Toxicology division of the emergency department at noon on 26 March 2024 and received the answer told of this outbreak highly impressed of *Bongkrekic acid* poisoning (BAP) within 2 h analysis because the presentation is so fulminant and they all ate the same food, pan-fried wet rice noodles at the same restaurant.

For this outbreak in eastern Taipei, Taiwan was difficult to early detect because the pan-fried wet rice noodles remained unchanged in odor, and appearance which interfered with people's judgment about the safety of the food. It does not like the spoilage manifests as changes in food color, smell, and taste, such as a putrid sour smell, but microorganisms in food may also produce toxins already [3]. A hypothesis was made as to why this devastating foodborne poisoning outbreak for the first time and it never happened before in Taiwan. According to an Australian study in 2016, the bacteria species change when the climate changes owing to the global warm and an increase in daily counts of 1·3% on the overall number of salmonellosis cases per 1 °C rise in maximum temperature, with greater observed increases ranging from 3·4% to 4·4% in cases depending on the serotype and phage type [9]. The Central Weather Administration in Taiwan (CWA, Taiwan) said from 1991 to 2020, Taiwan's temperature rose by 0.29 Celsius every 10 years, higher than the global average of 0.21 C. Another research from Malaysia in year 2023 concluded that with a 1.0 °C rise in temperature, the excess risk of foodborne poisoning in each state can increase up to 74.1% [10]. These evidences compose the linkage between climate change by global warming and foodborne poisoning eventually leading to the first outbreak of BAP in Taiwan.

The toxidrome of Bongkrekic acid

BKA functions by inhibiting adenine nucleotide translocase (ANT), also known as ADP/ATP translocase or ADP/ATP carrier located on the mitochondrial inner membrane, which is responsible for transporting ADP into and ATP out of mitochondria [2,4–6,11]. Majorities of articles described that the lethal dose of Bongkrekic acid (BA) is 1.0–1.5 mg [4,7,and12]]. The median interval from pombe consumption to symptom onset was 16 h [4].

A toxidrome is a syndrome caused by the presence of toxins in the body. It can be recognized by several clinical features, such as vital signs, consciousness, size of the pupils, volume of secretions, motility of gastrointestinal tract, diarrhea or vomiting, urination difficulty or not, and sweating skin or dry [13]. The most common presentations of BAP are gastrointestinal and neurological symptoms, such as abdominal pain, watery diarrhea, nausea and vomiting, jaundice, headache, vertigo distal extremity paresthesia, weakness, irritability, and confusion with a sequence of initial gastrointestinal followed by neurologic symptoms. Some patients would present with fever, chest pain, or tightness even showing the ST T wave changes over the electrocardiogram mimicking an acute heart attack. Other non-specific subcutaneous hemorrhage, hematemesis, rhabdomyolysis, acute tubular necrosis-related hematuria high potassium, low blood pressure, shortness of breath, cyanosis of the lips and fingernails, and cardiac arrest might happen [7].

Table 1
Symptoms presentation in *Bongkrekic acid* poisoning patients.

System	Symptoms	References
Neurologic	Headache, vertigo, extremity paresthesia, weakness irritability, and confusion.	[2]
Cardiovascular	Chest pain, or tightness showing the ST T wave changes on electrocardiogram.	[2,4]
Respiratory	Dyspnea, shortness of breath	[2]
Liver	Jaundice, fulminant hepatitis	[1,7]
Gut	Abdominal pain, watery diarrhea, nausea and vomiting, hematemesis.	[1–4,6,7,14]
urinary	Oliguria, acute tubular necrosis, hematuria.	[1,7]
Endocrine	Hypoglycemia.	[1,8]
Musculoskeletal	Weakness, muscle ache, rhabdomyolysis.	[2,4,7,14]
Skin and conjunctiva	Hemorrhagic, ecchymosis, subcutaneous hemorrhage, cyanosis of the lips and fingernails.	[2,7]
Systemic	Fever, high potassium, low blood pressure, cardiac arrest.	[2,3,7]

Table 2
Fatality rate of documented Bongkrekic acid poisoning.

Year	Country	cases	fatality rate	references
2007	Indonesia	30	33.3%	[15]
2014	China	22	22.7%	[16]
2015	Mozambique	234	32.1%	[4]
2018	China	4	50.0%	[3]
2019	China	5	60.0%	[17]
2010–2020	China	146	29.5%	[7]
2020	China	9	100%	[8,12]
2024	Taiwan	33	15.2%	This article

The severe damage caused by BKA on the liver could include glucose metabolism, bilirubin metabolism, blood coagulation function, and body fluid circulation. Moreover, the disease progresses rapidly, leading to multiple organ failure, including the brain, liver, and kidney, and then mortality [2–4,6,7,14]. Symptoms presentation in Bongkrekic acid poisoning patients are listed in Table 1.

Table 2 shows the fatality rate of documented Bongkrekic acid poisoning events. Of them, some are Pro-MED alerts or were from established and reliable news sources. Tracing the history, the vehicles of BAP were commonly as wet rice noodles, the same as this outbreak, fermented coconut tempe, fermented corn flour products (ciba, fermented corn noodles, tang-yuan and cooked dough), auricularia auricula, tremella, and sweet potato flour and corn flour products (jelly), locally brewed alcoholic beverage made from corn flour and in a growth medium containing above 20% of oleic acid [1,3–5,7].

Laboratory tests for B. acid

The major sample for testing of *B. acid* is blood, and the other testing is urine and bronchial alveolar lavage (BAL) in this outbreak of eastern Taipei, Taiwan. The serum level of BKA is nearly ten-fold higher than in the urine and BAL samples. Currently used for detection of rice and noodle products, exhibiting its applicability and suitability for analysis BKA in rice and noodle products is the ultra-high liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) [18,19]. For this outbreak, an ultrahigh-performance liquid chromatography (UPLC) system paired with a high-resolution time-of-flight mass spectrometer (TOF-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) was taken the responsibility for analyzing the BKA levels.

These debilitated BAP patients showed exaggerated high levels of alanine aminotransferase (ALT) (some up to ten thousand IU/L

above), aspartate transaminase (AST), bilirubin, ammonia (some exceeding one thousandμmol/L). These presentations are quite different from other bacterial colitis, such as *Salmonella, Cholera, Staphylococcus,* and *Bacillus Cereus*. However, patients who received treatment and were discharged from the emergency department with a relatively low serum BKA level (6.9 ± 10.2 ng/ml).

Of these debilitated cases, we can see that the BKA level rebounds in the next time before plasma exchange, and the BKA disposition is characterized by a long half-life (t1/2 of 102 h) and AUC (AUC of 129,000 L/h·kg) after ingestion of contaminated food [14]. Little information is enough to realize the absorption profile and volume of distribution of BKA. The hypothesis is that the BKA deposits in the adipose tissue in organs and serum due to its fat-soluble characteristics [14]. The rebound of the BKA level may be associated with the redistribution of secondary compartments and the enterohepatic circulation and this is also described in a China report in 2023 [14].

Treatment strategy for B. acid poisoning

In toxicology, gastric lavage and gastrointestinal decontamination are suggested in patients who have been ingested within 1–2 h with extremely serious intoxication [20]. If the patient presents to the emergency department after ingesting a fatal dose of poison within 1 h of ingestion, then gastric emptying is to be considered using activated charcoal, gastric lavage using saline, and specific agents. BKA is an odorless, colorless, heat-stable foodborne toxin with a molecular weight of 486 kDa [2]. Owing to the BKA being odorless and colorless, the BAP patients seek medical help after being sick exceeding the golden time of gastrointestinal decontamination after the arrival of the emergency department.

In some cases, hypoglycemic episode was found due to the inability to proceed with gluconeogenesis by haptic failure, and dextrose might be helpful for patients who develop hypoglycemia [1]. For the BAP patients with systemic acidosis, a priority was placed on rapidly correcting acidosis by intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT) remains helpful in correcting systemic acidosis and hyperammonemia in the early stage of acidosis resulting from shock down of cell power plant. BKA has a slow elimination rate characterized by a long half-life and a high maximum plasma concentration. Clinically plasma exchange (PE) (plasmapheresis) treatments were significantly more effective than CRRT in accelerating the clearance of BKA. Subsequent therapy included two sets of coupled plasma filtration adsorption (CPFA) to target BKA removal [6,14].

The problem-based solving method is liver transplantation can save these debilitated cases' lives. Besides the aggressive supportive care mentioned above, the eventual necessity of liver transplantation is mandatory when the patient is free of concurrent inflammatory processes.

Outcome, prognosis, and prevention

The outcome of BAP depends on the doses ingested of BKA. There is no specific antidote in BAP. The treatment is based on aggressively supportive care. In a 10-year experience of 146 *B. acid* poisoning cases with a 29.5% mortality rate in the year 2023 [7]. Despite the aggressively supportive care, the fatal rate remains high. Till 8 June 2024, the mortality rate of BAP in Taipei, Taiwan is 15.2% (5 of 33). Food safety education should be strengthened so that homemade-starch-fermented food should be avoided in a not well-reserved environment and temperature. Meanwhile, training and teaching the clinical physicians to differentiate the BAP from the commonly seen infectious colitis to make timely accurate diagnoses and medical responses [12].

Conclusion

The primary health workers especially emergency physicians need to keep in mind of BAP is quite different in presentations from other infectious colitis commonly seen before. The contamination of *B. gladioli pathovar cocovenenans* (*B. cocovenenans*) leads to produce BKA poisoning and has emerged as a devasting and lethal food safety concern. Knowing the toxic-kinetic and toxic-dynamic mechanisms is important to farseeing the presentation of these BAP patients. Throughout this outbreak, we gathered abundant experiences in mitigating and manage these debilitated patients. Aggressively supportive care and early liver transplantation if there is no concurrent inflammatory process and the patient's condition is tolerable to surgical intervention saves lives. For food safety education, it is crucial to enhance our understanding of inhibiting BKA production and promote proper food preservation methods and a suitable environment to ensure food safety.

Declaration of competing interest

I declared there is no conflict of interest statement.

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Review Article

Genetic counseling of mosaicism for balanced or unbalanced translocation with a normal cell line at amniocentesis

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ABSTRACT

Genetic counseling of mosaicism for balanced translocation with a normal cell line at amniocentesis is not difficult because most of the reported cases have normal phenotypes. However, genetic counseling of mosaicism for unbalanced translocation with a normal cell line at amniocentesis remains difficult because cases with mosaic unbalanced translocation with a normal cell line at prenatal diagnosis have been reported to be associated with either normal or abnormal phenotype. This article makes a comprehensive review of the reported cases of *de novo* or familial mosaic unbalanced translocation with a normal cell line and various counseling issues such as meiotic event, post-zygotic mitotic event, culture artefact, chimerism, uniparental disomy (UPD), jumping translocation, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the unbalanced translocation cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Introduction

Genetic counseling of mosaicism for balanced translocation with a normal cell line at amniocentesis is not difficult because most of the reported cases have normal phenotypes. However, genetic counseling of mosaicism for unbalanced translocation with a normal cell line at amniocentesis remains difficult because cases with mosaic unbalanced translocation with a normal cell line at prenatal diagnosis have been reported to be associated with either normal or abnormal phenotype. This article makes a comprehensive review of the reported cases of *de novo* or familial mosaic unbalanced translocation with a normal cell line and various counseling issues such as meiotic event, post-zygotic mitotic event, culture artefact, chimerism, uniparental disomy (UPD), jumping translocation, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the unbalanced translocation cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Mosaicism for balanced translocation with a normal cell line at amniocentesis

Balanced reciprocal translocation mosaicism (BRTM) with a normal cell line

BRTM is an extremely rare condition that is predominantly reported in the cases of phenotypically normal individuals with offspring with unbalanced chromosomal rearrangements, or reproductive failure of infertility, sterility and pregnancy loss [1–9]. BRTM occurs in a frequency from 0.06/1000 individuals [10] to 0.2/1000 individuals [8]. BRTM can be caused by a pre-zygotic event [11], a post-zygotic event [12] or chimerism [13]. Prenatal diagnosis of mosaicism with a 46, XX cell line should exclude the possibility of maternal cell contamination.

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BRTM with a normal cell line and normal phenotype

Hsu et al. [14] reported an accumulation of 13 cases with mosaicism for various BRTM at amniocentesis, and all 11 liveborns and the two abortuses were phenotypically normal.

46,XY,t (6; 14) (q16.3; q13)/46,XY

Golden et al. [15] reported prenatal diagnosis of 46,XY,t (6; 14) (q16.3; q13)/46, XY in a pregnancy with a normal liveborn. Mosaicism was confirmed in foreskin, cord blood and placenta.

46,XY,t (4; 10) (q12; p12.32)/46,XY

Chen [16] reported BRTM of 46,XY,t (4; 10) (q12; p12.32)/46, XY at amniocentesis in a pregnancy with a favorable outcome and no prominent perinatal decrease of the balanced translocation cell line. The parental karyotypes were normal, and the BRTM was confirmed in the cord blood and peripheral blood at age two months with the similar levels of mosaicism. In that case, amniocentesis revealed a karyotype of 46,XY,t (4; 10) (q12; p12.32) [21]/46, XY [4]. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed no genomic imbalance. A phenotypically normal baby was delivered at 38 weeks of gestation. The cord blood had a karyotype of 46,XY,t (4; 10) (q12; p12.32) [30]/46, XY [10], and at age two months, the phenotypically normal infant was, and the peripheral blood had a karyotype of 46,XY,t (4; 10) (q12; p12.32) [32]/46, XY [8]. In that case, the BRTM at prenatal diagnosis was associated with no prominent perinatal decrease of the cell line with the balanced reciprocal translocation, *i.e.*, 84% (21/25 colonies) mosaicism for t (4; 10) (q12; p12.32) at amniocentesis at 16 weeks of gestation, 75% (30/40 cells) mosaicism for t (4; 10) (q12; p12.32) at birth in the cord blood at 38 weeks of gestation, and 80% (32/40 cells) mosaicism for t (4; 10) (q12; p12.32) in the peripheral blood at age two months.

46,XY,t (7; 8) (q31.2; p23.1)/46,XY

Chen et al. [17] reported incidental detection of familial 8p23.2 microduplication encompassing *CSMD1* associated with mosaic 46,XY,t (7; 8) (q31.2; p23.1)/46, XY at amniocentesis in a pregnancy with no apparent phenotypic abnormality and a favorable outcome. In that case, amniocentesis at 19 weeks of gestation revealed a karyotype of 46,XY,t (7; 8) (q31.2; p23.1) [2]/46, XY [20]. Prenatal ultrasound findings and the parental karyotypes were normal. aCGH analysis on cultured amniocytes and parental bloods revealed familial 8p23.2 microduplication. The pregnancy was carried to 38 weeks of gestation, and a phenotypically normal baby was delivered. All of the cord blood, umbilical cord and placenta had the karyotype of 46.XY. When follow-up at age six months, the neonate was normal in phenotype and development.

46,XY,t (1; 3) (q42; q25)/46,XY

Zhang et al. [9] reported prenatal diagnosis of *de novo* 46,XY,t (1; 3) (q42; q25) [40]/46, XY [39] at amniocentesis. The cord blood had similar level of mosaicism. The father had a karyotype of 46,XY,t (12; 14) (q22; q13), and the mother's karyotype was normal. A phenotypically normal baby was delivered and was normal in phenotype and development at age 21 months.

BRTM with a normal cell line and abnormal phenotype

Warburton [18] reported a 6% (n = 163) risk of a serious congenital anomaly associated with a *de novo* non-mosaic BRTM at amniocentesis. Congenital anomaly in mosaic BRTM has occasionally been reported.

46,XY,t (8; 12) (p23.2; q13.3)/46,XY

Saura et al. [19] reported postnatal diagnosis of BRTM of 46,XY,t (8; 12) (p23.2; q13.3)/46, XY in skin fibroblasts and lymphocytes in a 6-month-old infant with facial dysmorphism.

46,XX,t (7; 11) (q36; p11)/46,XX

Aughton et al. [20] reported BRTM in a 6-month-old infant with an abnormal phenotype of macrocephaly, facial dysmorphism, clinodactyly, agenesis of the corpus callosum and a karyotype of 46,XX,t (7; 11) (q36; p11)/46,XX. The parental karyotypes were normal.

Balanced whole-arm translocation mosaicism with a normal cell line

Balanced whole-arm translocation mosaicism has been reported in normal individuals [21,22].

46,XX,t (10; 16) (q11.2; q11.1)/46,XX

Wang et al. [21] reported a normal mother with mosaicism for a whole-arm translocation of 46,XX,t (10; 16) (q11.2; q11.1)/46, XX and her child with maternal UPD 16 and the karyotype of 46,XY,t (10; 16) (q11.2; q11.1)mat [22]/47,idem,+16 [4] at prenatal diagnosis.

46,XY,t (1; 5) (p10; q10)/46,XY

Gardner and Amor [22] reported 46,XY,t (1; 5) (p10; q10)/46, XY at amniocentesis and a normal child on follow-up at age four years.

Balanced complex chromosome rearrangement mosaicism with a normal cell line

46,XX,t (3; 10) (p13; q21.1), inv (6) (p23q12)/46,XX

Hastings et al. [23] reported prenatal finding of mild cerebral ventriculomegaly in a fetus with mosaicism for two balanced *de novo* chromosome rearrangements of 46,XX,t (3; 10) (p13; q21.1), inv (6) (p23q12)/46,XX. The cord blood sampling had the karyotype of 46,XX,t (3; 10) (p13; q21.1), inv (6) (p23q12). The pregnancy was subsequently terminated, and a fetus was delivered with an atrial septal defect, abnormal segmentation of the lungs, a high arched palate and small low-set ears. Cytogenetic analysis of the skin revealed 46,XX,t (3; 10) (p13; q21.1),inv (6) (p23q12) [6]/46, XX [26].

Balanced Robertsonian translocation mosaicism with a normal cell line

Warburton [18] reported a 3.7% (n = 51) risk of a serious congenital anomaly associated with a *de novo* non-mosaic Robertsonian translocation at amniocentesis. Hsu et al. [14] reported four cases (two with 13q/14q translocation, one with 13q/22q translocation and one with 14q/21q translocation) of mosaic Robertsonian translocation, and all four cases had phenotypically normal liveborns.

Zhao et al. [24] reported mos 45,XX,der (22; 22) (q10; q10)/46, XX in a 21-year-old female, mos 45,XX,der (14; 21) (q10; q10)/46, XX in a 22-year-old female and mos 45,XX,der (21; 21) (q10; q10)/46, XX in a 33-year-old female. Balanced Robertsonian translocation mosaicism can be detected in individuals with infertility, miscarriage or offspring with chromosomal abnormalities. In an overview of 872 Robertsonian translocations identified in a diagnostic laboratory, Zhao et al. [24] identified three mosaic balanced

Robertsonian translocations in adults, three unbalanced der (21; 21) mosaic trisomy 21 in children and one unbalanced der (21; 21) mosaic trisomy 21 in adult. Lu et al. [25] identified 192 Robertsonian translocation carriers (including 189 balanced Robertsonian translocations and three mosaic Robertsonian translocations) among 84,569 pregnancies. The three cases with mosaic balanced Robertsonian translocations included 45,XX,der (14; 22)/46,XX, 45,XX,der (15; 21)/46, XX and 45,XY,der (21; 21)/46,XY.

45,XY,der (13; 21) (q10; q10)/46,XY

Chen [26] reported 45,XY,der (13; 21) (q10; q10)/46, XY and no genomic imbalance by aCGH at amniocentesis in a pregnancy with a normal phenotype in the fetus. The cord blood at birth and the peripheral blood at the age of 4½ years had the similar level of mosaicism and no perinatal decrease of the cell line with the balanced Robertsonian translocation. In that case, amniocentesis revealed a karyotype of 45,XY,der (13; 21) (q10; q10) [7]/46, XY [22] (7/29 colonies = 24% mosaicism). The cord blood had a karyotype of 45,XY,der (13; 21) (q10; q10) [10]/46, XY [30] (10/40 cells = 25% mosaicism), and the peripheral blood had a karyotype of 45,XY,der (13; 21) (q10; q10) [12]/46, XY [28] (12/40 cells = 30% mosaicism).

Mosaicism for unbalanced translocation with a normal cell line at amniocentesis

Unbalanced reciprocal translocation mosaicism with a normal cell line at amniocentesis associated with a favorable fetal outcome

46,XX,der (4)t (4; 5) (q34; q12)/46,XX

Cotter et al. [27] first reported a case of unbalanced reciprocal translocation mosaicism at amniocentesis associated with a favorable fetal outcome. In that case, amniocentesis at 16 weeks of gestation revealed a karyotype of 46,XX,der (4)t (4; 5) (q34; q12) [10]/46,XX [52], consistent with 16% (10/62 cells) mosaicism for the der (4). Fluorescence *in situ* hybridization (FISH) confirmed that the extra material on the der (4) chromosome was derived from chromosome 5 and caused mosaic 5q duplication. Repeat amniocentesis performed at 18 weeks of gestation revealed a mosaic der (4) level of 32.5% (13/40 cells). Cord blood at 20 weeks of gestation revealed no mosaicism (0/100 cells). Amniocentesis at 20 weeks of gestation revealed a mosaic der (4) level of 17% (26/152 cells). Prenatal ultrasound findings and the parental karyotypes were normal. The pregnancy was carried to term, and a phenotypically normal baby was delivered. Cytogenetic analysis of the cord blood and placenta revealed a normal karyotype. At age two years, the infant showed no phenotypic or developmental anomalies.

46,XY,der (15)t (6; 15) (q25.1; p12)/46,XY

Chen et al. [28] reported mosaic 6q (6q25.1→qter) duplication due to 46,XY,der (15)t (6; 15) (q25.1; p12)/46, XY at amniocentesis in a pregnancy associated with a favorable fetal outcome and postnatal decrease of the aneuploid cell line with the unbalanced translocation. In that case, the mosaic levels for the der (15) cells with partial trisomy 6q25.1→qter in cultured amniocytes at 17, 19, 24 and 27 weeks of gestation were 77% (17/22 colonies), 60% (12/20 colonies), 95.8% (23/24 colonies) and 80.8% (21/26 colonies), respectively. However, the mosaic levels for partial trisomy 6q in uncultured amniocytes were 40% by aCGH at 19 weeks of gestation, 50% by aCGH and 51% (51/100 cells) by FISH at 24 weeks of gestation, and 46% by aCGH and 35% (35/100 cells) by FISH at 27 weeks of gestation. There was cytogenetic discrepancy between cultured and uncultured amniocytes in that case. Prenatal ultrasound findings and the parental karyotypes were normal. The pregnancy was carried to term, and a phenotypically normal baby was delivered. When follow-up at age one month, the neonate was phenotypically normal, the peripheral blood had a karyotype of 46, XY (40/40 cells), and FISH analysis showed 5% (5/105 cells) mosaicism in buccal mucosal cells, compared with 2% mosaicism (2/100 cells) in the normal control.

46,XX,der (9)t (9; 13) (p24; q12)/46,XX

Chen [29] reported mosaic 46,XX,der (9)t (9; 13) (p24; q12)/46, XX at amniocentesis in a pregnancy associated with a favorable fetal outcome and a likely culture artefact. In that case, amniocentesis at 17 weeks of gestation revealed 15.8% (3/19 colonies) mosaicism for der (9)t (9; 13) (p24; q12). Repeat amniocentesis at 22 weeks of gestation revealed normal results in cultured amniocytes by conventional cytogenetic analysis and uncultured amniocytes by aCGH. A phenotypically normal baby was delivered with a normal karyotype in cord blood and no phenotypic abnormality.

46,XY,der (14)t (13; 14) (q32.2; p13)/46,XY

Chen et al. [30] reported mosaic distal 13q duplication due to mosaic unbalanced translocation of 46,XY,der (14)t (13; 14) (q32.2; p13)/46, XY at amniocentesis in a pregnancy associated with a favorable fetal outcome, perinatal progressive decrease of the aneuploid cell line and cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes. In that case, amniocentesis at 17 weeks of gestation revealed 56.6% (17/30 colonies) mosaicism for der (14) in cultured amniocytes and 45% mosaicism by aCGH in uncultured amniocytes. Repeat amniocentesis at 24 weeks of gestation revealed 46.6% (13/30 colonies) mosaicism in cultured amniocytes, and 30–40% mosaicism by aCGH and 22.8% (23/101 cells) mosaicism by interphase FISH in uncultured amniocytes. Prenatal ultrasound findings and the parental karyotypes were normal. A phenotypically normal baby was delivered at term. At birth, the cord blood, umbilical cord and placenta had the mosaic levels of 50% (20/40 cells), 35% (14/40 cells) and 0% (40/40 cells), respectively. When follow-up at age 4½ months, the mosaic levels of peripheral blood and buccal mucosal cells were 45% (18/40 cells) and 2.7% (3/110 cells), respectively, and the neonate was normal in phenotype and development.

Unbalanced Robertsonian translocation mosaicism with a normal cell line at amniocentesis associated with a normal fetus and/or a favorable fetal outcome

45,XY,der (15; 22) (q10; q10)mat/46,XY,i (15) (q10)/46,XY

Chen et al. [31] reported mosaicism for Robertsonian jumping translocation of 45,XY,der (15; 22) (q10; q10)mat/46,XY,i (15) (q10)/46, XY at amniocentesis in a pregnancy with a favorable fetal outcome. In that case, amniocentesis at 19 weeks of gestation revealed a karyotype of 45,XY, der (15; 22) (q10; q10) [29]/46,XY,i (15) (q10) [3]/46, XY [5]. aCGH analysis on uncultured amniocytes revealed no genomic imbalance. The mother had a karyotype of 45,XX,der (15; 22) (q10; q10), and the father had a karyotype of 46,XY. Prenatal ultrasound findings were normal. Repeat amniocentesis performed at 23 weeks of gestation revealed 45,XY,der (15; 22) (q10; q10)mat [23]/45,XY,-22 [2], and aCGH analysis on uncultured amniocytes revealed no genomic imbalance. Polymorphic DNA marker analysis excluded UPD 15, and FISH analysis detected three 15q signals in 3.8% (4/104 cells) in uncultured amniocytes. A phenotypically normal baby was delivered at 38 weeks of gestation. The umbilical cord had a karyotype of 45,XY,der (15; 22) (q10; q10). When follow-up at age seven months, the neonate was normal in phenotype and development. The peripheral blood had the karyotype of 45,XY,der (15; 22) (q10; q10) (40/40 cells), and the buccal mucosal cells had normal signals in all 100 cells by interphase FISH analysis.

46,XX,+21,der (21; 21) (q10; q10)/46,XX

Long et al. [32] and Hsu et al. [14] reported prenatal diagnosis of 46,XX,+21,der (21; 21) (q10; q10)/46, XX at amniocentesis with 85.2% mosaicism for trisomy 21 in a pregnancy with a normal abortus, and the mosaicism was confirmed in the fetus.

46,XY,+14,der (14; 14) (q10; q10)/46,XY

Hsu et al. [14] reported 46,XY,+14,der (14; 14) (q10; q10)/46, XY at amniocentesis with 4% mosaicism for trisomy 14 in a pregnancy with a normal liveborn and 46, XY in the blood and placenta.

46,N,+14,der (14; 21) (q10; q10)/46,N

Worton and Stern et al. [33] and Hsu et al. [14] reported prenatal diagnosis of 46,N,+14,der (14; 21) (q10; q10)/46,N at amniocentesis with 30% mosaicism for trisomy 14 in a pregnancy with a normal liveborn who had 9% mosaicism for trisomy 14 in the blood.

45,XY,t (21; 21) (q10; q10)

Yan et al. [34] reported a 45,XY,t (21; 21) (q10; q10) homologous Robertsonian translocation carrier who had an approximately normal offspring with a mosaic karyotype of 46,XX,t (21; 21) (q10; q10) [14]/46,XX, [86].

46,XX,+21,der (21; 21) (q10; q10)/46,XX

Chen et al. [35] reported 46,XX,+21,der (21; 21) (q10; q10) [8]/46, XX [18] at amniocentesis at 17 weeks of gestation with 30.8% (8/26 colonies) mosaicism for trisomy 21. aCGH analysis on uncultured amniocytes revealed no genomic imbalance. Repeat amniocentesis with cord blood sampling at 21 weeks of gestation revealed a normal 46, XX karyotype in cord blood and 7.4% (2/27 colonies) mosaicism for trisomy 21 in cultured amniocytes. Repeat cord blood sampling at 21 weeks of gestation revealed a karyotype of 46,XX. A phenotypically normal baby was delivered. At birth, the cord blood had 2.5% (1/40 cells) mosaicism for 46,XX,+21,der (21; 21) (q10; q10), and the placenta had the karyotype of 46,XX,+21,der (21; 21) (q10; q10). When follow-up at age two months, the neonate was normal in phenotype and development. The peripheral blood had a karyotype of 46, XX (40/40 cells), and aCGH analysis on buccal mucosal cells revealed no genomic imbalance.

Unbalanced reciprocal translocation mosaicism with a normal cell line at amniocentesis associated with fetal abnormality

46,XY,der (1)t (1; 7) (p36.3; q11)/46,XY

Hsu et al. [14] reported prenatal diagnosis of 46,XY,der (1)t (1; 7) (p36.3; q11)/46, XY at amniocentesis with 82.8% mosaicism for partial trisomy 7q in a pregnancy with delivery of an abnormal liveborn manifesting low-set ears, imperforate anus, dysmorphism and mental retardation. The blood in the patient had 3% mosaicism for der (1).

46,XX,der (15)t (2; 15) (p10; q10) (WCP2+)/46,XX

Pipiras et al. [36] reported prenatal diagnosis of 46,XX,add (15) (p10).ish t (2; 15) (p10; q10) (WCP2+) [3]/46, XX [27] by amniocentesis at 30 weeks of gestation in a pregnancy with fetal intrauterine growth restriction. The pregnancy was terminated, and the fetus had dolichocephaly, hypertelorism, high forehead, low-set ears with prominent anthelix and a small nose characteristic of trisomy 2p.

46,X,der(Y)t (Y; 1) (q12; q12)/46,XY

Zeng et al. [37] reported prenatal diagnosis of 57% mosaicism for trisomy 1q due to an unbalanced translocation of 46,X,der(Y)t (Y; 1) (q12; q12) [12]/46, XY [9] at amniocentesis at 18 weeks of gestation in a twin pregnancy with the abnormalities decreased amniotic fluid, absent stomach, small cerebellum, dilated ventricles, increased nuchal fold and congenital diaphragmatic hernia in one fetus. A malformed baby was delivered at 33 weeks of gestation and died after birth with facial dysmorphism, camptodactyly, syndactyly, left diaphragmatic hernia and cleft palate. Molecular analysis confirmed a postzygotic mitotic error.

46,XX,der (3) (qter→q24::p26.3→qter)/46,XX

Chen et al. [38] reported prenatal molecular cytogenetic diagnosis of mosaic deletion-duplication syndrome of chromosome 3 with mosaic 3p26.3qter deletion and mosaic 3q24q29 duplication using cultured and uncultured amniocytes and the association with fetoplacental discrepancy. In that case, amniocentesis at 21 weeks of gestation revealed 20% (5/25 colonies) mosaicism for add (3) (p26). Repeated amniocentesis detected 3p26.3 deletion and 3q24q29 duplication in uncultured amniocytes by aCGH analysis, and 27.3% mosaicism (12/44 cells) in uncultured amniocytes and 23.3% mosaicism (7/30 cells) in cultured amniocytes by FISH analysis. The cultured amniocytes had the karyotype of 46,XX,der (3) (qter→q24::p26.3→qter) [10]/46, XX [20], consistent with 33% (10/30 colonies) mosaicism for der (3). Cordocentesis showed 12.5% (5/40 cells) mosaicism for der (3) in the cord blood. The pregnancy was subsequently terminated, and a malformed fetus was delivered at 24 weeks of gestation with characteristic facial dysmorphism and clinodactyly. The mosaic levels for der (3) in the placenta, membrane and umbilical cord were 0% (0/40 cells), 25% (10/40 cells) and 50% (20/40 cells), respectively.

Unbalanced Robertsonian translocation mosaicism with a normal cell line at amniocentesis associated with fetal abnormality

46,XX,+14,der (14; 14) (q10; q10)/46,XX

Lambert et al. [39] and Hsu et al. [14] reported prenatal diagnosis of 46,XX,+14,der (14; 14) (q10; q10)/46, XX at amniocentesis with 64.7% mosaicism for trisomy 14 in a pregnancy with an abnormal abortus manifesting micrognathia and hyperlobation of the lungs. In that case, the msoaicism was found in the fetal skin (12.9%), ovary (32%) and kidney (4%).

Mosaic unbalanced translocation with a normal cell line associated with familial balanced translocation

The mechanism of mosaic unbalanced translocation with a normal cell line associated with familial balanced translocation has been well reported [40,41]. The proposed mechanisms include: (1) A mitotic exchange of non-homologous chromatids followed by the loss of one of the translocated chromatids, resulting in a normal cell line and an unbalanced cell line in the subsequent segregation [42]. (2) An unbalanced zygote followed by loss of the abnormal chromosome and a subsequent monosomic rescue by the duplication of the normal chromosome resulting isodisomy for this chromosome [43]. (3) Asymmetric 3:1 segregation with the derivative chromosome and two normal associated chromosomes. Two different cell lines result from the loss of a normal chromosome in one cell and loss of the derivative chromosome in the other cell [44]. (4) Chimerism with the presence of two genetically different cell lines in one individual derived from two different zygotes [45].

UPD associated with familial balanced translocation

The risk of UPD due to Robertsonian translocation involving chromosomes 14 or 15 is estimated to be less than 1% [46,47]. Berend et al. [46] estimated that 0.8% of the heterozygous Robertsonian translocation carriers are likely to be UPD. Wang et al. [48] reported mosaic isochromosome 15q and maternal

uniparental isodisomy for chromosome 15 in a patient with morbid obesity and variant Prader–Willi syndrome-like phenotype. Homologous Robertsonian translocations of der (14; 14) or i (14q) and der (15; 15) or i (15q) are likely to be associated with UPD 14 or UPD 15 imprinting disorders [24]. Bruyère et al. [49] reported the risk of 1/738 with 0.02–0.76% (95% confidence interval) in UPD, and the risk of 3/169 (95% confidence interval: 0.1–3 %) confidence interval) in mosaic trisomy with the prenatal diagnosis of a non-homologous Robertsonian translocation carrier. Blanluet et al. [50] reported recurrence of an early postzygotic rescue of an inherited unbalanced translocation of t (2; 11) (q35; q25) in two siblings with mosaic segmental uniparental isodisomy of chromosome 11q.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Genetic counseling of mosaicism for a duplication due to partial trisomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis

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ABSTRACT

Genetic counseling of mosaicism for a duplication due to partial trisomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis remains difficult because mosaic duplication due to partial trisomy has been reported to be associated with either normal or abnormal phenotype in prenatal diagnosis. This article makes a comprehensive review of the reported cases of mosaicism for a duplication due to partial trisomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis and various counseling issues such as culture artefact, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the abnormal cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Introduction

Genetic counseling of mosaicism for a duplication due to partial trisomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis remains difficult because mosaic duplication due to partial trisomy has been reported to be associated with either normal or abnormal phenotype in prenatal diagnosis. This article makes a comprehensive review of the reported cases of mosaicism for a duplication due to partial trisomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis and various counseling issues such as culture artefact, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the abnormal cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Mosaicism for partial trisomy due to a segmental duplication with a normal cell line at amniocentesis and a favorable outcome

Mosaic 15q11.2 microduplication

Chen et al. [1] reported mosaicism for a 15q11.2 microduplication with a normal cell line at amniocentesis in a pregnancy with a favorable fetal outcome and postnatal decrease of the aneuploid cell line with the microduplication. In that case, amniocentesis at 17 weeks of gestation revealed a karyotype of 46, XY in cultured amniocytes by conventional cytogenetic analysis, and 33.76% mosaicism for a 15q11.2 microduplication in uncultured amniocytes by array comparative genomic hybridization (aCGH) analysis. Repeat amniocentesis at 23 weeks of gestation revealed a karyotype of 46, XY in cultured amniocytes by conventional cytogenetic analysis, 40%–45% mosaicism for a 15q11.2 microduplication in uncultured amniocytes by aCGH analysis, and 19% (19/100 cells) mosaicism for a 15q11.2 microduplication in uncultured amniocytes by fluorescence *in situ* hybridization (FISH) analysis. Polymorphic DNA marker analysis excluded uniparental disomy (UPD) 15. Prenatal ultrasound findings were normal. The

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pregnancy was carried to term, and a phenotypically normal baby was delivered. aCGH analysis on the DNA extracted from cord blood at birth and buccal mucosal cells at age four months revealed no genomic imbalance. Interphase FISH analysis on the buccal mucosal cells at age four months revealed 4% (4/104 cells) mosaicism for a 15q11.2 duplication. The neonate was normal in the development and phenotype at age four months.

Mosaic 14q12q22.3 duplication

Chen et al. [2] reported mosaic 46,XY,dup(14) (q12q22.3)/46, XY at amniocentesis in a pregnancy associated with a favorable fetal outcome and cytogenetic discrepancy in various tissues. In that case, amniocentesis at 17 weeks of gestation revealed a karyotype of 46,XY,dup(14) (q12q22.3)[7]/46,XY[13], consistent with 35% (7/20 colonies) mosaicism for a partial 14q duplication, and 25% mosaicism for a partial 14q duplication by aCGH analysis in uncultured amniocytes. Repeat amniocentesis at 22 weeks of gestation revealed a karyotype of 46,XY,dup(14) (q12q22.3)[6]/46,XY[14], consistent with 30% (6/20 colonies) mosaicism for a partial 14q duplication, 30% mosaicism for a partial 14q duplication by aCGH analysis in uncultured amniocytes and 19.4% (24/124 cells) mosaicism for a partial 14q duplication by FISH analysis in uncultured amniocytes. Polymorphic DNA marker analysis excluded UPD 14. Prenatal ultrasound findings and the parental karyotypes were normal. A phenotypically normal baby was delivered at term with the mosaic partial 14q duplication levels of 35% (14/40 cells), 17.5% (7/40 cells) and 7.5% (3/40 cells) in cord blood, umbilical cord and placenta, respectively by conventional cytogenetic analysis of the cultured cells. When follow-up at age four months, the phenotypically normal neonate showed 67.5% (27/40 cells) mosaicism for a partial 14q duplication in the peripheral blood by conventional cytogenetic analysis and 4.8% (5/105 cells) mosaicism for a partial 14q duplication in the buccal mucosal cells by interphase FISH analysis, When follow-up at age nine months, the phenotypically normal infant showed 62.5% (25/40 cells) mosaicism for a partial 14q duplication in the peripheral blood by conventional cytogenetic analysis.

Mosaic 9q22.3q34.1 duplication

Chen et al. [3] reported cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes in mosaic 46,XX,dup(9) (q22.3q34.1)/46, XX at amniocentesis in a pregnancy with a favorable outcome. In that case, amniocentesis at 18 weeks of gestation revealed a karyotype of 46,XX,dup(9) (q22.3q34.1)[8]/46,XX[16] in cultured amniocytes, consistent with 33.3% (8/24 colonies) mosaicism for a partial 9q duplication. Repeat amniocentesis at 21 weeks of gestation revealed a karyotype of 46,XX,dup(9) (q22.3q34.1)[7]/46,XX[25] in cultured amniocytes, consistent with 21.9% (7/32 colonies) mosaicism for a partial 9q duplication, no genomic imbalance by aCGH analysis in uncultured amniocytes and 1% (1/105 cells) mosaicism for a partial 9q duplication by interphase FISH analysis. Prenatal ultrasound was normal. A phenotypically normal baby was delivered at 37 weeks of gestation. The mosaic levels of a partial 9q duplication at birth in the cord blood, umbilical cord and placenta were 10% (4/40 cells), 5% (2/40 cells) and 0% (0/40 cells), respectively. When follow-up at age 2½ months, the neonate was normal, and the mosaic levels of a partial 9q duplication in peripheral blood and buccal mucosal cells were 10% (4/40 cells) and 0% (0/40 cells), respectively.

Mosaic Xq22.1q22.2, Xq25q22.3 duplication

Chen et al. [4] reported mosaic Xq duplication of 46,X,der(X) dup(X) (q22.1q22.2)dup(X) (q25q22.3)/46, XX at amniocentesis in a pregnancy with a favorable fetal outcome. In that case, amniocentesis at 16 weeks of gestation revealed a karyotype of 46,X,der(X)dup(X) (q22.1q22.2) dup(X) (q25q22.3)[7]/46,XX[20] in cultured amniocytes, consistent with 25.9% (7/27 colonies) mosaicism for a partial Xq duplication and no genomic imbalance by aCGH analysis in uncultured amniocytes. The mother had a karyotype of 46,XX. Repeat amniocentesis at 22 weeks of gestation revealed a karyotype of 46, XX in cultured amniocytes and no genomic imbalance by aCGH analysis in uncultured amniocytes. Prenatal ultrasound was normal. A phenotypically normal baby was delivered at 39 weeks of gestation with 7.5% (3/40 cells) mosaicism for a partial Xq duplication by conventional cytogenetic analysis in the cord blood. When follow-up at age nine months, the infant showed normal phenotype and development with 2.5% (1/40 cells) mosaicism for a partial Xq duplication in peripheral blood by conventional cytogenetic analysis and 0% (0/40 cells) mosaicism for a partial Xq duplication in buccal mucosal cells by FISH analysis.

Mosaicism for partial trisomy due to a segmental duplication with a normal cell line at amniocentesis and fetal abnormality

Mosaic 3q23q27 duplication

Gardner et al. [5] and Hsu et al. [6] reported prenatal diagnosis of 46,XX, dir dup(3) (q23q27)[64]/46,XX[36] by amniocentesis with 64% mosaicism for a partial duplication of 3q23q27 in an female infant with Cornelia de Lange syndrome and hypomelanosis of Ito. The peripheral blood also had the mosaicism.

Mosaic 12p duplication

Jewell et al. [7] and Hsu et al. [6] reported prenatal diagnosis of 46,XY,dup(12p)/46, XY by amniocentesis with 80% mosaicism for a duplication of 12p in a liveborn with micrognathia, prominent nose and hypotonia. The mosaicism was confirmed in the blood but not in the chorionic villi and chorionic membrane.

Mosaic 1q31.3q32.3 duplication

Chen et al. [8] reported prenatal diagnosis of mosaic 1q31.3q32.1 trisomy associated with occipital encephalocele. In that case, amniocentesis at 19 weeks of gestation revealed a karyotype 46,XX,dup(1) (q31.3q32.1)[18]/46,XX[2] in cultured amniocytes, consistent with 90% (18/20 colonies) mosaicism for 1q31.3q32.1 duplication. The parental karyotypes were normal. Prenatal ultrasound showed occipital encephalocele and ventriculomegaly. Repeated amniocentesis at 22 weeks of gestation revealed a karyotype 46,XX,dup(1) (q31.3q32.1)[21]/46,XX[9], consistent with 70% (21/30 colonies) mosaicism for a 1q31.3q32.1 duplication. The pregnancy was subsequently terminated, and a malformed fetus was delivered with facial dysmorphism and occipital encephalocele. The mosaic levels of the partial 1q duplication in the cord blood, umbilical cord, placenta and skin were 35% (14/40 cells), 65% (26/40 cells), 0% (0/40 cells) and 70% (28/40 cells), respectively. The duplication of 1q31.3q32.1 was confirmed by FISH analysis and aCGH analysis.

Mosaic 1q21qter duplication

Karaoguz et al. [9] reported prenatal diagnosis of 46,XX,dup(1) (q21qter)[21]/46,XX[77] by amniocentesis at 19 weeks of gestation in a pregnancy with fetal ventriculomegaly. The parental karyotypes were normal. The pregnancy was terminated, and a malformed fetus was delivered with craniofacial dysmorphism and

digit abnormality. Autopsy confirmed ventriculomegaly. Postmortem cytogenetic analysis of cord blood, intracardiac blood and skin showed the mosaic levels for a partial 1q duplication were 2%, 4% and 16%, respectively.

Mosaicism for partial trisomy due to an unbalanced translocation with a normal cell line at amniocentesis and a favorable outcome

Mosaic 5q12qter duplication

Cotter et al. [10] first reported a case of unbalanced reciprocal translocation mosaicism at amniocentesis associated with a favorable fetal outcome. In that case, amniocentesis at 16 weeks of gestation revealed a karyotype of 46,XX,der(4)t(4; 5) (q34; q12) [10]/46,XX[52], consistent with 16% (10/62 cells) mosaicism for the der(4). FISH confirmed that the extra material on the der(4) chromosome was derived from chromosome 5 and caused mosaic 5q duplication. Repeat amniocentesis performed at 18 weeks of gestation revealed a mosaic der(4) level of 32.5% (13/40 cells). Cord blood at 20 weeks of gestation revealed no mosaicism (0/100 cells). Amniocentesis at 20 weeks of gestation revealed a mosaic der(4) level of 17% (26/152 cells). Prenatal ultrasound findings and the parental karyotypes were normal. The pregnancy was carried to term, and a phenotypically normal baby was delivered. Cytogenetic analysis of the cord blood and placenta revealed a normal karyotype. At age two years, the infant showed no phenotypic or developmental anomalies.

Mosaic 6q25.1qter duplication

Chen et al. [11] reported mosaic 6q (6q25.1→qter) duplication due to 46,XY,der(15)t(6; 15) (q25.1; p12)/46, XY at amniocentesis in a pregnancy associated with a favorable fetal outcome and postnatal decrease of the aneuploid cell line with the unbalanced translocation. In that case, the mosaic levels for the der(15) cells with partial trisomy 6q25.1→qter in cultured amniocytes at 17, 19, 24 and 27 weeks of gestation were 77% (17/22 colonies), 60% (12/20 colonies), 95.8% (23/24 colonies) and 80.8% (21/26 colonies), respectively. However, the mosaic levels for partial trisomy 6q in uncultured amniocytes were 40% by aCGH at 19 weeks of gestation, 50% by aCGH and 51% (51/100 cells) by FISH at 24 weeks of gestation, and 46% by aCGH and 35% (35/100 cells) by FISH at 27 weeks of gestation. There was cytogenetic discrepancy between cultured and uncultured amniocytes in that case. Prenatal ultrasound findings and the parental karyotypes were normal. The pregnancy was carried to term, and a phenotypically normal baby was delivered. When follow-up at age one month, the neonate was phenotypically normal, the peripheral blood had a karyotype of 46, XY (40/40 cells), and FISH analysis showed 5% (5/105 cells) mosaicism in buccal mucosal cells, compared with 2% mosaicism (2/100 cells) in the normal control.

Mosaic 9p24pter duplication

Chen [12] reported mosaic 46,XX,der(9)t(9; 13) (p24; q12)/46, XX at amniocentesis in a pregnancy associated with a favorable fetal outcome and a likely culture artefact. In that case, amniocentesis at 17 weeks of gestation revealed 15.8% (3/19 colonies) mosaicism for der(9)t(9; 13) (p24; q12). Repeat amniocentesis at 22 weeks of gestation revealed normal results in cultured amniocytes by conventional cytogenetic analysis and uncultured amniocytes by aCGH. A phenotypically normal baby was delivered with a normal karyotype in cord blood and no phenotypic abnormality.

Mosaic 13q32.2qter duplication

Chen et al. [13] reported mosaic distal 13q duplication due to mosaic unbalanced translocation of 46,XY,der(14)t(13; 14) (q32.2; p13)/46, XY at amniocentesis in a pregnancy associated with a favorable fetal outcome, perinatal progressive decrease of the aneuploid cell line and cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes. In that case, amniocentesis at 17 weeks of gestation revealed 56.6% (17/30 colonies) mosaicism for der(14) in cultured amniocytes and 45% mosaicism by aCGH in uncultured amniocytes. Repeat amniocentesis at 24 weeks of gestation revealed 46.6% (13/30 colonies) mosaicism in cultured amniocytes, and 30-40% mosaicism by aCGH and 22.8% (23/101 cells) mosaicism by interphase FISH in uncultured amniocytes. Prenatal ultrasound findings and the parental karyotypes were normal. A phenotypically normal baby was delivered at term. At birth, the cord blood, umbilical cord and placenta had the mosaic levels of 50% (20/40 cells), 35% (14/40 cells) and 0% (40/40 cells), respectively. When follow-up at age 4½ months, the mosaic levels of peripheral blood and buccal mucosal cells were 45% (18/40 cells) and 2.7% (3/110 cells), respectively, and the neonate was normal in phenotype and development.

Mosaicism for partial trisomy due to an unbalanced translocation with a normal cell line at amniocentesis and fetal abnormality

Mosaic 7q11qter duplication

Hsu et al. [6] reported prenatal diagnosis of 46,XY,der(1)t(1; 7) (p36.3; q11)/46, XY at amniocentesis with 82.8% mosaicism for partial trisomy 7q in a pregnancy with delivery of an abnormal liveborn manifesting low-set ears, imperforate anus, dysmorphism and mental retardation. The blood in the patient had 3% mosaicism for der(1).

Mosaic 2p10pter duplication

Pipiras et al. [14] reported prenatal diagnosis of 46,XX,add(15)(p10).ish t(2; 15) (p10; q10) (WCP2+)[3]/46,XX[27] by amniocentesis at 30 weeks of gestation in a pregnancy with fetal intrauterine growth restriction. The pregnancy was terminated, and the fetus had dolichocephaly, hypertelorism, high forehead, low-set ears with prominent antihelix and a small nose characteristic of trisomy 2p.

Mosaic 1q12qter duplication

Zeng et al. [15] reported prenatal diagnosis of 57% mosaicism for trisomy 1q due to an unbalanced translocation of 46,X,der(Y)t(Y; 1)(q12; q12)[12]/46,XY[9] at amniocentesis at 18 weeks of gestation in a twin pregnancy with the abnormalities decreased amniotic fluid, absent stomach, small cerebellum, dilated ventricles, increased nuchal fold and congenital diaphragmatic hernia in one fetus. A malformed baby was delivered at 33 weeks of gestation and died after birth with facial dysmorphism, camptodactyly, syndactyly, left diaphragmatic hernia and cleft palate. Molecular analysis confirmed a postzygotic mitotic error.

Mosaic 1q11qter duplication

Pettenati et al. [16] reported prenatal diagnosis of complete sole trisomy 1q of 46,XY,der(14)t(1; 14) (q11; p11.1) by amniocentesis in a fetus with mosaic der(14)t(1; 14) (q11; p11.1) of 46,XY,der(14) t(1; 14) (q11; p11.1)[3]/46,XY[22] in cord blood, nuchal thickening,

bitemporal narrowing, a single choroid plexus cyst, mild ventriculomegaly, hyperechoic bowel, hydrops fetalis and left parietal encephalocele.

Mosaic 3p26.3qter deletion and mosaic 3q24q29 duplication

Chen et al. [17] reported prenatal molecular cytogenetic diagnosis of mosaic deletion-duplication syndrome of chromosome 3 using cultured and uncultured amniocytes and the association with fetoplacental discrepancy. In that case, amniocentesis at 21 weeks of gestation revealed 20% (5/25 colonies) mosaicism for add(3)(p26). Repeated amniocentesis detected 3p26.3 deletion and 3q24q29 duplication in uncultured amniocytes by aCGH analysis, and 27.3% mosaicism (12/44 cells) in uncultured amniocytes and 23.3% mosaicism (7/30 cells) in cultured amniocytes by FISH analysis. The cultured amniocytes had the karyotype of 46,XX,der(3)(qter→q24p26.3→qter)[10]/46,XX[20], consistent with 33% (10/30 colonies) mosaicism for der(3). Cordocentesis showed 12.5% (5/40 cells) mosaicism for der(3) in the cord blood. The pregnancy was subsequently terminated, and a malformed fetus was delivered at 24 weeks of gestation with characteristic facial dysmorphism and clinodactyly. The mosaic levels for der(3) in the placenta, membrane and umbilical cord were 0% (0/40 cells), 25% (10/40 cells) and 50% (20/40 cells), respectively.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

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Review Article

Genetic counseling of mosaicism for a deletion due to partial monosomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis

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ABSTRACT

Genetic counseling of mosaicism for a deletion due to partial monosomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis remains difficult because mosaic deletion due to partial monosomy has been reported to be associated with either normal or abnormal phenotype in prenatal diagnosis. This article makes a comprehensive review of the reported cases of mosaicism for a deletion due to partial monosomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis and various counseling issues such as culture artefact, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the abnormal cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Introduction

Genetic counseling of mosaicism for a deletion due to partial monosomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis remains difficult because mosaic deletion due to partial monosomy has been reported to be associated with either normal or abnormal phenotype in prenatal diagnosis. This article makes a comprehensive review of the reported cases of mosaicism for a deletion due to partial monosomy in a cell line with 46 chromosomes associated with a normal cell line at amniocentesis and various counseling issues such as culture artefact, cytogenetic discrepancy between cultured and uncultured amniocytes and among various tissues, perinatal progressive decrease of the abnormal cell line and a possible favorable fetal outcome. The information provided is useful for obstetricians and genetic counselors during genetic counseling of the parents who wish to keep the babies under such a circumstance.

Hsu et al. [1] reported 17 cases of mosaicism for a deletion and a normal cell line including the deletions of 1q (n = 1), 2q (n = 2), 4p (n = 1), 4q (n = 1); 9q (n = 1), 10q (n = 2), 11q (n = 1), 12p (n = 1), 16q (n = 1), 18p (n = 3), 18q (n = 2), and 18p/18q (n = 1). In their report, only four of the 17 cases (4/17 = 23.5%) were phenotypically abnormal. Of the 13 cases with normal phenotype, ten cases had a mosaic level less than 20%, and three cases were above 20%. Of the four cases with abnormal phenotype, two cases had a mosaic level over 20% (59% and 28%, respectively), and one case was less than 20%. The breakpoints of the deletion cases such as del(10q) in 10q23 and del(2q) in 2q11 and 2q31 were likely due to the common fragile sites of these chromosomes.

Mosaicism for partial monosomy due to a deletion with a normal cell line at amniocentesis and a favorable outcome

Mosaic 12p12.1p12.2 microdeletion

Chen et al. [2] reported mosaicism for a 12p12.1p12.2 microdeletion with a normal euploid cell line at amniocentesis in a pregnancy with a favorable outcome and postnatal decrease of the

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aneuploid cell line with microdeletion. In that case, amniocentesis at 17 weeks of gestation revealed 36% mosaicism for a 12p12.1p12.2 microdeletion by array comparative genomic hybridization (aCGH) analysis. At 22 weeks of gestation, cordocentesis revealed 36% mosaicism for a 12p12.1p12.2 microdeletion by aCGH analysis. A phenotypically normal baby was delivered at 38 weeks of gestation. When follow-up at age 1½ months, the neonate was normal in phenotype and development. The mosaic levels of 12p12.1p12.2 microdeletion were 10–15% by aCGH analysis in the peripheral blood and 17% (18/104 cells) by interphase fluorescence *in situ* hybridization (FISH) analysis in the buccal mucosal cells.

Mosaic 10q26.13q26.3 deletion

Chen et al. [3] reported mosaic distal 10q deletion or 46,XY,del(10)(q26.13)/46,XY at amniocentesis and cordocentesis in a pregnancy associated with cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, perinatal progressive decrease of the aneuploid cell line and a favorable fetal outcome. In that case, amniocentesis at 16 weeks of gestation revealed a karyotype of 46,XY,del(10)(q26.13)[6]/46,XY[17], consistent with 26.1% (6/23 colonies) mosaicism for del(10)(q26.13) in cultured amniocytes. aCGH analysis on the DNA extracted from uncultured amniocytes revealed 35% mosaicism for the 10q26.13q26.3 deletion. At 22 weeks of gestation, cordocentesis revealed a karyotype of 46,XY,del(10)(q26.13)[16]/46,XY[24], consistent with 40% (16/40 colonies) mosaicism for del(10)(q26.13). Repeat amniocentesis at 24 weeks of gestation showed the karyotype of 46,XY,del(10)(q26.13)[4]/46,XY[22], consistent with 15.4% (4/26 colonies) mosaicism for del(10)(q26.13) in cultured amniocytes. Polymorphic DNA marker analysis excluded uniparental disomy (UPD) 10. Molecular cytogenetic analysis on the uncultured amniocytes showed 40% mosaicism by aCGH analysis and 29.8% (31/104 cells) mosaicism for the 10q26.13q26.3 deletion by interphase FISH. Prenatal ultrasound findings and the parental karyotypes were normal. At 39 weeks of gestation, a phenotypically normal baby was delivered. The mosaic levels of distal 10q deletion in the cord blood, umbilical cord and placenta by conventional cytogenetic analysis were 15% (6/40 cells), 0% (0/40 cells) and 0% (0/40 cells), respectively. When follow-up at age four months, the neonate was normal in phenotype and development. The mosaic levels of distal 10q deletion were 12.5% (5/40 cells) by conventional cytogenetic analysis in the peripheral blood and 8% (8/102 cells) by interphase FISH analysis in buccal mucosal cells.

Mosaic 9p24.3p22 deletion

Chen et al. [4] reported mosaic distal 9p deletion or 46,XY,del(9)(p23)/46,XY at amniocentesis in a pregnancy associated with perinatal progressive decrease of the aneuploid cell line and a favorable fetal outcome. In that case, amniocentesis at 17 weeks of gestation revealed a karyotype of 46,XY,del(9)(p23)[8]/46,XY[17] in cultured amniocytes, consistent with 32% (8/25 colonies) mosaicism for a distal 9p deletion. aCGH analysis on uncultured amniocytes revealed 43% mosaicism for a 9p24.3p23 deletion. Prenatal ultrasound showed hypospadias and echogenic bowel. Repeat amniocentesis at 23 weeks of gestation revealed a karyotype of 46,XY,del(9)(p23)[10]/46,XY[10] in cultured amniocytes, consistent with 50% (10/20 colonies) mosaicism for a distal 9p deletion, and molecular cytogenetic analysis on the uncultured amniocytes showed 40–50% mosaicism for a 9p24.3p23 deletion by aCGH analysis. Parental karyotypes were normal. At 27 weeks of gestation, cytogenetic analysis on cultured amniocytes revealed a karyotype of 46,XY,del(9)(p23)[6]/46,XY[14], consistent with 30% (6/20 colonies) mosaicism for del(9)(p23), and aCGH analysis on uncultured amniocytes showed 35% mosaicism for a 9p24.3p23 deletion. At 41 weeks of gestation, a phenotypically normal baby was delivered. The mosaic levels of a distal 9p deletion in the cord blood, umbilical cord and placenta were 15.9% (7/44 cells), 42.5% (17/40 cells) and 0% (0/40 cells), respectively. When follow-up at age three months, the neonate was normal in phenotype and development. The mosaic levels of a distal 9p deletion in peripheral blood were 7.5% (3/40 cells) by conventional cytogenetic analysis in the peripheral blood and 13% (13/102 cells) by interphase FISH analysis in buccal mucosal cells.

Mosaic 1q22qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XX,del(l)(q22)/46,XX by amniocentesis with 8% mosaicism for del(l)(q22) in a pregnancy with a normal abortus with 46,XX in fetal blood and skin.

Mosaic 2q31qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(2)(q31)/46,XY by amniocentesis with 12.5% mosaicism for del(2)(q31) in a pregnancy with a normal liveborn who was normal at age 3½ years.

Mosaic 2q11.2qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(2)(q11.2)/46,XY by amniocentesis with 16.1% mosaicism for del(2)(q11.2) in a pregnancy with a normal liveborn with 46,XY in blood.

Mosaic 4p12pter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(4)(p12)/46,XY by amniocentesis with 13.3% mosaicism for del(4)(p12) in a pregnancy with a normal liveborn with 46,XY in blood and mosaicism in skin.

Mosaic 4p33pter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XX,del(4)(p33)/46,XX by amniocentesis with 64.4% mosaicism for del(4)(p33) in a pregnancy with a normal abortus with mosaicism in fetal xyphoid and placental tissues.

Mosaic 9q11qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(9)(q11)/46,XY by amniocentesis with 5.1% mosaicism for del(9)(q11) in a pregnancy with a normal liveborn.

Mosaic 10q23.2qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(10)(q23.2)/46,XY by amniocentesis with 8.6% mosaicism for del(10)(q23.2) in a pregnancy with a normal liveborn and 46,XY in cord blood at cordocentesis.

Mosaic 10q23qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(10)(q23)/46,XY by amniocentesis with 14.7% mosaicism for del(10)(q23) in a pregnancy with a normal liveborn.

Mosaic 12p12pter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(12)(p12)/46,XY by amniocentesis with 7.3% mosaicism for del(12)(p12) in a pregnancy with a normal liveborn who was normal at age two years and had a normal karyotype of 46,XY in cord blood.

Mosaic 18p11.2pter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XY,del(18)(p11.2)/46,XY by amniocentesis with 25.8% mosaicism for del(18)(p11.2) in a pregnancy with a normal liveborn.

Mosaic 18p deletion and monosomy 18

[1] reported prenatal diagnosis of 46,XY,18p-/45,XY,-18/46,XY by amniocentesis with 3.5% mosaicism for an 18p deletion and 1.8% mosaicism for monosomy 18 a pregnancy with a normal liveborn who was normal at age seven months and had 2% mosaicism for an 18p deletion in blood.

Mosaic 18q21q23 deletion

Hsu and Moertel et al. [1,5] reported prenatal diagnosis of 46,XY,del(18)(q21q23)/46,XY by amniocentesis with 26.7% mosaicism for del(18)(q21q23) in a pregnancy with a normal liveborn and 46,XY in blood.

Mosaic 18q11.1qter deletion, 18p1.1pter deletion and monosomy 18

Hsu et al. [1] reported prenatal diagnosis of 46,XX,del(l8)(q11.1)/46,XX,del(l8)(p11.1)/45,XX, −18/46,XX by amniocentesis with 6% mosaicism for an 18q deletion, 4% mosaicism for an 18p deletion and 18.8% mosaicism for monosomy 18 in a pregnancy with a normal liveborn.

Mosaicism for partial monosomy due to a deletion with a normal cell line at amniocentesis and fetal abnormality

Mosaic 11q24qter deletion

Hsu and Bui et al. [1,6] reported prenatal diagnosis of 46,XX,del(11)(q24)/46,XX by amniocentesis in a pregnancy with an abnormal liveborn with web neck, widely spaced nipples, rocker-bottom feet, systolic murmur and sacral dimple. The mosaicism was confirmed in the tissues.

Mosaic 16q23qter deletion

Hsu et al. [1] reported prenatal diagnosis of 46,XX,del(16)(q23)/46,XX by amniocentesis with 59% mosaicism for del(16)(q23) in a pregnancy with an abnormal abortus with cystic hygroma and 48% mosaicism for del(16) in the fetal tissues.

Mosaic 18p deletion and monosomy 18

Hsu et al. [1] reported prenatal diagnosis of 46,XX,18p-/45,XX,-18/46,XX by amniocentesis with 5.2% mosaicism for an 18p deletion and 12.3% mosaicism for monosomy 18 in a pregnancy with an abnormal abortus with microcephaly, mongoloid slant of eyes, pointed chin and gap between 1st and 2nd toes and 46,XX in skin.

Mosaic 18q12.2q21.1 deletion

Hsu and Wilson et al. [1,7] reported prenatal diagnosis of 46,XY,del(18)(q12.q21.1)/46,XY by amniocentesis with 28% mosaicism for del(18)(q12.q21.1) in a pregnancy with an abnormal abortus with facial dysmorphism, long broad thumbs, long broad big toes, large foramen ovale and contracture of mid-phalangeal joints. The mosaicism was confirmed in the fetal tissues.

Mosaic 11q23qter deletion

Valduga et al. [8] reported prenatal diagnosis of 46,XY,del(11)(q23)/46,XY with 15.8% (3/19 colonies) mosaicism for del(11)(q23) by the first amniocentesis at 21 weeks of gestation, and 19.4% (7/36 colonies) mosaicism for del(11)(q23) at repeat amniocentesis at 24 weeks of gestation. During repeat amniocentesis, simultaneous FISH and cordocentesis showed 20% mosaicism for the distal 11q deletion. The pregnancy was terminated. The fetus manifested no true facial dysmorphism, dolichocephaly and mild bilateral dilated ureters. The mosaicism was confirmed in the fetal tissues.

Mosaic 11q24.2qter deletion

Porter et al. [9] reported prenatal diagnosis of 46,XY,del(11)(q24.2)/46,XY by amniocentesis with 76% (38/50 cells) mosaicism for del(11)(q24.2) in a pregnancy with an fetal abnormalities of absence of digits on the right hand, facial dysmorphism, cleft palate, left ventricular hypoplasia with no outflow tract, a common aorta and pulmonary trunk from the right ventricle and a subpulmonary ventricular septal defect. The muscle of the abortus had 65% (13/20 cells) mosaicism for the deletion.

Mosaic 15q11.1q11.2 deletion

Chen et al. [10] reported detection of mosaic 15q11.1-q11.2 deletion encompassing *NBEAP1* and *POTEB* in a fetus with diffuse lymphangiomatosis. In that case, amniocentesis revealed a karyotype of 46,XX,del(15)(q11.1q11.2)[9]/46,XX[26], consistent with 25.7% (9/35 colonies) mosaicism for del(15)(q11.1q11.2). The parental karyotypes were normal. The pregnancy was terminated, and a malformed fetus was delivered with diffuse lymphangiomatosis over the left abdomen, thigh and vulva. The mosaic levels for del(15)(q11.1q11.2) in the cord blood and placenta were 60% (24/40 cells) and 57.5% (23/40 cells), respectively.

Mosaic 3p26.3qter deletion and mosaic 3q24q29 duplication

Chen et al. [11] reported prenatal molecular cytogenetic diagnosis of mosaic deletion-duplication syndrome of chromosome 3 using cultured and uncultured amniocytes and the association with fetoplacental discrepancy. In that case, amniocentesis at 21 weeks of gestation revealed 20% (5/25 colonies) mosaicism for add(3)(p26). Repeated amniocentesis detected 3p26.3 deletion and 3q24q29 duplication in uncultured amniocytes by aCGH analysis, and 27.3% mosaicism (12/44 cells) in uncultured amniocytes and 23.3% mosaicism (7/30 cells) in cultured amniocytes by FISH analysis. The cultured amniocytes had the karyotype of 46,XX,der(3)(qter→q24p26.3→qter)[10]/46,XX[20], consistent with 33% (10/30 colonies) mosaicism for der(3). Cordocentesis showed 12.5% (5/40 cells) mosaicism for der(3) in the cord blood. The pregnancy was subsequently terminated, and a malformed fetus was delivered at 24 weeks of gestation with characteristic facial dysmorphism and clinodactyly. The mosaic levels for der(3) in the placenta, membrane and umbilical cord were 0% (0/40 cells), 25% (10/40 cells) and 50% (20/40 cells), respectively.

Mosaic 18p11.32p11.21 deletion and mosaic 18q21.2q23 deletion due to mosaic r(18)

Chen et al. [12] reported prenatal diagnosis of mosaicism for ring chromosome 18, monosomy 18, ring chromosome 18 duplication and disomy 18 in a fetus with multiple congenital anomalies. In that case, amniocentesis revealed 46,XY,r(18)[27]/45,XY,-18[5]/46,XY[5], consistent with 73% (27/37 colonies) mosaicism for r(18) and 13.5% (5/37 colonies) mosaicism for monosomy 18. Prenatal ultrasound showed ventriculomegaly. At 38 gestational weeks, a malformed fetus was delivered with microcephaly, hypertelorism, epicanthal folds, cleft palate, a broad flat nose, simian creases, broad hands, tapered fingers, clubfeet, micropenis, a sacral dimple, hypotonia, ventriculomegaly and a ventricular septal defect. The peripheral blood had a karyotype of 46,XY,r(18)[81]/45,XY,-18[3]/46,XY,idic r(18)[3]/46,XY[13].

Mosaic 18q21.3qter deletion

Chen et al. [13] reported prenatal diagnosis of *de novo* mosaic distal 18q deletion associated with congenital anomalies. In that case, prenatal ultrasound showed microcephaly and facial cleft. Amniocentesis at 21 weeks of gestation revealed the karyotype of 46,XY,del(18) (q21.3)[18]/46,XY[6], consistent with 75% (18/24 colonies) mosaicism for a distal 18q deletion. The parental karyotypes were normal. The pregnancy was subsequently terminated, and a malformed fetus was delivered with median facial cleft and facial dysmorphism. The mosaic levels for del(18) (q21.3) were 62.5% (25/40 cells) in the blood and 80% (16/20 cells) in liver.

Mosaic 13q13.3qter deletion

Widschwendter et al. [14] reported prenatal diagnosis of *de novo* mosaic distal 13q deletion associated with multiple anomalies. In that case, prenatal ultrasound at 25 weeks of gestation showed bilateral hydronephrosis, posterior meningoencephalocele, sloping forehead, microcephaly, syndactyly and hypoplastic thumbs. Amniocentesis showed chromosome 13q deletion in 18% ($n = 49$) of uncultured amniocytes. Cordocentesis showed the karyotype of 46,XY,del(13) (q13.3)/46,XY with 18% mosaicism for del(13) (q13.3). The parental karyotypes were normal. The pregnancy was subsequently terminated, and a malformed fetus was delivered with additional abnormalities of agenesis of corpus callosum, hypoplastic cerebellum and macroglossia. Postmortem fibroblast cultures showed 27% (8/30 cells) mosaicism for del(13) (q13.3).

Mosaic 5p15.1pter deletion

Chen et al. [15] reported discrepancy between the fetus and extra-embryonic tissues in prenatally detected mosaic distal 5p deletion. In that case, amniocentesis at 20 weeks of gestation because of advanced maternal age detected the karyotype of 46,XY,del(5) (p15.1)[4]/46,XY[26], consistent with 13.3% (4/30 colonies) mosaicism for del(5) (p15.1). The pregnancy was subsequently terminated, and a malformed fetus was delivered with mild facial dysmorphism. The mosaic levels for del(5) (p15.1) were 8.3% (2/24 cells) in liver, 28.6% (8/28 cells) in lungs, 6.7% (2/30 cells) in skin and 38% (19/50 cells) in cord blood.

Mosaic 5p15.1pter deletion

Chen et al. [16] reported prenatal diagnosis of mosaic distal 5p deletion in a pregnancy because of advanced maternal age. In that case, amniocentesis at 17 weeks of gestation detected the karyotype of 46,XX,del(5) (p15.1)[23]/46,XX[23], consistent with 50% (23/46 colonies) mosaicism for del(5) (p15.1). Repeat amniocentesis at 19 weeks of gestation showed 44.4% (12/27 colonies) mosaicism for del(5) (p15.1). The pregnancy was terminated, and a fetus was delivered with mild facial dysmorphism. The mosaic levels for del(5) (p15.1) were 57.5% (23/40 cells) in cord blood, 45% (18/40 cells) in liver and lungs, and 42.5% (17/40 cells) in skin. The placenta had a karyotype of 46,XX,dup(5) (qter→p15.3p15.3→p10)[23]/46,XX[17], and the amnion had a karyotype of 46,XX,del(5) (p15.1)[7]/46,XX,dup(5) (qter→p15.3p15.3→p10)[18]/46,XX,trp(5) (qter→p15.3p15.3→p10p10→p15.3)[6]/46,XX[21].

Mosaic 22q11.2 microdeletion

Chen et al. [17] reported prenatal diagnosis of mosaic 22q11.2 microdeletion in a pregnancy with tetralogy of Fallot on fetal ultrasound at 32 weeks of gestation. In that case, amniocentesis revealed a karyotype of 46,XY.ish del(22) (q11.2q11.2) (D22S553−)[5]/46,XY.ish 22q11.2 (D22S553 × 2)[1], consistent with 83.3% (5/6 colonies) mosaicism for 22q11.2 microdeletion. A mosaic level of 61% (61/100 cells) for 22q11.2 microdeletion was found in 100 interphase amniocytes. A baby with DiGeorge syndrome was delivered at term with tetralogy of Fallot. The cord blood had 55% (11/20 cells) mosaicism for 22q11.2 microdeletion. The paternal blood had 27.3% (3/11 cells) mosaicism for 22q11.2 microdeletion in metaphase lymphocytes, and 19% (19/100 cells) mosaicism for 22q11.2 microdeletion in interphase lymphocytes. The maternal karyotype was normal. Quantitative fluorescent polymerase chain reaction (QF-PCR) determined the maternal origin of the 22q11.2 microdeletion.

Mosaicism for partial monosomy due to a deletion with a normal cell line at amniocentesis and unknown fetal outcome

Mosaic 22q13.3qter deletion

Phelan et al. [18] reported prenatal diagnosis of mosaicism for deletion 22q13.3 in a pregnancy with an abnormal maternal serum screening result. In that case, amniocentesis at 17 weeks of gestation revealed 95% (19/20 cells) mosaicism for 22q13.3 deletion in cultured amniocytes by G-bands and 94% (47/50 cells) mosaicism by FISH. The pregnancy was terminated. The cord blood had 37% (11/30 cells) mosaicism for 22q13.3 deletion by G-bands and 26% (26/100 cells) mosaicism by FISH. G-banded analysis on the umbilical cord cultures revealed 97% (29/30 cells) mosaicism for 22q13.3 deletion.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Genetic counseling of mosaic and non-mosaic tetrasomy 9p at prenatal diagnosis

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ABSTRACT

Genetic counseling of mosaic and non-mosaic tetrasomy 9p remains difficult because of the possible associated congenital abnormalities, cytogenetic discrepancy in various tissues, true-positive and false-positive diagnosis in non-invasive prenatal testing (NIPT), uniparental disomy (UPD) 9, tissue-limited mosaicism, perinatal progressive decrease of the aneuploid cell line, phenotypic normal carriers and possible favorable fetal outcome in the cases with mosaic tetrasomy 9p at amniocentesis. This article presents a comprehensive review of various counseling issues concerning mosaic and non-mosaic tetrasomy 9p at prenatal diagnosis, and the information provided is very useful for genetic counseling under such circumstances.

Introduction

Tetrasomy 9p, or supernumerary isochromosome 9p [i(9p)], is a rare chromosome abnormality resulting from a supernumerary isochromosome 9p that may involve the entire 9p only; the entire 9p with part of the heterochromatic region of 9q; or the entire 9p with heterochromatic region of 9q and part of the euchromatic region of 9q [1–4]. Tetrasomy 9p has been characterized by clinical features of intrauterine growth restriction (IUGR), developmental delay, ventriculomegaly, Dandy-Walker malformation, facial dysmorphism of a bulbous/beaked nose, hypertelorism, micrognathia, ear malformations, and cleft lip/palate, congenital heart defects, hypoplasia of the digits and nails, joint dislocations, and urogenital abnormalities; and the severity of phenotype associated with tetrasomy 9p is influenced by the size of the isochromosome involved, the degree of mosaicism and the presence of tissue mosaicism [1,5–14]. Prenatal diagnosis of mosaic or non-mosaic tetrasomy 9p is unusual, and the frequency of prenatally detected tetrasomy 9p at amniocentesis is estimated to be 0.002% [15]. For example, Forabosco et al. [15] found eight cases with isochromosomes in a population-based study of 88,965 amniocenteses and found only two cases with i(9p).

Mosaic and non-mosaic Tetrasomy 9p at prenatal diagnosis have been reported to be associated with abnormal fetal ultrasound. Chen et al. [3] reported that fetuses with tetrasomy 9p may present increased nuchal translucency in the first trimester and cystic hygroma in the second trimester as well as fetal ascites, hydrops fetalis, polyhydramnios, oligohydramnios, IUGR, Dandy-Walker variant or malformation, ventriculomegaly, skeletal abnormalities, cleft lip and palate, hydronephrosis and congenital heart defects. In a review of 19 fetuses with tetrasomy 9p, Nakamura-Pereira et al. [16] summarized the common prenatal ultrasound findings of tetrasomy 9p as in the following: IUGR (58%), ventriculomegaly (58%), genitourinary anomaly (47%), hypoplastic/absent vermis (42%), cleft lip and palate (42%), limb malformations (42%), cardiac anomaly (26%) and polyhydramnios (21%). In a systematic clinical review of prenatally diagnosed tetrasomy 9p, Vinkšel et al. [17] found that the most common characteristics of prenatally-detected tetrasomy 9p are IUGR (57.0%), central nervous system abnormalities (59.0%), skeletal anomalies (29.0%), genitourinary and renal anomalies (29.0%) and cardiac defects (29.0%).

True-positive non-invasive prenatal testing (NIPT) diagnosis

Yu et al. [18] reported prenatal diagnosis of a fetus with tetrasomy 9p without obvious phenotypic manifestations by true-positive NIPT in a 37-year-old woman at 15 weeks of gestation.

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NIPT revealed the gain of 9p24.3-9p11 with the size of 46.36 Mb, chromosome microarray (CMA) and fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes at amniocentesis at 18 weeks of gestation revealed tetrasomic of 9p24.3-q13 and a dicentric isochromosome consisted of two copies of the 9p. The karyotype by conventional cytogenetic analysis was 47,XY,+idic(9)(q13). Unfortunately, the pregnancy was subsequently terminated. Zhang et al. [19] reported prenatal diagnosis of a fetus of mosaic tetrasomy 9p by true-positive NIPT in a 32-year-old woman at 13 weeks of gestation. NIPT revealed duplicated 9p with a Z-score-of 4.3 and the gain of 45.76-Mb 9p24.3-p11.2. CMA and FISH analysis on uncultured amniocytes at amniocentesis at 22 weeks of gestation revealed the 64.9-Mb gain of 9p24.3p13.2 × 2.43, consistent with 21.5% mosaicism for 9p24.3p13.2 by CMA and 25% (25/100 cells) mosaicism for 9p24.3p13.2 by FISH. Cytogenetic analysis of cultured amniocytes revealed the karyotype of 47,XX,+der(9)del(9) (q21q34) dup(9) (p12p24) [10]/46,XX[90], consistent with 10% mosaicism for tetrasomy 9p. Prenatal ultrasound at 30 weeks of gestation showed strong light spot in left ventricle, and no other abnormalities could be found. The pregnancy was carried to term, and a 2700-g phenotypically normal baby was delivered. When follow-up at the age of 2½ years, the child manifested normal phenotype and normal psychomotor and language development.

False-positive NIPT diagnosis

Mosaic tetrasomy 9p has been well reported in phenotypically normal carriers [14,20–26]. Shu et al. [26] reported the first case of maternal mosaic tetrasomy 9p incidentally detected by NIPT. Shu et al. [26] reported prenatal diagnosis of false-positive NIPT for elevation in DNA from chromosome 9p in two NIPT tests at 11 and 15 gestational weeks, respectively, and in repeat NIPT six days and one month post-delivery in a 33-year-old woman. Amniocentesis and CMA showed normal results in the fetus. Multiplex ligation-dependent probe amplification (MLPA) on buccal swab and on uncultured maternal blood showed normal result in buccal swab of the neonate and mosaic tetrasomy 9p in the maternal blood. The mother and the child were phenotypically normal. The maternal blood had a karyotype of 47,XX,+dic(9; 9)(q21.1; q21.1) [24]/46,XX [9] with 76% mosaicism for tetrasomy 9p.

Phenotypically normal or near normal carriers of mosaic tetrasomy 9p

Sait and Wetzler [20] reported a 41-year-old phenotypically normal male with hypereosinophilia and a karyotype of 47,XY,+i(9)(p10) in the peripheral blood and 43% mosaicism for tetrasomy 9p in the skin. McAuliffe et al. [14] reported a 37-year-old phenotypically normal male with oligospermia and a karyotype of 47,XY,+i(9)(p10) [4]/46,XY [16] with 20% mosaicism for tetrasomy 9p in the peripheral blood. Ogino et al. [21] reported a 10-year-old phenotypically near normal boy with 6% mosaicism for tetrasomy 9p in the peripheral blood, 5% mosaicism for tetrasomy 9p in buccal mucosal cells and a concealed penis mimicking Klinefelter syndrome. Baronchelli et al. [22] reported a phenotypically normal female with premature ovarian failure and a karyotype of 47,XX,+i(9)(p10)[72]/46,XX [28] with 72% mosaicism for tetrasomy 9p in the peripheral blood. Papoulidis et al. [23] reported two females with mosaic tetrasomy 9p and a normal phenotype. One case was a 20-ear-old female who had 100% tetrasomy 9p in the peripheral blood and 65% mosaicism in buccal mucosal cells. The other one was a 28-ear-old female who had 94% (34/36 cells) mosaicism for i(9)(p10) in the peripheral blood. In a systemic review of normal phenotypes in carriers of small supernumerary marker chromosomes (sSMC) with known adverse outcome, Liehr and Al-Rikabi [24] found that ~1%–30% of the sSMC carriers showed no clinical signs. Bellil et al. [25] reported a 41-year-old male with moderate oligozoospermia but no phenotypic abnormality and a karyotype of 47,XY,+i(9)(p11)[6]/46,XY [18] with 25% mosaicism for tetrasomy 9p in the peripheral blood. Shu et al. [26] a 33-year-old female who was incidentally found to have a karyotype of 47,XX,+dic(9; 9)(q21.1; q21.1) [24]/46,XX [9] with 76% mosaicism for tetrasomy 9p in the peripheral blood and a normal MLPA result in the buccal mucosal cells following prenatal diagnosis of false-positive NIPT.

Phenotypically normal neonates in the cases with mosaic tetrasomy 9p at amniocentesis

Zhang et al. [19] reported a 2½ year-old phenotypically normal female neonate with 10% mosaicism for tetrasomy 9p in cultured amniocytes at amniocentesis and 25% mosaicism for tetrasomy 9p by FISH and 21.5% mosaicism for 9p by CMA in uncultured amniocytes at amniocentesis. Chen et al. [4] reported a 7-month-old phenotypically normal female neonate with 26.7%, 5.9% and 0% mosaicism for tetrasomy 9p at 18, 23 and 27 weeks of gestation, respectively in cultured amniocytes at amniocentesis, and 50% mosaicism for 9p by CMA and 22.6% mosaicism for tetrasomy 9p by FISH at 23 weeks of gestation and 20% mosaicism for tetrasomy 9p by FISH at 27 weeks of gestation in uncultured amniocytes at amniocentesis. FISH analysis on buccal mucosal cells at the age of two months showed 1% mosaicism for tetrasomy 9p, and peripheral blood at the age of two months and seven months showed 45% mosaicism for tetrasomy 9p and 35% mosaicism for tetrasomy 9p, respectively.

Tissue-limited mosaicism, cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, cytogenetic discrepancy among various tissues and perinatal progressive decrease of the tetrasomy 9p cell line in mosaic tetrasomy 9p at amniocentesis

Tetrasomy 9p due to i(9p) has a strong propensity to tissue-limited mosaicism with the abnormal cell line predominantly in the blood [1,3,4,27]. Prenatal diagnosis by chorionic villus sampling (CVS) using cultured chorionic villi cells or by amniocentesis using cultured amniocytes may obtain a false-negative result in pregnancies with fetal mosaic tetrasomy 9p [1,3,4,27–29]. Grass et al. [28] reported 75% mosaicism for tetrasomy 9p in blood cells in a boy with mild manifestations but a normal karyotype of 46,XY at CVS. Eggermann et al. [29] reported 32% mosaicism for tetrasomy 9p in blood cells in a girl with multiple abnormalities but a normal karyotype of 46,XX at amniocentesis. Shehab et al. [27] suggested that tetrasomy 9p is well tolerated in lymphocytes, and the supernumerary i(9p) is often found in all or a very high frequency of blood cells. Chen et al. [1] reported prenatal diagnosis of mosaic tetrasomy 9p by amniocentesis in a 38-year-old woman. Amniocentesis at 18 and 22 weeks of gestation revealed 20% and 16.7% mosaicism for tetrasomy 9p, respectively in cultured amniocytes. Cytogenetic analysis of skin and lung revealed normal karyotypes with no tetrasomy 9p, whereas the cord blood had 48% mosaicism for tetrasomy 9p. Chen et al. [3] reported prenatal diagnosis of mosaic tetrasomy 9p by amniocentesis in a 37-year-old woman. Amniocentesis at 20 and 23 weeks of gestation revealed 21.4% and 16.7% mosaicism for tetrasomy 9p, respectively in cultured amniocytes. Uncultured amniocytes at 23 weeks of gestation had 47.1% mosaicism for tetrasomy 9p by FISH. The fetal blood had 32.5% mosaicism for tetrasomy 9p. The fetus had IUGR, fetal ascites and hydrops fetalis. Chen et al. [4] reported prenatal diagnosis of mosaic

tetrasomy 9p by amniocentesis in a 33-year-old woman. Amniocentesis at 23 and 27 weeks of gestation revealed 5.9% and 0% mosaicism for tetrasomy 9p, respectively in cultured amniocytes. However, uncultured amniocytes revealed 22.6% mosaicism for tetrasomy 9p by FISH and 50% mosaicism for tetrasomy 9p by aCGH at 23 weeks of gestation and 20% mosaicism for tetrasomy 9p by FISH at 27 weeks of gestation. The cord blood at 20 and 39 weeks of gestation had 31.8% and 47.5% mosaicism for tetrasomy 9p, respectively. The umbilical cord and placenta at birth had mosaicism of 2.5% and 10%, respectively. The buccal mucosal cells at the age of two months had 1% mosaicism for tetrasomy 9p. The peripheral blood had 45% and 35% mosaicism for tetrasomy 9p at the age of two months and seven months, respectively. The observation by Chen et al. [1,3,4] indicates that there is cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes in the mosaic levels detected by conventional cytogenetic analysis in cultured amniocytes and molecular genetic analysis in uncultured amniocytes. The latter results obtained by molecular analysis may be higher in mosaic levels than the former results obtained by conventional cytogenetic analysis. This indicates that molecular genetic analysis on uncultured amniocytes during repeat amniocentesis should not replace conventional cytogenetic analysis on cultured amniocytes in case of mosaic tetrasomy 9p at amniocentesis. Furthermore, there is progressive decrease of the aneuploid cell line with tetrasomy 9p at prenatal diagnosis [4]. This indicates that mosaic tetrasomy 9p at amniocentesis without fetal anomalies can be a transient and benign condition, and the fetus can be associated with a favorable outcome. This information is very useful for genetic counselors and obstetricians during genetic counseling of the parents who wish to keep the babies under such a circumstance [4].

Uniparental disomy (UPD) 9

Prenatal diagnosis of mosaicism for i(9p), i(9q), sSMC(9) and trisomy 9 should include a differential diagnosis of UPD and the application of polymorphic DNA marker analysis to exclude UPD 9, especially uniparental isodisomy 9. The chromosome 9 contains no genomic imprinting gene. However, if the associated chromosome 9 in UPD 9 contains genetic defects involving autosomal recessive disorders, uniparental isodisomy 9 can be associated with genetic disorders [30–34]. For examples, Sulisalo et al. [30] reported autosomal recessive cartilage-hair hypoplasia (OMIM 250250) associated with *RMRP* (OMIM 157660) at 9p13.3 in two probands transmitted by UPD 9. Tiranti et al. [31] reported autosomal recessive Leigh syndrome or mitochondrial complex IV deficiency, nuclear type 1 (OMIM 220110) associated with *SURF-1* (OMIM 185620) at 9q34.2 in a proband transmitted by maternal uniparental isodisomy 9. Castanet et al. [32] reported Bamforth-Lazarus syndrome (OMIM 241850) or autosomal recessive syndromic congenital hypothyroidism associated with *FOXE1* (OMIM 602617) at 9q22.33 in a proband transmitted by maternal uniparental isodisomy 9. Xiao et al. [33] reported autosomal recessive Leigh syndrome or mitochondrial complex IV deficiency, nuclear type 1 (OMIM 220110) associated with *SURF-1* (OMIM 185620) at 9q34.2 in a proband transmitted by paternal uniparental isodisomy 9. Nishimura et al. [34] reported autosomal recessive craniosynostosis and dental anomaly (OMIM 614188) associated with *IL1*1RA (OMIM 600939) at 9p13.3 in a proband transmitted by maternal uniparental isodisomy 9. Chen et al. [35,36] reported detection of maternal UPD 9 associated with mosaic trisomy 9 at amniocentesis with favorable outcomes and normal karyotypes. Chen et al. [37], reported detection of paternal UPD 9 in a phenotypically normal neonate with perntally detected mosaicism for an sSMC(9) and a supernumerary ring chromosome 9. Amniocentesis revealed a karyotype of 47,XY,+mar [25]/48,XY,+mar,+r(9) [4]/47,XY,+r(9) [1]/46,XY [6]. The marker chromosome was sSMC(9). Anderlid et al. [38] reported maternal heterodisomy 9 in a neonate with moderate mental retardation, speech delay, no obvious dysmorphism and the karyotype of 47,XX,+mar (34%)/46,XX (66%) with mosaic supernumerary r(9) (p12→q10). Björck et al. [39] reported isochromosomes for i(9p) and i(9q) and maternal uniparental isodisomy with no clinical symptoms. The 34-year-old woman was ascertained because of repeated spontaneous abortions. Her karyotype was 46,XX,i(9) (p10),i(9) (q10).

Conclusion

Genetic counseling of mosaic and non-mosaic tetrasomy 9p remains difficult because of the possible associated congenital abnormalities, cytogenetic discrepancy in various tissues, true-positive and false-positive diagnosis in NIPT, UPD 9, tissue-limited mosaicism, perinatal progressive decrease of the aneuploid cell line, phenotypic normal carriers and possible favorable fetal outcome in the cases with mosaic tetrasomy 9p at amniocentesis. This article presents a comprehensive review of various counseling issues concerning mosaic and non-mosaic tetrasomy 9p at prenatal diagnosis, and the information provided is very useful for genetic counseling under such circumstances.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Review Article

Cervical cancer: Part II the landscape of treatment for persistent, recurrent and metastatic diseases (I)

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ABSTRACT

The WHO (World Health Organization) conducted an elimination of cervical cancer program using triple pillar intervention strategy to target 90%-70%-90% of women before the year 2030, including (1) a full vaccination of HPV (human papillomavirus) vaccine to 90% of girls <15 years of age; (2) a high-performance screening procedure to 70% of women during the reproductive age (at the age of 35 and 45 years of age); and (3) an appropriate and adequate treatment to 90% of women with confirmed diagnosis of cervical lesions. Among the aforementioned three pillars, a full HPV vaccination has been introduced in our previous review, of which we have discussed the policy and strategy of HPV vaccination in the world and also reviewed the efficacy of HPV vaccination, with a successful reduction of over 90% of HPV-associated neoplasms. The aims of the current review will target another pillar-an appropriate and adequate treatment to 90% of women with confirmed diagnosis of cervical lesions. Since the early-stage cervical cancer has a favorable outcome and the treatment recommendation has been established, therefore, the current review focuses on women with persistent, recurrent and metastatic cervical cancers (advanced cervical cancers), which are still a biggest challenge based on its extremely worse outcomes before the introduction of immune checkpoint inhibitors (ICIs). Integration of ICIs into conventional chemotherapy (paclitaxel-cisplatin) has become the new standard therapy for those patients with advanced cervical cancers. The recent clinical trials, such as KENOTE 826 and KENOTE A18 showing a dramatical improvement of both progression free survival and overall survival have approved the therapeutic efficacy of this combination as ICI plus paclitaxel-platinum (cisplatin or carboplatin) with/without bevacizumab to women with persistent, recurrent and metastatic cervical cancers.

Introduction

The burden of cervical cancers has been well recognized, since cervical cancer is not only a cause contributing to the disability of diseased women but also associated with high mortality rates, which significantly impair equilibrium of relationship between patients and family and subsequently cause enormous losses of family, society and world [1–7]. Cervical cancers-related huge socio-economic damage is involved in the high-income countries and this trouble is particularly apparent in the low- and middle-income countries (the poverty world), not only with a very high incidence of cervical cancer in those low- and middle-income countries but also with a high proportion of patients died of diseases in these countries [8]. An estimated number of 604,000 women were diagnosed with cervical cancer annually and finally 342,000 women will die of diseases, which may reach to 847,000 and 524,000, respectively in 2040 in particular in low- and middle-income countries, where nearly half of

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mortality cases occurred with a more than four-fold increase than those in the developed countries [9–13]. Many causes may contribute to the high incidence and high death rates in low socio-demographic index countries, including limited women's access to screening, no vaccination, and inadequate treatment-knowledge and deficient or defecting health-care systems, reflected by resource scarcity, lack of skilled staff, high client loads, lack of preventive oncology policy, territorial disputes, and lack of national guidelines were identified as barriers to the services [8,14]. Additionally, there are many following obstacles, such as limited health system capacity, heavier workload, longer waiting time, lack of coordination and inadequate treatment after the confirmed diagnosis needing to be overcome [14].

The risk factors associated with cervical cancer include persistent human papilloma virus (HPV) infection, particularly for those high-risk HPV (hrHPV) infections (types 16,18,31,33,35,39,45,51,52,56,58, and 59), smoking, presence of sexual transmitted disease (STD), such as human immunodeficiency virus (HIV) or chlamydia infection, unprotected or early exposure of sexual activity (<18 years of age), multiple sexual partners, sexual partner who is considered high risk (someone with HPV infection or who has many sexual partner), long-term use of oral contraceptives (birth control pills), multiple full-term pregnancies, young age at first full-term pregnancy (<20 years of age), low economic status (limited access to health care), a diet low in fruits and vegetables, diethylstilbestrol exposure, and family history of cervical cancer [15,16].

In part I, we have introduced the effective relief of cancer-related tension by conducting HPV vaccination program, which is the first and most important recommendation by WHO (World Health Organization) [8,9]. In brief, hrHPV is the "necessary" cause of the development of cervical cancer and HPV 16 and HPV 18 account for 71% of cervical cancer cases; while HPV types 31,33,45, and 58 account for another 19% of cases [8,17,18]. Nearly 90% of incident HPV infections are cleared within a period of two years from the acquisition of infection and 10% will persistent. Repeated same-type and multiple-type HPV infection is common in women with active sexual activity. Young-age has a stronger immune response to HPV vaccine compared to older age. The purpose of HPV vaccination is against cancer not correlated with sex. More than 36,000 HPV-related cancer are effectively prevented by HPV vaccination annually. HPV vaccination can be given earlier at 9 years of age with best efficacy to prevent six cancers. HPV-related cancers are involved in girls, boys, women and men. The adequate information for education and awareness of the reality, safety, and efficacy of HPV vaccination should be widely spread, such as a dramatical decline of cervical cancer from 538 among unvaccinated women to only 19 among vaccinated women in a Swedish study [8,17,18].

The current review entitling "Cervical Cancer: Part II the landscape of treatment for persistent, recurrent and metastatic diseases" will discuss the strategy to ameliorate the cancer-related as well as treatment-associated sequelae and further enhance the efficacy of treatment and subsequently decrease the cancer- or therapy-related morbidities and mortalities.

General principle for management of women with cervical cancer (Non-fertility sparing) (Table 1)

Cervical cancer is assigned a clinical staging system by FIGO (the International Federation of Gynaecology and Obstetrics) since 1958 and the updated FIGO staging system for cervical cancer was made in 2021, which is closely aligned with the latest TNM (tumor-node-metastasis) staging and allocated after all imaging and pathology reports are available and not to be altered later, for example at recurrence [18]. Similar to cancers of all female genital organs [18–25], four stages of cervical cancers are classified, including stage I (IA1 & IA2 as well as IB1, 2, & 3), II (IIA1 & IIA2 as well as IIB), III (IIIA, IIIB, and IIIC1 & IIIC2), IV (IVA and IVB) [18]. Based on the recommended treatment from the new update NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024—May 6, 2024, it has clearly suggested that cervical cancer treatment can be made according to the FIGO staging system [25].

Women with cervical cancer at the very early stage needing fertility sparing surgery, such as stage IA1 (no lymphovascular space invasion [LVSI]), stage IA2-IB1 with following criteria as no LVSI, negative cone margins, squamous cell (any grade) or usual type adenocarcinoma (grade 1 or 2 only), tumor size $\leq$ 2 cm, depth invasion $\leq$ 10 mm, negative imaging for metastatic disease, can be managed by cone biopsy with negative margins, with or without pelvic lymphadenectomy (PLND) or sentinel lymph node (SLN) mapping [25]. However, all aforementioned recommendations belonged to category 2A unless otherwise indicated [25]. For women with diagnosed stage IA1-IA2 cervical cancer and LVSI, radical trachelectomy plus PLND or SLN mapping can be an alternative therapy in those women needing fertility preservation and this recommendation is also a category 2A [3,25].

Women with stage IB1 not meeting conservative surgery criteria or stage IB2 or stage IIA1, radical hysterectomy (RH) plus PLND (category 1) or pelvic external beam radiotherapy (EBRT) plus brachytherapy with or without concurrent platinum-containing chemotherapy (with concurrent platinum-containing [cisplatin as a single agent or carboplatin if cisplatin intolerant] chemotherapy calling as concurrent chemoradiation [CCRT]) is a standard therapy [25].

When women are diagnosed as locally advanced cervical cancer, such as stage IB3, stage IIA2, treatment had better be used by CCRT plus brachytherapy (category 1) [25]. In some highly-selected population, other individualized modified approaches are also indicated, although these recommendations belong to the category 2B [25]. For women with more advanced (regional) cervical cancer, such as FIGO 2014 stage III-IVA, the standard therapy is a concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin a single agent as recommended therapy [25]. Additionally, NCCN has favored the adding pembrolizumab into the conventional CCRT [25], which will be discussed in detail in the following section. For women with persistent, recurrent or metastatic cervical cancer, systemic therapy can be considered [25]. However, since the curability is low, the best supportive care is also highly recommended by NCCN guideline [25]. All suggest that there are still big gaps or challenges for physicians and patients if the advanced cervical cancers (persistent, recurrent or metastatic cancers) are diagnosed.

The updates in Version 3.2024 of the NCCN guidelines for cervical cancer from Version 2.2024 mainly focus on the use of cisplatin for CCRT (or carboplatin if cisplatin intolerant) and the introduction of immune checkpoint inhibitors (ICIs) into the modern systemic treatment or CCRT programs [25]. Additionally, maintenance therapy by ICIs and/or monoclonal antibodies (Abs) has been also suggested, and the therapy can be referred to the original study protocol for maintenance therapy dosing schedules [25]. The brief summary of FIGO cervical cancer stage and recommended therapies is shown in Table 1.

Why the aforementioned updated information is so important? This can be well explained by distribution of the cervical cancer stage. In the United States, an estimated 51% of patients with cervical cancer have regional (defined by spread to regional lymph nodes) or distant (metastatic) disease at diagnosis by Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute (NCI) [26]. In Taiwan, more than 55% of invasive

Table 1
2021 FIGO staging for cervical cancer and the recommended therapy.

Stage and the disease status		Treatment
IA1	No LVSI	Cone margin free: Extrafascial hysterectomy (medically inoperable: observation) Cone positive margin: • Extrafascial or modified radical hysterectomy + BPLND/SNL mapping if margin with carcinoma • Repeat cone to evaluate depth of invasion or (medically inoperable: Brachytherapy ± pelvic EBRT)
	With LVSI	• modified radical hysterectomy + BPLND/SNL mapping • Pelvic EBRT + brachytherapy
IA2		• modified radical hysterectomy + BPLND/SNL mapping • Pelvic EBRT + brachytherapy
	Meet conservative criteria: no LVSI, SCC or usual type adenocarcinoma	• Extrafascial hysterectomy + BPLND/SNL mapping
IB1		• Radical hysterectomy + BPLND ± para-aortic lymphadenectomy • Pelvic EBRT + brachytherapy ± CCRT
	Meet conservative criteria: no LVSI, SCC or usual type adenocarcinoma, Depth of invasion ≤10 mm	• Extrafascial hysterectomy + BPLND/SNL mapping
IB2		• Radical hysterectomy + BPLND ± para-aortic lymphadenectomy • Pelvic EBRT + brachytherapy ± CCRT
IB3		• Pelvic EBRT + CCRT + brachytherapy • Radical hysterectomy + BPLND ± para-aortic lymphadenectomy
IIA1		• Radical hysterectomy + BPLND ± para-aortic lymphadenectomy • Pelvic EBRT + brachytherapy ± CCRT
IIA2		• Pelvic EBRT + CCRT + brachytherapy • Radical hysterectomy + BPLND ± para-aortic lymphadenectomy
IIB		• Pelvic EBRT + CCRT + brachytherapy
IIIA		• Pelvic EBRT + CCRT + brachytherapy
IIIB		• Pelvic EBRT + CCRT + brachytherapy
IIIC1		• Pelvic EBRT + CCRT + brachytherapy
IIIC2		• Extended-field EBRT + CCRT + brachytherapy
IVA		• Pelvic EBRT + CCRT + brachytherapy • Extended-field EBRT + CCRT + brachytherapy
IVB		• Systemic therapy + individualized RT

Abbreviations: LVSI, lymphovascular space invasion or involvement; BPLND/SNL, bilateral pelvic lymph node dissection/sentinel lymph node; EBRT, external beam radiation; CCRT, cisplatin-based concurrent chemoradiation.

cervical cancer patients (n = 723) are classified as regional or distant (metastatic) disease at diagnosis by Cancer Registry Annual Report, 2021 Taiwan of the Health Promotion Administration, Ministry of Health and Welfare [27]. In fact, these women with advanced cervical cancer have been treated with systemic therapy, including chemotherapy and targeted therapy (Fig. 1); however, the outcomes seemed to be very disappointing, since nearly half of patients (608/1310) finally died of cancers. All suggest that these therapies do not satisfy the clinical or medical needs [27].

Conventional systemic therapy for cervical cancer

Chemotherapy, working by preventing malignant cells from proliferation and growth aiming to disrupt various stages of the cell cycle and prevent uncontrolled proliferation is a standard and preferred choice for neoplasm treatment, when local or regional therapy can not cover the extensively invasion or disseminated distribution of cancer status of patients. Although the development of anti-cancer chemotherapeutic agents is continuous, there is no

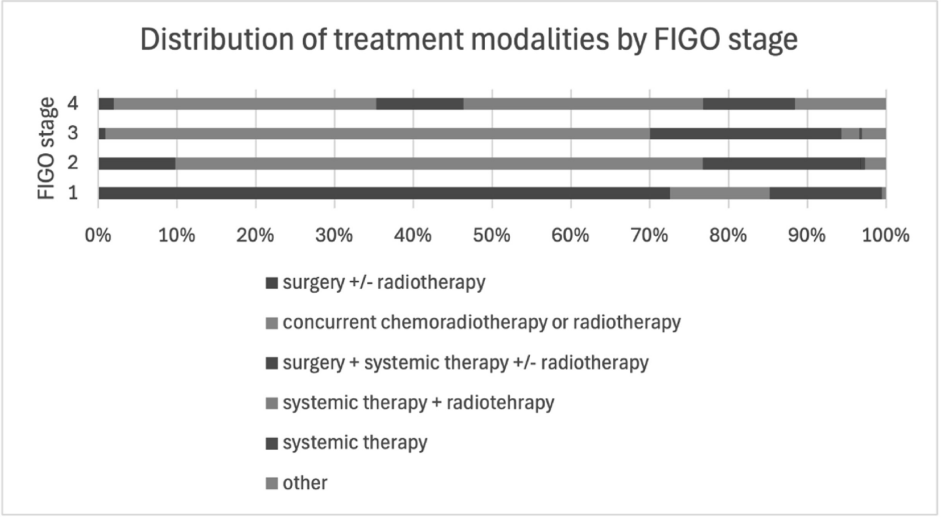

Fig. 1. Distribution of treatment modalities by FIGO stage in Taiwan (data from 2021 cancer registry annual report).

doubt the standard chemotherapy for cervical cancer has not been changed in the past ten years. Cisplatin is the most important and well-known therapy of choice for cervical cancer, which has been used for more than forty years [28–30]. Cisplatin is not only the key agent used alone for the management of patients with cervical cancers, but also plays a backbone to integrate other agent to form an effective multi-agent regimen for cervical cancer treatment [28–30]. The clinical use of cisplatin is so widely and in broad, which is applied as neoadjuvant, adjuvant, rescue, or palliative role. Additionally, cisplatin is the most essential and effective agent to work in cooperation of radiation therapy (radio-sensitizer) to form the concurrent chemoradiation (platinum-based CCRT, often using cisplatin as a best choice) to treat the localized diseases or in combination of radiotherapy in the management of patients with extensive diseases [28–30]. The most frequently clinically used dose of cisplatin is defined as 50 mg/m^2 or above 40 mg/m^2, which was suggested by Bonomi's study [28]. A 100 mg/m^2 single dose may produce a statistically significant higher response rate than the 50 mg/m^2, but this 100 mg/m^2 dosage of cisplatin failed to produce any appreciable differences in complete remission rate, response duration, progression free survival (PFS) and overall survival (OS) [28]. By contrast, the higher dose affects fast-proliferating normal cells, including bone marrow, gastrointestinal tract cells, hair follicles, mesenchymal or endothelial cells of glomerulus structure of kidney or peripheral neuron sheath cells, resulting in greater myelosuppression and nephrotoxicity [28]. Therefore, the clinically recommended and preferred dosage of cisplatin was established as 50 mg/m^2, not only with not inferior to the therapeutic effect by 100 mg/m^2 but also with lower risk of occurrence of adverse events (AEs) [28].

In 2005, cisplatin-based multiple-agent combination therapy has been approved to offer both PFS and OS compared to cisplatin single agent therapy (median PFS 4.6 months 2.9 months; medial OS 9.4 months vs. 6.5 months, respectively) [31]. Moreover, after introduction of paclitaxel in the management of various kinds of gynecologic cancers, which were associated with significantly improved outcomes [20,21,32–41], the combination of paclitaxel and cisplatin (PC) has been recognized the more effective and less toxic regimen in the management of patients with cervical cancer needing systemic therapy compared to other three valuable or effective combined regimens (vinorelbine plus cisplatin [VC], gemcitabine plus cisplatin [GC] and topotecan plus cisplatin [TC]) [42]. The advantages of PC regimen compared to VC, GC, and TC regimens have been demonstrated by achieving the better PFS or OS [42]. The hazard ratios (HR) of experimental-to-PC was 1.36 (95% confidence interval [CI] 0.97–1.90 for VC), 1.39 (95% CI 0.99–1.96 for GC) and 1.27 (95% CI 0.90–1.78 for TC), respectively in term of PFS [42]. The aforementioned benefit from PFS was also reproducible in OS with 1.15 (95% CI 0.79–1.67 for VC), 1.32 (95% CI 0.91–1.92 for GC) and 1.26 (95% CI 0.86–1.82 for TC), respectively, suggesting that VC, GC, and TC are not superior to PC [42]. By contrast, the trend in response rate, PFS and OS favors PC regimen compared to the other three combinations (VC, GC, and TC) [42]. Even though the application of PC for patients with advanced cervical cancer seemed to be workable and favorable, the median PFS was 5.82 months (95% CI 4.53–7.59 months) and the median OS was only 12.9 months, respectively [42], suggesting that PC regimen did not meet the clinical and medical needs.

To enhance the therapeutic efficacy of PC regimen in the management of patients with advanced cervical cancers, tri-agent containing with other chemotherapy was tried. Unfortunately, adding more chemotherapy agents did not have a better response and by contrast, toxicity was dramatically increased. In fact, the above-findings have been easily explained by the own AEs of chemotherapy, since the damage has been equally applied to normal tissue along with cancer tissue. Therefore, new novel or modern therapy may be needed. Hanahan modified by the original six acquired capabilities-Hallmarks of Cancer-proposed in 2000 to produce a 2022 new hallmarks of cancer may aid in differentiating tumor and normal tissue characteristics and suggest better treatment options, including enabling replicative immortality, tumor-promoting inflammation, activating invasion and metastasis, inducing or accessing vasculature (angiogenesis), genome instability and mutation, resisting cell death, deregulating cellar metabolism, sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, unlocking phenotypic plasticity, and senescent cells as well as two enabling characteristics of non-mutational epigenetic reprogramming and polymorphic microbiomes [43]. Among the above, targeted the inducing or accessing vasculature (anti-angiogenesis) may offer a better option for cancer treatment, contributing to the development of a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab) mainly targeting VEGF-A which is a critical factor to enhance and finish the angiogenesis process. The benefits of using bevacizumab has been well-known in the present-day treatment options for various kinds of cancers, such as epithelial ovarian cancers (EOC), colon cancer, and many others [20,21,41,43–47].

Integration of bevacizumab into conventional chemotherapy and following maintenance of therapy has offered a dramatical and amazing success in significantly prolonging PFS or even OS [20,21,41,43–47], which is also successfully copied to the treatment for cervical cancer, which also present an exciting and promising result [48–51]. In 2014, GOG 240 (the Gynecologic Oncology Group), a phase 3, randomized trial was conducted to test the incorporation of bevacizumab and the use of nonplatinum combination chemotherapy in the treatment of persistent, recurrent and metastatic cervical cancer [48–50]. First, GOG 240 identified PC regimen as a better choice for the standard chemotherapy therapy compared to PT (paclitaxel and topotecan) regimen, since PT was not superior to PC (HR 1.20) [48]. Second, bevacizumab plus chemotherapy (either PC or PT) was associated with increased OS (17.0 months vs. 13.3 months; HR 0.71, 98% CI 0.54–0.95) and higher response rates (48% vs. 36%) [48]. All support the PC regimen as a standard systemic therapy for cervical cancers.

However, the proverb showing “no pain and no gain” is a real reflective in using bevacizumab plus chemotherapy for treating cervical cancers. In 2021, Cochrane review in 2021 has first raised the concern about this protocol containing bevacizumab in the treatment for cervical cancer [52]. Additionally, the authors considered favoring the use of bevacizumab plus chemotherapy is based on low-certainty evidence [52]. The next section will discuss the specific and non-specific AEs of using bevacizumab plus chemotherapy in the management of patients with cervical cancer. Before ending of this section, Table 2 is a summary of recent advance of chemotherapy in the management of advanced cervical cancer.

The AEs of anti-angiogenetic agents for cervical cancers

The bevacizumab-containing chemotherapy is associated with an improvement of 3.7 months in median OS and lower risk of death with HR of 0.77 (95% CI 0.62–0.95) compared to chemotherapy alone [48,52]. However, adding bevacizumab into the conventional chemotherapy (PC or PT) probably increases specific AEs and serious AEs, with an increased incidence of hypertension of grade 2 or higher (25% vs. 2% with risk ratio (RR) 13.75, 95% CI 5.07–37.29), serious thromboembolic events of grade 3 or higher (8% vs. 1%, with RR 4.5, 95% CI 1.55–13.08), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%, with RR 18.00, 95% CI

Table 2
Recent advance of chemotherapy treating advanced cervical cancer.

Study	Year	Main finding
Bonomi et al. [28]	1985	Identify the optimal dosage of cisplatin as 50 mg/m^2 or above 40 mg/m^2.
Long et al. [31]	2005	Cisplatin-based multiple-agent combination therapy had improved PFS and OS using compared to single-agent.
Monk et al. [42]	2009	The combination of paclitaxel and cisplatin is superior to vinorelbine plus cisplatin, gemcitabine plus cisplatin, and topotecan plus cisplatin.
GOG 240 [48]	2014	Increased OS and response rates were found in the combination of bevacizumab and chemotherapy.

Abbreviations: PFS, progression free survival; OS, overall survival.

2.42–133.67), compared with chemotherapy alone [48,52]. There is also a higher incidence of serious haemorrhage (RR 5.00, 95% CI 1.11–22.56) [52]. To summary all AEs, a higher incidence of serious AEs was identified in patients treated with bevacizumab plus chemotherapy compared to those with chemotherapy alone (RR 1.44, 95% CI 1.16–1.79) [52].

With aforementioned survival benefits but possibly potential AE risks, the question is raised that does it really benefit to advanced cervical cancer patients treated with bevacizumab plus chemotherapy. It is relatively difficult to respond to this question. In fact, the above concerns have been evaluated in GOG 240 study, which attempted to assess the primary quality of life (QoL) of patients using the score on the Functional Assessment of Cancer Therapy-Cervix Trial Outcome Index (FACT-Cx TOI) [49]. A short-term evaluation of patients was assessed before treatment cycles 1, 2, and 5, and at 6 and 9 months after the start of cycle 1, with the FACT-Cx TOI, items from the FACT-GOG-Neurotoxicity subscale, and a worst pain item from the Brief Pain Inventory [49]. Compared with patients who received chemotherapy alone, patients who received chemotherapy plus bevacizumab reported FACT-Cx TOI scores that were an average of 1.2 points lower, suggesting that improvements of PFS and OS in patients attributed to the incorporation of bevacizumab into the treatment of advanced cervical cancer were not accompanied by any significant deterioration in health-related QoL [49]. However, Cochrane review seemed to argue the above findings and additionally, the authors found the incremental cost-effectiveness ratio as USD 295,164 per quality-adjusted life-year [52], suggesting that the concept for routine use or practical use of bevacizumab plus chemotherapy for cervical cancer patients needs more studies to verify its ratio between the benefits and the risks.

The bevacizumab-specific AEs may cause the permanent injuries of patients, such as the development of GI or GU fistulae, which may subsequently impair the QoL in their remaining lives. Nobody will argue about the poor QoL of the cancer patients without treatment; however, cancer treatment may be not always associated with an improvement of QoL, since therapy may destroy the diseased organs and/or further damage the surrounding tissues or organs. Some of them may be severe to disturb the patients' living, contributing to deteriorating the existed poor QoL of these patients. This concern is particularly important or worthy of our attention to patients who are expected to have a short lifespan. For those patients, the palliative treatment by the best supportive care may be a therapy of choice. Therefore, when we design any new strategies to manage the patients with advanced cervical cancer, we should always consider their better efficacy without significantly increasing the therapy-related AEs or developing new onset of AEs, particularly for avoiding therapy-induced permanent injuries, which may further exacerbate the existed poor QoL of patients. In fact, looking forward to improving the better QoL, regardless which disease is belonged is always the priority before decision of treatment for patients [53–60].

Based on the aforementioned concerns and to avoid the therapy-related severe AEs, what can we do? First, is it possible to identify what's proportion of the patients vulnerable to developing bevacizumab-specific AEs? To respond to this question, previous study may give some hints. In the final OS and AE analysis of GOG 240, patients with fistula (any grade) always had a prior irradiated therapy, although the incidence was particularly higher in the bevacizumab plus chemotherapy groups than chemotherapy-alone groups (32 [15%] of 220 versus three [1%] of 220) [50]. Additionally, much severe form of fistula was also frequently noted in the bevacizumab plus chemotherapy group compared to chemotherapy alone group (in term of grade 3 fistula, 13 [6%] in the bevacizumab plus chemotherapy groups versus one [<1%] in the chemotherapy alone groups) [50]. All suggest that bevacizumab-based therapy really increased the risk of development of fistula (any grade) and also was associated with more severe form of fistula (grade 3) when fistula occurred.

The next question is raised- "was radiation itself an independent essential factor involving in the fistula formation?". Based on the results of GOG 240, the answer may be "yes", since all patients complicated with any grade of fistula have been irradiated before. One recent meta-analysis further supported both bevacizumab and radiation were a critical cause inducing the occurrence of fistula [2]. Bevacizumab dramatically increases the risk of gastrointestinal/genitourinary (GI or GU) fistula or perforation in cervical cancer patients, particularly for those with prior exposure to radiotherapy, which demonstrated a nearly five-fold increase (odd ratios [OR] 4.03, 95% CI 1.76–9.20 for GI fistula or perforation and OR 4.71, 95% CI 1.51–14.70 for GU fistula or perforation, respectively) [2].

Even though we can identify the essential factor contributing to an increased risk of development of GI or GU fistula or perforation, all we can do are so limited. Unlike other two main gynecologic organ cancers (uterine cancer and ovarian cancer), of which surgery is a cornerstone in the comprehensive approach to both types cancer treatment [19–21,32–34,61–65], radiation therapy is a crucial component in the treatment of cervical cancer utilizing high dose of radiation to target and destroy cancer cells by resulting in double-strand breaks in the DNA helix, initiating a cascade of cellular response and subsequently disrupting the ability of cancer cells to divide and grow, ultimately leading to the cell death [7,18,43]. At first, nearly all patients with any-stage invasive cervical cancer can be primarily treated by radiation with or without cisplatin [18,25], which is used as radio-sensitizer. Second, nearly all patients being treated with incomplete or inadequate surgical approach or having been undergoing the curative therapy (radical hysterectomy as an example) but coexisting identified surgical-pathological risk factors can be managed by postoperative radiation as an essentially effective rescue method [25,66–68]. However, a certain percentage of the patients will be recurrent, persistent and metastatic during and after the definite therapy, and many of them have been exposed to prior radiotherapy. The patients with persistent, recurrent or metastatic cervical cancers after radiation therapy may be one of the most challenging situations, since only a very few patients can be managed by surgical approach and nearly all of them should be treated with systemic therapy and/or palliative therapy with an aim of best support care. Bevacizumab plus PC could offer advantages of

prolongation of both PFS and OS; however, the occurrence of anti-angiogenetic agents-related complications such as fistula formation may be a nightmare [69]. Therefore, the unmet medical needs encourage the development of new therapeutic strategies.

The recent advanced technology has been continuously improved, such as molecular methods for biomarkers testing in solid tumors to dissect into three main parts, including host, cancer cells, and tumor microenvironment (TME), and each of them included biological sex, polymorphisms affecting the immune response, HLA heterozygosity for the host factors; genomic background, immune-sensitivity or immune-resistance, neoantigen sources, somatic mutations, onco-viral antigens, and cancer testis antigens, antigen presentation and immune evasion as impaired response to checkpoint blockage for the cancer cells; and immune-resistance, tumor infiltration as better outcomes/sensitivity to immune checkpoint inhibitors (ICIs) and associated with immunosuppressive environment, as macrophage M2 cells and myeloid derived suppressor cells for TME [43,70]. These tumor-agnostic therapies (also known as pan-tumor or histology-independent therapies) is classified broadly as novel/modern therapy and can be guided by many modern technological tools, such as immunohistochemistry (IHC) [4,37,71–73], fluorescence *in situ* hybridization (FISH) [74,75], polymerase chain reaction (PCR) [37,76,77], next-generation sequencing (NGS) [5,78–80], and gene expression profiling (GEP) [75,81–83], to offer a more precise and tailored strategy to combat cancers by identifying the "more specific" or "more precise" molecules involved in cancer growth and survival and by producing bullets which can attack cancers directly [70,84].

These tissue-agonistic drugs have really opened a new cancer treatment modality that focuses on targeting specific genetic mutations or alternations that drive tumor growth rather than treating tumors based on their location or tissue of origin [84]. To date, the tissue-agonistic drugs or targets contain at least six biomarkers to generate indications to patients with advanced solid tumors, which include tyrosine receptor kinase-TRK (Larotrectinib or entrectinib applied by NTRK gene fusion), programmed cell death 1 or programmed cell death ligand 1 or 2 (PD-1, PD-L1, PD-L2, pembrolizumab or dostarlimab according to presence of MSI-H [microsatellite instability high], dMMR [mismatch repair deficiency], or TMB-H [tumor mutational burden high] $\geq$ 10 mut/Mb), BRAF (V-raf murine sarcoma viral oncogene homolog B1, dabrafenib or trametinib indicated by BRAF V600E mutation [substitution of valine to glutamic acid at position 600 of the BRAF protein]), RET (rearranged during transfection, selpercatinib based on RET gene fusion), and HER-2 (human epidermal growth factor receptor 2, trastuzumab deruxtecan, based on HER2/neu overexpression) [84]. Besides the above, others include cell surface-expressed tissue factor (tisotumab vedotin [TV]) and many others [85].

Additionally, according to Hallmarks of Cancer-proposal suggesting precise treatment options, "avoiding immune destruction" may be an alternative choice in the management of cancers [43]. Additionally, complexities of cancer can be considered as a systemic disease, including tumor initiation and promotion, tumor micro- and immune macro-environments, aging, metabolism and obesity, cancer cachexia, circadian rhythms, nervous system interactions, tumor-related thrombosis and the microbiome [86]. Among these, tumor-induced perturbations of the immune system may be one of most critical determining factors to establish the cancer growth, invasion and metastasis in distinct ways by production of paracrine or autocrine molecules from cancer cells, immune cells and non-immune stroma cells in driving an immunosuppressive microenvironment, contributing to requirement a comprehensive understanding of the molecular underpinnings of the interplay between local and systemic immunity [86]. Therefore, avoiding immune destruction, one of the core hallmark capabilities constituting a theoretical framework that has proved to be of enduring utility for rationalizing the vast complexity of cancer and its underlying mechanisms and thereby, identifying the immune checkpoint proteins [86]. ICIs is a blockage to immune checkpoint protein. Using ICIs alone or ICI-based backbone therapy in the management of women with various kinds of tumors, including cervical cancer have been tested in many clinical trials [86–104]. Many of them showed a very exciting and promising result because these therapies have significantly prolonged the patients' lifespan [39,40,84,87–105]. The following section will focus on ICIs, either using alone or in combination of other therapeutic strategy in the management of women with cervical cancer.

Immune checkpoint inhibitors (ICIs)

Cancer variants with a high proliferation fraction respond well to conventional chemotherapy (chemotherapy-sensitive) and are curable, but it is rare to cure advanced solid tumor by chemotherapy and recurrence rate secondary to appearance of resistant strain of cancer variants is high, resulting in therapeutic failure [87]. Therefore, based on targeting the hallmarks of cancer, immunotherapy represents a paradigm shift from traditional cancer treatment to groundbreaking approach in the field of cancer treatment, utilizing the host natural defense mechanisms and enhancing the power of host immune system to recognize, target and finally clean cancer cells [86]. Cancer cells often develop mechanisms, called as tumor immunosuppression effects to escape from surveillance of host immune system. Immune checkpoint (ICP) is a kind of signal (stimulatory or inhibitory) for regulating the antigen recognition of T cell receptors in the process of immune response of attacking pathogens and protecting the normal tissue from damage (the intensity and duration of immune responses), and often considered as "brakes" to prevent overactivation of the immune system and maintain self-tolerance [88].

During the cancer transformation, cancer cells upregulate the expression of immune checkpoint proteins or their ligands to suppress T cell activity, avoid immune detection and establish an immunosuppressive TME [88]. There are many immune checkpoint proteins playing a crucial roles in regulating the immune response, including programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), PD-L2, cytotoxic T-lymphocyte-associated antigen-4 (CLTA-4), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein-3 (TIM-3), V-domain immunoglobulin suppressor of T cell activation (VISTA), T cell immunoreceptor with immunoglobulin and ITIM (immunoreceptor tyrosine-based inhibitory motif) domain (TIGIT), B- and T-lymphocytes attenuator (BTLA), signal-regulatory protein alpha (SIRPa), CD40/CD40L (CD154), Ox34 (CD134), Siglec-15, and 4-IBB (CD137) [88,90]. Therefore, restoration of functioning immune system can be achieved by using agonists to stimulatory signals or antagonists of inhibitory signals. Among both, drugs designed to block these inhibitory signals (PD-1/PD-L1 pathway), thereby unleashing the immune system to recognize and attack cancer cells have shown remarkable success in treating various cancers, including melanoma, lung cancer, renal cell cancer, endometrial cancer, as well as cervical cancers [25,39,70,87–105]. The next section will discuss the current advance in using ICIs alone or acting as backbone to integrate other modality strategies in the management of women with advanced cervical cancers (persistent, recurrent or metastatic cervical cancers).

Clinical trials of using ICIs alone or acting as backbone in the management of women with advanced cervical cancer

Table 3 summarizes important clinical trials of ICIs. Each trial and ICI will be discussed in detail below.

Table 3
Summary of important clinical trials of immune checkpoint inhibitors.

Clinical trial	Study design	Sample size	Patient Eligibility	Treatment arms	Primary endpoint(s)	Medium follow up period (months)
NCT01693783 2018 JAMA oncology [106]	Phase1 (run-in cohort) and phase 2, single-arm	42	Metastatic with measurable disease and progression after at least 1 line of platinum chemotherapy	Ipilimumab 3 mg/kg, every 21 days for 4 cycle or ipilimumab, 10 mg/kg, every 21 days for 4 cycles and then 4 cycles of maintenance therapy every 12 weeks	Grade 3 AEs: 4/42, 9.5% ORR: 1/34, 2.9%	N/A
NCT02628067 KEYNOTE-158 [109]	Phase 2 basket study	98	Progression during or intolerance to≧1 line of standard therapy	Pembrolizumab 200 mg every 3 weeks for up to 2 years	Overall ORR: 12/98, 12.2% PD-L1 positive ORR: 12/82, 14.6% (interim result, medium follow up period 10.2months)	10.2
NCT03635567 KEYNOTE-826 [103,110−112]	Phase 3, double-blind	617	Persistent, recurrent, or metastatic cervical cancer First-line treatment	Pembrolizumab 200 mg + paclitaxel + carboplatin/ cisplatin ± bevacizumab every 3 weeks for up to 35 cycles Placebo + paclitaxel + carboplatin/ cisplatin ± bevacizumab every 3 weeks for up to 35 cycles	PFS: 10.4 vs. 8.2 months HR: 0.61; 95% CI, 0.50−0.74, $p < 0.001$ OS: 26.4 vs. 16.8 months HR: 0.63; 95% CI, 0.52−0.77, $p < 0.001$	39.1
NCT04221945 ENGOT-cx11/GOG-3047/ KEYNOTE-A18 [101]	Phase 3 Double-blind	1060	Newly diagnosed, high-risk, locally advanced, stage IB2−IIB with node-positive disease or stage III−IVA regardless of nodal status (FIGO 2014)	5 cycles of pembrolizumab 200 mg every 3 weeks plus chemoradiotherapy, followed by 15 cycles of pembrolizumab 400 mg every 6 weeks 5 cycles of placebo every 3 weeks plus chemoradiotherapy, followed by 15 cycles of placebo every 6 weeks	PFS: Not reached in either group HR: 0.70; 95% CI, 0.55−0.89, $p = 0.002$ (88.5% information fraction) PFS Rates at 24 months: 68% vs. 57% OS: Follow-up for overall survival is continuing HR: 0.73; 95% CI, 0.49−1.07 (42.9% information fraction) OS rates at 24 months: 87% vs. 81%	17.9 months
NCT02257528 NRG-GY002 [113]	Phase 2 Single-arm	26	Persistent, recurrent cervical cancer One prior systemic therapy	4 doses of IV nivolumab (3 mg/kg every 2 weeks), followed by an additional 42 doses 3 mg/kg every 2 weeks for a maximum of 46 doses	ORR: 1/22, 4% Duration of response: 3.8 months AE: 21/25, 84% Gr3 AE: 6/25, 24%	32
NCT03298893 NiCOL [97]	Phase 1 Single-arm	16	Stage IB3 to IVA (FIGO 2018) With an indication for curative intent CCRT	Nivolumab 240 mg every 2 weeks with CCRT and maintain for a total of 13 cycles	DLT: 3/15, 20%	23.8
NCT02488759 CheckMate 358 [100]	Phase 1/2 Open-label	193	Recurrent or metastatic cervical cancer	Nivolumab monotherapy: Nivolumab 240 mg every 2 weeks NIVO3 plus IPI1: Nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks NIVO1 plus IPI3: nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles, followed by nivolumab 240 mg every 2 weeks	ORR: Nivolumab monotherapy: 5/19, 26% NIVO3 plus IPI1: 14/45, 31% NIVO1 plus IPI3: 43/112, 38%	Median follow-up: 19.0 months/ 12.6months/ 16.7months
NCT03816553 CLAP trial [114]	Phase 2 Single-arm	45	Progression after at least one line of systemic therapy	Camrelizumab 200 mg every 2 weeks and apatinib 250 mg once per day continuously in 4-week cycles	ORR: 25/45, 55.6%	11.3

(*continued on next page*)

Table 3 (*continued*)

Clinical trial	Study design	Sample size	Patient Eligibility	Treatment arms	Primary endpoint(s)	Medium follow up period (months)
				(maximum of 24 months camrelizumab treatment)		
NCT03104699 [91]	Phase 2 Single-arm	161	Recurrent and/or metastatic cervical cancer and who had relapsed after a prior platinum-based treatment regimen for advanced disease	Balstilimab 3 mg/kg once every two weeks up to 24 months	ORR: 21/140, 15% ORR by PD-L1 status: Positive: 17/85, 20% Negative: 3/38, 7.9%	10.2
NCT03495882 [115]	Phase 2 Single-arm	155	Recurrent and/or metastatic cervical cancer who relapsed after prior platinum-based therapy	Balstilimab 3 mg/kg once every 2 weeks and zalifrelimab 1 mg/kg once every 6 weeks, for up to 24 months.	ORR: 32/125, 25.6% ORR by PD-L1 status: Positive: 22/67, 32.8% Negative: 3/33, 9.1%	21
NCT03257267 EMPOWER- Cervical 1/ GOG-3016/ENGOT-cx9 [117]	Phase 3 Open-label	608	Progression after first-line platinum-containing chemotherapy, regardless of their programmed cell death ligand 1 (PD-L1) status.	Cemiplimab (350 mg every 3 weeks) Single-agent chemotherapy	OS: 12.0 vs. 8.5 months HR: 0.69; 95% CI, 0.56−0.84, $p < 0.001$	18.2
NCT03830866 CALLA trial [118]	Phase 3 Double-blind	770	Untreated locally advanced IB2 −IIB lymph node positive, stage ≥ III any lymph node status (FIGO 2009)	Durvalumab (1500 mg intravenously once every 4 weeks) or placebo with and following chemoradiotherapy, for up to 24 cycles	PFS: Not reached in either group PFS Rates at 12 months: 76.0% vs. 73.3%	18.5 in durvalumab group, 18.4 in placebo group
NCT03852251 COMPASSION-03 [96]	Phase 1b/2 Open-label	111 (the cervical cancer cohort)	Unresectable advanced solid tumours	Cadonilimab monotherapy	Grade 3 AEs: 67/240, 28% (Total of the cohorts) ORR: 32/99, 32.3% (the cervical cancer cohort)	14.6 (the cervical cancer cohort)
NCT04868708 COMPASSION-13 [94]	Phase 2 Open-label	45	Recurrent or metastatic cervical cancer	cohort A-15: cadonilimab 15 mg/kg every 3 weeks plus chemotherapy cohort A-10: cadonilimab 10 mg/kg every 3 weeks plus chemotherapy cohort B-10: cadonilimab 10 mg/kg every 3 weeks plus chemotherapy and bevacizumab	AE: 45/45, 100% Gr3 AE: 33/45, 73.3% Immune-related AE: 29/45, 64.4%	18.3/20.24/15.01 in 3 cohorts
NCT03556839 BEATcc (ENGOT-Cx10 −GEICO 68-C−JGOG1084 −GOG-3030) [90]	Phase 3 Open-label	410	Unrtreated, metastatic (stage IVB), persistent, or recurrent cervical cancer	Atezolizumab 1200 mg + cisplatin/ carbolpatin + paclitaxel + bevacizumab every 3 weeks Cisplatin/ carbolpatin + paclitaxel + bevacizumab every 3 weeks	Median PFS: 13.7 vs. 10.4 months HR: 0.62; 95% CI, 0.49−0.78, $p < 0.0001$ Median OS: 32.1 vs. 22.8 months HR: 0.68; 95% CI, 0.52−0.88, $p < 0.0046$	32.9
NCT04300647 SKYSCRAPER-04 [119]	Phase 2 Open-label	171	Second or third-line therapy for PD-L1-positive recurrent/ persistent cervical cancer	Atezolizumab 1200 mg alone every 3 weeks Atezolizumab 1200 mg + tiragolumab 600 mg every 3 weeks	ORR: 7/45, 15.6% vs. 24/ 126,19.0%	8.5
NCT03438396 InnovaTV 204/GOG-3023/ ENGOT-cx6 [120]	Phase 2 Single-arm	102	Recurrent or metastatic cervical cancer	TV 2.0 mg/kg once every 3 weeks	ORR: 24/101, 24%	10.0
NCT03786081 InnovaTV 205/GOG-3024/ ENGOT-cx8 [85]	Phase 2	142	Recurrent or metastatic cervical cancer	TV plus bevacizumab or pembrolizumab or carboplatin (Only TV plus pembrolizumb or carboplatin in dose expansion arms)	ORR: 1st line TV + carboplatin: 18/33, 54.5% 1st line TV + pembrolizumab: 13/	17.8/21.7/15.0

					32, 40.6% 2nd/3rd line TV + pembrolizumab: 12/34, 35.3%	
NCT04697628 InnovaTV 301/ENGOT-cx12/GOG-3057 [121]	Phase 3 Open-label	502	Previously treated recurrent or metastatic cervical cancer	TV monotherapy Topotecan or vinorelbine or gemcitabine or irinotecan or pemetrexed	OS: 11.5 vs. 9.5 months HR: 0.70; 95% CI, 0.54–0.89, p = 0.0038	10.8
NCT03972722 [95]	Phase 2 Single-arm	105	PD-L1-positive recurrent or metastatic cervical cancer Progression ≧1 line chemotherapy	Zimberelimab (240 mg every 2 weeks up to 2 years	ORR: 29/105, 27.6%	16.9
NCT00292955 [92]	Phase 2	21	Newly-diagnosed, stage IB-IVB invasive carcinoma of the uterine cervix	Cetuximab monotherapy as neoadjuvant chemotherapy and concurrent with CRT	CMR of LACC patients: 11/12, 91.7% PMR of LACC patients: 1/12, 8.3%	≧48
NCT03059823 POD1UM-101 [93]	Phase 1	35 (the cervical cancer cohort)	Locally advanced or metastatic solid tumors	Retifanlimab monotherapy for up to 2 years	Immune-related AE: 19/35, 54% (the cervical cancer cohort)	17.6 (the cervical cancer cohort)

Abbreviations: ORR, Objective response rate; CRT, chemoradiation; AE, adverse events; PFS, progression-free survival; OS, overall survival; N/A, not available; vs., versus; CCRT, concurrent chemoradiotherapy; DLT, dose-limiting toxicities; LACC, locally-advanced cervical cancer; CMR, complete metabolic response; PMR, partial metabolic response; TV, tisotumab vedotin.

Ipilimumab

Ipilimumab is a monoclonal antibody targeting against CTL antigen 4 (CTLA-4). Ipilimumab is proven by the US Food and Drug Administration (FDA) for various cancers, including melanoma, renal cell carcinoma, colorectal cancer, hepatocellular carcinoma and non-small cell lung cancer [105]. A phase 1/2 trial in the recurrent and metastatic cervical cancer setting enrolled 42 patients treated with ipilimumab monotherapy. The grade 3 toxic effect rate was 9.5%, but the objective response rate (ORR) was only 2.9%. This study did not demonstrate the single-agent benefit of ipilimumab in cervical cancer [106].

Pembrolizumab

Pembrolizumab, which binding to the PD-1 receptor on lymphocytes then interrupting the interaction with PD-L1 and PD-L2, is one of the most well-known immunotherapies in the gynecologic oncology field. Pembrolizumab along with chemotherapy, with or without bevacizumab was approved by the FDA in 2021 for persistent, recurrent, or metastatic cervical cancer patients who have PD-L1 expression tumors (CPS≧1) [107]. Further, FDA approves pembrolizumab in combination with chemoradiotherapy for FIGO 2014 stage III to IVA cervical cancer in 2024 [108]. KEYNOTE-158 is a phase 2 basket study, which enrolled patients with advanced solid tumors that have failed at least one line of therapy. The study treatment was pembrolizumab 200 mg every 3 weeks for up to 2 years. The interim results for 98 advanced cervical cancer individuals reported an overall ORR of 12.2%. Among the eligible participants, 83.7% were PD-L1 expression positive. The ORR of PD-L1 positive patients was 14.6%. Further, all of the 12 responders were with PD-L1 positive tumors [109]. KEYNOTE-826 is a phase 3 double-blind trial randomized the participants into pembrolizumab 200 mg every 3 weeks or placebo, in combination with chemotherapy with or without bevacizumab [110]. The results demonstrate a significant PFS and OS benefit in the group that added pembrolizumab in all-comer, CPS≧1 or CPS≧10. However, the report published in 2021 showed that the population of CPS<1 had PFS and OS HR close to 1 [110]. The final survival results reported in 2023 revealed that PFS and OS were significantly longer with pembrolizumab than placebo [111]. In the all-comer, CPS ≥1, and CPS ≥10 populations, median PFS was 10.4 versus 8.2 months (HR, 0.61 [95% CI, 0.50 to 0.74]), 10.5 versus 8.2 months (HR, 0.58 [95% CI, 0.47 to 0.71]), and 10.4 versus 8.1 months (HR, 0.52 [95% CI, 0.40 to 0.68]), respectively [112]. The median OS was 26.4 versus 16.8 months (HR, 0.63 [95% CI, 0.52 to 0.71]), 28.6 versus 16.5 months (HR, 0.60 [95% CI, 0.49 to 0.74]), and 29.6 versus 17.4 months (HR, 0.58 [95% CI, 0.44 to 0.78]) in order of all-comer, CPS ≥1, and CPS ≥10 [112]. The subgroup analysis of KETNOTE-826 classified the participants by use of bevacizumab, choice of platinum (carboplatin or cisplatin), prior chemoradiotherapy exposure only (yes or no), and histologic type, which found improved OS throughout subgroups [103]. ENGOT-cx11/GOG-3047/KEYNOTE-A18 study assesses the efficacy of pembrolizumab with chemoradiotherapy in newly diagnosed, locally advanced cervical cancer. The study arms were pembrolizumab (200 mg every 3 weeks) or placebo plus chemoradiotherapy, followed by 15 cycles of pembrolizumab (400 mg every 6 weeks) or placebo. The results showed significantly improved PFS in the population of pembrolizumab with chemoradiotherapy compared to placebo plus chemoradiotherapy (HR: 0.70; 95% CI, 0.55–0.89, p = 0.002) [101]. In addition, the study also demonstrates a similar safety profile between groups, with 75% grade 3 or higher AE rates in the pembrolizumab plus chemoradiotherapy group, and 69% in the placebo plus chemoradiotherapy group [101]. This result prompts the FDA

approval of pembrolizumab plus chemoradiotherapy for locally advanced cervical cancer [108].

Nivolumab ± ipilimumab

Nivolumab is another checkpoint inhibitor targeting the PD-1 receptor. NRG-GY002 is a single-arm phase 2 trial exploring the efficacy of nivolumab monotherapy in persistent or recurrent cervical cancer. This study showed a limited antitumor activity, with response rate of 4% and the duration of response of 3.8 months [113]. CheckMate 358 trial investigates the efficacy of nivolumab-based monotherapy and nivolumab in combination with ipilimumab, an anti-CTLA-4 antibody, in recurrent or metastatic cervical cancer. Nivolumab alone or in tandem with ipilimumab has been approved for various tumor types, including melanoma, head, and neck squamous cell carcinoma, and non-small cell lung cancer. CheckMate 358 trial demonstrates objective response rates of 26% for nivolumab monotherapy, 31% for nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (NIVO3 plus IPI1), and 38% for nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for four cycles then nivolumab 240 mg every 2 weeks (NIVO1 plus IPI3) [100]. Grade 3 or higher AEs were more frequent in the group with higher doses of ipilimumab but were manageable [100]. NICOL trial, a phase 1 trial, aimed to determine the safety profile and appropriate dose of nivolumab in combination with and following CCRT. It supports the recommended dose of nivolumab 240 mg every 2 weeks with and following CCRT [97].

Camrelizumab

Camrelizumab is another anti PD-1 antibody, and apatinib is a tyrosine kinase inhibitor targeting on vascular endothelial growth factor receptor-2 (VEGFR-2). CLAP trial, an open-label, single-arm trial, evaluated the anti-tumor activity of camrelizumab in combination with apatinib for recurrent cervical cancer. The trial reported a promising result with an object response rate of 55.6% [114].

Balstilimab ± Zalifrelimab

Balstilimab, also known as AGEN2034, is an antibody binding to PD-1. A phase 2 study (NCT03104699) investigated the efficacy of balstilimab monotherapy in recurrent and/or metastatic cervical cancer patients after prior platinum-based therapy. The overall response rate was 15%, and the median duration of response was 15.4 months. The subgroup of PD-L1 positive patients had a response rate of 20%, while the PD-L1 negative individuals had a response rate of 7.9% [91]. A phase 2 trial (NCT03495882) evaluated the anti-tumor activity of the combination of balstilimab and zalifrelimab. Zalifrelimab (AGEN1884) is an antibody targeting on CTLA-4. This trial also focused on the population of recurrent and/or metastatic cervical cancer patients after prior platinum-based therapy. The overall response rate was 25.6%, and the median duration of response was not reached. The subgroup of PD-L1 positive patients had a response rate of 32.8%, while the PD-L1 negative individuals had a response rate of 9.1% [115]. Comparing the above two trials, combination therapy of balstilimab plus zalifrelimab seems to display a higher treatment response. RaPiDS (GOG-3028) (NCT03894215) is an ongoing randomized phase 2 trial aimed to evaluate the efficacy and safety of balstilimab monotherapy and balstilimab in combination with zalifrelimab [116].

Cemiplimab

Cemiplimab is a fully human PD-1 antibody approved for lung and skin cancers. EMPOWER- Cervical 1/GOG-3016/ENGOT-cx9 trial aims to assess the activity of cemiplimab toward recurrent cervical cancer. The participants were randomized into cemiplimab group and single-agent chemotherapy group. The overall survival was longer in the cemiplimab group than single-agent chemotherapy group (12.0 vs. 8.5 months with a HR of 0.69, 95% CI, 0.56–0.84, $p < 0.001$) [117].

Durvalumab

Durvalumab, targeting on PD-L1, is an antibody approved for patients with dMMR endometrial cancer, lung cancer, hepatocellular carcinoma and biliary tract cancer. CALLA trial investigates the efficacy of durvalumab with and following chemoradiotherapy for newly diagnosed locally advanced cervical cancer, regardless of PD-L1 expression status. This trial is a double-blind, randomized trial comparing durvalumab and placebo. The PFS was not reached in either group, and PFS rates at 12 months were 76.0% and 73.3%, with the median follow-up period of 18 months [118]. According to the CALLA trial with the setting of an all-comers population, durvalumab did not provide PFS benefits.

Cadonilimab

Cadonilimab is an immune checkpoint inhibitor targeting both PD-1 and CTLA-4. COMPASSION-03 trial demonstrates a promising tumor response rate and safety profile of cadonilimab for the treatment of recurrent advanced solid tumors, including cervical cancer, esophageal squamous cell carcinoma, and hepatocellular carcinoma [96]. In the cervical cancer cohort of COMPASSION-03 trial, the objective response rate was 32.3% (32 of 99) with a median follow-up of 14.6 months [96]. Further, the COMPASSION-13 trial investigates cadonilimab with the primary endpoint of the safety profile. All of the participants developed treatment-related AEs (45/45, 100%), 33 of them were grade 3 AE (33/45, 73.3%), and 29 of them were immune-related AE (29/45, 64.4%). Seven patients (7/45, 15.6%) discontinued cadonilimab treatment owing to AE, and there was one patient death [94].

Atezolizumab ± tiragolumab

BEATcc trial (ENGOT-Cx10-GEICO 68-C-JGOG1084-GOG-3030) is a phase 3 trial to assess the addition of atezolizumab, a PD-L1 inhibitor with chemotherapy, with bevacizumab for untreated, metastatic, persistent, or recurrent cervical cancer. This trial provides evidence of significantly longer PFS and OS in the group adding atezolizumab. Patients receiving atezolizumab plus chemotherapy with bevaciumab had a median OS of 32.8 months [90]. Tiragolumab is an immune checkpoint inhibitor targeting T-cell immunoreceptor with immunoglobulin and immuno-receptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT). SKYSCRAPER-04 trial investigates the antitumor acidity of tiragolumab plus atezolizumab among second or third-line therapy for PD-L1-positive persistent/recurrent cervical cancer individuals. The results showed that the combination of tiragolumab and atezolizumab did not have a significant benefit in objective response rates compared to the results observed in the PD-L1 positive population in the KEYNOTE-158 trial (19.0% vs. 14.6%) [109,119]. Further study is warranted to identify the population suitable for dual blockade of PD-L1 and TIGIT.

Tisotumab vedotin

TV is an antibody-drug conjugate (ADC) directed against tissue factor (TF). InnovaTV 204/GOG-3023/ENGOT-cx6 trial is a key trial that provides evidence of the optimal efficacy of TV on recurrent or

metastatic cervical cancer. This trial demonstrated 24% (24/101) objective response rate of TV monotherapy within the 10.0 months of the follow-up period [120]. InnovaTV 205/GOG-3024/ENGOT-cx8 evaluates TV as the backbone plus chemotherapy, pembrolizumab, or bevacizumab. TV had objective response rates ranging from 35.5% to 54.5% in different arms and a manageable toxicity profile [85]. InnovaTV 301/ENGOT-cx12/GOG-3057 randomized previously treated cervical cancer patients into treatments of TV monotherapy or chemotherapy. The median OS was 11.5 months in the TV monotherapy group, within 10.8 months of the median follow-up period [121]. This pivotal trial leads to FDA approval for treated recurrent or metastatic cervical cancer [122].

Zimberelimab

Zimberelimab is an anti-PD-1 monoclonal antibody. The single-arm, phase 2 study (NCT03972722) evaluates the efficacy of zimberelimab for previously treated, recurrent, metastatic cervical cancer patients. The objective response rate was 27.6% (29/105) with a not-reached median duration of response during a median follow-up period of 16.9 months [95]. This trial demonstrated the durable anti-tumor activity of zimberelimab.

Cetuximab

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor which has been approved for several malignant tumors. The combination of cetuximab with radiotherapy was previously approved to prolong the OS in patients with squamous cell carcinoma of head and neck cancer. Therefore, the usage of cetuximab is explored by the NCT00292955 trial. This trial evaluates the efficacy and optimal dosage of cetuximab with CCRT for cervical cancer using the method of [18F] fluorodeoxyglucose-PET/CT (FDG-PET/CT). The result provided evidence of early assessment of response to neoadjuvant cetuximab by FDG-PET/CT. Among the locally advancer cervical cancer population, the complete metabolic response rate was 91.7% (11/12). In addition, the combination of cetuximab with cisplatin 30 mg/m^2 and radiotherapy had a manageable adverse event profile [92].

Retifanlimab

Retifanlimab is an antibody blocking PD-1 on the cell surface. POD1UM-101 trial is a phase 1 trial to evaluate the safety profile of retifanlimab for advanced solid tumors, including cervical cancer. This trial enrolled 35 cervical cancer patients, and immune-related AEs occurred in 19 (54%) of these patients [93]. The response rate of the cervical cancer cohort was 20% (7/35), the median PFS was 3.6 months, and the median OS was 18.1 months during a median follow-up period of 17.6 months [93]. These results encourage further study on retifanlimab as monotherapy or backbone immunotherapy.

Conclusion

Immunotherapy (IO) brings the treatment of cervical cancer into a new era. Antibodies targeting PD-1 or PD-L1 are the primary components of immunotherapy. Other drugs include inhibitors targeting on CTLA-4, EGFR and ADC targeting on TF. Currently, only pembrolizumab, TV have received FDA approval. Further research is essential for investigating the efficacy and toxicities of immunotherapy, as well as identifying the subgroups that will benefit most from the therapy.

Declaration of competing interest

Dr. Peng-Hui Wang and Dr. Szu-Ting Yang, editorial board members at Taiwanese Journal of Obstetrics and Gynecology, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Review Article

Surgery-based radiation-free multimodality treatment for locally advanced cervical cancer

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ABSTRACT

The current review described a 55-year woman using 28 months to finish her surgery-based radiation-free multimodality treatment journey to fight International Federation of Gynaecology & Obstetrics (FIGO) 2018 clinical stage IIA2 (cT2aN0M0) squamous cell carcinoma (SCC) of the cervix. She received six cycles of perioperative adjuvant therapy, including three cycles of neoadjuvant therapy (NAT) and three cycles of postoperative adjuvant therapy by using combination of dose-dense chemotherapy (CT, weekly paclitaxel 80 mg/m^2+triweekly cisplatin 40 mg/m^2), immunotherapy (IO, triweekly pembrolizumab 200 mg) and half-dose anti-angiogenic agent (triweekly bevacizumab 7.5 mg/kg) plus interval radical surgery (radical hysterectomy + bilateral salpingo-oophorectomy + bilateral pelvic lymph node dissection + para-aortic lymph node sampling) and following maintenance therapy with monthly 22 cycles of half-dose of IO (pembrolizumab 100 mg) and concomitant 4 cycles of single-agent CT (paclitaxel 175 mg/m^2) and 18 cycles of half-dose anti-angiogenic agent (bevacizumab 7.5 mg/kg). During the cervical SCC fighting journey, two unwanted adverse events (AEs) occurred. One was pseudo-progressive disease during the NAT treatment and pathology-confirmed upgrading FIGO stage IIIC1p (ypT2a1N1M0) after radical surgery and the other was the occurrence of hypothyroidism during the post operative adjuvant therapy. Based on this case we presented, we review the recent trend in the management of women with locally advanced cervical cancer (LACC) using the radiation-free but surgery-based multimodality strategy and highlight the strengths and limitations about perioperative adjuvant therapy with dose-dense CT + IO + half-dose anti-angiogenic agent and maintenance treatment of half-dose IO combining with short-term single agent CT and following long-term half-dose anti-angiogenic agent. All underscore the possibility that women with LACC have an opportunity to receive surgery-based RT-free multi-modality strategy to manage their diseases with satisfactory results. Additionally, the evolving role of IO plus CT with/without anti-angiogenic agent functioning as either primary treatment or adjuvant therapy for the treatment of advanced CC has been in process continuously. Moreover, the patient's positive response to IO, pembrolizumab as an example, both during the primary and maintenance therapy, highlights the importance of integrating IO into CT regimens for CC, especially in cases where conventional therapies, RT as an example, are insufficient or who do not want to receive RT-based treatment. The sustained disease-free status of the patient over several years reinforces the potential of IO to significantly increase long-term survival outcomes in CC patients, particularly for those with LACC.

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Introduction

Cervical cancer (CC) is one of the most common and significant causes of death among gynecological patients [1–3]. According to reports from many previous studies, there were approximately 604000 new cases of CC and 342000 CC-related deaths, which may reach 847000 and 524000, respectively in 2040 especially in low- and middle-income countries, where nearly half of the mortality cases occurred [1–4]. Additionally, the mortality rate in low- and middle-income countries was in a four-fold increase than that in the developed countries [1–4]. Furthermore, CC and other gynecological cancers show significant difference in nature, with the most notable difference being that "squamous cell carcinoma (SCC)" constitutes the majority of CC cases, while adenocarcinoma is relatively rare but more aggressive in clinical course and worse outcome, partly because of its difficulty to being detected by conventional cytology examination in the pre-cancer or early-stage cancer status and partly because of its relative resistance to conventional chemotherapy (CT) and/or radiotherapy (RT) [4–8]. In contrast, other gynecological cancers, such as ovary- and uterus-related cancers mainly belong to the adenocarcinoma types [9–13]. Moreover, the staging system of the cervix is different from the other two main gynecological organs (ovary and uterus)-related cancers, since the former is based on the clinical staging system (surgery is only limited to early-stage CC or a highly selected clinical situations) and the latter is according to complete and thorough surgical staging system [4,9–17], contributing to the unique initial treatment to CC patients compared to non-CC gynecological cancers [18–20]. Although RT-based primary treatment can be applied to every stages of invasive CC, persistent, recurrent and metastatic diseases preceded by a RT is much complicated and hard to manage, resulting in a biggest challenge for both physicians and patients [18–20].

Reviewing the treatment history of CC, due to the predominance of SCC, treatment options have evolved, with predecessors often favoring treatments similar to those used for other organ-originated SCC [20–24]. Head and neck cancers (HNC) may be the most well-known example, which reveals that the choice of surgical approach is only limited to the highly selected patients (often in the early stage or indicating other clinical indications), and predecessors usually considered RT to be a primary, standard of care (SOC) or better choice [21–24]. RT not only takes advantages for SOC treatment for SCC, regardless which organ is a primary site, based on its much effectiveness, less traumatic injury as well as better local controls compared to other non-RT treatment. Additionally, when clinically, it is very hard to identify the tumor border (unsafe or unclear tumor margin), particularly for those infiltrating-type SCC, complete safe resection is seldom to reach, resulting in the positive resection end (positive cut end), which often needs further RT and is associated with increased post-operative and post-RT complications (adverse events [AEs]). Additionally, incomplete resection is in long-term considered as the most determinate factor contributing to the worst prognosis. This risk is always present in any surgical treatment, regardless which type of surgery is performed or which type of tumor belongs [25–27]. However, there is no doubt that the worst prognosis occurs in SCC type compared to other non-SCC histological types. The concerns of therapeutic failure after or before RT are always present, because they involves in a much increase of AEs and also increased AEs and is also associated with strongly negative impact on the outcome [25–27].

To increase the response and therapeutic effects of RT, RT augmented simultaneously or concurrently either by chemicals or pharmaceutical agents (radio-sensitizing agents, enhancing the killing effect on tumor cells by accelerating DNA damage and producing free radicals indirectly when combined with RT, achieve greater tumor inactivation than would have been expected from the additive or synergistic effect of each modality, including (1) suppression of intracellular thiols or other endogenous radioprotective substances; (2) formation of cytotoxic substances by radiolysis of the radiosensitizer; (3) inhibitors of repair of biomolecules; (4) thymine analogs that can incorporate into DNA; and (5) oxygen mimics that have electrophilic activity [28]. Among these, chemoradiation (CRT, containing either concurrent CRT [CCRT] or combination of CT and RT) may be most popular and well-known. Recently, immune-modification agents are showing an impressive therapeutic effect either using alone or using by combinations as RT, CT or targeted therapy [18,29–35].

By contrast, the role of application of systemic therapy to CC was often regarded as second line treatment [18,20]. According to the NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024—May 6, 2024, primary treatment by RT is recommended for stage IVA or earlier, while patients with stage IVB CC or recurrent CC can proceed to systemic therapy [20]. However, for those CC patients with persistent, recurrent or metastatic lesions, the therapeutic effects by systemic treatment is still disappointing even after introduction of immunotherapy (IO), such as immune checkpoint inhibitors (ICIs), and therefore for those patients, another treatment of choice is considered the better hospice care [20]. All suggest that the advance of the current treatment still fails to satisfy the urgent medical need or positive impact on favorable outcomes of CC patients.

Reviewing the role of systemic therapy in CC, the standard of medical care for persistent, recurrent or metastatic CC was platinum-based CT (paclitaxel plus cisplatin: TP) until 2014, when the United States (US) Food and Drug Administration (FDA) approved the addition of bevacizumab, an anti-angiogenic agent targeting vascular endothelial growth factor (VEGF), to SOC treatment of cytotoxic CT for patients with persistent or recurrent or metastatic CC, based on the significant improvement of both progression-free survival (PFS) and overall survival (OS) (8.2 vs. 5.9 months; hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.54–0.82 and 16.8 vs. 13.3 months; HR 0.77, 95% CI 0.62–0.95, respectively) [18,36–38]. The advantages of systemic therapy may overcome the limitation of local and regional treatment which is performed by either surgical approach or RT, since the latter cannot cover the extensive invasion or disseminated distribution of cancer. However, non-specific cytotoxic killing effects are the main limitation of using conventional CT, which works by disrupting various stages of the cell cycle and subsequently stopping the tumor-associated uncontrolled proliferation. At the same time, the normal cells, particularly those with rapid turnover rate and high proliferation rate, such as hematological system, gastrointestinal mucosa, and others are vulnerable to the aforementioned cytotoxic agents, contributing to equal application of the damage to normal tissue and cancer tissue, and further resulting in the AEs secondary to cytotoxic agents. Additionally, integration of anti-angiogenic agent targeting VEGF into the SOC paclitaxel plus cisplatin (PT) CT may significantly increase the risk of specific AEs and serious AEs which make patients in trouble and possibly in lethal or catastrophic emergency, including hypertension, serious thromboembolic events, serious haemorrhage and perforation and fistula formation, and the latter two severe AEs (perforation or fistula) occur much frequently in particularly for those patients having been treated with prior RT [2,18].

In our previous meta-analysis, we found that an anti-angiogenic agent targeting VEGF dramatically increases the risk of gastrointestinal/genitourinary (GI or GU) fistula or perforation in CC patients, particularly for those with prior exposure to RT, which

demonstrated a nearly five-fold increase (odd ratios [OR] 4.03, 95% CI 1.76–9.20 for GI fistula or perforation and OR 4.71, 95% CI 1.51–14.70 for GU fistula or perforation, respectively) [2,18]. In fact, as early as 2021, Cochrane review has first raised the concern about this protocol containing bevacizumab in the treatment for CC [39], suggesting the current treatment strategy may not satisfy the clinical need and encourage the development of new strategies [18].

To explore the new strategy for CC treatment, hallmarks of cancer-proposal may offer the better and precise treatment options [40]. Among these, one of the core hallmark capabilities, "avoiding immune destruction" may be a target to develop the new vision in the field of cancer treatment [41]. "Avoiding immune destruction" constitutes a theoretical framework that has proved to be of enduring utility for rationalizing the vast complexity of cancer and its underlying mechanisms and thereby, identifying the immune checkpoint proteins [41]. Immunotherapy (IO) using ICIs targeting immune checkpoint proteins represents a paradigm shift from traditional cancer treatment to a groundbreaking approach in the field of cancer treatment, utilizing the host natural defense mechanisms and enhancing the power of host immune system to recognize, target and finally clean cancer cells [18,41,42].

However, although the revised FIGO staging of CC (2018) [4] and NCCN guideline Version 3.2024–May 6, 2024 [20] for CC are excellent tools to suggest the therapeutic plan for patients with cervical cancer, in clinical routine practice, cervical cancer can be classified as early-stage CC, locally advanced cervical cancer (LACC) and far advanced or metastatic CC. Additionally, the frequency of LACC is still high in low-income countries where sufficient radiotherapy facilities are often lacking [43,44]. Therefore, this article aims to share clinical experiences based on a journey of a patient with LACC who was successfully managed by surgery-based RT-free multimodality treatment.

History and course

In January 2019, the patient first sought medical attention at a local hospital, where transvaginal ultrasound (TVS) and physical examination (PV) revealed a 4-cm cervical mass. A subsequent biopsy confirmed the presence of malignancy. She visited the gynecology outpatient department (GYN OPD) in February 2019, for a second opinion, where further tests confirmed the diagnosis of SCC of the cervix. The tumor was clinically staged as cT2a2N0M0 (tumor size $\geq$ 4 cm, as LACC according to clinical evaluation and imaging studies (revised FIGO stage of cervical cancer-2018 [4]) and on schedule for CRT either by CCRT or by combination of CT and RT (CT + RT) (Figs. 1 and 2). However, the patient was against this suggestion, and she did not want to any exposure to RT. By contrast, she preferred the definite surgical treatment. After sharing decision-making, the following surgery-based RT-free multimodality treatment was planned and the patient started her journey to fight the LACC.

1. Neoadjuvant Treatment (NAT) with Combination of CT, IO (pembrolizumab) and Anti-angiogenic Agent (Bevacizumab, B) Therapy in 2019 (Fig. 3)
   - The patient initially received neoadjuvant treatment (NAT) with combination of CT, IO and anti-angiogenic agent (bevacizumab) therapy in February 2019. The regimen contained a dose-dense CT consisting of weekly paclitaxel (T, 80 mg/m^2), tri-weekly cisplatin (P, 40 mg/m^2), and half-dose anti-angiogenic agent (B, tri-weekly bevacizumab [avastin], 7.5 mg/kg) and ICIs (triweekly pembrolizumab, 200 mg). The aim was to reduce tumor size and down-stage of cancer status fitting for surgical intervention (rationale 1).

Rationale 1 and challenge 1

For FIGO stages IB3 and IIA2, external-beam RT (EBRT) associated with concurrent platinum-based CT (CCRT) followed by intracavitary brachytherapy (ICBT) is highly recommended with favorable outcome and acceptable AEs (Category 1) (Fig. 2) [20]. Primary surgery is seldom considered as a priority of treatment (category 2b) (Fig. 2) [20]. With consideration of RT-free treatment for this subject with FIGO IIA2, direct primary surgical treatment was not recommended based the category 2b status. To achieve the goal fitting definite surgical intervention, down-stage or shrinkage of tumor to FIGO IIA1 or below should be done. Therefore, the concept of NAT has been developed. NAT, especially for neoadjuvant chemotherapy (NACT) in cancer is an interesting approach for locally advanced cancer disease and has been applied in different types of cancer with aiming not only to decrease the tumor burden as well as shrink large local lesions, to make surgery or RT less extensively, which may be beneficial for cosmetic purposes and preserve an organ or maintain the function (fewer vaginal injuries caused by radical surgeries or RT induced fibrosis, better outcomes for quality of life [QoL] and better ovarian functions for premenopausal women), and in situations such as unresectable disease without access to RT, to enable definite surgical treatment to kill the majority of cancers and then continue to destroy resistant cells using either surgery or RT making the chance of subsequent dissemination less likely [43–59], but also to treat the metastatic disease from its original tumor area and offer an idea or server a predictor for the biology and outcome of the tumor [45], which makes physicians with much understanding the sensitivity of cancers to CT regimen based on the patient's response and pathological specimens to better formulate the next treatment strategy, referring the reference to guide the better choice for further treatment [53].

However, so far, many debated issues existed to argue the benefits of NAT before definite surgery (NAT-S) or even before CRT (NAT-CRT) compared with direct CRT [43–53], and this challenge is apparently and particularly applied to those patients who are selected for surgical intervention (NACT-S) [53]. Some issues are always highlighted, including that NACT-S cannot avoid a large proportion of patients undergoing postoperative adjuvant CRT (at least 30% and more), which not only dramatically prolongs the treatment period (delaying the surgical resection process as well as the extension therapeutic time in patients who need postoperative adjuvant CCRT) but also contributes to increase risks significantly of acute and late AEs and long-term toxicities, compared to patients treated with direct CRT [45]. Moreover, so far, no evidence supports the better outcome after NACT-S compared to direct CRT [45]. However, NACT-S is still being practiced in many parts of the world, particularly in developing or low-income countries, because those countries (for example, half of countries in Africa) do not have offered RT due to absence of RT facilities [44,57]. Since the subject in the current report refused to receive any RT, therefore, we should re-consider the no-RT therapy and hope the outcome should not be inferior to standard of care CCRT.

Hu et al. conducted a multicenter, prospective, randomized controlled trial (RCT) enrolling 774 patients with FIGO stage IB3 and IIA2 CC to assess prognostic differences between NACT-S and primary radical surgery and the results showed NACT-S is not inferior to direct surgery [59], suggesting that similar to primary radical surgery, NACT-S is not a standard of care therapy for patients with LACC (IB3 and IIA2).

Moreover, the EORTC (European Organization for Research and Treatment of Cancer Gynecological Cancer Group)-55994 attempted to compare the outcomes in FIGO IB2-IIB CC patients either treated with NACT-S (n = 314) and primary CCRT (n = 312) and the

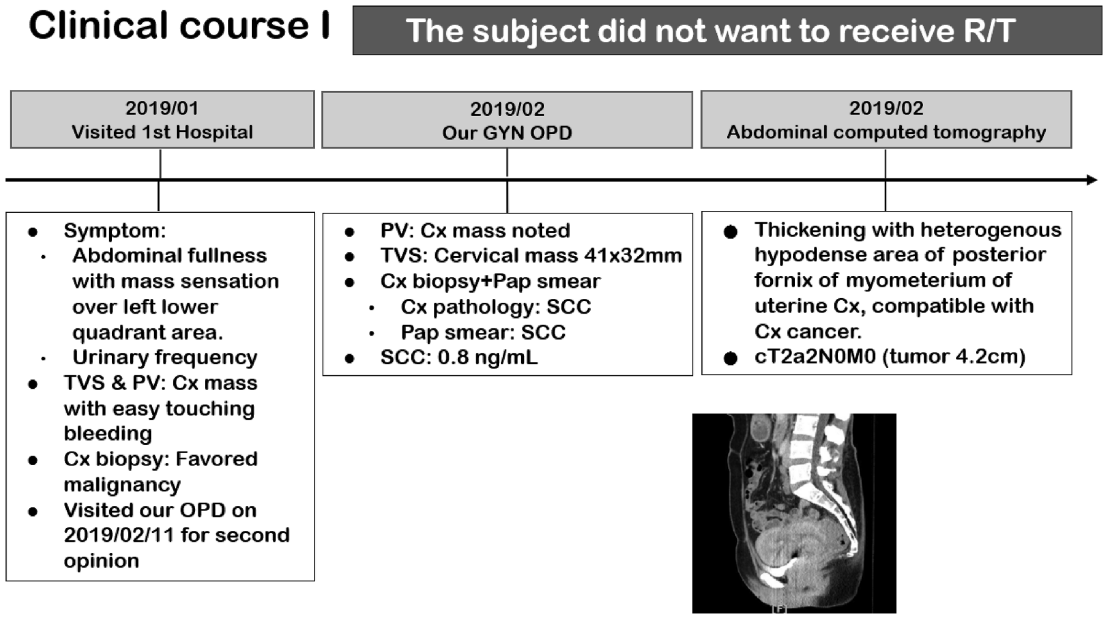

Fig. 1. The history and pre-treatment evaluation. Abbreviation: TVS (transvaginal ultrasound), PV (pelvic examination), GYN (gynecology), OPD (outpatient clinics), Cx (Cervix), SCC (squamous cell carcinoma).

results showed no significant difference of five-year OS (72% vs. 76%, 95% CI 66–77% vs. 70–80%) between two groups [43]. Based on failure to demonstrate superiority in favor of the NACT-S arm, primary CCRT is still recommended as a standard of care [43]. However, it is very interesting to find that short-term severe AEs ($\geq$ 3 grade 3) occurred more often with NACT-S (41% vs. 23%) but long-term severe AEs occurred more frequently with primary CCRT (21% vs. 15%) [43]. Although the authors concluded that patients either treated with NAT-S or treated with primary CCRT had an acceptable morbidity rate and similar health-related QoL (HRQoL), they still suggested that primary CCRT remains the standard of care in this LACC setting in their randomized trial [43].

In our institute, NACT-S was also applied in some of selected patients with LACC. In 2014, we retrospectively evaluated 60 patients with bulky size ($\geq$ 6 cm) of LACC, undergoing NACT-S (n = 35, with three courses of weekly single agent cisplatin 50 mg/m^2 and following primary radical surgery) and primary radical surgery (n = 25), and found the median survival was 143.8 months in the NACT-S group and 129.8 months in the primary radical surgery group, respectively, which did not reach the

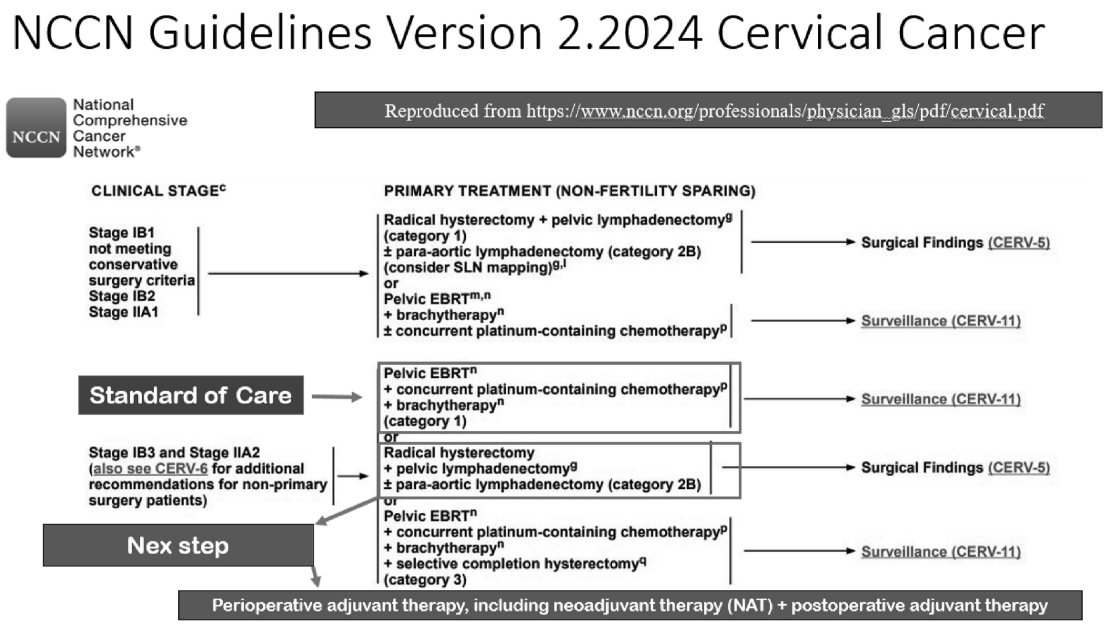

Fig. 2. NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024–May 6, 2024 Cervical Cancer recommends the standard of care for patients with stage IB3 and stage IIA2 favoring pelvic external beam radiotherapy (EBRT) + concurrent platinum-containing chemotherapy + brachytherapy (category 1). The secondary choice as the primary surgery by radical hysterectomy + pelvic lymphadenectomy with/without para-aortic lymphadenectomy (category 2B). The least recommendation is pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy + selective completion hysterectomy (category 3).

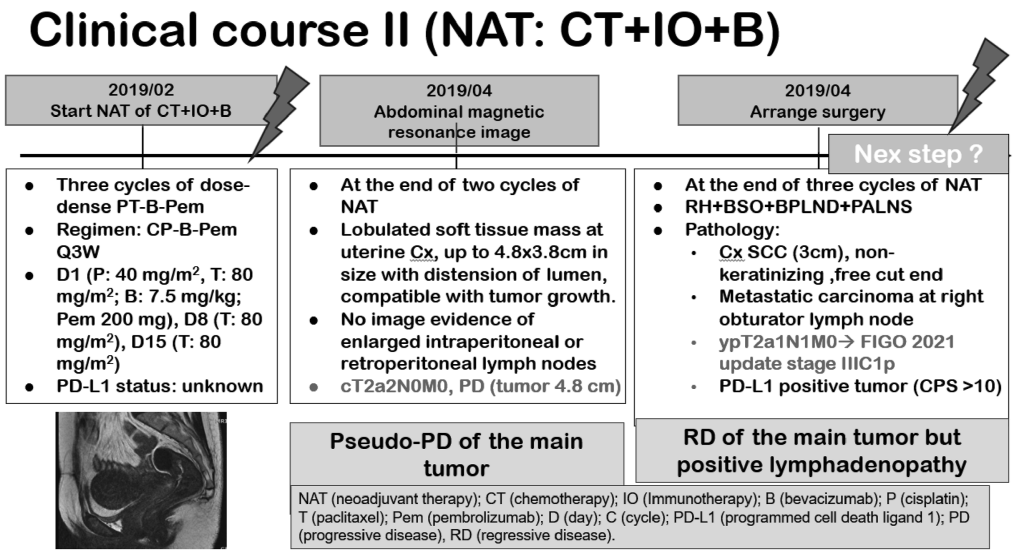

Fig. 3. The clinical course of the patient showed the neoadjuvant therapy (NAT) by chemotherapy (CT) (dose-dense chemotherapy with cisplatin 40 mg/m^2 triweekly plus paclitaxel 80 mg/m^2 weekly) + immunotherapy (IO) (pembrolizumab 200 mg triweekly) + half-dose anti-angiogenic agent (bevacizumab [avastin] 7.5 mg/kg triweekly). The NAT was completed by three cycles. Then, radical hysterectomy + bilateral salpingo-oophorectomy + pelvic lymphadenectomy + para-aortic lymph node sampling (RH + BSO + BPLND + PALNS) was performed after completion of three cycles of NAT. Abbreviation: NAT (neoadjuvant therapy), CT (chemotherapy), IO (immunotherapy), B (anti-angiogenesis agent − bevacizumab [avastin]), P (cisplatin), T (paclitaxel), Pemb (pembrolizumab), Q3W (triweekly), D (day), PD-L1 (programmed cell death ligand 1), Cx (cervix), TNM (tumor, lymph node, metastasis), PD (progressive disease), RD (regressive disease), SCC (squamous cell carcinoma), FIGO (International Federation of Gynaecology & Obstetrics).

statistically significant difference between two groups [60]. Furthermore, we found large pathological tumor size (HR 10.7, 95% CI 2.9–38.8) and the presence of para-aortic lymphadenopathy (lymph node metastases [LNM]) (HR 8.3, 95% CI 1.7–42.8) as well as the presence of immediate complication (surgery-related morbidity) (HR 4.6, 95% CI 1.4–15.3) contributed to a worse outcome, supporting the feasibility of this approach [60].

Moreover, the study comparing the outcomes of women with LACC (between IB3 and IIB) treated with NACT-S (multi-agent CT following radical surgery either by robotic approach [n = 18] or conventional exploratory approach [n = 21]) showed NACT following robotic approach associated with worse outcomes even though these subjects had a better response to NACT (downstage or shrinkage of the tumor volume) compared to NACT following conventional radical surgery [61], suggesting that minimally invasive surgery (MIS) should not be performed in patients with LACC, although MIS has extensively been accessed in the many kinds of diseases in place of the original conventional exploratory laparotomy [12,15,62–65]. Additionally, we demonstrated that FIGO IIB may not be suitable for NACT-S approach [61]. Nearly half of the patients with clinical stage IIB CC had enlarged lymphadenopathies (>10 mm) identified during pretreatment radiologic evaluation, which negatively impacted prognosis, suggesting the need to incorporate computed tomography- or magnetic resonance image (MRI)-based lymph node assessment before treatment for stage IIB CC [66].

All suggest that NACT shouldn't be used routinely in patients with LACC before radical surgery, particularly for those patients with LACC FIGO stage IIB and above, and might be also fitting to the lower staging LACC but associated with bulky size tumors, such as FIGO IB3 and IIA2 [20,43,49,52]. This is a challenge 1 in this issue.

However, the aforementioned recommendation may not be reproducible in patients undergoing NACT-CCRT status, since evidence supports the significant benefits of NAT on the patients with LACC who are planned to underwent CCRT as primary choice of treatment. Recently, the results of the GCIG INTERLACE trial at the 2023 congress of the European Society of Medical Oncology (ESMO) is likely to change the therapy for LACC, because six cycles of NACT administered dose-dense weekly carboplatin AUC2 (area under the concentration−time curve, 2 mg per ml min) and paclitaxel 80 mg/m^2 followed by definitive CCRT with pelvic radiotherapy (40~50.4 Gy) and cisplatin (40 mg/m^2 weekly for five weeks) and brachytherapy (total dose EQD2 [equivalent dose in 2-Gy fractions] at least 78 Gy at point A) (experimental arm) were compared with definitive CCRT alone (standard arm) in patients with LACC (FIGO 2008 stage IB1/node positive, IB2, II, IIIB and IVA) and was found to be significantly superior to conventional and direct CCRT with significantly longer PFS rates (HR 0.65, 95% CI 0.46–0.91) and significantly longer OS rates (HR 0.61, 95% CI 0.40–0.91) after 5 years' follow-up [45,52].

Since the potential limitation of therapeutic effect was expected if we used conventional NACT-S for treatment of the subject with the current clinical condition (FIGO IIA2), another alternative approach should be applied as rescue strategy to enhance the possibility of complete resection without further postoperative adjuvant RT. Therefore, is it possible to use the more effective and powerful strategy to satisfy the need of our patients and offer the rationale to perform NAT-S for this subject without compromising the therapeutic outcome? Therefore, more active and effectiveness-convinced NAT should be explored [45]. Anti-angiogenic drugs (bevacizumab, avastin) and IO (ICIs, for example pembrolizumab) have been demonstrated a promising and active combination in the management of advanced diseases, particularly combining with CT [32–38,45,46]. IO will enhance the systemic T-cell response to tumor antigens, amplified by CT, that can detect and kill micro-metastatic tumors and, with the tumor in place, presentation to, and thus priming of, more tumor-specific circulating T cells than in an adjuvant setting and additionally, some active associations of ICIs and CT in NAT settings have already been reported—eg, in breast carcinoma—with improvement of pathological response [45,67,68].

The ENGOT-cx11/GOG-3047/KEYNOTE-A18 study of pembrolizumab (IO) plus CCRT versus placebo-based CCRT showed the HR for PD or death was 0.70 (95% CI 0.55–0.89) and information fraction 42.9% of OS at 24 months (87% vs. 81%) with HR for death of 0.73 (95% CI 0.49–1.07) [69]. By contrast, the CALLA study

compared LACC patients treated with durvalumab (ICIs, anti-programmed cell death ligand 1 [anti-PD-L1]) plus CCRT versus CCRT alone failed to demonstrate any survival benefits of this population [70]. Although all aforementioned data have conflicts and the role of ICIs is still uncertain and it may be secondary to different mechanisms of ICIs, such as the different targets as anti-programmed cell death (anti-PD-1) and its ligand (anti-PD-L1) [71], the integration of CT with/without anti-angiogenic agent (bevacizumab) into ICIs (particularly for anti-PD-1, such as pembrolizumab) might offer a substantial therapeutic benefit for patients with LACC.

In fact, according to Dr. Li's evidence before publishing the first trial to assess the activity and safety of NAT by camrelizumab (IO, ICIs, anti-PD-1) plus CT following surgery for the treatment of LACC, they found no published research studies investigated immune-based NAT-S for CC, although two phase II trials are going [72]. One (NCT04799639, https://clinicaltrials.gov/study/http://clinicaltrials.gov/show/NCT04799639) attempted to examine the activity of three cycles of sintilimab (IO, ICIs, anti-PD-1) plus CT as a NAT and found an objective response rate of 95% and a pathological complete response rate of 35% [46,72]. Meanwhile, the other single arm multicenter phase II trial: MITO CERV3 (NCT04238988, https://clinicaltrials.gov/study/NCT04238988), attempted to evaluate the role of pembrolizumab (IO, ICIs, anti-PD-1) in combination with CT in FIGO stage IB2-IIB CC patients, who will receive three cycles of NAT of carboplatin AUC 5, paclitaxel 175 mg/m^2, and pembrolizumab 200 mg triweekly, followed by radical surgery in patients without PD (progressive disease); however, so far, reported data has not been found [46,72].

Dr. Li's phase II trial named as NACI study using one cycle of neoadjuvant nab-paclitaxel at a dose of 260 mg/m^2 and cisplatin at a dose of 75–80 mg/m^2 (nab-TP regimen) and two additional cycles of nab-PC regimen plus camrelizumab at a dose of 200 mg (ICIs) and following surgery for LACC patients (n = 85) found objective response (83 [98%, 95% CI 92–100] of 85 patients, including 16 [19%] with a complete response and 67 [79%] with a partial response), with 32 (38%) patients having a pathological complete response, although the median follow-up is too short (11.0 months [interquartile range (IQR) 6.0–14.5]) and cannot draw any conclusions about final outcomes [45,46]. With supporting by NACI study, we offered this strategy with combination of CT + IO + anti-angiogenic agent to our subject with LACC (FIGO IIA2) as a rationale 1.

2. Image Tumor Progression (Fig. 3)
   - After two courses of NAT containing dose-dense cisplatin and paclitaxel (PT) plus pembrolizumab (IO) and bevacizumab (anti-angiogenic agent) (PT + pem + B), the follow-up imaging in April 2019, indicated an enlarged tumor size, which increased the size to 4.8 × 3.8 cm, hinting the possibility of progressive disease (PD) of primary tumor, although the abovementioned image evaluation needed further validation.

Rationale 2 and challenge 2

The evaluation of response, particularly in the first follow-up, in patients initially treated with IO with/without other agents (CT and anti-angiogenic agent) sometimes may be challenged, because it may be confusing to distinguish the progressive disease (PD) from pseudo-progressive disease (pseudo-PD) in immune unconfirmed progressive disease (iUPD) based on the observation that RECIST is prone to misjudgment due to the high number of immune cells infiltrating early in IO [73–75]. However, the use of image to predict the therapeutic outcome of NAT may face this struggle and dilemma since pseudo-PD may confuse physicians' decision about NAT-related therapeutic response and planning of next step therapy.

In the MITO CERV 3 Trial (single arm multicenter phase II study), a total of 45 patients with FIGO stage IB2-IIB CC underwent three cycles of platinum-based NACT with concomitant administration of pembrolizumab 200 mg triweekly and if PD was absent, patients subsequently receive radical surgery [76], suggesting that NAT may not always work for these LACC patients, and additionally, PD after NAT may be contraindicated for radical surgery, and by contrast, cisplatin-based CCRT may be a better alternative in such situations. Therefore, how to precisely diagnose PD for these patients is of the critical importance and without clear and definite distinguishment between PD and pseudo-PD, these LACC patients will loss opportunity to receive definite radical surgery (complete safe resection of tumors). This potential risk should be always in concern and also a biggest challenge (the challenge 2) that we should take into consideration.

It is relatively difficult to make an accurate confirmation about PD, as the clinical evolution of the patients does not always correlate with the PD at a molecular, microscopic or even macroscopic levels [77]. The pattern of response to treatment as well as the pattern of side effects with IO differ from those with traditional CT and targeted therapy [78]. The response to IO may take considerably longer to be observed radiologically compared with CT and targeted therapy [78]. However, the other specific to IO is hyper-progressive diseases (hyper-PD), and the predictive factors of hyper-PD are largely unknown, which is a phenomenon of extraordinarily rapid tumor progression which confers a worse prognosis to cancer patients and continuation of IO beyond progression for patients with apparent clinical deterioration is not recommended [78]. By contrast, patients who show signs of hyper-PD should stop IO treatment and consider alternative therapy and early palliative care [78]. Therefore, the importance of post-treatment evaluation of cancers underscores a critical dimension of research, particularly in evaluating the efficacy of new treatment of CC like the current NAT using the combination regimen, including CT, IO and anti-angiogenic agent for this subject.

One meta-analysis enrolling 18 IO clinical trials (ten cancer types) of total 287 patients showed the rate of the pseudo-PD was 15%, and most often in the first timepoint after baseline than later in treatment and nontarget lesions were significantly more frequent the cause of iUPD than change in target lesions size [73]. Therefore, the specific radiological assessment criteria were developed, including immune-related Response Criteria (irRC), immune-related RECIST (irRECIST), immuno-RECIST (iRECIST), and the immune PET Response Criteria in Solid Tumors (iPERCIST criteria), which are an extension of RECIST 1.1 aiming to address the unique patterns of response observed in patients undergoing IO [73–75].

Regrettably, even with improved assessment and classification, clear guidance on the appropriate timeframe and interval for patient monitoring during and after IO remains elusive [74,75]. For example, many of the evaluated items, such as complete response, partial response and stable disease are identical between RECIST 1.1 and iRECIST, but the definition of PD and new lesions were different [73]. In conventional RECIST 1.1 response criteria showed $\geq$20% increase in SOD (sum of diameters) relative to nadir and 5 mm absolute increase and unequivocal progression of any non-target lesions as PD status; however, for iRECIST, although initial progression criteria are the same as RECIST1.1, the true PD should require confirmatory scan 4–8 weeks later which must meet additional growth criteria to confirm progression [73].

In the current case report, we found this subject had a typical presentation of pseudo-PD at the end of two cycles of NAT containing CT + IO + anti-angiogenic agent. Similar to other reports

showing that the patients receiving IO may demonstrate a period of disease stabilization or even transient worsening of radiologic lesions before radiologic tumor regression occurs [78], the current subject was also misdiagnosed as worsening of radiological lesions.

In fact, the final pathology report of the current case was 3 cm in size of the main tumor compared to the original size up to 4 cm above, suggesting this NAT strategy containing CT + IO + anti-angiogenic agent indeed intimately links to the shrinkage of tumor and down-stages FIGOIIA2 to FIGO IIA1, suggesting that advanced imaging and classification techniques for posttreatment image studies are urgently needed. Some cautions are generally taken by oncologists' experienced in IO not to stop IO prematurely so that potential benefit from IO would not be compromised [78]. For example, recently, images utilizing LASSO and EL- SVM for biopsy image classification or integrating deep convolutional features through AF-SENet or ViT-AMC networks, that help contribute significantly to the precision and interpretability of diagnoses [77,79,80], which not only increases the accuracy of tumor grading but also increases a more nuanced understanding of tumor behavior and pathology-related diagnosis, and all of them are essential for tailoring treatment strategies [76].

3. Surgical Intervention (Fig. 3)
   - After three courses of NAT containing CT + IO + half-dose anti-angiogenic agent and in April 2019, the patient underwent radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and para-aortic lymph node sampling (RAH + BSO + BPLND + PALNS). Pathology reports confirmed the presence of non-keratinizing SCC (tumor size of 3-cm) with metastatic spread to the right obturator lymph node (ypT2a1N1M0), and according to 2021 FIGO update cervical cancer stage IIIC1p. This PD-L1 positive SCC was represented by a tumor proportion score (TPS, [number of PD-L1 positive tumor cells/total number of viable tumor cells] x100 by PD-L1 IHC 22C3 pharmDx [Dako/Agilent]) > 1 and the combined positive score (CPS, [number of PD-L1 positive cells (tumor cells, lymphocytes, macrophages)/ total number of viable tumor cells] x100) > 10.

Challenge 3

CC is most often associated with pelvic LNM, up to 20% according to previous studies when the bulky size tumor is found (FIGO stages IB3 and IIA2) [50,60,61,66]. Since early-stage CC is associated with various risk of LNM, the 2018 FIGO staging system (2021 FIGO update again) emphasizes the significance of lymph node status in prognosis and the recognition of diverse prognostic outcomes within this group [4]. In this case report, she was pathologically confirmed to have pelvic LNM and specifically labeled as stage IIIC1p. Stage IIIC1p CC is in marked heterogeneity with much variability in the postoperative prognosis based on US Surveillance, Epidemiology, and End Results (SEER) Program (SEER) showing that patients with stage IIIC1p disease have a higher disease-specific survival rate than patients with stage IIIA-IIIB disease and furthermore, the survival rate within the stage IIIC1p group decreased as the T stage increased (5-year OS rates were 74.8% for T1, 58.7% for T2, and 39.3% for T3) [81,82]. Furthermore, no post-operative adjuvant therapy was an independent risk contributing to worse prognosis (poor OS and DFS) in patients with stage IIIC1p CC [81,82]. Although according to NCCN guideline, the SOC of this group of patients was EBRT + concurrent platinum-containing CT (CRT) with/without brachytherapy (Fig. 4) [20,81], the patient refused to receive this suggestion, contributing to raising the question what is the next potential alternative in place of SOC of RT-based adjuvant therapy without compromising the therapeutic oncologic outcome. This is a challenge 3.

4. Postoperative RT-free Multimodality Adjuvant Therapy (Figs. 3–5)
   - Postoperatively, the SOC for the patient was postoperative adjuvant CCRT with/without vaginal brachytherapy according to the NCCN guideline (Fig. 4) [20], but the subject still refused this suggestion. Based on the observation for this subject having a metastatic lesion (LNM), systemic therapy could be applied in place of RT for local control and possibly for better distant control (Fig. 5). The subject received three additional cycles of postoperative adjuvant therapy with the same

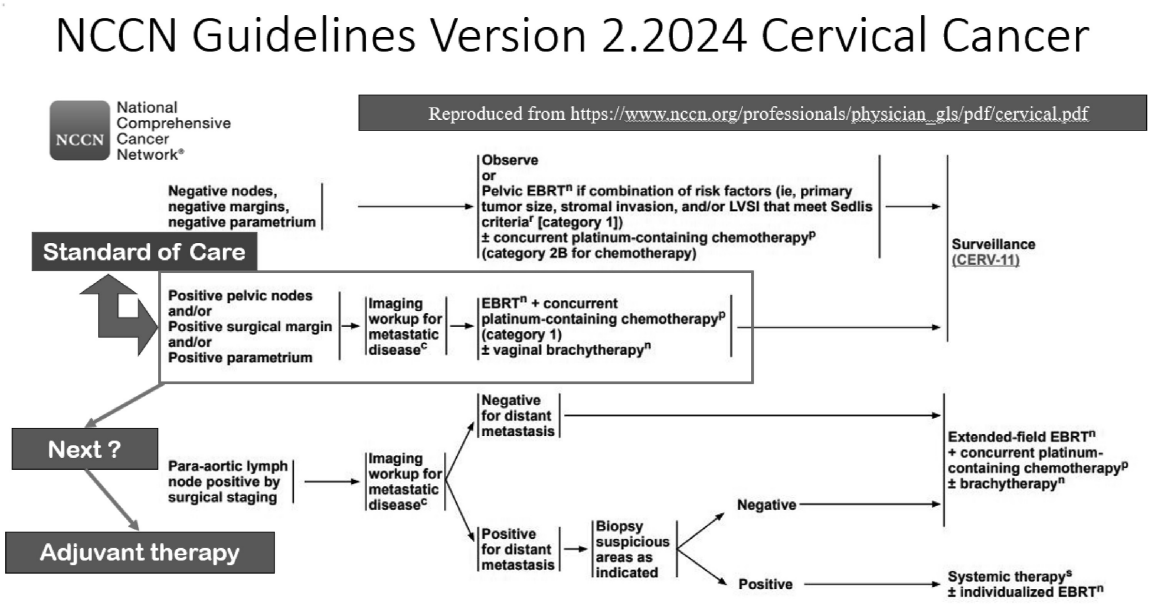

Fig. 4. NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024—May 6, 2024 Cervical Cancer recommends the standard of care for patients with positive pelvic lymph node but negative para-aortic lymph node after radical hysterectomy + pelvic lymphadenectomy + para-aortic lymph node sampling (or dissection) favoring pelvic external beam radiotherapy (EBRT) + concurrent platinum-containing chemotherapy (category 1) with/without vaginal brachytherapy. Only distant metastatic status suggests systemic therapy with/without individualized EBRT.

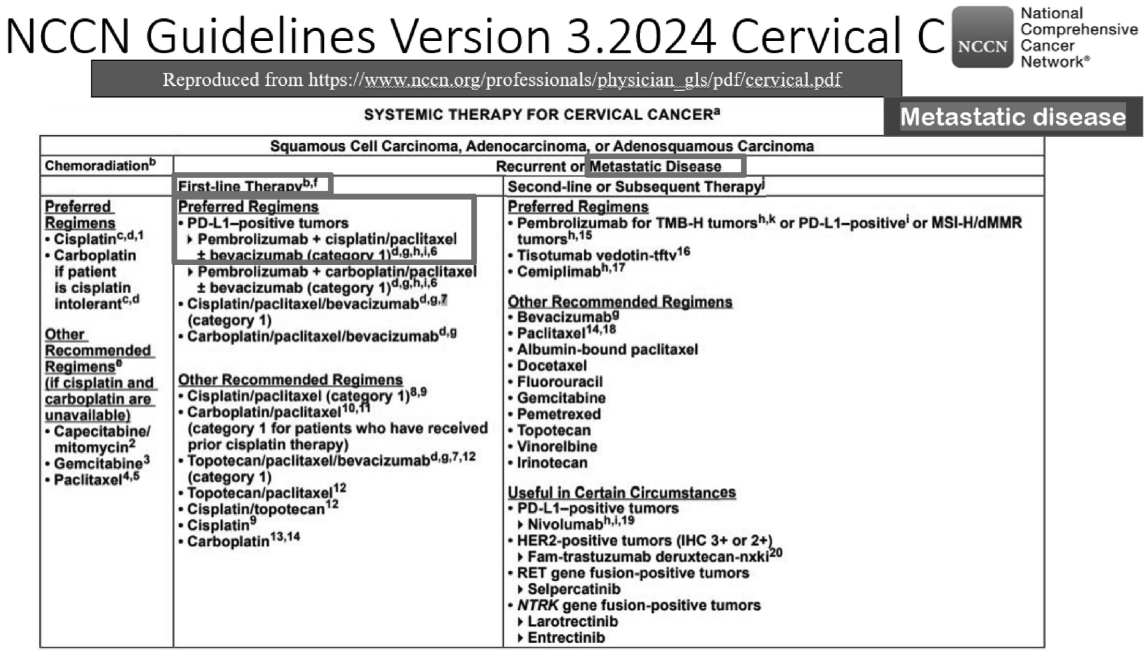

Fig. 5. NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024—May 6, 2024 Cervical Cancer recommends the systemic therapy for metastatic PD-L1 cervical cancer patients by using first-line therapy as pembrolizumab + cisplatin/paclitaxel with/without bevacizumab (category 1).

regimen as described above. Combination of three cycles of NAT and three cycles of postoperative adjuvant therapy is called a perioperative therapy (a total of six cycles of dose-dense CT + IO + half-dose anti-angiogenic agent treatment). The outcome was excellent with a complete free-of-disease status after perioperative adjuvant therapy plus radical surgery (Fig. 6). However, she was attacked by hypothyroidism during the time period.

Rationale 3 and challenge 4

Recurrent, persistent or metastatic CC is still the biggest challenge for both physicians and patients, since the outcome is very poor with five-year OS rates of less than one-fifth, contributing to urgent need for new avenues for improving outcomes in these highly lethal diseases [77]. This is a challenge 4. As shown above, PD-1 and possible PD-L1 inhibitors (ICIs) have shown efficacy and

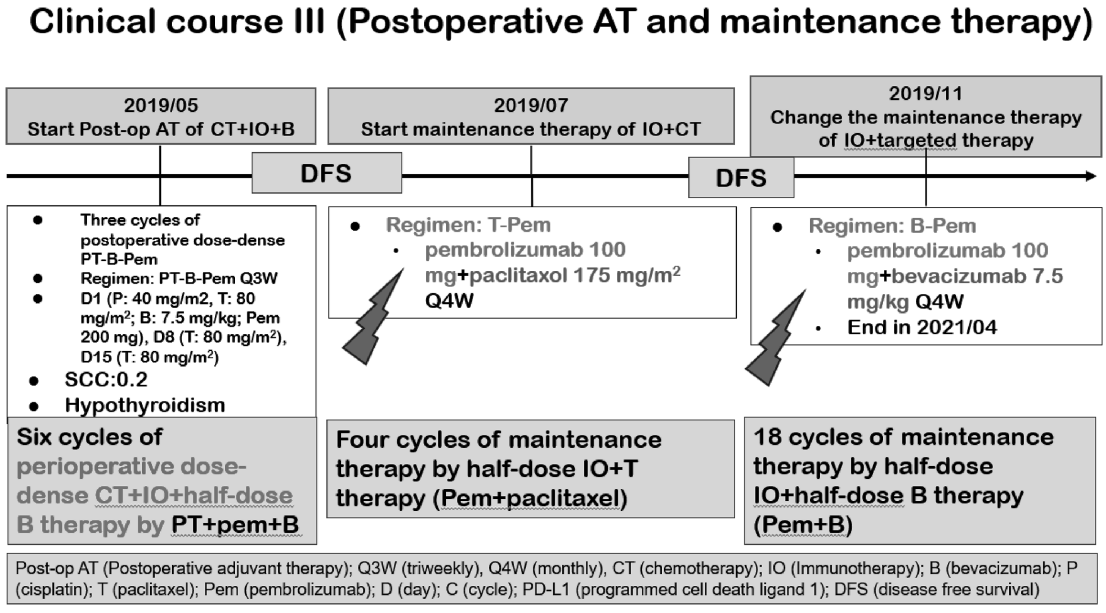

Fig. 6. The clinical course of patient after three cycles of neoadjuvant therapy by dose-dense chemotherapy (triweekly cisplatin 40 mg/m^2+weekly paclitaxel 80 mg/m^2) + pembrolizumab (triweekly immunotherapy [IO] 200 mg) + bevacizumab (triweekly anti-angiogenesis agent avastin 7.5 mg/kg) and radical hysterectomy showed the additional three cycles of dose-dense chemotherapy (triweekly cisplatin 40 mg/m^2+weekly paclitaxel 80 mg/m^2) + pembrolizumab (triweekly immunotherapy [IT] 200 mg) + half-dose bevacizumab (triweekly anti-angiogenic agent bevacizumab 7.5 mg/kg). Then, maintenance therapy was administered by 4 cycles of pembrolizumab 100 mg monthly + paclitaxel 175 mg/m^2 monthly and followed by 18 cycles of maintenance therapy with monthly pembrolizumab 100 mg and monthly bevacizumab 7.5 mg/kg).

safety profiles in CC [33–36,46,47,69–72,77], although in individual studies of gynecological cancers, including CC, endometrial cancer, and ovarian cancer, showing the conflicting or inconsistent results have been reported concerning the association between PD-L1 expression and patient's survival outcomes [83].

According to the findings obtained from several meta-analyses aiming to clarify the relationship between PD-L1 expression and survival outcomes in gynecological cancers, results have also yielded incongruent and contradictory results [83], suggesting that the interaction between IO and host factor, or others such as PD-L1 expression and tumor history or behaviors is relatively complex and worthy of further investigation [77]. Besides, patients with PD-L1 positive tumors, represented by a TPS (available to non-small cell lung cancer) or the CPS (available to head and neck SCC, gastric cancer, esophageal SCC, CC, and triple-negative breast cancer [TNBC]), showed better outcomes in the monotherapy setting, supporting the potential for personalized and precise medicine approaches in optimizing treatment plans for patients with persistent, recurrent or metastatic CC by biomarker-driven treatment strategies [77,83–85]. Additionally, recent clinical trials, including phase 3 trials examining ICIs for CC revealed nuanced findings regarding their efficacy and safety profiles [32–36,45–47,52,67–69,72,77]. Based on the impressive results and exciting findings of KEYNOTE-828 (NCT 03635567) [32–35,86], the phase III, RCT of pembrolizumab 200 mg or placebo once triweekly for up to 35 cycles plus platinum-based CT, with or without bevacizumab, showed statistically significant survival benefits with the addition of pembrolizumab for patients with persistent, recurrent, or metastatic CC (primary data cutoff: May 3, 2021) [35]. The updated 2023 and 2024 articles report the protocol-specified final OS results tested in the PD-L1 CPS $\geq$1, all-comer, and CPS $\geq$10 populations with the median study follow-up duration was 39.1 months (range, 32.1–46.5 months) on October 3, 2022 [86]. In the PD-L1 CPS $\geq$1 (n = 548), all-comer (n = 617), and CPS $\geq$10 (n = 317) populations, median OS with pembrolizumab-CT versus placebo-CT was 28.6 months versus 16.5 months (HR for death, 0.60 [95% CI 0.49–0.74]), 26.4 months versus 16.8 months (HR, 0.63 [95% CI 0.52–0.77]), and 29.6 months versus 17.4 months (HR, 0.58 [95% CI, 0.44 to 0.78]), respectively [32,86]. Additionally, in the CPS $\geq$1 population, HRs for OS favored the pembrolizumab group in all subgroups: with bevacizumab (HR 0.62, 95% CI 0.45–0.87) and without bevacizumab (HR 0.67, 95% CI 0.47–0.96), use of carboplatin (HR 0.65, 95% CI 0.50–0.85) and cisplatin (HR 0.53, 95% CI 0.27–1.04), with prior CRT only (HR 0.56, 95% CI 0.39–0.81) and without prior CRT only (HR 0.72, 95%CI 0.52–1.00), and SCC (HR 0.60, 95% CI 0.46–0.79) and non-SCC (HR 0.70, 95% CI 0.41–1.20) histologic type [32]. In the current subject, the tumor was PD-L1 positive SCC with CPS >10, suggesting that this combination of CT + IO + bevacizumab may offer the better benefits to this subject, including bevacizumab (HR 0.62 [yes] vs. 0.67 [no]), cisplatin (HR 0.53 vs. 0.65 [carboplatin]), and SCC (HR 0.60 vs. 0.70 [nonSCC]). Although the HR was 0.56 in patients with prior CRT compared to those without CRT as 0.72, it suggested that this combination will be better in patients with prior CRT. However, compared to patients with prior CRT, patients without prior CRT had a favorable OS, regardless of IO was added into CT or not [32]. All suggest that the current subject fulfilled all favoring predictor markers to achieve the best therapeutic response as supposed. In fact, the aforementioned regimen (CT + IO with/without bevacizumab) was approved by the FDA on 13 October 2021, for patients with persistent or recurrent or metastatic CC with a PD-L1 CPS $\geq$1 and has since become the standard of care. This is a rationale 3.

5. Long-Term Maintenance Therapy with Short-Term Therapy of Combination of Single Agent-Paclitaxel and Half Dose of IT and Sequent Half-Dose of IT and Anti-Angiogenic Agent (Figs. 7 and 8)
   - Maintenance therapy with 22 cycles of monthly IO (pembrolizumab 100 mg) and concomittent with either four cycles of single agent CT (paclitaxel 175 mg/m^2) or 18 cycles of B (bevacizumab 7.5 mg/kg was administered to this patient.

Rationale 4 and challenge 5

According to the original design of KEYNOTE-826 (NCT 03635567) [35], patients were randomly assigned in a 1:1 ratio to receive pembrolizumab (200 mg) or placebo triweekly for up to 35 cycles. All the patients received paclitaxel (175 mg/m^2) and the investigator's choice of cisplatin (50 mg/m^2) or carboplatin (AUC 5) triweekly. At the request of a global regulatory authority, the second protocol amendment (approved on June 25, 2019) limited chemotherapy to six cycles, although patients with ongoing clinical benefits who received CT without unacceptable side effects could continue beyond six cycles after consultation with the sponsor. Patients could receive bevacizumab at a dose of 15 mg/kg triweekly

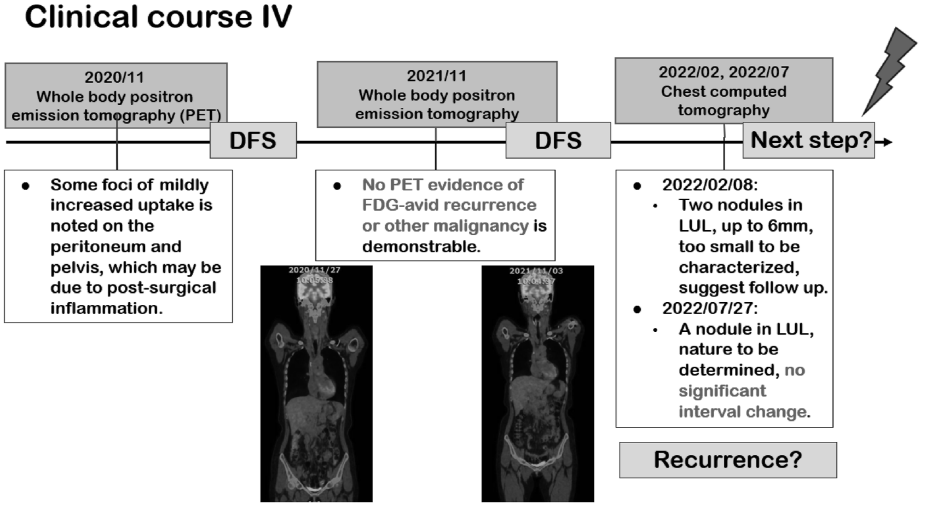

Fig. 7. Postoperative follow-up showed the subject was free of disease during the one and two-year follow-up, although some unusual but neglected findings were found during the follow-up. Abbreviation: DFS (disease-free survival), LUL (left upper lung).

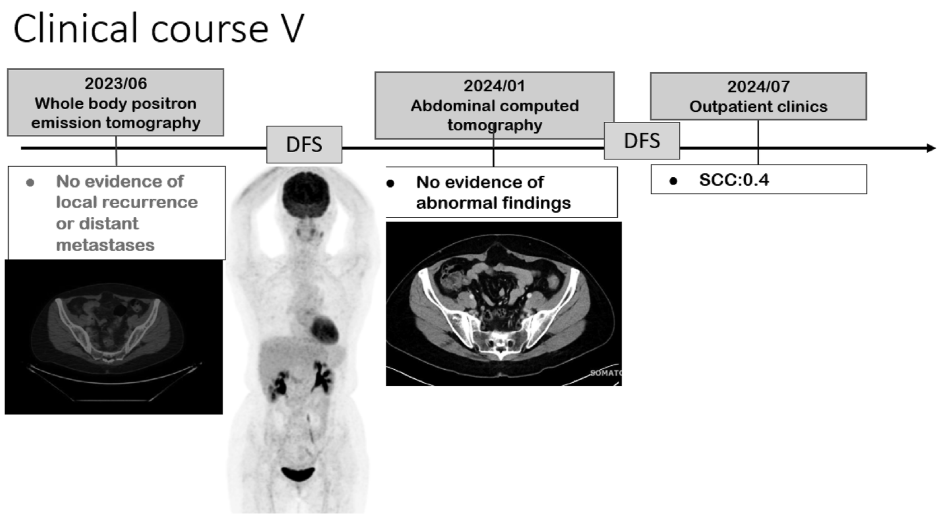

Fig. 8. Postoperative follow-up showed the subject was free of disease during the three- and four-year follow-up. SCC (squamous cell cancer antigen).

according to local practice at the investigator's discretion [35]. Therefore, the challenge 5 containing six deviations and one severe IO-related AE is present in the management of this patient with LACC. First, bevacizumab dosage was used 7.5 mg/kg (not 15 mg/kg) and the cisplatin dose was 40 mg/m^2 (not 50 mg/m^2). Second, dose-dense CT was used (not conventional triweekly CT). Third, half dose of pembrolizumab 100 mg was used during the maintenance therapy and a total of 28 cycles of pembrolizumab (200 mg for 6 cycles and 100 mg for 22 cycles), based on KEYNOTE-826 protocol needing 35 cycles of full-dose pembrolizumab (200 mg) [35]. Fourth, the time interval of the maintenance therapy was extended from three weeks to four weeks. Fifth, additional single agent CT with paclitaxel (175 mg/m^2) was used for additional four cycles (not CT-free in the maintenance therapy). Sixth, bevacizumab was applied for additional 18 cycles for maintenance therapy (not bevacizumab-free maintenance therapy). Severe AE (hypothyroidism) attacked this subject.

First, the dose of bevacizumab applied to treat CC is 15 mg/kg, based on original design of GOG 240 (NCT00803062) and is used every three weeks (triweekly) [37,38]. Although many studies favored the dose of 15 mg/kg for bevacizumab in combination with other agents (CT, IO, or new investigated agents) [87–89], some studies using a dose of 7.5 mg/kg to combine other common agents, such as CT or IO for CC treatment revealed good response and acceptable toxicity [90]. Dr. Yang's group explored the long-term efficacy and safety of 7.5 mg/kg bevacizumab combined with NACT and CCRT in 62 refractory CC and found the OS rate was 78.6%, the local region-free survival rate was 91.3%, the disease-free survival (DFS) rate was 70.6%, and the distant metastasis-free survival rate was 81.4% at four-years follow-up [87]. A total of 29 patients (46.8%) experienced grade 3/4 hematological toxicity, 3 patients (4.8%) experienced grade 3 gastrointestinal toxicities, and none experienced grade 5 AEs. All suggesting that bevacizumab at the dose of 7.5 mg/kg combined with NACT and CCRT significantly improved complete clinical response and OS in refractory CC with acceptable toxicity [90].

In our previous study, we also found that the 1-, 2-, and 3-year PFS rates (95% CI) were 36.24% (95% CI 22.0–50.5), 20.7% (95% CI 9.8–34.2), and 17.7% (95% CI 7.7–31.1) for the cisplatin-based CT group; and 71.4% (95% CI 47.1–86.0), 51.0% (95% CI 27.9–70.1), and 51.0% (95% CI 27.9–70.1) for the cisplatin-based CT + bevacizumab 7.5 mg/kg group, respectively [91]. The 1-, 2-, and 3-year OS rates were 62.6% (95% CI 46.4–75.18), 32.4% (95% CI 18.8–46.9), and 23.2% (95% CI 11.2–37.6) for the cisplatin-based CT group; and 85.7% (95% CI 61.9–95.1), 66.6% (95% CI 42.5–82.5), and 55.5% (95% CI 27.1–76.7) for the cisplatin-based CT + bevacizumab 7.5 mg/kg group, respectively. Additionally, the cisplatin-based CT + bevacizumab 7.5 mg/kg group presented higher PFS and OS rates compared with cisplatin-based CT alone group, $p = 0.003$ and $p = 0.005$, respectively [91]. The aforementioned findings support the rational 4 in this issue.

Second, a dose-dense CT regimen for advanced CC has been tested by phase II/III RCT (JCOG1311, Japan Clinical Study Group) [87]. At the two-year follow-up period, the 2-year OS in the conventional arm was 37.5% (95% CI 25.4%–49.4%) versus 38.9% (95% CI 26.7%–50.9%) in the dose-dense arm [87]. Additionally, median OS time of patients treated with the conventional PT + bevacizumab regimen, dose-dense PT + bevacizumab regimen, conventional PT regimen, or dose-dense PT regimen was 18.5 months (95% CI 12.2 to not estimatable), 21.5 months (95% CI 15.5 to not estimatable), 11.3 months (95% CI 2.5–23.0), and 15.4 months (95% CI 8.3–27.3), respectively [87]. Since dose-dense regimen did not improve OS in these advanced CC patients statistically significantly compared to conventional regimen, it was confirmed that dose-dense PT for metastatic or recurrent cervical carcinoma is not superior to conventional PT regimen [87]. However, we found either dose-dense or conventional PT + bevacizumab had a better outcome compared to dose-dense or conventional PT alone, in agreement with advantages from PT + bevacizumab recommended by GOG 240 trial [37,38]. Although the study failed to demonstrate superiority of dose-dense PT ± bevacizumab regimen to conventional PT ± bevacizumab regimen, we still favored this dose-dense PT regimen to this subject with LACC, similar to our previous publication addressing the benefits of dose-dense CT for other kinds of gynecologic cancers [92–94].

Third, to explore the maintaining therapeutic effect of half dose of pembrolizumab, a recent RCT may respond to this argument [95]. Dr. Peer using an interventional pharmacoeconomic approach tried to evaluate minimum effective concentration (MEC) for both drugs by less frequent dosing of pembrolizumab and nivolumab based on its long half-lives and no evidence of a relationship of dose to efficacy and the results showed extended dosing regimens of nivolumab 240 mg every 4 weeks and 480 mg every 8 weeks along with pembrolizumab 200 mg every 6 weeks were simulated, showing that >95% of patients maintained MEC or greater, suggesting the potential to reduce drug exposure by at least 50%, thus substantially reducing patient visits (as well as costs), while maintaining

equivalent efficacy [95]. Although the scientific justification for an ongoing RCT comparing standard dose with half-dose or standard interval fixed dosing with extended interval fixed dosing, and ultimately an efficacy-driven comparative trial [95]. Additionally, Dr. Low attempted to assess the efficacy of pembrolizumab 100 mg vs. pembrolizumab 200 mg upon survival outcomes, toxicity and cost in an average-sized Asia patient with advanced non-small cell lung cancer and the results showed no difference in PFS and OS between pembrolizumab 100 mg and pembrolizumab 200 mg as a single agent (PFS: 6.8 vs 4.2 months, HR 0.72, 95% CI 0.36–1.46; 9 month OS: 58% vs 63%, HR 1.08, 95% CI 0.48–2.41) and when combined with CT (9-month PFS: 60% vs 50%, HR 0.84, 95% CI 0.34–2.08; 9-month OS: 85% vs 58%, HR 0.27, 95% CI 0.062–1.20), suggesting the further RCT should be done to investigate a lower dose of pembrolizumab [96]. Although no guidelines recommend dose reduction of IO due to any causes, such as concerns of cost or development of irAEs (IO-related adverse events), we observe remarkable maintaining complete clinical remission and mild toxicities of half dose of pembrolizumab in this case we presented. In fact, the current patient had hypothyroidism during the perioperative adjuvant therapy and was treated with thyroxin replacement therapy. This may be an explanation to rationale 4 and challenge 5.

Fourth, although no evidence supports the current strategy to extended interval for treatment, similar to the response as shown in prior section, if half-lives of therapeutic agents is long, efficacy may not be compromised if extended interval is limited. However, this hypothesis still needs further validation.

Fifth, there are controversies about the optimal number of NACT, adjuvant CT, or perioperative adjuvant CT cycles applied to cancer patients. So far, even for those incurable cancer diseased patients, nobody knows when the CT should be ceased. Although this concern frequently exists, particularly for those patients undergoing NACT-S and/or primary cytoreductive surgery with minimal or invisible residual tumors (maximum safe surgical resection), there is no consensus or guideline responding to this question. In Medscape website, cervical cancer treatment protocols are provided [97]. Using the similar clinical situations to guide the current case report we presented, treatment recommendations for advanced stage disease (including stage IB3, IIA2, IIB, IIIA, IIIB, IVA), cisplatin-based multiagent CT were limited to maximum six cycles [97]. Even for far advanced stage cervical cancer (stage IVB), it is hard to know optimal cycles of CT for this group patients. Long-term use of CT may not increase OS but by contrast, CT-associated AEs are apparent. Moreover, in GOG 240 trial, treatment was discontinued at the onset of disease progression or the development of unacceptable toxic effects, or if the patient had a complete response [37]. The median number of cycles for patients treated with CT alone was 6 (range, 0 to 20) and for those who received CT plus bevacizumab, the median was 7 (range, 0 to 36) [37]. The GOG 240 study also confirmed bevacizumab monotherapy deserves some consideration, particularly among patients intolerable to CT, despite several dose reductions ultimately requiring peeling back of CT [38].

No study was conducted to compare the standard cycles (maximum six cycles) and extended cycles of CT, particularly among the patients with complete remission or after definite complete surgical resection (without residual tumors). Therefore, CT for other cancers may be used as reference. One RCT aimed to compare the survival benefits of 12 cycles against 6 cycles of adjuvant temozolomide in adults with newly diagnosed high-grade gliomas and found that the median PFS of 6 cycles and 12 cycles groups was 18 months (95% CI 14.8–21.1) and 16 months (95% CI 11.0–20.9), respectively, suggesting the definite complete surgical resection may not be beneficial from extended adjuvant temozolomide beyond six cycles [98].

For ovarian cancer, from the reported randomized trials using different durations or different numbers of CT cycles, none of these showed improvement in survival beyond 6 cycles and data from the literature do not support a relationship between the number of cycles and response or between the cumulative dose and response [99]. Although statistically significant differences in PFS were found in patients who achieved a clinically defined complete clinical remission to a PT-based CT and who continued single-agent paclitaxel for an extended period, notably, this randomized trial most likely did not offer any survival advantage, as it was closed prematurely by the Data Safety Monitoring Committee in accordance with the guidelines planned for interim analysis of primary endpoints [99]. Therefore, six cycles of perioperative adjuvant therapy are the standard of care, and if the extended cycles are needed, single agent-paclitaxel may be a better choice.

Sixth, bevacizumab monotherapy for consolidation or maintenance therapy is acceptable in many kinds of cancers, such as ovary, cervix and others [37,99–101]. According to clinical trials for ovarian cancer, a total 22 cycles or less (including concurrent and maintenance) of bevacizumab were used [100,101]. The rationale of combination of IO and anti-angiogenic agent can be supported by the BEATcc trial (ENGOT-Cx10-GEICO 68-C-JGOG1084-GOG-3030) [102,103], which clearly introduced the treatment protocol, including ceased time. Treatment was continued until disease progression, unacceptable toxicity, patient withdrawal, or death, whichever occurred first [103]. Patients with a complete response after at least six cycles could discontinue CT and continue bevacizumab (and atezolizumab in the experimental group) as maintenance therapy [103]. In the BEATcc trial, median treatment duration was 12.7 months (IQR 7.6–24.8) in the experimental group versus 8.5 months (IQR 5.1–13.9) in the standard group [103]. Median duration of CT was also six cycles (IQR 6–8) in both groups, whereas median bevacizumab duration was longer in the experimental group (14 cycles [IQR 7–25]) than in the standard group (ten cycles [6–18]) [103]. Median atezolizumab duration was 16 cycles (IQR 8–32) [103]. Based on the aforementioned trial, maintenance of pembrolizumab and bevacizumab for 18 cycles may be reasonable for the current case we presented. In fact, this subject had received a total 24 cycles of bevacizumab treatment during this journey.

6. Follow-up and Current Status
   - The patient had finished her journey to fight LACC in April 2021. The last follow-up of the patient was July 2024 and she is alive with totally free of disease.

Adverse events

During the journey of this subject fighting the LACC, from perioperative adjuvant therapy, including NAT and postoperative adjuvant therapy with dose-dense CT (triweekly cisplatin + weekly paclitaxel) + triweekly standard dose IO + half-dose bevacizumab (7.5 mg/kg), radical surgery (RAH + BSO + BPLND + PALNS), and maintenance therapy with 22 cycles of monthly half-dose IO (pembrolizumab 100 mg) concomittent with either four cycles of full-dose paclitaxel (175 mg/m2) or 18 cycles of half-dose anti-angiogenetic agent (bevacizumab 7.5 mg/kg), she had severe irAE (IO-related adverse events) by hypothyroidism. Since treatment-related AEs are a big issue, the further discussion will be introduced in our next article.

Conclusion

In summary, this review underscores the possibility to offer RT-free multi-modality strategy in the management of patient with

LACC. Additionally, it also highlighted the evolving role of ICIs plus anti-angiogenetic agent in the treatment of advanced CC. Moreover, the patient's positive response to IO, pembrolizumab as an example, both as a primary and maintenance therapy, highlights the importance of integrating ICIs into treatment regimens for CC, especially in cases where conventional therapies, RT as an example, are insufficient. The sustained disease-free status of the patient over several years reinforces the potential of ICIs to significantly improve long-term outcomes in CC management.

Declaration of competing interest

Dr. Peng-Hui Wang and Dr. Szu-Ting Yang, editorial board members at Taiwanese Journal of Obstetrics and Gynecology, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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Original Article

Risk and protective factors for postpartum depressive symptoms among women in postpartum nursing center

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ABSTRACT

Objectives: In Taiwan, many women receive postpartum care at postpartum nursing centers for one month. However, limited research has examined the postpartum depressive symptoms in women residing in postpartum nursing center. The objectives of this study were to investigate the prevalence of postpartum depressive symptoms and to identify the risk factors and protective factors for postpartum depressive symptoms in postpartum nursing center.

Materials and methods: This was an observational study. Postpartum women who were over 20 years old and able to speak Mandarin Chinese or Taiwanese, and had delivered singleton, live infants at term were recruited between January 2020 and June 2020 from a postpartum nursing center in central Taiwan. A questionnaire including sociodemographic characteristics, the Edinburgh Postnatal Depression Scale, and a pain scale was administered at first week and last week in the postpartum nursing center.

Results: A total of 60 postpartum women participated in the study. The prevalence rates of postpartum depressive symptoms after admission and before discharge from a postpartum nursing center were 13% and 8%, respectively. The postpartum depressive symptoms and postpartum pain intensity (including perineum pain and postoperative pain after caesarean delivery) scores were significantly decreased after staying at the postpartum nursing center. The risk factors for postpartum depressive symptoms were previous abortion experience and postpartum pain, while the protective factors were having child care arrangements after return home and having 8–11 h of sleep per day.

Conclusions: There is a need for the early detection and management of postpartum depressive symptoms in postpartum nursing center.

Introduction

After childbirth, women may experience significant physical and psychological changes [1,2], which may take longer than six weeks to recover [3]. Among common postpartum symptoms, depressive symptoms, perineal pain and pain at abdominal incision have been reported as highly prevalent after vaginal delivery and caesarean delivery (3). The prevalence of postpartum depression (PPD) ranges from 10% to 19% worldwide [4–6] and 3.5%–63.3% in Asian countries [7]. In Taiwan, the estimated prevalence of PPD symptoms defined using a cut-off score of 13 on the Edinburgh Postnatal Depression Scale (EPDS) [8] was 17.3% before childbirth and 24.1% after childbirth [9]. The length of time for PPD recovery varies, with 8% of women may still have moderate depressive symptoms at 12 months postpartum [10]. A previous study examined the relationships between PPD prevalence and postpartum practices [11] and demonstrated that PPD occurred in a variety of countries despite a global variation in postpartum practices, with technocentric cultures (no formalized traditions or norms after 24–48 h monitoring immediately postpartum) being commonly practiced in the United States, Canada, the United Kingdom, Western Europe, New Zealand and Australia, and ethnokinship cultures (family and social support rituals maintained for 30–40 days postpartum) in Korean, Chinese, Japanese, Hmong, Mexican, African, Arabic, and Amish [11].

"Doing the month", "Zuo Yuezi", or postpartum confinement is a traditional ritual women practice after giving birth in Taiwan. Postpartum women may not be allowed to go outside, wash hair

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and body, drink cold water and take cold food (e.g., cabbage, turnips, etc.) for one month after childbirth [12,13]. While "doing the month" is perceived as supportive and protective of the physical recovery of postpartum women to restore balance of yin and yang, studies reported that some activities (e.g. going outside of their homes, average sleep of 6 h or less per night, never or rarely opened the windows, restriction on bathing or showering, squatting) are associated with higher risk of postpartum depression (PPD) [14,15]. In addition, prolonged rest with restricted activity during the postpartum confinement may increase the risk of venous thromboembolism [16]. Consumption of a traditional alcoholic chicken soup during 'doing-the-month' may have impact on lactation [17]. Furthermore, adherence to "doing the month" was negatively correlated with aerobic endurance [18].

The "doing the month" practice has recently been shifted from performing at home to a postpartum nursing centre (PNC) [19,20]. Previous studies have shown that 72%–78% of women received postpartum care at home and 20% at PNC [15,18]. An ethnographic study reported that postpartum women preferred carrying out "doing the month" at the PNC, which allowed them to rest properly, learn child care skills, avoid traditional hygiene practices, and make their own decision [19]. Services provided by PNCs may include but not limited to assessments of vital signs for new mothers and babies, promotion of sleep and rest for new mothers, nutrition management, nursing, and educational classes [19,20]. A recent study reported that practice of "doing-the-month" in PNC had beneficial effects on milk microbiota [21]. Huang et al. reported that staying at a postpartum care institution had an independent effect on EPDS score; women (n = 130) stayed at a postpartum care institution had lower depression scores compared with women (n = 122) who did not stay at a postpartum care institution [22]. Hung et al. also found that PNC has an important role in helping women to decrease postpartum stress and improve general health [23].

The risk and protective factors for PPD have been well documented [24–26]. The risk factors identified include poverty, antenatal depression, depressive history, psychiatric morbidity, maternal self-esteem, unwanted pregnancy, caesarean section, preference of infants' gender, preterm and low birth-weight infants, multiple births, negative birth experience, lack of social support, riboflavin consumption, vitamin D deficiency, violence and abuse, immigration status, gestational diabetes, obese and overweight, postpartum anaemia, postpartum sleep disruption and poor postpartum sleep, and traditional dietary pattern (Japanese, Indian, United Kingdom, and Brazilian dietary pattern) [7,9,27,28 29], as well as child care stress, life stress, prenatal anxiety, low marital satisfaction, history of depression, and difficulty infant temperament [30,31]. On the other hand, greater seafood consumption, healthy dietary patterns, multivitamin supplementation, fish and polyunsaturated fatty acid intake, higher concentrations of docosahexaenoic acid in mothers' milk, calcium, zinc, Vitamin D, selenium, the relationship with partner, skin-to-skin care, and self-confidence have been found to be protective factors for PPD [27,28].

Previous studies have demonstrated associations between PPD, pain, negative maternal physical and psychological health, mothering role and poor quality of life [32–34]. PPD may impact on the maternal–infant interactions, cognitive process, perceptions of women competence, and adherence to the recommended preventive health service schedules [33,35]. PPD is a great challenge for mothers [36] and may need to be considered as a major public health issue [37] due to the healthcare and societal economic costs associated with PPD [38–42].

The primary aim of this study was to investigate the prevalence of PPD symptoms among women in PNC. The secondary aims were to compare depressive symptoms and pain after admission and before discharge from the PNC and to identify the risk factors and protective factors for PPD symptoms in PNC. Given the increasing number of new mothers choosing to receive postpartum care in contemporary healthcare services, this research is important to demonstrate the prevalence and the factors associated with PPD symptoms to understand the need of postpartum women in postpartum centre and may provide a foundation for future research investigating the effects of different treatment options for PPD symptoms in such setting.

Methods

This observational study was conducted from January 2020 to June 2020 at a PNC in central Taiwan. Postpartum women were eligible for participation if they were over 20 years old and able to speak Mandarin Chinese or Taiwanese, and delivered singleton, live infants at term. The exclusion criteria were postpartum women with psychiatric disorders, newborn with physical deficiencies, preterm infants less than 35-week gestational age, and preterm infants with birth weight less than 2500 g. One hundred forty-six eligible postpartum women were invited to participate at their admission to the PNC. The informed consent was obtained from postpartum women who agreed to participate in the study. Participants were told that they could withdraw from the study at any time during the data collection. This study was approved by the Institutional Review Board of the Jen-Ai Hospital (No. 108-81).

Data were collected from participants using questionnaires administered at first week and last week in the PNC. Participants were asked to complete the questionnaires which included sociodemographic characteristics such as age, marital status, education level, religion, employment status, household income, parity, number of previous abortions, whether the pregnancy was planned, child care arrangements, newborn sex, newborn weight, low birth weight, labour complications, type of delivery, breastfeeding, sleep hours, length of stay in the PNC, EPDS, and a pain scale.

The EPDS was one of the most frequently used screening instruments of PPD symptoms [8]. The Chinese version of the EPDS was developed by Lee et al. in Hong Kong [43] and Heh and Tseng in Taiwan [44,45]. The EPDS is a 10-item self–report scale. It assesses depressive symptoms in the past week, including inability to laugh, inability to look forward with enjoyment to things, blaming oneself unnecessarily, feeling anxious or worried, feeling scared or panicky, inability to cope, having difficulty sleeping, feeling sad or miserable, feeling unhappy and crying, and intention to harm oneself. Each item is scored from 0 ("no, not at all") to 3 ("yes, quite often") according to the severity of symptoms with a total score of 30 points. In this study, the cut-off score of greater than or equal to 10 indicates that women might have depression [8,46]. Sensitivity and specificity of the Chinese version of the EPDS were reported as 82% and 86% respectively [43]. Internal consistency (Cronbach's α) coefficients of the EPDS ranged from 0.73 to 0.87 [43,44].

The Numeric Rating Scale (NRS) for pain was used to measure pain intensity [47,48]. The participants were asked to circle the number between 0 ("no pain at all") and 10 ("the worst pain imaginable") on a horizontal line that describes best to their postpartum pain intensity, including perineum pain or postoperative pain following Caesarean delivery [49,50]. High test-retest reliability has been tested in both literate (Pearson correlation coefficient = 0.96) and illiterate (Pearson correlation coefficient = 0.95) patients with rheumatoid arthritis [51].

All statistical analyses were conducted with SPSS Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to analyse the sociodemographic characteristics and prevalence of PPD symptoms among participants. All data were expressed as the

frequency (percentage) or mean ± standard deviation (SD). The paired-sample t-test was used to compare the means of EPDS score and pain intensity after admission and before discharge from the PNC. Multiple linear regression model was used for calculating the measures of association between risk factors and the occurrence of PPD symptoms. Cox proportional hazards regression model was performed to investigate the associations between sociodemographic factors and time-to-event outcomes (no PPD symptoms) in this study. Kaplan–Meier survival curve was conducted to estimate the proportion of participants having PPD symptoms. The event of interest was having no PPD symptoms, and the time of the event was censored for participants who were still having PPD symptoms at the end of stay in the PNC. A *p*-value of less than or equal to 0.05 was considered statistically significant.

Results

Between January 1 and June 10, 2020, a total of 146 women attended the PNC in central Taiwan. Among them, 15 women did not meet the inclusion criteria and 71 women refused to participate in the study. Therefore, a total of 60 postpartum women completed the structured questionnaires. Fig. 1 shows the recruitment of participants.

Among those who completed the questionnaires, the average age was 32.7 years (SD 3.9). Most were married (98.3%), and the majority had an education level of university or less (76.7 %). Moreover, 75% of the participants were career women, and 35% had a total household income ranged from NTD 90,000 to NTD 119,999 per month (Table 1).

Approximately 55% of participants were primiparous women, and a small proportion of postpartum women had abortion experience (6.7%). Most of the pregnancies were planned (80%) and the majority had child care arrangements after return home from the PNC (95%). The most common type of delivery was normal spontaneous delivery (55%), followed by Caesarean section (38.3%). Approximately, seventy-seven percent of the postpartum women initiated breastfeeding. The average length of stay in the PNC was 25.5 days (SD 5.0). The average sleep hours per day ranged from 4 to 7 h in the first week and 8–11 h in the last week of PNC (Table 1).

The means of EPDS scores in the first week and the last week of PNC were 6.5 (SD 3.4) and 4.5 (SD 3.5), respectively. Eight (13.3%) postpartum women reported having PPD symptoms (EPDS score $\geq$10) at first week and five (8.3%) at last week in the PNC. Among 60 postpartum women, the mean pain intensity in the first week and the last week of PNC were 3.0 (SD 1.6) and 0.1 (SD 0.3), respectively. Paired-sample t-tests showed significant changes in the PPD symptoms and pain intensity after staying at the PNC ($p < 0.001$) (Table 2).

After adjusting for all possible risk factors (i.e. age, marital status, education, religion, employment status, total household income per month, parity, planned pregnancy, newborn sex, newborn weight, labour complications, type of delivery, breastfeeding, and length of stay in the PNC), previous abortion experience and higher pain intensity score were significant risk factors of increasing PPD symptoms in PNC. On the other hand, having child care arrangements after return home and getting 8–11 h of sleep per day were protective factors of PPD symptoms (Table 3). The adjusted R^2 of multivariate linear regression model showed a predictive value of these factors of 56% for PPD symptoms.

The results of the multivariate Cox proportional hazards model are shown in Table 4. All sociodemographic variables were put into the model for adjustment. After adjusting for all possible factors, the factor associated with higher predicted probability of having no PPD symptoms before discharge from PNC as determined by the Cox model was caesarean section (hazard ratio = 2.04, $p = 0.04$). In addition, decreased pain intensity predicted having no PPD symptoms at last week in the PNC (hazard ratio = 0.07, $p = 0.01$).

Fig. 2 summarizes the estimated probability of having PPD symptoms in the PNC. Kaplan–Meier survival estimates revealed that the probability of having PPD symptoms started to decrease from 14 to 40 days in the PNC. As an example, the estimated probability of having PPD symptoms at 14 days after PNC admission was 96% and was reduced to 48% at 25 days after admission.

Discussion

This observational study identified a prevalence rate of 13% of PPD symptoms after admission and 8% before discharge from a PNC. These findings are similar to those reported in previous studies [5,22,27]. In addition to the decreased prevalence rate of PPD symptoms, the symptom severity was significantly reduced after attending a PNC. Our results indicate not only postpartum sleep hours, previous abortion experiences, child care arrangements, and pain were significantly associated with PPD symptoms in the PNC. The significant predictive variables for no PPD symptoms at discharge in this study were having caesarean section and low pain intensity before discharge from PNC.

The finding that less participants reported PPD symptoms before discharge from PNC compared to the first week in PNC and the probability of having PPD symptoms decreased from 14 to 40 days in the PNC is consistent with a previous study [52] which showed that the odds of having PPD symptoms were significantly

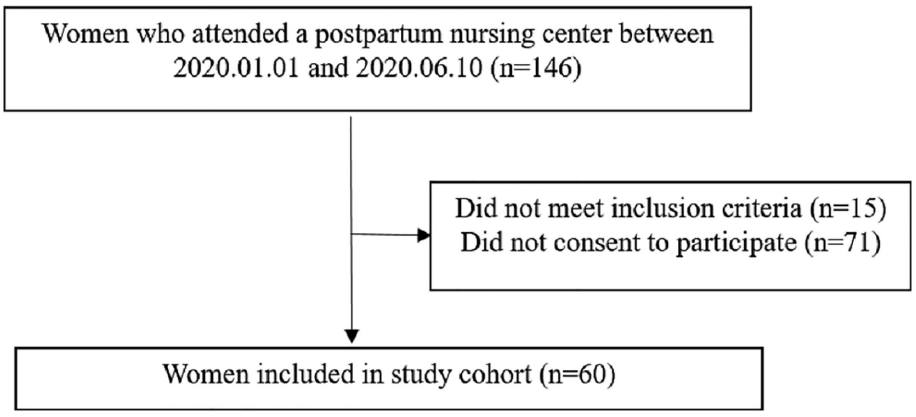

Fig. 1. Study flowchart.

Table 1
Socio-demographic characteristics of participants in the postpartum nursing center (n = 60).

Variables	N (%)
Age, years (mean ± SD)	32.70 ± 3.91
Marital status	
Married	59 (98.33)
Single	1 (1.67)
Education	
≤University	46 (76.67)
≥Graduate school	14 (23.33)
Religion	
No	33 (55.00)
Yes	27 (45.00)
Employment status	
No	15 (25.00)
Yes	45 (75.00)
Total household income per month	
<NT 60,000	14 (23.33)
NT 60,000 ≤ income < NT 90,000	17 (28.33)
NT 90,000 ≤ income < NT 120,000	21 (35.00)
≥NT 120,000	8 (13.33)
Parity	
Primiparous	33 (55.00)
Multiparous	27 (45.00)
Number of previous abortions	
0	56 (93.33)
≥1	4 (6.67)
This pregnancy was planned	
No	12 (20.00)
Yes	48 (80.00)
Arrangement for newborn back home	
No	3 (5.00)
Yes	57 (95.00)
Newborn sex	
Male	29 (48.30)
Female	31 (51.70)
Newborn weight, grams (mean ± SD)	3020.43 (310.99)
Low birth weight	
No	58 (96.70)
Yes	2 (3.30)
Labour complications	
No	55 (91.70)
Yes	5 (8.30)
Type of delivery	
Normal spontaneous delivery	33 (55.00)
Vacuum extraction delivery	4 (6.70)
Caesarean section	23 (38.30)
Breastfeeding	
No	14 (23.30)
Yes	46 (76.70)
Average sleep times per day in the first week of PNC, hours	
<4	9 (15.00)
4-7	37 (61.67)
8-11	13 (21.67)
≥12	1 (1.67)
Average sleep times per day in the last week of PNC, hours	
<4	3 (5.00)
4-7	18 (30.00)
8-11	36 (60.00)
≥12	3 (5.00)
Length of stay in the PNC, days (mean ± SD)	25.50 ± 5.09

NT: New Taiwan Dollar; PNC: Postpartum Nursing Center; SD: Standard Deviation.

lower among women who attended a PNC. The longitudinal study by Huang et al. which investigated the effect of stay in a postpartum care institution on postpartum depression reported that women who stayed at a postpartum care institution had lower PPD symptom scores compared to those who did not stay at a postpartum care institution [22]. Huang et al. also found that staying at a postpartum care institution was the only factor correlated with the PPD symptom score [22]. In Taiwan, the model of care provided in the PNC is similar to those in the hospital; several healthcare professionals including medical doctors, nurses and allied health

Table 2
The results of different paired-sample t-tests on the scores of Edinburgh Postnatal Depression Scale and pain intensity.

	First week (mean±SD)	Last week (mean±SD)	Paired difference			P-value
			Mean difference	95% CI of the difference		
				Lower	Upper	
EPDS score	6.52 ± 3.43	4.50 ± 3.45	−2.02	−2.84	−1.19	<0.001
Pain intensity	2.97 ± 1.61	0.07 ± 0.25	−2.90	−3.32	−2.48	<0.001

CI: Confidence Interval; EPDS: Edinburgh Postnatal Depression Scale; SD: Standard Deviation.

Table 3
Multiple linear regression model for postpartum depressive symptoms.

Variables	EPDS (last week)	
	B (95% CI)	*P*-value
Age, years	−0.15 (−0.36–0.05)	0.14
Marital status		
Married (reference)	–	
Single	−0.54 (−6.79–5.71)	0.86
Education		
≤University (reference)	–	
≥Graduate school	−0.69 (−2.43–1.05)	0.43
Religion		
No (reference)	–	
Yes	0.17 (−1.44–1.78)	0.83
Employment status		
No (reference)	–	
Yes	−1.46 (−3.19–0.28)	0.10
Total household income per month		
<NT 60,000 (reference)	–	
NT 60,000 ≤ income < NT 90,000	−0.04 (−2.10–2.02)	0.97
NT 90,000 ≤ income < NT 120,000	0.17 (−1.83–2.17)	0.87
≥NT 120,000	−0.48 (−3.12–2.15)	0.71
Parity		
Primiparous (reference)	–	
Multiparous	−0.58 (−2.23–1.08)	0.48
Number of previous abortions		
0 (reference)	–	
≥1	3.43 (0.49–6.91)	0.04
This pregnancy was planned		
No (reference)	–	
Yes	1.60 (−0.34–3.53)	0.10
Arrangement for newborn back home		
No (reference)	–	
Yes	−4.54 (−8.57–0.50)	0.03
Newborn sex		
Male (reference)	–	
Female	0.27 (−1.32–1.86)	0.73
Newborn weight, grams	0.000094 (−0.002–0.003)	0.94
Labour complications		
No (reference)	–	
Yes	0.09 (−3.18–3.35)	0.96
Type of delivery		
Normal spontaneous delivery (reference)	–	
Vacuum extraction delivery	−2.49 (−5.94–0.97)	0.15
Caesarean section	0.54 (−0.91–2.00)	0.45
Breastfeeding		
No (reference)	–	
Yes	−0.72 (−2.79–1.35)	0.48
Average sleep times per day in the last week of PNC, hours		
<4 (reference)	–	
4-7	−3.36 (−7.34–0.62)	0.10
8-11	−5.24 (−9.00–1.48)	0.01
≥12	−4.12 (−8.93–0.69)	0.09
Pain score (last week in the PNC)	6.70 (3.63–9.76)	<0.001
Length of stay in the PNC, days	−0.03 (−0.18–0.12)	0.70

CI: Confidence Interval; EPDS: Edinburgh Postnatal Depression Scale; NT: New Taiwan Dollar; PNC: Postpartum Nursing Center.

Table 4
The multivariate Cox proportional hazards model of having no postpartum depressive symptoms.

Variables	Adjusted hazard ratio (95% CI)	*P*-value
Age, years	1.06 (0.97–1.17)	0.18
Marital status		
Married (reference)	1.00	
Single	0.18 (0.01–3.18)	0.24
Education		
≤University (reference)	1.00	
≥Graduate school	1.51 (0.67–3.40)	0.32
Religion		
No (reference)	1.00	
Yes	0.80 (0.39–1.65)	0.54
Employment status		
No (reference)	1.00	
Yes	2.30 (0.88–5.97)	0.09
Total household income per month		
<NT 60,000 (reference)	1.00	
NT 60,000 ≤ income < NT 90,000	1.99 (0.72–5.50)	0.19
NT 90,000 ≤ income < NT 120,000	1.05 (0.41–2.71)	0.92
≥NT 120,000	0.93 (0.27–3.14)	0.90
Parity		
Primiparous (reference)	1.00	
Multiparous	0.65 (0.29–1.43)	0.28
Number of previous abortions		
0 (reference)	1.00	
≥1	0.49 (0.08–3.07)	0.44
This pregnancy was planned		
No (reference)	1.00	
Yes	0.75 (0.27–2.06)	0.58
Arrangement for newborn back home		
No (reference)	1.00	
Yes	4.34 (0.49–8.81)	0.19
Newborn sex		
Male (reference)	1.00	
Female	0.56 (0.26–1.21)	0.14
Newborn weight, grams	1.0 (0.99–1.00)	0.70
Labour complications		
No (reference)	1.00	
Yes	0.79 (0.13–4.63)	0.79
Type of delivery		
Normal spontaneous delivery (reference)	1.00	
Vacuum extraction delivery	2.95 (0.49–17.93)	0.24
Caesarean section	2.04 (1.01–4.14)	0.04
Breastfeeding		
No (reference)	1.00	
Yes	0.65 (0.26–1.67)	0.37
Average sleep times per day in the last week of PNC, hours		
<4 (reference)		
4-7	0.79 (0.09–6.60)	0.83
8-11	0.90 (0.13–6.35)	0.92
≥12	0.78 (0.08–7.87)	0.83
Pain intensity (last week in the PNC)	0.07 (0.01–0.58)	0.01

CI: Confidence Interval; NT: New Taiwan Dollar; PNC: Postpartum Nursing Center.

professionals are involved to provide holistic care to meet the individual needs of mother and baby, to promote health recovery and to educate mothering skills [20]. While several studies reported the beneficial effects of exercise-based interventions [53] and psychological interventions [54] for PPD symptoms, only one longitudinal cohort study examined trends of PPD symptoms at first, second and third trimesters and at 6 weeks postpartum [22] and compared the PPD symptom scores between those stayed and not stayed at a postpartum care institution. Future randomized controlled trial should investigate the long-term effects of a PNC program on PPD symptoms.

In contrary to previous studies [55,56] which reported that abortion does not increase women's risk of depression at postpartum period, we found that previous abortion experience was a significant risk factor for PPD symptoms when controlling for other variables. However, it should be noted that the number of women who reported having abortion experience was low (6.7%) in our study. A study by Giannandrea et al. [57] showed that women with a history of pregnancy loss were at increased risk for postpartum psychiatric disorders including depression. These inconsistent findings indicate the need to explore other psychological variables (e.g. anxiety and depression during pregnancy [58]) associated with abortion and PPD symptoms in this population with large sample size.

In accordance with previous research [59,60], we found that sleep 8–11 h/day acts as a protective factor against PPD symptoms. Insufficient sleep during early postpartum had been shown to be associated with accelerated biological aging, fatigue and breastfeeding [61,62] and the importance of sleep for the prevention of PPD was highlighted in recent studies [62,63]. Therefore, women were encouraged to have more sleep when they stayed at the PNC; this was shown in our study with increased average sleep hours per day from the first week to last week of PNC (mean increase of 4 h per day). Furthermore, we found a significant association between child care arrangements and PPD symptoms. Previous studies reported that women who had worries about child care were at risk of developing PPD [64] and that problems regarding child care arrangements may be indicators of long-term high levels of depressive symptoms among mothers [65]. Furthermore, mothers' perceptions of good care options were associated with reduced maternal depressive symptoms, which was possibly attributable to the feeling of flexibility in child care arrangement [66]. As to date, no study has examined the relationships between child care arrangement after discharge from PNC with PPD symptoms, it is not possible to compare our finding with other studies. However, a previous study has shown significant inverse correlations between postpartum depressive symptoms and readiness to care for family, infant, and self [67]. Future research could focus more in details on the relationships between post-PNC discharge child care plan, self-efficacy and PPD symptoms.

Most interestingly, we found that employment, caesarean section and low pain intensity were significant predictors of no PPD symptoms before discharge from PNC. While our findings confirm with previous studies that severity of postpartum pain and employment were linked to PPD symptoms [32,68–71], it is surprising that caesarean section was found to be a predictor of no PPD symptoms in this study. A meta-analysis found significant associations between emergency caesarean section and increased risk of PPD and not between elective caesarean section and PPD risk [72]. As the information about the type of caesarean section (i.e. elective or emergency) was not collected in our study, it is not possible to know the proportion of each and their impact on PPD symptoms. Furthermore, a longitudinal study reported that several mediators were present in the associations between mode of delivery and risk of PPD [73]. Future research studies may investigate the predictors of no PPD symptoms in the PNC setting by considering possible confounders (e.g. history of depression and fear of delivery [73], etc.) in the analysis.

Limitations of the study

Several limitations of this study should be taken into consideration. The convenience sampling method may limit the generalizability of our result to all postpartum women in the PNC, and the response rate of 41% (60/146) may give rise to potential non-response bias. However, the distribution of age, marital status, type of delivery, newborn sex and lengths of stay were similar between those completed the questionnaire and those who did not (data not shown). Therefore, the potential underestimation and issue of representativeness might not be significant. Furthermore,

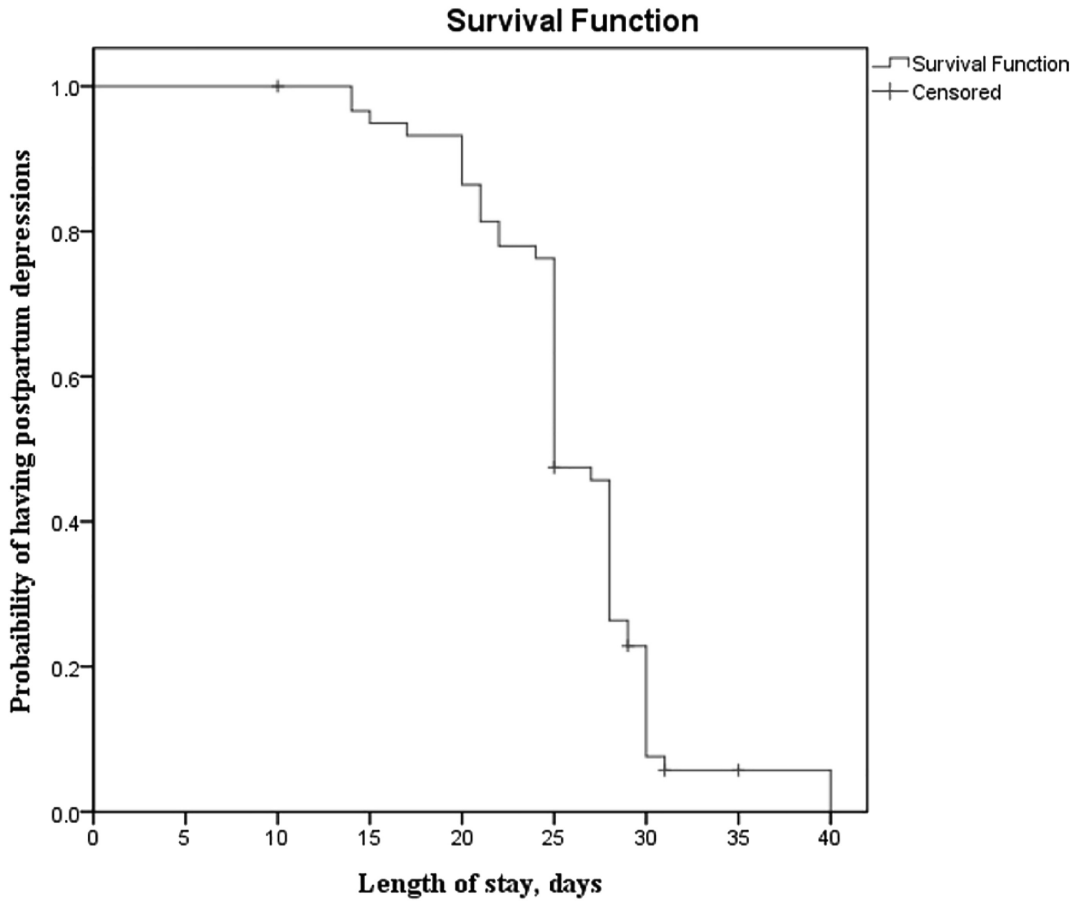

Fig. 2. Probability of having postpartum depressive symptoms.

the nature of an observational study design limits our ability to determine causal relationships between staying in the PNC and PPD symptoms. Other limitations include small sample size, lack of other potential predictors in the questionnaire (e.g. complications during pregnancy, stressful life events, anxiety, incontinence [74], frequency of sleep disturbance [75], neonatal outcomes [i.e. preterm and illness] [76], and self-consciousness, etc. [25,26]), use of self-report questionnaires, and being a single-centre study. While the EPDS and NRS have been extensively used in similar research, they have been criticized for their potential limitations (e.g. symptoms measured by the EPDS are highly transient throughout the perinatal period) [77], and NRS only has modest accuracy for identifying patients with clinically important pain) [78]. Future studies should consider including more comprehensive measures of depression (e.g. centre for epidemiologic studies of depression instrument and Beck Depression Inventory) [79] and pain (e.g. Brief Pain Inventory and McGill Pain Questionnaire) [80].

Conclusions

The findings of this study suggest that PPD symptoms was prevalent in women who attended the PNC and was associated with previous abortion experience and postpartum pain, while having child care arrangements after return home and 8–11 h of sleep per day were protective. Postpartum women who had caesarean section and low pain intensity were more likely to have no PPD symptoms before discharge from the PNC. This study also found that PPD symptoms could be decreased depending on the duration of stay in PNC. However, given the limitations of this study, our results should be interpreted with caution. The identification of risk and protective factors associated with PPD symptoms and predictors of no PPD symptoms before discharge from the PNC may allow for early identification/screening and intervention of PPD symptoms when women are admitted to the PNC. Future research is needed to confirm the findings of our study and to establish the effectiveness of a PNC program on PPD symptoms in this population.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Original Article

The relationship between serum vitamin D, testosterone, and oxidative stress levels in women with sexual dysfunction: A case-controlled study

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ABSTRACT

Objective: Female sexual dysfunction (FSD) is highly prevalent and can result from hypovitaminosis D. Besides the role of vitamin D in normal bone development, studies showed it could reduce oxidative stress and lipid peroxidation. This prospective study aims to evaluate the relationship between serum vitamin D, testosterone, and oxidative stress levels in women with FSD.

Materials and methods: In this cross-sectional study, a total of 40 women with FSD (age range: 18–45 years) were randomly assigned into two groups of intervention and control. In the intervention group, patients received vitamin D 300,000 IU intramuscularly (IM) and then 50,000 IU orally once a week for four weeks. We measured the serum vitamin D, testosterone, and oxidative stress levels, as well as the Female Sexual Function Index (FSFI) at baseline and monthly for three months.

Results: Serum testosterone levels significantly increased in the intervention group at the end of the third month ($P = 0.014$). Also, FSFI scores significantly improved ($P < 0.01$) in the intervention group compared to the control group. While there was positive a correlation between serum vitamin D levels with glutathione, total antioxidant capacity (TAC), testosterone, and FSFI score, there was a negative correlation between serum vitamin D levels with malondialdehyde (MDA), protein carbonyl, and nitric oxide.

Conclusion: We witnessed that women with FSD had low serum vitamin D levels. So, modifying serum vitamin D levels must be considered as a treatment option. Moreover, vitamin D supplementation improved testosterone, serum oxidative stress, and sexual function.

Introduction

Female sexual dysfunction (FSD) is a highly prevalent condition that can be categorized into three primary domains based on the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): female sexual interest/arousal disorder (FSIAD), genito-pelvic pain/penetration disorder (GPPD), and female orgasmic disorder (FOD) [1]. These sexual concerns are considered as dysfunctions only if they lead to distress [2]. The prevalence of FSD has been reported in the range of 30–50%, which is likely influenced by social stigma [3].

The etiology of FSD includes biological, psychological, socio-cultural, and relational factors [4]. Several chronic illnesses (e.g., vascular disease, diabetes mellitus, neurologic disease, and malignancies), as well as psychoactive substance or medication as biological factors, can impact sexual health directly or indirectly [5]. Other biological factors, pregnancy, lactation, and aging are associated with a decline in sexual responsiveness and libido. To evaluate the multifactorial nature of FSD, multidisciplinary approaches, as well as pharmacological and nonpharmacological strategies have been used [6,7].

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The role of 25-Hydroxyvitamin D3 (25[OH]D), cholecalciferol, is well understood in normal bone development and calcium and phosphorus balance. Furthermore, 1,25-dihydroxycholecalciferol (1,25[OH]2D) (calcitriol), the hormonally active form of vitamin D3, which is produced by the effect of 1-α-hydroxylase on 25-OH VD, showed pleiotropic effects in different tissues and organs [8]. These effects include regulation of cellular growth and differentiation, glucose metabolism, and immune function through specific receptors in the brain, muscles, chest, bones, and gastrointestinal tract [9–12]. It has been reported that 25[OH]D insufficiency could result in cancer, cardiovascular diseases, insulin resistance, diabetes, autoimmune diseases (such as rheumatoid arthritis, systemic lupus erythematosus, and chronic pain), infectious diseases, psychological disorders (such as depression) cognitive deficits, and mortality [13–16]. Also, different studies showed the predisposing effect of low 25[OH]D level in the development of endometriosis, polycystic ovary syndrome, infertility, breast and ovarian cancer, as well as gestational diabetes mellitus and preeclampsia [17]. These problems are due to the presence of 1,25(OH)2D receptors (vitamin D receptors, or VDRs) in many other tissues than bone [18,19]. Also, vitamin D has a neuroprotective role, and one of its mechanisms is nerve damage reduction caused by hydrogen peroxide (H2O2) [20]. A recent study revealed that vitamin D supplementation can reduce oxidative stress and lipid peroxidation by increasing total antioxidant capacity (TAC) and glutathione and decreasing malondialdehyde (MDA) [21]. Calcitriol also has beneficial effects in upregulating the expression of some anti-inflammatory cytokines and antioxidants [22]. In addition, it can regulate the reactive oxygen species (ROS) level and mitochondrial-based expression of antioxidants through its anti-inflammatory effects and cell-signaling pathways [23,24]. Therefore, it can protect tissues from toxins, disorders associated with micronutrient deficiency, and microorganisms-induced stresses [25].

Nowadays, the rate of vitamin D testing has increased [26]. According to recent large observational studies, approximately 40% of Europeans are vitamin D deficient, and about 13% are severely deficient [27]. Iran is no exception, where some recent systematic review and meta-analysis studies showed the prevalence of vitamin D deficiency as %57. Besides, the gender-based analysis revealed the 64% prevalence of vitamin D deficiency in Iranian women [28]. Krysiak et al. reported a correlation between vitamin D deficiency and insufficiency with FSD and depressive symptoms [29]. Also, a case–control study demonstrated the relationship between low levels of vitamin D and FSD based on the Female Sexual Function Index (FSFI) questionnaire [30]. Another study in this regard indicated the beneficial effects of vitamin D supplementation on female sexual functioning and mood in women with low vitamin D levels [31].

Considering the increasing incidence of vitamin D deficiency in the Iranian population, the increasing prevalence of FSD, as well as the relationship between oxidative stress with low vitamin D levels, the present study aimed to evaluate the relationship between serum vitamin D, testosterone, and oxidative stress levels in women with FSD.

Materials and methods

Research design and ethics

This case–control study was approved by the Medical Ethics Committee of the Research Deputy of Mazandaran University of Medical Sciences, Sari, Iran (code: IR.MAZUMS.REC.1396.2218). We included all women diagnosed with sexual dysfunction referred to Bagheban clinic (a tertiary medical center) in Sari, Iran from October 2018 to March 2019.

Sampling and initial assessment

In this cross-sectional study, we included a total of 40 women with FSD (age range: 18–45 years). All patients were diagnosed with sexual dysfunction by a gynecologist and signed an informed consent prior to inclusion in the study. The exclusion criteria were as follows: comorbidities causing sexual dysfunction, including depression, anxiety, substance use, Parkinson's disease, and epilepsy; history of drug use with sexual adverse effects such as selective serotonin reuptake inhibitors, antiandrogens, opioids, cimetidine, spironolactone, thiazides, and ketoconazole; and alcohol consumption.

The severity of sexual dysfunction was assessed based on the interview and FSFI questionnaire at baseline. The FSFI consists of 19 items in six areas and yields domain scores in sexual desire, arousal, lubrication, orgasm, satisfaction, and pain for assessing sexual function over the past four weeks; it was developed as a self-report instrument to evaluate key dimensions of sexual function in women [32]. The serum concentration of 25OHD3 was evaluated by radioimmunoassay.

The subjects were randomly assigned into two groups of intervention and control. Patients in control group received only local conservative routine treatment for vitamin D deficiency, 50.000 international unit (IU) of vitamin D orally once a month. Meanwhile, in the intervention group, patients who were vitamin D insufficient (<30 ng/dL) or deficient (<20 ng/dL) received vitamin D 300.000 IU intramuscularly and then 50.000 IU orally once a week for four doses and then monthly. The oral usage form of vitamin D was pearl (soft gelatin capsules containing 50.000 IU). Oral vitamin D was obtained from Daana Pharma Co. (Iran) and its injectable dosage form was obtained from Darou Pakhsh Co. (Iran). All patients were reevaluated monthly after the initiation of vitamin D administration for three months. Patients' characteristics, including age, weight, serum concentration of 25OHD3, testosterone, estrogen, prolactin, TSH, and FSH were recorded at baseline. Also, the serum levels of 25OHD3, testosterone and FSFI score were assessed at the end of the first, second, and third months of the study [33].

Measurement of oxidative stress parameters

Data normalization: Determination of serum protein level was performed by Bradford method. The activity can be normalized in terms of serum protein for each of the parameters.

Measurement of serum carbonyl protein

The serum carbonyl protein was measured using the 2,4-dinitrophenyl-hydrazine (DNPH) reagent. After measuring the serum carbonyl protein, 500 μL of trichloroacetic acid (20% w/v) was added to 250 μg of serum and stored at 4 °C for 15 min. The precipitated proteins were then centrifuged at 6500×*g* for 10 min and the supernatant was discarded. The bottom precipitate layer was completely dispersed in 500 μL of 0.1 M NaOH, and 500 μL of 10 mM DNPH dissolved in 2 M HCl was added to the samples. A blank was also prepared by adding 500 μL of 2 M HCl without DNPH to the protein sample. The samples were then incubated at room temperature for 30 min away from light, and then 500 μL of trichloroacetic acid (20% w/v) was added. The supernatant was discarded after collection of protein precipitate by centrifugation at 6500×*g* for 10 min. The bottom layer was combined with 1 mL of a 1:1 (v/v) mixture of ethanol and ethyl acetate, and centrifuged again at 6500×*g* for 10 min to remove the supernatant [34]. The amount of carbonyl protein was measured by absorption at 365 nm with an absorption coefficient of 22,000 M^{-1} cm^{-1}, expressed as mmol of DNPH per milligram of protein [34].

Measurement of lipid peroxidation

The amount of lipid peroxidation was measured based on the thiobarbituric acid method. Out of 0.1 mL of TBA reagent including 0.5 normal HCl, 15% TCA and 0.3% TBA was added to 0.2 mL of serum, mixed well, then incubated in a hot water bath for 30 min. After cooling, 0.2 mL of n-butanol was added, shaken well, and centrifuged at 3500 rpm for 10 min [35]. The n-butanol layer was isolated for measurement at 532 nm and the amount of TBARs was calculated using the standard curve [36].

Measurement of glutathione

Amount of 0.25 mL of 20% trichloroacetic acid was added to 1 mL of diluted serum and centrifuged at 1000×*g* for 20 min after vortexing. Two mL of 0.3 M hydrogen phosphate (50) and 0.5 mL of 0.4% DTNB were added to 1 mL of the clear supernatant and then vortexed and incubated for 15 min to obtain a complete reaction [37]. Absorption was measured at 412 nm and glutathione concentration was obtained using the standard glutathione curve in nmol/mL [2].

Measurement of nitric oxide (NO)

The measurement of NO is difficult due to its short half-life. Thus, the serum levels of its stable metabolites (nitrite and nitrate) were assessed, which provides a reliable estimate of NO in vivo. The amount of nitrite in the serum or cell culture supernatant was determined by the grease reaction. During the first stage of the mentioned reaction, the nitrite reacts with sulfanilic acid to produce diazonium ions. In the second stage of this reaction, the ion pairs with the N- (1-naphthyl) ethylene diamine compound to form azo derivatives in pink. Laboratory steps were performed according to the instructions of Sibistephan company's kit.

Total antioxidant capacity (TAC)

The serum TAC was measured using the FRAP (ferric reducing the ability of plasma) method.

Statistical analysis

All statistical analysis was performed using SPSS v.21 software. An independent sample t-test or Mann–Whitney U-test was used to compare the mean of the parametric or nonparametric values between the two groups. P-value <0.05 was considered significant.

Results

Out of a total of 78 patients who met the inclusion criteria, 40 women accepted to be enrolled in this analytical cross-sectional study (20 with FSD and 20 in the control group). At baseline, the mean age of patients in the intervention and control groups was 32.8 ± 6.97 and 34.5 ± 7.81, respectively (P = 0.47). No statistically significant differences were observed in the averages of age and body mass index (BMI) between the two groups at the beginning of the study (Table 1). Also, there were no significant differences between the two groups in case of testosterone, vitamin D plasma levels, and sexual dysfunction parameters using FSFI questionnaire at the baseline (Table 1).

As shown in Table 2, there was a significant difference between intervention and control groups in serum vitamin D concentration at the end of first, second, and third months of the study (P < 0.01). Furthermore, serum testosterone levels significantly increased in the intervention group during the study and at the end of the third month (P = 0.014). While all the sexual areas (desire, arousal, lubrication, orgasm, satisfaction, and pain) partially improved, the FSFI scores significantly improved (P < 0.01) among the patients in the intervention group during the three months of the study (Table 3).

The mean changes in serum levels of oxidative stress, vitamin D, and testosterone were shown in Table 4. There were significant differences in the serum levels of intervention and control groups (P < 0.01).

The correlation between the mean serum vitamin D levels and the mean of oxidative stress and testosterone were shown in Table 5. While an increase in the vitamin D level raised the levels of glutathione, TAC, testosterone, and FSFI score, there was a decrease in serum MDA, protein carbonyl, and NO levels.

Discussion

According to the results of this study, the mean serum levels of vitamin D in both control and intervention groups were lower than normal at baseline. This finding indicated that vitamin D deficiency was very common in the study region, which was similar to other parts of Iran [28]. Also, sexual dysfunction was significantly related to the serum levels of vitamin D and oxidative stress parameters. The lower levels of vitamin D were associated with a decrease in the FSFI score and more severe disorder. These results are in line with a study that reported a low serum vitamin D level was associated with impaired sexual functioning and the degree of FSD directly depended on the severity of vitamin D deficiency [29]. In the mentioned study, women with vitamin D deficiency had worse scores in three domains of FSFI, including orgasm, desire, and satisfaction, which is consistent with our findings. Interestingly, the researchers noticed that lower serum vitamin D levels negatively affected the women's mood, Beck Depression Inventory II (BDI-II) score, as well as depressive symptoms [29]. In a recent study,

Table 1
The baseline characteristics of participants.

	Intervention (20)	Control (20)	P-value
Age (years) Mean ± SD	32.8 ± 6.97	34.5 ± 7.81	0.47
Body Mass Index (kg/m^2) Mean ± SD	25.75 ± 2.63	25.55 ± 1.85	0.78
Estrogen (mIU/mL) Mean ± SD	97.40 ± 63.22	107.96 ± 72.89	0.62
Progesterone (mIU/mL) Mean ± SD	10.79 ± 6.66	7.36 ± 7.30	0.13
Testosterone (mIU/mL) Mean ± SD	0.16 ± 0.10	0.17 ± 0.11	0.78
FSH (mIU/mL) Mean ± SD	6.46 ± 5.85	6.72 ± 4.70	0.87
LH (mIU/mL) Mean ± SD	4.43 ± 3.63	5.79 ± 5.58	0.36
TSH (mIU/mL) Mean ± SD	1.43 ± 0.84	2.00 ± 1.64	0.17
FT4 (mIU/mL) Mean ± SD	16.15 ± 1.56	15.91 ± 2.48	0.71
Plasma vitamin D level (ng/dL) Mean ± SD	18.85 ± 3.04	17.70 ± 3.37	0.26
FSFI score Mean ± SD	16.10 ± 1.48	15.52 ± 1.26	0.18

FSFI: Female Sexual Function Index.
P-value less than 0.05 was considered statistically significant.

Table 2
Average serum levels of vitamin D and testosterone concentrations at baseline and at the end of first, second, and third month of the study in the intervention and control groups.

		At baseline (mean ± SD)	At the end of first month (mean ± SD)	At the end of second month (mean ± SD)	At the end of third month (mean ± SD)
Vitamin D level (ng/mL)	Intervention (n = 20)	18.9 ± 3.04	23.7 ± 2.6	26.49 ± 2	28.9 ± 2.7
	Control (n = 20)	17.7 ± 3.37	19.4 ± 3.5	18.9 ± 3.9	19.1 ± 3.8
P-value		0.26	<0.01	<0.01	<0.01
Testosterone level (ng/mL)	Intervention (n = 20)	0.16 ± 0.11	0.19 ± 0.11	0.24 ± 0.12	0.31 ± 0.11
	Control (n = 20)	0.17 ± 0.12	0.16 ± 0.08	0.19 ± 0.09	0.22 ± 0.08
P-value		0.78	0.27	0.19	0.014

Table 3
Total sexual dysfunction score at baseline and during 3 months of the study in the intervention and control group.

	Group	At the baseline (mean ± SD)	At the end of 1st month (mean ± SD)	At the end of 2nd month (mean ± SD)	At the end of 3rd month (mean ± SD)
Total sexual dysfunction score	Intervention	16.1 ± 1.5	20.94 ± 1.9	23.35 ± 2.2	25.77 ± 2.4
	Control	15.5 ± 1.3	18.62 ± 1.5	20.49 ± 1.7	21.11 ± 1.7
	P-value	0.58	0.09	<0.01	<0.01

Krysiaket al. showed that sexual desire, orgasm, and sexual satisfaction increased in women with vitamin D deficiency; also, sexual desire was improved in women with vitamin D insufficiency after vitamin D supplementation. In addition, we witnessed a positive correlation between BDI-II score and depressive symptoms with vitamin D deficiency and vitamin D insufficiency [31]. The wide distribution of vitamin D receptors in different parts of brain, including the thalamus, hypothalamus prefrontal cortex, and hippocampus, may play a role in the pathogenesis of depression [38]. The results of this study also confirm the findings of our study on the relationship between FSD and vitamin D status.

A significant improvement in glutathione and FRAP status and reduction in MDA, carbonyl protein, and NO serum concentrations were observed with the administration of vitamin D in the intervention group compared to the control group. The exact mechanism by which vitamin D may affect oxidant/antioxidant balance is unclear. Several studies have shown that vitamin D may reduce the lipid peroxidation, which ultimately leads to increased glutathione levels and TAC [39,40]. A study on pregnant women showed that TAC and total glutathione concentrations increased in patients who received vitamin D supplement compared to the placebo group. Other beneficial effects of vitamin D in the mentioned study were as follows: reduction in systolic and diastolic blood pressure; reduction in the concentrations of serum high-sensitivity C-reactive protein, fasting plasma glucose, and insulin; and increased quantitative insulin sensitivity check index (QUICKI) score, serum vitamin D, and calcium levels [41].

Several other studies demonstrated the relationship between low serum level of vitamin D and increased oxidative stress biomarkers [42–44]. The thiol groups of proteins are one of the most important antioxidants and main reducing agents in both the cells and extracellular tissue. The amount of thiol groups in proteins and total thiols in the body indicates the antioxidant status of the body. Regarding the direct relationship between the increasing productions of free radicals and reducing the amount of thiol groups, measuring the amount of total thiol can be useful in assessing the level of oxidative stress. Glutathione depletion may lead to increased lipid peroxidation, proteins, and DNA damage, and decreased resistance to oxidative damage. Free radicals' reaction with phospholipid unsaturated fatty acid chains can result in double bond breakage, peroxidation, and destruction of lipid membranes. MDA is one of the latest lipid peroxidation products in cell membranes, which is used as a marker of lipid oxidation.

Oxidative stress makes proteins susceptible to proteolysis. Carbonyl proteins are one of the most important biomarkers of protein oxidation and are produced by direct oxidation of amino acids or by secondary reaction with primary products of carbohydrate and lipids oxidation. These oxidative effects change the structure and function of proteins.

In general, we witnessed that an increase in oxidative stress decreased the antioxidants levels in people with sexual disorders. A study showed that vitamin D may stabilize plasma membranes against lipid peroxidation and increase the expression of the antioxidant system through nuclear receptors [45]. Also, another study showed that vitamin D could increase the production of NO in the endothelium, especially in people with vitamin D deficiency [46].

The main limitation of this study was the lack of expression of sexual disorders by patients for cultural reasons. A significant number of subjects tried not to show the disorder very clearly and

Table 4
The mean changes in oxidative stress parameters from the baseline to the end of the study.

Parameter	Group		P-value
	Intervention	Control	
Glutathione (nM)	0.12 ± 0.06	0.05 ± 0.04	<0.01
Malondialdehyde (mM)	−0.13 ± 0.12	−0.04 ± 0.06	0.014
Protein carbonyl (mM)	−0.07 ± 0.06	−0.02 ± 0.04	<0.01
Nitric oxide (μmol/mL)	−0.12 ± 0.09	−0.02 ± 0.9	<0.01
Total antioxidant capacity (μmol $FeSO_4$/L)	0.15 ± 0.12	−0.016 ± 0.05	<0.01
Vitamin D	10.1 ± 2.2	1.4 ± 2.4	<0.01
Testosterone	0.15 ± 0.12	0.05 ± 0.0.9	0.005
FSFI score	9.7 ± 1.9	5.6 ± 1.5	<0.01

FSFI: Female Sexual Function Index.

Table 5
The correlation between serum vitamin D with testosterone, stress oxidative, and FSFI score.

First parameter	Second parameter	r	P-value
Vitamin D	Glutathione	0.62	<0.001
	Malondialdehyde	−0.38	0.016
	Protein carbonyl	−0.32	0.036
	Nitric oxide	−0.35	0.029
	Total antioxidant capacity	0.57	<0.001
Vitamin D	Testosterone	0.33	0.038
Vitamin D	FSFI score	0.85	<0.001
Testosterone	FSFI score	0.415	0.008

FSFI: Female Sexual Function Index.

were reluctant to enter the study. Therefore, they were excluded from the study.

In conclusion, this study showed that low serum vitamin D levels were prevalent in women with sexual dysfunction. So, modification of serum vitamin D levels must be considered as a successful treatment option. In addition, vitamin D supplementation improved serum levels of testosterone, oxidative stress, and sexual function in women.

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Conflicts of interest

The authors declared no conflict of interest.

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Original Article

Prognostic factors and survival of endometrial cancer: An 11-year retrospective cohort study in southern Taiwan

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ABSTRACT

Objective: Endometrial cancer (EC) is the most common gynecological malignancy in high-income countries. In Taiwan, the incidence of EC increased from 1.69 in 1980 to 11.36 per 100,000 women/year in 2010. Therefore, we aimed to study the prognostic factors and survival of patients with EC in southern Taiwan.

Materials and methods: This study included patients with EC who underwent hysterectomy-based surgery at our hospital between 2010 and 2020. The primary outcome was 5-year progression-free survival (PFS) and overall survival (OS) of patients diagnosed with EC. The secondary outcome was the prognostic factors associated with 5-year PFS and OS in patients with EC. We used the chi-square test to assess categorical variables and the independent t-test to assess continuous variables. The Kaplan–Meier method was used to estimate survival outcomes. Cox regression analysis was conducted to examine the factors associated with PFS and OS.

Results: A total of 133 patients were enrolled in this study. The mean age of the patients was 56.5 ± 10.71 years. The mean body mass index was 26.4 ± 5.21 kg/m^2. The 5-year PFS and OS were 90.3% and 94.53%, respectively. In terms of PFS, endometrioid histology was linked to more favorable outcomes (hazard ratio [HR] = 0.02, 95% confidence interval [CI]:0.001–0.59), while lymph-vascular space invasion (LVSI) was associated with adverse results (HR = 9.11, 95% CI: 1.07–77.44). Initial analyses revealed no significant correlations between OS and various factors, including age, BMI, parity, DM, hypertension, age at last birth, and tumor grade. However, univariate analysis found grade 3 tumor differentiation, LVSI, and lymph node invasion associated with poorer OS. Laparoscopy was associated with better OS. Nevertheless, subsequent multivariate analysis did not reveal any factor significantly associated with OS. Most patients with EC (76.69%) underwent laparoscopic surgery.

Conclusion: In conclusion, endometrioid histology was linked to more favorable PFS, while LVSI was related to adverse PFS. Our study did not identify any factors associated with OS. Two-thirds of the patients underwent minimally invasive surgery.

Introduction

Endometrial cancer (EC) is the most common gynecological malignancy in high-income countries, with more than 40,000 newly diagnosed cases in 2020 worldwide [1]. The prevalence of EC in the United States is 25.7/100,000 per year, and its incidence has been rising rapidly, particularly in Asian countries such as Japan and Singapore [2]. In Taiwan, the incidence of EC increased from 1.69 per 100,000 women/year in 1980 to 11.36 per 100,000 women/year in 2010 [3]. Several factors have contributed to this trend. One possible reason could be the decreased fertility rate resulting from socioeconomic transition, which is a risk factor for EC [4]. Another possible reason could be increased body weight and physical inactivity in younger generations [5].

EC usually presents with postmenopausal vaginal bleeding in approximately 90% of patients [6]. Therefore, early detection of EC is often possible [1]. The gold-standard treatment for EC is a

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surgical approach that includes total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy [7]. Laparoscopic surgery has become a popular treatment option for patients with EC [8]. Patients with advanced-stage EC or known risk factors for recurrence will receive postoperative adjuvant radiotherapy or chemotherapy [9].

Previous studies have identified several prognostic factors of EC. It has long been established that multiple histological findings, including myometrial invasion, cervical involvement, uterine serosal involvement, and lymph-vascular space invasion (LVSI), are crucial prognostic factors [10]. In addition to pathological staging, clinical factors such as race, body mass index (BMI), age, and certain medical conditions such as diabetes mellitus (DM) are considered prognostic factors for EC [11,12].

Although the disease is highly curable at an early stage with a 5-year overall survival of up to 80%, the 5-year overall survival can be as low as 20% in patients with late-stage endometrial cancer [13]. The mean time to recurrence is approximately 22.5 months, with age, International Federation of Gynecology and Obstetrics (FIGO) stage, and initial treatment as independent risk factors for recurrence [11,14,15]. Therefore, we need to determine the important prognostic factors affecting the survival of patients with EC and determine the best treatment.

Previous studies have explored the prognostic factors and their relevance to patient survival. However, the survival and prognosis of patients with EC are multifactorial. Therefore, we aimed to study the prognostic factors and survival rates of patients with EC in southern Taiwan.

Methods

Ethics

This study was approved by the Research Ethics Committee of the Dalin Tzu Chi Hospital, Chiayi, Taiwan (IRB B1110219). We retrospectively analyzed patients who underwent hysterectomy-based surgical treatment for EC (C54.1 ICD-10-CM) between 2010 and 2020 at our hospital.

Study population

This study included 133 patients with EC who underwent hysterectomy-based surgery at our hospital between 2010 and 2020. The exclusion criteria for our study included patients who did not receive surgical treatment, those with incomplete pathological data, and those with missing information regarding the age of their first pregnancy. The diagnosis of EC was confirmed by a pathologist.

Data collection

We collected the patients' clinical information using electronic medical records in our hospital's information system. Patients diagnosed with malignant neoplasm of the endometrium (C54.1 ICD-10-CM) who underwent hysterectomy-based surgery at our hospital were selected for the study. We also collected clinical information such as (1) basic details, including age at the time of surgery, height, weight, history of hypertension and DM, and smoking status; (2) reproductive history including age at menarche, age at menopause, age at first birth, and parity status; (3) surgical history, including date, route, and type of hysterectomy; (4) pathological data including histological type, tumor grade, LVSI, lymph node (LN) invasion, clinical stage, and FIGO stage.

Primary outcome

The primary outcome was the progression-free survival (PFS) and overall survival (OS) of patients diagnosed with EC at Dalin Tzu Chi Hospital. PFS was defined as the time from the surgery date to the recurrence date. OS was defined as the time from the date of hysterectomy-based surgery to the date of death or last follow-up.

Secondary outcome

The secondary outcome of this study was to evaluate the prognostic factors associated with PFS and OS in patients with EC, including age, BMI, parity, DM, hypertension, histology, tumor grade, LVSI, LN invasion, and operation route. The risk factors related to PFS and OS were also analyzed.

Statistical analysis

We used the chi-square test to assess categorical variables and the independent t-test to assess continuous variables. We utilized the website (https://riskcalc.org/samplesize/) to compute the required sample size. Our selected parameters were as follows: alpha set at 0.05, power at 0.8, a ratio of unexposed to exposed of 1, and a hypothesized hazard ratio of 3. Additionally, we assumed the probability of the event in the unexposed group (p1) to be 0.2 and the probability of the event in the exposed group (p2) to be 0.4. Ultimately, our calculation yielded a total required sample size of 98. The Kaplan–Meier (K-M) method was used to estimate survival outcomes. Cox regression analysis was conducted to examine the factors associated with cancer mortality. All statistical analyses were performed using SPSS (version 24.0; IBM Corp., Armonk, NY, USA), with the significance level set at $p < 0.05$.

Results

Basic characteristics

A total of 133 patients were enrolled in this study. All patients underwent staging surgery, including hysterectomy and bilateral salpingo-oophorectomy. The demographics of all patients are listed in Table 1. The mean age of the patients was 56.5 years (standard deviation (SD): 10.71 years). The mean BMI was 26.4 (SD: 5.21). Most patients had their first pregnancy between 20 and 24 years. Of the 133 patients, 23% had DM, 43% had hypertension. Seventy-eight percent of patients had stage 1 EC, followed by stage 3 (14.29%), stage 2 (4.51%), and stage 4 (2.26%). Most patients (87.22%) had endometrioid histology, followed by mixed cell carcinoma (6.02%), endometrioid with squamous differentiation (4.51%), and clear cell carcinoma (1.5%). The tumor differentiation grades of grade 1 and 2 tumors were noted in 44.36% and 36.84% of the patients, respectively. Lymph node invasion was observed in 13.53% of patients. Most patients with EC (76.69%) underwent laparoscopic surgery. Regarding adjuvant therapy, the majority received radiotherapy ($n = 38$, 35.51%), followed by chemotherapy ($n = 20$, 18.69%), while hormone therapy ($n = 1$, 0.93%) was less frequently administered.

Progression-free survival

Table 2 presents the results of the univariate analysis of PFS of EC on various variables. Notably, factors such as FIGO stage (stage 3,4, HR: 5.46, 95% CI: 1.578–18.89), endometrioid histology (HR: 0.07, 95% CI: 0.02–0.262), endometrioid grade 3 (HR: 5.72, 95% CI: 1.64–40.40), lymphovascular invasion (HR = 12.15, 95% CI:

Table 1
Basic characteristics of the study cohort.

Variable	N = 133	
Basic data		
Age (in years, mean, SD)	56.5	10.71
BMI (mean, SD)	26.4	5.21
Reproductive history		
Pregnancy History (N, %)	108	81.2
Age at first pregnancy (in years, mean, SD)	24.6	3.90
< 20	7	5.26
20-24	50	37.59
25-29	37	27.82
30-34	13	9.77
≥ 35	1	0.75
Disease		
DM N,%	23	17.29
HTN N,%	43	32.33
FIGO stage N,%		
FIGO stage 1	105	78.95
FIGO stage 2	6	4.51
FIGO stage 3	19	14.29
FIGO stage 4	3	2.26
Histology N,%		
Clear cell carcinoma	2	1.5
Mixed cell carcinoma	8	6.02
Endometrioid	116	87.22
Serous carcinoma	1	0.75
Endometrioid with squamous	6	4.51
Endometrioid Grade N,%		
Grade 1	59	44.36
Grade 2	49	36.84
Grade 3	25	18.8
Lymphovascular invasion N,%	35	26.32
LN invasion N,%	18	13.53
OP route, N, %		
Open	31	23.31
Laparoscopy	102	76.69
Adjuvant therapy, N, %		
Radiotherapy	38	35.51
Chemotherapy	20	18.69
Hormone therapy	1	0.93

SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; OP, operation.

Table 2
Univariate analysis of progression-free survival.

Variables	HR	95% CI		P value
Basic data				
Age	1.03	0.97	1.10	0.325
BMI	0.95	0.83	1.09	0.473
Parity	1.47	0.89	2.43	0.135
Reproductive history				
Age at last birth <30	REF			
Age at last birth ≥ 30	0.66	0.19	2.28	0.511
Disease				
DM (ref = 0)	1.90	0.49	7.36	0.352
HTN (ref = 0)	1.22	0.35	4.34	0.755
FIGO stage				
FIGO stage 1,2	REF			
FIGO stage 3,4	5.46	1.578	18.89	0.007
Histology				
clear cell carcinoma	–	–	–	–
mixed cell carcinoma	REF			
endometrioid	0.07	0.02	0.262	<0.0001
serous carcinoma	–	–	–	–
endometrioid with squamous	–	–	–	–
Endometrioid Grade				
Grade 1	REF			
Grade 2	1.11	0.16	7.87	0.918
Grade 3	8.15	1.64	40.40	0.010
Lymphovascular invasion (ref = 0)	12.15	2.57	57.31	0.002
LN invasion (ref = 0)	4.72	1.33	16.786	0.016
OP route				
Open	REF			
Laparoscopy	0.24	0.07	0.82	0.023
Adjuvant therapy, N, %				
Radiotherapy (ref = 0)	2.84	0.80	10.07	0.11
Chemotherapy (ref = 0)	7.00	1.97	24.88	0.00
Hormone therapy (ref = 0)	–	–	–	–

HR: hazard ratio; CI: confidence interval; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; OP, operation.

2.57–57.31), LN invasion (HR: 4.72, 95% CI: 1.33–16.786), and the laparoscopy (HR = 0.24, 95% CI: 0.07–0.82) demonstrate notable impact in predicting PFS outcomes in EC. Patients who received chemotherapy had a worse PFS (HR = 7.00, 95% CI: 1.97–24.88).

Table 3 outlines the results of the multivariate analysis for PFS of EC in various variables. Noteworthy associations such as endometrioid histology (HR: 0.02, 95% CI: 0.001–0.59) and LVSI (HR: 9.11, 95% CI: 1.07–77.44) were observed, providing valuable insights for predicting PFS outcomes in EC.

Fig. 1A illustrates that the 5-year PFS was 90.3%.

Overall survival

Univariate analysis of the factors associated with OS is listed in Table 4. Age, BMI, parity, DM, and hypertension were not associated with OS. Endometrioid histology was associated with better survival than mixed-cell carcinoma (hazard ratio [HR]: 0.09, $p < 0.001$). Grade 3 tumor differentiation, LVSI, and LN invasion were associated with poor survival. Laparoscopic surgery had a lower HR (0.11, $p = 0.01$) than open surgery. The prognosis of endometrioid histology was better than that of mixed cell carcinoma (HR = 0.09, 95% CI: 0.02–0.38). Patients who received chemotherapy had a worse overall survival (HR = 11.79, 95% CI: 2.28–60.97).

Table 5 illustrates a multivariate analysis of all the factors associated with overall survival. After multivariate analysis, there was no association between these factors and OS.

The K-M plot illustrates that the 5-year OS was 94.53% (Fig. 1B).

Discussion

In this retrospective cohort study, we aimed to investigate the OS and PFS of patients diagnosed with EC at Dalin Tzu Chi Hospital between 2010 and 2020. Initial analyses revealed no significant correlations between OS and various factors, including age, BMI, parity, DM, hypertension, age at last birth, and tumor grade. However, certain prognostic factors were identified through univariate analysis. Grade 3 tumor differentiation, LVSI, and lymph node invasion were associated with poorer OS. Laparoscopy was associated with better OS. Nevertheless, subsequent multivariate analysis did not reveal any factor significantly associated with OS. Regarding PFS, endometrioid histology was linked to more favorable outcomes, while LVSI was associated with adverse results.

Tejerizo-García et al. found that tumor grade was an independent prognostic factor for OS in patients with EC [16]. Moreover, the endometrioid subtype, LVSI, and LN invasion also played important roles in survival outcomes. A retrospective cohort study investigating LVSI and survival in patients with EC also concluded that patients with initially positive LVSI had lower OS than those with negative LVSI [17]. A similar result was also observed in a study conducted by Oliver-Perez et al., in which a lower disease-free survival was observed in patients with EC with positive LVSI [18]. Our results showed that tumor grade, LVSI, and LN metastasis were

Table 3
Multivariate analysis of progression-free survival.

Variables	HR	95% CI		P value
Basic data				
Age	0.96	0.87	1.06	0.47
BMI	0.98	0.83	1.16	0.84
Parity	1.35	0.51	3.55	0.55
Reproductive history				
Age at last birth <30	REF			
Age at last birth ≥ 30	1.03	0.16	6.65	0.973
Disease				
DM (ref = 0)	1.23	0.09	17.55	0.880
HTN (ref = 0)	0.71	0.06	8.59	0.787
FIGO stage				
FIGO stage 1、2	REF			
FIGO stage 3、4	0.19	0.010	3.65	0.269
Histology				
clear cell carcinoma	–	–	–	–
mixed cell carcinoma	REF			
endometrioid	0.02	0.001	0.59	0.023
serous carcinoma	–	–	–	–
endometrioid with squamous	–	–	–	–
Endometrioid Grade				
Grade 1	REF			
Grade 2	0.44	0.04	5.52	0.527
Grade 3	0.31	0.02	6.37	0.447
Lymphovascular invasion (ref = 0)	9.11	1.07	77.44	0.043
LN invasion (ref = 0)	14.18	0.84	238.23	0.065
OP route				
Open	REF			
Laparoscopy	0.51	0.07	3.93	0.515
Adjuvant therapy, N, %				
Radiotherapy (ref = 0)	0.87	0.07	11.07	0.91
Chemotherapy (ref = 0)	1.81	0.06	57.01	0.74
Hormone therapy (ref = 0)	–	–	–	–

HR: hazard ratio; CI: confidence interval; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; OP, operation.

Table 4
Univariate analysis of overall survival.

Variables	HR	95% CI		P value
Basic data				
Age	1.06	0.99	1.14	0.12
BMI	0.95	0.81	1.11	0.50
Reproductive history				
Nulliparous	REF			
Parous	–	–	–	–
Disease				
DM (ref = 0)	1.97	0.38	10.17	0.42
HTN (ref = 0)	1.65	0.37	7.38	0.51
FIGO stage				
FIGO stage 1	REF			
FIGO stage 2	0.74	0.001	688.44	0.93
FIGO stage 3	1.61	0.11	24.54	0.73
FIGO stage 4	–	–	–	–
Histology				
Clear cell carcinoma	–	–	–	–
Mixed cell carcinoma	REF			
Endometrioid	0.09	0.02	0.38	0.001
Serous carcinoma	–	–	–	–
Endometrioid with squamous	–	–	–	–
Endometrioid Grade				
Grade 1	REF			
Grade 2	1.16	0.07	18.47	0.92
Grade 3	12.06	1.41	103.33	0.02
Lymphovascular invasion (ref = 0)	17.86	2.15	148.47	0.01
LN invasion (ref = 0)	9.37	2.09	41.93	0.003
OP route				
Open	REF			
Laparoscopy	0.11	0.02	0.58	0.01
Adjuvant therapy, N, %				
Radiotherapy (ref = 0)	2.45	0.55	10.93	0.24
Chemotherapy (ref = 0)	11.79	2.28	60.97	0.00
Hormone therapy (ref = 0)	–	–	–	–

SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; OP, operation; ref, reference.

risk factors for EC prognosis, which is consistent with the results of previous studies.

Different histologies of EC are associated with different OS and PFS. In our study, most patients (87.22%) had endometrioid histology, followed by mixed cell carcinoma (6.02%), endometrioid with squamous differentiation (4.51%), and clear cell carcinoma (1.5%). The composition is correlated with a previous study that revealed endometrioid cancer constitutes most of EC [19]. The previous study also showed clear cell and serous carcinoma associated with worse OS than endometrioid carcinoma [19]. Our study also showed endometrioid histology was associated with better PFS.

In our previous study regarding the prognostic factors of EC in Eastern Taiwan, we found that DM and a monocyte/lymphocyte ratio >0.2386 were associated with cancer death, poor OS, and PFS [20]. However, in the results of the current study, we found no significant relationship between age, diabetes, and OS. Several studies have shown that older age is an important negative prognostic factor for EC [21]. Zhang et al. concluded in their

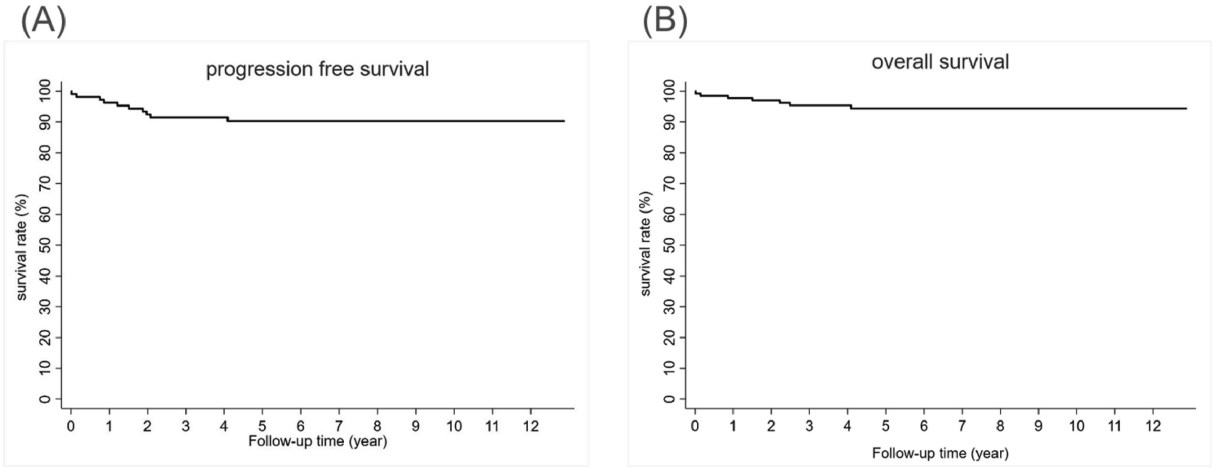

Fig. 1. Kaplan–Meier curve of survival in patients with endometrial cancer. (A) Progression-free survival. (B) Overall survival.

Table 5
Multivariate analysis of overall survival.

Variable	HR	95% CI		P value
Basic data				
Age	1.01	0.89	1.15	0.87
BMI	0.99	0.78	1.25	0.94
Reproductive history				
Nulliparity	REF			
Parous	–	–	–	–
Disease				
DM (ref = 0)	1.24	0.03	55.74	0.91
HTN (ref = 0)	1.14	0.04	31.10	0.94
FIGO stage				
FIGO stage 1	REF			
FIGO stage 2	0.66	0.001	541.13	0.90
FIGO stage 3	0.99	0.01	142.91	1.00
FIGO stage 4	–	–	–	–
Histology				
clear cell carcinoma	–	–	–	–
mixed cell carcinoma	REF			
endometrioid	0.40	0.01	15.63	0.626
serous carcinoma	–	–	–	–
endometrioid with squamous	–	–	–	–
Endometrioid Grade				
grade 1	REF			
grade 2	0.81	0.02	29.32	0.91
grade 3	2.05	0.05	77.10	0.70
Lymphovascular invasion (ref = 0)	2.04	0.05	81.81	0.71
LN invasion (ref = 0)	2.40	0.02	261.80	0.71
OP route				
Open	REF			
Laparoscopy	0.48	0.02	10.16	0.64
Adjuvant therapy, N, %				
Radiotherapy (ref = 0)	0.07	0.00	9.26	0.29
Chemotherapy (ref = 0)	110.40	0.11	>999.99	0.18
Hormone therapy (ref = 0)	–	–	–	–

SD: standard deviation, BMI: body mass index, Preg: pregnancy, DM: diabetes mellitus, HTN: hypertension, FIGO: International Federation of Gynecology and Obstetrics, LN: lymph node, OP: operation.

retrospective study that age and race were significantly correlated with OS and cancer-specific survival [22]. Apart from age, a previous meta-analysis reported that patients with diabetes had poorer OS than those without diabetes [11,22].

Age at last birth and parity are considered risk factors for EC. A recent study included 1005 patients with EC among 332625 women; a greater number of childbirths was linked to a progressively reduced risk of EC [23]. Similarly, another study concluded that parity was negatively correlated with the onset of EC and showed no significant association with the incidence of specific EC subtypes [24]. Late age at last childbirth was independently associated with a decreased risk of EC, and this reduced risk endured for an extended period [25]. According to a previous meta-analysis, there appears to be a potential link between parity and reduced risk of endometrial cancer [26]. However, our study did not find an association between parity, age at last birth, and EC development. This may have been due to the small sample size.

Laparoscopic staging surgery is the standard surgical method for patients with EC [27]. The laparoscopic approach resulted in reduced intraoperative blood loss, extended operative time, decreased uterine weight, fewer removed lymph nodes, and shorter hospital stays [28]. A previous investigation has shown that minimally invasive surgery has become the primary surgical approach for patients with EC [29]. In addition, minimally invasive surgery has demonstrated better in-hospital outcomes than laparotomy. Furthermore, the utilization of robot-assisted laparoscopic surgery, which exhibits a comparable in-hospital safety profile in comparison to conventional laparoscopy, is increasing [29]. A previous study's findings support the advantages of laparoscopic surgery and confirm its safe and effective application in cases of intermediate and high-risk EC [30]. Our study correlated with previous studies in that most patients with EC received laparoscopic surgery.

When utilizing BMI as an indicator of obesity, previous research has revealed that individuals classified as obese (BMI of 30–35 kg/m^2) had a 2.6-fold rise in their risk of EC [31]. In contrast, those classified as severely obese (BMI >35 kg/m^2) had a 4.7-fold increase in risk compared to that of women of normal weight (BMI <25 kg/m^2) [31]. Findings from a previous meta-analysis demonstrated a robust connection between BMI and a heightened risk of endometrial cancer [32]. The mean BMI of females in Taiwan is 22.9 ± 3.4 kg/m^2 [33]. In our study, the mean BMI was 26.4 (SD: 5.21), which was higher than the mean BMI in Taiwanese females.

This study had several strengths and limitations. In this retrospective cohort study, data were extracted from our hospital database. We enrolled patients with comprehensive medical records that provided thorough personal profiles, medical histories, and laboratory information. This approach effectively mitigated recall bias. However, it is important to acknowledge one limitation of this study, its relatively small sample size.

Conclusion

In conclusion, our study did not identify any factors associated with OS. Endometrioid histology was linked to more favorable PFS, while LVSI was associated with adverse PFS. Most of our patients underwent minimally invasive surgery. These findings underscore the importance of recognizing specific prognostic factors and highlight the increasing use of minimally invasive surgical approaches to manage EC.

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Declaration of Generative AI and AI-assisted technologies in the writing process

We used AI for grammar checking.

Declaration of competing interest

The authors declare no conflict of interest relevant to this article.

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Original Article

Single incision mini sling for the treatment of urodynamic stress incontinence: Surgical outcomes and preoperative predictors of failure☆

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ABSTRACT

Objective: To evaluate the surgical outcomes and predictors of failure of Single Incision Mini Sling (Ophira) in women with urodynamic stress incontinence.
Materials and methods: Records of 115 women underwent anti-incontinence procedure using Ophira Mini Sling from June 2019 to September 2020 reviewed. Subjective evaluation was assessed using validated IIQ-7, UDI-6, POPDI-6 and PISQ-12 questionnaires. Multichannel urodynamics, 1-h pad test and 72-h voiding diary was performed as objective evaluation. Primary outcome was the objective cure rate of negative urine leak on provocative filling cystometry and 1-h pad test weight <2 g, and subjective cure rate was negative response to question 3 of UDI-6. Secondary outcome was to identify risk factors associated with failure for Ophira.
Results: Total of 108 women were evaluated. The objective cure rate was 91.7% with subjective cure rate of 86.1%. Comparison of clinical outcome shows significant improvement of USI post-operatively ($p < 0.001$) and reflected in 1-h pad test ($p < 0.001$). Improvement in all subjective evaluation parameters is seen except for POPDI-6. Failure of Ophira correlate significantly in women age >66 years, presence of asthma, pre-operative Intrinsic Sphincter Deficiency (ISD), and Maximum Urethral Closure Pressure (MUCP) value < 40 cmH20.
Conclusion: Ophira Single Incision Mini Sling is safe and effective treatment option for USI, showing high objective and subjective cure rates with low incidence of complications. Non-modifiable risks of age ≥66 years, asthma status, pre-operative intrinsic sphincteric deficiency and low maximal urethral closure pressure were the factors of failure for Ophira.

Introduction

Through midurethral theory [1], surgical treatment of stress urinary incontinence (SUI) have progressively developed. Traditional invasive anti-incontinence surgeries that carry inevitable risk of complications and post-operative voiding difficulties are being replaced by midurethral sling (MUS) tension-free vaginal tape (TVT) and transobturator tape (TOT), proving to be as effective with fewer complications. The emergence of single incision midurethral sling (SIMS) are designed to be minimally invasive, requiring less dissection and avoiding trocar passage through obturator foramen and retropubic allows for a safer surgery.

Earlier SIMS were inconsistent in terms of placement techniques, resulting incomparable result with prior MUS, thus withdrawn from clinical use [2,3]. New generation of slings were

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designed to be shorter (in length) and do not penetrate the tissues as deeply. Despite the findings of meta-analysis on effectiveness and complications of SIMS being non-inferior in patient-reported outcomes and objective cure rates to standard MUS, lower post-operative pain score and earlier return to normal activity were achieved in SIMS group [4]. Ophira® Mini Sling System (Promedon Group, Argentina) is an innovative mini sling with its main features being single incision method, equipped with multipoint fishbone-like polypropylene fixation device that improves surgical effect.

Despite the availability of various SIMS, data are limited, with short term follow up. The existing studies are small-scale involving heterogenous group of patients. Therefore, the primary objective of this study is to evaluate the objective and subjective cure rate of SUI using Ophira in homogenous group of patients and to identify the preoperative predictors that contributes to its failure as the secondary aim.

Materials and Methods

The medical records of 115 patients with clinically confirmed SUI and urodynamic stress incontinence (USI), who underwent anti-incontinence surgery using Ophira, without needing concurrent procedures from June 2019 to September 2020, with at least one year follow up post-operatively were reviewed, after obtaining institutional review board approval (IRB:202101921B0). Exclusion criteria were patients with SUI symptoms without diagnosis of USI on urodynamic studies (UDS), stage II or more genital prolapse according to Pelvic Organ Prolapse Quantification System, Detrusor Overactivity (DO), neurogenic bladder dysfunction, pre-operative PVR >100 ml and patients requiring concomitant prolapse surgery.

Pre-operative evaluation

All patients followed a standardized pre-operative institutional protocol comprising of medical history, physical and pelvic examination, 72-h voiding diary, multichannel urodynamic study, and urine analysis. Subjective evaluation performed through validated Incontinence Impact Questionnaire-7(IIQ-7), Urogenital Distress Inventory-6(UDI-6), Pelvic Organ Prolapse Distress Inventory 6(POPDI-6), Colorectal Anal Distress Inventory-8(CRADI-8) and Pelvic organ prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Objective evaluation comprises multichannel UDS testing following standardized protocol set by International Continence Society (ICS) [5], 1-h pad test and 72-h voiding diary. All conditions and definitions of lower urinary symptoms, methods, definitions, and units conform to the standards recommended by the International Urogynaecological Association and the ICS [6].

USI was diagnosed when there was demonstrable involuntary leakage of urine during increased abdominal pressure in the absence of detrusor contraction during filling cystometry. Patients having urine leakage on Valsalva leak point pressure <45 cmH2O in symptomatically full bladder were diagnosed as Intrinsic sphincter deficiency (ISD) [7]. Bladder Outlet Obstruction (BOO) was determined using a BOO nomogram [8]. Diagnosis of DO applies when there is involuntary detrusor contraction during filling phase which maybe spontaneous or provoked.

Surgical procedure

The surgical application of Ophira device was carried out in the similar manner previously describe by Lo et al. upon using MiniArc and Solyx devices [9–11] (Fig. 2). TRS [12] was added replacing the blue loosening sutures using 1–0 absorbable polyglactin suture placed on one end of the sling, as adapted in previous studies [12,13]. The sling was placed in close contact with vaginal tissue below the mid-urethra. No provocative stress test facilitating the adjustment of the vaginal tape performed intraoperatively. Cystoscopy was performed at the end of surgery to ensure bladder integrity. Bladder was drained post-cystoscopy with no catheter indwelled. Patients is required to achieve PVR <20% of the voided

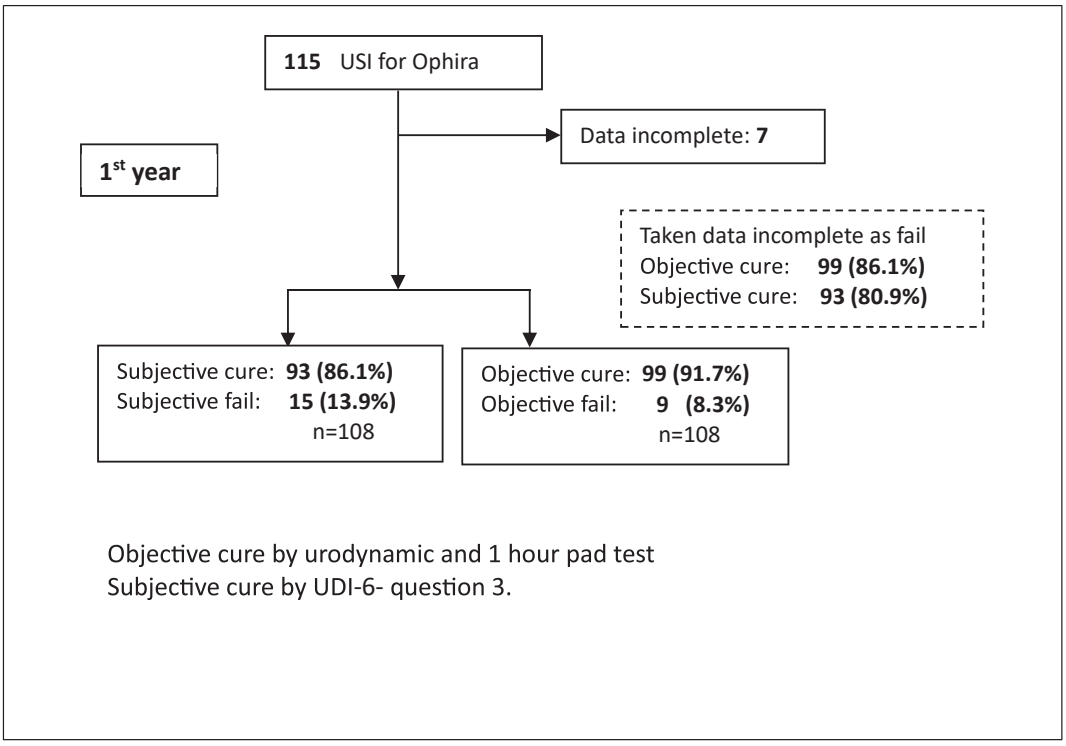

Fig. 1. Flow chart on study design and patient outcomes.

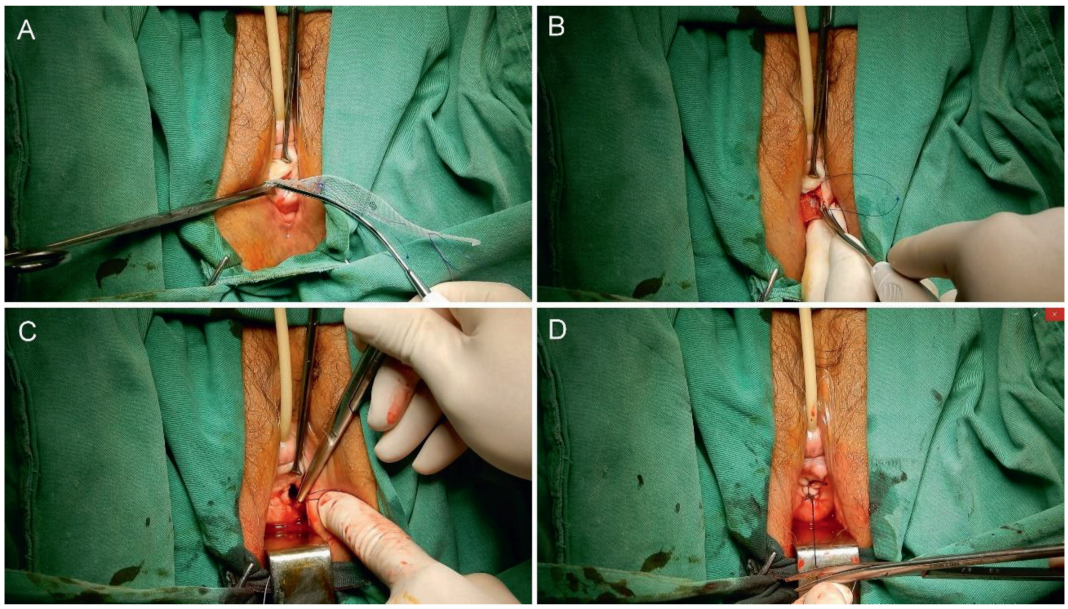

Fig. 2. Surgical procedure for Ophira surgery in brief.
A. The right arm of the Mini Sling attached to the internal obturator muscle at the level of the right arcus tendineus. **B**. Then left arm of the Mini Sling attached to the internal obturator muscle at the level of the left arcus tendineus. **C**. The insertion depth for the left fixation arm was defined using a tension-free test, by inserting a pair of Metzenbaum scissors that verifies the absence of tension on the urethra. When undue tension was anticipated, the tension of the Mini Sling would be released by slowly pulling on the blue thread that is attached to one of the Mini Sling arms. **D**. The free end of the TRS exteriorized in the anterior vaginal wall.

volume and/or <100 ml prior discharge. For patients with immediate voiding dysfunction postoperatively, transperineal urethral ultrasound was performed to check for over-tensioned slings. Gentle downward pull of TRS using hemostatic clamp was done for over-tensioned sling. In patients with high PVR and no urethral indentation, sterile intermittent catheterization was performed. Anticholinergic and Beta 3 adrenergic drugs were prescribed for patients with overactive bladder (OAB), if indicated.

All patients were followed up for 1 week, 1 month, 3 months, 6 months, and annually following institution protocol. During each follow up, PVR urine measurements, urinalysis, pelvic examinations were performed. Multichannel UDS and validated subjective questionnaires was performed preoperatively and post-operatively at 1 year. Shall the patient unable to participate in clinic set-up, telephone consult by credentialed nurse was done.

Outcome measures

The primary outcome measured the objective cure, defined as no demonstrable involuntary leakage of urine during the multichannel UDS testing and a 1-h pad test weight <2 g. The presence of USI and pad weight >2 g signified failure. Subjective cure was defined as negative response to UDI-6 question 3 (no leakage on coughing, sneezing, or laughing); a score >1 on this question indicates failure. Presence of surgical complications and mesh related complications following Ophira procedure identified.

The secondary outcomes are to identify the different risk factors for failure following Ophira procedure.

Statistical analysis

A post hoc sample size calculation of 76 subjects needed to detect the difference in failure rate of 15%, with a confidence level of 95% and statistical power of 80%. Descriptive statistics were used for demographics and perioperative data. The paired sample *t*-test and McNemar test were applied for comparison of continuous and categoric data, respectively. The chi-square test was used to compare the success and failure groups to identify potential risk factors of failure.

Patient age and parity were grouped in categories for analysis, while other preoperative parameter was analyzed as binary variables. When the data violated the chi-square assumptions (if more than 1 cell had an expected count of less than 1 or greater than 20% of the cells had an anticipated count of less than 5), Fisher's exact test was applied.

Variables evaluated in the univariate analysis as possible predictors of Ophira failure includes age, menopausal status, prior prolapse surgery, diabetes mellitus, ISD, low Maximum Urethral Closure Pressure (MUCP), and short Functional Urethral Length (FUL). Multivariate logistic regression model was then performed with independent risk factors for failure identified with ORs and 95% CIs. A p value < 00.05 was considered statistically significant. All statistical methods were performed using SPSS Version 17(SPSS Inc, Chicago,IL).

Results

Ophira was performed on 115 women with USI during the index period. Complete data were available for 108 women, with the median follow-up of 19.8 ± 4.5 months. The objective cure rate was at 91.7% and subjective cure rate of 86.1%. Analysis on Intention to treat shows objective cure rate of 86.1% and subjective cure rate of 80.9% (Fig. 1).

Population characteristic, clinical and urodynamic features at the time of surgery are shown in Table 1. The mean age of the cohort was 54.3 ± 11.2 years with the mean BMI of 25.0 ± 3.2 kg/m^2. Forty-seven (43.5%) women had prior pelvic surgery and 64 (59.3%) were menopaused.

The mean operating time is 26.7 ± 8.9 min, with mean intraoperative blood loss of 14.4 ± 13.3 ml. No intraoperative complications and mesh-related complications found during the follow up period.

Table 1
Baseline characteristic and outcomes of **108** USI patients undergoing Ophira surgery.

	Ophira,	n = 108
Mean age (year)	54.3 ± 11.2	(52.2–56.5)
Median parity	3	(0–6)
Mean BMI (kg/m^2)	25.0 ± 3.2	(24.4–25.6)
Urodynamic		
USI	104	
USI & ISD	4	
Prior pelvic surgery	47	(43.5%)
VH + Surelift™ + A-P	2	
VH + Uphold™	1	
AH	11	
LH	9	
TVT-O	2	
Burch	2	
C/S	20	
Medical disease		
DM	15	(13.9%)
HT	27	(25.0%)
Asthma	3	(2.8%)
Lung cancer	2	(1.9%)
Stroke	1	(0.9%)
Parkinsonism	1	(0.9%)
SLE	1	(0.9%)
Breast cancer	3	(2.8%)
Sicca syndrome	2	(1.9%)
Post-menopause	64	(59.3%)
Mean operating time (min)	26.7 ± 8.9	(24.0–29.4)
Mean intraoperative blood loss (ml)	14.4 ± 13.3	(11.9–17.0)
Mean hemoglobin difference (g/dl)	0.61 ± 0.60	(0.48–0.74)
Mean post-OP hospital stay (days)	1.0 ± 0.1	(0.9–1.1)
Mean period of follow-up (months)	19.8 ± 4.5	(18.9–20.7)
Complications, Major	0	0
Repeat MUS	0	(0%)
Mesh extrusion	0	(0%)
Obj. cure (n) at 1 year (n = 108)		
cure	99	(91.7%)
fail	9	(8.3%)
Sub. cure (n) at 1 year (n = 108)		
cure	93	(86.1%)
fail	15	(13.9%)

Data listed as mean ± standard deviation (95 % confidence interval), median and range within parentheses, incidence and 100 percentiles within parentheses.
BMI, body mass index; USI, Urodynamic stress incontinence; ISD, intrinsic sphincter deficiency; VH, vaginal hysterectomy; A-P, anterior and posterior colporrhaphy; AH, total abdominal hysterectomy; LH, laparoscopic hysterectomy; TVT-O, trans-obturator mid-urethral sling vaginal tape obturator system (Gynecare TVT-Obturator System; Ethicon, Inc.); C/S, Cesarean section; DM, Diabetic mellitus; HT, hypertension; SLE, Systemic lupus erythematosus; MUS, mid-urethral sling; Obj, objective; Sub, subjective.

Four women had immediate voiding dysfunction and managed with TRS manipulation, which resulted with resumption of normal PVR. The average post-operative hospital stay length was 1.0 ± 0.1 days.

Table 2 display the comparison of pre- and post-clinical outcome. The peak flow rate (Qmax) and residual urine volume were within normal limits with no significant change post-operatively. However, there was significant improvement of USI post-operatively ($p < 0.001$). Despite not statistically significant, women with ISD shows improvement during the 1-year follow-up ($p = 0.342$). USI recurred in 9 (8.3%) women; however, the symptoms were tolerable and require no repeat surgery. Post-operative detrusor overactivity (DO) was diagnosed in one woman and treated medically. None developed BOO. There were no significant UDS parameter changes pre- and post operatively, which reflects that Ophira posed no obstructive effect at the lower urinary tract system. The 1-h pad test, as an adjunct assessment on severity of urinary incontinence shows significant improvement ($p < 00.001$) from preoperative mean weight of 23.7 ± 29.7 g to 2.0 ± 6.2 g.

Table 2
Comparison of pre and post clinical outcomes.

UD parameter	Pre-OP, n = 108		Post-OP 1st year, n = 108		*p*-value
Qmax	23.7 ± 8.5	(22.1–25.3)	22.5 ± 8.1	(20.9–24.1)	0.191[a]
RU	25.7 ± 33.7	(19.3–32.1)	30.8 ± 33.7	(24.4–37.2)	0.265[a]
CC	367.7 ± 126.3	(343.6–363.7)	377.3 ± 122.0	(345.1–400.6)	0.382[a]
MUCP	57.2 ± 22.0	(53.0–61.4)	56.8 ± 24.1	(52.2–61.4)	0.813[a]
FUL	24.9 ± 6.2	(23.8–26.1)	23.9 ± 6.6	(22.6–25.2)	0.166[a]
Dmax	14.8 ± 11.5	(12.6–16.9)	16.2 ± 10.3	(14.2–18.2)	0.226[a]
UD diagnosis	n = 108		n = 108		
USI	108	(100%)	9	(8.3%)	**<0.001**[b]
ISD	4	(3.7%)	2	(1.9%)	0.342[b]
DO/DOI	0/0		1/0	(0.9%)	0.316[b]
BOO	0		0		–
1 h pad test	n = 108		n = 108		
	23.7 ± 29.7	(18.0–29.3)	2.0 ± 6.2	(0.8–3.2)	**<0.001**[a]

Data listed as mean ± standard deviation (95 % confidence interval), incidence and 100 percentiles within parentheses.
UD, urodynamics; Qmax, maximum urinary flow (m/s); RU, postvoid residual urine (ml); CC, cystometric capacity (ml); MUCP, maximum urethral closure pressure (cmH_2O); FUL, functional urethral length (cm); Dmax, detrusor pressure at maximum flow (cmH_2O); USI, urodynamic stress incontinence; ISD, intrinsic sphincter deficiency; DO, detrusor overactivity; DOI, detrusor overactivity incontinence; BOO, bladder outlet obstruction.
The value in bold signifies statistically significant in which $P < 0.05$.
[a] Paired-samples t test.
[b] McNemar's test.

Table 3
UDI-6, IIQ-7, POPDI-6 and PISQ-12 scores pre and postoperative.

	Pre- operative, n = 108		Post-operative, n = 108		P value
UDI-6	9.9 ± 2.7	(9.1–10.7)	4.3 ± 2.4	(3.7–5.0)	**<0.001**
IIQ-7	11.2 ± 3.5	(10.7–11.7)	3.0 ± 3.3	(2.0–3.9)	**<0.001**
POPDI-6	3.1 ± 2.2	(2.6–3.5)	2.9 ± 1.9	(2.2–3.4)	0.261
CRADI-8	3.4 ± 2.4	(2.6–3.0)	2.6 ± 2.3	(2.1–3.3)	**0.001**
PISQ-12 n = 33	26.7 ± 5.2	(23.3–29.6)	29.0 ± 6.1	(18.3–37.3)	**0.007**

Data listed as mean ± standard deviation with 95% CI in parentheses.
UDI-6, Urinary Distress Inventory; IIQ-7, Incontinence Impact Questionnaire; POPDI-6, Pelvic Organ Prolapse Distress Inventory 6; CRADI-8, Colorectal-Anal Distress Inventory 8; PISQ-12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire.
Paired-samples t test; The value in bold signifies statistically significant in which $P < 0.05$.

Subjective assessment on quality of life, urinary symptoms, and sexual activity were measured using validated questionnaires (Table 3). Results showed significant improvement in all parameters except for POPDI-6.

Table 4 analyzes the factors associated with success and failure of Ophira. Univariate and Multivariate analysis of these risk factors significantly shown that failure of Ophira is correlated with age >66 years old presence of asthma, pre-operative ISD, and MUCP value < 40 cmH2O (Table 5). This analysis was confirmed with the multivariate logistic regression model where all these factors were associated with failure of MUS (Table 6).

Discussion

Despite the controversies of SIMS for female SUI, they are as effective as other MUS procedures in female SUI [14]. In this study, the objective cure rate of 91.7 % and subjective cure rate of 86.1%. Although the median follow-up at 19.8 ± 4.5 months, the cure rate was assessed and based on the cut-off 1-year evaluation.

Table 4
Patients undergoing Ophira surgery divided according to success and failure of the procedure.

Variables		Success group n = 99, (%)	Failure group n = 9, (%)	p value	P[b] value
Age (years)				**0.007**[c]	
28-46	n = 28	27	1		(reference)
47-65	n = 61	58	3		0.776
≧66	n = 19	14	5		**0.033**[d]
Parity				0.374[c]	
0-2	n = 54	51	3		
3-5	n = 53	47	6		
≧6	n = 1	1	0		
BMI (kg/m2)				0.113[c]	
17-23	n = 35	32	1		
23.1–29	n = 65	56	5		
≧29.1	n = 13	11	3		
Menopause					
with	n = 64	56	8	0.080[d]	
without	n = 44	43	1		
Prior prolapse surgery					
with	n = 3	2	1	0.232[d]	
without	n = 105	97	8		
Prior anti-SUI surgery					
with	n = 4	3	1	0.298[d]	
without	n = 104	96	8		
Prior C/S					
with	n = 20	19	1	0.475[d]	
without	n = 88	80	8		
Prior hysterectomy					
with	n = 23	20	3	0.398[d]	
without	n = 85	79	6		
Diabetes mellitus					
with	n = 15	12	3	0.109[d]	
without	n = 93	87	6		
Neurogenic disease [a]					
with	n = 2	1	1	0.160[d]	
without	n = 106	98	8		
Asthma					
with	n = 3	1	2	**0.018**[d]	
without	n = 105	98	7		
ISD, pre-OP					
with	n = 4	1	3	**0.002**[d]	
without	n = 104	98	6		
MUCP, pre-OP					
≧40 cmH_2O	n = 80	76	4	**0.002**[d]	
<40 cmH_2O	n = 28	23	5		
FUL					
≧2 cm	n = 94	88	6	0.091[d]	
<2 cm	n = 14	11	3		

BMI, body mass index; SUI, stress urinary incontinence; ISD, intrinsic deficiency; MUCP, maximum urethral closure pressure; FUL, functional urethral length.
The value in bold signifies statistically significant in which $P < 0.05$.
[a] Stroke and Parkinsonian.
[b] values for comparison between subgroups.
[c] Chi-square test.
[d] Fisher exact test.

Table 5
Univariate and multivariate analysis of factors associated with post-operative failure.

Covariate	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Age ≥ 66	1.31	1.11–1.73	0.022	1.79	1.21–3.14	0.042
Asthma	1.27	0.90–1.81	0.118			
ISD	1.96	1.39–3.79	0.002	2.16	1.55–4.11	0.012
MUCP < 40 cmH_2O	3.46	2.01–11.78	<0.001	3.91	2.51–12.82	<0.001

Covariate	Odds ratio	95% CI
Age		
28-46	1	(Reference group)
47-65	1.01	0.83–1.11
≥66	1.31	1.11–1.73
Asthma	1.27	0.90–1.81
ISD	1.96	1.39–3.79
MUCP < 40 cmH_2O	3.46	2.01–11.78

ISD, intrinsic deficiency; MUCP, maximum urethral closure pressure.
CI, confidence interval; ISD, intrinsic sphincter deficiency.

Table 6
Multivariable logistic regression model for predictors of post-operative failure for Ophira surgery.

Covariate	Odds ratio	95% CI
Age		
28–46	1	(Reference group)
47-65	1.01	0.92–1.21
≥66	1.79	1.21–3.14
Asthma	1.17	0.84–1.41
ISD	2.16	1.55–4.11
MUCP < 40 cmH_2O	3.91	2.51–12.82

CI, confidence interval; ISD, intrinsic sphincter deficiency.

The success rate of this study is consistent with published reports [15,16]. Despite the long term follow-up study on 40 patients by Gon [15] that shows success objective rate of 85%, it is performed on heterogenous group. This present study is conducted in a larger number of homogenous patients, giving the study power and strength in the evaluation of Ophira as treatment for patients with pure SUI.

The high cure rate of Ophira could be attributed to the concept of tissue fixation by bilaterally anchoring a low-tension suburethral tape to the obturator internus muscle at the level of the tendinous arc. Ophira is built with blue loosening sutures at the base of both fixation arms which offers the ability to correct excessive tension during the procedure for optimum suburethral support, however author omits these loosening sutures to implement TRS. Through TRS manipulation, immediate voiding dysfunction from over-tensioned sling is corrected. This allows for customization of the implant to patient, and yields a successful postoperative result and better outcome.

Various factors have been associated with failure of anti-incontinence surgery. In this study, age >66 years have negative impact on the success of continence surgery. Pelvic floor disorders thru age-related connective tissue and neuromuscular changes, as well as deteriorating function of female bladder and urethral function [17], explains the risk of failure of MUS surgery with the increasing age. Presence of asthma is one of the risks of failure for anti-incontinence surgery, regardless of severity of the disease, chronic cough and sneezing induces rapid increased in intra-bdominal pressure leading to forced expiration which in turn places high demand on the continence system. However, the presence of asthma and failure of MUS surgery needs to be interpreted with cautious as the number of subjects is low. A larger subject size may be needed to show the true effect.

ISD also contributes to the cause of failures for all type of MUS [18]. Continence from MUS is dependent on good urethral mobility as the sling act as fulcrum for dynamic of kinking to occur during Valsalva or increased abdominal pressure [19]. This study demonstrated how preoperative ISD leads to failure of MUS. This is in line with Wlazlak et al., which reported reduced cure rates in ISD patients with hypomobile urethra [20].

Patients with low MUCP has been associated with poor urethral function and worse outcome of MUS surgery [21]. Despite it is difficult to standardize and implement the use of MUCP as clinical parameter, low MUCP of 40cmH2O is a predictor of poor outcomes for anti-incontinence surgery [22]. Prior studies showed that in patients with MUCP <42cmH20, TOT was 6 times more likely to fail than TVT at 3 months post-operatively [23,24]. With these data, one can infer that regardless of the type of MUS used, failure of MUS is

associated with bladder neck hypomobility and poor urethral function.

In this study, ISD and low MUCP were regard as independent risk factors as ISD has a multifactorial basis. ISD can occur in a low MUCP and/or low Vasalva Leak Point Pressure (VLPP). However, they comprise different mechanism where MUCP defines the factors acting extrinsically on the mid rather than the proximal urethra, while VLPP is lowered in Blaivas's type III where there is deficiency in mucosal sealing over the intrinsic proximal component of bladder neck [25]. These two mechanisms may act alone or in combination, thus altering the indicators of ISD.

Lower urinary tract symptoms occurred despite good clinical outcomes. Incidence of voiding dysfunction reaches 40% from bladder outlet obstruction after any anti-incontinence procedure [26]. Both urethral compression and kinking phenomenon are key features for the continence effect [27].

De Novo detrusor overactivity and urgency can occur after MUS insertion. Independent risk factors include age >66 years old, increased bladder sensation, lower bladder capacity, lower MUCP, greater pad loss, and diabetes mellitus [28]. Detrusor Overactivity (DO) could also occur as a result of clinical obstruction, leading to changes in detrusor muscle [29]. Although numerous factors may influence detrusor function, performing continence surgery will worsen the pre-existing detrusor instability that was already damaged by the weakened endopelvic fascia that caused SUI to begin with [30].

Strength and limitation

The strength of this study are homogenous patients that require no concurrent prolapse procedure, use of standardized institution-wide perioperative evaluation protocol, similar to that of a prospective case-control. This study also able to provide the pre-operative failure predictors that will be useful in determining patient selection for future incontinence surgery. The limitation of the study is single-arm, retrospective design, duration of 1-year follow-up; which may not be sufficient to draw a substantial conclusion.

Despite Ophira being not quite a new procedure, it is not commonly performed, thus it is crucial to continue reporting the outcome, both good and bad.

Ophira SIMS is a minimally-invasive, safe, and effective treatment option for women with USI, showing high objective and subjective cure rates with low incidence of complications. Age ≥66 years, asthma status, pre-operative ISD and low MUCP were the risk factor predicting failure for Ophira. Further investigation with large scale, long-term follow-up periods to define its place in the new SIS system for the treatment of SUI is recommended.

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Registry and registration number of the study in public trials registry

Not Applicable.

Animal study

Not applicable.

Declaration of competing interest

The authors declare they have no competing interest.

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Original Article

What maximal urethral closure pressure threshold predicts failure of mid-urethral sling surgery?

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A R T I C L E I N F O

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A B S T R A C T

Objective: Low Maximal Urethral Closure Pressure (MUCP) is linked to unfavourable outcome of anti-incontinence surgery, however the cut-off value varied within studies. This study aimed to predict the cut-off value of MUCP that contributes to poor outcome of Mid-Urethral Sling (MUS) surgery in Urinary Stress Incontinence (USI) patients.
Materials and methods: Records of 729 women underwent MUS procedure from January 2004 to April 2017 reviewed. Patients were divided into four MUCP groups, which were <20 cmH2O (≥20 and < 40) cmH2O (≥40 and ≤ 60) cmH2O and >60 cmH2O. Objective evaluation comprising 72-h voiding diary, multichannel urodynamic study (UDS) and post-operative bladder neck angle measurement. Subjective evaluation through validated urinary symptoms questionnaires. Primary outcome was objective cure rate of negative urine leak on provocative filling cystometry and 1-h pad test weight <2 g, and subjective cure rate was negative response to question 3 of UDI-6. Secondary outcome was identifying risk factors of cure failure for MUS in low MUCP groups. To identify the risk factors of cure failure, MUCP groups were narrowed down into <40 cmH2O or ≥40 cmH2O.
Results: Total of 688 women evaluated. Overall objective cure rate was 88.2% with subjective cure rate of 85.9%. Objective and subjective cure rates were lower in groups with low MUCP <40 cmH2O. Failure of MUS correlate significantly in patients with low MUCP <40 cmH20, bladder neck angle <30° and Functional urethral length (FUL) < 2 cm.
Conclusion: Women with MUCP <40cmH2O, bladder neck angle <30° and FUL < 2 cm are more likely to have unfavorable outcome following MUS surgery. We proposed the cut-off low MUCP <40cmH2O as predictor for fail MUS surgery in SUI patients.

Introduction

The practice of Multichannel Urodynamic Study (UDS), let alone the measurement of Maximal Urethral Closure Pressure (MUCP) are not routinely performed for all patients undergoing anti-incontinence surgery. MUCP, which is the highest pressure generated along the length of urethra above baseline intravesical pressure, is believed to correspond to the rhabdosphincter at the level of midurethra and represent the ability of urethra to resist leakage [1]. De' Lancey reveals through ROSE study that urethral function was the parameter most strongly associated with urinary stress incontinence in which MUCP were found to be lower in women with stress urinary incontinence(SUI) [2]. Despite most clinician does not rely on MUCP as part of urodynamic evaluation, it is the predominant factor associated with stress incontinence and has

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important clinical implications, especially on predicting the outcome of anti-incontinence surgery. Anti-incontinence surgery improves urethral support, however do not typically change urethral closure pressure [3]. Failure of anti-incontinence surgery were quoted to be 5–20% [4] with most studies attributing to low MUCP.

Various studies, including TOMUS trial have confirmed the link of low MUCP with SUI, intrinsic sphincter deficiency (ISD) as well as failure for anti-incontinence surgery [5–8]. International Continence Society (ICS) state the MUCP value of <20 cmH2O is suggestive of ISD. Yet, there were no agreed value to define how low is low for MUCP to give an impact to the outcome of Mid-urethral sling (MUS) surgery. Threshold values for low-pressure urethra varies from <20 cmH2O to 40 cmH2O [9,10]. Variation and combination linked to type of perfusion catheter, gynecologic position and bladder volume leads to different cut-off point of MUCP measurement. Hence, establishing the value of pre-operative MUCP with the outcome of MUS surgery may provide the prognostic worth in future anti-incontinence surgery.

In this regard, this present study was performed to investigate the possible range of pre-operative MUCP value associated with outcome of MUS surgery, and preoperative predictors that contributes to its failure.

Materials and methods

This is a retrospective study performed in a tertiary referral center. The medical records of 729 patients who underwent anti-incontinence surgery MUS from January 2004 to July 2017 were reviewed, after obtaining institutional review board approval (IRB:201700320B0C601). Patients with clinically confirmed SUI and urodynamic stress incontinence (USI) without needing concurrent procedures were included. Exclusion criteria were patients with SUI symptoms without USI on UDS, POP-Q stage II or more genital prolapse according to Pelvic Quantification System, detrusor overactivity (DO), mixed urinary incontinence, neurogenic bladder dysfunction, PVR >100 ml, previous pelvic malignancy and radiation and patients requiring concomitant prolapse surgery.

Pre-operative evaluation followed institutional protocol comprising medical history, physical and pelvic examination, 72-h voiding diary, multichannel urodynamic study (UDS), and urine analysis. Subjective evaluation performed through validated Incontinence Impact Questionnaire-7(IIQ-7), Urogenital Distress Inventory-6(UDI-6), Pelvic Organ Prolapse Distress Inventory 6(POPDI-6), Colorectal Anal Distress Inventory-8(CRADI-8) and Pelvic organ prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Objective evaluation comprises multichannel UDS testing following standardized protocol set by International Continence Society (ICS) [11], 1-h pad test and 72-h voiding diary.

All patients undergone MUS surgery had preoperative UDS, which include urethral pressure profilometry to measure MUCP using cm H2O. Implementing the MUCP cut-off level of 20 cmH2O as the low level and >60 cmH2O as the high level, patients were group into <20 cmH2O (≥20 to <40) cmH2O (≥40 to ≤60) cmH2O, and >60 cmH2O.

USI was diagnosed when there was demonstrable involuntary leakage of urine during increased abdominal pressure in the absence of detrusor contraction during filling cystometry. Patients having urine leakage on Valsalva leak point pressure (VLPP) < 45 cmH2O in symptomatically full bladder were diagnosed as Intrinsic sphincter deficiency (ISD). Patients with low MUCP, however with VLPP of >45 cmH2O does not fulfil the diagnosis of ISD. Diagnosis of DO applies when there is involuntary detrusor contraction during filling phase which maybe spontaneous or provoked.

All conditions and definitions of lower urinary symptoms, methods, definitions, and units conform to the standards recommended by the International Urogynaecological Association and the ICS [12].

Surgical procedure

All surgical procedure was performed under general anaesthesia by one urogynaecologist. Patient were subjected randomly to either one of the MUS of retropubic mid-urethral sling (Gynecare TVT™; Ethicon,USA), trans-obturator tape (TOT) (Monarc™; American Medical Systems, USA) or one of these 2 types of single-incision sling (SIS) (Solyx™; Boston Scientific Corporation,USA or Mini-Arc®; American Medical Systems, USA). The choice of MUS kit utilized depended on the availability at the time of scheduled surgery and patient's choice in which TOT is under National Health Insurance (NHI) while SIS is self-purchase. The sling was placed in close contact with vaginal tissue below the mid-urethra. No provocative stress test facilitating the adjustment of the vaginal tape performed intraoperatively. Cystoscopy was performed at the end of surgery to ensure bladder integrity. Bladder was drained post-cystoscopy with no catheter indwelled. Patients is required to achieve PVR <20% of the voided volume and/or <100 ml prior discharge. In patients with high PVR and no urethral indentation, sterile intermittent catheterization was performed. Anticholinergic and Beta 3 adrenergic drugs were prescribed for patients with de novo overactive bladder (OAB), if indicated.

All patients were followed up for 1 week, 1 month, 3 months, 6 months, and annually following institution protocol. During each follow up, PVR urine measurements, urinalysis, pelvic examinations were performed. Multichannel UDS inclusive of functional urethral length (FUL), and validated subjective questionnaires was performed preoperatively and post-operatively at 1 year. Transperineal ultrasonography examination on bladder neck angle is evaluated at 1-year post-operative, as per previous study [13]. Shall the patient unable to participate in clinic set-up, telephone consult by credentialed nurse was done.

Outcome measures

The primary outcome measured the objective cure, defined as no demonstrable involuntary leakage of urine during the multichannel UDS testing and a 1-h pad test weight <2g. The presence of USI and/or pad weight >2g signified failure. Subjective cure was defined as negative response to UDI-6 question 3 (no leakage on coughing, sneezing, or laughing); a score >1 on this question indicates failure.

The secondary outcomes are to compare the factors associated with failure after MUS between groups pre-operative MUCP.

Statistical analysis

A post hoc sample size calculation of 76 subjects needed to detect the difference in failure rate of 15%, with a confidence level of 95% and statistical power of 80%. Descriptive statistics were used for demographics and perioperative data. The paired sample *t*-test and McNemar test were applied for comparison of continuous and categoric data, respectively. The chi-square test was used to compare the success and failure groups to identify potential risk factors of failure.

Patient age and parity were grouped in categories for analysis, while other preoperative parameter was analyzed as binary variables. When the data violated the chi-square assumptions (if more than 1 cell had an expected count of less than 1 or greater than 20% of the cells had an anticipated count of less than 5), Fisher's exact test was applied.

Variables evaluated in the univariate analysis as possible predictors of MUS failure includes age, parity, menopausal status, prior prolapse surgery, prior SUI surgery, diabetes mellitus, pre-operative ISD diagnosis, transperineal ultrasound measurement of bladder neck angle, and functional urethral length (FUL). Multivariate logistic regression model was then performed with independent risk factors for failure identified with ORs and 95% CIs. A p value < 0.05 was considered statistically significant. All statistical methods were performed using SPSS Version 17(SPSS Inc, Chicago, IL).

Results

MUS was performed on 729 women with USI during the index period. Complete data were available for 688 women, evaluated at 1-year post-operative. Of the 688 patients undergone MUS surgery, 342 patients had SIS with either Solyx or MiniArc, 257 had TOT-Monarc and 89 patients had TVT.

Based on measurement of MUCP preoperatively, patients were sub-group into 4 group of MUCP <20 cmH2O (n = 16), MUCP (≥20 to <40) cmH2O (n = 119), MUCP (≥40 to ≤60) cmH2O (n = 198) and MUCP >60 cmH2O (n = 355). The overall objective cure rate was at 88.2 % and subjective cure rate of 85.9% (Fig. 1). Both objective and subjective cure rate is lower in group of patients with low MUCP <20 cmH2O compared to 3 other group.

Population characteristic, clinical and urodynamic features at the time of surgery are shown in Table 1. The mean age of the groups differs with higher age group seen in MUCP <20 cmH2O group of (63.8 ± 12.0) years. The mean BMI is similar among groups. Thirty-seven (5.37%) women had prior failed anti-incontinence surgery and 392 (57%) were menopaused.

Table 2 display the objective and subjective success after surgery at 1-year follow up. Objective and subjective cure rate were found to be higher in MUCP >60 cmH2O group.

Urodynamic parameter of Qmax, Cytometric capacity, MUCP measurements, and FUL as well as subjective assessment urinary and incontinence symptoms were compared pre- and 1-year post-operatively (Table 3). No significant changes observed on Qmax, cystometric capacity in all group pre- and post-operatively. However, statistically significant higher MUCP and FUL measurement were seen in MUCP <20 cmH2O, MUCP (≥20 and < 40) cmH2O and MUCP (>40 and ≤ 60 cmH2O group post-operatively. The diagnosis of USI post-operatively remains only in 75 (10.9%), while de novo DO were diagnosed in 16 patients (2.3%), significantly in MUCP >60 cmH2O and MUCP (≥40 and ≤ 60) cmH2O group. Subjective parameters with UDI-6 and IIQ-7 shows significant improvement in all groups.

Table 4 analyzes the factors associated with success and failure of MUS specifically in low MUCP groups. Statistically significant risk factors contributing to success and failure of MUS is seen in those with bladder neck angle of <30°, FUL < 2 cm and with ISD in MUCP (≥20 and ≤ 40) cmH2O group, and bladder neck angle of <30° in MUCP (≥40 and ≤ 60) cmH2O group. Univariate and Multivariate analysis of risk factors associated with post-operative failure after MUS surgery identifies bladder neck angle of <30°, ISD and FUL < 2 cm in MUCP (≥20 and < 40) cmH2O group, and bladder neck angle <30° in MUCP (≥40 and ≤ 60) cmH2O group (Table 5 and Table 6).

Intraoperative complication of bladder injury occurred in 1 patient during Monarc procedure which was repaired immediately and Foley catheter removed after 72 h. Patient had uneventful postoperative recovery. One patient had vaginal mesh exposure, diagnosed based on the symptoms and pelvic examination, and classified according to the Joint International Urogynaecological, Association/ICS working Group on Complications Terminology [14]. The patients underwent excision of the exposed mesh postoperatively in outpatient setting with no persistent mesh exposure thereafter.

Discussion

This study has shown the relationship between MUCP and the outcome of MUS surgery. The MUCP grouping is to narrow down the boundary threshold measurement of MUCP in order to evaluate the outcome of MUS surgery in each category, in which the universally agreeable cut-off value of <20 cmH2O and the upper limit of >60 cmH20 is used. The value of MUCP is not evaluated as continuum, as it would not provide impact in determining the outcome of MUS surgery. Patients with pre-operative low MUCP <20 cmH2O was found to have lower objective and subjective cure rate. Highest cure rate was seen in MUCP >60 cmH2O group. Two other group of MUCP (≥20 and < 40) cmH2O, and MUCP (≥40 and ≤ 60) cmH2O also shows good cure rate, both objective and subjectively, with a better cure percentage seen in group with higher MUCP measurement. This is in agreement with other studies where ISD patients with low MUCP were attributed to poor outcome of MUS surgery [15]. Thus, MUCP values before anti-incontinence surgery can be utilize to predict the risk rate of MUS treatment.

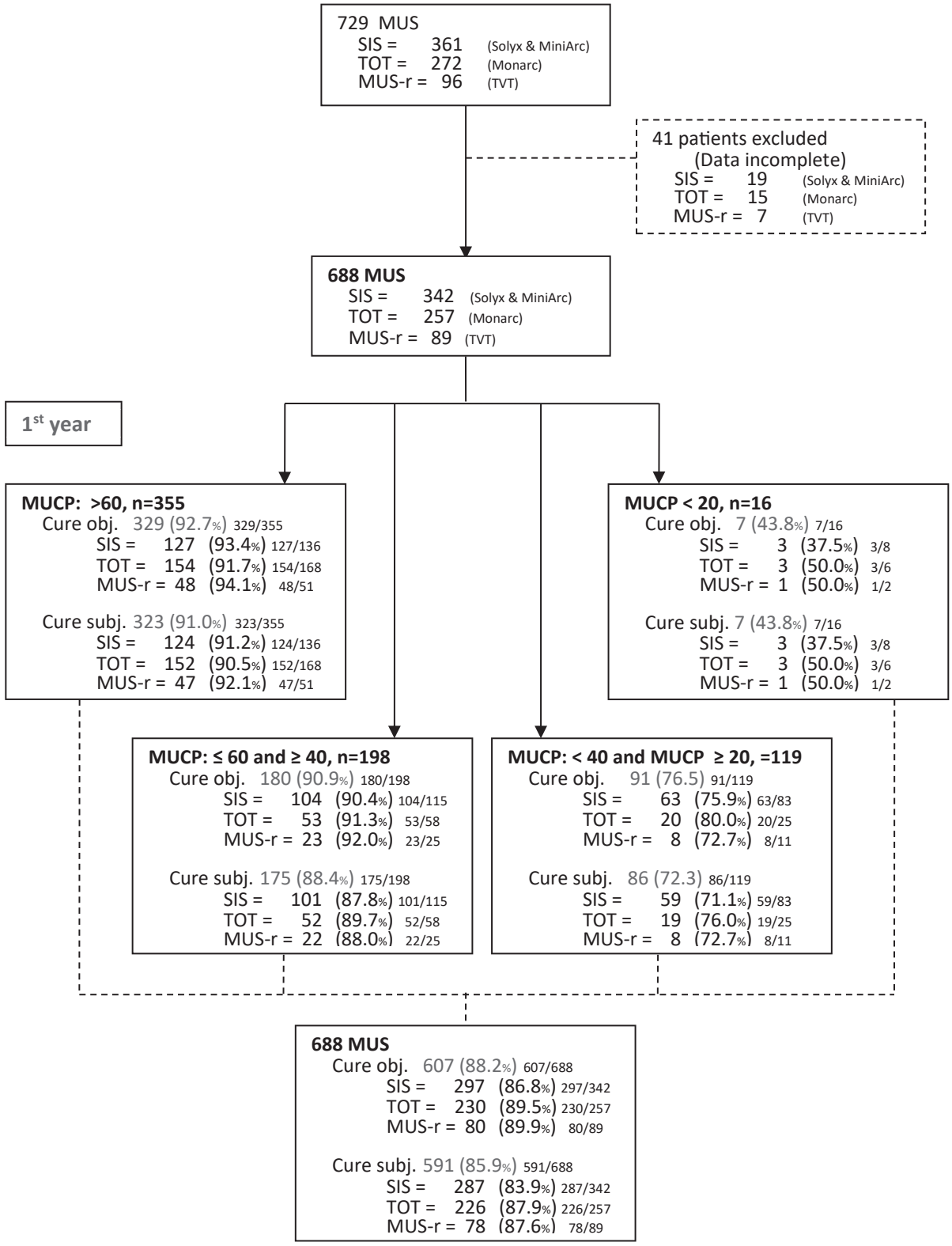
Most frequently, MUCP and Valsalva Leak Point Pressure (VLPP) are the urodynamic parameters use to grade the severity of SUI, however VLPP was excluded from the evaluation items as the straining ability of many patients was not reproducible or relatively poor, in addition to VLPP as a stand-alone value was not shown to be a useful index of ISD [16]. ISD and low MUCP were regard separately as ISD has multifactorial basis, in which it can occur in low MUCP and/or low VLPP. However, they comprise different mechanism where MUCP defines factors acting extrinsically on the mid rather than the proximal urethra, while VLPP is lowered in Blaivas's type III where there is deficiency in mucosal sealing over intrinsic proximal component of bladder neck [9]. These two mechanisms may act alone or in combination, thus altering the indicators of ISD.

In this study, ISD was not only observed in patients with MUCP <20 cmH2O, significant number were found to belong to patients in MUCP (≥20 and < 40) cmH2O group. This suggest a wider range of pre-operative MUCP measurement with a higher cut-off point of <40 cmH2O might be a better value in prediction of MUS failure.

Despite the various type of MUS surgery performed for this cohort, the association of MUCP and surgery type is not in context of this study. It is worth mentioning that the usage of retropubic MUS, is not a common practice in female SUI nowadays, contributing to the least number of patients in this study.

Through this study, ISD, postoperative bladder neck angle <30° and FUL <2 cm are significant predictors for MUS surgery failure in patients with MUCP <40 cmH_2O. This is in agreement with previous study by Lo evaluating surgical outcome of repeat MUS in failed incontinence surgery [17]. Bladder neck angle measurement is applicable in clinical practice in which women with bladder neck hypermobility were more likely to remain continent after MUS surgery, owing to dynamic kinking mechanism that result in compression effect on the urethra during increased intra-abdominal pressure [18,19].

Low MUCP values were associated with reduced urethral functional length, in which combination contribute to USI. FUL, defined as length of urethra along which urethral pressure exceeds intravesical pressure, presumably represents the location of urethral sphincter. Several studies, found greater FUL in continent than in stress-incontinence women, and shorter FUL appears to be associated with greater severity of SUI, which is in line with this study [20,21].



Objective cure by urodynamic and 1 hour pad test
Subjective cure by UDI-6- question 3
SIS, single incision sling; **TOT**, trans-obturator sling; **MUS-r**, retropubic mid-urethral sling; **obj.**, objective; **subj.**, subjective

Fig. 1. Flow chart on study design and patient outcomes.

Table 1
Preoperative demographics of patients undergoing mid-urethral slings according to MUCP n = 688.

Overall cure	MUCP: >60, n = 355	MUCP: ≤60 and ≥40, n = 198	P value*	MUCP: <40 and ≥20, n = 119	P value*	MUCP: <20, n = 16	P value*
Age (years)	51.0 ± 9.5 (50.0–52.0)	55.8 ± 10.1 (54.5–57.5)	0.001[a]	61.4 ± 11.5 (51.3–60.0)	<0.001[a]	63.8 ± 12.0 (50.0–60.8)	<0.001[a]
BMI (Kg/m^2)	25.4 ± 3.7 (25.0–25.8)	24.9 ± 3.5 (24.0–25.2)	0.108[a]	25.5 ± 3.7 (26.8–27.2)	0.772[a]	26.0 ± 4.4 (31.8–32.8)	0.506[a]
Parity (n)	3 (0–9)	3 (1–9)	0.436[b]	3 (1–10)	0.578[b]	3 (1–7)	0.262[b]
Postmenopausal status (n) n = 392	173 (48.7%)	119 (60.1%)	0.001[c]	87 (73.1%)	<0.001[c]	13 (81.3%)	0.019[d]
Prior prolapse surgery (n)							
With n = 50	17 (5.1%)	20 (9.6%)	0.032[c]	10 (8.4%)	0.169[c]	3 (18.8%)	0.048[d]
Without	338	178		109		13	
Prior SUI surgery (n)							
With n = 37	18 (5.1%)	10 (5.1%)	0.992[c]	8 (6.7%)	0.493[c]	1 (6.3%)	0.588[d]
Without	337	188		111		15	
Diabetes mellitus (n)							
With n = 101	51 (14.4%)	22 (11.1%)	0.278[c]	20 (16.8%)	0.519[c]	3 (18.8%)	0.714[c]
Without	304	176		99		13	
ISD, pre-op (n)							
With n = 48	0	0	x	36 (30.3%)	<0.001[d]	12 (75%)	<0.001[d]
Without	355	198		83		4	
FUL (n)							
<2 cm n = 166	60 (16.9%)	55 (27.8%)	0.003[c]	38 (31.9%)	<0.001[c]	13 (81.3%)	<0.001[d]
≥2 cm	295	143		81		3	
Angle							
<30°	15 (4.2%)	10 (5.1%)	0.654[c]	34 (28.6%)	<0.001[c]	7 (43.8%)	<0.001[d]
≥30°	340	188		85		9	
MUS							
SIS n = 342	136	115	0.133[c]	83	0.103[c]	8	0.642[c]
TOT n = 257	168	58		25		6	
MUS-r n = 89	51	25		11		2	
OP time, (min)	36.4 ± 20.0 (34.3–38.5)	34.6 ± 17.9 (32.0–37.2)	0.297[a]	35.1 ± 21.6 (34.5–40.6)	0.551[a]	34.2 ± 6.8 (29.6–37.9)	0.115[a]
Blood loss (ml)	27.1 ± 24.1 (24.6–29.6)	24.5 ± 29.1 (20.9–28.9)	0.263[a]	24.1 ± 24.2 (22.8–34.4)	0.214[a]	21.7 ± 14.7 (14.3–25.7)	0.291[a]
Hb diff, (g/dL)	−0.7 ± 0.7 (−0.8–0.6)	−0.7 ± 0.6 (−0.9–0.5)	0.686[a]	−0.6 ± 0.6 (−0.8–0.6)	0.382[a]	−0.6 ± 0.7 (−1.0–0.6)	0.382[a]
Post-operative hospital stay (days)	1.3 ± 1.0 (1.2–1.4)	1.2 ± 0.9 (1.2–1.4)	0.131[a]	1.3 ± 0.7 (1.3–1.4)	0.342[a]	1.4 ± 0.6 (1.1–1.5)	0.288[a]
Complications							
Mesh exposure(n)	1 (0.3%)**	0	0.642[d]	0	0.749[d]	0	0.957[d]
Bladder injury (n)	1 (0.3%)***	0	0.642[d]	0	0.749[d]	0	0.957[d]

SUI, stress urinary incontinence; ISD, intrinsic sphincter deficiency; pre-op, pre-operatively; SIS, single incision sling; TOT, trans-obturator sling; MUS-r, retro-public mid-urethral sling; TVT, tension-free vagina tape; MUCP, maximum urethral closure pressure (cmH_2O); FUL, functional urethral length (cm); OP, operation; Hb diff., Hemoglobin difference.
Data listed as mean ± standard deviation (95 % confidence interval), Median and range within parentheses, incidence and 100 percentile within parentheses.
*P values for comparison between MUCP: >60 and MUCP: ≤60 and ≥40 or MUCP: <40 and ≥20 or MUCP: <20.
**P < 0.05 was considered statistically significant.
***Intra-operative bladder injury Monarc procedure: Foley maintained for 3 days.
[a] Independent-samples t test.
[b] Mann–Whitney U.
[c] Chi-square test.
[d] Fisher exact test.

Table 2
Objective and subjective success after surgery according to MUCP at follow up of 1 year, n = 688.

Overall cure	MUCP: >60, n = 355	MUCP: ≤60 and ≥40, n = 198	P value*	MUCP: <40 and ≥20, n = 119	P value*	MUCP: <20, n = 16	P value*
Obj. cure (n) n = 607	329/355 (92.7%)	180/198 (90.9%)	0.462[a]	91/119 (76.5%)	<0.001[a]	7/16 (43.8%)	<0.001[b]
SIS n = 297/342	127/136 (93.4%)	104/115 (90.4%)	0.390[a]	63/83 (75.9%)	0.001[a]	3/8 (37.5%)	<0.001[b]
(Solyx) n = 106/122	33/34 (97.1%)	45/50 (90.0%)		27/35 (77.1%)		1/3 (33.3%)	
(MiniArc) n = 191/220	94/102 (92.3%)	59/65 (90.8%)		36/48 (75.0%)		2/5 (40.0%)	
TOT(Monarc) n = 230/257	154/168 (91.7%)	53/58 (91.3%)	0.946[b]	20/25 (80.0%)	0.018[a]	3/6 (50.0%)	0.013[b]
MUS-r (TVT) n = 80/89	48/51 (94.1%)	23/25 (92.0%)	0.535[b]	8/11 (72.7%)	0.030[b]	1/2 (50.0%)	0.021[b]
P value (between MUS)	0.776a	0.959[a]		0.872[a]		0.881[a]	
Subj. cure (n) n = 591	323/355 (91.0%)	175/198 (88.4%)	0.327[a]	86/119 (72.3%)	<0.001[a]	7/16 (43.8%)	<0.001[b]
SIS n = 287	124/136 (91.2%)	101/115 (87.8%)	0.385[a]	59/83 (71.1%)	<0.001[a]	3/8 (37.5%)	0.001[b]
(Solyx) n = 101	32/34 (94.1%)	43/50 (90.0%)		25/35 (71.4%)		1/3 (33.3%)	
(MiniArc) n = 186	92/102 (90.2%)	58/65 (89.2%)		34/48 (70.8%)		2/5 (40.0%)	
TOT (Monarc) n = 226	152/168 (90.5%)	52/58 (89.7%)	0.856[a]	19/25 (76.0%)	0.034[a]	3/6 (50.0%)	0.018[b]
MUS-r (TVT) n = 78	47/51 (92.1%)	22/25 (88.0%)	0.678[b]	8/11 (72.7%)	0.099[b]	1/2 (50.0%)	0.045[b]
P value (between MUS)**	0.930a	0.937[a]		0.890[a]		0.881[a]	

Obj. cure, objective cure; Subj. cure, subjective cure; SIS, single incision sling; MUS-r, retro-pubic mid-urethral sling; TVT, tension-free vagina tape; TOT, trans-obturator sling.
Objective cure at 1 year, no involuntary urine leakage during filling cystometry and a 1-h pad test < 2 g.
Subjective cure at 1 year, a negative response to question 3 on UDI-6, with no urine leakage related to physical activity, coughing or sneezing.
*P values for comparison between normal and overweight or Obese of association with cure.
**P values for comparison between SIS, TOT and MUS-r of association with cure.
[a] Chi-square test.
[b] Fisher exact test.

Table 3
Urodynamic and subjective questionnaire (UDI-6, IIQ-7) outcomes after surgery according to MUCP at follow up of 1 year, n = 688.

	MUCP: >60, n = 355	MUCP: ≤60 and ≥40, n = 198	P value*	MUCP: <40 and ≥20, n = 119	P value*	MUCP: <20, n = 16	P value*
Qmax							
Pre-	24.1 ± 9.1 (22.2–25.1)	23.5 ± 10.8 (22.0–25.0)	0.340[a]	23.8 ± 9.7 (23.6–26.5)	0.836[a]	22.1 ± 12.4 (21.3–27.2)	0.393[a]
Post-	23.3 ± 9.4 (22.2–24.2)	22.3 ± 9.8 (22.1–24.9)	0.2.7[a]	21.9 ± 10.0 (21.5–23.7)	0.165[a]	21.1 ± 8.9 (19.8–25.1)	0.180[a]
P value (within group)**	0.347[c]	0.190[c]		0.104[c]		0.503[c]	
RU							
Pre-	34.5 ± 30.3 (31.4–37.7)	31.1 ± 30.2 (29.4–35.6)	0.605[a]	32.3 ± 27.7 (24.4–34.7)	0.932[a]	37.0 ± 32.4 (26.4–42.8)	0.568[a]
Post-	36.6 ± 28.1 (33.7–39.5)	35.8 ± 31.4 (30.9–39.5)	0.761[a]	34.5 ± 33.4 (28.0–37.0)	0.551[a]	33.4 ± 23.0 (23.0–41.4)	0.657[a]
P value (within group)**	0.161[c]	0.216[c]		0.847[c]		0.573[c]	
CC							
Pre-	408.1 ± 122.1 (395.4–420.8)	404.4 ± 129.5 (384.8–421.9)	0.737[a]	383.7 ± 126.8 (380.1–410.4)	0.062[a]	346.4 ± 86.8 (366.4–416.3)	0.146[a]
Post-	395.5 ± 118.9 (383.1–407.9)	387.0 ± 131.2 (367.7–406.3)	0.479[a]	373.0 ± 122.8 (369.4–411.1)	0.143[a]	354.3 ± 113.8 (351.3–403.7)	0.175[a]
P value (within group)**	0.2633[c]	0.146[c]		0.603[c]		0.452[c]	
MUCP							
Pre-	87.5 ± 20.8 (85.4–89.7)	51.8 ± 9.1 (50.4–53.3)	<0.001[a]	33.5 ± 8.6 (64.3–72.0)	<0.001[a]	16.3 ± 3.3 (59.1–70.7)	<0.001[a]
Post-	80.4 ± 28.0 (77.5–83.4)	52.5 ± 16.6 (50.1–55.0)	<0.001[a]	40.1 ± 19.0 (62.5–69.7)	<0.001[a]	29.3 ± 12.2 (56.5–69.3)	<0.001[a]
P value (within group)**	0.101[c]	0.576[c]		0.001[c]		0.002[c]	
FUL							
Pre-	25.6 ± 6.6 (24.9–26.4)	23.8 ± 7.1 (22.7–24.9)	0.035[a]	21.5 ± 7.8 (23.3–25.1)	<0.001[a]	18.6 ± 4.7 (22.6–25.8)	<0.001[a]
Post-	25.5 ± 6.6 (24.8–26.2)	23.4 ± 5.6 (22.6–24.2)	0.002[a]	22.3 ± 6.0 (23.4–24.9)	<0.001[a]	20.0 ± 7.6 (23.3–26.3)	0.003[a]
P value (within group)**	0.906[c]	0.471[c]		0.3255[c]		0.542[c]	
USI							
Pre-	355 (100%)	198 (100%)		119 (100%)	x	16 (100%)	
Post- n = 75	23 (3.0%)	17 (8.6%)	0.359[b]	26 (21.8%)	<0.001[b]	9 (56.3%)	<0.001[b]
P value (within group)**	<0.001[d]	<0.001[d]		<0.001[d]		<0.007[d]	
DO[DOI]							
Pre-	0 (0%)	0 (0%)		0 (0%)		0 (0%)	
Post-n = 16 (6)	7 [4] (2.0%)	5 [0] (2.0%)	0.440[e]	3 [2] (2.0%)	0.478[e]	1 [0] (5.3%)	0.300[e]
P value (within group)**	0.008[d]	0.024[d]		0.081[d]		0.310[d]	
UDI-6							
Pre-	9.9 ± 3.4 (9.5–10.3)	11.3 ± 3.1 (10.8–11.7)	<0.001[a]	12.2 ± 2.5 (11.7–12.6)	<0.001[a]	13.3 ± 2.1 (12.2–14.4)	<0.001[a]
Post-	3.5 ± 2.4 (3.3–3.8)	3.9 ± 2.0 (3.6–4.2)	0.073[a]	6.4 ± 2.2 (6.0–6.8)	<0.001[a]	8.0 ± 3.2 (6.3–9.7)	<0.001[a]
P value (within group)**	<0.001[c]	<0.001[c]		<0.001[c]		<0.001[c]	
Difference [% change]	−6.4 ± 1.5 (−6.5–6.2)	−7.4 ± 1.6 (−7.6–7.2)	<0.001[a]	−5.8 ± 0.8 (−5.9–5.6)	<0.001[a]	−5.3 ± 2.3 (−6.5–4.1)	0.008[a]
IIQ-7							
Pre-	12.0 ± 3.3 (11.7–12.4)	13.5 ± 2.8 (13.1–13.9)	<0.001[a]	14.0 ± 2.1 (13.5–14.4)	<0.001[a]	15.6 ± 1.9 (14.6–16.3)	<0.001[a]
Post-	4.0 ± 2.4 (3.7–4.2)	4.3 ± 2.3 (4.0–4.7)	0.057[a]	5.5 ± 2.2 (5.1–5.90)	<0.001[a]	8.0 ± 2.1 (6.9–9.1)	<0.001[a]
P value (within group)**	<0.001[c]	<0.001[c]		<0.001[c]		<0.001[c]	
Difference [% change]	−8.1 ± 1.9 (−8.3–7.9)	−9.1 ± 1.3 (−9.3–8.9)	0.069[a]	−8.5 ± 1.4 (−8.7–8.2)	0.241[a]	−7.6 ± 0.7 (−8.0–7.2)	0.236[a]

Data listed as mean ± standard deviation with 95% CI in parentheses.
Qmax, maximum urinary low(m/s); RU, postvoid residual urine (mL); CC, cystometric capacity (mL); MUCP, maximum urethral closure pressure (cmH2O); FUL, functional urethral length (cm); USI, urodynamic stress incontinence; DO, Detrusor overactivity; DOI, detrusor overactivity incontinence; BOO, bladder outlet obstruction; UDI-6, Urinary Distress Inventory; Q-2, question 2 (Do you experience, and, if so, how much are you bothered by urine leakage related to the feeling of urgency?); Q-3, question 3 (Do you experience, and, if so, how much are you bothered by urine leakage related to physical activity, coughing, or sneezing?); IIQ-7, Incontinence Impact Questionnaire
*P values (between group) for comparison between normal and overweight or Obese.
**P values (within group) for comparison between pre-operative and post-operative values.
P < 0.05 was considered statistically significant.
[a] Independent-samples t test.
[b] Chi-square test.
[c] Paired t-test.
[d] McNemar's test.
[e] Fisher exact test.

Table 4
Low MUCP patients undergoing mid-urethral sling surgery divided according to success and failure of the procedure at 1 year.

Variables	MUCP: ≤60 and ≥40, n = 198			MUCP: <40 and ≥20, n = 119			MUCP: <20, n = 16		
Variables	Success group n = 180, (90.9%)	Failure group n = 18, (9.1%)	p value*	Success group n = 91, (76.5%)	Failure group n = 28, (23.5%)	p value*	Success group n = 7, (43.8%)	Failure group n = 9, (46.3%)	p value*
Age (years)			*0.053[a]			*0.322[a]			*0.460[a]
28–46	n = 39 37	2		n = 10 9	1		n = 1 1	0	
47–65	n = 123 114	9		n = 62 49	13		n = 6 2	4	
≥66	n = 38 29	7		n = 47 33	14		n = 9 4	5	
Parity			*0.382[a]			*0.097[a]			*0.121[a]
0-2	n = 85 80	5		n = 37 35	2		n = 5 4	1	
3-5	n = 106 94	12		n = 75 51	24		n = 10 3	7	
≥ 6	n-7 6	1		n = 7 5	2		n = 1 0	1	
Menopause									
with	n = 119 108	11	0.927[a]	n = 87 73	14	0.435[b]	n = 13 6	7	0.600[b]
without	n = 79 72	7		n = 32 28	4		n = 3 1	2	
Prior prolapse surgery									
with	n = 20 17	3	0.332[b]	n = 10 8	2	0.569[b]	n = 3 2	1	0.400[b]
without	n = 178 163	15		n = 109 83	26		n = 13 5	8	
Prior									
SUI surgery									
with	n = 10 9	1	0.623[b]	n = 8 6	2	0.493[b]	n = 1 0	1	0.563[b]
without	n = 188 171	17		n = 111 53	26		n = 15 7	8	
Diabetes mellitus									
with	n = 22 18	4	0.122[b]	n = 20 13	7	0.185[a]	n = 3 1	2	0.600[b]
without	n = 176 162	14		n = 99 78	21		n = 13 6	7	
Angle									
<30°	n = 10 6	4	**<0.007**[b]	n = 34 21	13	**<0.017**[a]	n = 7 2	5	0.500[b]
≥30°	n = 188 174	14		n = 85 70	15		n = 9 3	4	
ISD, pre-op									
with	n = 0 0	0	x	n = 36 20	16	**<0.001**[a]	n = 12 5	7	0.608[b]
without	n = 198 180	18		n = 83 71	12		n = 4 2	2	
FUL (all = 166)									
≥ 2 cm	n = 143 131	12	0.581[a]	n = 78 65	13	**0.015**[a]	n = 6 4	2	0.182[b]
<2 cm	n = 55 49	6		n = 41 26	15		n = 10 3	7	
Types of MUS			*0.121[a]			*0.872[a]			*0.881[a]
SIS	n = 115 104	11		n = 83 63	20		n = 8 3	5	
TOT	n = 58 53	5		n = 25 20	5		n = 6 3	3	
MUS-r	n = 25 23	2		n = 11 8	3		n = 2 1	1	

SUI, stress urinary incontinence; ISD, intrinsic sphincter deficiency; MUCP, maximum urethral closure pressure; FUL, functional urethral length; pre-op, pre-operative.
*P values for three subgroups comparison.
[a] Chi-square test.
[b] Fisher exact test.

Table 5
Univariate logistic regression of factors associated with failure after mid-urethral slings.

	MUCP: ≤60 and ≥40		MUCP: <40 and ≥20	
Covariate	Odds ratio	95% CI	Odds ratio	95% CI
Angle < 30°	5.3	2.16–13.36	2.17	2.16–4.06
ISD	–	–	3.07	1.62–5.82
FUL < 2 cm	–	–	1.31	1.02–1.69

CI, confidence interval.
Angle, Change of inclination angle at post-operative; ISD, intrinsic sphincter deficiency; FUL, functional urethral length.

Table 6
Multivariable logistic regression model for predictors of failure after mid-urethral slings.

	MUCP: ≤60 and ≥40		MUCP: <40 and ≥20	
Covariate	Odds ratio	95% CI	Odds ratio	95% CI
Angle < 30°	5.3	2.16–13.36	2.29	2.02–4.23
ISD	–	–	2.51	1.62–4.32
FUL < 2 cm	–	–	1.40	1.13–2.09

CI, confidence interval.
Angle, Change of inclination angle at post-operative; ISD, intrinsic sphincter deficiency; FUL, functional urethral length.

Interestingly, de novo Detrusor Overactivity (DO) were found to be significantly more in those with higher MUCP groups (MUCP (>40 to <60)cmH2O and >60 cmH2O). This is contradictory to most study that link low MUCP with de novo DO. It could be postulated that myogenic DO could be the result of cautionary tale against placing undue tension during MUS insertion, which was also reflected in previous study [22].

Strength and limitation

The strength of this study are large sample size patients that underwent solely MUS surgery with no concurrent prolapse procedure, use of standardized institution-wide perioperative evaluation protocol with the usage of multiple validated QOL questionnaires and UDS, similar to that of a prospective

case–control, where cure assessment consistently performed at pre- and 1 year post-operatively. This study also able to provide the cut-off value for MUCP to determine poor outcome of MUS surgery as well as pre-operative failure predictors that will be useful in clinical practice for future incontinence surgery.

The limitation of the study is single-arm, retrospective design, duration of 1-year follow-up; which may not be sufficient to draw a substantial conclusion. The utilization of different type of MUS may represent the possibility of non-randomized bias, though not being the focus of this study, however it does not contribute to significant difference in any MUCP grouping (Table 1). The single surgeon experience-although ensure consistent and standardize surgical technique, may not be generalizable to others. Uneven distribution of patients based on the type of MUS surgery performed may have diluted the strength of the findings. Sonographic measurement of bladder neck angle was only assessed post-operatively, as non-significant variation was anticipated, as per previous study [22]. It would be ideal to have pre-operative measurement to enable comparison.

There is no doubt that MUS procedure performed in patient with SUI will generate good outcome, however determining its cause of failure, including preoperative diagnostic parameters is crucial. Based on this study, we proposed a higher cut-off value of pre-operative MUCP <40 cmH2O as a predictor of failure in MUS surgery, in addition to bladder neck angle <30° and FUL < 2 cm.

Conclusion

Women with pre-operative MUCP <40 cmH2O, bladder neck angle <30° and FUL < 2 cm are more likely to have unfavorable outcome following MUS surgery.

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The authors report none.

Author contributions

TS Lo: Protocol/Project development, Data collection, Data analysis, Manuscript editing.

F Harun: Manuscript writing and Manuscript editing.

HB Zakaria: Manuscript writing.

YL Tan: Manuscript editing.

WC Hsieh: Data collection.

Al-Zabidi AAA: Manuscript editing.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Original Article

Unraveling fetal venous disorders: An integrated approach in fetal echocardiography and their clinical significance

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ABSTRACT

Objective: Fetal venous system malformations frequently coincide with cardiac or extracardiac anomalies. This study explores our experience with an integrated fetal echocardiography approach and analyzes the characteristics and outcomes of fetal venous system disorders.

Materials and methods: We conducted a retrospective study with 7048 pregnant women (7255 fetuses) who underwent complete two-dimensional (2D) fetal echocardiographic examinations. We primarily employed an integrated 2D approach. Three-/four-dimensional (3D/4D) spatiotemporal image correlation was supplemental. Fetal venous disorders were classified into 3 groups: cardinal (Group 1), umbilical and vitelline (Group 2), and pulmonary (Group 3) systems, based on embryological-anatomical considerations. Maternofetal data were recorded alongside imaging diagnoses.

Results: Congenital venous malformations were identified in 98 fetuses, yielding a prevalence of 1.35% (98/7255). Six participants had coexisting venous disorders from different groups. Group 1 included 48 fetuses with persistent left superior vena cava (LSVC) and 3 others (unidentified brachiocephalic vein, left inferior vena cava (IVC), and interrupted IVC with azygous continuation to SVC). Group 2 had 39 fetuses with persistent right umbilical vein and 7 with umbilical-portal-ductus venosus disorders. Group 3 had 7 fetuses with pulmonary venous return disorders. Group 2 showed the most favorable outcomes (alive and without neonatal death), while Group 3 exhibited the poorest. Associated cardiac defects were observed in 43.1% of Group 1, 8.7% of Group 2, and 57.1% of Group 3 ($P < 0.001$), displaying a broad spectrum of non-specific anomalies. Meanwhile, Group 2 had a greater occurrence of a single venous disorder (93.5%) compared to Group 1 (88.2%) and Group 3 (57.1%) ($P = 0.020$).

Conclusion: Our approach offers an integrated strategy for assessing the fetal venous system during fetal echocardiography, providing multiple views to characterize venous anomalies. The presence of a fetal venous disorder may indicate the coexistence of more severe abnormalities, and the prognosis depends on associated anomalies or the venous disorders per se.

Introduction

Fetal echocardiography, as a non-invasive imaging modality, plays a pivotal role in the early detection and assessment of congenital heart defects. Achieving a comprehensive diagnosis of these disorders necessitates equal consideration and evaluation of the fetal venous system. By the fourth weeks of embryological development, 4 venous systems — cardinal (draining the body), umbilical (draining the chorion), vitelline (draining the yolk sac), and pulmonary systems — connect to the heart [1,2]. The embryology of fetal venous systems is complex, marked by diverse developmental abnormalities and morphological variations. Disruptions in development can occur through primary failure to create critical anastomoses or via secondary occlusion of an already transformed system [1].

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Congenital venous malformations occur sporadically and have been associated with various cardiac and extracardiac defects [3]. Due to the anatomical complexity and variability among individuals, congenital venous anomalies frequently go unnoticed prenatally if not specifically focused on during fetal scans. This underscores the need for a more organized and efficient way to identifying anomalies in the fetal venous system during fetal echocardiography.

The focus of our study is to unravel fetal venous disorders through an integrated approach during routine two-dimensional (2D) fetal echocardiography. Utilizing three-/four-dimensional spatiotemporal image correlation (3D/4D STIC) imaging as an adjunct tool enhances the capability to assess complexities associated with fetal venous disorders. Our goal is to provide a comprehensive understanding of developmental abnormalities and morphological variations in the fetal venous system, while also exploring potential associations with both cardiac and extracardiac defects. Through this organized approach, our study aims to contribute valuable insights to the field of fetal echocardiography, ultimately enabling enhanced prenatal detection, diagnosis, and management of fetal venous disorders.

Materials and methods

Study population

We conducted a retrospective study of 7624 consecutive fetal echocardiographic examinations performed at Taichung Veterans General Hospital, a tertiary referral center, and Your Ultrasound Clinic, a specialized fetal ultrasound center, between November 2015 and May 2022. Fetuses underwent detailed cardiac and extracardiac ultrasound scans during the second or third trimester. Exclusion criteria were applied to ensure data quality, which led to the exclusion of 51 fetuses with incomplete studies, 6 fetuses with inconclusive prenatal diagnoses, and 312 repeated follow-up examinations. The repeated follow-up examinations were usually done for cases complicated with associated cardiac or extracardiac defects. We also performed functional heart studies to detect the absence or presence of early signs for fetal cardiac dysfunction and determined timing of delivery. After these exclusions, a total of 7255 fetuses remained eligible for analysis, including 6841 singleton and 414 twin fetuses (Fig. 1). We categorized the study population into 3 groups based on embryological-anatomical

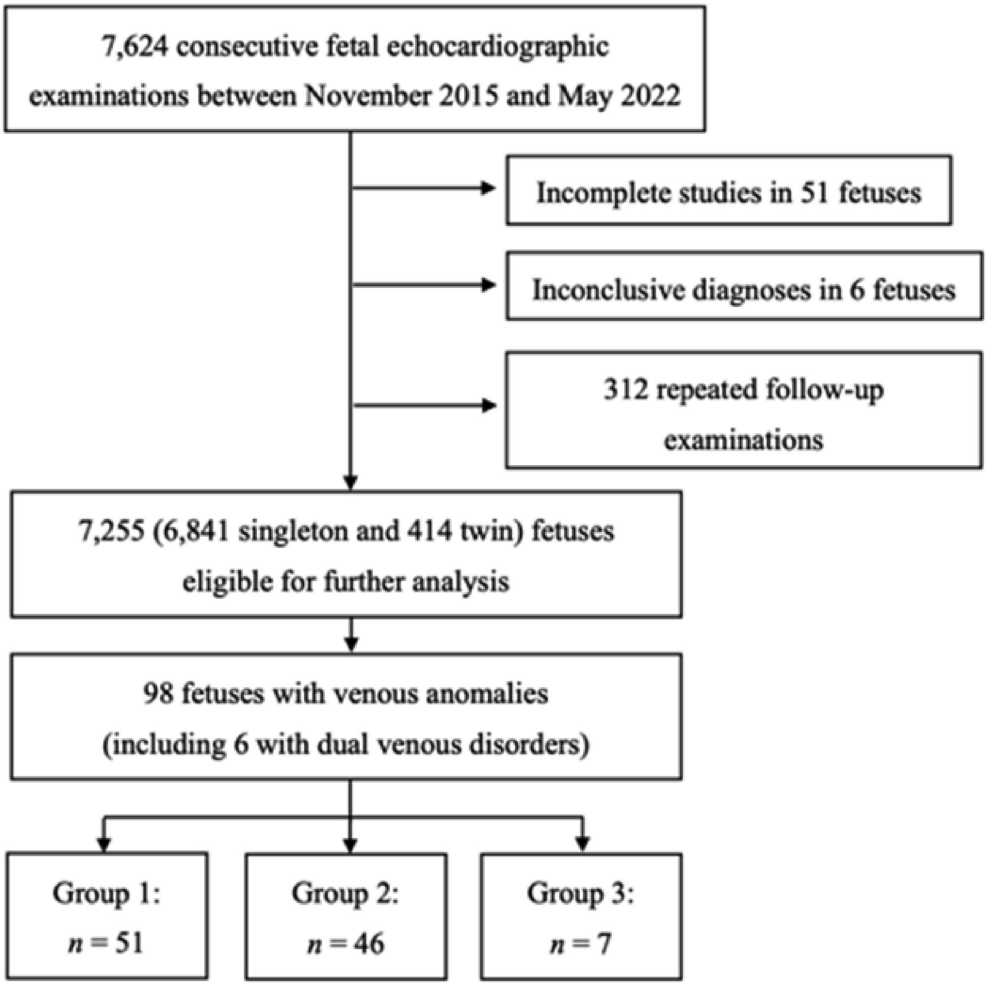

Fig. 1. Subject enrollment.

considerations. Ethical approval was obtained from the institutional review board at Taichung Veterans General Hospital (approval number CE21449B), and informed consent was waived.

Data collection

Data were collected from our fetal echocardiographic database and medical charts. Fetuses diagnosed with venous malformations in utero were categorized into 3 groups: cardinal (Group 1), umbilical and vitelline (umbilico-porto-ductus venosus complex) (Group 2), and pulmonary (Group 3) venous systems. We combined the umbilical (chorion drainage) and vitelline (yolk sac drainage) systems into a single group due to concurrent developmental changes and functional inseparability, despite their embryological distinctness [2,4]. Parents received counseling, and each fetus with a congenital venous disorder was periodically followed up 2 to 4 times before birth, depending on the type of malformation and associated anomalies. Data collected included maternal age, gestational age (GA) at diagnosis, GA at delivery, birthweight, twin pregnancies, delivery mode, genetic disorders, associated anomalies, gender, and neonatal outcomes. Favorable outcomes were measured as individuals who were alive without neonatal death, while unfavorable outcomes included termination of pregnancy, in utero death, and neonatal death (due to associated malformations or postoperative complications). Live newborns underwent examinations by a certified pediatric cardiologist (S.L.J). For postnatal examinations conducted elsewhere, we obtained outcome data by contacting parents through telephone or outreach clinics, including any additional intracardiac and extracardiac anomalies detected and any that were missed during prenatal ultrasound. We continued to follow cases for a period ranging from 1 to 7.5 years.

Fetal echocardiography

Each examination, comprising comprehensive cardiac and extracardiac evaluations, was conducted by one of two highly experienced obstetricians (J.J.T or H.C.L), each with over 27 years of experience in fetal ultrasound. All 2D echocar-diographic examinations were performed in a standardized manner [5,6]. Fetal positions were dorso-posterior, allowing apical, right-sided, or left-sided heart insonation. Throughout the study, we consistently utilized the Voluson E8 or S6 ultrasound machines (GE Healthcare, Zipf, Austria). Adjustments were made to the ultrasound equipment presets for each study. In cases with abnormal findings, a diagnostic consensus was reached between J.J.T and either H.C.L or S.L.J to ensure the robustness of our results.

The integrated approach represented a comprehensive study for fetal cardio-vascular system during fetal echocardiography. To systematically evaluate the fetal venous systems, we employed a comprehensive 2D approach, including abdominal, 4-chamber, complete 3-vessel and high mediastinal, and parasagittal views (Fig. 2). In addition to gray scale, color Doppler was applied to identify venous flow directions and waveforms. The abdominal view (transverse and longitudinal) served as a foundational plane, allowing a full display of the inferior vena cava (IVC), umbilico-porto-hepatic system, and ductus venosus (DV) through slight cephalic, caudal, or lateral angulations of the transducer. The 4-chamber view demonstrated the pulmonary veins returning to the left atrium and identified the drainage of the coronary sinus (CS) into the right atrium by gently shifting back and forth or making slight caudal adjustments of the transducer. The complete 3-vessel view, including the 3-vessel view, ductal arch view, aortic-isthmal view, and 3-vessel and trachea view (3VT), was obtained by moving the transducer cephalad and slightly oblique from the 4-chamber view. The superior vena cava (SVC) and trachea positioned to the right of the aortic arch, and the azygous vein drained into the SVC. In the high mediastinum, we observed the drainage of the left brachiocephalic vein (LBCV) into the SVC and the orientation of the aortic branching and vessels surrounding the thymus. Parasagittal views at the bicaval plane displayed the SVC and IVC entering the right atrium, illustrating their relationship with other venous components. If unsolved conditions occurred, the use of 3D/4D imaging attempted to provide a full anatomic description of the more complex fetal venous problems.

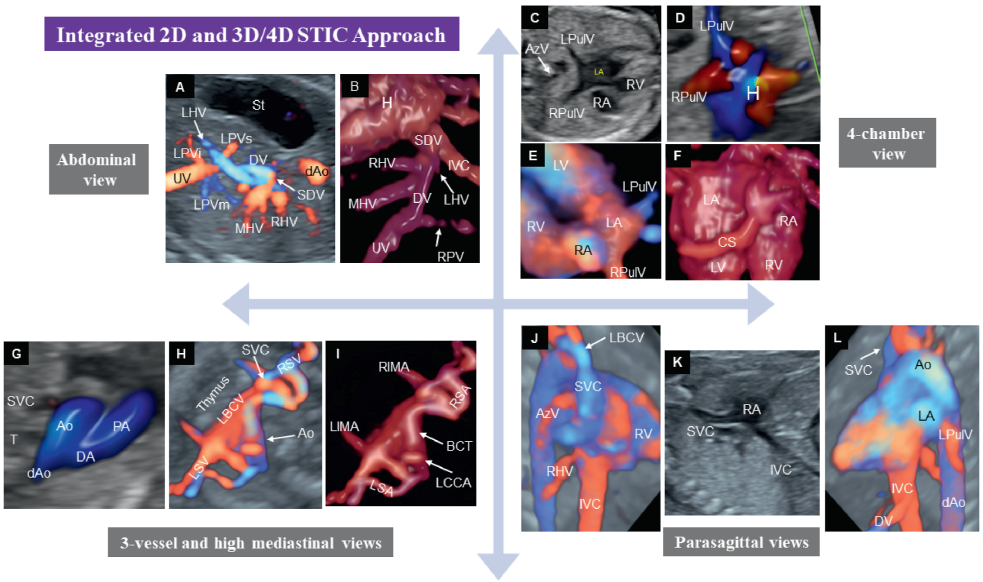

Fig. 2. The integrated 2D and 3D/4D echocardiographic ultrasound offers diverse perspectives for understanding fetal venous systems. Ao, aortic arch; AzV, azygous vein; BCT, brachiocephalic trunk; CS, coronary sinus; dAo, descending aorta; DA, ductus arteriosus; DV, ductus venosus; H, heart; IVC, inferior vena cava; LA, left atrium; LBCV, left brachiocephalic vein; LCCA, left common carotid artery; LHV, left hepatic vein; LIMA, left internal mammary artery; LPulV, left pulmonary vein; LPVi, inferior left portal vein; LPVm, medial left portal vein; LPVs, superior left portal vein; LSA, left subclavian artery; LSV, left subclavian vein; LV, left ventricle; MHV, middle hepatic vein; PA, main pulmonary artery; RA, right atrium; RHV, right hepatic vein; RIMA, right internal mammary artery; RPV, right portal vein; RPulV, right pulmonary vein; RSA, right subclavian artery; RSV, right subclavian vein; RV, right ventricle; SDV, subdiaphragmatic vestibulum; St, stomach; SVC, superior vena cava; T, trachea; UV, umbilical vein.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS version 22.0; International Business Machines Corp, New York, USA). Continuous data were presented as median with interquartile range, while categorical data were presented as number (n) and percentage (%). Mann–Whitney U or Kruskal–Wallis tests were employed for continuous variable comparisons, depending on data distribution. For categorical variables, Chi-Square or Fisher's exact tests were used. A probability value of $P < 0.05$ was considered statistically significant.

Results

General data

Congenital venous malformations affected 98 fetuses, with a prevalence of 1.35% (98/7255). These cases were categorized into 3 distinct groups (Fig. 1). Among the study cohort, 6 participants had coexisting venous disorders from different groups. Three fetuses had disorders from both Group 1 and Group 2, while the remaining 3 had disorders from both Group 1 and Group 3. In Group 1 (51/7255; 0.70%), there were 48 cases of persistent left superior vena cava (LSVC) and 3 other cases (unidentified brachiocephalic vein, left IVC, and interrupted IVC with azygous continuation to SVC). Group 2 (46/7255; 0.63%) had 39 cases of persistent right umbilical vein (PRUV) and 7 other cases with disorders related to the umbilical-portal-DV complex. Group 3 (7/7255; 0.10%) exclusively comprised total anomalous pulmonary venous connections (TAPVC). Twin fetuses in Group 1 had a significantly higher prevalence of cardinal venous anomalies (1.93%) compared to singleton fetuses (0.63%) ($P = 0.008$). The occurrence of a singular venous disorder was higher in Group 2 (93.5%) compared to Group 1 (88.2%) and Group 3 (57.1%) ($P = 0.020$).

Integrated and systematic approach

Our study utilized a comprehensive strategy to depict the fetal venous system in detail, employing 2D and 3D/4D imaging techniques (Fig. 2). While obtaining all 2D standard views may not be feasible in every fetus during a single scan, our comprehensive approach facilitated this process, even if it required additional studies on occasion. In most cases, pivotal veins, except the CS and smaller veins like internal mammary and subclavian veins in the upper mediastinum, could be readily identified using 2D grayscale and color Doppler imaging techniques. Additionally, in 12 cases with uncertain or doubtful 2D findings, we employed advanced 3D/4D STIC modality for more detailed exploration of venous disorders or associated cardiac anomalies.

Clinical characteristics

Table 1 summarizes the clinical characteristics. Group 2 had the youngest latest GA at delivery, with a median of 39.0 weeks (range, 36.0–40.0). Additionally, Group 2 had the highest birthweight, with a median of 2660.0 g (range, 2260.0–3297.5), and the lowest incidence of associated cardiac anomalies (8.7%). Consequently, Group 2 exhibited the most favorable outcome (87.5%) compared to the other two groups. Three pregnancies were terminated due to associated anomalies. Conversely, Group 3 had the earliest GA at delivery, with a median of 26.0 weeks (range, 22.0–37.0), the lowest birthweight, with a median of 1247.5 g (range, 493.8–2789.0), and the highest incidence of associated cardiac anomalies (57.1%) among the 3 groups, resulting in the least favorable outcome. Genetic analyses were performed in 43 cases of Group 1, 33 cases of Group 2, and 7 cases of Group 3, with abnormal results observed in 9.3%, 9.1%, and 14.3%, respectively ($P = 0.909$). Associated cardiac anomalies were 43.1%, 8.7%, and 57.1% in Group 1, Group 2, and Group 3, respectively ($P < 0.001$). The associated cardiac defects displayed a broad spectrum of non-specific anomalies, including, in Group 1, right aortic arch or aberrant subclavian artery (5 cases), coarctation of the aorta or interrupted aortic arch (4 cases), isolated ventricular septal defect (4 cases), tetralogy of Fallot or pulmonary atresia with ventricular septal defect (3 cases), pulmonary stenosis (2 cases), univentricular atrioventricular connection (2 cases), double outlet right ventricle (1 case), and hypoplastic left heart syndrome (1 case); in Group 2, right aortic arch or aberrant subclavian artery (3 cases) and critical pulmonary stenosis (1 case); in Group 3, aberrant subclavian artery (1 case), common arterial trunk (1 case), hypoplastic left heart syndrome (1 case), and left atrial isomerism (1 case). However, the comparison of associated extracardiac anomalies between groups were not significant.

Table 1
Comparison of clinical characteristics among 3 groups: Group 1, cardinal venous anomalies, Group 2, umbilical/vitelline venous anomalies, and Group 3, pulmonary venous anomalies.

Characteristics	Group 1 ($n = 51$)		Group 2 ($n = 46$)		Group 3 ($n = 7$)		*P* value
Maternal age (years)	34	(32–39)	32	(29–35.3)	34	(32–38)	0.035
GA at diagnosis (weeks)	23	(22–24)	22	(21–23)	23	(21–25)	0.079
GA at delivery (weeks)[a]	37	(28.3–38.3)	39	(36–40)	26	(22–37)	0.009
Birthweight (g)[a]	2152.5	(1205–2765)	2660	(2260–3297.5)	1247.5	(493.8–2789)	0.011
Twin fetuses	8/51	(15.7)	1/46	(2.2)	1/7	(14.3)	0.072
Mode of delivery[a]							0.172
TOP	10/39	(25.6)	3/23	(13.0)	4/7	(57.1)	
VD	13/39	(33.3)	11/23	(47.8)	1/7	(14.3)	
CS	16/39	(41.0)	9/23	(39.1)	2/7	(28.6)	
Genetic disorder[b]	4/43	(9.3)	3/33	(9.1)	1/7	(14.3)	0.909
Associated anomalies							
Cardiac	22/51	(43.1)	4/46	(8.7)	4/7	(57.1)	<0.001
Extracardiac	6/51	(11.8)	10/46	(21.7)	2/7	(28.6)	0.309
Male gender	20/51	(39.2)	23/45	(51.1)	2/7	(28.6)	0.355
Outcome							0.008
Favorable	25/39	(64.1)	21/24	(87.5)	2/7	(28.6)	
Unfavorable[c]	14/39	(35.9)	3/24	(12.5)	5/7	(71.4)	

Data are given as median (range) or *n* (%).
TOP, termination of pregnancy; VD, vaginal delivery.
[a] Excluding cases with no available birthweight. Categorical data are presented as *n*/*N* (%) with percentages calculated against the *N* for which information is available.
[b] Including conventional karyotyping and/or array comparative genomic hybridization results.
[c] Including termination of pregnancy, in utero death, and neonatal death. CS, cesarean section; GA, gestational age.

Table 2
Comparison of clinical characteristics between persistent left superior vena cava (LSVC) and persistent right umbilical vein (PRUV).

Characteristics	LSVC ($n = 48$)		PRUV ($n = 39$)		*P* value
Maternal age (years)	34.5	(32.3–39)	32	(29–35)	0.004
GA at diagnosis (weeks)	23	(22–24)	22	(21–23)	0.030
GA at delivery (weeks)[a]	37	(27.5–38)	39	(36–40)	0.017
Birthweight (g)[a]	2115	(1120–2770)	2650	(2250–3281.3)	0.015
Twin fetuses	8	(16.7)	1	(2.6)	0.038
Mode of delivery[a]					0.310
TOP	9/37	(24.3)	2/17	(11.8)	
VD	12/37	(32.4)	9/17	(52.9)	
CS	16/37	(43.2)	6/17	(35.3)	
Genetic disorder[a,b]	4/41	(9.8)	2/26	(7.7)	1.000
Associated anomalies					
Cardiac	21	(43.8)	3	(7.7)	<0.001
Extracardiac	5	(10.4)	8	(20.5)	0.312
Male gender[a]	18	(37.5)	20	(51.3)	0.236
Outcome[a]					0.105
Favorable	24/37	(64.9)	16/18	(88.9)	
Unfavorable[c]	13/37	(35.1)	2/18	(11.1)	

Data are given as median (range) or *n* (%).
[a] Excluding cases with no available birthweight. Categorical data are presented as *n/N* (%) with percentages calculated against the *N* for which information is available.
[b] Including chromosomal and genetic results.
[c] Including termination of pregnancy, in utero death, and neonatal death. CS, cesarean section; GA, gestational age; TOP, termination of pregnancy; VD, vaginal delivery.

Prevalent venous disorders

The 2 most common venous disorders were LSVC in Group 1 and PRUV in Group 2, with a prevalence of 0.66% (48/7255) and 0.54% (39/7255), respectively. Table 2 summarizes their clinical characteristics. PRUV was associated with a younger maternal age at diagnosis, with a median age of 32.0 years (range, 29.0–35.0), an earlier GA at diagnosis, with a median of 22.0 weeks (range, 21.0–23.0), a later GA at delivery, with a median of 39.0 weeks (range, 36.0–40.0), and a higher birthweight, with a median of 2650.0 g (range, 2250.0–3281.3). LSVC showed a higher incidence in twin fetuses (16.7% vs. 2.6%, $P = 0.038$) and a higher rate of associated cardiac anomalies (43.8% vs. 7.7%, $P < 0.001$) with an odds ratio of 0.11 (95% CI 0.03–0.40, $P = 0.001$). However, the prevalence of associated extracardiac anomalies did not significantly differ between LSVC and PRUV (10.4% vs. 20.5%, $P = 0.312$). Genetic analyses were conducted in 41 cases of LSVC and 26 cases of PRUV, with positive results observed in 9.8% and 7.7% of fetuses, respectively ($P = 1.000$).

LSVC could be observed with or without a right SVC, as depicted in Fig. 3. In Fig. 3A–C, a fetus exhibited both a right SVC and LSVC with a dilated CS, allowing for the identification of an additional vessel on the left side of the main pulmonary artery (4 vessels) in the 3VT view. The 3D reconstructed image provided valuable information about the course of the LSVC and its drainage into the CS. In the only one case of a fetus with LSVC in the absence of a right SVC (Fig. 3D–F), only 3 vessels were recognized, and the course of the brachiocephalic vein could be highlighted, illustrating blood flow from the head and right arm towards the LSVC. A wide spectrum of associated congenital heart defects was identified in fetuses with LSVC (Figs. 4 and 5).

PRUV was diagnosed through axial plane imaging of the upper abdomen, which revealed the UV directing towards the fetal stomach. 3D imaging demonstrated spatial visualization of the IVC, umbilico-porto-hepatic system, DV, and associated cardiac anomalies (Fig. 6).

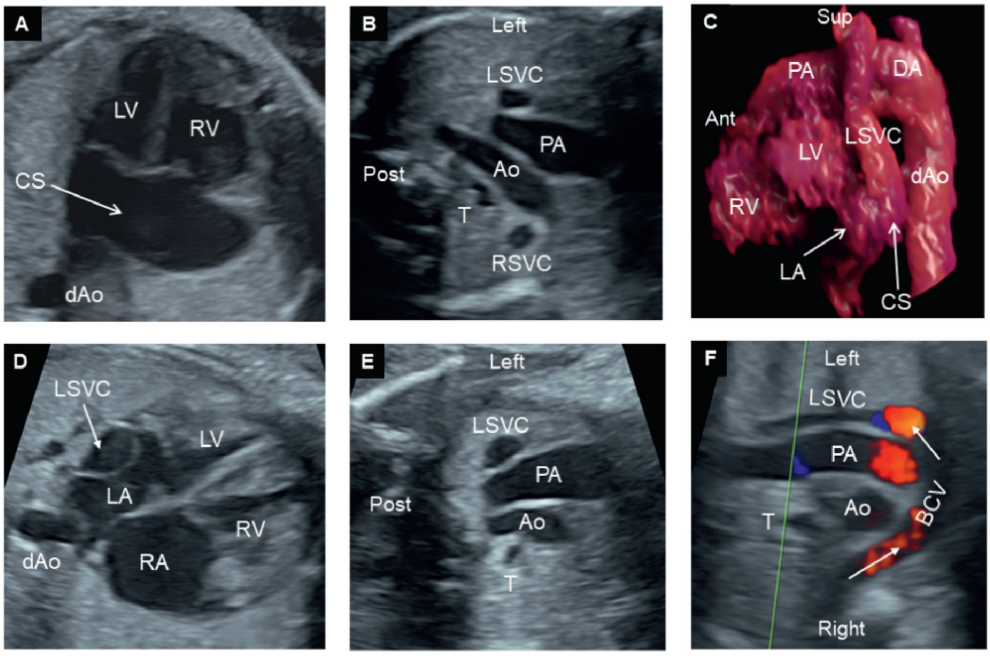

Fig. 3. Two fetuses with persistent left superior vena cava (LSVC) are shown. In the first case (31 $\frac{4}{7}$ weeks' gestation) (A–C), both LSVC and right superior vena cava (RSVC) are present. (A) shows a dilated coronary sinus (CS) just below the 4-chamber view. (B) illustrates 4 vessels in the 3-vessel-and-trachea (3VT) view. (C) presents a 3D HDlive flow monochromatic image from the left parasagittal view of the heart, displaying the course of the LSVC and its drainage into the CS. In the second case (36 $\frac{5}{7}$ weeks' gestation) (D–F), only LSVC is present; RSVC is absent. (D) displays the LSVC in cross-section at the left border of the left atrium (LA). (E) shows recognition of only 3 vessels in the 3VT view. (F) highlights the course of the brachiocephalic vein (BCV) on color Doppler, indicating the direction of blood flow from the head and right arm toward the LSVC at the plane between the 3VT and upper mediastinum. Ant, anterior; Ao, aortic arch; DA, ductus arteriosus; dAo, descending aorta; LV, left ventricle; PA, main pulmonary aorta; Post, posterior; RA, right atrium; RV, right ventricle; Sup, superior; T, trachea.

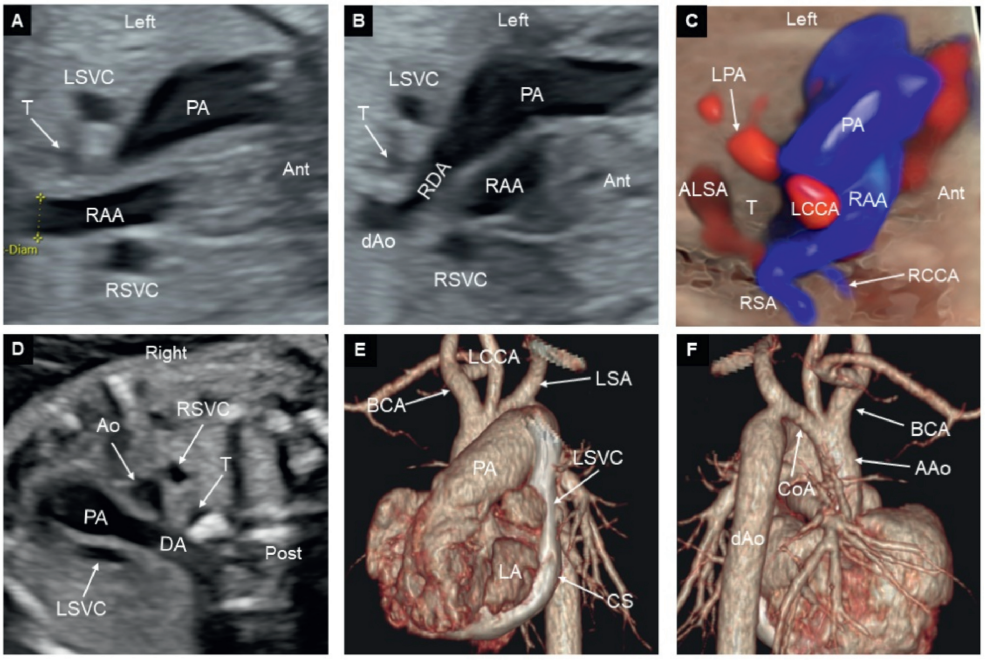

Fig. 4. Two fetuses with persistent left superior vena cava (LSVC) in combination with congenital heart disorders are depicted. In the first case (20 $\frac{6}{7}$ weeks' gestation), (A,B) grayscale 3-vessel-and-trachea (3VT) views display both right-sided aortic arch (RAA) and right-sided ductus arteriosus (RDA) and (C) a 3D HDlive flow image reveals both the aortic and ductal arches point towards the right side of the trachea. The left common carotid artery (LCCA), right common carotid artery (RCCA), right subclavian artery (RSA), and aberrant left subclavian artery (ALSA) can be clearly visualized in an anterior to posterior direction relative to the heart. The newborn was well and uneventful. In the second case, (D) the grayscale 3VT view at 24 weeks' gestation shows a hypoplastic segment of the transverse arch (Ao) and (E,F) multidetector computed tomography of the heart after birth reveals the presence of LSVC in combination with CoA between the brachiocephalic artery (BCA) and the ductus arteriosus. At 7-day-old, the aortic arch was repaired using an autologous pulmonary artery patch. AAo, ascending aorta; Ant, anterior; CS, coronary sinus; dAo, descending aorta; LA, left atrium; LPA, left pulmonary artery; LSA, left subclavian artery; PA, main pulmonary artery; Post, posterior; RSVC, right superior vena cava; T, trachea.

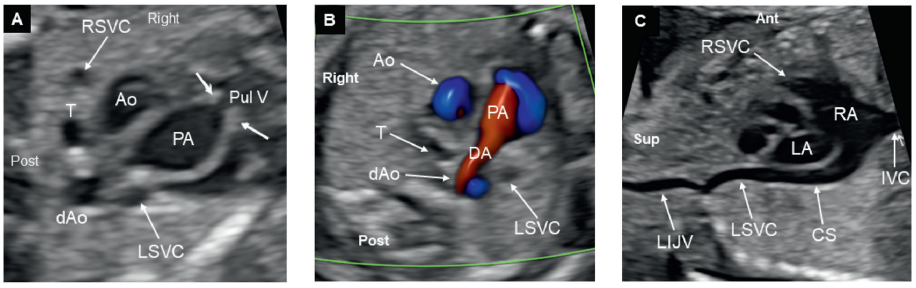

Fig. 5. Images depict a fetus at 25 $\frac{5}{7}$ weeks' gestation with persistent left superior vena cava (LSVC) and critical pulmonary stenosis (valvular and supravalvular). (A) A grayscale transverse view of the upper chest reveals postvalvular dilatation of the main pulmonary artery (PA) and a thickened, echogenic pulmonary valve (Pul V). (B) Radiant flow display records turbulent flow across the pulmonary valve and retrograde flow from the ductus arteriosus (DA). (C) The left parasagittal plane image displays the course of the LSVC and its drainage into the coronary sinus (CS). At 2 days old, percutaneous transluminal pulmonary valvuloplasty was performed. Ant, anterior; Ao, aortic arch; dAo, descending aorta; IVC, inferior vena cava; LA, left atrium; LIJV, left internal jugular vein; Post, posterior; RA, right atrium; Sup, superior; RSVC, right superior vena cava; T, trachea.

Rarer venous disorders

Rare and subtle venous anomalies exhibited distinct features and outcomes. For instance, one fetus had a DV-systemic shunt (Fig. 7A and B), with the DV draining into the CS, but it was born full-term and develops normally. Conversely, another fetus with an umbilical-systemic shunt (Fig. 7C and D) faced complications, including cardiomegaly, poor portal system development, agenesis of the DV, and preauricular tags, leading to pregnancy termination. In a separate case, a fetus exhibited both intrahepatic portal-systemic shunt and DV-systemic shunt (Fig. 7E–G). Despite being growth-restricted, the baby was born full-term, and postnatal imaging confirmed the presence of portosystemic communications (Fig. 7H). These shunts resolved by 6 months, with transient neonatal hyperammonemia and elevated liver enzyme levels. Another 2 fetuses with isolated DV agenesis but no portosystemic shunt had a favorable outcome.

In addition, a case of cardiac-type TAPVC revealed a common posterior pulmonary vein with no connection to the left atrium, accompanied by an enlarged retro-atrial space (Fig. 8A and B). A direct connection was observed between the vertical vein and the right atrium (Fig. 8C). This fetus also presented other malformations, including a common arterial trunk (type A1), right aortic arch with a U-shaped vascular ring, and congenital high airway obstruction syndrome (Fig. 8D–F), which led to pregnancy termination.

Discussion

The current study provided valuable insights regarding a wide spectrum of venous abnormalities in a cohort of well-studied

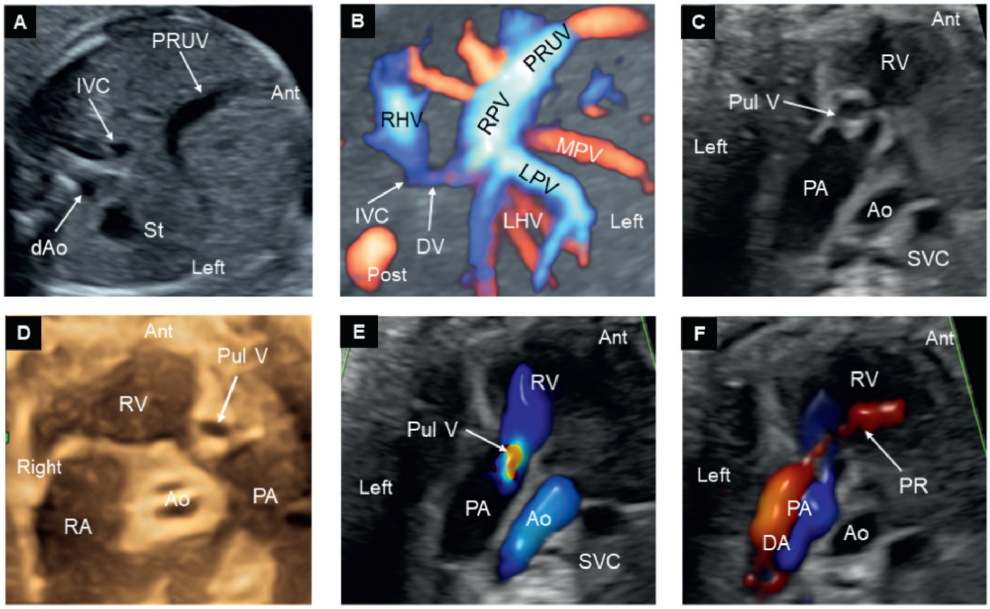

Fig. 6. Images depict a fetus with persistent right umbilical vein (PRUV) and severe pulmonary stenosis (valvular). At 21 $\frac{6}{7}$ weeks' gestation, (A) grayscale and (B) 3D glass body mode transverse views of the upper abdomen reveal the umbilical vein curving toward the fetal stomach (St). These images also provide the spatial relationship between the inferior vena cava (IVC), umbilico-porto-hepatic system, and ductus venosus (DV). At 35 $\frac{5}{7}$ weeks' gestation, (C) the grayscale 3VT view and (D) the short axis view in 3D glass body mode highlight the presence of thickened and stenotic pulmonary valve (Pul V). (E) The radiant flow display demonstrates color aliasing across the pulmonary valve, indicating turbulent blood flow. Furthermore, (F) the presence of pulmonary regurgitation (PR) suggests a dysplastic nature of the Pul V. Percutaneous transluminal pulmonary valvuloplasty was performed when the neonate was 2 days old. Ant, anterior; Ao, aortic arch; dAo, descending aorta; LHV, left hepatic vein; LPV, left portal vein; PA, main pulmonary artery; MPV, main portal vein; Post, posterior; RA, right atrium; RHV, right hepatic vein; RPV, right portal vein; RV, right ventricle; SVC, superior vena cava.

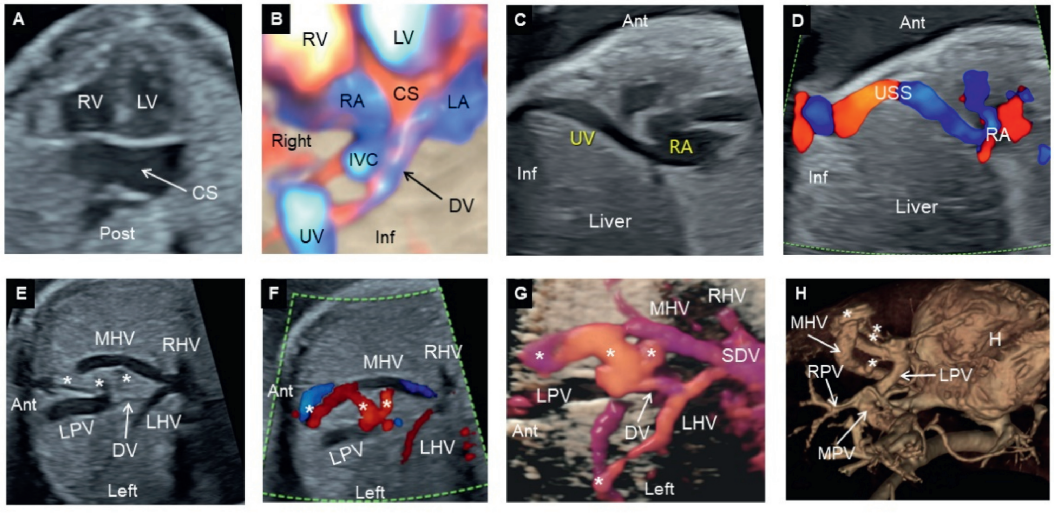

Fig. 7. Images show 3 fetuses with umbilico-portal-systemic shunts. In the case of ductus venosus-systemic shunt (DVSS) at 21 $\frac{5}{7}$ weeks' gestation, (A) shows a prominent coronary sinus (CS) can be visualized slightly inferior to the 4-chamber view. (B) depicts the ductus venosus (DV) draining into the CS in the sagittal plane, captured using a 3D HDlive flow image. The baby was born full-term and uneventful. In the case of umbilical-systemic shunt (USS) at 24 $\frac{2}{7}$ weeks' gestation, (C) reveals a direct connection between the umbilical vein (UV) and the right atrium (RA) in the sagittal planes, both in the grayscale image and the color Doppler image (D). This pregnancy was terminated. In the case of intrahepatic portal-systemic shunt, combined with DVSS, at 33 $\frac{6}{7}$ weeks' gestation, (E) displays multiple shunts between the left portal vein (LPV) and the middle and left hepatic vein (MHV and LHV), marked with (*), as well as DV direct drainage into the LHV in the grayscale image, the color Doppler image in (F), and the 3D HDlive flow monochromatic image in (G). Postnatally, multidetector computed tomography of the abdominal vessels reveals the presence of multiple portosystemic communications (*) between the portal and hepatic veins in various hepatic segments, as demonstrated in (H). The shunts resolved at 6 months of age. Ant, anterior; H, heart; HV, hepatic vein; Inf, inferior; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MPV, main portal vein; Post, posterior; RHV, right hepatic vein; RPV, right portal vein; RV, right ventricle; SDV, subdiaphragmatic vestibulum.

subjects prenatally. Fetal venous malformations occurred in 1.35% of cases in our study. We discovered various associated cardiac and extracardiac defects with diverse manifestations and outcomes. High-resolution ultrasonography with color Doppler imaging was invaluable for assessing the venous system's complexities [1,2]. Our comprehensive fetal venous system evaluation during fetal echocardiographic examinations employed a strategic 2D ultrasound technique, consistently delivering informative data. Integrating the 3D/4D STIC modality allowed us to study subtle or uncertain venous problems (Figs. 3, 4, and 6-8), particularly umbilico-portal-DV (Fig. 7) and pulmonary venous return disorders (Fig. 8).

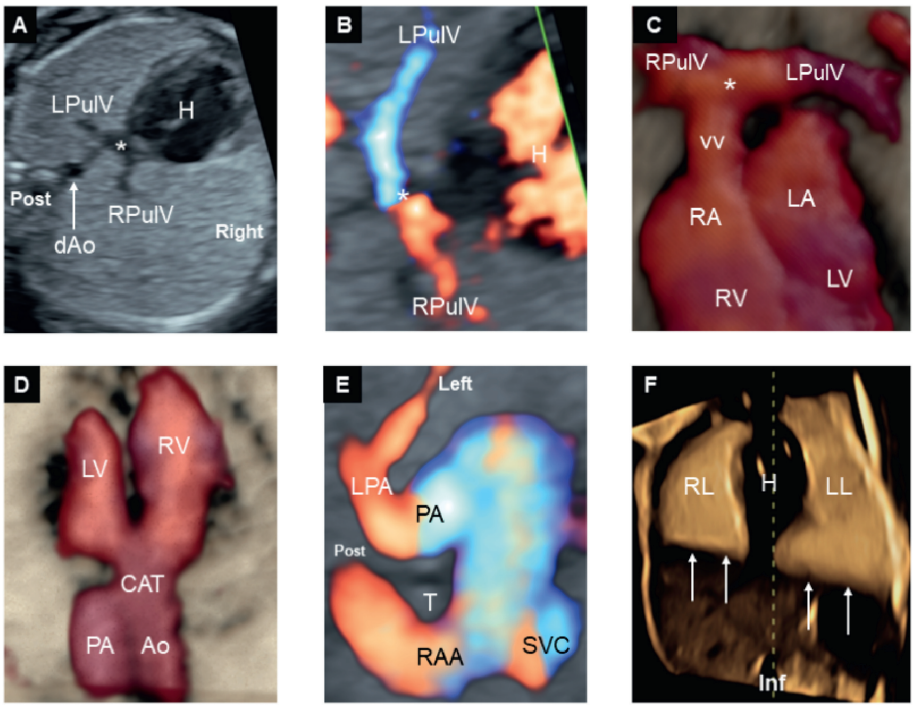

Fig. 8. Images depict a fetus at 22 $\frac{6}{7}$ weeks' gestation with total anomalous pulmonary venous connection (TAPVC) and multiple malformations. The 4-chamber views in (A) grayscale and (B) color Doppler images reveal a common pulmonary vein (*) situated posterior to the heart, lacking a connection to the left atrium (LA), and causing an enlarged retro-atrial space. (C) A 3D HDlive flow monochromatic image displays the direct connection of the vertical vein (vv) to the right atrium (RA). This fetus with cardiac type TAPVC also presents associated malformations, including (D) common arterial trunk (CAT) type A1, (E) right aortic arch (RAA) with a U-shaped vascular ring, and (F) congenital high airway obstruction syndrome featuring hyperechogenic lungs (RL and LL), diaphragmatic flattening (arrows), and a midline positioned, compressed heart (H). This pregnancy was terminated. Ao, aortic arch; Inf, inferior; LPA, left pulmonary artery; LPulV, left pulmonary vein; LV, left ventricle; PA, main pulmonary artery; Post, posterior; RPulV, right pulmonary vein; RV, right ventricle; SVC, superior vena cava; T, trachea.

Unraveling fetal venous disorders with modified approach

Traditionally, the fetal heart examinations did not widely evaluate the fetal venous conditions [5,6]. Our study, conducted from November 2015 to May 2022, represents a significant advancement in expanding existing knowledge. In 2023, Moon-Grady et al. highlighted the importance of assessing systemic (umbilical vein, DV, hepatic veins, SVC, and IVC) and pulmonary venous anatomy in fetal echocardiography [7]. Therefore, our integrated u ltrasound technique systematically enhanced our understanding of the fetal venous disorders, with a focus on diagnostic accuracy over time efficiency.

Unlike the systematic approach published in 2013 [8], our retrospective cohort study introduced key differences: (1) exclusion of the CS view due to its rarity of anomalies and technical complexity, (2) a strong emphasis on the complete 3-vessel view rather than only 3VT view, and (3) the incorporation of 3D/4D STIC modality. Instead of the challenging CS view, we found practically in the 4-chamber or 3V/3VT views, which allowed for amendable diagnoses of various malformations related to CS. In cases of abnormal 2D findings (12 cases), we transitioned to the advanced 3D/4D STIC modality for an in-depth exploration. Furthermore, the usefulness of 3D anatomical landmarks within the high mediastinum offered clear visualization of neighboring vessels around the thymus box.

Diverse manifestations and outcomes

LSVC, the most common anomalous systemic venous return, occurs in 0.3%–0.5% of the general population [9]. In our prenatal series, LSVC was identified in 0.66% of cases, with 56.2% being isolated findings. Associated cardiac malformations were broad spectrum and observed in 43.8% of LSVC cases. Isolated LSVC is generally benign but requires caution when associated with a dilated CS due to potential aortic coarctation [9,10]. Furthermore, the prevalence of PRUV in fetuses was reported at 0.38%, with 76.6% being isolated and 8.7% having associated cardiac defects [11]. Our study found a 0.54% prevalence of PRUV cases, with 71.8% being isolated and showing favorable outcomes. In non-isolated PRUV cases, 7.7% had concurrent, non-specific cardiac anomalies. Isolated PRUV cases with normal DV and portal system branching displayed unremarkable hemodynamics [12]. Similar to LSVC cases, a PRUV diagnosis warrant comprehensive fetal morphology assessment, particularly focusing on the cardiovascular system.

Our prenatal study revealed a 0.10% prevalence of disorders involving the umbilical-portal-DV complex, leading to varying outcomes. Accurate assessment of the relationship between portal veins, hepatic veins, and shunting is crucial, aided by targeted color Doppler examination and even 3D imaging. To avoid missing the target, the upper abdominal plane with slight cephalic and caudal angulations can visualize a shunt from the portal system to the systemic veins. According to Achiron et al. (2016) [4], umbilical-portal-systemic venous shunts were classified as umbilico-systemic shunt (type I), DV-systemic shunt (type II), intrahepatic porto-systemic shunt (type IIIa), and extrahepatic porto-systemic shunt (type IIIb). This proposed in utero classification was based on the embryological-anatomical origin of the shunt and applied in our study. Prognosis depends on the presence of portosystemic shunts and the status of portal venous circulation [13]. However, fetal cardiac dysfunction signs (e.g., cardiomegaly and hydrops)

necessitates timely delivery. Postnatal angiography remains superior to prenatal ultrasound for identifying subtle anatomical or morphological changes [14]. Isolated DV agenesis generally carries a good prognosis [15].

TAPVC and partial anomalous pulmonary venous connections (PAPVC) are very rare anomalies, with a low detection rate (<2%) [16,17]. In our cohort, a prevalence of 0.10% cases with anomalous pulmonary venous connections was identified. 3D image was straightforward and informative (Fig. 8C). Supracardiac TAPVC is the most common type, followed by infracardiac, cardiac, and mixed type [18]. Key echocardiographic signs include ventricular disproportion, an increased area behind the left atrium, and the presence of a vertical vein [16]. Prognosis depends on the presence of pulmonary venous obstruction, associated cardiac anomalies (e.g., heterotaxy syndrome), and the extent of right-to-left intracardiac shunting [16,18,19].

Clinical implications

Under normal circumstances, during routine fetal echocardiography, fetal venous system and intracardiac structure survey could be concomitantly performed effectively. We recommend fetal venous screening is part of routine 2nd trimester fetal cardiovascular examination. The significance of conducting a thorough assessment and optimizing postnatal care for fetal venous disorders is underscored by the existence of concurrent anomalies. Employing an integrated fetal echocardiographic approach facilitates a thorough examination and enhances the detection rate of these disorders.

Study limitations

This study has several limitations that should be acknowledged. Firstly, our study population consisted of individuals with relatively high–risk profiles, which could potentially introduce bias into the calculation of malformation rates. Secondly, due to various maternal or fetal factors, complete examinations were not feasible for all cases, potentially leading to the oversight or underdiagnosis of some venous disorders during the prenatal period. This limitation could impact the comprehensiveness of our data. Thirdly, because of the retrospective nature of our study, inherent limitations such as incomplete or missing information may exist, which could introduce potential statistical bias and affecting the accuracy and reliability of our findings.

Conclusion

Fetal venous system embryology is intricate, encompassing a wide range of developmental abnormalities and morphological variations. In this extensive retrospective study, we employed an integrated and systematic approach to comprehensively assess the fetal venous system, providing insights into various venous anomalies. This study contributes to the ongoing advancement of prenatal cardiac assessment, ultimately aiding in the improved care of affected fetuses and neonates.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Original Article

A nomogram to predict platinum-sensitivity and survival outcome in women with advanced epithelial ovarian cancer

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ABSTRACT

Objective: This study presents the development and validation of a nomogram aimed at predicting platinum-sensitivity and survival outcomes in women with advanced epithelial ovarian cancer (EOC).
Materials and methods: Data from a retrospective cohort of women diagnosed with stage III/IV EOC between Jan 2011 and Dec 2021 treated at our institute were collected. Clinical and pathological characteristics were analyzed using logistic regression analysis to identify independent predictors of platinum-sensitivity. Impact on progression-free (PFS) and overall survival (OS) was determined by Kaplan–Meier and Cox regression analysis. A nomogram was constructed based on the significant predictors, and its performance was evaluated using calibration, discrimination, and validation analyses.
Results: Of the 210 patients, 139 (66.19%) had platinum-sensitive and 71 (33.81%) were platinum-resistant disease. On multivariate analysis, platinum-resistance correlated with neoadjuvant chemotherapy (OR 2.15; 95% CI 1.10–4.21), clear cell/mucinous histology (OR 5.04; 95% CI 2.20–11.54), and suboptimal debulking status (OR 3.37; 95% CI 1.44–7.91). Median PFS and OS were also significantly shorter for patients with neoadjuvant chemotherapy (23 vs. 10 months and 69 vs. 29 months, respectively), clear cell/mucinous histology (15 vs. 3 months and 63 vs. 11 months, respectively), and suboptimal debulking (26 vs. 5 months and 78 vs. 24 months, respectively). The nomogram demonstrated good predictive accuracy for platinum-sensitivity in the cohort as indicated by high concordance index of 0.745. Calibration plots showed excellent agreement and internal validation further confirmed the reliability of the nomogram's performance.
Conclusion: A novel predictive nomogram based on type of initial treatment, histology, and debulking status was developed, which provides a friendly and reliable tool for predicting platinum-sensitivity and survival outcomes in women with advanced EOC. Its application may assist clinicians in individualizing treatment decisions.

Introduction

Epithelial ovarian cancer (EOC) accounts for the majority of ovarian cancer cases, constituting approximately 90% of all ovarian malignancies [1]. Most patients are diagnosed at a late stage due to several factors, including the absence of specific early symptoms and effective screening tests [2]. The aggressive nature of advanced EOC and its widespread involvement within the peritoneal cavity make surgical resection more complexity, contributing to its status as a formidable challenge in the field of gynecologic oncology. Cytoreductive surgery followed by platinum-based chemotherapy has been the cornerstone of treatment for decades; however, the development of platinum resistance remains a major obstacle, leading to limited treatment options and poorer outcomes with a medium survival of only 6–12 months [3]. On average, the 5-year survival rate for stage III and IV EOC ranges from approximately 20%–30% [4].

Although there are several strategies aimed at overcoming platinum-sensitivity, platinum resistance still remains a significant challenge [5]. Additionally, there is significant heterogeneity in patient responses to platinum-based therapies, with some women showing exceptional sensitivity to treatment, while others experience early progression and reduced survival. In light of these clinical complexities, there is a critical need for accurate and reliable

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predictive tools to identify patients who are likely to respond favorably to platinum-based therapies and to estimate individual survival outcomes. Traditional clinical and pathological factors alone may not be sufficient to adequately stratify patients and guide treatment decisions. The prediction of chemosensitivity often involves considering multiple factors in combination. Recent studies have demonstrated that hemogram data, such as platelet count and neutrophil-to-lymphocyte (N/L) ratio, can serve as prognostic parameters in EOC, highlighting the significant role of inflammation in carcinogenesis [6,7]. However, our literature review revealed that only a limited number of researchers have developed and consolidated prediction models incorporating these pretreatment hemogram data.

A nomogram, as a multifactorial predictive model, offers the potential to integrate a wide range of clinical, pathological, and molecular characteristics to provide individualized risk estimates for both platinum-sensitivity and survival outcomes [8]. The development of such a nomogram can help clinicians tailor treatment strategies, select appropriate therapeutic combinations, and identify patients who may benefit from alternative or investigational therapies. In this study, we attempted to construct and validate a novel nomogram for predicting platinum-sensitivity and survival outcomes in a cohort of women with advanced EOC. By utilization an extensive dataset with inclusion of hemogram data and employing advanced statistical methods, we aimed to identify independent predictors and develop an easily interpretable nomogram that can aid clinical decision-making and improve patient outcomes.

Material and methods

This study employed a retrospective cohort design to investigate the predictive capabilities of a nomogram for platinum-sensitivity and survival outcomes in women with newly diagnosed advanced EOC who underwent cytoreductive surgery and platinum-based chemotherapy. Data from women diagnosed with stage III/IV EOC between Jan 2011 and Dec 2021 treated at Kaohsiung Chang Gung Memorial Hospital were collected. Relevant clinical, pathological, and treatment data were retrieved from medical records, including age at diagnosis, parity, histological subtype, FIGO stage, preoperative CA-125 levels, platelet counts, N/L ratios, and details of surgical and platinum-based chemotherapy (e.g., residual disease and the addition of bevacizumab, response to therapy). Patients with non-EOC, without undergoing cytoreductive surgery, lacking complete clinical and treatment data, or those chemotherapy less than 6 cycles were excluded. Patients who underwent neoadjuvant chemotherapy (NACT) followed by interval debulking surgery were also eligible for inclusion. Treatment outcomes were retrospectively reviewed using RECIST and Gynecological Cancer Intergroup CA125 related-response criteria [9]. In present study, platinum-resistance refers to disease that progresses or recurs within six months of completing platinum-based treatment. This study was conducted in compliance with relevant ethical guidelines and approved by the Institutional Review Board of Chang Gung Memorial Hospital (No.202301253B0).

Descriptive statistics were used to summarize patient characteristics and clinicopathological factors. We used receiver operating characteristic (ROC) curve analysis, area under the curve (AUC) calculation, and Youden's index to identify potential cutoff points of CA-125 levels, platelet counts, and N/L ratios that could be used to predict platinum-sensitivity. Univariate and multivariate logistic regression analyses were then performed to identify independent predictors by calculating the odds ratio (ORs) and corresponding 95% confidence intervals (CIs). Impact of independent predictors on progression-free (PFS) and overall survival (OS) was determined by Kaplan–Meier analysis and the significance of difference was calculated by log rank test. Those of significant predictors were also included in multivariate Cox regression analysis to identify independent prognostic factors. PFS and OS were defined as the time from the start of treatment until the disease progresses and until death from any cause, respectively. A nomogram was constructed to calculate individualized probabilities of platinum-sensitivity based on the significant predictors, and its performance was evaluated using calibration, discrimination, and validation analyses. Briefly, calibration plots were generated to compare predicted probabilities against observed outcomes. Internal validation was performed using 300 bootstrapping techniques to assess the nomogram's accuracy and discrimination within the study cohort. Discrimination analysis was conducted by calculating the area under the ROC curve to evaluate the nomogram's ability to differentiate between platinum-sensitive and resistant cases and to estimate probabilities. We calculated the concordance index (c-index) for each bootstrap sample, which represents the model's predictive accuracy. Data management and analysis were performed using SPSS software for Windows version 22 and MedCalc software version 22.003. A p-value less than 0.05 was considered statistically significant. The statistical analysis of nomogram was performed using R 4.1.0 software, available online.

Results

Initially, a total of 817 patients with newly diagnosed ovarian cancer during the study interval were recruited. After screening of these patients, 210 women with advanced EOC who met the inclusion criteria were finally included in this study. Among them, 139 patients (66.19%) were classified as having platinum-sensitive disease, while 71 patients (33.81%) were categorized as platinum-resistant. Fig. 1 shows the flowchart of study cases enrollment. The median age of the entire cohort was 54 years (interquartile range 49–63), and most of patients were FIGO stage III (64.76%) disease. Serous carcinoma accounted for 63.81% while clear cell (CCC) and mucinous carcinoma (MUC) accounted for 20% of our study populations. Forty percent of patients received NACT followed by interval debulking surgery. Optimal debulking surgery with residual tumor less than 1 cm was achieved in 120 patients (57.14%). Only 36 patients (17.14%) had bevacizumab combination treatment. Detailed demographic characteristics of patients in terms of platinum-sensitivity is shown in Table 1.

The medium PFS and OS rates of the entire cohort were 13 months (95% CI 8.01–17.99) and 55 months (95% CI 39.91–70.09), respectively. The optimal cutoff values of CA-125, platelet count, and N/L ratio for prediction of platinum-sensitivity were 2910 U/mL (AUC 0.536), 327,000/mm3 (AUC 0.535), and 5.725 (AUC 0.540), respectively. On univariate analysis, stage IV, NACT, CCC or MUC histology, CA-125 > 2910 U/mL, N/L ratio >5.725, and suboptimal debulking were significantly associated with platinum-resistant disease. However, NACT (OR 2.15; 95% CI 1.10–4.21), CCC or MUC histology (OR 5.04; 95% CI 2.20–11.54), and sub-optimal debulking status (OR 3.37; 95% CI 1.44–7.91) were the only independent predictors associated with platinum-sensitivity on multivariate analysis (Table 2). After a median follow up of 55 months, PFS and OS were significant shorter with NACT group, CCC or MUC histology, and suboptimal debulking status. These 3 variables were further confirmed as independent prognostic factors for both PFS and OS (Fig. 2). The median PFS were 10 months versus 23 months in NACT and no NACT arms (HR 1.71, 95% CI 1.19–2.45), 3 months versus 15 months in the CCC or MUC and non-CCC or -MUC arms (HR 1.74 95% CI 1.14–2.65), and 5 months versus 26 months in the suboptimal and optimal debulking arms (HR 1.75, 95% CI 1.08–2.81) (Fig. 3A). The median OS were 29 months versus 69 months in NACT and no NACT arms (HR 1.62, 95% CI 1.02–2.56), 11

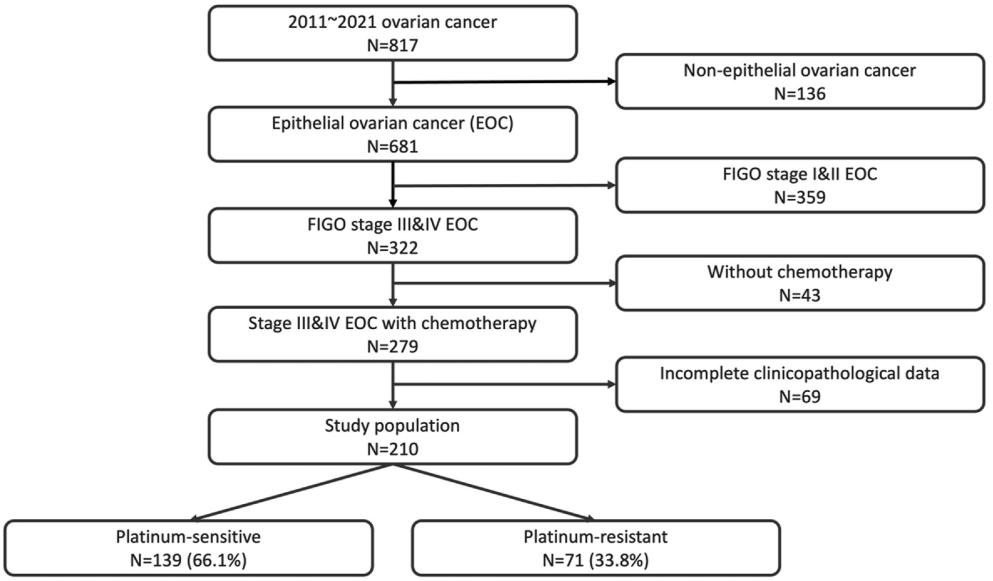

Fig. 1. CONSORT flow diagram of study population enrollment.

months versus 63 months in the CCC or MUC and non-CCC or -MUC arms (HR 3.27, 95% CI 2.01–5.30), and 24 months versus 78 months in the suboptimal and optimal debulking arms (HR 2.27, 95% CI 1.28–4.02) (Fig. 3B).

We used initial treatment mode (NACT or not), histologic type (CCC/MUC or not), and debulking status (suboptimal or not) to construct a nomogram for predicting the risk of platinum-resistance. The nomogram demonstrated good predictive

Table 1
Clinicopathological characteristics of the study population, in related to platinum-sensitivity.

	Total (N = 210)	Platinum sensitive, n (%)	Platinum resistant, n (%)
Age (years) (n = 210, median = 54, IQR = 49–63)			
<55	96	63 (65.6)	33 (34.4)
≥55	114	76 (66.7)	38 (33.3)
Parity (n = 208, median = 2, IQR = 1–3)			
<2	58	36 (62.1)	22 (37.9)
≥2	150	102 (68)	48 (32)
FIGO stage (n = 210)			
III	136	101 (74.3)	35 (25.7)
IV	74	38 (51.4)	36 (48.6)
Neoadjuvant chemotherapy (n = 210)			
No	126	91 (72.2)	35 (27.7)
Yes	84	48 (57.1)	36 (42.8)
Histology (n = 210)			
High grade serous	125	88 (70.4)	37 (29.6)
Low grade serous	9	9 (100)	0
Clear cell	35	17 (48.6)	18 (51.4)
Endometrioid	20	15 (75)	5 (25)
Mucinous	7	1 (14.3)	6 (85.7)
Mixed serous	8	7 (87.5)	1 (12.5)
Adenocarcinoma	6	2 (33.3)	4 (66.7)
Histology (n = 210)			
Non-clear cell, non-mucinous	168	121 (72)	47 (28)
Clear cell or mucinous	42	18 (42.9)	24 (57.1)
CA-125 (U/mL) (n = 204, median = 874.15, IQR = 323.75–2714.4)			
<2910	156	110 (70.5)	46 (29.5)
≥2910	48	26 (54.2)	22 (45.8)
Platelet (1000/μL) (n = 207, median = 343, IQR = 278–437)			
<327	86	64 (74.4)	22 (25.6)
≥327	121	74 (61.2)	47 (38.8)
N/L ratio (n = 191, median = 4.12, IQR = 2.93–5.54)			
<5.725	168	117 (69.6)	51 (30.4)
≥5.725	42	22 (52.4)	20 (47.6)
Residual disease (n = 210)			
Optimal	120	120 (79.2)	25 (20.8)
Suboptimal	90	44 (48.9)	46 (51.1)
Adjuvant chemotherapy with Bevacizumab (n = 210)			
Yes	36	27 (75)	9 (25)
No	174	112 (64.4)	62 (35.6)

CA-125, cancer antigen 125; IQR, interquartile range; N/L, neutrophile/lymphocyte.

Table 2
Logistic regression analysis of the risk factors for platinum-resistant advanced ovarian cancer.

	Univariate			Multivariate		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age ≥55 years	0.96	0.54–1.69	0.874	–	–	–
Parity ≥2	0.77	0.41–1.45	0.418	–	–	–
FIGO stage IV	2.73	1.51–4.69	0.001*	1.12	0.48–2.64	0.795
NACT	1.95	1.09–3.49	0.025*	2.15	1.10–4.21	0.026*
CCC or MUC	3.43	1.71–6.90	0.001*	5.04	2.20–11.54	<0.001*
CA-125 ≥ 2910 U/mL	2.02	1.04–3.93	0.037*	1.60	0.75–3.43	0.223
Platelet ≥$327*10^3$/μL	1.85	1.01–3.39	0.05	–	–	–
N/L ratio ≥5.725	2.09	1.05–4.15	0.037*	1.725	0.78–3.79	0.175
Suboptimal debulking	3.97	2.17–7.27	<0.001*	3.37	1.44–7.91	0.005*
No Bevacizumab	0.60	0.27–1.36	0.223	–	–	–

* *p* value less than 0.05.
CA-125, cancer antigen 125; CCC, clear cell carcinoma; CI, confidence interval; MUC, mucinous carcinoma; NACT, neoadjuvant chemotherapy; N/L, neutrophile/lymphocyte; OR, odds ratio.

accuracy for platinum-sensitivity in the cohort as indicated by high concordance index of 0.745. Calibration plots indicated a high level of agreement between the predicted probabilities and the observed outcomes, supporting the reliability of the nomogram's predictions.

The final results of internal validation further indicated well-calibrated, accurately discriminating between platinum-sensitive and platinum-resistant cases (Fig. 4B). For example, a CCC or MUC patient (100 points) who received a NACT (52 points) followed by

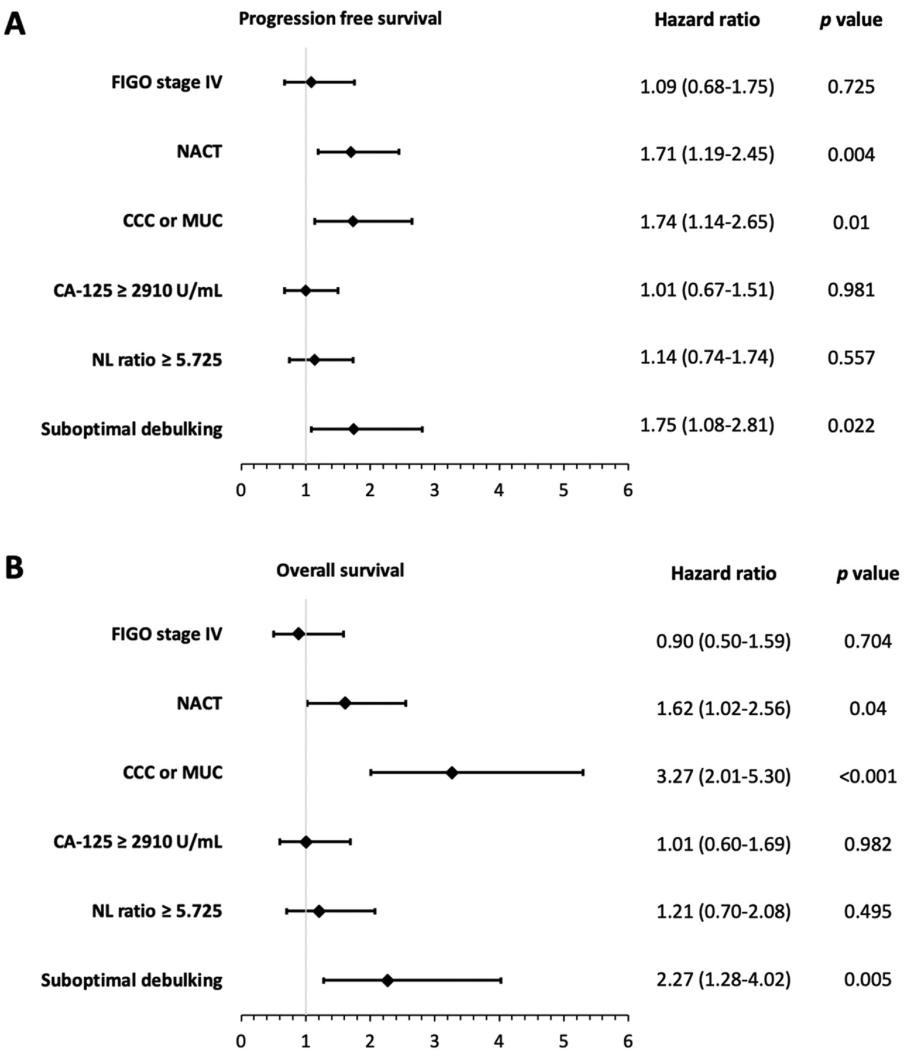

Fig. 2. Multivariate Cox regression model to identify independent prognostic factors. Clear cell/mucinous carcinoma, suboptimal debulking, and neoadjuvant chemotherapy were found to be independently associated with progression-free (A) and overall survival (B).

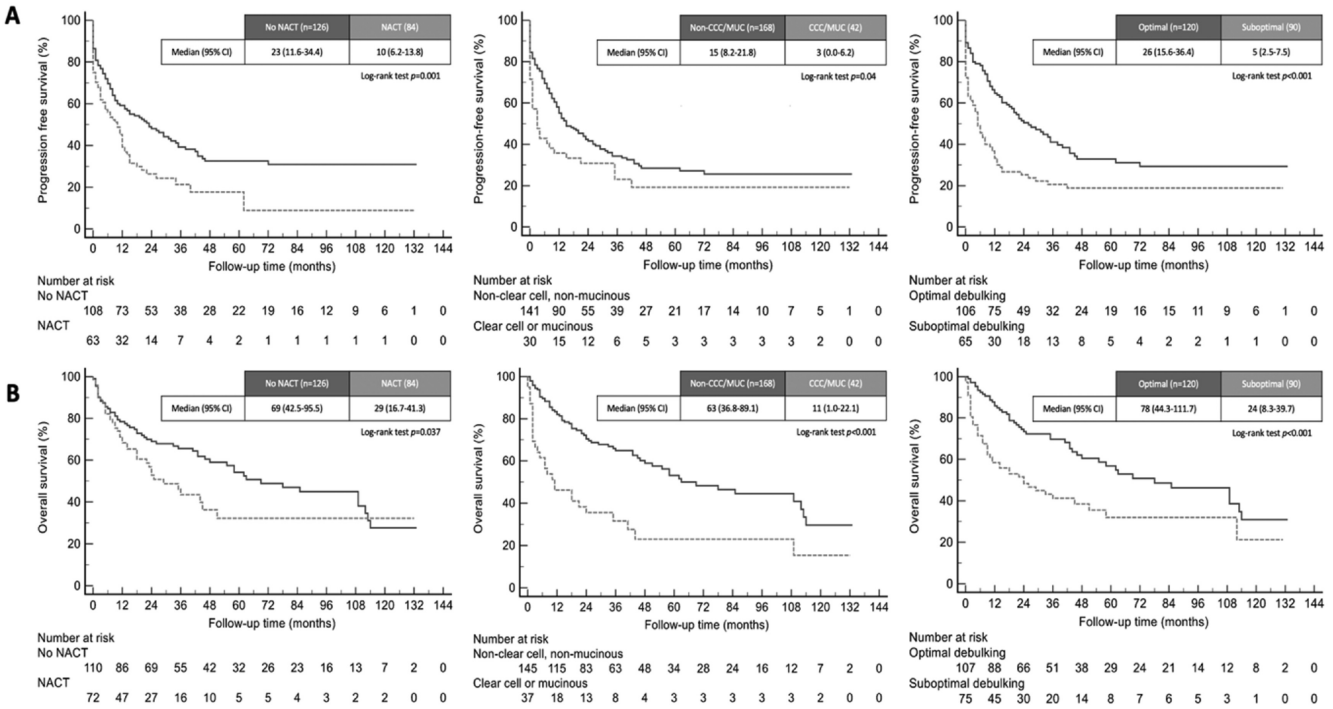

Fig. 3. Kaplan–Meier curves of progression-free (A) and overall survival (B) in the study population according to different subgroups.

suboptimal interval debulking surgery (87 points) would accumulate approximately 239 total points in the model. By projecting 239 points to the bottom risk axis, a platinum-resistant probability of 0.86 can be estimated (Fig. 4A). In contrast, a patient diagnosed with high-grade serous carcinoma, accruing zero points due to their subtype, who underwent initial cytoreductive surgery (0 points) resulting in complete resection without residual tumor (0 points), followed by adjuvant chemotherapy. In this case, the patient would accumulate zero points in the model. By projecting zero points onto the bottom risk axis, the estimated probability of platinum resistance would be nearly zero (Fig. 4A).

Discussion

The present study investigated the intricate interplay among various clinicopathological factors as potential predictors of platinum-sensitivity in advanced EOC. We observed potential associations between NACT, CCC or MUC histology, and suboptimal debulking surgery with a diminished response to platinum-based chemotherapy. These three factors could be used for the development of a prediction model to assess the likelihood of platinum-sensitivity, yielding promising predictive outcomes.

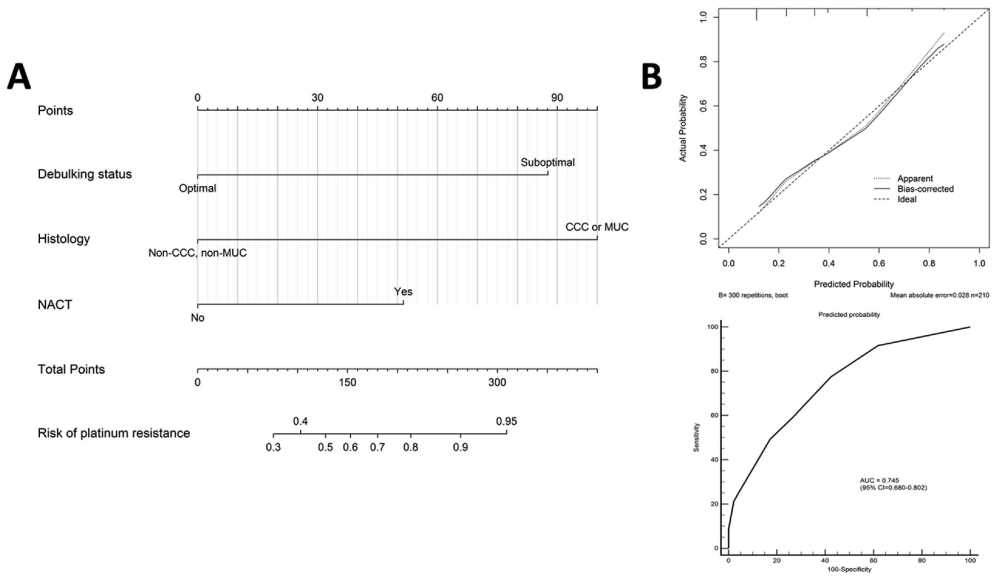

Fig. 4. (A) nomogram predicting the probability of platinum-resistant disease in patients with advanced epithelial ovarian cancer (B) The calibration plot for the prediction model, the C-index (concordance index) was 0.745 and mean absolute error was 0.028.

Several retrospective studies generally concur that advanced-stage ovarian CCC is associated with an unfavorable prognosis, marked by reduced sensitivity to platinum-based chemotherapy compared to serous EOC. Only 11%–27% of CCC patients exhibit responsiveness to platinum-based chemotherapy, in contrast to patients with high-grade serous carcinoma (HGSC), who manifest substantially higher response rates ranging from 73% to 81% [10,11]. The similar findings were also observed in ovarian MUC [12]. Despite exhibiting a diminished response rate attributed to its inherent resistance to conventional platinum-based chemotherapy, the treatment approach for CCC or MUC still parallels that of HGSC [13]. The complex mechanisms driving CCC or MUC's chemotherapy resistance remain incompletely elucidated. Presently, there exists a prevailing understanding that the immune microenvironment significantly contributes to CCC development and pathogenesis. In a prior analysis, programmed death-ligand 1 (PD-L1) expression and deficiency in mismatch repair (MMR) mechanisms were identified in 57% and 67% of CCC cases, respectively [14]. Multiple clinical trials involving PD-1 and PD-L1 monoclonal antibodies are currently in progress. Across the four completed trials involving avelumab, durvalumab, pembrolizumab, and nivolumab, notable efficacy has been observed, emphasizing the potential therapeutic viability of immune checkpoint inhibitors [15–18]. Although these clinical trials had relatively small CCC sample sizes and needs further validation, anti-PD-1 or -PD-L1 antibodies hold promise as novel therapeutic agents for ovarian CCC patients. Unlike CCC, MUC is presently categorized as immunologically 'cold.' In a recent study encompassing 126 MUC patients, 86% exhibited an immune-depleted (cold) phenotype, while a mere 14% displayed an immune-inflamed (hot) status characterized by T cell and PD-L1 infiltrates [19]. These findings suggest that MUCs might exhibit limited responsiveness to existing immunotherapeutic approaches. Recently, the biomarkers for ovarian MUC, including the *KRAS* and *HER2-neu* genes, *MEK*, and *PI3K*, and their corresponding molecular target drugs such as trastuzumab, lapatinib, and cetuximab have been gaining attention [20]. In a small series genotype-matched clinical trial, 2 MUC patients with *KRAS* mutation experienced partial response to *MEK*-based combination therapy demonstrating an active therapeutic strategy [21]. Additional prospective studies with more cases are warranted.

Neoadjuvant chemotherapy followed by interval debulking surgery has been established as an alternative treatment approach for advanced-stage EOC based on two randomized controlled trials [22,23]. While NACT offers advantages such as reduced intraoperative complications and increased rates of achieving optimal debulking, the relationship between the timing of surgery and platinum-sensitivity remains understudied. Following these two trials, researchers have sought to investigate the potential correlation between NACT and the subsequent likelihood of platinum-resistance in EOC patients. Rauh-Hain et al. were the pioneers in demonstrating that patients receiving NACT faced an elevated risk of developing platinum-resistant disease (44.2% vs. 31.2%) in comparison to upfront surgery [24]. Similarly, Petrillo et al. observed a noteworthy discrepancy in the incidence of platinum-resistant disease (36% vs. 5%) and a shorter platinum-free interval [25]. Luo et al. found that NACT was an independent risk factor for platinum-resistant recurrence with an OR of 2.95 (95% CI 1.57–5.54)—a finding consistent with our own result [26]. da Costa et al. extended the investigation by using time to platinum-resistant recurrence as the endpoint. Their findings aligned with prior research, confirming that NACT was associated with an elevated risk of platinum-resistant disease [27]. The underlying mechanism behind the propensity of NACT to induce platinum-resistance lies in the fact that patients undergoing NACT often present with large-volume unresectable disease prior to treatment. Such substantial tumors may lead to a higher probability of housing resistant clones by enriching cancer stem cells when subjected to initial platinum-based treatment rather than surgical intervention [28,29].

It is well established that platinum-resistant disease stands as a significant independent prognostic factor. Such patients exhibit diminished response rates to subsequent lines of chemotherapy, translating to poorer survival compared to platinum-sensitive counterparts. Therefore, factors predictive of platinum-sensitivity are theoretically intertwined with survival outcomes. Notably, suboptimal debulking and CCC/MUC are well recognized predictors of platinum-resistant recurrence, coinciding with their prognostic significance—findings that agree with our study's observations. Interesting, our results not only establish NACT as an independent predictor for heightened platinum-resistant risk but also underscore its implications on survival. However, this contradicts with the majority of previous studies [24–27]. The rationale behind this discrepancy might be the higher rate of optimal interval debulking surgery following NACT, which potentially counteracts the unfavorable platinum-resistant effect induced by NACT. In our study, the rates of optimal debulking were 62.7% and 48.8% for the NACT and primary surgery groups, respectively. Although statistically significant ($p = 0.046$), this difference was remarkably smaller than in Luo et al.'s study (84.5% vs. 46.3%, $p < 0.001$) and similar to da Costa et al.'s findings (76.7% vs. 62.3%, $p = 0.022$) and Rauh-Hain et al.'s results (91.5% vs. 82.7%, $p = 0.03$) [24,26,27]. While the exact magnitude of the impact of optimal debulking rate disparity on neutralizing the adverse chemo-resistant effect prompted by NACT remains uncertain, evidence suggests a proportional relationship—the larger the difference, the lesser the impact on survival. For example, the p-values for OS differences were 0.25 for Luo et al. suggesting no difference [26], 0.07 and 0.08 favoring the primary surgery group in Rauh-Hain et al. and da Costa et al. respectively [24,27], and a significant improvement in the primary surgery group ($p = 0.037$) in our study. A recent database study including 5522 patients further validated that survival outcomes were inferior in the NACT group when complete resection was not attainable. The study authors concluded that the primary goal when using NACT should be the achievement of complete resection for all residual disease, rather than only reducing residual disease to less than 1 cm [30]. Another interesting finding is the considerable variation in NACT rates across various study cohorts, ranging from as low as 17% to as high as 77% [24–27]. Such substantial disparities might be attributed to the absence of stringent NACT selection criteria in real-world clinical practice.

A similar scenario could also be observed in the utilization of bevacizumab. Bevacizumab was shown to be most effective in patients with poorly chemo-sensitive advanced EOC and to reduce platinum-resistant recurrence [31,32]. Nevertheless, the current non-reimbursement of this drug in Taiwan's National Health Insurance program resulted in a substantial proportion of patients (82.8% in our study) not receiving bevacizumab as part of their treatment regimen. Moreover, our study revealed no discernible disparity in bevacizumab use between the optimal and suboptimal debulking groups (16.7% vs. 17.8%, $p = 0.83$). Taken together, these findings provide context for the lack of significant association between bevacizumab usage and both platinum-sensitivity and survival, which is opposite to the results observed in several prior well-designed studies [33,34].

It is essential to acknowledge certain limitations inherent in our study. First, the retrospective single center chart review nature introduces the potential for unmeasured confounders. Second, our study has a relatively smaller sample size than similar studies performed in this domain. Third, we lacked external validation in independent cohorts to ensure the accuracy of our prediction

model. Forth, homologous recombination deficiency status (BRCA 1/2 mutation etc.), which is an indicator of better response to platinum-based chemotherapy and better prognosis [35,36], was not checked or recorded as a parameter in this study. Hence, in order to confirm these findings, it is imperative to conduct a comprehensive, multicenter study on a larger scale to validate our findings.

In conclusion, we developed a novel predictive nomogram based on type of initial treatment (NACT vs. primary surgery), histologic type (CCC/MUC vs. non-CCC/MUC), and debulking status (optimal vs. suboptimal), which provides a friendly and reliable tool for predicting platinum-sensitivity and survival outcomes in women with advanced EOC. Our study emphasizes the significance of prioritizing initial debulking surgery followed by adjuvant chemotherapy in patients with advanced EOC, particularly those with CCC or MUC histologic subtypes. For individuals undergoing NACT, achieving complete debulking with no residual disease remains imperative. Moreover, patients identified as having a high likelihood of platinum-resistance should be considered for enrollment in relevant clinical trial protocols. By integrating multiple clinical and pathological factors, our nomogram holds the potential in designing future clinical trial protocols, optimizing treatment decisions, and improving patient care for this challenging patient population in the near future. Further external validation in independent cohorts is warranted to strengthen the nomogram's utility and enhance its clinical impact.

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Declaration of competing interest

The authors have no conflict of interest relevant to this article.

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Original Article

Prenatal diagnosis and outcome of congenital dacryocystoceles

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ABSTRACT

Objective: To determine the incidence and present our experience with prenatal diagnosis and postnatal outcome of dacryocystocele.
Material and methods: All cases of congenital dacryocystocele diagnosed in our center between 2020 and 2022 were identified in our database to establish the incidence of these defects. The medical records were then reviewed for gestational age, gender, size, and side of dacryocystocele and postnatal outcome.
Results: A total of 26 cases with dacryocystoceles were found at a mean gestation age of 30 weeks (range, 29–33 weeks). The overall incidence was 1.35%, there was an obvious female predominance (73%), 69% of cases were unilateral and 31% were bilateral. There were no serious associated anomalies. The postnatal outcome was obtained in 88% of cases (23/26), in 39% (9 out of 23) cases the dacryocystocele was confirmed postnatally, and in 7 (77%) of these it was complicated by dacryocystitis. The spontaneous resolution was more likely in the right-sided lesions, and this was statistically significant. The treatment in cases with dacryocystitis involved massage and local antibiotics and was successful in 71% of cases. 2 cases (29%) suffer from recurrent dacryocystitis and are followed up with recurrent probing and local antibiotics. No breathing difficulties were described postnatally in our study group.
Conclusion: The overall prenatal incidence of dacryocystocele was 1.35%. The outcome is favorable, 61% of dacryocystoceles in our study resolved spontaneously and in no case postnatal breathing complications were reported. Dacryocystitis was common in persisting cases but was usually treated successfully by massage and antibiotics. The right-sided dacryocystoceles are more likely to resolve spontaneously than left-sided, and this was the only significant factor predicting persistence.

Introduction

Dacryocystocele is a rare congenital defect characterized by cystic distension of the nasolacrimal sac due to the obstruction of lacrimal drainage, both above and below the sac [1–3]. In the neonate, it develops as a cystic bluish swelling in the medial canthal area within the first 12 weeks of life [1,3]. Although prenatally diagnosed dacryocystocele have usually a good prognosis and spontaneously resolve during prenatal or postnatal life, potential complications of dacryocystocele include acute dacryocystitis, orbital cellulitis and respiratory distress when they extend intranasally and form large intranasal cysts in the inferior meatus [2,4].

The treatment of dacryocystocele remains controversial. It can resolve spontaneously, thus in uncomplicated cases some authors suggest conservative treatment [3]. Some others advocate rather surgery ranging from nasolacrimal ducts probing to endoscopic marsupialization [3,5,6]. Treatment of dacryocystitis complicating dacryocystocele is also controversial, with some suggesting initial massage with antibiotics, and others recommending early surgical treatment [3].

Prenatal diagnosis of dacryocystocele has been reported, but there are only a few studies involving more cases [1,4,7]. Thus, convincing data about the incidence, development, and postnatal outcome are missing [2,7]. The study aimed to report the incidence, ultrasound findings, development, postnatal outcome, and management of dacryocystoceles diagnosed in our center.

Material and methods

Cases of congenital dacryocystocele diagnosed prenatally by ultrasound between January 2018 and August 2023 were identified by a review of our database. No patients were excluded from the study.

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All ultrasound examinations were performed in our center by 4 experienced FMF-certified fetal medicine specialists using Samsung Hera W10 Elite or Samsung Hera W9 (Samsung Medison, Seoul, Republic of Korea). Standard anatomic views (routine facial coronal, sagittal, and transverse planes in the level of orbits) were used to scan the fetal facial structures including orbits, nose, upper and lower lip, and chin. These views were applied not only during routine anomaly scans in the second trimester but also during the third trimester.

The ultrasound diagnosis was established by 2D ultrasound by detection of a cystic smooth-wall lesion with anechoic content in the medial and inferior part of the fetal orbit. Color Doppler was used to confirm the absence of blood flow signals within and around the mass.

For each case of prenatally detected dacryocystocele, the following characteristics were recorded: gestational age at diagnosis, size and side of the cyst, fetal gender, result of follow-up scan if performed, postnatal outcome, and management.

Our analysis included the calculation of prenatal incidence and comparison of cases with persistent and postnatally resolved dacryocystoceles.

Average incidence and incidence in individual gestational weeks were calculated. Because dacryocystocele was diagnosed by prenatal scan from 28 gestational weeks onwards in this study, the incidence was calculated from the number of singleton pregnancies that underwent prenatal ultrasound at or after 28 gestational weeks. The number of pregnancies older than 36 weeks was small, thus they were grouped as 36+ gestational weeks for the statistical analysis.

Comparison of data between neonates with spontaneously resolved dacryocystoceles and the neonates with persistent dacryocystoceles was performed by Fisher's Exact Test, F-test, and Two-sample t-test. A value of $P < 0.05$ was considered statistically significant.

Results

In total, 26 cases with dacryocystocele were found at a mean gestation age of 30 weeks (range, 29–33weeks).

In 10 cases a follow-up scan was performed in more advanced gestational age, in none of these cases dacryocystocele resolved between the first and the follow-up scan. None of these cases was referred to us for the suspected anomaly, all dacryocystoceles were first detected during the third-trimester scan in our center.

During the study period, 3263 third-trimester scans were performed (range 38–42 weeks) in 1912 third-trimester unique pregnancies. The overall incidence was 1.35%, being the highest at 31 (2.09%) and 34 (2.29%) weeks. You can see the distribution of the fetuses with dacryocystocele in the study group in Table 1. The incidence of fetuses with dacryocystocele both in percentage and in number of cases is displayed in Fig. 1a and b.

Table 1
The distribution of the fetuses with dacryocystocele in the study group.

Gestational week	All exams	Unique pregnancies	Dacryocystoceles	Incidence
28	143	140	0	0,00%
29	277	265	3	1,13%
30	1240	1180	13	1,10%
31	439	431	9	2,09%
32	185	181	1	0,55%
33	204	197	3	1,52%
34	278	262	6	2,29%
35	135	131	1	0,76%
36+	362	209	1	0,48%

As for the associated anomalies, there was a mild tricuspid regurgitation in one case, no other associated anomalies were found. In one of the cases, there was dacryocystocele detected prenatally and confirmed postnatally in the older sibling too.

There was an obvious female predominance, the dacryocystocele was found in 19 (73%) female and only in 7 (27%) male fetuses. In 69% (18/26) of cases the dacryocystocele was unilateral (Fig. 2), in 8 cases left-sided and in 10 cases right-sided. In 31% (10/26) the dacryocystocele was found in both eye corners (Fig. 3). The size of dacryocystocele was between 4.1 and 7.5 mm (median 5.7 mm).

The postnatal outcome was obtained in 88% of cases (23/26), in 17 female and 6 male fetuses. The mean gestation age at delivery was 39 weeks (37–41 weeks). In 39% (9 out of 23) cases the dacryocystocele was confirmed postnatally and in 7 (77%) of these it was complicated with dacryocystitis. The treatment in all cases of dacryocystitis involved massage and local antibiotics and was successful in 71% of cases. 2 cases (29%) suffer from recurrent dacryocystitis and are followed up with recurrent probing and local antibiotics.

We compared the data between fetuses with spontaneously resolved dacryocystoceles and those with persistent dacryocystoceles postnatally. We found the only significant difference in the laterality of the dacryocystocele – it is much more likely that the right-sided dacryocystocele resolves spontaneously than the left-sided (p 0.043). In the other variables (maternal age, fetal gender, gestational age at delivery, gestational age at first detection, and size of the dacryocystocele) there was no significant difference between persistent and resolving cases. The comparison of both groups is displayed in Table 2.

Discussion

Congenital dacryocystocele is a rare congenital defect resulting from congenital lacrimal and/or nasolacrimal duct obstruction [7,8] typically diagnosed in the third trimester [9]. Clinically it is characterized postnatally by the appearance of a cystic mass below the median canthus of the eye [7]. Associated clinical symptoms described during the first week of life include dacryocystitis, facial cellulitis, and breathing difficulties [2,6,7]. Breathing and breast-feeding difficulties may be due to an associated intranasal cyst, which can be missed on ultrasound. If suspected, the diagnosis should be confirmed by magnetic resonance [10].

The development of the efferent lacrimal pathways was well described with fetal magnetic resonance performed at 19–40weeks [8]. Although there is a great variability in the timing of events, it is clear, that their visualization with fetal magnetic resonance reflects the net effect of two processes: opening the eyelids and subsequent patency of the lacrimal puncta, leading to fluid accumulation, and opening of Hasner's membrane creating a valve. Production of fluid/mucous within the nasolacrimal system by goblet cells will certainly add to the content of the lacrimal sac, however, their number is variable, and their distribution among the fetal population is unknown. The fluid accumulation and opening of the Hasner's membrane usually happen between 28 and 32 weeks, which reflects also the peak of visualization of efferent lacrimal pathways by magnetic resonance [8]. However, the distal end of lacrimal drainage at the level of Hasner's membrane may canalize at birth or even later. In the event of the early onset production of goblet cells, mucinous secretion may lead to the distension of the lacrimal drainage system. This causes the changes in anatomical orientation of the proximal end of the lacrimal sac, which acts as a check-valve system that only permits the fluid to enter the sac leading to further distension. This cystic distension is designated as a dacryocystocele [2,4]. Fluid accumulation within the closed lacrimal drainage system enforces perforation of the

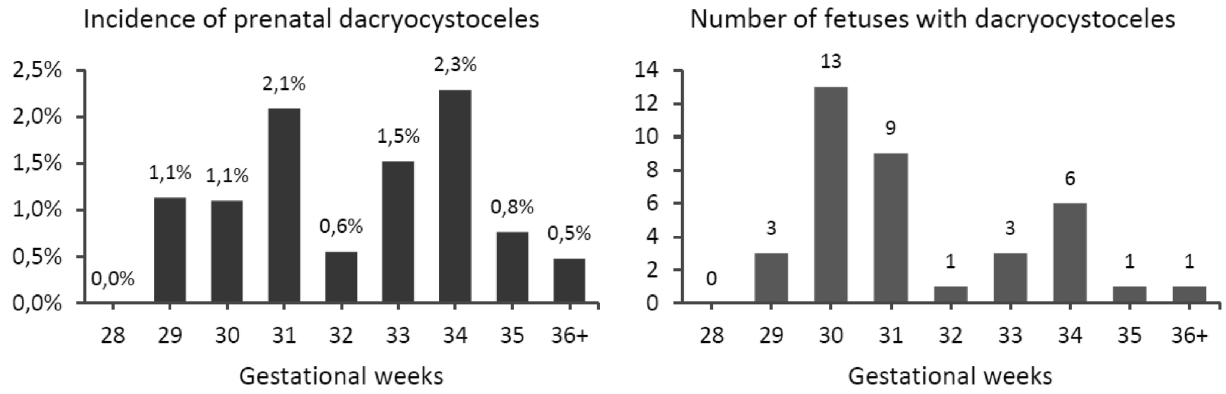

Fig. 1. Incidence of prenatal dacryocystoceles by gestational age both in percentage and in absolute number.

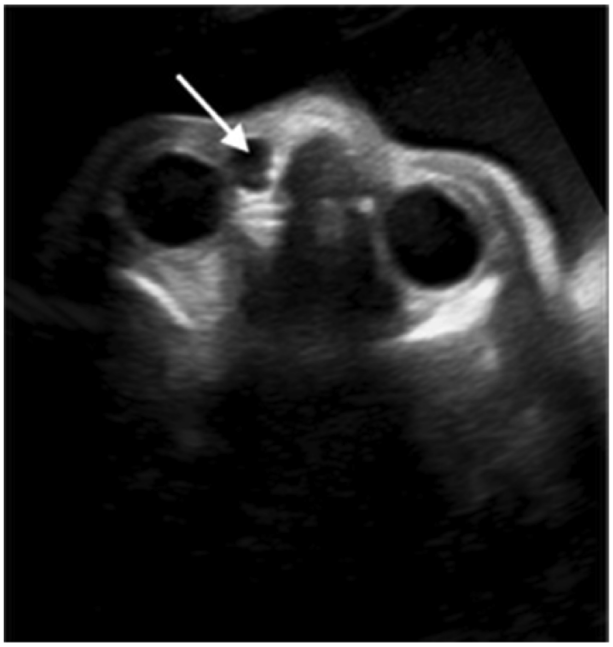

Fig. 2. Ultrasound image of prenatally diagnosed unilateral dacryocystocele (arrow).

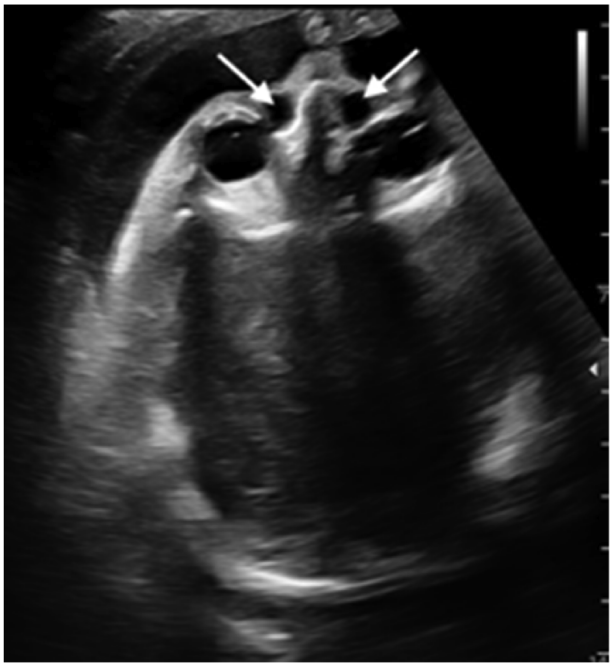

Fig. 3. Ultrasound image of prenatally diagnosed bilateral dacryocystocele (arrows).

membrane at the distal end of the nasolacrimal duct, the valve of Hasner, with a resolution of dacryocystocele [2,4,7,8]. Thus, a non-perforated Hasner's valve does not represent a cause of dacryocystocele, however it is certainly responsible for its resolution.

The exact frequency of congenital dacryocystocele in the fetal population is unknown, as there is only one systematic study about the development of fetal efferent lacrimal system performed by Brugger et al. using fetal magnetic resonance. He suggested defining dacryocystocele as cystic distension of the lacrimal sac/with a diameter of more than 5 mm and reported an incidence of 2.76% [8]. As for ultrasound studies, there are only a few involving more cases and report much lower incidence, respectively between 0.1% and 0.5% [1,2,4,7]. Some of them used the cut-off of 5 mm and more suggested by Brugger et al. [8], and some of them did not. We defined dacryocystocele as cystic distension of the lacrimal sac/duct with a diameter of more than 4 mm as we had a case with

Table 2
Comparison of the data between fetuses with spontaneously resolved dacryocystocele and those with persistent dacryocystoceles postnatally.

Variable	Spontaneous resolution (n = 14)	Persisted (n = 9)	P
Maternal age (years)	32,4	32,0	0,835
Gender of neonate			
Male	4	2	0,565
Female	10	7	
GA at delivery (weeks)	39,4	40,0	0,320
GA of first detection (weeks)	30,9 (30, –32)	30,8 (29,4–33,9)	0,909
Size (mm)	5,8	5,6	0,612
Laterality			
Bilateral	3	3	0,435
Unilateral	11	6	
Unilateral-right	8	1	**0,043**
Unilateral-left	3	5	

Bold represents P less than 0.05 is statistically significant.

dacryocystocele with a diameter of 4.1 mm confirmed postnatally. The size of dacryocystocele in our study ranged from 4.1 to 7.5 mm (median 5.7 mm), interestingly being 5.6 mm in the postnatally resolved cases while only 5.4 mm in persisting cases. In our study group, the earliest detection of dacryocystocele was at 29 weeks (3 cases), and the last one was seen at 38 weeks (1 case). This timing corresponds with the development of the lacrimal pathway and with the data in other studies [2,8]. The overall incidence in our study group was 1.35%, being the highest at 31 (2.09%) and 34 (2.29%) weeks. Our incidence is higher than reported in the other ultrasound studies, however lower than in the study by Brugger using fetal magnetic resonance [8]. This can be explained by the fact, that in many centers the ultrasound examination of fetal eyes does not belong to the protocol for the third-trimester scan, and the resolution of the fetal magnetic resonance is much higher than of the ultrasound. Additionally, imaging of fetal eyes with fetal magnetic resonance is not limited by fetal position as in the ultrasound. Our distribution of incidence, which was more than 2% at 31 and 34 weeks, can be explained by the number of scans at individual weeks in our center. In our country, the third-trimester scan is routinely performed between 30 and 32 weeks. Thus, the majority of dacryocystoceles were diagnosed between 30 and 32 weeks. The cases with increased risk of fetal growth restriction, really small-for-gestational-age and fetal growth-restricted fetuses, and fetuses in mothers suffering from gestation diabetes we usually rescan at 34 weeks, which explains the second peak of incidence.

As reported in previous studies we also found an obvious female predominance [2,7,11], the dacryocystocele was found in 73% of female and only in 27% of male fetuses. This is considered to be connected with the fact that the nasolacrimal duct is narrower in girls than in boys [6]. In agreement with previous studies, 69% of our cases with dacryocystocele were unilateral and only 31% bilateral. The laterality did not differ significantly between the right and left eye [2,4,7,8]. Although some authors describe about 5–10% risk of associated anomalies [2,7], apart from uneventful mild tricuspid regurgitation there was no associated congenital defect in our study group. Interestingly in our study group, there was a case connected with a family history of dacryocystocele (older sibling), that was not reported in any study before.

The postnatal outcome was obtained in 88% of cases (23/26), in 17 female and 6 male fetuses. The mean of gestation age at delivery was 39 weeks (37–41 weeks). In our study, 61% of dacryocystoceles spontaneously resolved before birth. This is in agreement with data in other studies, that the majority (49–90%) of dacryocystoceles resolve antenatally or at birth [2,7]. It can be explained by mechanical disruption and rupture of the Hasner's valve at the time of delivery [7]. Kim et al. described spontaneous resolution before a follow-up scan at a mean age of 33 weeks in 8 out of 11 re-scanned fetuses, however, we re-scanned 10 cases with dacryocystocele in about 4 weeks (at 34–35weeks) from the first diagnosis and all of them were present during follow-up scan. In 39% (9 out of 23) of our cases, the dacryocystocele was confirmed postnatally, and 7 (77%) of these were complicated by dacryocystitis. Although several authors mention association with severe complications such as respiratory distress and breastfeeding difficulties due to nasal obstruction by intranasal cyst [2,3,12], there were none of these in our study. Our data are in agreement with the so far largest study by Li et al. [7], who also did not show any respiratory distress in newborns born with dacryocystocele. Dacryocystitis has been described by many authors with a frequency between 30 and 75% [3,7].

The treatment of congenital dacryocystocele remains controversial [3]. Some authors recommend conservative management with massage and antibiotics, while others advocate early intervention ranging from nasolacrimal duct probing to endoscopic marsupialization [3]. In our study, 23% of persisting congenital dacryocystoceles resolved after massage, and the remaining 77% were complicated with dacryocystitis. The treatment in all cases of dacryocystitis involved massage and local antibiotics and was successful in 71% of cases. 2 cases (29%) suffer from recurrent dacryocystitis and are followed up with recurrent probing and local antibiotics.

So far, except for the bilaterality and intranasal extension of dacryocystocele, there was no reported association between the size and laterality and the need for surgical treatment [2]. Better outcomes were found to be related to early detection in utero and giving birth at more advanced gestation age [4]. This study by Kim et al. was the only prenatal study trying to find an association between several variables (maternal age, fetal gender, delivery mode and gestational age at delivery, gestational age of the first detection, size and laterality of the dacryocystocele) and spontaneous resolution of the congenital dacryocystocele before or at the birth [4]. We also compared the data between fetuses with spontaneously resolved dacryocystocele and those with persistent dacryocystoceles postnatally and used the same variables used by Kim et al. Against him, we found the only significant difference in the laterality of the dacryocystocele – it is much more likely that the right-sided dacryocystocele resolves spontaneously than the left-sided (p 0.043). In the other variables (maternal age, fetal gender, gestational age at delivery, gestational age at first detection, and size of the dacryocystocele) there was no significant between persistent and resolving cases.

To conclude, the overall incidence of dacryocystocele was 1.35%, more than in other prenatal ultrasound studies. We believe this is due to the lack of examination of fetal eyes in the protocol for third-trimester scans in many centers. We suggest including this examination to inform parents about the risk of this congenital defect. They should be informed about good prognosis as many dacryocystoceles spontaneously resolve and if persisting, early massage with antibiotics may prevent the need for surgical information. According to our study spontaneous resolution is much more likely to resolve if unilateral and right-sided. Further studies are needed to confirm our data and maybe find some other variables predicting prognosis.

Declaration of competing interest

No declaration of interest.

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Original Article

Clinical, radiological, and pathological features of mitotically active cellular fibroma of ovary: A review of cases with literature review

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ABSTRACT

Objective: Mitotically active cellular fibroma (MACF) of the ovary, characterized by relatively high mitotic activity without severe atypia, was first described in the WHO classification in 2014. However, due to its rarity, the clinicopathological characteristics of ovarian MACF have not been established. This study was performed to describe the clinical, radiological, and pathological features of MACF by analyzing 11 cases of ovarian MACF.

Materials and methods: Between 2015 and 2022, 11 patients with ovarian MACFs underwent surgical treatment at our institution. Clinicopathologic data of the patients were retrospectively reviewed from their medical records.

Results: Median patient age was 53.7 years (range 21–77 years), and median tumor diameter was 7.8 cm (range 4.3–14.0 cm). Preoperative CA125 was elevated in 4 cases. Four of the eleven patients had abdominal pain, and two presented with vulvar pain or a palpable abdominal mass, respectively. Preoperative radiological impressions included fibroma, fibrothecoma, stromal tumor, and cystadenocarcinoma. A laparoscopic approach was adopted in 7 cases (64%). Intraoperative frozen section was performed in 5 patients, and all demonstrated the presence of a benign, fibromatous stromal tumor. Three patients underwent fertility-sparing surgery, including laparoscopic ovarian cystectomy and unilateral salpingo-oophorectomy. Median follow-up was 37.7 months (range 2–84 months), and no patient experienced disease relapse or died of their disease.

Conclusion: This study shows that ovarian MACF has a benign clinical course. Fertility-sparing surgery provides a safe therapeutic option for MACF, which can be managed safely by laparoscopy. Imaging findings and final pathological diagnosis were not well matched. Intraoperative frozen section is important for determining surgical extent in mitotically active cellular fibroma of the ovary.

Introduction

In 2003 the WHO classified ovarian fibromatous tumors as benign fibroma or malignant fibrosarcoma, and in 1981, Prat and Scully reported mitotic activity was the most important criterion for classifying ovarian fibroma [1]. Ovarian cellular fibroma was defined as having low mitotic activity at <4/10 HPFs (high-power fields) without moderate to severe cytological atypia and fibrosarcoma as having increased mitotic activity (≥4 per 10 HPFs) and moderate to severe atypia [2]. However, ovarian fibromas with mitotic activities of ≥4/10 HPFs but no moderate to severe atypia are not categorized. These mitotically active cellular fibromas (MACFs) were often previously diagnosed as fibrosarcoma [3], but the clinicopathologic characteristics and prognosis of these tumors differ significantly from those of ovarian fibrosarcoma [4], because

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MACFs are generally considered to be clinically indolent, whereas ovarian fibrosarcoma has a malignant disposition and an extremely poor prognosis. In 2006, Irving et al. first differentiated MACF and fibrosarcoma and reported that MACF has a more favorable prognosis [5]. Accordingly, the 2014 WHO classification of tumors of the breast and female genital organs defined MACF as having a mitotic activity of ≥4 per 10 HPFs without moderate to severe atypia [6].

Several case reports have been published since this reclassification by the WHO [3,7–9]. However, the biological nature of this tumor is not well understood, and limited data is available on long-term survival rates. Furthermore, the clinicopathologic characteristics of MACF have not been documented, and its optimal management is not well established. In this study, we retrospectively reviewed 11 ovarian MACF cases to investigate its clinical, radiological, and pathological features and outcomes and establish its biological nature and optimal treatment strategies.

Materials & methods

The clinicopathologic features and imaging findings of 11 patients that underwent surgery under a diagnosis of MACF between 2015 and 2022 were retrospectively analyzed by reviewing medical records. Clinical details, age at diagnosis, obstetric history, presenting symptoms, co-existing medical conditions, preoperative tumor markers, operative findings, follow-up duration, current status, and preoperative imaging findings were reviewed. Pathological findings regarding tumor size, necrosis and hemorrhage, mitotic count, cytological atypia, immunohistochemistry analysis, and co-existing pathological findings, and operative findings regarding location, greatest dimension, component, operative method, ascites, preoperative rupture, and adhesion were collected. Surgery was performed as open surgery or laparoscopic surgery. During laparoscopic surgery, the tumor mass was removed without spillage using an endobag. This study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (IRB #2210-010-119).

Results

The data of eleven ovarian MACF patients treated surgically were analyzed. Median patient age at diagnosis was 53.7 years (range 21–77 years), and median follow-up duration was 37.7 months (range 2–84 months). Greatest tumor diameters ranged from 4.3 to 14.0 cm (median 7.8 cm). In all cases, MACF was unilateral. Detailed clinical characteristics of the 11 patients are shown in Table 1. Patients ranged from premenopausal to postmenopausal. Four had abdominal pain, one presented with vulvar pain, and another with a palpable abdominal mass. Five patients were asymptomatic. Laboratory examinations revealed an elevated serum CA125 level in four cases, and of these, two had a high ROMA score (cases 4 and 7), raising suspicion of an ovarian malignancy, which was also suspected based on CT and MRI findings. Meig's syndrome with pleural effusion was found in one patient.

Preoperative radiological impressions of ovarian MACFs are shown in Table 1. Fibroma or fibrothecoma was suspected when radiologic imaging depicted only a solid component. On the other hand, malignancy was suspected when tumors contained mixed solid and cystic components or a predominant cystic component. Representative image findings are shown in Figs. 1–4. Case 10 was typical and appeared to be a fibromatous tumor, such as fibroma or fibrothecoma by MR (Fig. 2). Case 3 was an indeterminate solid tumor, and CT could not determine whether it was benign or malignant (Fig. 1B). Case 1 was interpreted as epithelial ovarian cancer by MRI because it had imaging findings similar to those of ovarian cancer (Fig. 3, Table 1). In case 5, MRI showed a 14 cm-sized predominant cystic mass with multiple enhancing mural nodules in the ovary, suggestive of ovarian malignancy (Fig. 4).

Operative findings are summarized in Table 2. In all 11 cases, MACF was confined to one ovary, and 8 patients had right-sided ovarian MACF. Solid components were observed in 7 cases (64%). Two of the remaining four cases were mixed solid/cystic types, and the other 2 were of the cystic type. Laparoscopic procedures were performed in 7 cases (64%) (Fig. 5), and laparotomy was performed in 4 cases suspicious of ovarian malignancy by CT or MRI. Frozen section was performed in 5 patients, and all revealed benign fibromatous stromal tumors without atypical cells. Three patients had significant ascites, but all were negative for malignancy by cytology. No rupture occurred before operations, and two cases showed mild ovarian surface adhesions. Operative procedures are described in Table 2. Three patients underwent fertility-sparing surgery, including laparoscopic ovarian cystectomy and unilateral salpingo-oophorectomy. No further treatment was performed postoperatively in any of the 11 patients, and at final follow-up, all were alive without recurrence.

Pathological features of the 11 patients are provided in Table 3. Mitotic counts ranged from 4 to 14/10 HPFs. Mild cytological atypia was observed in three cases, but no moderate to severe cytologic atypia was detected. Infarct-type necrosis with hemorrhage was present in one case and hemorrhage in two cases. Co-existing pathological findings included paratubal cyst, endometrial cancer, and hydrosalpinx. Representative gross and microscopic findings are shown in Fig. 6. Grossly, tumor masses were well-circumscribed and external surfaces were smooth, glistening, and pink-to-yellow colored. The cut surface of the solid tumor was tan to yellow. Histologically, neither intratumoral hemorrhage nor necrosis were observed in the solid tumor, which was very uniform and hypercellular with some collagenous stroma in lower power view. Mild nuclear atypia and increased mitotic activity were observed, but atypical mitosis and necrosis were absent.

Discussion

Previously, ovarian fibromatous tumors were simply classified as benign fibromas or malignant fibrosarcomas. Prat and Scully recommended that fibrosarcoma be diagnosed based on a mitotic index of ≥4/10 HPFs [1]. However, nuclear pleomorphism and severe cytologic atypia were subsequently added [5]. As classified by the WHO in 2014, MACF is a rare type of ovarian fibromatous tumor characterized by increased mitotic activity (≥4/10 HPFs) and the absence of moderate to severe cytologic atypia [6]. The clinicopathologic features of this tumor differ from those of malignant fibrosarcoma, as MACF is less aggressive and follows a more indolent clinical course. Mitotic activity and nuclear atypia are important for predicting the aggressiveness of ovarian fibromatous tumors, but even when the mitotic count is high and nuclear atypia is minimal, outcomes are relatively favorable. In this study, we describe the clinicopathological characteristics and surgical outcomes of 11 patients with ovarian MACF.

Due to its rarity, the natural history of MACF is largely unknown. The age distribution and presenting symptoms of the 11 MACF patients included in the present study were comparable to those previously reported, that is, median age was 53.7 years (range 21–77 years) in the present study and 42.3 years (range 14–93 years) in a previous report [5], and presenting symptoms were attributed to tumor mass effects [5.7], sometimes including abdominal pain, acute abdomen due to torsion, menometrorrhagia, and ascites. In a large study conducted by Irving et al., all cases were unilateral. At presentation, 10% of MACFs were associated with ovarian surface adhesions or rupture and 13% with extraovarian involvement, which was probably due to the implantation of

Table 1
Clinical features of each patient with MACF.

Patient	Age (years)	G-P-A-L	Presenting symptoms	Medical statement	Preoperative tumor marker	Radiological impression	Follow up duration (month)	Current status
1	37	1-1-0-0	RLQ pain	Pleural effusion	CA-125 : 59.6 IU/ml HE4 : 52.1 pM ROMA: Low CA19-9 : 4.6 IU/ml AFP: 2.05 ng/ml β-hCG: 1.2 mIU/ml	Cystadenocarcinoma or Meig's syndrome (MRI)	17	NED
2	65	5-3-2-3	Low abdominal pain	None	CA-125 : 25.5 IU/ml HE4 : 46.4 pM ROMA: Low CA19-9 : 5.0 IU/ml	Parasitic myoma or Indeterminate ovarian tumor (MRI)	26	NED
3	61	1-0-1-0	None	HTN	CA-125 : 8.6 IU/ml HE4 : 50.8 pM ROMA: Low	r/o Malignant ovarian tumor (CT)	30	NED
4	77	10-5-5-5	Vulvar pain	HTN	CA-125 : 107 IU/ml HE4 : 74.5 pM ROMA: High	Malignant ovarian tumor (MRI) Suspicious ovarian cancer (PET-CT)	60	NED
5	46	2-1-1-1	Palpable abdominal mass	None	CA-125 : 13.1 IU/ml CA-19-9 : 10.6 IU/ml CEA: 0.8 ng/ml Inhibin: 2.30 pg/ml	Cystadenocarcinoma (MRI)	66	NED
6	59	3-2-1-2	Low abdominal pain	None	CA-125 : 13.67 IU/ml CA-19-9 : 4.38 IU/ml	Fibroma or fibrothecoma (CT)	84	NED
7	43	NA	Abdominal pain	None	CA-125 : 432.4 IU/ml HE4 : 49 pM ROMA: High CA 19-9 : 3.7 IU/ml	r/o Malignant ovarian tumor (CT)	54	NED
8	53	5-2-3-2	None	None	CA-125 : 7.4 IU/ml HE4 : 54.3 pM ROMA: Low CA 19-9 : 4.3 IU/ml	Fibroma or Subserosal myoma (USG)	46	NED
9	66	4-0-4-4	None	HTN Dyslipidemia	CA-125 : 46.6 IU/ml CA 19-9 : 2.82 IU/ml CEA: 2.74 ng/ml	Malignant ovarian tumor or Stromal ovarian tumor (MRI)	27	NED
10	21	0-0-0-0	None	None	CA-125 : 17.1 IU/ml HE4 : 41.1 pM ROMA: Low CA-19-9 : 5.4 IU/ml	Fibroma or fibrothecoma (MRI)	3	NED
11	63	3-3-0-3	None	HTN DM	CA-125 : 17.4 IU/ml HE4 : 112.0 pM ROMA: Low	Fibrothecoma (CT)	2	NED

AFP: alpha-fetoprotein; CA-125: cancer antigen-125; CA 19-9: cancer antigen 19-9; CEA: carcino-embryonic antigen; CT: computed tomography; DM: diabetes mellitus; G-P-A-L: gravidity-parity-abortion-live children; HE4: human epididymis protein 4; HTN: hypertension; MRI: magnetic resonance imaging; PET-CT: positron-emission tomography; RLQ: right lower quadrant; ROMA: risk of malignancy algorithm; USG: ultrasonography.

detached tumor fragments in peritoneal surfaces [5]. In our series, 6 of the 11 patients presented symptoms associated with a pelvic mass, such as lower abdominal pain, and the mean tumor diameter was 7.8 cm (range 4.3–14.0 cm) and 9.4 cm (range 1.0–18 cm) in a previous study [5]. Furthermore, it has been reported that MACF has no specific associated tumor markers, though CA125 was elevated in some cases [8].

It is important to differentiate ovarian tumors radiologically because the surgical methods used to treat pelvic masses frequently depend on preoperative imaging results; in the present

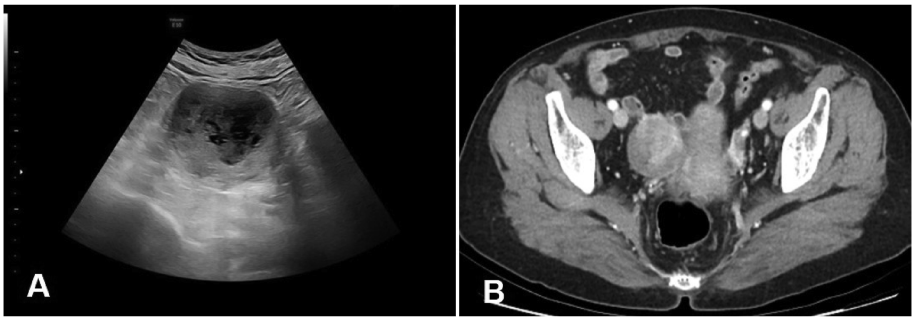

Fig. 1. (A) Transvaginal ultrasonography revealed a well-defined, mixed solid/cystic mass on the left ovary (~6.5 cm in diameter, case 11). (B) Contrast-enhanced CT image showing a 4 cm-sized heterogeneous solid tumor in the right adnexa (case 3).

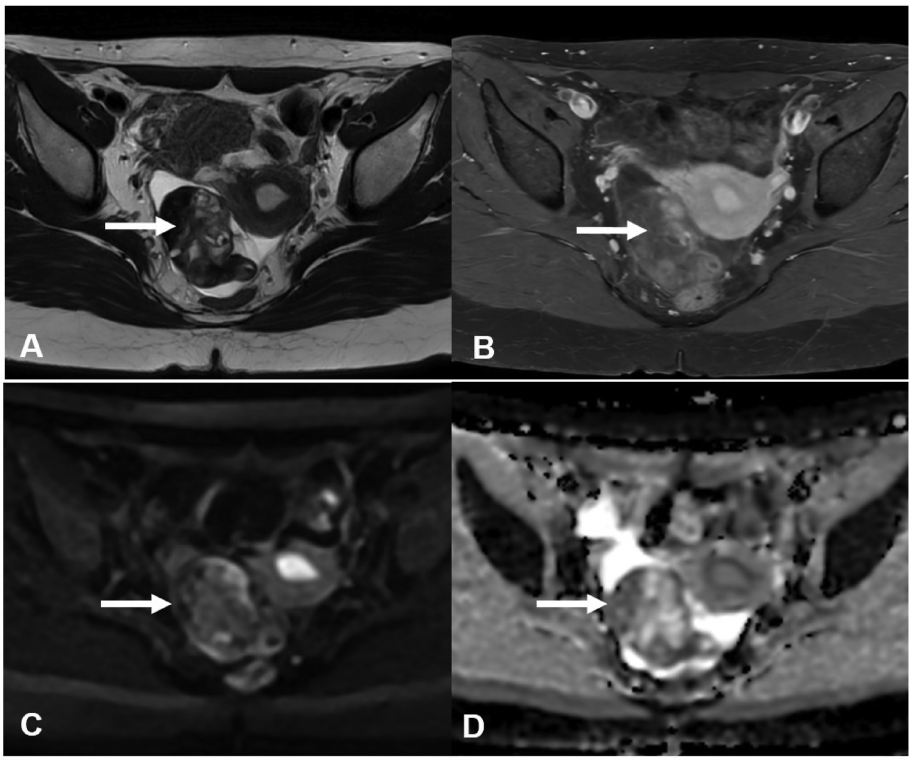

Fig. 2. (A) T2-weighted MR image showing a 5-cm sized predominantly hypointense tumor with several small hyperintense cystic regions in the right ovary. (B) Contrast-enhanced T1-weighted MR image showing hypovascularity of the right ovarian tumor, (C–D) DWI (b value, 1000 s/mm^2) and ADC maps showing hypointensity, the so-called 'T2-blackout' effect (case 10).

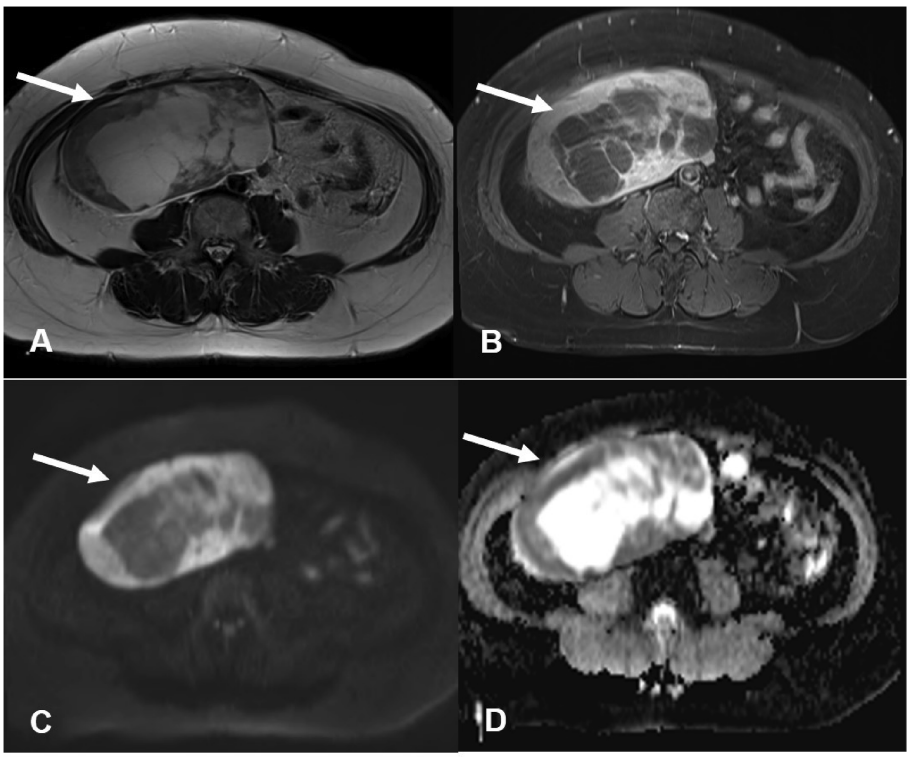

Fig. 3. (A) T2-weighted MR image showing a 14-cm sized heterogenous multiseptated mixed cystic/solid tumor in the right ovary. (B) Contrast-enhanced T1-weighted MR image showing hypervascularity of the right ovarian tumor. (C–D) DWI (b value, 1000 s/mm^2) and ADC maps showing hyperintensity and hypointensity (at the peripheral solid portion, indicating restricted diffusion), respectively (case 1).

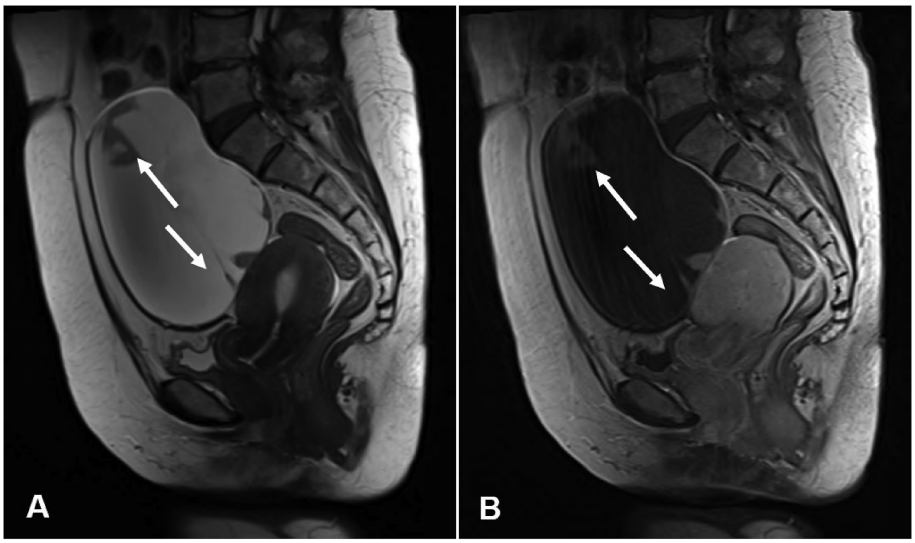

Fig. 4. Sagittal T2-weighted image (A) and contrast-enhanced T1-weighted image (B) showing a 14-cm sized predominant cystic mass with multiple enhancing mural nodules (arrows) in the ovary, suggestive of ovarian malignancy (case 5).

Table 2
Operative findings of each patient with MACF.

Patient	Location	Greatest dimension (cm)	Component	Operative procedures (frozen biopsy results)	Ascites	Pre-operation Rupture	Adhesion
1	Right	14.0	Solid and Cystic	RSO (frozen: stromal tumor, mesenchymal tumor)	(+)	(−)	(−)
2	Right	5.2	Solid	Laparoscopic BSO	(−)	(−)	(−)
3	Right	4.3	Solid	BSO (frozen: stromal tumor)	(−)	(−)	Periovarian adhesion
4	Left	8.7	Solid and Cystic	TAH BSO (frozen: stromal tumor, more likely benign)	(+)	(−)	(−)
5	Right	14	Cystic	TLH BSO	(−)	(−)	(−)
6	Right	5.3	Solid	Laparoscopic BSO	(−)	(−)	(−)
7	Right	13	Cystic	RSO (frozen: stromal tumor, more likely benign)	(+)	(−)	(−)
8	Right	4.9	Solid	Laparoscopic RSO	(−)	(−)	(−)
9	Left	4.5	Solid	TLH BSO	(−)	(−)	(−)
10	Right	5	Solid	Laparoscopic ovarian cystectomy	(−)	(−)	(−)
11	Left	6.5	Solid	Laparoscopic BSO (frozen: stromal tumor)	(−)	(−)	(−)

BSO: bilateral salpingo-oophorectomy; RSO: right salpingo-oophorectomy; TAH: transabdominal hysterectomy; TLH: total laparoscopic hysterectomy.

study, different imaging modalities (CT, MRI, or PET) were used to establish a preoperative clinical diagnosis. However, imaging findings and final pathological results were not well-matched. Preoperative radiological impressions included fibroma, fibrothecoma, another stromal tumor, cystadenocarcinoma, or uterine subserosal myoma (Table 1). Ovarian malignancy was suspected in 6 of the 11 cases, and imaging appearances ranged from fibroma to ovarian malignancy-like. Solid MACF tumors are difficult to distinguish from solid pelvic tumors such as malignant ovarian tumors and uterine myoma [8], and the presence of a large pelvic mass, ascites, and an elevated CA 125 level may raise suspicion of ovarian malignancy [9]. In our study, four patients had an elevated serum CA-125 level and two of these had high ROMA score, which raised suspicion of ovarian malignancy and supported CT and MRI findings (cases 4, 7). In these two cases, serum CA-125 levels were significantly elevated (107 and 432.4 IU/ml, respectively), and ROMA scores were high (at 45.3; normal <29.9% and 59.8; normal <11.4 %, respectively). Finally, postoperative serum levels of CA125

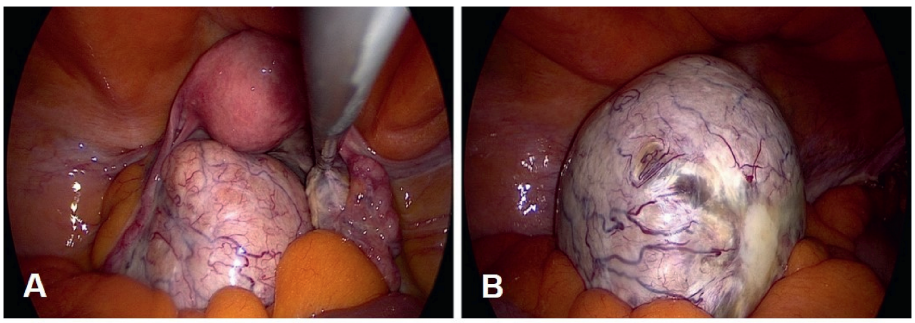

Fig. 5. Laparoscopic image showing a 6.5 × 5.0 × 5.0 cm solid smooth mass in the left ovary without adhesion (case 11).

Table 3
Pathological features of each patient with MACF.

Patient	Necrosis	Hemorrhage	Mitotic count (per 10 HPFs)	Cytological atypia	Immunohistochemistry	Coexisting pathological findings
1	(+) Infarct type necrosis	(+)	6	(−)	Positive: WT-1, inhibin, ER(focal weak) Negative: desmin, CD10, calretinin	Paratubal cyst
2	(−)	(−)	14	(−)	Positive: WT-1 Negative: desmin Ki-67 index: 4%	None
3	(−)	(−)	4	Mild	Special stain: reticulin	Paratubal cyst
4	(−)	(+)	6	(−)	Ki-67 : 5%	None
5	(−)	(−)	7	(−)	Positive: inhibin Negative: PANCK, EMA	None
6	(−)	(−)	4	Mild	Not applicable	None
7	(−)	(−)	5	(−)	Positive: SMA, inhibin, calretinin	None
8	(−)	(−)	5	(−)	Positive: inhibin Negative: CD99, CD10 Ki-67 index: 10%	None
9	(−)	(−)	5	(−)	Not applicable	Endometrial cancer
10	(−)	(+)	4	(−)	Positive: WT1 Negative: inhibin	Right hydrosalpinx
11	(−)	(−)	5	Mild	Positive: inhibin a, WT-1, calretinin, ER Negative: CD99 Special stain: reticulin	None

returned to normal range in all cases (#1, 4, 7 and 9). Thus, our findings indicate that imaging-based preoperative prediction of ovarian MACF is limited and that intraoperative evaluation and confirmatory postoperative histopathological examination are required to make an accurate diagnosis.

Grossly, the external surfaces of tumors were smooth, glistening, and pink-to-gray and cut surfaces were fleshy and tan-to-yellow colored. Tumors were predominantly solid or mixed solid/cystic lesions. In a previous study, two-thirds were solid, and the remainder were mixed solid/cystic [5], and in another study, more than half of cases had mixed solid/cystic lesions or cystic lesions [7], which hinted at the frequency of cystic change in these tumors [5.7]. Microscopically, tumors are typically comprised of densely packed, spindle-shaped fibroblastic-like cells and arranged in a fascicular pattern. Furthermore, the histologic features of MACFs and CFs are similar (Table 4), though MACFs are often associated with higher mitotic counts and more diffuse cellularity. In a previous study, mean mitotic count ranged from 4 to 19/10 HPFs for MACFs and from 1 to 3/10 HPFs for CFs.[5] In our series, two cases were mixed solid/cystic types, and the other two had only a cystic

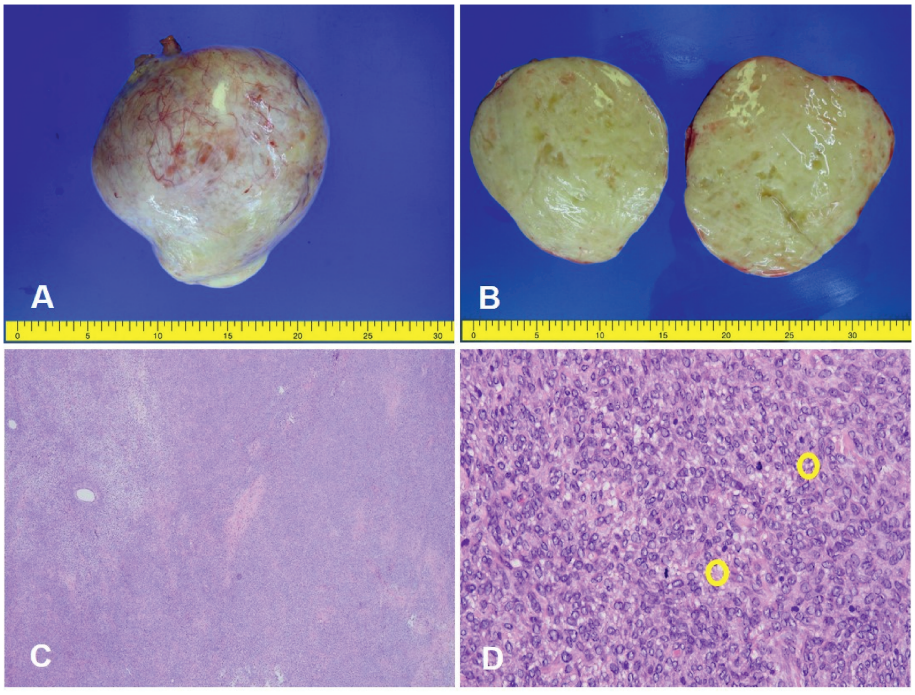

Fig. 6. Gross and microscopic findings. (A) Grossly, tumors were well-circumscribed with a smooth, glistening, pink-to-yellow colored external surface. (B) The cut surface of the tumor revealed a tan to yellow-colored solid mass. Neither hemorrhage nor necrosis was present. (C) At lower power, tumors were uniform and hypercellular with little collagenous stroma (original magnification, x40). (D) Tumor cells had mild nuclear atypia with vesicular chromatin, irregular nuclear membranes, and inconspicuous nucleoli. Increased mitotic activity was identified, but atypical mitosis and necrosis were absent. Yellow circles indicate mitosis (original magnification, x400) (case 8).

Table 4
Clinicopathologic differences between Cellular Fibroblastic Tumors of the Ovary.

	CF	MACF	Fibrosarcoma
Pathologic	increased cellularity	increased cellularity,	markedly increased cellularity,
	mitotic activity <3/10 HPFs	increased mitotic activity ≥4/10 HPFs	increased mitotic activity ≥4/10 HPFs
	no severe nuclear atypia	mild to moderate nuclear atypia	diffuse moderate-to-severe atypia
	fascicular growth pattern	fewer collagen fibers	extensive necrosis and hemorrhage
	large amount of collagen fibers	diffuse growth pattern	infiltrative margins
	tumor cell necrosis (−)	tumor cell necrosis (−)	metastasis at presentation
Clinical	benign	benign ~ low malignant potential	malignant
		indolent behaviour	aggressive behaviour
		possible local recurrence	higher recurrence rate
		rupture & adhere to the peritoneum	usually lead to death within 2 years
	usually confined to one ovary	usually confined to one ovary	often spread beyond the ovary

portion due to extensive hyaline degeneration, as described in a previous case series [7]. No significant nuclear atypia and no gross necrosis or hemorrhage were observed in tumors, though infarct type necrosis was noted in one case (case 1) and microscopic hemorrhage in three (cases 1, 4, and 10). The mitotic counts ranged from 4 to 14/10 HPFs (mean 5.9).

Clinicopathologic differences between cellular fibroblastic tumors of ovary are summarized in Table 4. The differential diagnosis of MACF and fibrosarcoma is possible based on degree of nuclear atypia and the presence of necrosis and hemorrhage because fibrosarcoma usually has diffuse moderate-to-severe atypia, extensive necrosis and hemorrhage, and infiltrative margins. However, the differential diagnosis of MACF and adult granulosa cell tumor (AGCT) is challenging [10]. A prominent diffuse cellular fibromatous background in AGCT may resemble MACF findings. It has been suggested that FOXL2 mutation analysis is a useful adjunct for differentiating diffuse AGCT (mutation present) and CF (mutation absent) [10], and that reticulin staining patterns and the presence of vesicular nuclei or nuclear grooves may be helpful for differentiating these two entities [7]. In the absence of a specific immunochemical stain for MACF, diagnoses are made by excluding tumors with negative immunohistochemical staining results [8].

The preoperative diagnosis of MACF remains challenging because it has no useful serum tumor markers or characteristic imaging findings at this time. Therefore, further investigation using a large patient cohort is essential to establish clinical features and imaging findings of ovarian MACF, a relatively newly defined entity (Table 4). Thus, intraoperative diagnosis by frozen section plays an important role in determining surgical treatment. Kim et al. recommended that surgical excision and subsequent histological evaluation are necessary because imaging studies cannot accurately diagnose ovarian MACF [7]. Yamada et al. also highlighted the significance of histological diagnosis, including intraoperative consultation [8]. Therefore, we suggest that frozen section during surgery is crucial for determining surgical practice when the CA125 level or ROMA score is high and imaging findings raise suspicion of ovarian malignancy. We performed frozen section in five of the eleven cases and all five were ovarian benign fibrous stromal tumors without atypical cells. However, a literature search revealed that frozen results indicated the presence of malignancy in four MACF cases (Table 5), which cautions that care is required when performing frozen section.

No optimal treatment guideline for MACF has been established due to its rarity. However, aggressive treatment is not recommended because most cases mentioned in the literature followed a benign clinical course. Thus, surgical resection of the tumor is the mainstay treatment. Fertility-sparing surgery might be reasonable for young reproductive patients with MACF [4]. Furthermore, cosmetic factors are also important in young patients scheduled for surgery. Fortunately, minimally invasive surgery is acceptable for patients with MACFs [3,8] and has been well adopted over recent years for gynecologic surgeries [13]. However, operators are often reluctant to use minimally invasive surgery in patients with an ovarian fibromatous tumor due to the presence of a solid component, a large tumor size, and a preoperative imaging diagnosis indicating the possibility of a malignant ovarian tumor. Nonetheless, minimally invasive surgery would be acceptable if the resected tumor was placed in an endobag and removed without tumor spillage. Yamada et al. reported the first case of MACF of the ovary treated by laparoscopic surgery [8], and in our series, laparoscopic procedures were performed in 7 patients (64%). Furthermore, no further treatment was performed, and at last follow-up, all remained alive without recurrence. Accordingly, our results indicate minimally invasive surgery is not associated with a poor prognosis.

Prognostic factors of ovarian MACF have not been adequately identified due to a lack of long-term clinical follow-up data. Local recurrence has been reported in a few cases, and risk factors of recurrence, such as moderate nuclear atypia, intraoperative rupture, dense adhesion to pelvic/abdominal organs, incomplete excision, infarction with extraovarian involvement, histological features of tumor necrosis and hemorrhage, have been suggested [12,13]. However, MACFs with these risk factors do not always recur, and the absence of these factors does not exclude relapse [12]. The

Table 5
Intraoperative frozen section in MACFs showing malignancy.

Authors (year)	Age	Frozen section results	Operative procedures	Final results	
				Mitotic counts/10HPFs	Cytological atypia
Monteiro et al. (2012) [9]	13	malignant, poorly differentiated, stromal tumor	RSO, OMT, mPB	5–7	no
Zong et al. (2014) [4]	39	malignancy	TAH, BSO, OMT, PLD	3–5	mild
Wu et al. (2014) [11]	76	malignancy (Sertoli-Leydig stromal cell tumor)	TAH, BSO	5–9	mild
Olivadese et al. (2021) [12]	34	spindle cell tumor invading the intestine (GIST)	Anterior sigmoid-rectal resection	2 (Recurrence) 4 (Primary tumor)	absent to mild

RSO: right salpingo-oophorectomy; OMT: omentectomy; mPB: multiple peritoneal biopsies; TAH: transabdominal hysterectomy; BSO: bilateral salpingo-oophorectomy. PLD: pelvic lymphadenectomy.

Table 6
Recurrence cases of mitotically active cellular fibroma of the ovary.

Authors (year)	Age	Interval (year)	Previous surgery	Pathologic findings		Clinical course in recurrence
				at primary surgery	at recurrence surgery	
Prat & Scully (1981) [1]	75	1	BO	adhesion (omentum, pelvic wall)	not done	Died at 2.75 yr
	82	7	O	>4 cm rupture	not done	Died of pneumonia at 7 yr, recurrence at autopsy
Bucella et al. (2009) [14]	65	6	TH, BSO	10 cm no rupture incomplete resection due to very low position in pelvis	10 cm 4 mitoses/10 HPFs significant atypia or necrosis (−)	second recurrence after 6 mo NED for 6 mo after second recurrence
Bi et al. (2013) [15]	65	7.8	TH, BSO, Om	15 cm 8 mitoses/10 HPFs mild/moderate atypia		NED for 121 mo
Haroon et al. (2013) [16]	NA	1.2	NA	NA	NA	NA
Olivadese et al. (2021) [12]	34	16	UO	9 cm mild atypia 4 mitoses/10 HPFs mild atypia adhesion(−), rupture(−)	5 cm peritoneal nodule 2 mitoses/10 HPFs pericellular reticulin staining Necrosis and hemorrhage (−)	NED for 96 mo

UO, unilateral oophorectomy; BO, bilateral oophorectomy; BSO. bilateral salpinpo-oophorectomy, TH, total hysterectomy; Om, omentectomy; HPF, high power fields; NED, no evidence of disease.

consistent risk factors have not been established due to the lack of adequate follow-up of MACF and a limited number of recurrence cases. Histologic features of recurred tumors differ slightly from those of primary tumors in terms of mitotic counts and infiltration of adjacent intestines [12]. Some authors have suggested that adjuvant treatment and long-term follow-up should be considered when patients have poor prognostic factors [13.14], and some cases have received adjuvant radiotherapy due to poor prognostic factors (adhesion, tumor rupture, or residual mass (<1 cm)) or hormonal therapy due to incomplete resection [14]. In our study, rupture did not occur, and two cases showed mild ovarian surface adhesions. All 11 cases received complete cytoreduction with no rupture of the tumor capsule, and postoperative adjuvant therapy was not administered. No evidence of recurrence was observed at last follow-up.

We performed a literature review on recurrent MACFs and identified 6 cases (Table 6), in which recurrence occurred in patients with or without pathological prognostic factors. Times to recurrence varied widely from 1 to 16 years. In an early report, deaths were reported in cases of recurrence, but no death was subsequently reported. Therefore, despite the more favorable prognosis of MACF than fibrosarcoma and complete surgical resection without rupture or in the absence of adherence, reports strongly suggest MACF requires a long-term clinical follow-up.

Few cases of ovarian MACF have reported in the literature, and this study is the largest case series to be published after the first reclassification of MACF from fibrosarcoma by Irving et al. [5]. Due to the lack of clinically meaningful serum tumor markers and distinctive imaging findings, the preoperative diagnosis of MACF remains challenging, and thus, histological diagnosis and pathologic consultation during surgery are important.

The major limitation of the study is the small sample size of patients with MACF, due to its rarity. Because of such limitation, it is difficult to draw firm conclusions with regard to the clinical, radiological, and pathological features and optimal treatment strategies.

In summary, ovarian fibromatous tumor with a high mitotic count and low nuclear atypia has been reclassified as MACF, which represents a newly-recognized subtype of ovarian cellular fibromatous tumor. Here, we detail the clinical, radiological, and pathological features of ovarian MACF. The preoperative or intraoperative differentiation of MACF and fibrosarcoma are important to avoid misdiagnosis and overtreatment. Imaging findings and final pathological diagnoses were discordant in many cases. However, increased cellularity, frequent mitotic figures, and mild cytological atypia are suggestive of MACF. Laparoscopic surgery might be acceptable if a tumor is removed without tumor spillage. Further large-scale studies are required to understand better the biological nature, to identify its pathological prognostic factors, and to improve the preoperative imaging diagnosis of ovarian MACF.

Conflicts of interest

The authors declare no conflicts of interest related to this manuscript.

Acknowledgments

None.

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Original Article

Comparison of maternal and neonatal morbidity in transvaginal versus transabdominal cerclage patients: A retrospective study from two tertiary hospitals

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ABSTRACT

Objective: To compare the maternal and neonatal morbidity in patients with transvaginal (TVC) versus transabdominal (TAC) cerclage.

Materials and methods: Retrospective analysis of patients who received cervical cerclage and terminated the pregnancy in the second trimester or third trimester in two tertiary hospitals. Data on basic clinical characteristics, predelivery maternal morbidity, intrapartum morbidity, postpartum morbidity and neonatal morbidity of TVC patients and TAC patients were analysed and compared.

Results: Seventy-two TVC patients and 120 TAC patients were included. The rates of abnormal fetal presentation and placental disorders were significantly higher in TAC patients than that in TVC patients (21.67% vs 5.56% and 18.33% vs 4.17%, respectively). The rates of premature rupture of membranes and intrauterine infection were significantly higher in TVC patients than that in TAC patients (25.00% vs 2.50% and 11.23% vs 3.33%, respectively). Compared with TVC patients, the rates of estimated intrapartum hemorrhage $\geq$500 ml, uterine rupture and cesarean delivery in the third trimester were significantly higher in TAC patients than in TVC patients. Gestational age at delivery and neonatal morbidity were comparable between TVC patients and TAC patients.

Conclusion: Compared with TVC patients, TAC patients were associated with a significantly higher incidence of maternal morbidity in placental disorders, abnormal fetal presentation, intrapartum hemorrhage $\geq$500 ml and uterine rupture.

Introduction

Preterm birth is the leading cause of neonatal morbidity and mortality. Cervical insufficiency (CI) refers to the inability of the cervix to maintain a pregnancy in the second or early third trimester, characterised by painless cervical dilation and shortening, resulting in pregnancy loss [1–5]. CI is the most common etiology of second trimester fetal loss, with the incidence of CI estimated to be approximately 1% of all pregnancies [3,5]. Several risk factors can lead to CI, including a history of cervical trauma or surgery, maternal exposure to diethylstilbestrol in utero, congenital uterine anomaly, and cervical length less than 25 mm measured by transvaginal ultrasound before 24 weeks [3,6].

Treatments for CI include conservative treatment and surgical treatment. Studies have shown that conservative management of CI with progesterone or a cervical pessary may be beneficial in preventing preterm birth in selected patients [3,6]. Cervical cerclage is the preferred surgical treatment of CI, it is a surgical procedure in which a suture is placed in the cervix to prevent premature cervical dilation in patients at high risk of CI [1,2]. Many studies have shown that cervical cerclage, either transvaginal or transabdominal, is an effective and safe treatment option for CI in preventing preterm birth [3,4,7,8]. However, results from some studies suggest that neonatal and maternal morbidity may increase in the subsequent pregnancy [9,10]. Therefore, a comparison of the impacts of different types of cervical cerclage on maternal and neonatal morbidity during pregnancy and delivery is needed.

The objective of our study is to compare the maternal and neonatal morbidity in patients with transvaginal versus transabdominal cerclage in two tertiary hospitals.

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Materials and methods

Patients

This was a retrospective study of patients who received TVC/TAC and subsequently terminated their pregnancy in the second trimester or third trimester at two centers between 1 January 2010 and 31 December 2019. Patients with multiple pregnancies, those who terminated the pregnancy due to fetal abnormality were excluded.

Patients were divided into two groups according to the technique of cervical cerclage received: the TVC group and the TAC group. As the surgical procedures of cervical cerclage and perioperative treatments have been comprehensively described by our colleagues in previous studies [11,12], details of the surgical procedures and perioperative treatments were not repeated.

Data collection

All maternal and neonatal medical records were reviewed. Baseline clinical characteristics including age, gravidity, previous delivery, abortion, mode of conception, previous cervical cerclage, mean gestational age before cerclage and indication for cerclage were collected. Maternal and neonatal morbidity was collected, including abnormal fetal position, placental disorders, pregnancy complications, intrapartum hemorrhage, postpartum hemorrhage, uterine rupture, hemostasis measures, mode of delivery, NICU admission, Apgar score and other neonatal complications. All data were analysed and compared between the two groups.

Ethical approval

This retrospective observational study was based on medical records, patients were not involved in the development of this study, informed consent on using clinical data for scientific study was obtained from all patients in admission. This study was approved by the Medical Ethics Committee of our hospitals. (NO. 2022ZSLYEC-510).

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS version 19, IBM, Armonk, NY, USA). Continuous variables are presented as the mean ± SD, and categorical data are expressed as frequencies and percentages. Comparisons of continuous variables between the two groups was made using the T-test or Mann–Whitney U-test as appropriate. Pearson's chi-squared test, Fisher's exact test or the Mann–Whitney U-test were used to assess categorical data as appropriate. $P < 0.05$ was considered statistically significant.

Results

As shown in Fig. 1, a total of 192 patients were included, of whom 72 patients received TVC treatment and 120 patients received TAC treatment. The baseline clinical characteristics of all patients are shown in Table 1. In the TVC group, 7 patients received a Shirodkar cerclage and the other 65 patients received a McDonald cerclage, the mean gestational age at cerclage during pregnancy was 15.62 ± 1.03 weeks. Indications for cerclage were typical painless second trimester fetal loss history in 58 patients, cervical length <25 mm before 24 weeks' gestation by transvaginal sonography in 10 patients and previous radical cervical surgery (loop electrosurgical excision procedures, LEEP) for high-grade squamous intraepithelial lesions in 4 patients. In the TAC group, 1 patient underwent laparotomy cervical cerclage at 7 weeks gestation, 24 patients underwent postconceptional laparoscopic cervical cerclage at a mean gestational age of 8.3 ± 1.43 weeks, and the other 95 patients underwent preconceptional laparoscopic cervical cerclage. Indications for cerclage were previous radical cervical surgery in 9 patients,

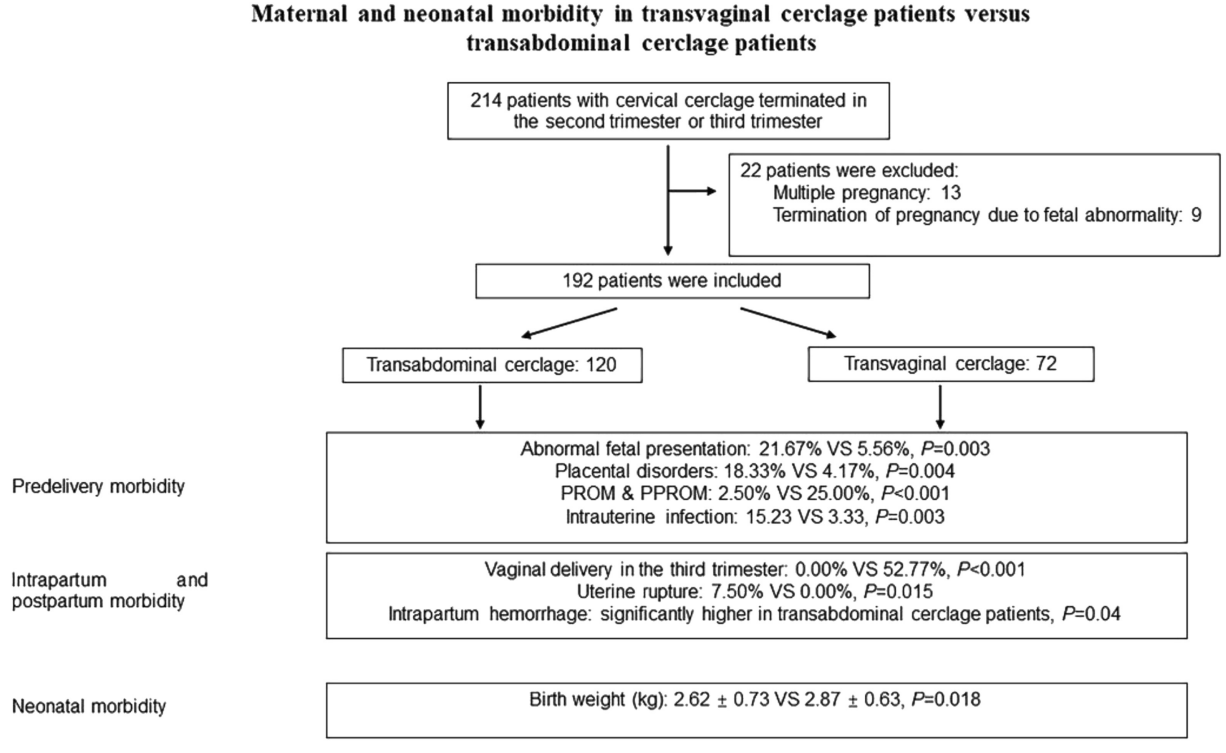

Fig. 1. Patient flowchart and key results of this study.

Table 1
Baseline clinical characteristics of all patients.

	Total patients, n = 192	TVC group, n = 72	TAC group, n = 120	*P* value
Age	33.02 ± 4.31	32.97 ± 4.48	33.04 ± 4.22	0.914
Gravida	3.39 ± 1.22	3.31 ± 1.31	3.44 ± 1.26	0.457
Mode of conception				
Spontaneously	154 (80.21)	62 (86.11)	92 (76.67)	0.112
ART[a]	38 (19.79)	10 (13.89)	28 (23.33)	
Previous delivery	56 (29.16)	23 (31.94)	33 (27.50)	0.512
Cesarean section	25 (13.02)	7 (9.72)	18 (15.00)	0.293
Vaginal birth	31 (16.15)	16 (22.22)	15 (12.50)	0.076
Abortion	1.98 ± 1.14	1.82 ± 1.01	2.08 ± 1.20	0.131
Previous second-trimester spontaneous abortion				
0	23 (11.98)	14 (19.44)	9 (7.50)	**0.014**
≥1	169 (88.02)	58 (80.56)	111 (92.50)	
Previous cerclage	29 (15.10)	10 (13.89)	19 (15.83)	0.716
Transvaginal	24 (12.50)	10 (13.89)	14 (11.67)	0.652
Transabdominal	5 (2.60)	0 (0.00)	5 (4.17)	0.159

Since $P < 0.05$ is considered statistically significant, we bolded those numeric which is minor than 0.05.
[a] ART: assisted reproductive technology. Data are expressed as mean ± SD or numbers (percentages).

including radical trachelectomy for cervical cancer (phase IA2) in 2 patients, cold knife conization and LEEP for high-grade squamous intraepithelial lesions in 6 patients and 1 patients, respectively,and typical painless second trimester fetal loss history in the other 111 patients. Compared with the TVC group, the rate of previous second-trimester spontaneous abortion ≥1 was significantly higher in the TAC group. There were no statistical significances in other baseline clinical characteristics between the two groups.

The results of pre-delivery maternal morbidity for all patients are shown in Table 2 and Table 3. One patient in the TAC group received a rescue TVC at 18 weeks' gestation due to membrane prolapse into the vagina. We found that the rates of abnormal fetal presentation and placental disorders were significantly higher in the TAC group than that in the TVC group, 5.56% versus 21.67% and 4.17% versus 18.33%, respectively, both with $P < 0.05$. The rates of premature rupture of membranes (PROM) and intrauterine infection were significantly higher in TVC patients than that in TAC patients, 25.00% vs 2.50% and 11.23% vs 3.33%, respectively, with $P < 0.05$. No statistical significance was found between the two groups for the other pre-delivery morbidity.

Table 2
Predelivery maternal morbidities of all patients.

	Total patients, n = 192	TVC group, n = 72	TAC group, n = 120	*P* value
Abnormal fetal presentation[a]	30 (15.63)	4 (5.56)	26 (21.67)	**0.003**
Breech presentation	16 (8.33)	4 (5.56)	12 (10.00)	0.281
Shoulder presentation	14 (7.29)	0 (0.00)	14 (11.67)	**0.003**
Placental disorders[b]	25 (13.02)	3 (4.17)	22 (18.33)	**0.004**
Placental previa	17 (8.85)	2 (2.78)	15 (12.50)	**0.022**
Low-lying placenta	8 (4.17)	1 (1.39)	7 (5.83)	0.262
Placenta increta	8 (4.17)	2 (2.78)	6 (5.00)	0.712
Hypertensive disorder	18 (9.38)	4 (5.56)	14 (11.67)	0.160
Diabetes mellitus	65 (33.85)	23 (31.94)	42 (35.00)	0.665
Scarred uterus	40 (20.83)	10 (13.89)	30 (25.00)	0.066
Uterine fibroids	24 (12.50)	10 (13.89)	14 (11.67)	0.652
Polyhydramnios	6 (3.13)	0 (0.00)	6 (5.00)	0.085
Oligohydramnios	1 (0.52)	0 (0.00)	1 (0.83)	1.000
PROM & PPROM	21 (10.94)	18 (25.00)	3 (2.50)	**<0.001**
Intrauterine infection	15 (7.81)	11 (15.23)	4 (3.33)	**0.003**
Fetal growth restriction	7 (3.65)	1 (1.39)	6 (5.00)	0.259
Macrosomia	2 (1.04)	0 (0.00)	2 (1.67)	0.529
Hypothyroidism	7 (3.65)	1 (1.39)	6 (5.00)	0.259
Hyperthyroidism	5 (2.60)	2 (2.78)	3 (2.50)	>0.999
Placental abruption	1 (0.52)	1 (1.39)	0 (0.00)	0.375

Since $P < 0.05$ is considered statistically significant, we bolded those numeric which is minor than 0.05.
[a] Fetal presentation was determined by four maneuvers of Leopold before delivery.
[b] Predelivery placental disorders were diagnosed by the last ultrasound examination before the termination of pregnancy, low-lying placenta is defined as the placental edge less than 2 cm from the internal os but not covering the internal os. PROM:premature rupture of membranes. PPROM: preterm premature rupture of membranes. Data are expressed as numbers (percentages).

Table 3
Subgroup analysis of abnormal fetal presentation and Placental disorders.

	Total patients, n = 192	TVC group, n = 72	TAC group, n = 120	*P* value
Abnormal fetal presentation				
<34 weeks	11 (5.73)	2 (2.78)	9 (7.50)	**0.214**
≥34 weeks	19 (9.90)	2 (2.78)	17 (14.17)	**0.011**
Placental disorders[a]				
Placental previa				
<28weeks	3 (1.56)	1 (1.39)	2 (1.67)	>0.999
≥28 weeks	14 (9.29)	1 (1.39)	13 (10.83)	**0.015**
Low-lying placenta				
<28weeks	1 (0.52)	0 (0.00)	1 (0.83)	>0.999
≥28 weeks	7 (3.64)	1 (0.83)	6 (5.00)	0.259

Since $P < 0.05$ is considered statistically significant, we bolded those numeric which is minor than 0.05.
[a] Predelivery placental disorders were diagnosed by the last ultrasound examination before the termination of pregnancy, low-lying placenta is defined as the placental edge less than 2 cm from the internal os but not covering the internal os. Data are expressed as numbers (percentages).

Pregnancy outcomes, intrapartum morbidities and postpartum morbidities are shown in Table 4 and Table 5. Compared with the TVC group, estimated intrapartum hemorrhage, estimated postpartum hemorrhage and the rate of uterine rupture were higher in the TAC group. We found no statistical significance between the two groups for mean gestational age at delivery, gestational age gained after cervical cerclage, additional hemostasis measures, type of uterine incision at cesarean section, preterm delivery rate and mode of delivery in the second trimester between the two groups. There were no vaginal deliveries in the third trimester in the TAC group, in contrast to the 52.77% vaginal delivery rate in the TVC group. Twenty-two patients terminated their pregnancy in the second trimester, 7 in the TVC group and 15 in the TAC group, all 7 patients in the TVC group had an intrauterine infection due to PPROM, whereas in the TAC group, 8 patients complicated with a dead fetus or miscarriage, 4 patients complicated with PPROM, 2 patients suffered membrane prolapse into the vagina, 1 patient complicated with severe maternal complications. In the TAC group, an inverted T-incision of the lower uterine segment was performed in 3 patients due to the difficulty in delivering the fetus during cesarean section, and a transverse incision of the uterine body was performed in 2 patients due to dysplasia of the lower uterine segment. In the TAC group, complete uterine rupture and incomplete uterine rupture were observed in 4 patients and in 5 patients during cesarean section, among which 2 patients were complicated with scar uterus and the other 7 patients were with intact uterus. No uterine rupture was observed in the TVC group. Cervical laceration was not observed in either group.

Neonatal morbidity of all patients is shown in Table 6. The mean birth weight in the TVC group was significantly lower than that in the TAC group. There were 2 neonatal deaths before discharge, both were in the TAC group, 1 was delivery at 25 + 3/7 weeks' gestation, and the other was delivery at 28 + 6/7 weeks' gestation. There were no statistically significant differences in other neonatal morbidities between the two groups.

Discussion

Cervical cerclage is the preferred surgical treatment option for CI, both TVC and TAC are optional treatments for patients

Table 4
Pregnancy outcomes, intrapartum and postpartum morbidities of all patients.

	Total patients, n = 192	TVC group, n = 72	TAC group, n = 120	*P* value
Mean gestational age at delivery (weeks)	34.59 ± 4.60	35.17 ± 5.35	34.24 ± 7.25	0.347
Gestational age gained[a]	12.56 ± 7.14	12.33 ± 6.15	12.69 ± 7.64	0.759
Gestational age at delivery				
<28	22 (11.46)	7 (9.72)	15 (12.50)	0.559
<34	45 (11.98)	21 (29.17)	24 (20.00)	0.147
<37	79 (17.71)	33 (45.83)	46 (38.33)	0.307
≥37	113 (82.29)	39 (55.17)	74 (61.67)	0.307
Mode of delivery				
Second-trimester	22 (11.46)	7 (9.72)	15 (12.50)	0.603
Vaginal delivery	14 (7.29)	6 (8.33)	8 (6.67)	0.193
Cesarean delivery	8 (4.17)	1 (1.39)	7 (5.83)	
Third-trimester	170 (88.54)	65 (90.28)	105 (87.5)	0.603
Vaginal delivery	38 (19.79)	38 (52.77)	0 (0.00)	**<0.001**
Cesarean delivery	132 (68.75)	27 (37.50)	105 (87.5)	
Estimated intrapartum hemorrhage (ml)				
<500	173 (90.10)	69 (95.83)	104 (86.67)	**0.039**
≥500	19 (9.90)	3 (4.17)	16 (13.33)	
Estimated postpartum hemorrhage (ml)				
<500	156 (81.25)	62 (86.11)	94 (78.33)	0.181
≥500	36 (18.75)	10 (13.89)	26 (21.67)	
Additional hemostasis measures[b]	14 (7.29)	4 (5.56)	13 (10.83)	0.213
Intrauterine balloon	10 (5.21)	4 (5.56)	6 (5.00)	> 0.999
Bilateral uterine artery ligation	9 (4.69)	1 (1.39)	8 (6.67)	0.157
Uterine compression sutrues	1 (0.52)	0 (0.00)	1 (0.83)	> 0.999
Uterine rupture[c]	9 (4.69)	0 (0.00)	9 (7.50)	**0.015**
Complete	4 (2.08)	0 (0.00)	4 (3.33)	0.299
Incomplete	5 (2.60)	0 (0.00)	5 (4.17)	0.159
Uterine incision during Cesarean section				
Low transverse	135 (70.31)	28 (38.89)	107 (89.17)	0.583
Others	5 (2.60)	0 (0.00%)	5 (4.17)	
Blood transfusion	7 (3.65)	2 (2.78)	5 (4.17)	0.713

Since $P < 0.05$ is considered statistically significant, we bolded those numeric which is minor than 0.05.

[a] Gestational age gained was defined as gestational age at delivery post cervical cerclage minus gestational age of previous second trimester fetal loss. Patients without previous second trimester fetal loss were not calculated.

[b] Bilateral uterine artery ligation and intrauterine balloon were performed in 2 patients in TAC group and 1 patient in TVC group due to massive intrapartum hemorrhage during cesarean section.

[c] Incomplete uterine rupture was diagnosed when a subperitoneal dehiscence of the myometrium was observed, a complete uterine rupture refers to the destroy of visceral peritoneum and uterine myometrium, resulting in direct communication between the amniotic and peritoneal cavities. Data are expressed as mean ± SD or numbers (percentages).

Table 5
Subgroup analysis of postpartum hemorrhage.

	Postpartum hemorrhage		*P* value
	Yes	No	
Vaginal delivery			
TVC group	4 (9.09)	40 (90.91)	>0.999
TAC group	1 (12.50)	7 (87.50)	
Cesarean delivery			
TVC group	1 (3.57)	27 (96.43)	>0.999
TAC group	5 (4.47)	107 (95.53)	

Data are expressed as numbers (percentages).

Table 6
Neonatal morbidities of all patients.

	Total patients, n = 192	TVC group, n = 72	TAC group, n = 120	*P* value
Live birth	170 (88.54)	66 (91.67)	104 (86.67)	0.292
Birth weight (kg)	2.77 ± 0.68	2.62 ± 0.73	2.87 ± 0.63	**0.018**
NICU admission	58 (34.12)	28 (42.42)	30 (28.85)	0.069
1 min Apgar score <7	14 (8.24)	7 (10.61)	7 (6.73)	0.370
5 min Apgar score <7	4 (2.35)	3 (4.55)	1 (0.96)	0.300
Respiratory distress syndrome	31 (18.24)	16 (24.24)	15 (14.42)	0.106
Intraventricular hemorrhage	3 (1.76)	1 (1.51)	2 (1.92)	> 0.999
Necrotizing enterocolitis	5 (2.94)	3 (4.55)	2 (1.92)	0.378
Retinopathy of prematurity	7 (4.12)	5 (7.58)	2 (1.92)	0.110
Sepsis	2 (1.18)	1 (1.51)	1 (0.96)	0.999
Neonatal infection	15 (8.82)	5 (7.58)	10 (9.62)	0.648
Hyperbilirubinemia	51 (30.00)	24 (36.36)	27 (25.96)	0.149
Acute renal injury	3 (1.76)	2 (3.03)	1 (0.96)	0.561
Bronchopulmonary dysplasia	2 (1.18)	1 (1.51)	1 (0.96)	> 0.999
Neonatal death before discharge	2 (1.18)	0 (0.00)	2 (1.92)	0.522
Retinal hemorrhage	3 (1.76)	2 (3.03)	1 (0.96)	0.561

Data are expressed as mean ± SD or numbers (percentages).

diagnosed with CI. TVC is the first-line surgical treatment option for CI. Indications for TVC cerclage placement include the following: firstly, a history of one or more previous second-trimester pregnancy losses or preterm deliveries. Secondly, women had a history of spontaneous loss or preterm delivery, and cervical length <25 mm on transvaginal sonography at less than 24 weeks gestation. Thirdly, cervical dilation or prolapse of the membranes into the vagina on physical examination [1–4]. TVC includes the McDonald technique and the Shirodkar technique. In the McDonald technique, the suture is placed at the exo-cervical isthmus junction, whereas in the Shirodkar technique, the bladder is mobilized and the suture is placed above the level of the cardinal ligaments. There is currently no data to indicate which of the above two techniques is better than the other [1–3,14]. The advantages of TVC include ease of performance and the possibility of vaginal delivery after the suture removal. It is a consensus in the SOGC, RCOG, ACOG and FIGO guidelines that TAC is reserved as a second-line treatment option for CI, and that TAC should be considered in patients who have previously failed TVC or who have a history of radical cervical surgery [1–4,8]. Recently, the results of a multicenter randomized control trial comparing TAC and TVC suggest that TAC is the preferred treatment of patients with failed vaginal cerclage [14]. In our study, the indication for cerclage was not comparable between the two groups, the higher rate of history-indicated cerclage in the TAC group was due to patient preference after consultation about TAC and TVC, there was no ultrasound-indication of cerclage in the TAC group since all TAC procedures were performed before pregnancy or in early pregnancy.

The results of our study indicate that TAC patients were associated with significantly higher rates of abnormal fetal presentation and placental disorders than TVC patients, to the best of our knowledge, no studies have reported similar results to ours. According to the literature, breech presentation and transverse presentation at delivery affect approximately 3%–5% and 0.5% of all pregnancies respectively [16,17]; in our study, the incidence of breech presentation and transverse presentation in TVC patients was similar to that previously reported, in contrast to the abnormally higher incidence in TAC patients. Previous studies have shown that maternal age, uterine fibroids, previous cesarean delivery, multiparity, placenta previa, prematurity and fetal growth restriction are associated risk factors for abnormal fetal presentation [15], in our study, all the above risk factors except for placenta previa were comparable between two groups. Therefore, we speculate that the higher rate of abnormal fetal presentation in the TAC group was due to the higher rate of placenta previa. Previous studies reported that the prevalence of placenta previa is 2.7–12.2 per 1000 pregnancies worldwide [17–19], in our study, the rate of placenta previa was up to 12.50% and 2.78% in TAC patients and TVC

patients respectively. Several risk factors for placenta previa have been identified, including maternal age, multiparity, previous cesarean delivery, chronic hypertension, diabetes and assisted reproductive technology [17,19]. In our study, the incidence of placental previa in the TAC patients was significantly higher than that in TVC patients, while the risk factors for placental previa were comparable between two groups, we speculate that the reason may be the higher suture site of the cervix in the TAC technique. In the McDonald technique, the suture is placed around the exo-cervix in the vagina, while in the Shirodkar technique, the suture is placed above the level of the cardinal ligaments, whereas in the TAC technique, the suture is placed at the level of the uterine blood vessels, thus the suture site of the TVC technique is lower than that of the TAC technique [2,11,13,14,20]. However, the exact pathogenesis of the increased incidence of abnormal fetal presentation and placental previa in TAC patients is still unknown, and further studies are needed.

Our study shows a significantly lower rate of PPROM, PROM and intrauterine infection rate in TAC patients than that in TVC patients, which is consistent with previous studies [4,9,21]. The lower incidence of PPROM, PROM and intrauterine infection in TAC patients may be due to several reasons. Firstly, in TAC patients, the mersilene tape is placed in the abdomen, which provides a sterile environment during pregnancy, whereas in TVC patients, the mersilene tape is placed in the exo-cervix using the McDonald approach, which increases the risk of infection due to the non-sterile nature of the vagina, leading to an increase in PPROM, PROM and intrauterine infection [2,4,13]. Secondly, more patients in the TAC group opted for an elective cesarean section delivery due to the nature of the TAC technique, whereas most patients in the TVC group had a trial of labor after cerclage removal.

Our study shows that TAC patients had significantly higher rates of caesarean delivery in the third trimester, estimated intrapartum hemorrhage $\geq$500 ml and uterine rupture, which have not been reported in previous studies. The reason for the significantly higher risk of cesarean section delivery in the third trimester was due to the nature of the TAC procedure itself, in which a cesarean section is required to deliver the fetus [1,2,4,14]. However, in TVC patients, a cesarean section is only required in patients with indications for cesarean section [1–4,13,14]. According to the literature, many causes and risk factors contribute to postpartum hemorrhage [22], the higher risks of intrapartum hemorrhage and postpartum hemorrhage in TAC patients in our study may be the result of the higher incidence of placenta previa, cesarean section and uterine rupture in TAC patients. So far, only 4 cases of uterine rupture in TAC patients have been reported, and in the cases presented by Burger and Dandapani, there were no risk factors for uterine rupture except for cervical cerclage and uterine contractions [23–26]. However, in our study, 9 patients in the TAC group suffered uterine rupture, only 2 patients were complicated with scar uterus, the other patients had intact uterus. Taken together, we agree with Dandapani that TAC may be a potential risk factor for uterine rupture.

To date, no randomized controlled trials have directly compared TVC and TAC in the treatment of all CI patients, the results of our retrospective study show that there were comparable gestational age, gestational age gain and neonatal complications between TVC patients and TAC patients, which is consistent with previous studies [2,20,27]. Two studies have evaluated TVC and TAC in the treatment of CI patients with previous failed TVC, the results of the MAVRIC study showed that preterm birth at < 32 gestational weeks was significantly reduced in TAC patients, another study conducted by Davis et al. also showed a lower incidence of preterm birth in TAC patients [14,20]. Taken together, the results of our study and the above two studies further support the view that TAC should be reserved as a second-line treatment option for CI, with indications for TAC strictly limited to patients with failed TVC or a history of radical cervical surgery.

The strengths of our study include the relatively large number of patients and the comprehensive data collection. Medical records of cervical cerclage and pregnancy outcome were obtained for each patient, thus avoiding recall bias. however, as a retrospective study, our study has limitations. Firstly, some patients who received TVC/TAC did not terminate the pregnancy in our hospital; therefore, not all patients who underwent TAC/TVC were analyzed, which would lead to patient selection bias. Secondly, no comparison was made between patients who received cervical cerclage and those who did not.

Conclusion

Compared with TVC patients, TAC patients were associated with a significantly higher incidence of maternal morbidity in abnormal fetal presentation, placental disorders, intrapartum hemorrhage $\geq$500 ml and uterine rupture.

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Declaration of Generative AI and AI-assisted technologies in the writing process

We declare that AI-assisted technologies were not used in the writing process.

Declaration of competing interest

We declare that there are no potential conflicts of interest.

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Case Report

A case study of transneovaginal oocyte retrieval after novel Lee's neovaginoplasty in Mayer-Rokitansky-Küster-Hauser syndrome

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ABSTRACT

Objective: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital disorder that results in vaginal agenesis. Lee's neovaginoplasty is a novel surgery for reconstructing the vagina. Transneovaginal oocyte retrieval completely changes the scope of fertility for patients with MRKH syndrome who have undergone neovaginal reconstruction.

Case report: A 22-year-old female with type 1 MRKH syndrome underwent Lee's neovaginoplasty successfully. Four years later, she sought embryo cryopreservation consultation and underwent controlled ovarian hyperstimulation. Upon examination, her anti-Müllerian hormone level was 1.97 ng/ml and she had only eight antral follicles. The neovaginal length was 8 cm with elasticity and extensibility. Transneovaginal oocyte retrieval was performed under ultrasound guidance, and seven oocytes were retrieved. The follicle-to-oocyte index was 87.5%.

Conclusion: Lee's neovaginoplasty is a promising surgery for reconstructing the vagina in MRKH syndrome, and this case shows that transneovaginal oocyte retrieval can be successfully performed after vaginal reconstruction. This technique provides a minimally invasive option for retrieving oocytes in patients of MRKH syndrome.

Introduction

Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a congenital disorder that is the common cause of vaginal agenesis. It is characterized by the agenesis of the uterus and upper part of the vagina, resulting in primary amenorrhea, but maintaining normal reproductive endocrine function and typical external genital appearance with a female chromosomal pattern of 46, XX [1]. MRKH agenesis affects one in 4000 live female births [2]. Management options for vaginal agenesis include self-dilation (Frank's method) and vaginoplasty.

In 2014, Lee's neovaginoplasty was introduced as a surgical method for reconstructing the vagina using the rudimentary uterine horns serosa and peritoneum [3]. This surgical approach offers several benefits, such as reduced morbidity from graft usage, shorter hospitalization, a more elastic and stronger neovaginal wall, better recovery, and natural lubrication [4]. Despite neovaginal reconstruction, patients with MRKH syndrome remain infertile and require uterine transplantation or in vitro fertilization with a surrogate for offspring acquisition [5]. Therefore, the development of transneovaginal retrieval of oocytes changes the course of fertility for MRKH patients.

This case report describes a female patient with MRKH syndrome who underwent Lee's neovaginoplasty and successfully underwent transneovaginal oocyte retrieval, which to our knowledge, is the first case of transneovaginal ultrasound-guided oocyte retrieval after Lee's neovaginoplasty.

Case presentation

A 22-year-old female presented with primary amenorrhea and no urinary symptoms. Her secondary sexual characteristics were appropriate for her age. On gynecological examination, a blind-ended vaginal dimple (less than 1 cm in depth) was found. Transabdominal sonography showed a dysgenetic uterus with normal bilateral adnexa and kidneys. No other concurrent defects were identified. A diagnosis of type 1 MRKH syndrome was made, and Lee's neovaginoplasty was planned to facilitate intercourse.

Lee's neovaginoplasty is a surgical procedure that simultaneously approaches the abdomen and vagina. Under laparoscopic

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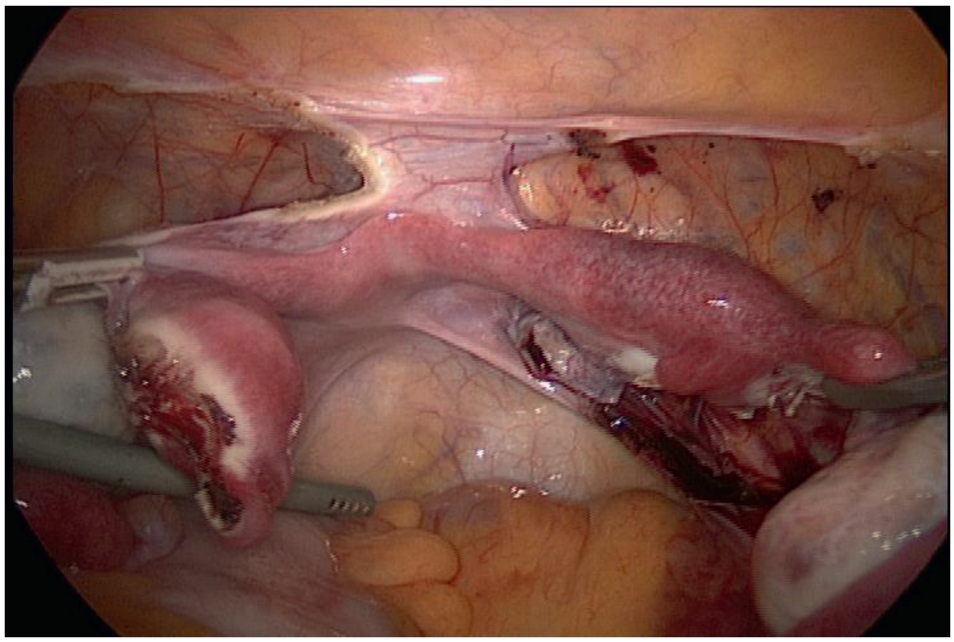

Fig. 1. Bilateral rudimentary uterine bodies were dissected free. The uterine serosa and peritoneum were used as a graft.

view, hypoplastic uterus and bilateral rudimentary uterine horns with bilateral adnexa were noted, confirming the diagnosis of MRKH syndrome. The surgical team made a vertical incision on the hymen in the area between the urethra and the rectum. The hymen was then opened with the artery forceps and a finger was inserted into the neovagina to manually distend the vaginal vault. At the same time, under the laparoscopic vision, an incision was then made on the distended vaginal vault, creating a 3 cm opening. The ovarian ligaments and Fallopian tubes were separated from the uterus, and the peritoneum attached to the uterus was harvested together with the uterus to the anterior edge of the vesical fold and posteriorly to the uterine arteries. The bilateral rudimentary uterine horns were dissected free and brought down into the vagina (Fig. 1). The myometrium of the bilateral rudimentary uterine horns that had been brought down into the vagina was trimmed away, leaving only the uterine serosa layer. The anterior and posterior vaginal walls were lined by uterine serosa, and the peritoneum was used for the lateral walls of the vagina. Stitches were placed between the uterine serosa and the vaginal opening to confirm they were tightly adhered. A 20 ml syringe was used as a stent for the neovagina (Fig. 2), and the vaginal vault was closed by suturing laparoscopically. At the nine-month follow-up, a patent neovagina with a length of 8 cm was observed, with adequate lubrication, and the patient had no dyspareunia during intercourse.

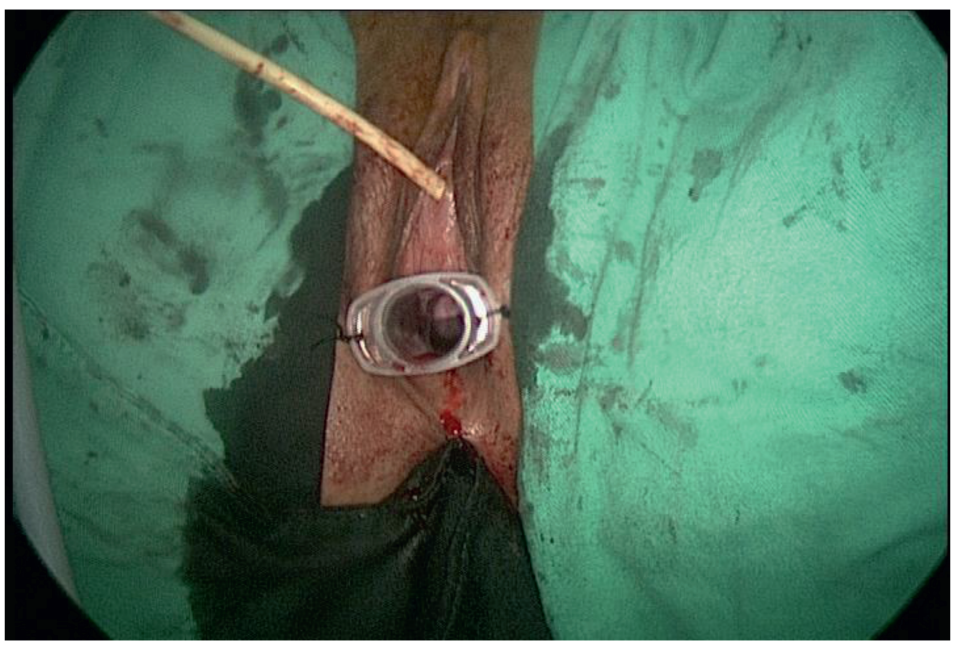

Fig. 2. Syringe as a neovaginal stent.

Four years after the Lee's neovaginoplasty, the patient sought embryo cryopreservation consultation. On gynecological examination, fair vaginal mucosa with a length of 8 cm was observed. Transneovaginal sonography showed normal bilateral adnexa with only eight antral follicles, and laboratory evaluation revealed normal hormonal assays and anti-Müllerian hormone level was 1.97 ng/ml. Controlled ovarian hyperstimulation (COH) was arranged using corifollitropin alfa 150 mcg (Elonva®) since the early follicular phase to start the gonadotropin releasing hormone antagonist protocol. Daily cetrorelix 0.25 mg (Cetrotide®) was then applied for four days after COH. When the diameter of the leading follicle approached 18 mm with serum estradiol levels reaching 1044 pg/ml, dual triggers with triptorelin 0.2 mg (Decapeptyl®) and recombinant human chorionic gonadotropin 250 mcg (Ovidrel®) were administered. Thirty-six hours later, transneovaginal oocyte retrieval was performed under ultrasound guidance (Fig. 3). A total of seven oocytes, with three from the right ovary and four from the left ovary, were retrieved smoothly. The follicle-to-oocyte index was 87.5%. Intracytoplasmic sperm injection was performed for insemination, and all embryos were cultured into blastocysts. Eventually, five blastocysts were cryopreserved with the grading 4BB, 5BB, 5AB, 5CC and 3CC.

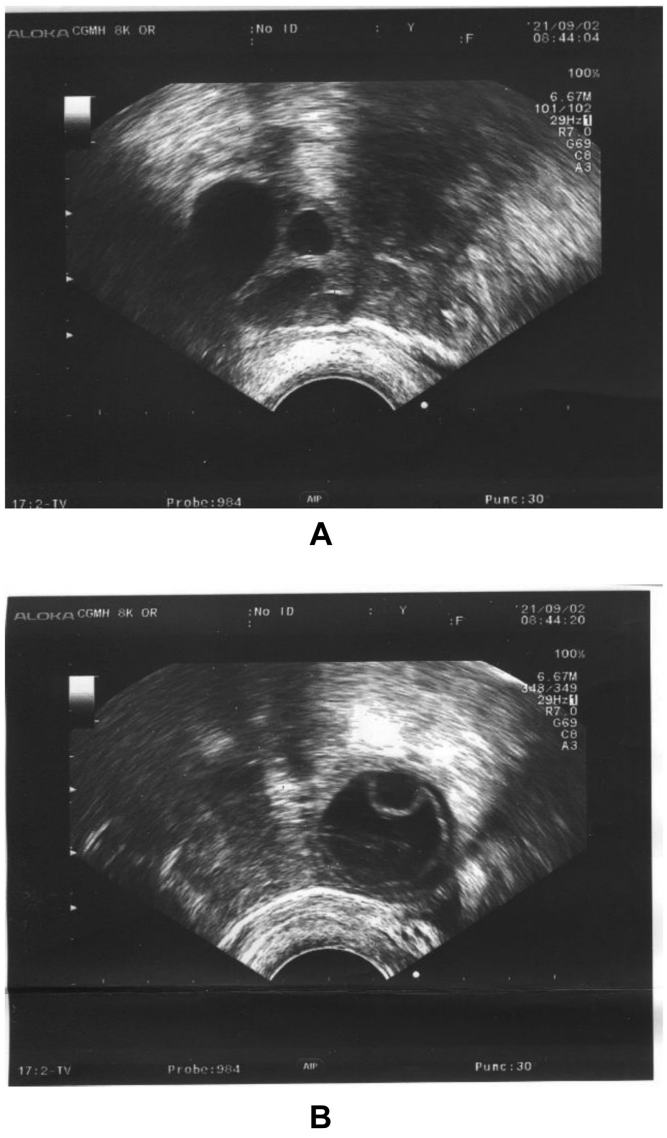

Fig. 3. Transneovaginal oocyte retrieval. A. Right ovary. B. Left ovary.

Discussion

Patients with MRKH syndrome who have vaginal agenesis often encounter difficulties during intercourse [6]. Vaginal dilation is a common first-line therapy for vaginal agenesis in some studies [7]; however, this approach has disadvantages such as physical discomfort and the potential risk of vaginal necrosis. Conventional neovaginoplasty using bowel, amnion, or artificial skin grafts can lead to a foul-smelling vagina, increasing the risk of infection, restenosis, and bowel perforation [8]. To address these issues, we opted for novel Lee's neovaginoplasty, which uses bilateral rudimentary uterine horns and uterine serosa to reconstruct the vagina [4]. Novel Lee's neovaginoplasty avoids discomfort from the traction device and provides the benefits of fast recovery, minimal invasion, and a more lubricated, flexible neovagina similar to that of a natural vagina [4,9].

Additionally, studies have shown that infertility can be the hardest psychological condition affecting the welfare of MRKH patients [10], and early counseling about fertility options is considered a keystone of care [11]. Advancements in reproductive medicine have provided MRKH patients with options for having children, such as uterine transplantation and surrogacy. However, there is no standard protocol for oocyte retrieval in these patients. Transvaginal techniques are challenging to perform in patients who have undergone conventional vaginoplasty due to the neovagina's poor elasticity. Recent reports have shown that combining laparoscopic oocyte retrieval with Davydov vaginoplasty provides minimal invasiveness [12]. However, this approach may not be suitable for underage patients or those who do not intend to become pregnant immediately. In this case, the patient initially did not plan to conceive after undergoing vaginal construction, but changed her mind after four years.

Some studies indicated that transvaginal oocyte retrieval is less traumatic and more effective than laparoscopic oocyte retrieval [13,14]. Therefore, we performed transneovaginal oocyte retrieval on this patient to address the aforementioned concerns. This innovative approach may be especially advantageous for individuals with MRKH who are experiencing emotional distress related to their infertility diagnosis [15].

The main limitations of our study are the limited possibility of generalising the validity of the study, the impossibility of establishing a cause-effect relationship, and the sample size. Therefore, it is important to note that this strategy for oocyte retrieval should be studied in a larger series of patients undergoing the same surgical approaches for the treatment of MRKH syndrome. Moreover, determining whether to perform vaginoplasty and oocyte retrieval in young MRKH patients should be personalized and based on their personal desires for willingness to adhere to post-operative dilation, emotional readiness, and fertility. Patients must meet specific requirements before undergoing these approaches, such as an evaluation of their emotional steadiness, the indication for vaginoplasty, and a desire to freeze oocytes despite the possibility of needing further invasive procedures for egg retrieval in the future.

Novel Lee's neovaginoplasty can reconstruct the neovagina with minimal morbidity and improve patients' life quality. Additionally, the additional uterine serosa makes the neovagina tougher and stronger. This case illustrates the potential of Lee's neovaginoplasty as a surgical option for restoring sexual function and achieving pregnancy in patients with MRKH syndrome who require fertility treatment. Transneovaginal oocyte retrieval represents an advancement in reproductive medicine, and its successful use in

this case highlights the importance of continued research and innovation in this field.

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Case Report

Duodenal stenosis due to small lymphocele after para-aortic lymphadenectomy: A case report and review of the literature

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ABSTRACT

Objective: We present an unusual case of a small para-aortic lymphocele causing duodenal stenosis after lymphadenectomy and discuss its treatment.
Case report: Our case involved a 57-year-old woman with endometrial cancer who underwent surgery, including para-aortic lymphadenectomy. On postoperative day 7, projectile vomiting occurred. Computed tomography (CT) revealed a small lymphocele in the dorsal duodenum, causing duodenal stenosis. Transpercutaneous and transduodenal puncture or surgical procedures were difficult because the cyst was too small. Per endoscopic and gastrointestinal series findings on the postoperative day 22, a liquid diet was presumed to be able to pass through the narrow portion. Hence, concentrated liquid food was administered orally; no vomiting occurred. At 2 months postoperatively, CT showed no lymphocele.
Conclusion: Conservative treatment involving waiting for spontaneous lymphocele reduction with a concentrated fluid diet may be considered in such cases if fluid passage is confirmed with endoscopy and gastrointestinal series.

Introduction

The incidence rate of lymphoceles after lymphadenectomy in gynecological malignancies is approximately 40% [1,2]. Lymphoceles develop more frequently in the pelvic area (76%) than in the para-aortic area (24%) [1]. Lymphoceles can be classified as symptomatic or asymptomatic. Although postoperative lymphoceles occur relatively frequently, most cases are asymptomatic and do not require intervention because they shrink spontaneously. In contrast, the most common complication of symptomatic lymphoceles is infection, with bowel stenosis being relatively rare.

Most symptomatic lymphoceles causing bowel stenosis are large and easily treatable by percutaneous puncture or surgery [3,4]. However, bowel stenosis can occur with small lymphoceles at specific sites. The duodenum is a retroperitoneal organ suspended by the ligament of Treitz; therefore, small lymphoceles in the dorsal duodenum can cause duodenal stenosis. However, these small lymphoceles are often difficult to approach using percutaneous puncture or surgery. There has been only one case reported of duodenal stenosis due to a lymphocele after gynecological surgery, in which the patient had a 10-cm lymphocele that could be treated surgically [5].

Herein, we report our experience with an unusual presentation of a 3–4-cm small para-aortic lymphocele causing duodenal stenosis in a patient who underwent para-aortic lymphadenectomy. We believe this is the first report of a small para-aortic lymphocele causing duodenal stenosis after gynecological surgery.

Case presentation

A 57-year-old woman was diagnosed with an endometrial carcinosarcoma. She also had a history of hypertension. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, para-aortic lymphadenectomy, pelvic lymphadenectomy, and partial omentectomy were performed. The surgery lasted 6 h and 40 min, with a total blood loss of 422 mL. During para-aortic lymphadenectomy, the view was developed through a median peritoneal incision along the inferior mesenteric vein. A complete para-aortic lymphadenectomy up to the left renal vein was performed. The upper and lower ends of the lymphatic vessels were ligated using synthetic absorbable threads and bipolar scissors, and vessel-sealing power-cutting devices were mainly used during

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lymphadenectomy. Peritoneal suturing was not performed, and no anti-adhesion material was used. Histopathological examination revealed endometrial carcinosarcoma with a tumor classification of stage IA, pT1a N0 M0.

The patient began ingesting food the day after surgery. Although no abdominal pain was noted on the 9th postoperative day, projectile vomiting occurred. Normal intestinal peristaltic sounds were auscultated on examination and the abdominal wall was not tender; defecation was normal. Abdominal radiography revealed a niveau formation in the duodenum. Computed tomography (CT) revealed a 42 × 24 mm lymphocele extending to the dorsal of the duodenum, causing compression (Fig. 1). Intestinal dilatation was not observed in the small intestine on the anal side of the ligament of Treitz. Percutaneous cystic puncture was considered too difficult to perform because the lymphocele was small and surrounded by major blood vessels, the upper gastrointestinal tract, pancreas, and kidneys. In anticipation of spontaneous lymphocele reduction, a nasogastric (NG) tube was inserted. On the 15th postoperative day, CT showed no remarkable changes in the lymphocele size. On the 21st postoperative day, transduodenal cyst puncture guided by endoscopic ultrasound was attempted. Endoscopic ultrasonography (EUS) was performed 2 h after NG tube removal. On EUS, cysts were detected on the dorsal side of the duodenum, which caused compression and duodenal tube narrowing. However, the transduodenal puncture failed because the cyst was too small and soft for a safe puncture. The endoscope was passed through the narrowed portion of the duodenum, and the absence of remnant gastric juice was confirmed. Based on these findings, we concluded that water or a liquid diet might pass through the narrowed portion of the duodenum. On the 22nd postoperative day, contrast medium was injected from the NG tube, and CT was performed 5 h later. We confirmed that the contrast medium reached the colon, although the contrast agent remained in the stomach. Given our confirmation that liquid nutritional supplements could physically pass through the duodenum, drinking was started on postoperative day 23, and oral concentrated liquid food intake was gradually increased. After confirming the necessary amount of nutrients was secured without vomiting, the patient was discharged on the 35th postoperative day. At 2 months postoperatively, CT showed an unclear lymphocele and the patient could consume normal meals without vomiting. At 4 years postoperatively, no duodenal stenosis, lymphocele, or cancer have recurred.

Discussion

Lymphoceles rarely stenose adjacent structures such as the bowel [2]. We reviewed the literature available in the PubMed and Scopus databases up to April 2024. Each of the terms “bowel obstruction,” “duodenal obstruction,” “bowel stenosis,” “duodenal stenosis,” and “ileus” in combination with “lymphocele” or “lymphocyst” or “lymphocele,” respectively, were used to search and collate relevant articles. Thus, we believe there has only been one other report published involving duodenal stenosis resulting from lymphocele compression following gynecological surgery [5]; other reports of duodenal stenosis due to lymphocele compression following digestive [6] and aortic [7] surgeries do exist (Table 1). Published reports may be scarce because bowel obstruction caused by large lymphocysts is treated with common symptomatic lymphocyst treatments such as percutaneous puncture aspiration, and therefore deemed to be of too little value to report. In the present case, the lymphocyst caused duodenal stenosis despite its small size and was therefore difficult to treat. Its characteristic symptoms, etiology, and treatment are discussed below.

Reasons for duodenal stenosis caused by small lymphoceles

In the present case, a median peritoneal incision was made. However, because of the absence of anti-adhesion agents and absence of suture closure of the median peritoneal incision, the retroperitoneal organs, including the inferior vena cava and inferior aorta, remained exposed. Therefore, postoperatively, the horizontal duodenal leg may have accidently adhered, resulting in small

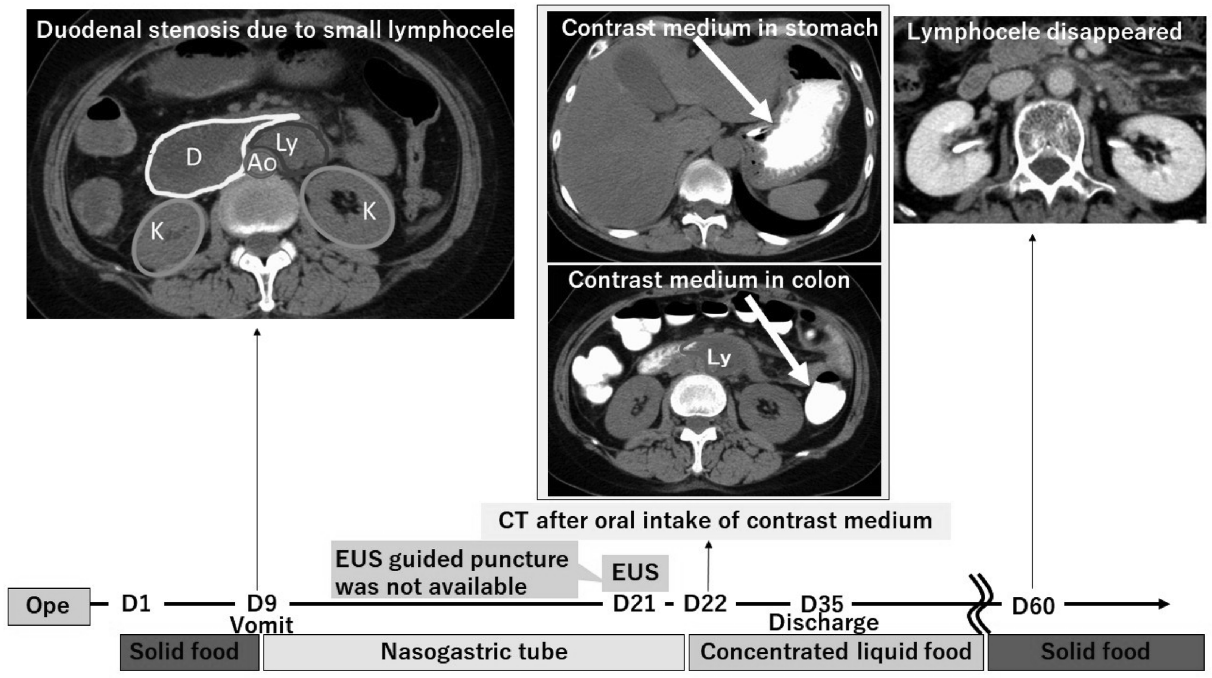

Fig. 1. Schema showing the clinical course of the case. Ope: operation, D: duodenum, Ao: aorta, Ly: lymphocele, K: kidney, CT: computed tomography, EUS: endoscopic ultrasonography, NG: nasogastric.

Table 1
Reported cases of duodenal stenosis due to a lymphocele after surgery.

Author	Patient age (years)	Clinical departments	Lymphocele causing surgery	Onset of duodenal stenosis	Symptoms	Size of lymphocele	Treatment of lymphocele
Nishibeppu et al. [6]	68	Digestive surgery	PALA	POD30	Intractable vomiting	Large	Conservative treatment: failure Percutaneous drainage + Sclerotherapy
Blessios et al. [7]	N. A	Cardiovascular surgery	Aortic synthetic graft	N. A.	N. A.	Large	Laparoscopic surgery
Radosa et al. [5]	62	Gynecology	PALA	POD29	Projectile vomiting (No abdominal pain) (Normal defecation) (Normal bowel movements)	90 × 100 mm	Laparotomy
The present case	57	Gynecology	PALA	POD9	Projectile vomiting (No abdominal pain) (Normal defecation) (Normal bowel movements)	24 × 42 mm	Liquid diet (Waiting for spontaneous shrinking of lymphocele)

N. A.: not applicable, PALA: para-aortic lymphadenectomy, POD: postoperative day.

lymphocytes. When a median peritoneal incision is made during para-aortic lymph node dissection, suture closure or the use of anti-adhesion agents may prevent complications such as those observed in the present case from arising.

Characteristic symptoms of duodenal stenosis

Duodenal stenosis may be diagnosed early by focusing on its characteristic symptoms. Postoperative vomiting is a complication caused mostly by paralytic ileus and rarely by strangulated ileus. Almost all cases involving the ileus have small bowel ileus, and upper gastrointestinal stenosis is very rare. In cases of paralytic and strangulated small bowel ileus, defecation and emesis cease, and the dilated small intestine causes flatulence and abdominal pain. On the other hand, duodenal stenosis is characterized by projectile vomiting immediately after eating and continuous defecation without flatulence or abdominal pain due to upper gastrointestinal stenosis (Table 1).

Relationship between lymphocele size and stenosis

Lymphoceles associated with small bowel stenosis are most likely large, and small lymphoceles usually do not cause small bowel stenosis. In contrast, small lymphoceles present in the dorsal duodenum may cause stenosis, given that the duodenum is a retroperitoneal organ suspended by the ligament of Treitz, which has no place for decompression.

General treatment for symptomatic lymphoceles

In general, there are five treatment options for symptomatic lymphoceles: percutaneous puncture, EUS-guided puncture, lymphatic embolization, lymphovenous anastomosis, and surgical fenestration, with the least invasive treatment method often given priority. Usually, the first treatment of choice is CT—or ultrasound-guided percutaneous needle aspiration and drainage of the lymphocele, which is occasionally combined with sclerotherapy. The recurrence rate is reduced from 59% to 31% in simple aspiration versus aspiration combined with sclerotherapy [8]. A meta-analysis revealed a pooled relative risk of 1.57 for percutaneous catheter drainage with delayed addition of sclerotherapy when compared to percutaneous catheter drainage alone [9]. EUS-guided puncture is a second option for lymphoceles attached to the upper gastrointestinal tract or colon [10,11]. Other minimally invasive therapeutic options include lymphatic embolization [12] and lymphovenous anastomosis [13]; however, these options are indicated only for lymphoceles in the pelvis, not those in the para-aortic region. Surgical fenestration via laparotomy or laparoscopy is the most reliable treatment option [4], albeit highly invasive.

Treatment for duodenal stenosis due to a para-aortic lymphocele in the dorsal duodenum

We present four treatment options for duodenum stenosis due to para-aortic lymphocele: percutaneous puncture, EUS-guided transduodenal puncture, surgery, and conservative treatment (Fig. 2). The size of the lymphocele is closely related to treatment options for duodenal stenosis due to lymphocele. Percutaneous drainage with or without sclerotherapy is available for large lymphoceles [6]. However, they are almost impossible to use in cases of small lymphoceles because of the upper gastrointestinal tract and pancreas on the ventral side and the kidney, and large blood vessels on the dorsal side. EUS uses an endoscope with an ultrasound imaging device attached to the end of it. This enables detailed observation of the walls of the digestive tract and adjacent organs such as the pancreas, bile duct, gallbladder, and lymph nodes. Needle biopsy, puncture aspiration, and drainage tube placement under ultrasound guidance can also be performed for these organs. Duodenal puncture guided by EUS with or without sclerotherapy may be useful for medium-sized lymphoceles but may be difficult for small cysts, as in our case. Surgical fenestration via laparotomy or laparoscopy has also been considered [4]. However, small lymphoceles are associated with an increased risk of recurrence after surgery and are more difficult to operate on due to the small fenestration size [14,15]. In addition, it should be noted that significantly more surgical complications occur after para-aortic lymph node dissection (24%) than after pelvic lymph node dissection (4%) [4]. Therefore, surgery should only be considered when all other treatment options have failed. On the other hand, nutritional management with a concentrated liquid diet is possible, provided that the cyst is small and allows liquid to pass through the duodenum. Upper gastrointestinal endoscopy, and CT after oral contrast medium administration may be useful for evaluating fluid passage through the duodenum. Conservative treatment is a characteristic treatment option for duodenum stenosis due to a lymphocele in the dorsal duodenum, as even small lymphoceles can cause bowel stenosis.

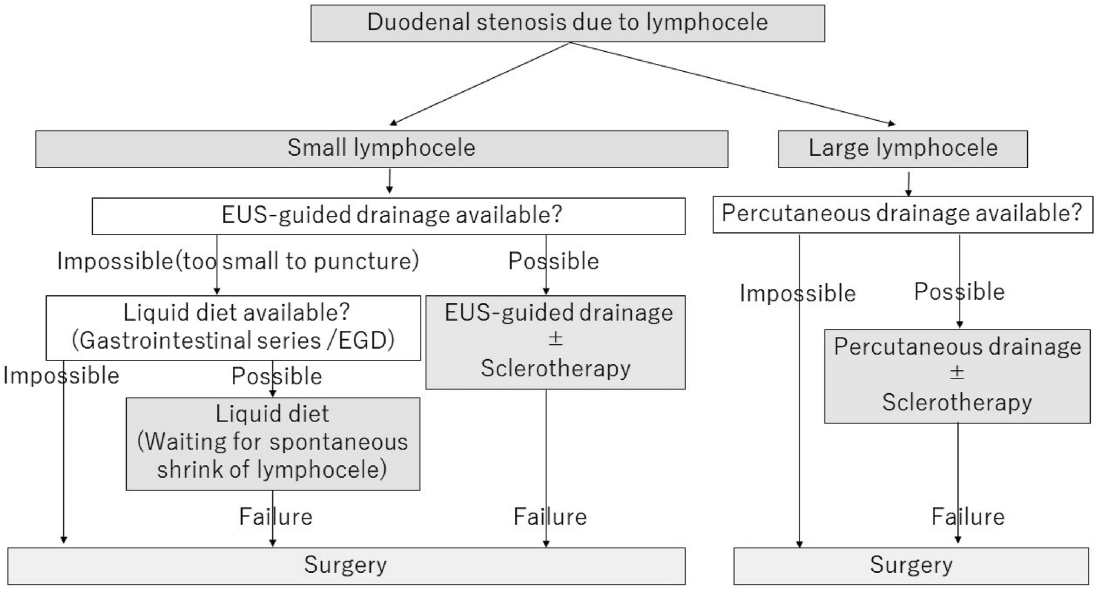

Fig. 2. Schema of treatment options for duodenal stenosis due to lymphocele. EGD: Esophagogastroduodenoscopy, EUS: Endoscopic ultrasonography.

In conclusion, unlike common pelvic lymphoceles, those that form on the dorsal portion of the duodenum can cause duodenal stenosis via compression, even when they are small in diameter. Small lymphoceles are challenging to treat via percutaneous or EUS-guided transduodenal puncture or surgical treatment. Therefore, conservative treatment involving waiting for spontaneous reduction of the lymphocele through long-term continuation of a concentrated liquid diet may be possible if passage through the duodenum is confirmed via endoscopy and CT after oral contrast medium administration assessment.

Declaration of competing interest

None.

Acknowledgment

None.

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Case Report

Detecting early-stage breast cancer with GATA3-positive circulating tumor cells

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ABSTRACT

Objective: This case demonstrated the possibility of using GATA3-positive circulating tumor cells (CTCs) to detect early-stage breast cancer (BrC).
Case report: The 86 years old female patient received a mammographic examination with no evidence of malignancy (Breast Imaging Reporting and Data System, (BI-RADS category 2). However, CTC testing on the same day revealed four GATA3-positive CTCs in 4 ml of peripheral blood. Core needle biopsy was performed in the suspicious area even with no evidence of malignant image on breast ultrasound. Pathologic examination showed invasive carcinoma of no special type of the breast. The patient then received an oncoplastic partial mastectomy of right breast and sentinel lymph node biopsy. The surgical staging was cT1N0M0. Post-operation follow-up examination showed absence of GATA3-positive CTCs and the presence of HER2/ER positive CTCs.
Conclusion: The role of GATA3-positive CTCs as a potential biomarker for early-stage BrC should be explored.

Introduction

Breast cancer (BrC) is one of the most common cancers in women in Taiwan. According to Taiwan Ministry of Health and Welfare statistics, about 15,400 new cases of breast cancer are diagnosed each year, accounting for about 25% of the incidence of cancer in women. BrC is also the 2nd-leading cause of cancer deaths in Taiwanese women, with about 2900 women dying from BrCr each year [1].

Breast ultrasound and screening mammography are common methods for diagnosing BrC and play an important role in detecting early-stage disease. The sensitivity of breast ultrasound alone for detecting BrC smaller than 1 cm size is 87%, while the sensitivity of mammography alone is 73%. However, combining breast ultrasound and mammography can increase the sensitivity to 93% [2].

Circulating tumor cells (CTCs) are tumor cells that shed from the original tumor sites and exist in the circulatory system. They can pass through the blood vessel wall into other organs and tissues to form metastases [3]. Currently, some studies have attempted to use CTC detection technology to detect early-stage BrC [4,5]. Detection of CTCs can be used for real-time monitoring of tumor, evaluation of tumor metastasis risk, helping the development of personalized treatment plans, and predicting treatment response and prognosis [3]. In addition, CTC detection methods are less invasive and easier to repeat than traditional tissue biopsy.

However, CTC testing has its limitations, including: 1). The scarcity of CTCs poses challenges to the sensitivity and specificity of detection, 2). The results of different CTC detection methods are not consistent, and 3). Many current tests only report the results of CTC enumeration, which only provides limited information.

Current advances in CTC technologies, especially microfluidic chip technology, have greatly improved the sensitivity and specificity of CTC testing. Our previous studies have demonstrated the sensitivity, stability, and efficiency of the CellReveal™ system in detecting CTCs [6–8]. The rapid development of CTC profiling and CTC single-cell sequencing can detect CTCs with specific cancer

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antigens and detect tumor-specific gene mutations in single cell level [6]. Therefore, the detection of CTCs with tumor-specific antigens can be used to detect BrC.

Here, we report a case of early-stage BrC that was suspected before positive imaging findings due to the detection of GATA-3 positive CTCs using automatic CellReveal™ devices.

Case presentation

The 86-year-old female patient has a history of cardiac arrhythmia, osteoporosis, and chronic hepatitis B. She had a pacemaker implanted due to cardiac arrhythmia. Currently, her liver function is normal. There is no family history of BrC. A screening mammography on Nov. 08, 2022 revealed no evidence of malignancy, (BI-RADS category 2). CTC testing was also done on the same day. Sixteen ml of peripheral blood was drawn for CTC testing. Four ml of the blood sample was used for tumor-associated immunocytochemistry staining for BrC after enrichment, including GATA3 and HER2 using an automatic CTC system (CellReveal™ machine, CytoAurora Biotechnologies Inc., Hsinchu, Taiwan) [7]. Tables 1 and 2 summarize the results of CTC testing. Three CTCs with immunohistochemistry (IHC) staining of PanCK-/GATA3+/HER2-/CD45-/DAPI+ and one CTC with PanCK+/GATA3+/HER2-/CD45-/DAPI+ were detected. The number of GATA3-positive CTCs was significantly higher than the range of 0–1 in 4 ml blood sample observed in normal individuals in our laboratory. Fig.1 shows the IHC standing of a GATA3+ CTC.

Breast ultrasound was performed on Dec. 07, 2022 due to the abnormal CTC findings. A right breast mass of 0.55*0.33*0.42 cm in size was detected with the impression of probably benign findings (category 3) (Fig. 2).

The patient underwent right breast core needle biopsy after a repeat breast ultrasound on March 1, 2023. Pathology revealed invasive ductal carcinoma. IHC staining of the biopsy sample was positive for ER (>90%) and PR (80%), but negative for HER2/Neu stain (1+). Ki-67/MIB-1 index was about 5% (Fig. 3).

Oncoplastic partial mastectomy of the right breast with sentinel lymph node biopsy was performed on March 23. 2023. The surgical staging classification was cT1N0M0 breast cancer, based on the American Joint Committee on Cancer (AJCC) cancer staging system. Results of immunohistochemistry staining confirmed the core needle biopsy diagnosis. The patient was then treated with hormone therapy and radiotherapy.

Follow-up CTC testing was performed on April 07, 2023. Two CTCs and one HER2-positive CTC were detected in the 4 ml peripheral blood sample. The IHC staining of an HER2-positive CTC is shown in Fig. 4. Follow-up CTC testing every three months was planned as an additional tool for monitoring the disease progression and treatment response.

On June 9, 2023, another CTC test was conducted. This time, the test utilized two blood samples to detect ER+/CK7+ CTCs and GATA3+/HER2+ CTCs separately. The results showed the presence of one ER-positive CTC in a 2 ml blood sample (Fig. 5), while no GATA3-positive CTCs or HER2-positive CTCs were detected in the additional 4 ml blood sample.

Discussion

This case report shows that GATA3-positive CTCs can be detected in patients with BrC before the tumor is identified by traditional imaging technologies. It shows that the detection of GATA3-positive CTCs has the potential to become a biomarker for the detection of early-stage BrC.

In the past, many studies have sought to explore the use of CTCs as biomarkers for diagnosing breast cancer. In 2023, a meta-analysis analyzed 14 studies on CTCs and breast cancer, finding that although the sensitivity of using CTCs for diagnosing breast cancer was low at 0.50, the specificity was high at 0.93. One of the major challenges in conducting meta-analyses of CTC-related studies stems from the significant variability in methods used to detect CTCs, which can influence the outcome of subgroup analysis.

Table 1
The results of pre-operation CTC testing from 4 ml of peripheral blood.

No.	IHC staining	Cell No.
1	PanCK+/GATA3-/HER2-	0
2	PanCK-/GATA3+/HER2-	3
3	PanCK+/GATA3+/HER2-	1
4	PanCK-/GATA3-/HER2+	0
5	PanCK+/GATA3-/HER2+	0
6	PanCK-/GATA3+/HER2+	0
7	PanCK+/GATA3+/HER2+	0

*IHC: immunocytochemistry.

Table 2
The cell size and characteristics of the PanCK-/GATA3+/HER2- CTCs.

No	Nuclear size (μm)	Nuclear area (μm^2)	Cytokeratin size (μm)	Cytokeratin area (μm^2)
1	7.86	38.35	10.41	58.58
2	13.70	74.02	15.93	86.07
3	7.76	32.81	8.92	37.71

Fig. 1. The IHC staining of a CTC of PanCK-/GATA3+ (red color)/HER2-/CD45-/DAPI+.

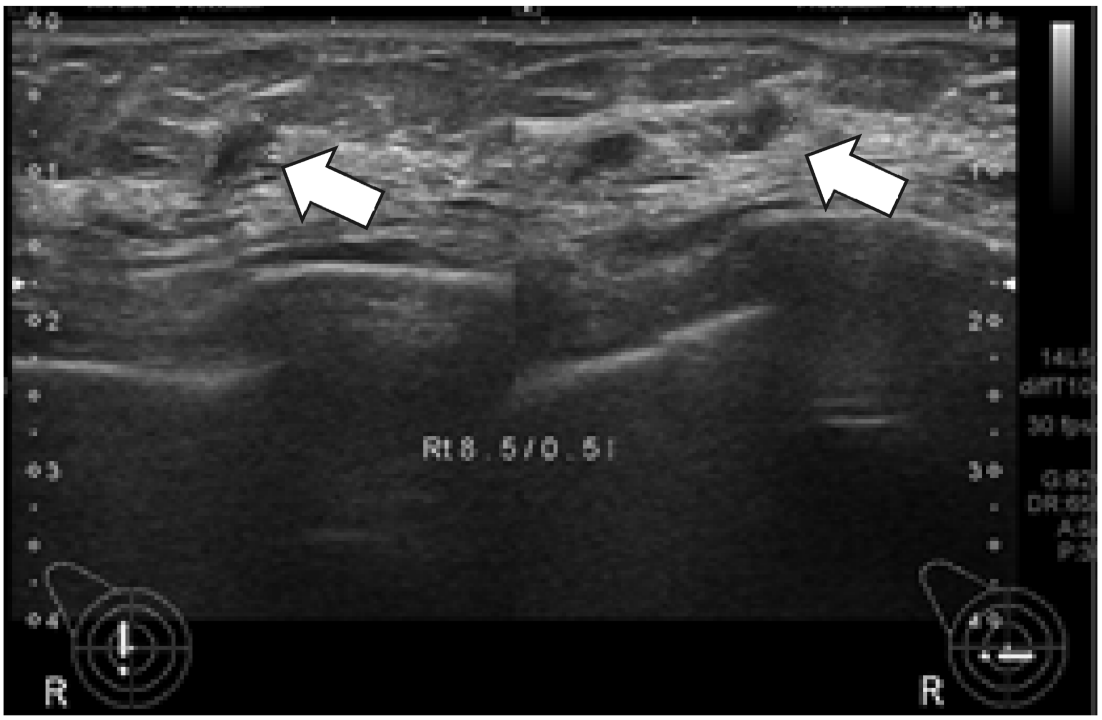

Fig. 2. The breast ultrasound revealed a hypoechoic mass in the right breast with size of 0.55*0.33*0.42 cm (arrows).

However, this meta-analysis also indicated the potential of CTC detection as a biomarker for diagnosing BrC [9].

GATA3 is a nuclear marker with expression in many epithelial neoplasms, including most BrC tumors. Researchers such as Liu et al. have found that 86% of urothelial carcinomas and 94% of BrC exhibit GATA3-positivity. Tumors of other organs rarely express GATA3 [10]. Currently, a limited number of studies investigate the association between GATA3-positive CTCs and BrC, aiming to determine whether the detection of GATA3-positive CTCs can serve as an effective biomarker for early-stage BrC. The study by Crook et al. has shown 100% specificity and 92.07% overall sensitivity in detecting and differentiating BrC cases from healthy women by profiling CTCs with GATA3 in combination with other three markers [5]. In another study, GATA3-positive CTCs were detected in one of three early-stage BrC cases [8]. The present case report reveals that GATA3-positive CTCs can be detected even in very early-stage BrC cases with benign imaging findings.

More and more evidence suggest that the number of CTCs can serve as an independent prognostic factor for cancer treatment [11–13]. A decrease in CTC count after surgery usually indicates a better prognosis. In this case, post-operative detection of GATA3-positive CTCs is absent, with only occasional occurrences of a few HER2-positive CTCs and ER-positive CTCs. This may suggest the absence or only a minimal presence of residual disease, indicating a more favorable prognosis.

The pathological examination with IHC testing was ER-positive but HER2/Neu-negative (1+). HER2/Neu-negative IHC testing indicates weak incomplete membrane staining in any proportion of tumor cells, or weak complete membrane staining in <10% of tumor cells [14]. There were no HER2-positive CTCs detected before the surgery in this case, which is consistent with the pathology report.

CTC profiling can provide much single-cell level information. This information can be useful for tumor monitoring, treatment selection, and prediction of drug resistance. More clinical data are emerging revealing the potential of CTC profiling as a real-time liquid biopsy in tumor therapy.

In the two postoperative follow-ups of this patient, one HER2-positive CTC was detected in 4 mL of blood on one occasion, and on the other occasion, one ER-positive CTC was detected in 2 mL of blood. In this case, HER2-positive CTC was detected after the surgery. CTCs are precursors of tumor metastasis, and they also represent the tumor heterogeneity and evolution. Joeger et al. have demonstrated the discrepancies in HER2 expression between the primary tumor and CTCs during the process of metastasis [15]. In the study by Ignatiadis et al., HER2-positive CTCs can be detected in cases of DCIS/LCIS or M0 BrC, irrespective of the HER2 status of the primary tumor [16].

The detection of HER2-positive CTCs in this patient has sparked new discussions on the treatment approach. Should we continue using anti-hormonal therapy based on the surgical pathology report, or should we add anti-HER2 drugs based on the post-operative CTC detection? Tumor metastasis is the leading cause of cancer-related deaths. Tumor cells enter the bloodstream in the form of circulating tumor cells (CTCs). If they evade attacks from the immune system and reach distant tissues, they can develop into metastatic lesions, which is a crucial mechanism of tumor metastasis. Primary tumors themselves exhibit intratumoral heterogeneity, and only a small portion of tumor cells enter the bloodstream, with these CTCs also displaying considerable heterogeneity. Liu et al. demonstrated favorable outcomes by targeting HER2-positive CTCs in metastatic breast cancer patients with anti-HER2 targeted therapy [17]. Typically, cancer patients undergo periodic CTCs examinations to monitor the likelihood of tumor recurrence. Additionally, CTC profiling is performed to monitor changes in CTC phenotype. In this case, the number of HER2-positive CTCs is not high, and there is no evidence of sustained increase, therefore maintaining the current treatment regimen and continuing to monitor CTCs would be appropriate. I believe that this issue still requires more data, and a consensus may not be reached in a short

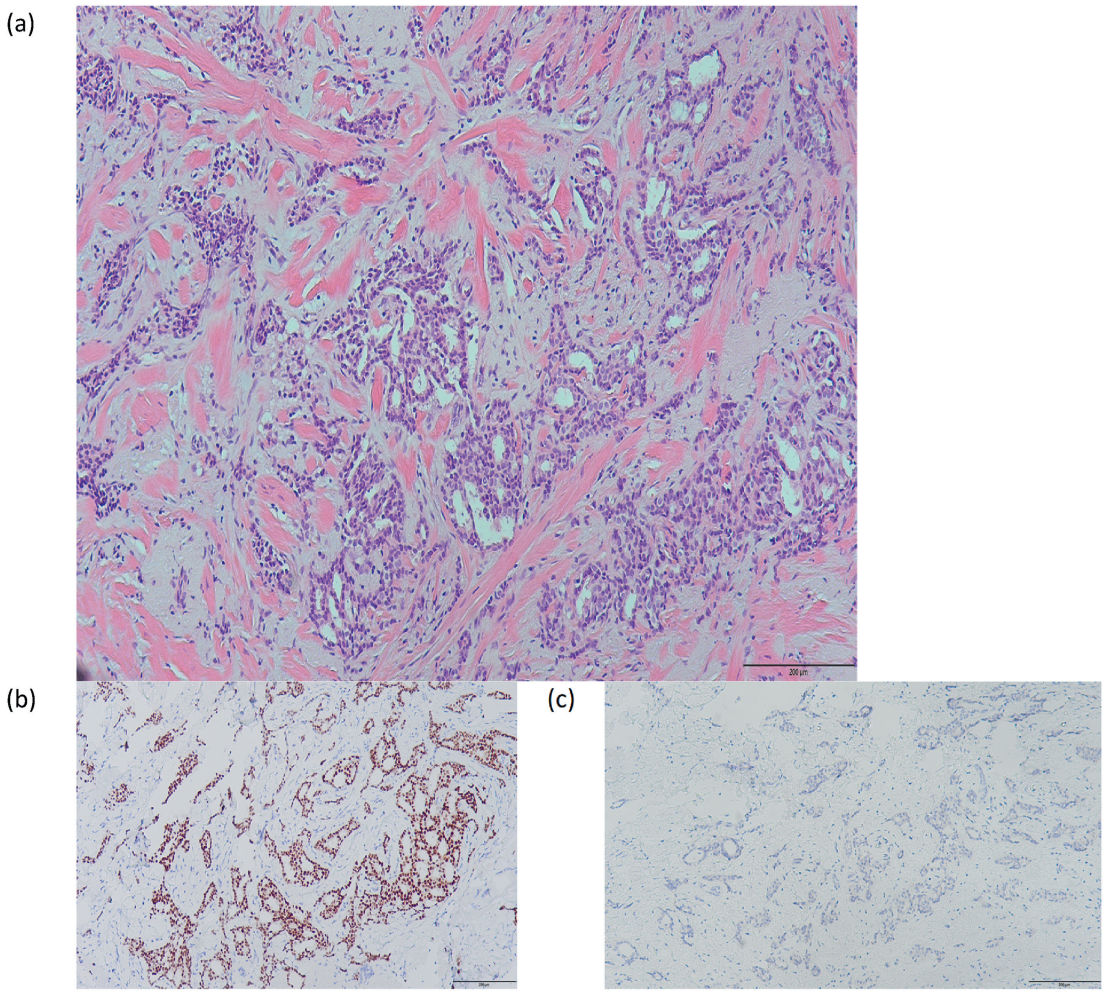

Fig. 3. Pathologic findings. (a) H&E staining. Section shows grade I invasive adenocarcinoma of the breast, no special type, in a desmoplastic stromal background. (b) The tumor cells are diffuse, and strong IHC positive for ER (>95%) and (c) The tumor cells are IHC negative for Her-2 Staining.

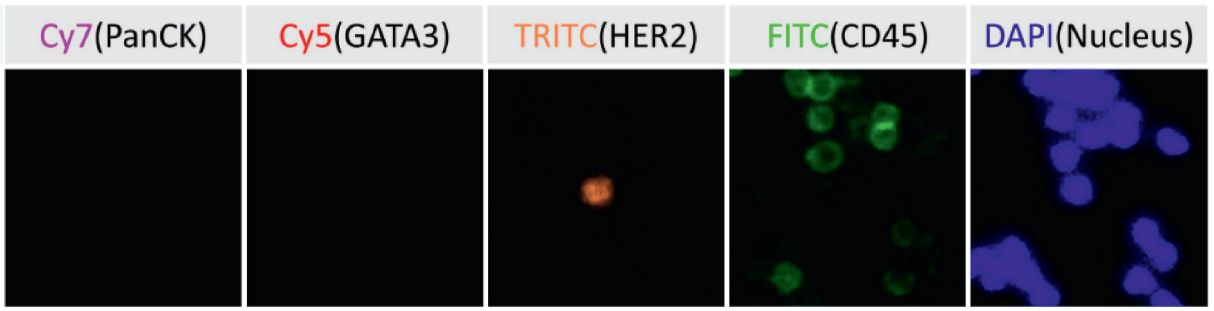

Fig. 4. IHC staining of an HER2 positive CTC.

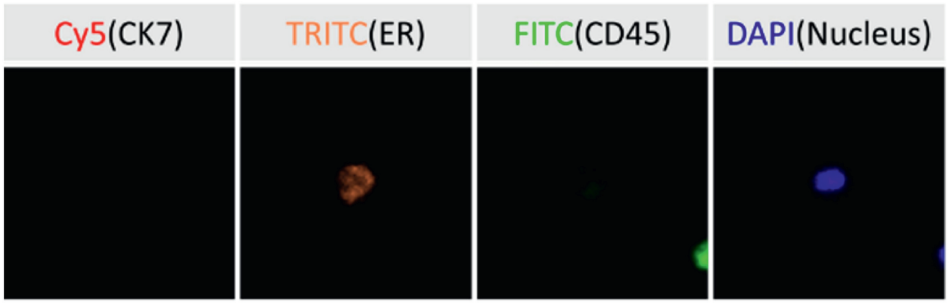

Fig. 5. ER-positive CTC.

period. However, Grigoryeva and colleagues have revealed that favorable responses to neoadjuvant chemotherapy occur when the chemotherapy regimen adequately targets the molecular subtype of CTCs [13].

In summary, we report a case where the detection of GATA3-positive CTCs prompted further clinical investigation and tissue biopsy, leading to the diagnosis of early-stage BrC. This case highlights the potential role of GATA3-positive CTCs in the detection of early-stage BrC. We utilized CTC detection to detect early BrC when both mammography and breast ultrasound showed benign results. Furthermore, we employed CTC detection as a real-time liquid biopsy to monitor disease progression, treatment response, assess prognosis, and detect minimal residual disease. Currently, there are limited reports on the relationship between GATA3-positive CTCs or other tumor-specific marker-positive CTCs and early-stage BrC. Although more data are needed to confirm the role of CTC detection in the diagnosis and treatment of breast cancer, we believe that CTC profiling will provide essential assistance in the treatment and monitoring of this condition. We believe that with the advancement and application of CTC technology, cancer treatment can truly achieve personalized medicine.

Conflicts of interest statement

Jou HJ declared that he was involved in the co-invention of certain intellectual property that was owned by CytoAurora Biotechnologies Inc., Hsinchu, Taiwan but received no benefits. All other authors declared no conflict of interests.

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Case Report

Mosaic distal 13q duplication due to mosaic unbalanced translocation of 46,XY,der(14)t(13;14)(q32.2;p13)/46,XY at amniocentesis in a pregnancy associated with a favorable fetal outcome, perinatal progressive decrease of the aneuploid cell line and cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes

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ABSTRACT

Objective: We present mosaic distal 13q duplication due to mosaic unbalanced translocation 46,XY,der(14)t(13;14)(q32.2;p13)/46,XY at amniocentesis in a pregnancy associated with a favorable fetal outcome.
Case report: A 37-year-old, gravida 2, para 0, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 46,XY, add(14)(p13)[17]/46,XY[13] (56.6% mosaicism). Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed arr 13q32.2q34 × 2~3, consistent with 45% mosaicism for distal 13q duplication. Repeat amniocentesis at 24 weeks of gestation revealed a karyotype of 46,XY,der(14)t(13;14)(q32.2;p13)[14]/46,XY[16] (46.6% mosaicism). The parental karyotypes were normal. aCGH analysis on the DNA extracted from uncultured amniocytes revealed arr 13q32.2q34 × 2.38, consistent with 30–40% mosaicism for distal 13q duplication. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes detected 22.8% (23/101 cells) mosaicism for distal 13q duplication. Prenatal ultrasound findings were unremarkable. At 39 weeks of gestation, a 3616-g phenotypically normal baby was delivered. The karyotypes of cord blood, umbilical cord and placenta were 46,XY,der(14)t(13;14)(q32.2;p13)[20]/46,XY[20] (50% mosaicism), 46,XY,der(14)t(13;14)(q32.2;p13)[14]/46,XY[26] (35% mosaicism) and 46,XY (40/40 cells) (0% mosaicism), respectively. When follow-ups at the age of 4½ months and the age of one year, the peripheral blood had the karyotype of 46,XY,der(14)t(13;14)(q32.2;p13)[18]/46,XY[22] (45% mosaicism). Interphase FISH analysis on buccal mucosal cells at the age of 4½ months revealed 2.7% (3/110 cells) mosaicism for distal 13q duplication, compared with 1% (1/100 cells) in the normal control. The neonate was normal in phenotype and development.
Conclusions: Mosaic unbalanced translocation at amniocentesis can be associated with a favorable fetal outcome, perinatal progressive decrease of the aneuploid cell line and cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes.

Introduction

We previously reported mosaicism for unbalanced translocations at amniocentesis in the pregnancy with favorable

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outcomes [1,2]. Here, we present an additional case with mosaic unbalanced translocation associated with mosaic distal 13q duplication. The information acquired in this presentation is useful for genetic counselors and obstetricians during genetic counseling as well as the parents who have very advanced maternal age, who have undergone difficult assisted reproductive technology and who wish to keep the babies under such a circumstance.

Case report

A 37-year-old, gravida 2, para 0, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 46,XY,add(14) (p13)[17]/46,XY[13] (56.6% mosaicism). Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed arr 13q32.2q34 × 2~3, consistent with 45% mosaicism for distal 13q duplication. Repeat amniocentesis at 24 weeks of gestation revealed a karyotype of 46,XY,der(14)t(13;14)(q32.2;p13)[14]/46,XY[16] (Figs. 1 and 2) (46.6% mosaicism). The parental karyotypes were normal. aCGH analysis on the DNA extracted from uncultured amniocytes revealed arr 13q32.2q34 × 2.38, consistent with 30–40% mosaicism for distal 13q duplication (Fig. 3). Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes detected 22.8% (23/101 cells) mosaicism for distal 13q duplication (Fig. 4). Prenatal ultrasound findings were unremarkable. At 39 weeks of gestation, a 3616-g phenotypically normal baby was delivered. The karyotypes of cord blood, umbilical cord and placenta were 46,XY,der(14)t(13;14)(q32.2;p13)[20]/46,XY[20] (50% mosaicism), 46,XY,der(14)t(13;14)(q32.2;p13)[14]/46,XY[26] (35% mosaicism) and 46,XY (40/40 cells) (0% mosaicism), respectively. When follow-ups at the age of 4½ months and the age of one year, the peripheral blood had the karyotype of 46,XY,der(14)t(13;14)(q32.2;p13)[18]/46,XY[22] (45% mosaicism). Interphase FISH analysis on buccal mucosal cells at the age of 4½ months revealed 2.7% (3/110 cells) mosaicism for distal 13q duplication, compared with 1% (1/100 cells) in the normal control. The neonate was normal in phenotype and development.

Discussion

The present case shows perinatal progressive decrease of the aneuploid cell line in case of mosaicism for distal 13q duplication at amniocentesis. In the present case, amniocentesis at 17 weeks of gestation revealed 56.6% (17/30 colonies) mosaicism in cultured amniocytes and 45% mosaicism by aCGH in uncultured amniocytes, repeat amniocentesis at 24 weeks of gestation revealed 46.6% (14/30 colonies) mosaicism in cultured amniocytes and 30–40% mosaicism by aCGH and 22.8% (23/101 cells) mosaicism by interphase FISH in uncultured amniocytes, and at the age of 4½ months, the peripheral blood had 45% (18/40 cells) mosaicism, and buccal mucosal cells had 2.7% (3/110 cells) mosaicism for distal 13q duplication.

The peculiar aspect of the present case is the cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes which shows that the aberrant aneuploid cells with the unbalanced translocation may overgrow during the culture process.

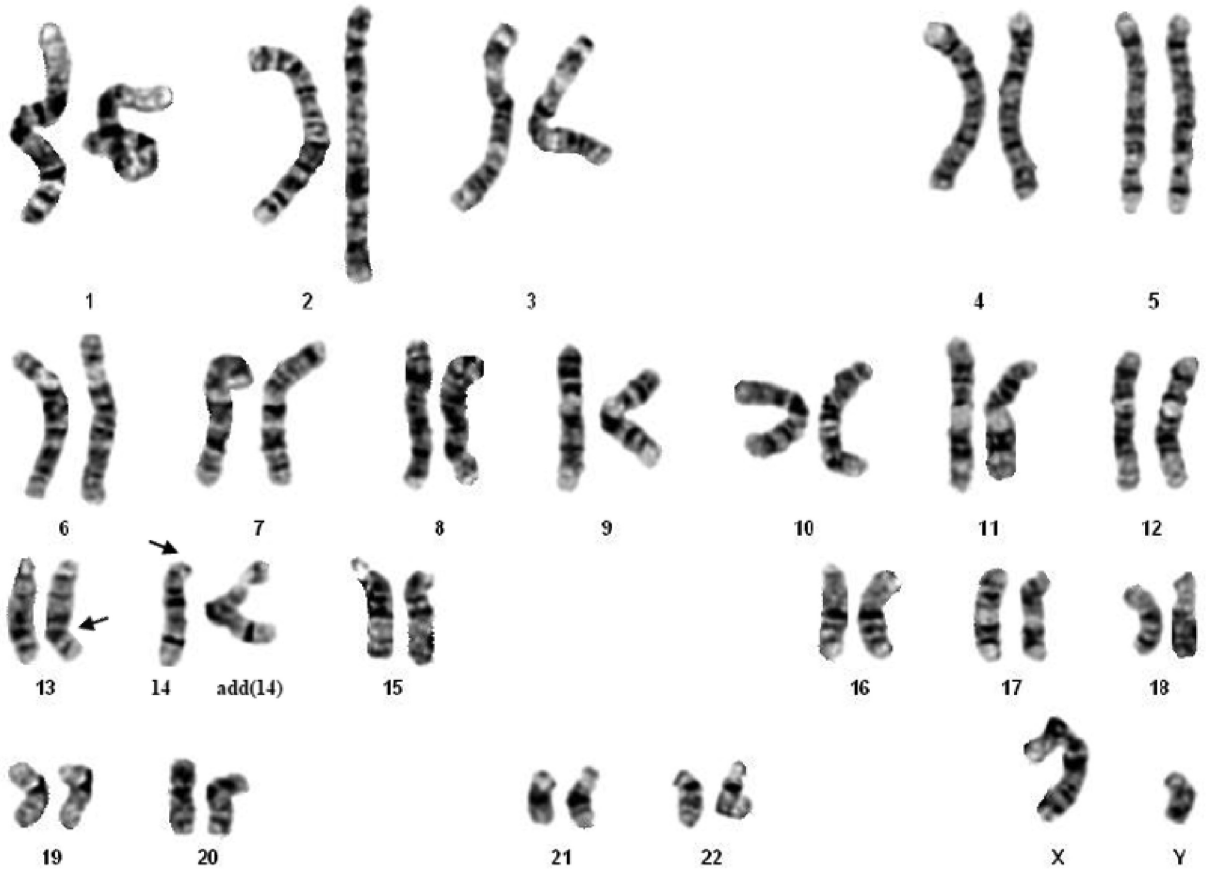

Fig. 1. A karyotype of 46,XY,der(14)t(13;14) (q32.2;p13). The chromosome add(14) is a der(14)t(13;14) (q32.2;p13). add = additional maternal of unknown origin, der = derivative, t = translocation.

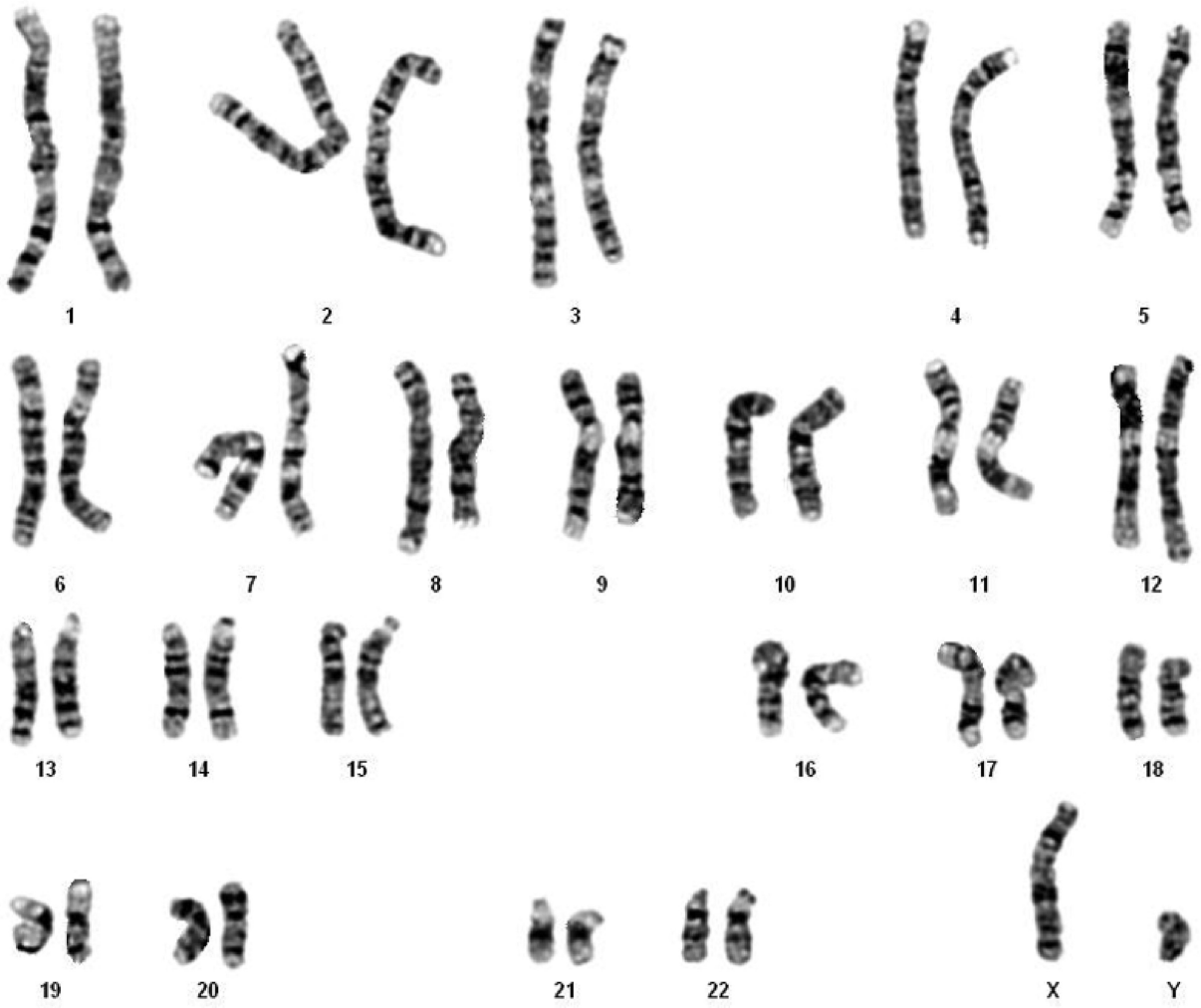

Fig. 2. A karyotype of 46,XY.

For examples, at 17 weeks of gestation at amniocentesis, the cultured amniocytes had 56.6% (17/30 colonies) mosaicism by conventional cytogenetic analysis, whereas the uncultured amniocytes had 45% mosaicism by aCGH. At 24 weeks of gestation at amniocentesis, the cultured amniocytes had 46.6% (13/30 colonies) mosaicism by conventional cytogenetic analysis, whereas the uncultured amniocytes had 30–40% mosaicism by aCGH, and 22.8% (23/101 cells) mosaicism by interphase FISH. This indicates that interphase FISH and aCGH analysis on uncultured amniocytes play important roles in the prenatal investigation of mosaic unbalanced translocation at amniocentesis. This is also true in the postnatal analysis of mosaic unbalanced translocation. For example, at the age of 4½ months, the peripheral blood had 45% (18/40 cells) mosaicism by conventional cytogenetic analysis, whereas buccal mucosal cells had only 2.7% (3/110 cells) mosaicism. Therefore, perinatal investigation of cytogenetic discrepancy in mosaicism between different methods, such as conventional cytogenetic analysis on cultured cells vs. molecular analysis on uncultured cells, should raise a consideration of overgrowth of the abnormal cells with the aberrant chromosome during the culture process.

The observation of overgrowth of the abnormal amniocytes with the aberrant unbalanced translocation during the culture process and perinatal progressive decrease of the aneuploid cell line in the present case has been described in our previous reports of mosaic unbalanced translocation at amniocentesis [1,2]. Chen et al. [2] previously reported mosaic 6q (6q25.1-q27) duplication due to 46,XY,der(15)t(6;15) (q25.1;p12)/46,XY at amniocentesis. In that case, the mosaic levels for the abnormal cells with partial trisomy 6q25.1→qter in cultured amniocytes at 17, 19, 24 and 27 weeks of gestation were 77%, 60%, 95.8% and 80.8%, respectively. However, the mosaic levels for partial trisomy 6q in uncultured amniocytes were 40% by aCGH at 19 weeks of gestation, 50% by aCGH and 51% by FISH at 24 weeks of gestation, and 46% by aCGH and 35% by FISH at 27 weeks of gestation. The mosaic levels of the umbilical cord, cold blood and placenta were 72.5%, 5% and 0%, respectively. The peripheral blood at the age of five months had a normal karyotype of 46,XY, and the buccal mucosal cells had 4.8% mosaicism for 6q25.1-q27 duplication. Chen [2] additionally reported mosaic der(9)t(9;13) (p24;q12) due to 46,XX,der(9)t(9;13) (p24;q12)/46,XX at amniocentesis. The aneuploid cell line was not detected at repeat amniocentesis and at birth. The unbalanced reciprocal translocation involving partial monosomy 9p (9p24→pter) and partial trisomy 13q (13q12→qter) in that report is likely caused by culture artefact during amniocyte culture process.

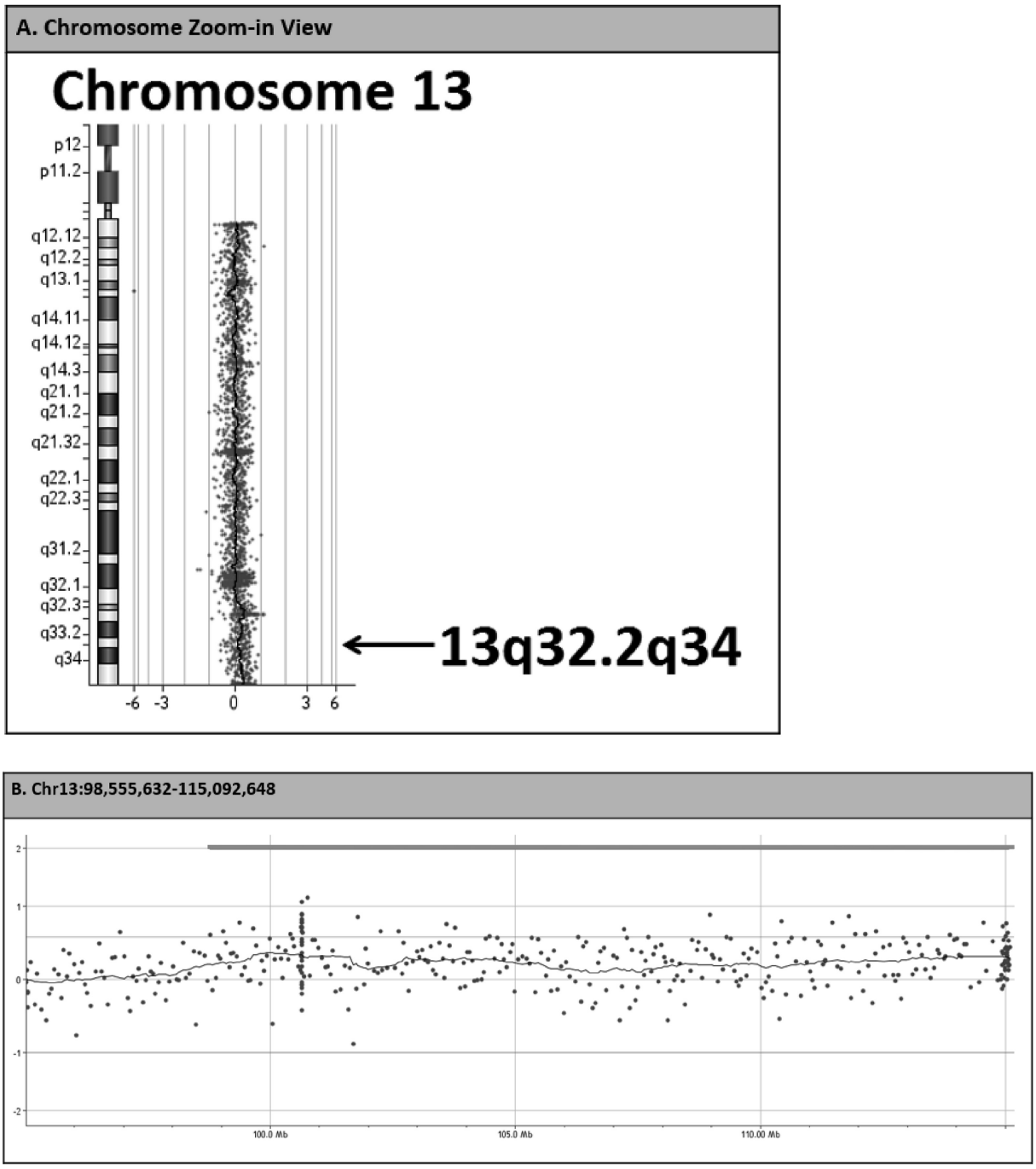

Fig. 3. (A) and (B) Array comparative genomic hybridization (aCGH) analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from uncultured amniocytes shows the result of 13q32.2q34 (98,555,632–115,092,648) × 2.38 [GRCh 37], consistent with 30–40% mosaicism for a 16.5-Mb duplication of 13q32.2-q34.

The present case also shows complete cytogenetic discrepancy between cord blood, umbilical cord and placenta. In the present case, the placenta had a normal karyotype. It is likely that mosaic unbalanced translocation at amniocentesis is caused by post-zygotic mitotic process, and the mosaicism is associated with the fetus only. This indicates that chorionic villus sampling (CVS) and non-invasive prenatal testing (NIPT) may play no role in the prenatal investigation of mosaic unbalanced translocation at amniocentesis.

In summary, we present mosaic distal 13q duplication due to mosaic unbalanced translocation at amniocentesis in a pregnancy associated with a favorable fetal outcome. Mosaic unbalanced translocation at amniocentesis can be associated with a favorable fetal outcome, perinatal progressive decrease of the aneuploid cell

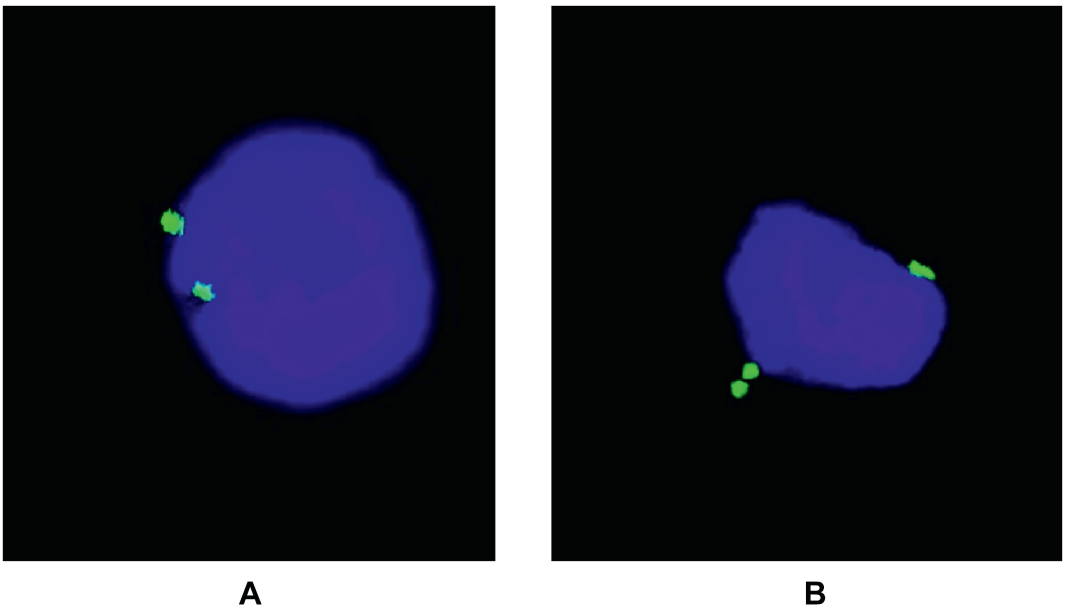

Fig. 4. Interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured amniocytes using the bacterial artificial chromosome (BAC) probe of RP11-60I24 [13q34; fluorescein isothiocyanate (FITC), spectrum green] shows (A) a normal cell with two 13q34 signals and (B) an abnormal cell with three 13q34 signals.

line and cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes.

Declaration of competing interest

The author has no conflicts of interest relevant to this article.

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Case Report

Low-level mosaic trisomy 14 at amniocentesis in a pregnancy associated with cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, positive non-invasive prenatal testing for trisomy 14, perinatal progressive decrease of the trisomy 14 cell line and a favorable fetal outcome

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ABSTRACT

Objective: We present low-level mosaic trisomy 14 at amniocentesis.
Case report: A 37-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. This pregnancy was conceived by *in vitro* fertilization and embryo transfer (IVF-ET). Amniocentesis revealed a karyotype of 47,XX,+14 [4]/46,XX [27], consistent with 12.9% mosaicism for trisomy 14. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr (1–22, X) × 2 with no genomic imbalance. Prenatal ultrasound findings were unremarkable. She was referred for genetic counseling at 21 weeks of gestation and was offered expanded non-invasive prenatal testing (NIPT) which was positive for trisomy 14. At 24 weeks of gestation, she underwent repeat amniocentesis which revealed a karyotype of 47,XX,+14 [2]/46,XX [26], consistent with 7% mosaicism for trisomy 14. The parental karyotypes were normal. Simultaneous aCGH analysis on the DNA extracted from uncultured amniocytes revealed no genomic imbalance. Polymorphic marker analysis excluded uniparental disomy (UPD) 14. Interphase fluorescence *in situ* hybridization (FISH) analysis on 104 uncultured amniocytes detected no trisomy 14 cell. At 35 weeks of gestation, a 2315-g phenotypically normal baby was delivered. The umbilical cord and placenta had the karyotype of 46, XX (40/40 cells). aCGH analysis on the DNA extracted from peripheral blood and buccal mucosal cells at the age of three months revealed no genomic imbalance. The neonate was normal in phenotype and development during postnatal follow-ups.
Conclusions: Low-level mosaic trisomy 14 at amniocentesis can be associated with cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, perinatal progressive decrease of the trisomy 14 cell line and a favorable fetal outcome.

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Introduction

We previously reported phenotypic abnormalities in two cases with mosaic trisomy 14 at amniocentesis [1,2]. Here, we present an additional case with low-level mosaic trisomy 14 at amniocentesis with cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, positive non-invasive prenatal testing (NIPT) for trisomy 14, perinatal progressive decrease of the trisomy 14 cell line and a favorable fetal outcome. The information provided in this case is very useful for genetic counselors, obstetricians and the parents who have very advanced maternal age, who have undergone difficult assisted reproductive technology and who wish to keep the babies under such a circumstance.

Case Report

A 37-year-old, gravida 2, para 1, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. This pregnancy was conceived by *in vitro* fertilization and embryo transfer (IVF-ET). Amniocentesis revealed a karyotype of 47,XX,+14 [4]/46,XX [27], consistent with 12.9% mosaicism for trisomy 14. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr (1–22, X) × 2 with no genomic imbalance. Prenatal ultrasound findings were unremarkable. She was referred for genetic counseling at 21 weeks of gestation and was offered expanded NIPT which was positive for trisomy 14. At 24 weeks of gestation, she underwent repeat amniocentesis which revealed a karyotype of 47,XX,+14 [2]/46,XX [26] (Figs. 1 and 2), consistent with 7% mosaicism for trisomy 14. The parental karyotypes were normal. Simultaneous aCGH analysis on the DNA extracted from uncultured amniocytes revealed no genomic imbalance. Polymorphic marker analysis excluded uniparental disomy (UPD) 14. Interphase fluorescence *in situ* hybridization (FISH) analysis on 104 uncultured amniocytes detected no trisomy 14 cell. At 35 weeks of gestation, a 2315-g phenotypically normal baby was delivered. The umbilical cord and placenta had the karyotype of 46, XX (40/40 cells). aCGH analysis on the DNA extracted from peripheral blood and buccal mucosal cells at the age of three months revealed no genomic imbalance. The neonate was normal in phenotype and development during postnatal follow-ups.

Discussion

The present case provides evidence that low-level mosaic trisomy 14 at amniocentesis can be associated with perinatal progressive decrease of the trisomy 14 cell line and a favorable fetal outcome. In the present case, amniocentesis at 18 weeks of gestation revealed a karyotype of 47,XX,+14 [4]/46,XX [27], consistent with 12.9% (4/31 colonies) mosaicism for trisomy 14. Repeat amniocentesis at 24 weeks of gestation revealed a karyotype of 47,XX,+14 [2]/46,XX [26], consistent with 7% (2/28 colonies) mosaicism for trisomy 14. aCGH on the DNA extracted from peripheral blood and buccal mucosal cells revealed arr (1–22) × 2, (X) × 2, (Y) × 0 with no genomic imbalance. The neonate was normal in phenotype and development during postnatal follow-ups.

The peculiar aspect of the present case is the cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes. In the present case, cultured amniocytes in two consecutive

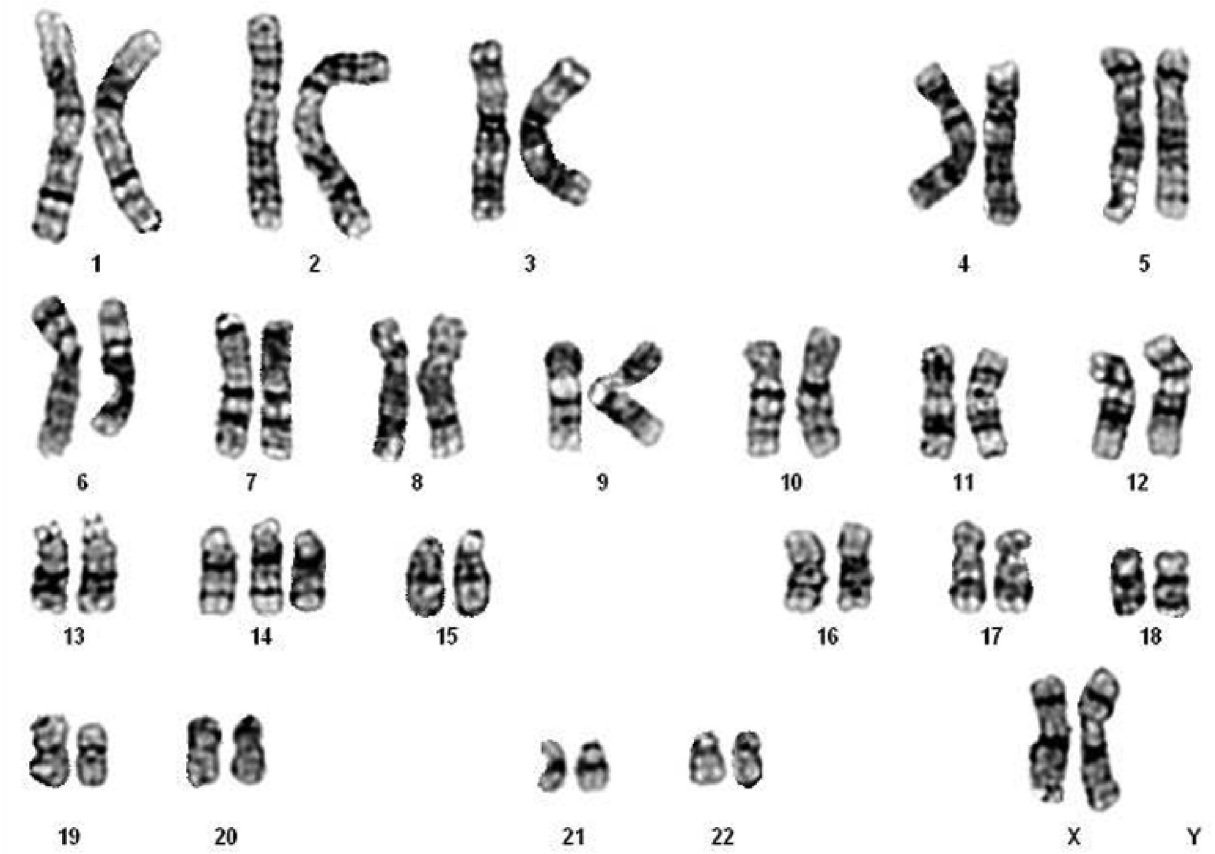

Fig. 1. A karyotype of 47,XX,+14.

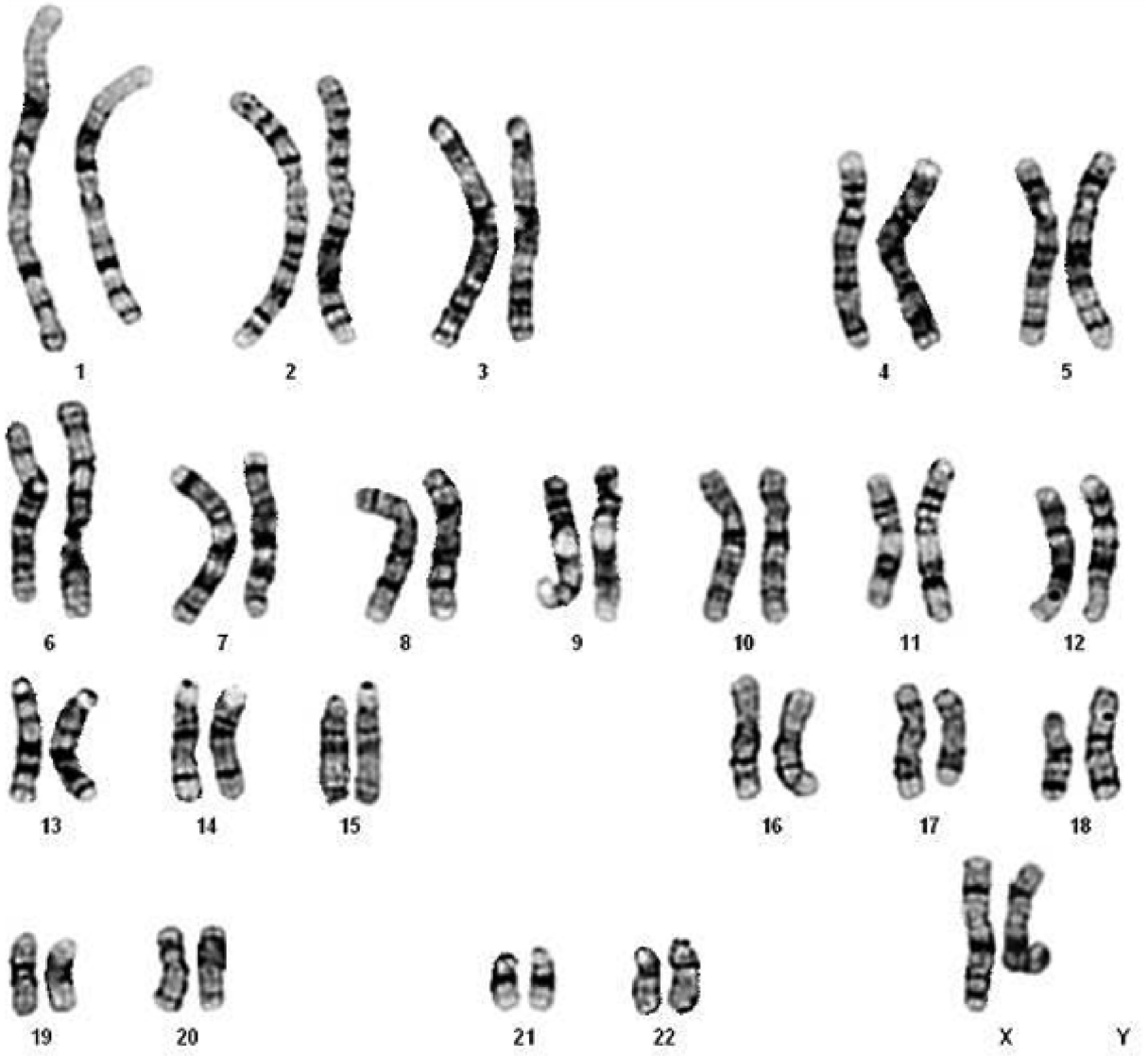

Fig. 2. A karyotype of 46,XX.

amniocenteses revealed mosaic trisomy 14, whereas simultaneous aCGH analysis on the DNA extracted from uncultured amniocytes and Interphase FISH analysis on uncultured amniocytes at repeat amniocentesis revealed normal results. This indicates that in case of mosaic trisomy 14, repeat amniocentesis should include conventional cytogenetic analysis, and molecular analysis on uncultured amniocytes should not replace karyotyping.

The present case was associated with positive NIPT for trisomy 14 at 21 weeks of gestation, and there was mosaic trisomy 14 at two consecutive amniocenteses in the second trimester. This indicates that expanded NIPT is useful for prenatal investigation of mosaic trisomy 14. In the present case, there were positive NIPT for trisomy 14 and normal karyotype of the cultured placental cells. The discrepancy in the cytogenetic result between NIPT and placental sampling may be due to incomplete postnatal sampling of the placental tissues at birth. In an overview of rare autosomal trisomies (RATs) detected by NIPT, Lannoo et al. [3] concluded that detection of trisomy 14 by NIPT has a relative frequency of 3.7% (95% CI: 2.1–4.5) in RATs, an absolute frequency of 0.007% (1/13042), a 93% meiotic occurrence (73% maternal, 20% paternal) and a 7% mitotic occurrence in case of fetal trisomy 14, a 1/18 (5.6%) (95% CI: 0.1–27) risk of fetal trisomy 14, a 7/11 (63.6%) frequency of abnormal outcome in case of fetal trisomy 14, a 6/11 (54.5%) frequency of major congenital anomalies in case of fetal trisomy 14 with no correlation to levels of trisomy 14 mosaicism, and a low risk of maternal UPD 14 or paternal UPD 14 (0/14) in case of fetal trisomy 14.

Low-level mosaic trisomy 14 at amniocentesis associated with a favorable fetal outcome has been previously reported [4]. Wu et al. [4] reported a case of a normal live born baby with a prenatal mosaic trisomy 14 of 46,XX,+14,der (14;21) (q10;q10) [4]/45,XX,der (14; 21) (q10; q10)[18] (18% mosaicism) at amniocentesis in a pregnancy with the maternal carrier of rob (14; 21). Polymorphic marker analysis excluded UPD 14. Prenatal ultrasound findings were normal. Postnatal study of cord blood, umbilical cord and placenta by FISH showed disomies 14 and 21 in the cord blood and umbilical cord, and 2% (2/100 cells) mosaicism for trisomy 14 in the placenta. The present case adds to the list of low-level mosaic trisomy 14 at amniocentesis associated with a favorable fetal outcome.

Prenatal diagnosis of trisomy 14 mosaicism should include a differential diagnosis of UPD 14. Maternal UPD 14 is associated with Temple syndrome (OMIM 616222) which is characterized by prenatal and postnatal growth restriction, muscular hypotonia, motor delay, hyperextensible joints, precocious puberty, truncal obesity, variable psychomotor retardation, small hands and feet, and adult short stature [5]. Paternal UPD 14 is associated with Kagami-Ogata syndrome (OMIM 608149) which is characterized by polyhydramnios, omphalocele, thoracic dysplasia (a coat-hanger sign), respiratory failure, poor growth, developmental delay, and facial abnormalities including full cheeks and protruding philtrum [5].

In summary, we present low-level mosaic trisomy 14 at amniocentesis. Low-level mosaic trisomy 14 at amniocentesis can be associated with cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes. Perinatal progressive decrease of the trisomy 14 cell line and a favorable fetal outcome.

Declaration of competing interest

The author has no conflicts of interest relevant to this article.

Acknowledgements

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Case Report

A case with rare complication of chronic puerperal uterine inversion and underwent operation reduction☆

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ABSTRACT

Objective: Puerperal uterine inversion is a rare and severe complication and is associated with short cord, uncontrolled cord traction, placenta accreta, or uterine atony.
Case report: A primigravida woman gave birth a 2770 gm newborn at term at our hospital, and clinically presented postpartum hemorrhage, hypovolemic shock, postpartum preeclampsia and urinary retention. She discharged 3 days postpartum, but she complained persist vaginal bleeding and lower abdominal pain for more than 1 month. Uterine inversion was diagnosed and laparoscope surgery for reduction was done.
Conclusion: The non-specific clinical presentation made diagnosis of uterine inversion more difficult. Except pelvic examination, sonographic and hysteroscopic images were record in this article. Surgical intervention was performed. A fundus incision was effective for reduction and had low risk of bladder and bowel injury.

Objective

Puerperal uterine inversion occurs about 1 in 3500–20000 deliveries [1,2]. Among these, only 13.9 % were chronic. It is a rare and severe complication often followed with massive hemorrhage. Diagnosis is usually made based on clinical presentation of lower abdominal pain, massive hemorrhage. Ultrasonography image signs such as target sign and recognizing an endometrial pseudostrip may help diagnosis [3]. Puerperal uterine inversion is associated with short cord, uncontrolled cord traction, placenta accreta, or uterine atony. Acute uterine inversion can be reduction with some manual; on the other hand, operation is often needed for reduction for a chronic uterine inversion.

In this article, we reported a case of chronic puerperal uterine inversion who had clinically presented postpartum hemorrhage with hypovolemic shock, postpartum preeclampsia and urinary retention initially. After diagnosed, the patient underwent a successful laparoscopic reduction.

Case

A 29-year-old primigravida woman had vacuum assistance delivery at 39 weeks of gestation, and delivered a 2770 gm female newborn. She then spontaneously delivered complete placenta of 610 gm 8 min later, and 2nd degree episiotomy wound was repaired satisfactorily. Initial estimated blood loss was 300 ml. During observation of postpartum period, persist vaginal bleeding and estimated blood loss 1250 ml was noted in 5 h postpartum. Besides, vital signs was taken and tachycardia up to 140 bpm and hypotension with blood pressure of 89/56 mmHg was noted. A hypovolemic shock was impressed. Resuscitation was done and uterotonic agents were prescribed, including Oxytocin 10U in 500 ml Lactate Ringer solution intravenous drip, with total 40U given, Methergin 0.2 mg intramuscular, Cytotec 800 mg from rectal route and 200 mg from sublingual route. Blood transfusion was prescribed with pRBC 4U, FFP 6U, and whole blood 2U. Ultrasonography showed smooth endometrium without retained placenta or blood clot; no abdominal free fluid was noted (Fig. 1). However, after bleeding ceased, elevated blood pressure was noted with proteinuria developed. Under impression of postpartum preeclampsia, MgSO4 pump was given for 24 h postpartum. After blood pressure controlled, she had fewer lochia, better uterine contraction and stable vital signs. On the next day of giving delivery, she had difficulty of urinary, and Foley catheter was placed

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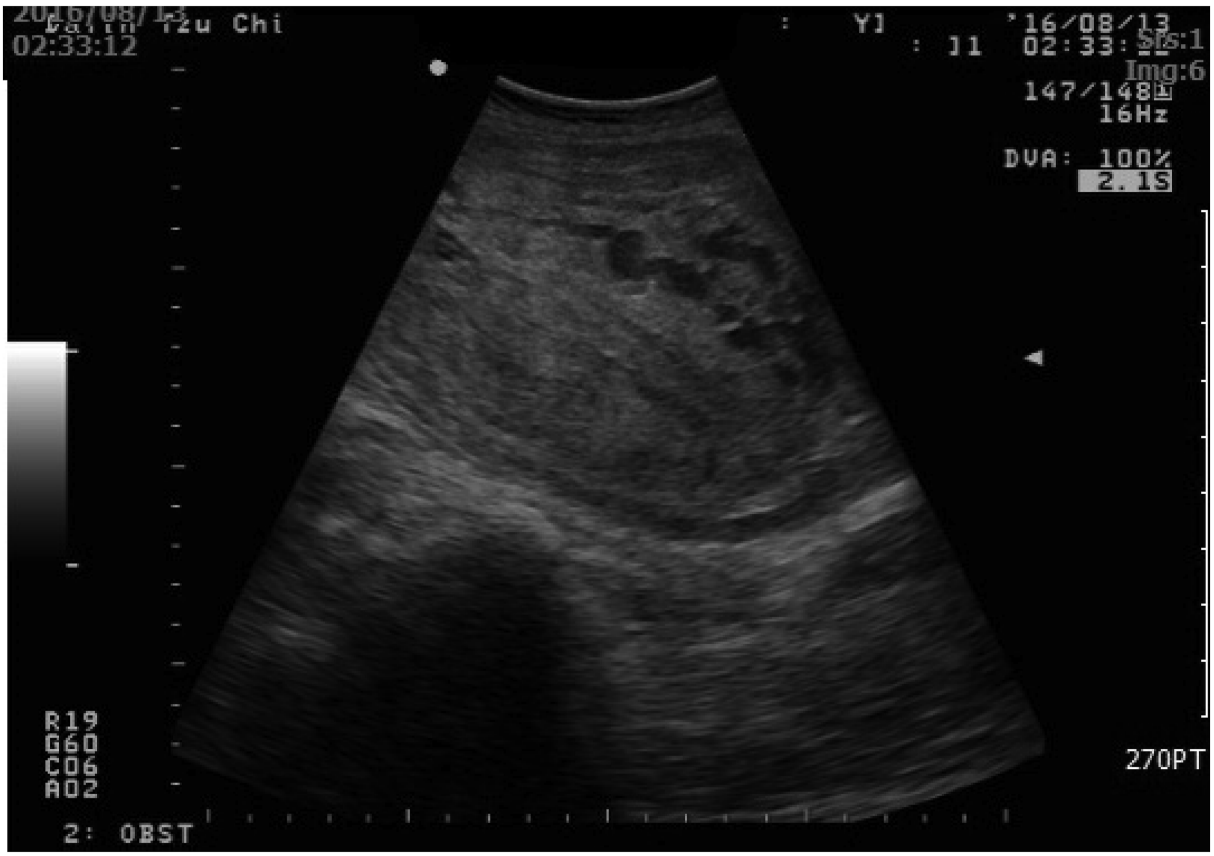

Fig. 1. Ultrasonographic picture while the patient was found with PPH.

for a week. After the patient was discharged, the Foley catheter was removed smoothly at out-patient department visit.

However, during further visit, she complained persist vaginal bleeding and lower abdominal dull pain for a month. Submucosal myoma was suspected by ultrasonographic image (Fig. 2). She was then admitted for hysteroscopy management 2 months post-partum. However, a protruding mass was noted while applying hysteroscopy (Fig. 3). Once the instrument reached the level of internal cervical os, the mass caused obstruction of the pathway and resulted in a failure hysteroscopy.Then we checked ultrasonographic image again (Fig. 4). As the picture showed, there was no uterine fundus noted, instead, adnexa was at the middle part of the uterus. Uterine inversion was diagnosed and laparoscope surgery reduction was arranged. A vertical incision at fundus was created from vagina route to loosen the contraction ring (Figs. 5 and 6). The incision was made under an unaided eye to avoid injury of bladder. Round ligament was pulled from laparoscopy; fundus incision was pushed by assistant from vaginal tract. Reduction of the uterine was done; followed with satisfactorily suture (Fig. 7). After operation she recovered well. The patient had pregnant 4 years later, and delivered by cesarean section at term.

Discussion

In this case, she presented postpartum hemorrhage with hypovolemic shock, postpartum preeclampsia, urinary retention right after delivery. After weeks, lower abdominal pain and persist lochia rubra were still complained. It's difficult to diagnose uterine inversion by nonspecific clinical representation. Besides direct pelvic examination touching the mass or inspection by speculum examination, we may diagnose uterine inversion with ultrasonography technique. A case report shared by Ida introduced some ultrasonographic signs, such as endometrial pseudostripe and target sign from transverse view [3]. In our patient, the mass mistaken for myoma might be the target sign of the inverted uterine fundus.

A cohort study based on the Nationwide Inpatient Sample (NIS) database in the US suggested some risk factors of puerperal uterine inversion including prolonged labor and severe preeclampsia, and the authors found the rate of abnormal placentation was significantly higher in women with a uterine inversion [4]. Uncontrolled cord traction, short umbilical cord and macrosomia were also included in predisposing factors in case reports [3,5]. Little article focused on the chronic puerperal uterine inversion separated from the acute one. A case report shared a woman received a Huntington's procedure for an acute puerperal uterine inversion. However, due to bad compliance of follow-up and ignorance, she suffered from fever, lower abdominal pain and persist vaginal bleeding for 4 weeks. Reinversion with endometritis caused a chronic uterine inversion was diagnosed [6]. As to our patient, she delivered the placenta spontaneously in 8 min. However, uterine atony and postpartum preeclampsia occurred. Although the initial ultrasonographic examination showed no obvious finding, we didn't recheck the image after preeclampsia was diagnosed and MgSO4 pump was applied. It was presumed that poor uterine contraction happened during the period of MgSO4 pump was given. Thus, we suggested to check the uterine contraction and lochia more closely for such PPH patient. If the bleeding and abdominal pain persist or progress, ultrasonographic examination might be performed to figure out the etiology.

After diagnosing a chronic uterine inversion, unlike acute inversion could be reduction by manual, a chronic one usually needed operation interventions for reduction due to contraction

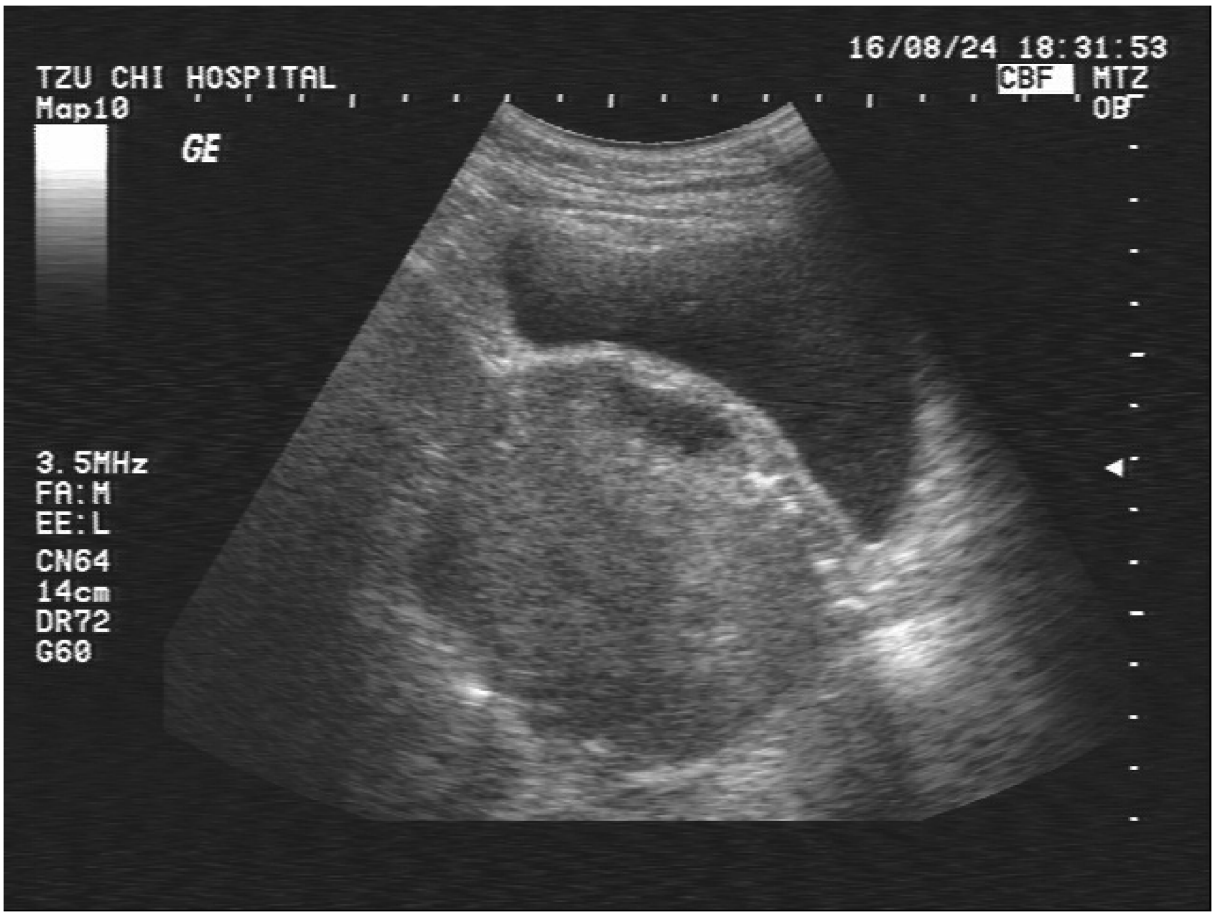

Fig. 2. Ultrasonographic picture obtained at OPD postpartum.

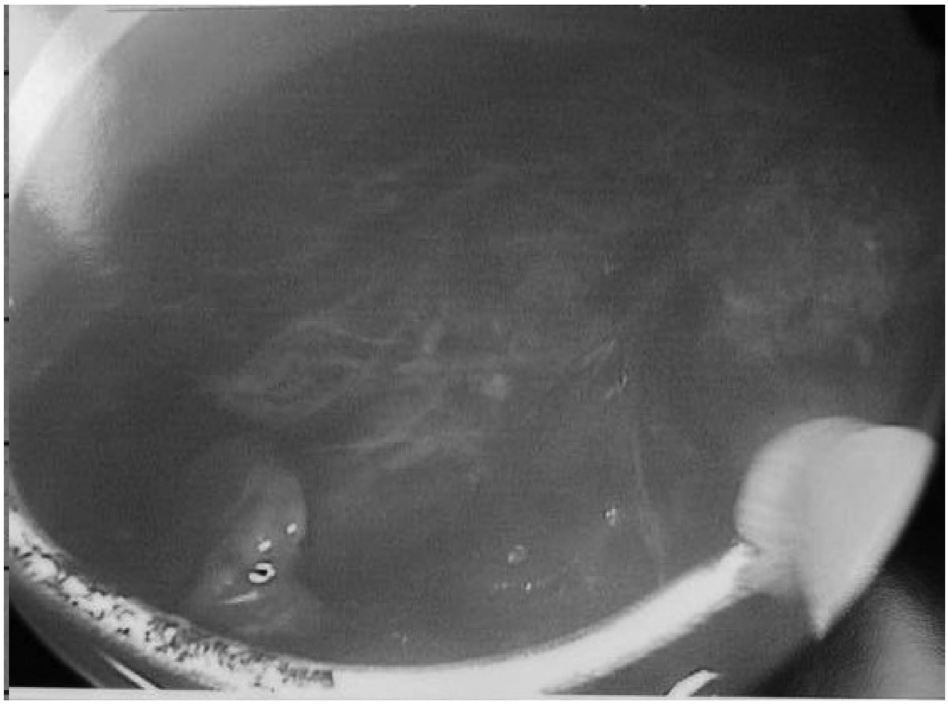

Fig. 3. A protruding mass was noted while applying hysteroscopy, the mass caused obstruction of the pathway and resulted in a failure hysteroscopy

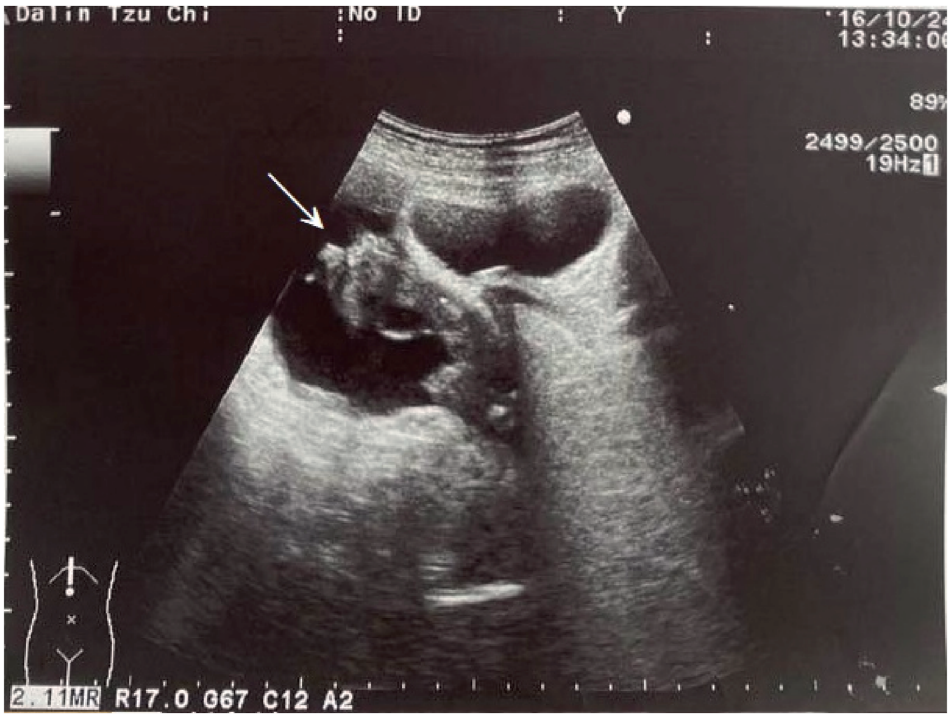

Fig. 4. Adnexa was at the middle part of the uterus (arrow) without fundus seen.

rings. Previous experience suggested us a vertical incision at posterior wall to avoid bladder injury, which called Haultain procedure. In our case, we created a vertical incision from vaginal route at uterine fundus to loose the contraction ring and we applied force on the incision to pushed it back and pull the round ligament from laparoscopic vision. Using this method could avoid bladder injury as well. Besides, we could apply force on incision from vagina to help reduction. Some previous reports suggested to apply an intrauterine balloon to prevent re-inversion [7]. In our case, we didn't place a balloon due to well contraction of the uterus and satisfactorily suture done under laparoscopy.

Based on the experience of the patient, we could diagnose uterine inversion more efficient and have effective way to reduction. Incision made at posterior wall or at fundus from vaginal tract are both safe; fundus incision provide a point for pushing force and thus helping reduction easier.

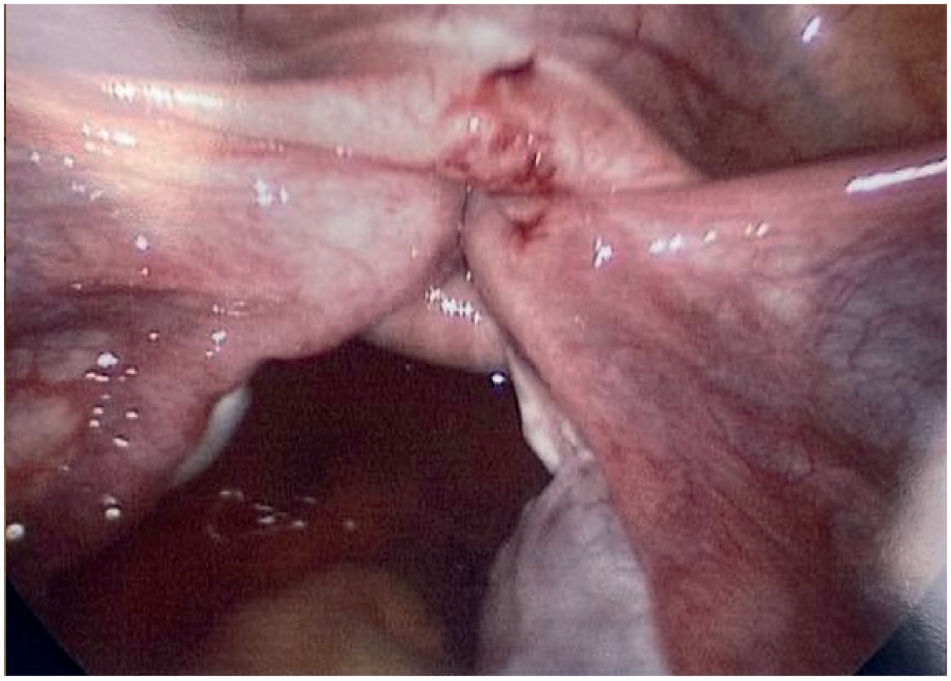

Fig. 5. Typical uterine inversion observed from laparoscopy.

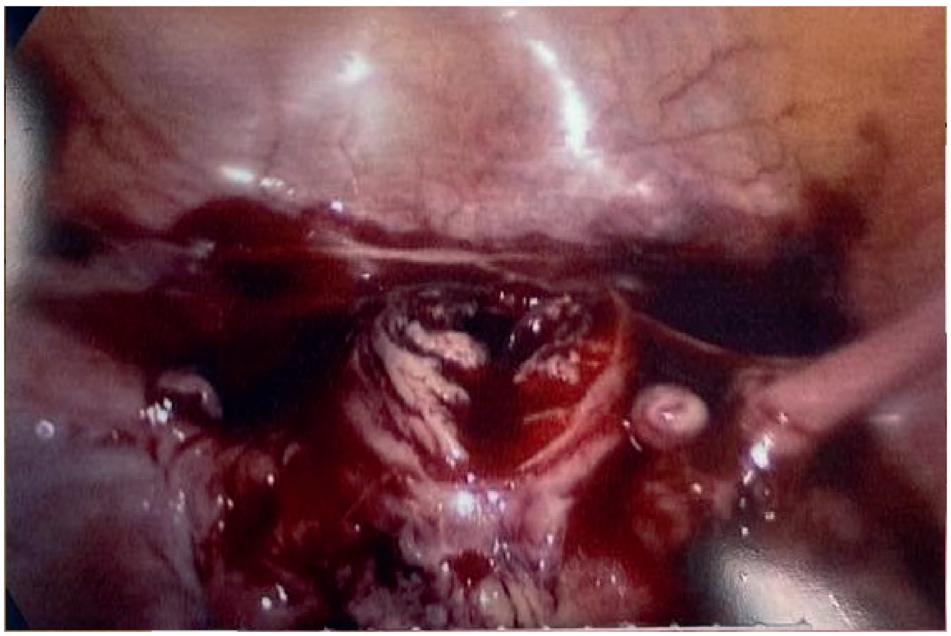

Fig. 6. Incision was made at fundus and the fundus was pushed back from vagina.

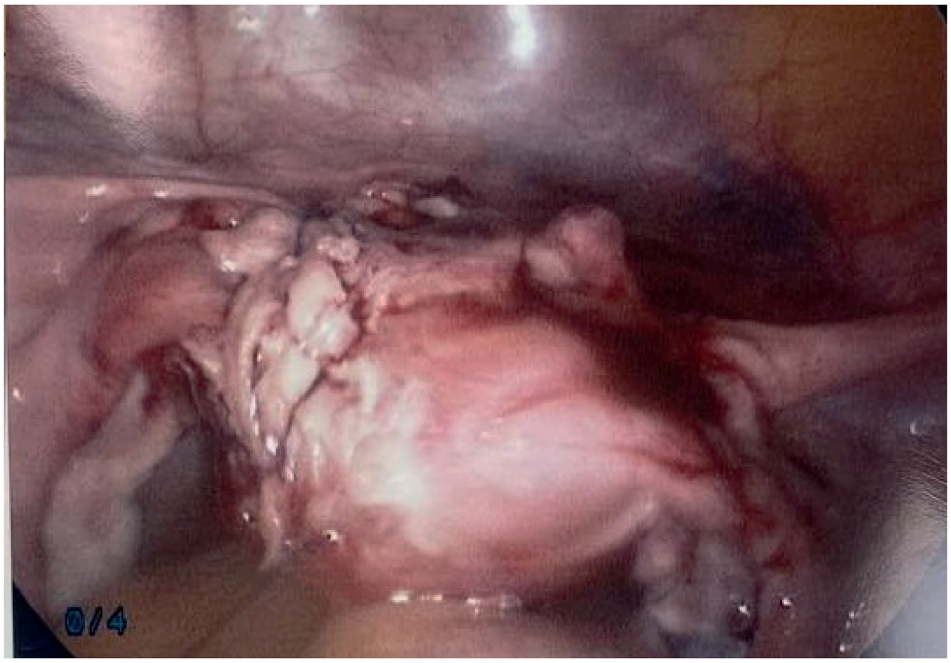

Fig. 7. Satisfactorily suture at the incision.

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Case Report

Clinical and genetic analysis of two phenotypically normal families carrying 4p16.1 microduplications

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ABSTRACT

Objective: To help determine the pathogenicity of 4p16.1 microduplications, we reported two asymptomatic families carrying this variation.
Case report: We present the prenatal diagnosis and genetic analysis of two normal families with 4p16.1 microduplications.
Conclusion: This paper highlights two families with clinically asymptomatic 4p16.1 microduplications that assisted in determining the pathogenicity of this fragment. The findings can be used as a reference for genetic counseling in cases of similar abnormalities encountered during future prenatal diagnosis.

Introduction

Prenatal diagnosis traditionally involves karyotyping, which can detect significant chromosome abnormalities but may miss smaller ones under 5 Mb [1,2]. To improve accuracy, researchers are turning to molecular genetic tools like chromosomal microarray analysis (CMA). Compared to karyotyping, CMA is much more sensitive in detecting microduplications and microdeletions [3]. Additionally, it does not require cell culture, which means that reporting times are shorter and the risk of mutations during cell culture is eliminated. However, CMA has difficulty identifying balanced translocations of chromosomes. As a result, combining karyotyping with CMA is a common clinical diagnosis approach.

Some chromosomal microduplications and microdeletions are not necessarily harmful. In clinical practice, there are many chromosomal microduplications and microdeletions with unclear clinical significance, including the 4p16.1 microduplications discussed in this paper. This study highlights two phenotypically normal families carrying 4p16.1 microduplications.

Case report

Case 1

A 35-year-old, gravida 2, para 1, woman underwent amniocentesis at 19 weeks of gestation because prenatal ultrasonography indicated the presence of bilateral hydronephrosis (Fig. 1-A) and echogenic intracardiac foci (Fig. 1-B). Her husband was 42-year-old. CMA, karyotype analysis and genetic counseling were performed.

Cultured amniocytes underwent cytogenetic analysis, which showed a normal karyotype of 46,XY. Uncultured amniocytes were subjected to CMA using the Affymetrix CytoScan 750K chip, which has 550k non-polymorphic markers and 200k SNP markers. CMA identified a 1.1 Mb chromosomal duplication in the 4p16.1 region (arr [hg19] 4p16.1 (9,734,061–10,878,115)x3) (Fig. 2-A). The parents' peripheral blood samples were also analyzed using CMA and conventional karyotyping, which showed normal karyotypes. The results of CMA showed that in addition to 4p16.1 microduplication similar to the fetus, the mother also carried an 8q11.1q11.21 microduplication (arr [hg19] 4p16.1 (9,756,767–10,794,960) x3,8q11.1q11.21 (46,839,736–48,151,265)x3). After a comprehensive physical examination on the parents failing to identify any abnormal features and genetic counseling, the parents opted to continue the pregnancy. The expectant mother gave birth to a male baby weighing 3400g via Caesarean section at 39 weeks of gestation. The baby underwent comprehensive physical examinations,

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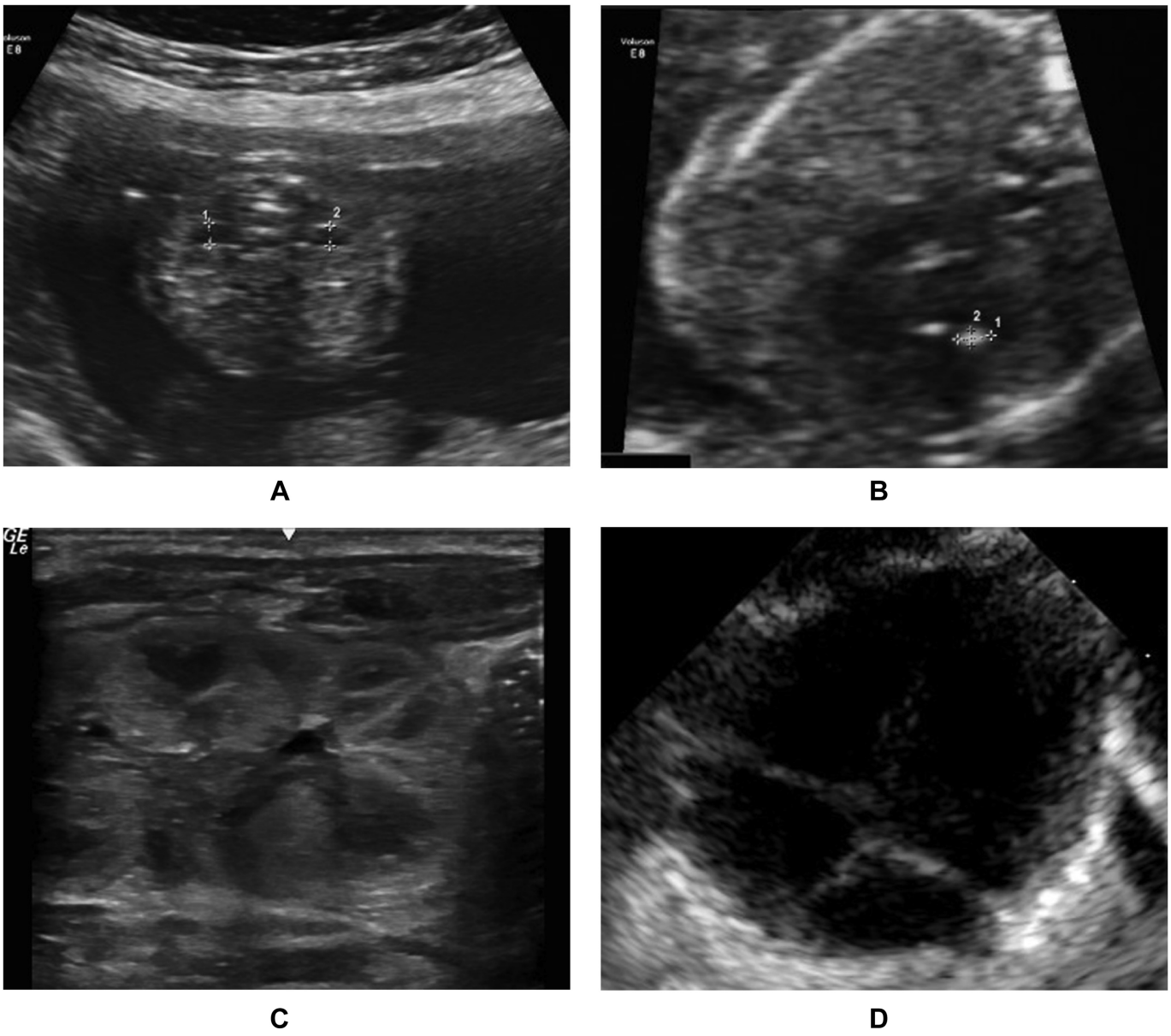

Fig. 1. A Bilateral hydronephrosis revealed by prenatal ultrasound, B Echogenic intracardiac foci revealed by prenatal ultrasound, C Ultrasound of kidney after birth, D Ultrasound of cardiac after birth.

which showed normal results. At the 16-month checkup, the baby's development was normal.

Case 2

A 30-year-old, gravida 1, para 0, woman underwent amniocentesis at 28 weeks of gestation due to prenatal ultrasonography indicating that the fetal nasal bone was not visible. Her husband was 35 years old.

CMA analysis was conducted on uncultured amniocytes after genetic counseling. The result of CMA showed that the fetus had an 872.9 Kb microduplication on chromosome 4p16.1 (arr [hg19] 4p16.1 (9,816,367–10,689,344)x3) (Fig. 2-B). Subsequently, the parents underwent CMA testing, which revealed that the father also had a similar mutation (arr [hg19] 4p16.1 (9,814,333–10,682,388) x3). Despite undergoing a comprehensive physical examination and genetic counseling, the parents decided to proceed with the pregnancy. The baby was born vaginally at 40 weeks of gestation and weighed 3950g. The baby underwent comprehensive physical examinations, which showed normal results. At the 22-month checkup, the baby's development was found to be normal.

Discussion

As molecular genetic diagnostic methods continue to advance, an increasing number of microdeletions and microduplications are being discovered. Although the pathogenicity of many of these genetic abnormalities remains uncertain [4], analyzing the genetic composition of families with microduplications and microdeletions and carefully documenting their clinical manifestations can provide valuable insight into the pathogenicity of these genetic variations.

The clinical significance of the 4p16.1 microduplications observed in the two families is still unclear after analyzing the data and querying the database (ClinGen, DECIPHER, ClinVar, PubMed,

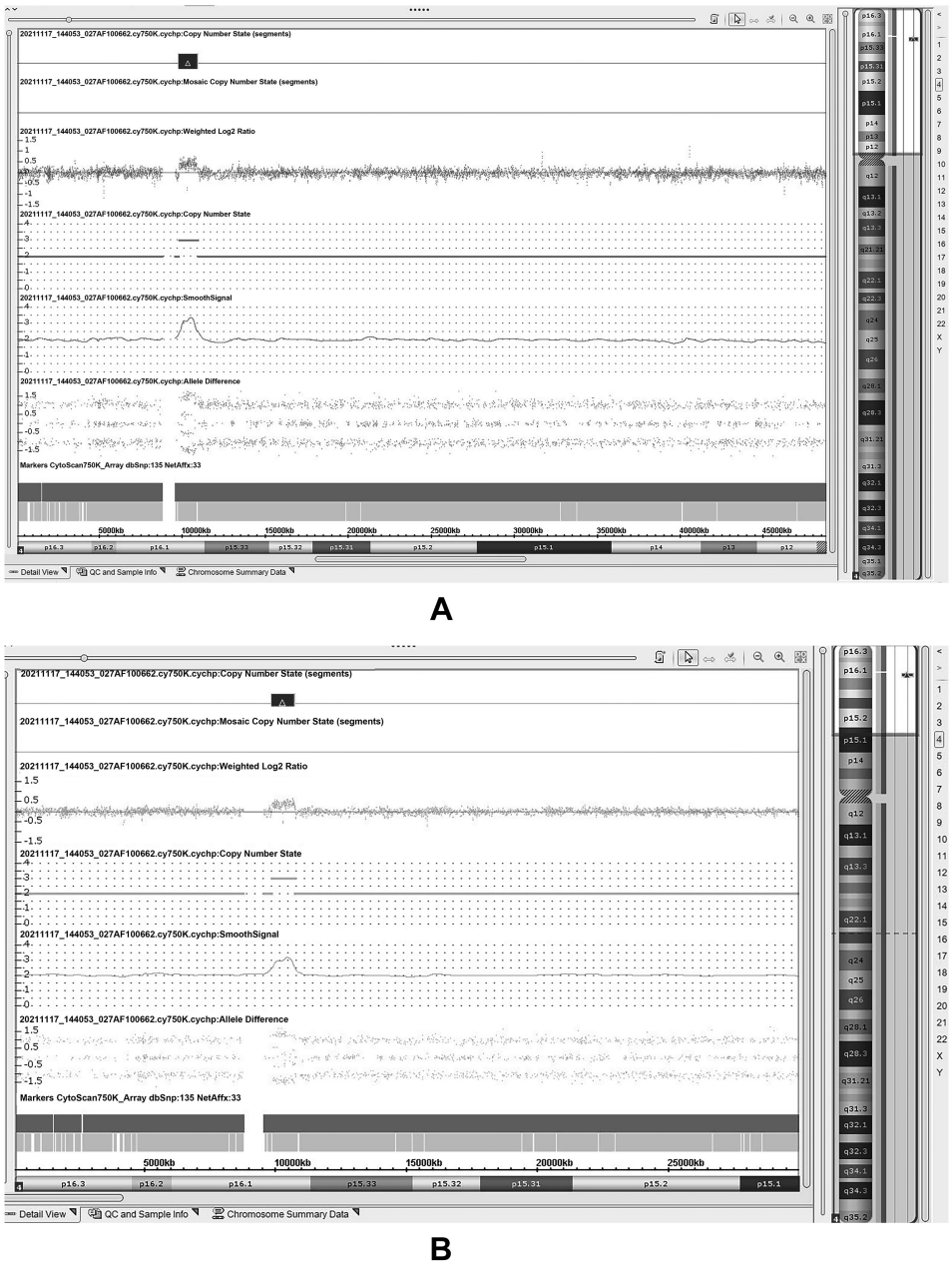

Fig. 2. A CMA detected a 1.1 Mb chromosomal duplication in the region of 4p16.1 (arr [hg19] 4p16.1 (9,734,061–10,878,115)x3), B CMA detected an 872.9 Kb chromosomal duplication in the region of 4p16.1 (arr [hg19]4p16.1 (9,816,367–10,689,344)x3).

OMIM) [5,6]. Evidence from the ClinGen database showing triple dose sensitivity to the genes contained in this segment is unclear. Similar fragment recurrences have been reported in other cases with various symptoms, such as developmental delays (https://www.ncbi.nlm.nih.gov/clinvar/variation/401006/), autism (https://www.deciphergenomics.org/patient/285840/overview/general), aphasia (https://www.ncbi.nlm.nih.gov/clinvar/variation/148806/), etc. However, there have also been cases with larger segment repeats and no abnormal clinical manifestations (https://www.ncbi.nlm.nih.gov/dbvar/variants/nsv4112182/, https://www.ncbi.nlm.nih.gov/dbvar/variants/nsv1014335/). What's more, no definitive reports on whether 4p16.1 microduplications were pathogenic were found in the PubMed database. The 4p16.1 microduplications involved in this paper contain five protein-coding genes, namely CLNK, DRD5, SLC2A9, WDR1 and ZNF518B. DRD5 is a gene that causes attention deficit-hyperactivity disorder and blepharospasm when mutated [7]. It is an autosomal dominant gene. WDR1 is an autosomal recessive gene, and patients with homozygous mutations suffer from periodic fever, immunodeficiency, and thrombocytopenia syndrome [8]. Mutations in SLC2A9 can cause hypouricemia [9].

In case 1, prenatal ultrasonography showed bilateral hydronephrosis and echogenic intracardiac foci, but these signs disappeared after the baby was born (Fig. 1-C,D) and the baby appeared normal, indicating that there may be little connection between these signs and genetic factors. The mother of case 1 also had an additional 8q11.1q11.21 microduplication of unknown clinical significance. However, this is likely benign as the mother does not have any abnormal clinical manifestations. In case 2, the nasal bone was not visible on ultrasound during the fetal period, but it developed

normally after birth. This was likely due to insufficient ossification of the nasal cartilage during fetal development.

We have known that in CMA analysis, the amplification or deletion of chromosome copy number was determined according to log2 ratio exceeding the preset threshold range. Due to factors such as the type of chip probe, GC content, hybridization efficiency, and segmental duplications in the hybridization region, the signal strength of the hybridization probe will fluctuate, resulting in fluctuations in the log2 ratio. As a result, there are some differences in the breakpoint of CNV fragment results, and the same fracture location cannot be accurately reached. With the increase of the density of the chip probe, the difference range of the fracture point of the detected CNV results will be smaller. Therefore, when conducting CNV analysis, the results of two CNV fragments are usually considered to be the same fragment results if the overlap in physical location exceeds 80%. So it is normal for parents and offspring to have slightly different CMA results in each family.

Overall, four patients in two families had microduplications on 4p16.1, but no significant clinical abnormalities were observed. Although there have been relevant reports on this genetic variation, current research is not sufficient to make a definitive judgment on its pathogenicity. The evidence presented in this paper suggests that the 4p16.1 microduplication may be considered a benign variation when additional similar evidence is gathered. This is beneficial for diagnosing and providing genetic counseling to patients who have similar genetic variations. Additionally, this paper highlights the importance of combining karyotype analysis, CMA, prenatal ultrasound and genetic counseling in prenatal diagnosis for the diagnosis of chromosomal abnormalities [10].

Declarations

This study was approved by the Ethics Committee of The Affiliated Weihai Second Municipal Hospital of Qingdao University (Weihai Maternity and Child Care Hospital). All the patients' guardians have signed the informed consents.

Consent for publication

All the patients' guardians have signed informed consents to the publication of this study.

Availability of data and materials

The data will be available upon request to the corresponding author.

Declaration of competing interest

All authors of this article certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Case Report

Postpartum hemoperitoneum – A rare case of uterine artery pseudoaneurysm rupture after uncomplicated vaginal delivery

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ABSTRACT

Objective: Our aim is to demonstrate a rare cause of hemoperitoneum without vaginal bleeding resulting from the rupture of a uterine artery pseudoaneurysm after uncomplicated vaginal delivery.
Case report: A 39-year-old woman who had experienced a normal vaginal delivery 8 days previously to being seen in our hospital, was presented to the emergency room with hypovolemic shock. Computed tomography angiography (CTA) showed massive internal bleeding and a ruptured pseudoaneurysm arising from the left uterine artery. The patient was successfully treated through transcatheter arterial embolization (TAE).
Conclusion: A pseudoaneurysm is a rare disease which can occur during an uncomplicated vaginal delivery. The clinical presentation can vary from asymptomatic, vaginal bleeding or hemoperitoneum. The diagnosis can be made by using Doppler sonography, CTA or Magnetic Resonance Imaging. The use of TAE is now the most common treatment option and possesses a high success rate.

Introduction

Spontaneous hemoperitoneum in pregnancy (SHiP) is a sudden case of non-traumatic intraperitoneal bleeding occurring during pregnancy and up to 42 days postpartum. This rare condition is associated with high perinatal morbidity and mortality. A recent prospective population-based cohort study involving an Italian population revealed an estimated incidence rate of 0.04 per 1000 births [1]. The incidence of a bleeding site in the uterine artery was 2 in 29 cases in their study. A pseudoaneurysm is a rare complication that arises when there is a rupture through one or more layers of an artery, resulting in blood leaking outside of the vessel and accumulating in a space confined by the adjacent tissue [2]. Rupture of a uterine artery pseudoaneurysm is an unusual, yet potentially life-threatening cause of delayed postpartum hemorrhage. In this report, we describe a case of uterine artery pseudoaneurysm rupture in a patient who was presented with hemoperitoneum and hypovolemic shock without vaginal bleeding eight days after an uncomplicated vaginal delivery.

Case presentation

A 39-year-old woman (gravida 4, para 1, spontaneous abortion 2, and artificial abortion 1 with medical termination) was presented to the emergency department, complaining of a sudden-onset of dizziness, near-syncope and cold sweating, without vaginal bleeding. She had previously delivered a female baby weighing 3,288g through a normal and smooth vaginal delivery eight days earlier without equipment assistance. The baby had Apgar scores of 7 and 9 in the first and fifth minutes, respectively. During the delivery, 300 mL of blood was lost, and the lochia in the first hour was 52g. The mother recovered smoothly and was discharged as scheduled two days later. Tracing back her history, she had undergone a laparoscopic left salpingectomy due to hydrosalpinx one year earlier. Drainage of the left endometrioma and cauterization for endometriosis implants in the cul-de-sac and pelvis wall were also then performed for secondary infertility treatment. She had natural pregnancy after the procedures 3 months later.

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Upon arrival at the emergency department, she appeared pale, diaphoretic, and was experiencing shallow breathing. Her initial vital signs were blood pressure 63/40 mmHg, heart rate 91 beats/min, respiratory rate 19 breaths/min, and body temperature 35.8 °C. An abdominal physical examination revealed tenderness over the hypogastric region, but no rebound tenderness or muscle guarding. A pelvic examination revealed a reduced amount of lochia rubra. Additionally, an abdominal sonography illustrated no retained tissue in the uterine cavity, and the patient's bilateral adnexa appeared unremarkable. However, massive ascites was seen over the bilateral gutter and Morrison's pouch.

Given the patient's presentation and examination findings, hypovolemic shock with internal bleeding was impressed. Laboratory data revealed hemoglobulin of 7.2 g/dL, hematocrit of 23.1%, fibrinogen degradation product (FDP) of 20.5 ug/mL, fibrinogen determination of 81.8 mg/dL, and D-dimer of 6.66 mg/L FEU. Initial resuscitation involved the administration of 2 L of isotonic crystalloid and 2 units of red blood. However, the patient's blood pressure dropped to 55/29 mmHg in a period of 90 min, while the patient also complained of severe upper abdominal cramping pain. An emergent abdominal computed tomography angiography showed a 1.4 cm pseudoaneurysm arising from the left uterine artery, with a heterogenous high attenuation of ascites (Fig. 1). Active bleeding from the pseudoaneurysm was suspected. The patient received further resuscitation using 2 L of isotonic crystalloid, 8 units of red blood, 4 units of fresh frozen plasma and 1 unit of single donor platelets. Her blood pressure improved to 85/52 mmHg, and she was sent for emergent transcatheter arterial embolization (TAE).

The TAE was performed through super selection of the bilateral uterine artery. The left uterine artery was embolized with an embolization coil (2 × 18S-3/2 TORNADO) and Gelfoam (Fig. 2), while the right uterine artery was injected with Gelfoam. The subsequent laboratory data showed hemoglobulin levels of 8.4 g/dL, FDP levels of 6.0 ug/mL, fibrinogen determination levels of 147.5 mg/dL and D-dimer levels of 2.05 mg/L FEU. The patient was sent to the ordinary ward after receiving TAE and was discharged five days later without any complications.

Discussion

A pseudoaneurysm is a vascular cavity that communicates with the arterial lumen. It is formed as a result of an incomplete arterial wall laceration. Besides iatrogenesis, its formation may be due to any process that affects and weakens the arterial wall, including chronic inflammation like endometriosis [3]. Uterine artery pseudoaneurysm (UAP) can occur after traumatic delivery, including cesarean section (CS), manual removal of the placenta, forceps delivery, vacuum extraction, dilatation and curettage (D&C), and even uncomplicated spontaneous vagina delivery [4,5]. The true incidence of UAP is not clear, with one retrospective observational study of 50 women with angiographically confirmed UAP who were treated by TAE revealing that it occurred in 3–6 of 1000 deliveries [6].

The clinical presentation of a ruptured pseudoaneurysm can vary depending on whether it communicates with the uterine cavity [7]. As reported previously, a postpartum hemorrhage with vaginal bleeding can occur. In our case, hemoperitoneum had occurred due to a pseudoaneurysm rupture into the intra-abdominal space. Owing to the increased accessibility of color Doppler sonography, more “once ruptured but possibly partly sealed” or “non-ruptured” UAPs have been diagnosed without symptoms.

Color Doppler ultrasound is an easily accessible tool in which findings of an intrauterine mass with swirling blood flow, a to-and-fro or yin-and-yang pattern, indicate a uterine artery pseudoaneurysm [8]. Computed tomography angiography (CTA) can confirm the presence of UAP with a narrow connection to the parent artery (uterine artery), while Magnetic resonance imaging (MRI) can reveal an enhanced, pseudoaneurysmal sac-like structure within the uterus [8]. The treatment of pseudoaneurysms has evolved over the years. In the past, the majority of uterine artery aneurysms were treated through a hysterectomy, with or without hypogastric artery ligation [9]. Recently, transcatheter arterial embolization (TAE), which was first popularized in the early 1970s, has become a mainstay treatment [10]. In a retrospective study, TAE allowed control of bleeding in all patients diagnosed

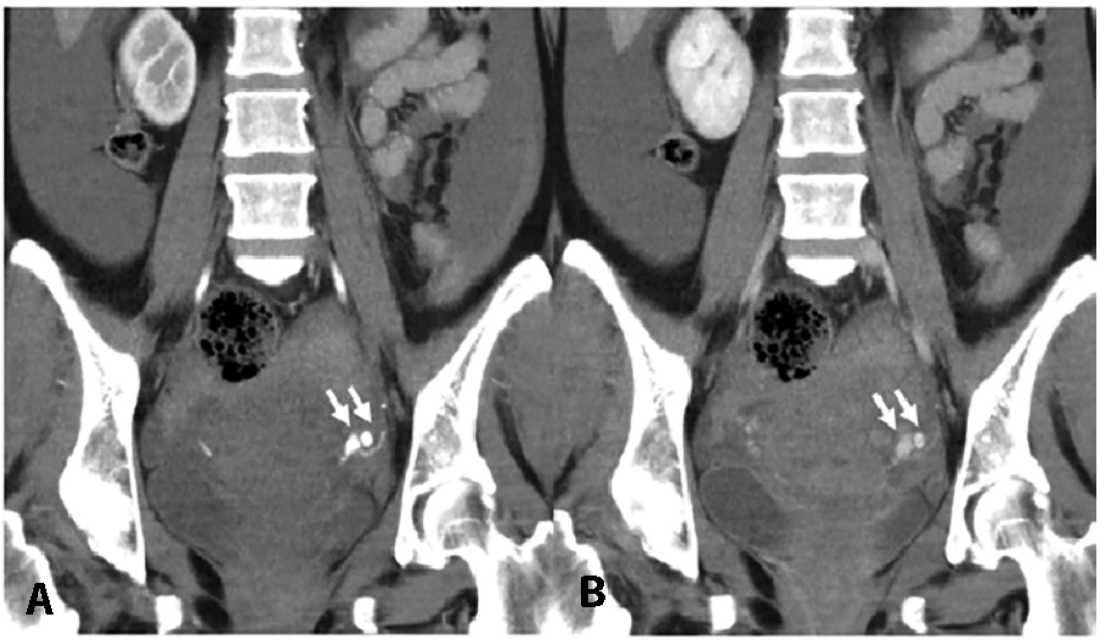

Fig. 1. The computed tomography angiography seen in the arterial phase (A) and venous phase (B) demonstrates high-attenuation ascites, which indicate hemoperitoneum, along with a 1.4 cm pseudoaneurysm (arrow) arising from the left uterine artery, related to the internal bleeding.

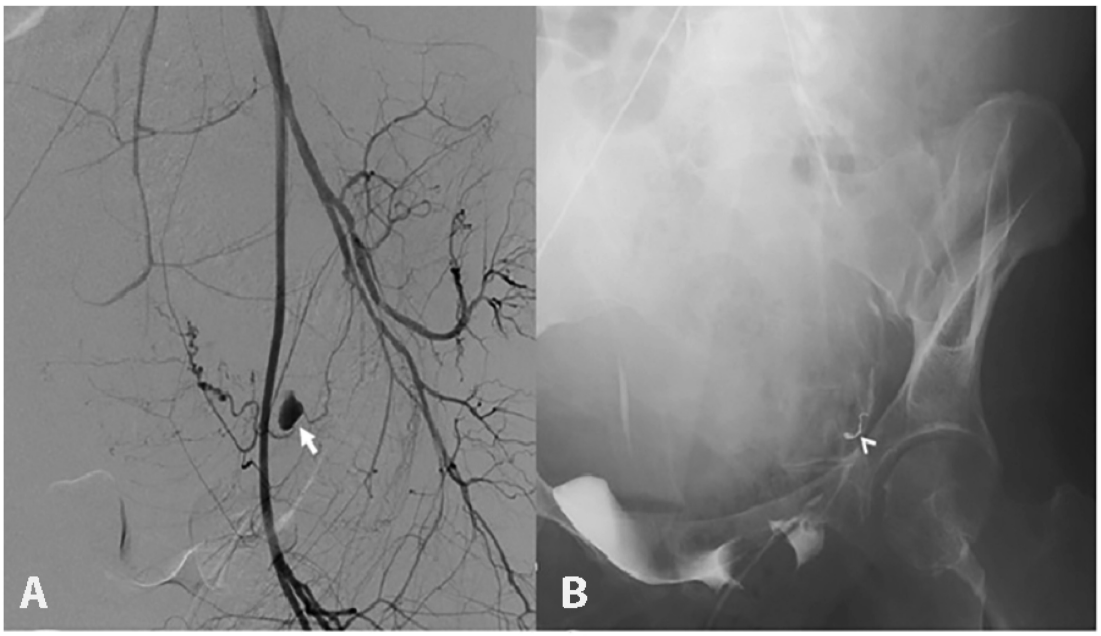

Fig. 2. The digital subtraction angiography (A) with super selective left internal iliac arteries and an LAO 45-degree decubitus view shows a pseudoaneurysm (arrow) arising from the left uterine artery. The post-TAE image (B) shows the retention of microcoils at the left uterine artery (arrowhead).

with a pseudoaneurysm after one or two embolization sessions in 17 of 18 (94 %) and 1 of 18 patients (6 %) respectively, without complications [11]. Few studies have reported on alternative options, including sono-guided direct thrombin injection into the pseudoaneurysm [9], laparoscopic vascular lesion removal after ligation of the artery branch, or stent graft repair with an endovascular approach [12].

Our case was presented to the emergency room as hypovolemic shock. The first impressions of delayed postpartum hemorrhage are retained products of conception, endometritis or sloughing of the placental site eschar [13]. However, there was no vaginal bleeding seen in our patient, which is a common presentation of delayed postpartum hemorrhage. Massive ascites were seen under bedside sonography, and severe internal bleeding was suspected. Subsequent computed tomography angiography gave us the definite diagnosis of a UAP rupture. Tracing back the patient's history, she has undergone laparoscopic left salpingectomy and left endometrioma drainage one year earlier. Some case reports have demonstrated the probable relationship between endometriosis and uterine artery pseudoaneurysm [14]. An Italian population-based prospective cohort study showed a higher risk of spontaneous hemoperitoneum in pregnancy for those at a maternal age >35 years, women with multiple pregnancies, and those involving assisted reproductive technology [1].

Uterine artery pseudoaneurysm is a life-threatening cause of late postpartum hemorrhage, which can be easily missed. The initial clue for diagnosis can be obtained by performing bedside color Doppler ultrasound. CTA is a valuable diagnostic tool for making an accurate diagnosis, and subsequent treatment involving TAE has a high success rate.

Declaration of competing interest

No authors have received support, financial or otherwise, from any organization that may have an interest in the submitted work. There are no other relationships or activities that could appear to have influenced the submitted work.

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Case Report

Perinatal lethal form Gaucher disease with compound heterozygosity of single nucleotide variants and copy number variations presenting as nonimmune hydrops fetalis and cerebellar hypoplasia: A case report

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ABSTRACT

Objective: To present the ultrasound imaging and genetic diagnosis of a fetus with prenatal lethal form of Gaucher disease.

Case report: A 37-year-old primiparous woman was pregnant at her 23 weeks of gestation and the prenatal fetal ultrasound revealed hydrops fetalis, cerebellum hypoplasia, and fetal immobility. The pregnancy was terminated due to major fetal anomaly, and whole exome sequencing (WES) analysis of fetal tissue and parental blood unveiled a pathogenic variant in exon 10 of the *GBA* gene (NM_001005741.3: c.1265T > G: p.L422R) originating from the mother. Additionally, a novel CNV (chr1: 155204785–155205635 deletion, 0.85 kb) spanning exon 10–12 in the *GBA* gene was identified from the father. This compound heterozygosity confirmed the diagnosis of prenatal lethal form of Gaucher disease and was informative for genetic counseling.

Conclusion: WES is a powerful tool to detect pathogenic variants among fetuses with nonimmune hydrops fetalis and complex abnormality from prenatal ultrasound. Compound heterozygosity consisted of single nucleotide variants (SNV) and copy number variations (CNVs) may lead rare inherited metabolic disorders including prenatal lethal form of Gaucher disease.

Introduction

Hydrops fetalis—the accumulation of fluid in at least two fetal compartments, such as the skin, pleura, pericardium, and abdomen—typically signifies an unfavorable fetal prognosis and major fetal abnormalities [1]. The etiology of hydrops fetalis can be categorized into immune hydrops and nonimmune hydrops (NIHF). Approximately 10% of hydrops fetalis cases are immunogenic, predominantly resulting from hemolysis related to Rh incompatibility. The remaining 90% are NIHF cases, the causes of which encompass cardio-pulmonary anomalies, severe fetal anemia (e.g., thalassemia or infection), and genetic aberrations [1–3].

Detailed prenatal ultrasonography enables the detection of hydrops fetalis as early as the late first trimester [1]. A comprehensive examination, including an assessment of fetal structures and Doppler velocimetry of the middle cerebral artery, can indicate the cause, such as cardiopulmonary abnormality or fetal anemia. Moreover, a detailed fetal scan can offer insights into complex genetic disorders affecting multiple systems. The term “genetic ultrasound” serves as a preliminary indicator, prompting physicians to consider performing prenatal genetic testing, including karyotyping, array-based comparative genomic hybridization (arrayCGH), and whole exome sequencing (WES) [4].

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Advancements in sequencing techniques, along with reductions in costs, have led to the popularization of next-generation sequencing (NGS)-based genetic diagnostics [4]. WES is a robust approach to comprehensively exploring the human genome. It identifies thousands of single nucleotide variants (SNVs) in an individual. In addition, by analyzing the counts of genetic fragments, WES can also detect structural variants (SVs) and copy number variations (CNVs) [5,6]. By comparing the extensive human genome database with the results of functional protein analysis, the pathogenic variants associated with specific diseases can be identified.

This report presents a case involving a mother carrying a hydropic fetus at 23 weeks of gestation with no reported fetal movement. Prenatal ultrasound revealed hydrops fetalis and cerebellar hypoplasia. Despite normal karyotyping and arrayCGH results, WES was conducted and revealed a perinatal lethal form of Gaucher disease (PLGD) characterized by compound heterozygosity involving two newly reported SNVs and CNVs.

Case presentation

A 37-year-old primiparous woman who underwent in-vitro fertilization and embryo transfer because of primary infertility for 5 years visited our clinic at the 23rd week of gestation. She reported hydrops fetalis, as identified in a thorough fetal scan at another hospital. Additionally, the mother noted an absence of fetal movement and kicking. Noninvasive prenatal screening using maternal plasma cell-free DNA was performed in the first trimester and indicated a low risk of trisomy 13, 18, and 21. Subsequent prenatal genetic diagnostics through amniocentesis, including karyotyping and arrayCGH, revealed no abnormalities and indicated a female fetus.

At our hospital, a general survey for hydrops fetalis was conducted through maternal blood typing, an indirect Coombs' test, and a TORCH (toxoplasma, rubella, cytomegalovirus, herpes, syphilis) survey, all of which yielded typical results. A detailed fetal ultrasound, repeated at our facility, indicated hydropic changes in the fetus, including scalp edema, pericardial effusion, pleural effusion, and ascites. Notably, the fetal stomach was absent, and multiple intracranial anomalies were discovered—cerebellum hypoplasia (size: 1.99 cm, 19 weeks 1 day, <1% for gestational age at 23 weeks), mild ventriculomegaly (posterior ventricle: 7.2 mm), and suspected lissencephaly characterized by absent gyration. The fetal middle cerebral artery–peak systolic velocity was a relatively high value of 43.09 cm/s (1.417 MoM), whereas the amniotic fluid level was typical, indicated by an amniotic fluid index of 9.68 cm. Despite the absence of fetal movement during the approximately 60-min examination, the fetal heart exhibited a proportional structure, correct connection with large vessels, and a normal axis. Other systems—including the lips, limbs, spine, stomach, gall bladder, kidneys, urinary bladder, genitalia, and placenta—were normal. Fetal growth was also within the expected range, with an estimated fetal weight of 573 g (Hadlock) and estimated gestational age of 23 weeks. However, no fetal movement was seen during the examination, which lasted approximately 60 min (Fig. 1).

The absence of fetal movement during the examination raised suspicion of neurological dysfunction due to severe hydrops fetalis and fetal brain anomalies. Subsequently, sampling for WES was conducted. After termination, the baby exhibited no anomalies in terms of appearance except for general edema (Fig. 2). The WES of the fetal blood and parental blood samples were processed as trios.

The WES results revealed compound heterozygosity of the *GBA* gene in the fetal genome, involving one SNV (NM_001005741.3: c.1265T > G: p.L422R) and one CNV (GRCh 37: chr1: 155204785–155205635 deletion, 0.85 kb). Subsequent analysis of the parental blood confirmed the compound heterozygosity phase, with the SNV being of maternal origin and the CNV being of paternal origin.

According to the American College of Medical Genetics and Genomics guidelines for the interpretation of genetic variants [7], the variant c.1265T > G in the *GBA* gene was deemed likely pathogenic on the basis of a report and in-silico analysis [8]. Sanger sequencing confirmed a hemizygous variant c.1265T > G in the *GBA* gene in the proband, with this variant being inherited from the mother (Fig. 3). The SNV was further confirmed through qPCR and discovered to be exclusively present in the *GBA* gene, not in the *GBAP* gene.

Furthermore, a novel CNV was identified through the WES-CNV test, revealing a suspected 0.85-kb deletion of exons 10–12 on the *GBA* gene. WES-CNV analysis indicated that both the proband and proband's father harbored the mutation, whereas the proband's mother did not. Notably, this CNV has not been reported in genomic databases—including gnomAD, ClinVar, ClinGen, and Decipher—or in any clinical case report. qPCR on exon 10 of the *GBA* gene confirmed decreased expression in the proband and proband's father (RQ value of proband: 0.51; proband's father: 0.42; proband's mother: 0.97; Fig. 4).

Discussion

Researchers have reported various instances of compound heterozygosity within the *GBA* gene leading to Gaucher disease. In a Tunisian case series, N370 S/RecNciI mutations were identified in five patients [9]. An Indonesian Chinese boy with type 2 Gaucher disease exhibited the L444P and RecNciI mutations [10]. Another case involved RecNcil plus R131C in a neonate with PLGD; the infant succumbed within 1 h of birth [11]. A cohort study reported 10 Chinese patients with type 2 Gaucher disease and compound heterozygosity, with L444P (p.Leu483Pro, c.1448T > C) found to be the most prevalent variant. L383R (p.Leu422Arg, c.1265T > G), identical to the variant in our patient, was also reported [8]. Notably, no prior reports have described compound heterozygosity involving a larger deletion encompassing exon 10 of the *GBA* gene, a potential contributor to Gaucher disease.

Perinatal Gaucher disease has been documented with presentations similar to those in our case, including cerebellar hypoplasia [12]. In an instance of an NIHF fetus exhibiting compound heterozygosity (c.1505 + 5 G > C and c.308-1G > A), fetal MRI revealed cerebellar hypoplasia and delayed cortical maturation. Additionally, prenatal ultrasound revealed ascites, pleural effusion, flattened nasofrontal angle, skin edema, clenched hands, ambiguous genitalia, and hepatosplenomegaly [13]. A systematic review identified cerebellar hypoplasia or fetal akinesia in 4 cases out of 12 literature sources [14].

Most NIHF cases have been reported as being idiopathic despite thorough physical and laboratory examinations being performed [15]. Through a systematic approach in which prenatal ultrasound is incorporated with basic genetic testing techniques such as karyotyping and arrayCGH, the etiology of NIHF can be determined in 72% of cases. The causes include hematologic diseases (28.4%), chromosomal anomalies (19.8%), lymphatic anomalies (7.8%), and cardiovascular disorders (4.1%). However, 28% of NIHF cases remain unexplained, and most diagnoses are phenotypic rather than genotypic [1].

Genetic sequencing technology, notably NGS, is extensively used in various scientific fields. NGS-based WES can successfully detect SNVs, small insertions/deletions (InDel), and CNVs [16]. Assuming adequate NGS sequencing coverage, the relative change in DNA content in the CNV region can be discerned by analyzing the number of reads [17]. WES-CNV, utilizing "the depth of coverage," can identify potential CNVs spanning multiple exons. The integration of NGS-based WES into prenatal diagnostic protocols has

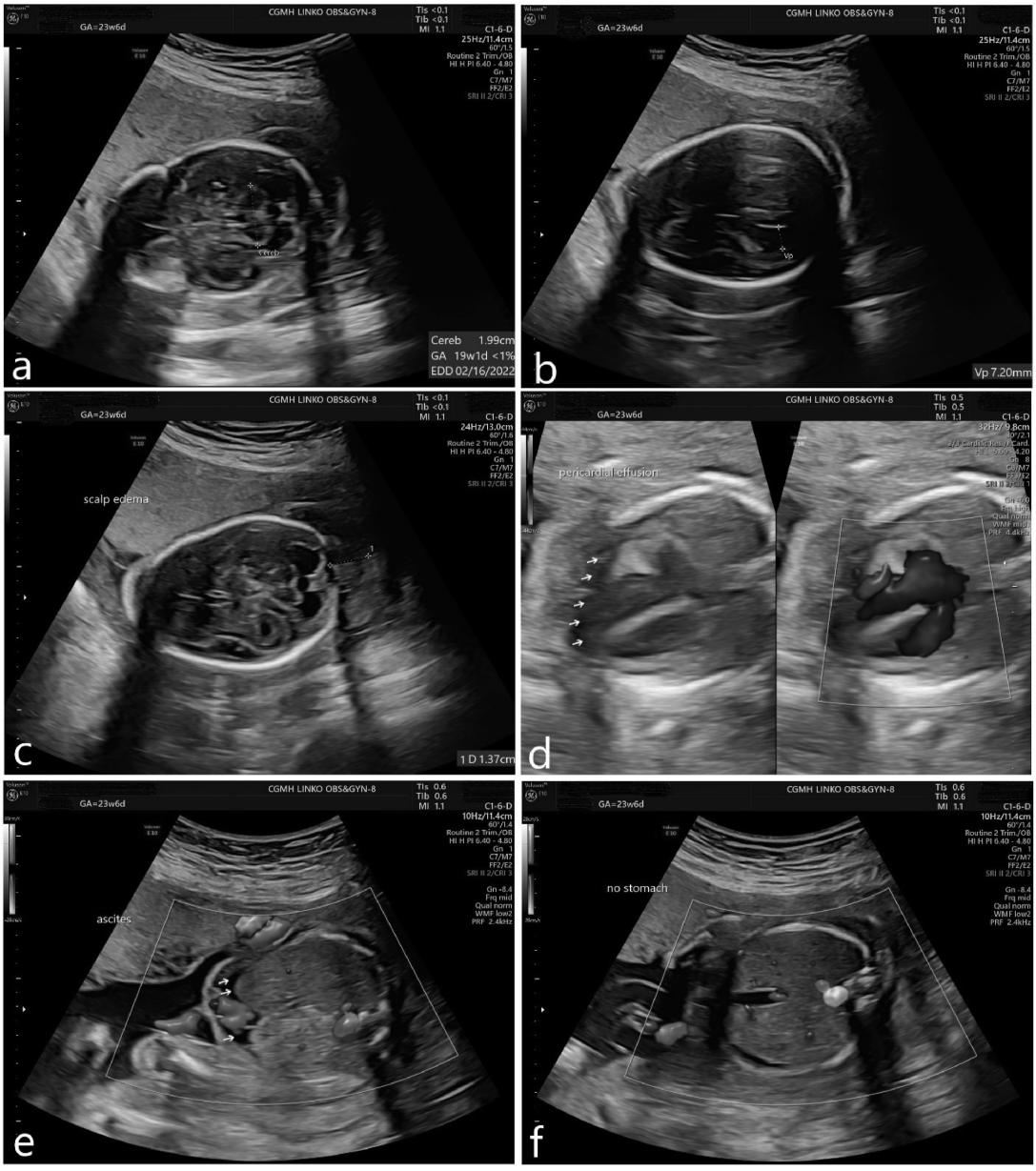

Fig. 1. Detailed fetal ultrasound revealed cerebellar hypoplasia (a), mild ventriculomegaly (b), smooth gyration and scalp edema (c), pericardial effusion (d), fetal ascites (e), and the absence of a stomach in the fetus (f), indicating fetal akinesia.

yielded definitive genetic diagnoses for an additional 9% of fetal structural anomalies [18]. However, large prospective trials specifically targeting NIHF have yet to be performed. In a genetic analysis cohort study of NIHF, positive findings on WES were obtained for only 3 out of 109 fetuses [2].

For a fetus with a family history of lysosomal storage disorder or characteristic sonographic presentations such as hydrops fetalis, hepatomegaly, and abnormal central nervous system findings, prenatal diagnosis of lysosomal storage disorder should be considered. Phenotypic evidence can be obtained through enzymatic assays on amniotic fluid cells, chorionic villi samples, or umbilical cord blood [19]. A cohort study employing NGS panels as a first-line survey for NIHF achieved five genotypic prenatal diagnoses of inborn errors of metabolism: Niemann-Pick type C (NPC), Barth syndrome, HNF1Beta deficiency, GM1 gangliosidosis, and Gaucher disease [5].

Gaucher disease is caused by deficiency of glucocerebrosidase, a lysosomal membrane protein encoded by the *GBA* gene. The loss of function results in abnormal accumulation of glucocerebrosides in various organs, including the spleen, liver, kidneys, lungs, brain, and bone marrow. A patient may present with hepatosplenomegaly, bone pain, pancytopenia, or neurologic symptoms, including convulsions, hypertonia, dementia, or intellectual disability. The disease is categorized into three types: type 1 (nonneuronopathic), type 2 (acute neuronopathic), and type 3 (subacute neuronopathic) [14]. The most severe form, PLGD, is type 2 Gaucher disease and onsets from the fetal stage to hours after birth. Affected babies typically exhibit hydropic changes and succumb either in utero (intrauterine fetal demise) or shortly after birth due to respiratory distress [20]. To date, no intrauterine fetal therapy has been proven successful. However, an animal model of an adeno-associated virus 9 vector carrying a reporter gene from

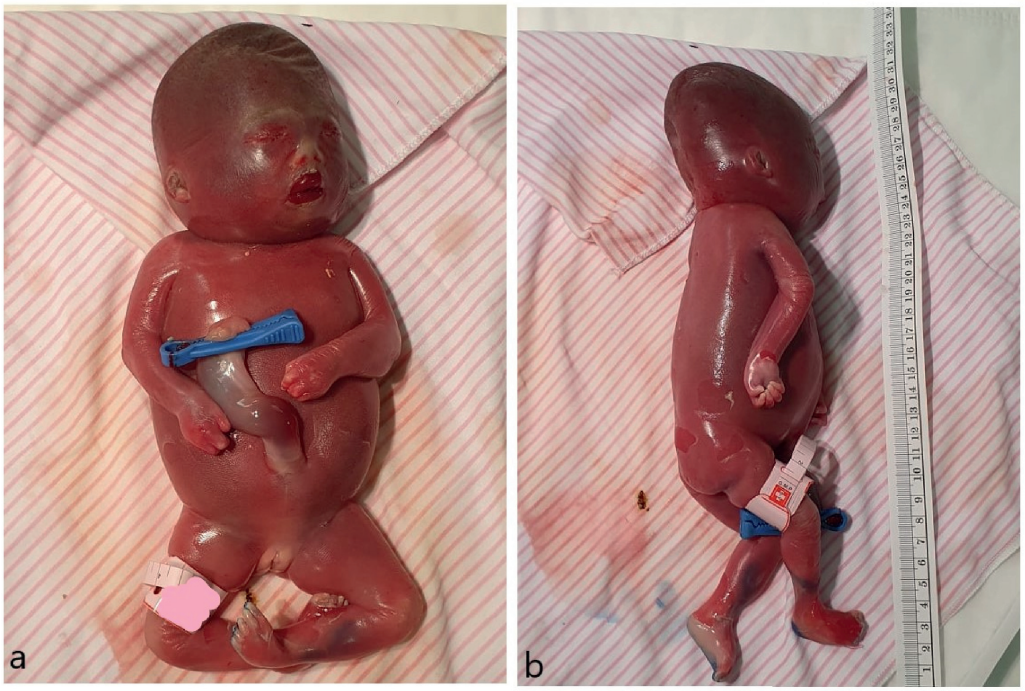

Fig. 2. Appearance of the abortus indicates generalized edema without evident trunk or limb deformities.

the human *GBA* gene was demonstrated to improve motor function and survival in *Gba*-mutant mice [21].

Specific genetic variants in the *GBA* gene are associated with PLGD, including L444P (c.1448T > C), A456P (c.1483G > C), V460V (1497G > C), H311R (c.1049A > G), V398F (c.1309G > T), E326K (c.1093G > A), P182L (c.662C > T), R463H (c.1505G > A), G234E (c.701G > A), and H413P (c.1238A > C) [20,22–26]. Most of these variants are found in a homozygous or compound heterozygous state, indicating a double-hit and loss-of-function mechanism. In a Chinese cohort study, novel mutations in the *GBA* gene were discovered in 10 unrelated patients with type 2 Gaucher disease; these mutations included P122L, Y363C, N382K, L383R, L385P, and M416V [8]. The Human Genome Variation Society nomenclature states that L383R is p.Leu422Arg, the same variant as exhibited by our patient. When combined with the other allele carrying SVs (chr1: 155204785–155205635 deletion, 0.85 kb) encompassing exon 10–12 in the *GBA* gene, the compound heterozygosity resulted in a nonimmune hydropic fetus, as detailed in our report.

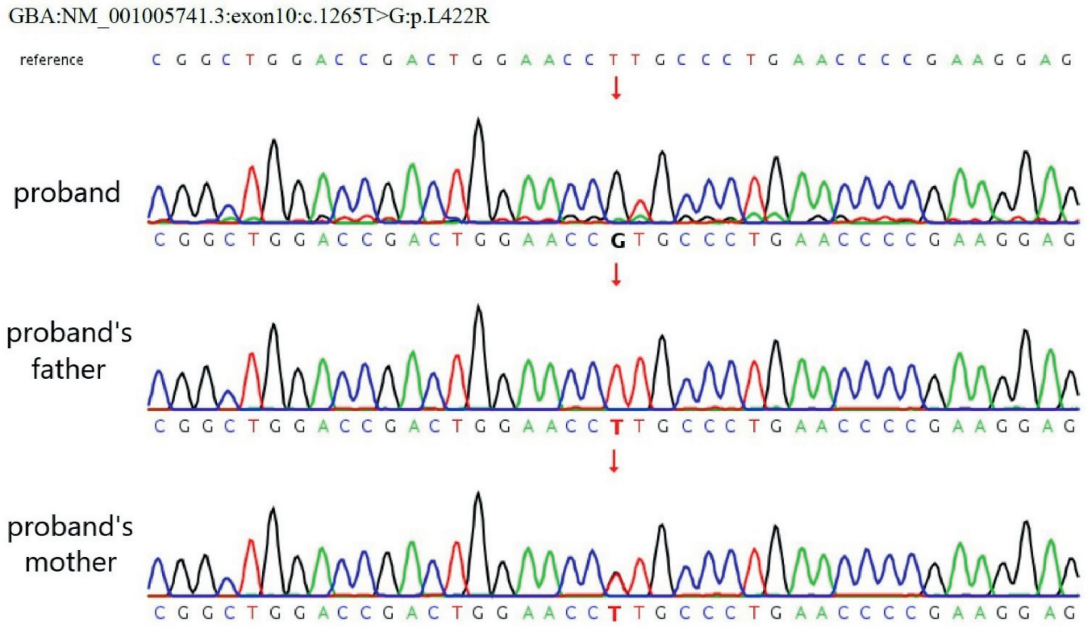

Fig. 3. Sanger sequencing of *GBA* gene exon 10: c.1265 T > G:p.L422R. The proband's father exhibited the wild type with T, the proband's mother exhibited heterozygous c.1265 T > G, and the proband exhibited hemizygous c.1265 T > G.

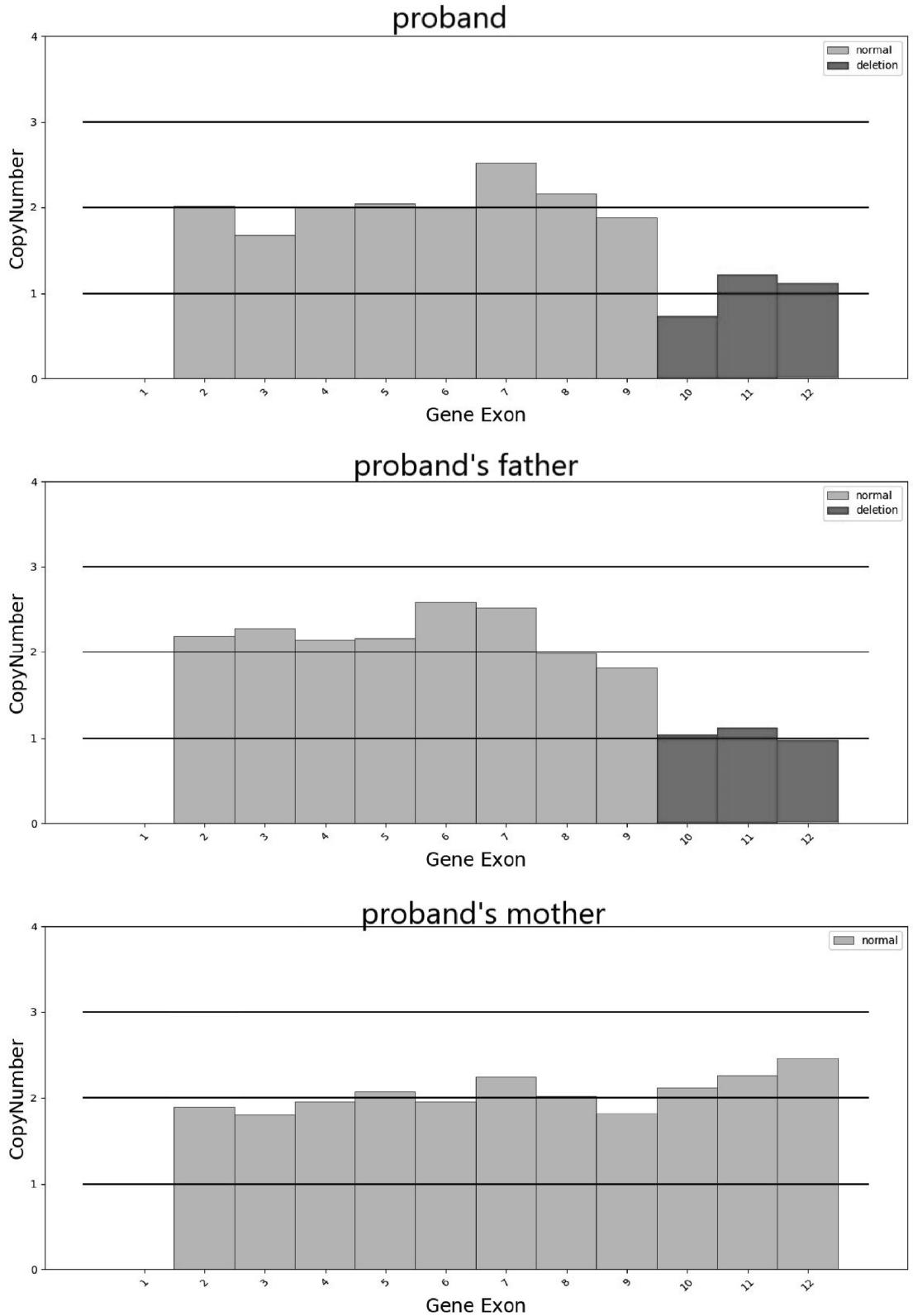

Fig. 4. WES-CNV reveals decreased expression in proband and proband's father on exon 10–12 of the *GBA* gene.

Conclusion

Gaucher disease was conclusively diagnosed in this case through WES, and compound heterozygosity involving an SNV and a CNV was discovered. This diagnosis was made despite normal karyotyping and arrayCGH results. The findings highlight the importance of considering Gaucher disease in the differential diagnosis of conditions characterized by

hydrops fetalis, cerebellum hypoplasia, and the absence of fetal movement.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board (IRB no. 202201153B0) of Chang Gung Memorial Hospital, Taoyuan City, Taiwan. Informed consent was waived due to the retrospective nature of the study, as endorsed by the aforementioned institutional review board.

Funding

No funding was applied for this study.

Authors' contributions

C–C H and N–C L drafted the manuscript. Y–H C and Y-L C designed the experimental protocols for the patient. C–F L prepared the figures and conducted the validation exams.

Consent for publication

Consent for publication was obtained from the patient on a signed document.

Availability of data and materials

All data and materials supporting the conclusions are included in the main paper.

Declaration of competing interest

No potential conflicts of interest are disclosed.

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Case Report

Laparoscopic modified simple ureteroneocystomy in iatrogenic lower third ureter injury during gynecology surgery

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ABSTRACT

Objective: Our objective was to propose a laparoscopic modified simple ureteroneocystostomy for repairing iatrogenic ureteral injuries. In laparoscopic modified simple ureteroneocystostomy, the highest point of the bladder was found by cystoscopy, then we implanted a "fish mouth" ureter end into the bladder, leaving at least 1 cm of ureter end in the bladder as an anti-reflux procedure.
Case report: We retrospectively reviewed a case series of lower third iatrogenic ureter injury during gynecology surgery of 11 patients who received laparoscopic modified simple ureteroneocystostomy at Da Lin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, from January 2011 to December 2020. One patient needs percutaneous nephrotomy due to infection and had the ureteroneocystostomy two months later. No obstruction, ureter stenosis/stricture, bladder leakage or other renal complications were noted after repair.
Conclusion: Laparoscopic modified simple ureteroneocystostomy is technically feasible for repairing lower third ureter injuries, with no major complications.

Introduction

Iatrogenic ureteral injury is a known complication of any gynecologic surgery, estimated at approximately 0.1–1.5% for benign procedures and approximately 5% for oncologic procedures [1]. The incidence of ureteral injury is 1 per 1000 in gynecologic hysterectomy: 13.9 per 1000 in laparoscopic, 0.4 per 1000 in total abdominal, 0.3 per 1000 in subtotal abdominal, and 0.2 per 1000 in vaginal hysterectomy [2]. Ureteroneocystostomy (UNC) or ureterovesical reimplantation refers to the reimplantation of the ureter into the bladder to correct lower third ureteral injuries close (3–5 cm) to the bladder.

Decades of experience in renal transplantation and ureteral repair have shown that vesicoureteral reflux (VUR), ureteral stricture, and fistula formation are the main concerns in ureteral reimplantation or anastomosis surgery. Repair failure can be complicated by recurrent infection, severe hydronephrosis, and renal failure. Therefore, anti-VUR procedures using submucosal tunneling in the bladder wall, such as extravesical Politano-Leadbetter technique and intravesical or extravesical Lich-Gregoir, have increased success rates to 90% [3,4]. Laparoscopic submucosal tunneling is technically difficult to perform and requires additional practice, although minimally invasive surgery has become the trend in recent decades [5]. The feasibility of laparoscopic UNC with submucosal tunneling technique has been demonstrated in pediatric VUR surgery, but the operative time is longer (>120 min) than for the open method and complications such as mucosal punctures during surgery have been reported [6–8]. Mitterdorfer et al. (1981) reported a simple intravesical UNC, a no-tunnel "drop-in" technique for renal transplantation, in which at least 1 cm of ureteral end was implanted into the bladder and sutured intravesically. Only 7.4% (6/81) of patients had VUR; 10.4% had postoperative complications such as urinary fistula (21/81) and ureteral obstruction (14/81) [9]. Based on this study, we propose an easier method that may involve fewer complications: laparoscopic modified simple UNC. Here we present the case series of laparoscopic modified simple UNC in lower third ureter injuries.

Case series presentation

Eleven cases of iatrogenic ureter injuries were identified, as shown in Table 1.

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Table 1
Characteristic and outcomes of iatrogenic ureter injury cases.

Age	Surgery	Indication	Injury	Time of recognition	Outcome	Reflux
60 y/o	LAVH + BSO	Anterior low seg myoma 7*7*5 cm	Lt	Post OP D2	No hydro IVU (−)	No
35 y/o	LAVH + DIE excision	Adenomyosis, DIE, E2a, E3b(L), E2c	Lt	Post OP D11	No hydro IVU (−)	No
43 y/o	LAVH + DIE excision	Adenomyosis, DIE, E2b (L + R)	Lt	Post OP D15	No hydro	nil
50 y/o	LAVH + bladder DIE excision	Low seg myoma 7.7 x 5.5 cm	Rt	Post OP D3	No hydro IVU (−)	No
63 y/o	Radical (Rt) Parametrectomy + BPLND + PALND	SCC of cervical Ca, rpT2N0 s/p TAH + BSO (Ib)	Rt	During OP	No hydro	nil -
48 y/o	LSC RAH + BPLND + PALND	Cervical SCC, pT1a2N0 (AJCC 8)	Rt	During OP	No hydro IVU (−)	nil
45 y/o	LAVH	Myoma, fundus 10 × 7cm	Rt	Post OP D7	No hydro IVU (−)	nil
42 y/o	LAVH	Low seg myoma 6 × 6cm near Rt ureter	Rt	Post OP 2 months (PCN)	No hydro	nil
40 y/o	LAVH	Adenomyosis, 6 cm	Rt	Post OP D5	No hydro IVU (−)	nil
41 y/o	LAVH + LSO	Adenomyosis + Bil endometrioma	Rt	Post OP D3	No hydro IVU (−)	No
55 y/o	APR with mesh and cervical amputation	Stage IV complete uterine prolapse	Rt	Post OP D8	No hydro IVU (−)	No

Rt: right, Lt: left, Hydro: hydronephrosis, confirmed by echo; IVU (−): intravenous urogram; Reflux was confirmed by Voiding Cystourethrography (VCUG), nil: not performed.
Abbreviations: LAVH: laparoscopic assisted vaginal hysterectomy; BSO: bilateral salpingo-ophorectomy; OP: operation; D: day; RAH: radical hysterectomy; BPLND: bilateral pelvic lymph node dissection; PALND: para-aortic lymph node dissection; DIE: deep infiltrating endometriosis; APR: anterior and posterior vaginal repair.

Patients were followed postoperatively for at least 3 months (median: 18 months, range 3–96 months). All patients had a good recovery after undergoing ureteral repair. The median and mean operation times were 120 and 118 ± 42 min, respectively. According to the collected data, no urine retention, severe hydronephrosis, or persistent kidney injury was observed in the patients after the repair. There were no instances of recurrent ureter obstruction, stenosis, stricture, or bladder leakage after the repair. The majority of injuries were detected within two weeks post-surgery. One patient experienced acute pyelonephritis due to delayed identification of ureter injury. An emergent percutaneous nephrostomy was performed as a management measure. The patient underwent ureter repair two months later. Follow-up for two years indicated grade 1 hydronephrosis.

Surgical procedure

The ureteral injuries were diagnosed and treated laparoscopically by a gynecology surgeon with the assistance of an urologist using operative cystoscopy. First, the injured ureter was dissected from the retroperitoneum to the common iliac levels to ensure sufficient ureteral length without tension. During dissection, the surgeon took care to avoid interrupting the vascular supply to the ureter, to prevent poor healing or tissue necrosis. Prior to implantation, the surgeon identified clear urine from the orifice of the ureteral end and made a “fish-mouth” incision. Next, the apex of the bladder was identified by cystoscopy with air bubbles as the site of implantation, and the wall of the bladder cut open with scissors from the abdomen (Fig. 1). Prior to implantation, we confirmed the

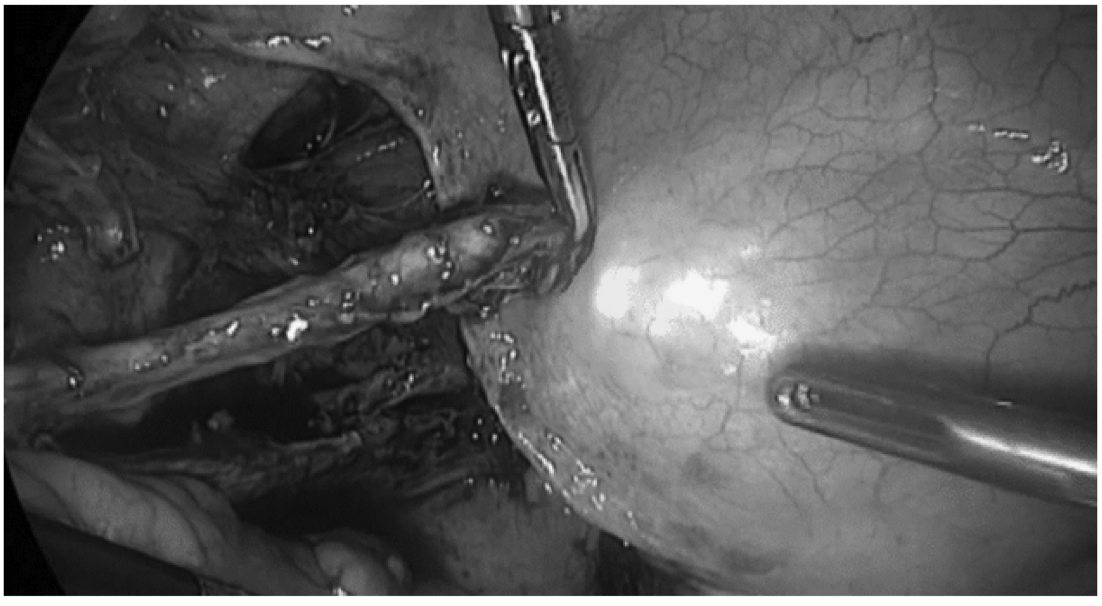

Fig. 1. Cystoscopy was used to achieve adequate length and find the apex of the bladder.

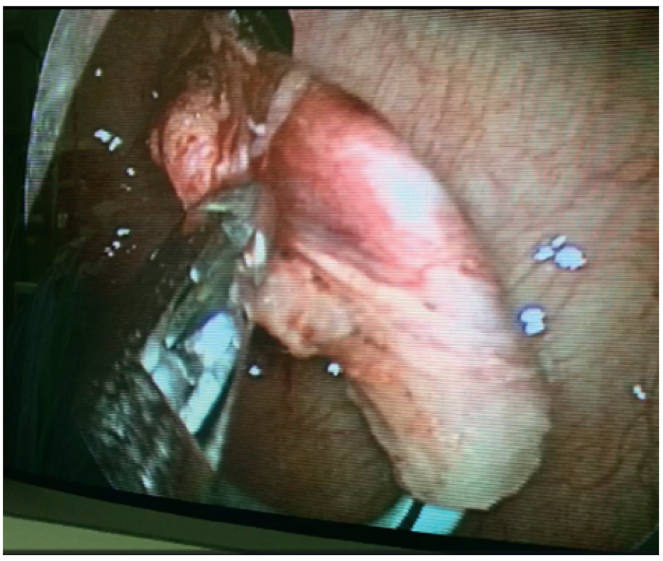

Fig. 2. An additional 1 cm at the ureter end with "fish mouth" opening was grasped from the bladder.

absence of any fluid leakage from the bladder. Any leakage from the bladder end of the injured ureter was treated by electrocoagulation. Using laparoscopy and cystoscopy, a ureteral stent was placed and the ureteral end inserted into the bladder. To prevent reflux, an additional centimeter of the end of the ureter was grasped inside the bladder by means of operative cystoscopy (Fig.2). Next, 3–5 stitches of 3–0 Vicryl were sutured around the ureter without penetrating the bladder or ureteral mucosa (Fig. 3). Finally, the bladder was tested with a minimum of 200 ml of water to confirm that there was no leakage from the suture site. To monitor possible postoperative leakage, Jackson–Pratt drains were placed; these were subsequently removed before discharge from the hospital. The ureteral stent was removed 3–6 months post-surgery. Following the operation, a urinary catheter was inserted for at least 8 days for healing purposes. During follow up, the patient underwent intravenous urography, renal sonography, and voiding cystography. All instances of hydronephrosis, urinary leakage, and VUR were documented in the medical records.

Discussion

No severe complications, such as VUR, severe hydronephrosis, or fistula were observed following surgery. Our modified technique differs from the simple no-tunnel "drop-in" technique, first, in that the ureteric end has a fish-mouth opening, which can prevent ureteric stricture or stenosis during the healing process. Second, the highest point of the bladder was found in the supine position, which can act as a natural valve against VUR. Third, extravesical suturing involving only the muscular layer of the bladder can prevent the formation of a fistula. As a result, perforation of the bladder can be avoided by not performing submucosal tunneling. This procedure is easier than extravesical Politano-Leadbetter or Lich-Gregoir. We adhere to the requirements of ureter repair mentioned by Png and Chapple (2000), which ensure good vascular supply and drainage of the ureter, complete excision of pathological lesions, and maintenance of a tension-free anastomosis. These factors are also attributes of our success [10]. Stepniewska et al. (2011) reported that, even with laparoscopic UNC with submucosal tunneling (Lich-Gregoir methods), 3 out of 20 patients still had VUR detected after 6 months [11]. Therefore, there is still room for improvement in VUR prevention. A modified simple UNC has the potential to demonstrate non-inferior or superior results. We consider the Psoas hitch or Boari flap technique as an alternative when the ureter is too short to reimplant into the bladder [12].

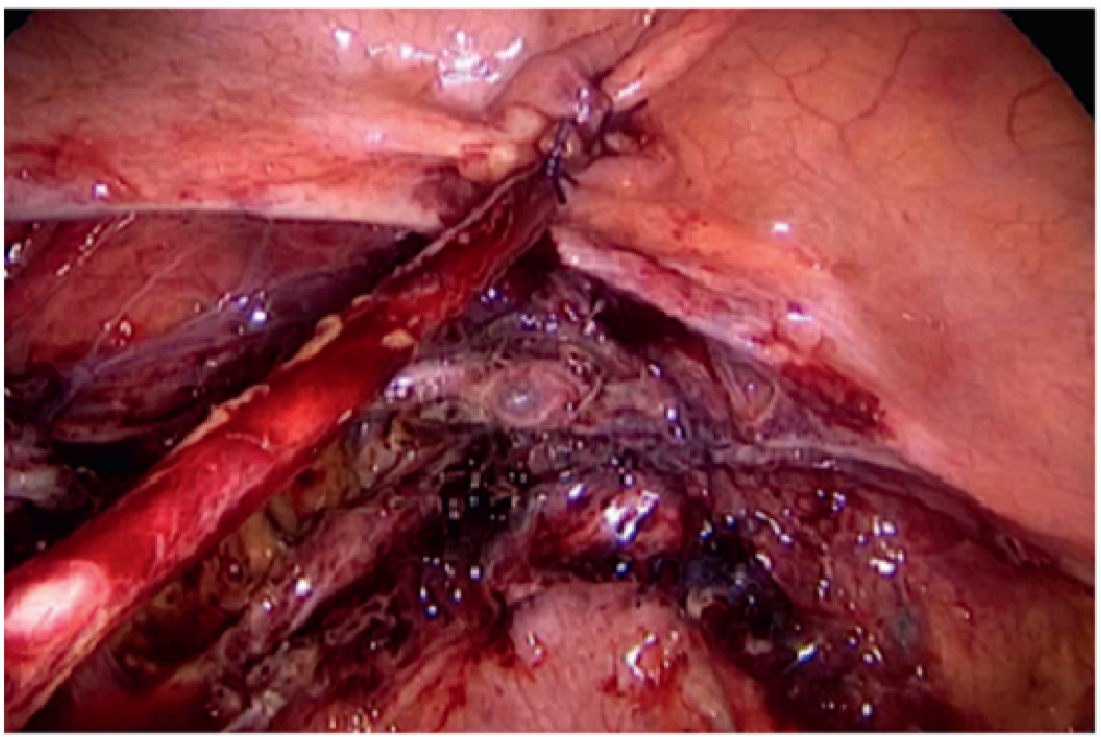

Fig. 3. Finally, 3–5 stiches using 3-0 Vicryl were sutured around the ureter without entering the bladder.

Following the anatomical route, the ureter crosses the ovarian vessel anteriorly; the right ureter then enters the pelvis, crossing the external iliac artery, while the left ureter crosses the common iliac artery. The ureters then descend medially towards the cardinal ligament and pass under the uterine artery (sometimes referred to as "water under the bridge") approximately 1.5–2 cm lateral to the cervix before entering the trigone of the bladder [13,14]. Of the cases observed, eight had ureteral injury during laparoscopically assisted vaginal hysterectomy, three had low-segment myoma, and three had deep infiltrating endometriosis (DIE). The location of the lower third of the ureter in close proximity to the uterus, as well as a protruding fibroid or a fatty low-segment uterus, make it particularly vulnerable to injury during gynecologic surgery. In the case of severe DIE, all three patients showed endometriotic lesions 1–3 cm thick near the uterosacral ligament; in some cases, the lesions involved the cardinal ligament and were observed near the uterine artery. These deep infiltrating endometriotic lesions cause thick and severe fibrosis that adheres to the periureteral area after inflammation [15]. The lysis of deep infiltrating endometriotic lesions can lead to either ureteral tearing or delayed rupture caused by tissue necrosis when an electrocoagulator is employed. Two patients diagnosed with cervical cancer underwent radical hysterectomy, which is a high-risk factor for ureter injury due to wide parametrectomy. To reduce the risk of injury, it is important to perform ureterolysis during surgery or place a ureter stent prior to surgery.

Early recognition and treatment of ureteral injuries are important to prevent morbidity. Laparoscopic modified simple UNC is a feasible means of repair of lower third ureteral injuries.

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2. Taipei International Convention Center
(c) 1.2020/08/01–2020/08/02 (oral presentation)
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Case Report

Urethral diverticulum in pregnancy: Rare case report and brief literature review

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ABSTRACT

Objective: Female urethral diverticulum (UD), an evagination of the urethral mucosa into the surrounding connective tissue, is extremely rare in pregnancy. No clear guidelines on the optimal management of UD have been established, except for a common conservative approach. Here, we discuss how to manage UD with pregnancy.
Case report: A 39-year-old gravida 4, para 0, abortion 3 (G4P0A3) woman at 34^{+0} gestational weeks (GW) visited our outpatient department with a 6-cm septate vaginal mass. Transvaginal ultrasound sonography (TVUS) revealed a 5.5 x 4.9-cm multicystic mass, which was confirmed as UD with pelvic MRI. She was admitted because of preterm labor. A cesarean section was performed at 36^{+5} GW due to a previous myomectomy, and a healthy male baby was born. UD was still observed in the patient two months after delivery. Periurethral diverticulectomy was performed, and pathological analysis revealed UD with chronic inflammation and edema.
Conclusion: Previous reports and our case report show that UD can develop during pregnancy and that pelvic MRI is suitable for its accurate diagnosis. Vaginal delivery is possible in pregnant women with the small size of the UD. UD aspiration can permit vaginal delivery in a few cases; however, pus can occur at the aspirated site after the operation. If UD is still observed after delivery, urethral diverticulectomy is recommended.

Introduction

Urethral diverticulum (UD) is an outpouching of the urethral mucosa into the periurethral tissue [1]. The exact etiology of acquired diverticula remains unknown; however, it is thought to originate from repeated urinary tract infections and subsequent obstruction of the periurethral glands [2]. As the periurethral glands predominate in the distal two-thirds of the urethra, most UDs occur in the distal or middle third of the urethral floor. UD has a variable appearance in terms of size, shape, and location [3]. UD can also be single or multiple and uni- or multiloculated [4].

UD is often difficult to diagnose. The classic triad of dyspareunia, dysuria, and urinary incontinence is regarded as a symptom of UD [3]. Most patients with UD have vague urinary symptoms or pelvic pain and are often refractory to treatment. Additional symptoms include urethral discharge and urinary dribbles. Differential diagnoses include Gartner's duct cyst, vaginal wall inclusion cyst, ectopic ureterocele, Skene's gland abscess, and urethral carcinoma or adenoma [5]. Complications of UD include stone formation, recurrent urinary tract infections, and, rarely, malignancy [6]. Preexisting UD can enlarge during pregnancy, causing pelvic dystocia, especially if it is associated with acute urinary retention [3]. However, there are no clear guidelines on the management of delivery in patients with UD or how to treat the disease during or after childbirth. Here, we report a rare case of UD during pregnancy along with a literature review.

Case report

A 39-year-old gravida 4, para 0, abortion 3 (G4P0A3) woman at 34^{+0} GW visited our hospital with a 6-cm multi-septate cystic mass in the vagina. She had previously undergone myomectomy and,

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subsequently, *in vitro* fertilization and embryonic transfer at a local clinic. She was being treated with a vaginal progesterone tablet (Utrogestan, a 100-mg tablet) to prevent preterm labor and the shortening of cervical length. She had also been diagnosed with gestational hypertension before two days. Her blood pressure on the day of the visit was 154/80 mmHg. She was prescribed a calcium channel blocker (Adalat, a 30-mg tablet) once daily until delivery to maintain her blood pressure.

She was experiencing discomfort due to a mass effect in vagina. Other symptoms, such as dyspareunia, frequency, or urgency, were not observed except a urinary dribbling. A blood test suggested microscopic hematuria: the C-reactive protein (CRP) level was 0.10 mg/dL and the white blood cell count was 7030 cells/mL. Transvaginal ultrasound sonography (TVUS) showed a 5.5 x 4.9-cm multicystic mass (Fig. 1a). Pelvic MRI confirmed the diagnosis of UD (Fig. 1b and c). After the observation of irregular uterine contractions through an NST monitor and a 15-mm T-shaped cervical length, she was admitted and treated with Ritodrine (Lavopa, a tocolytic agent), due to the risk of preterm labor. She was discharged four days later with no signs of preterm labor or further shortening of her cervical length.

We consulted with the urology department to determine if the optimal management of the UD should be during or after delivery. In urodynamic study, she has terminal urinary dribbling, which refers to the involuntary loss of urine immediately after urination. UD can rarely disappear spontaneously when the diverticulum ruptures and heals without a surgical procedure. Therefore, we planned to delay the surgical procedure until after delivery. Since the patient had preterm labor two weeks after discharge and a history of previous myomectomy, a cesarean section was performed at 36^{+5} GW, wherein a healthy male baby weighing 2890 g was born (APGAR scores of 10 and 10 after one and 5 min, respectively).

No abnormalities were observed in the uterus, tubes, ovary, appendix, or placenta during the surgery. The patient was discharged four days later without any postoperative complications. Her blood pressure was normal (124/73 mmHg), and therefore, all medications were discontinued.

UD was still observed two months after delivery with same symptoms; therefore, urethral diverticulectomy was performed four months after cesarean section by a urologist. A bulging mass was observed in the anterior vaginal wall. Urethroscopy revealed a urethral orifice skewed in the 7 o'clock direction toward the distal urethra. A Foley catheter was inserted, followed by an inverted U-shaped incision to dissect the surrounding tissue. Pathological analysis revealed chronic inflammation and edema in the dissected tissues. The patient was discharged from the hospital a week later with no signs of complications such as postoperative bleeding or infections. TVUS performed at the outpatient visit did not reveal UD recurrence (Fig. 1d).

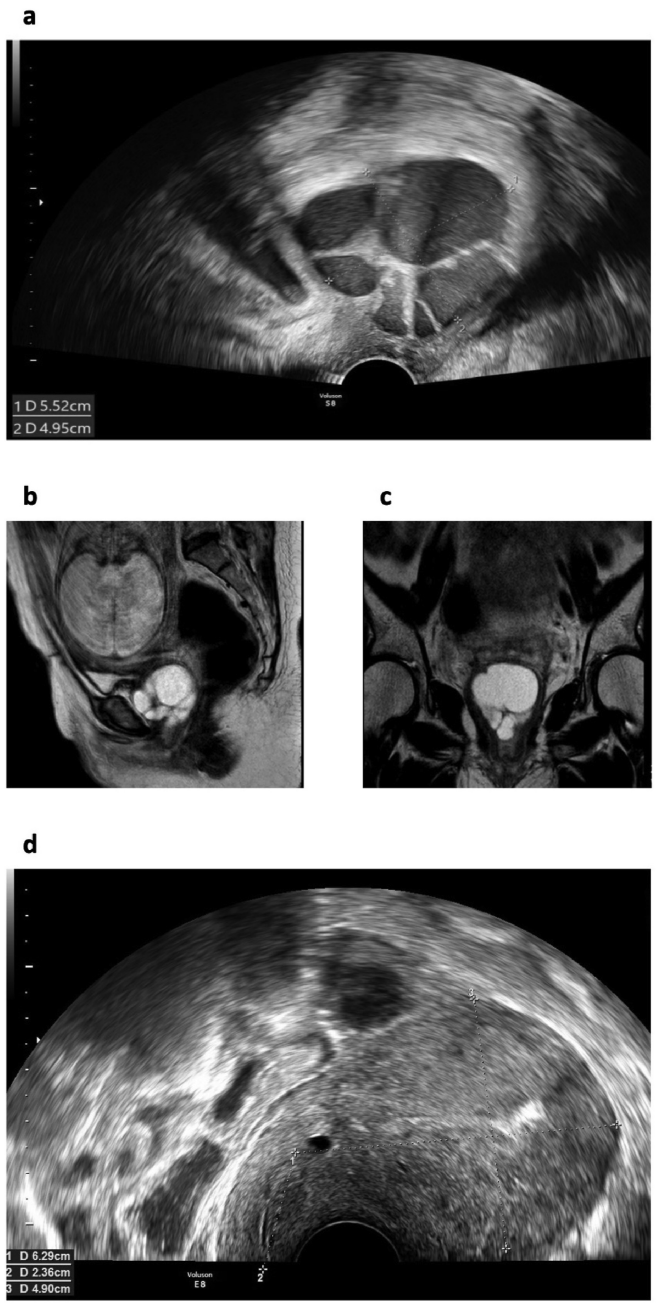

Fig. 1. Imaging presentation for urethral diverticulum in pregnancy.
a. Initial TVUS showing multiple cystic masses measuring 5.5 × 4.9 cm in size.
b and **c**. Sagittal (*B*) and coronal (*C*) images of pelvic MRI. This was performed for accurate diagnosis. The lesion was diagnosed as urethral diverticulum by MRI.
d. Post urethral diverticulectomy TVUS showing no recurrence of the lesion. The ultrasound was performed at the outpatient department of obstetrics and gynecology.

Conclusion

UD in pregnancy is rare and requires appropriate differential diagnosis and treatment; however, guidelines have not been clearly established. Advances in imaging technology have led to improvements in the diagnostic methods for UD and continue to supersede conventional modalities such as double-balloon cystoscopy and voiding cystourethrography [7]. For example, a pelvic MRI can provide the accurate information required for surgery, such as the size, configuration, and location of the ostium. In addition, an ultrasound technique such as TVUS can help to avoid possible fetal damage.

To comprehensively understand the current trends in the diagnosis and treatment of UD, we carefully reviewed previously published cases or articles. We first searched PubMed using the following Medical Subject Headings (MeSH) terms: “urethral diverticulum” AND “pregnancy” OR “women”; thereby, we identified seven articles with ten pregnant patients with UD that were published between 1997 and 2022 (Table 1).

The gestational weeks at which patients were diagnosed with UD varied from 6 to 38^{+4} GW. Various symptoms related to UD during pregnancy were described, including painless vaginal masses, suprapubic pain, incontinence, hematuria, urinary frequency, and dysuria. Diverticulectomy after delivery was performed in most patients, except in two: one that underwent

Table 1
Literature review of urethral diverticulum in pregnancy.

Authors	Symptoms	Diameter	Diagnostic modality (GW)	Treatment	Delivery method (GW)	Treatment after delivery
Iyer, et al. [2]	Painless vaginal mass	3~4 cm	TVUS (30^{+2})	Diverticulectomy under SA (31^{+2})	C/S for prevent fistula (39)	No recurrence
Moran, et al. [4]	Urethral pain	1. 2 cm	TVUS (2nd trimester)	Antibiotics	VD (NA)	Diverticulectomy
	None	1. NA 2. 3 cm	1. NA (30) 2. NA	1. Conservative Tx 2. Aspiration	1. C/S (38) 2. Repeated C/S (NA)	Diverticulectomy
	Hematuria	6 cm	TVUS (30)	Conservative Tx Aspiration during delivery	VD (NA)	Diverticulectomy
	Urinary frequency Dysuria	4 cm	Cystourethroscopy (6)	Antibiotics I&D Aspiration	C/S (37)	I&D
Artis, et al. [5]	1. None 2. Urinary incontinence, pain, renal stone 3. Pain, renal stone	1. 1 cm 2. ~2 cm 3. 1 cm	1. TVUS (33) 2. TVUS (26) 3. TVUS (NA)	1. Conservative Tx 2. Lithotripsy, ureteric stents, needle aspiration 3. Conservative Tx	1. VD (NA) 2. VD (NA) 3. VD (NA)	1. None 2. None 3. Diverticulectomy
Wittich AC [8]	Tender mass Dyspareunia	NA	Pelvic examination (19)	Excision of calculi	NA	No recurrence
Carswell FM [9].	Severe suprapubic pain	2 cm	MRI (11)	Cystoscopic drainage	VD (37)	Diverticulectomy
Xie, et al. [10]	Painless vaginal mass	2 cm	Aspiration (14)	Aspiration Antibiotics	Labor → C/S (NA)	Diverticulectomy
Magann, et al. [11]	None	~5 cm	TVUS (38^{+4})	Conservative Tx	C/S (39)	Reconstructive surgery

GW, gestational week; UD, Urethral diverticulum; C/S, Cesarean section; VD, vaginal delivery; TVUS, transvaginal ultrasound; I&D, incision and drainage; Tx, Treatment; SA, Spinal Anesthesia; NA, Not assigned; MRI, magnetic resonance imaging.

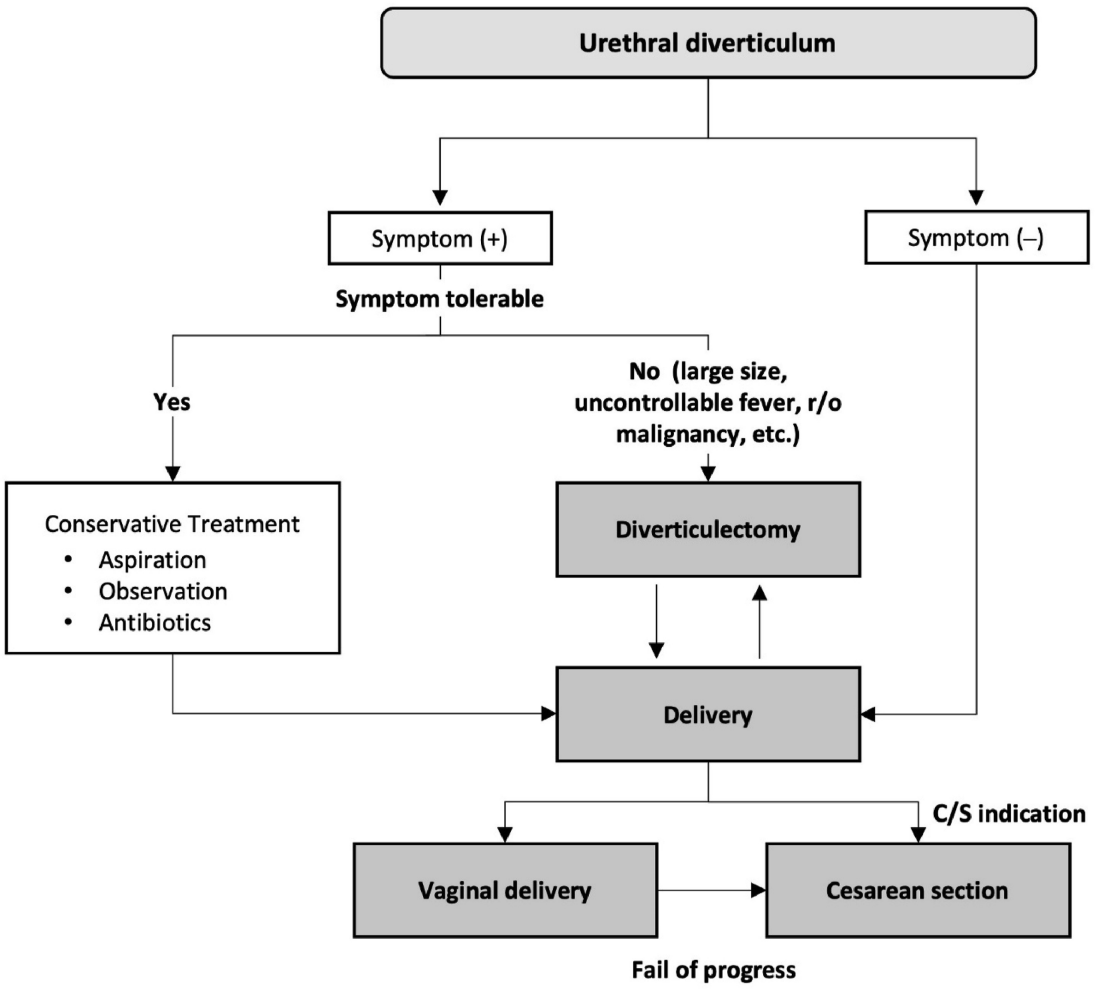

Fig. 2. Workflow for the treatment of urethral diverticulum in pregnancy.

diverticulectomy at 31^{+2} GW [2] and the other that underwent excision of calculi near 19 GW [8]. The former reported postoperative complications such as incomplete excision, stress incontinence, urethral stenosis, and urethrovaginal fistula; therefore, delivery was conducted by cesarean section to reduce complications [2]. The latter documented several symptoms, such as dyspareunia, vaginodynia, and urethral pressure [8]. Eight patients who underwent diverticulectomy after delivery were managed during pregnancy with conservative treatments, including aspiration (four patients), antibiotics (three patients), and/or cystoscopic drainage (one patient).

Four out of ten patients underwent childbirth through vaginal delivery (Table 1), among whom one patient was warned of complications such as recurrent urinary tract infection and the possibility of obstruction in the second stage of labor during vaginal delivery due to the large diverticulum [9]. One patient with UD gave birth by cesarean section due to failure in the progress of vaginal delivery because the inflammation caused by the aspiration of a distal periurethral diverticulum in the surrounding soft tissues might have obstructed the passage of labor [10]. Taken together with the aforementioned cases, including our case, surgical operations such as aspiration, marsupialization, and diverticulectomy are not recommended during pregnancy if vaginal delivery is considered [2,10]. Four patients except the one above underwent cesarean sections due to several reasons like repeated cesarean sections [4], diverticulectomy during pregnancy [2], breech presentation and fetal growth retardation [4], or the risk of fetal shoulder dystocia in a diabetic mother [11].

There was a patient who developed UD in three independent pregnancies [5]. She gave birth via vaginal delivery in all pregnancies. She had an asymptomatic anterior vaginal mass (1×1 cm) at 33 GW during the first pregnancy; however, diverticulectomy was not performed. In the second pregnancy, she had a 1×1 cm mass within the anterior vagina and suffered from symptoms such as urinary incontinence, pain, and renal stones. Later, the mass increased in size to 3×3 cm at 39 GW, and needle aspiration was performed to discard the fluid within the mass for immediate symptomatic relief. In the third pregnancy, the mass was removed via diverticulectomy after vaginal delivery. This implies that multiparous patients with UD without diverticulectomy have a high risk of severe symptoms and recurrence during the next pregnancy.

Based on previous and our cases of UD with pregnancy, we propose the workflow for UD treatment (Fig. 2). Tolerable symptoms are managed with conservative methods using appropriate antibiotics. If recurrent UTI is still observed, cystoscopic aspiration is followed to drain pus from UD. Diverticulectomy before childbirth can be an alternative if the patient still suffers from UTI after the drainage [2]. However, considering the risk of operation during pregnancy like hemorrhage, hematoma, inflammation, a pus pocket in the vaginal wall, obstruction of labor passage, and a fistula, diverticulectomy after delivery is more recommended [2,4,10]. When UD is well controlled with antibiotic treatment and/or aspiration, vaginal delivery is considered in principle. However, if a few clinical situations like large-size urethral diverticulum, uncontrollable fever, or r/o malignancy are suspected, a cesarean section before diverticulectomy is recommended to avoid the higher risk of complications. In conclusion, we recommend urethral diverticulectomy after delivery as the optimal method to manage UD in pregnant women.

Statement of ethics

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Ulsan University Hospital (IRB No 2023-07-058). Written informed consent was exempted by IRB.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Research Letter

Detection of tetrasomy 9p by chromosome microarray analysis and determination of maternal origin of the aberrant chromosome by quantitative fluorescent polymerase chain reaction in a second-trimester fetus with multiple anomalies on fetal ultrasound

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Dear Editor,

A 29-year-old primigravid woman was found to have multiple congenital anomalies on fetal ultrasound at 17 weeks of gestation. Prenatal ultrasound showed thicken nuchal folds, enlarged cisterna magna, left hydronephrosis and oligohydramnios. The pregnancy was subsequently terminated, and a 160-g malformed fetus was delivered with craniofacial dysmorphism of low-set ears, micrognathia, hypertelorism, median facial cleft lip and cleft palate. No perinatal cytogenetic analysis of the fetal tissues was made but elective array comparative genomic hybridization (aCGH) analysis on the DNA extracted from placenta was requested by the parents. aCGH revealed the result of arr 9p24.3p13.1 (204,193–38,815,475) × 4.0 [GRCh37] with a 38.61-Mb quadriplicaiton of 9p24.3-p13.1 encompassing 161 OMIM genes (Fig. 1). The parental karyotypes were normal. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from parental bloods, umbilical cord and placenta showed a maternal origin of the extra aberrant chromosome isochromosome 9p [i(9p)] (Fig. 2).

With advent of molecular and conventional cytogenetic analysis, mosaic and non-mosaic tetrasomy 9p can be diagnosed perinatally [1–3]. The present case was associated with oligohydramnios, enlarged cisterna magna, hydronephrosis, nuchal edema, cleft lip and palate and facial dysmorphism. Chen et al. [2] reported that fetuses with tetrasomy 9p may present increased nuchal translucency in the first trimester and cystic hygroma in the second trimester as well as fetal ascites, hydrops fetalis, polyhydramnios, oligohydramnios, intrauterine growth restriction (IUGR), Dandy-Walker variant or malformation, ventriculomegaly, skeletal abnormalities, cleft lip and palate, hydronephrosis and congenital heart defects. In a review of 19 fetuses with tetrasomy 9p, Nakamura-Pereira et al. [4] summarized the common prenatal ultrasound findings of tetrasomy 9p as in the following: IUGR (58%), ventriculomegaly (58%), genitourinary anomaly (47%), hypoplastic/absent vermis (42%), cleft lip and palate (42%), limb malformations (42%), cardiac anomaly (26%) and polyhydramnios (21%).

The present case demonstrates the usefulness of the application of chromosome microarray analysis (CMA) in the detection of tetrasomy 9p and QF-PCR in the determination of maternal origin of the aberrant chromosome of i(9p). The information acquired by molecular genetic analysis is very useful for genetic counseling of the parents concerning the pathogenesis of multiple congenital

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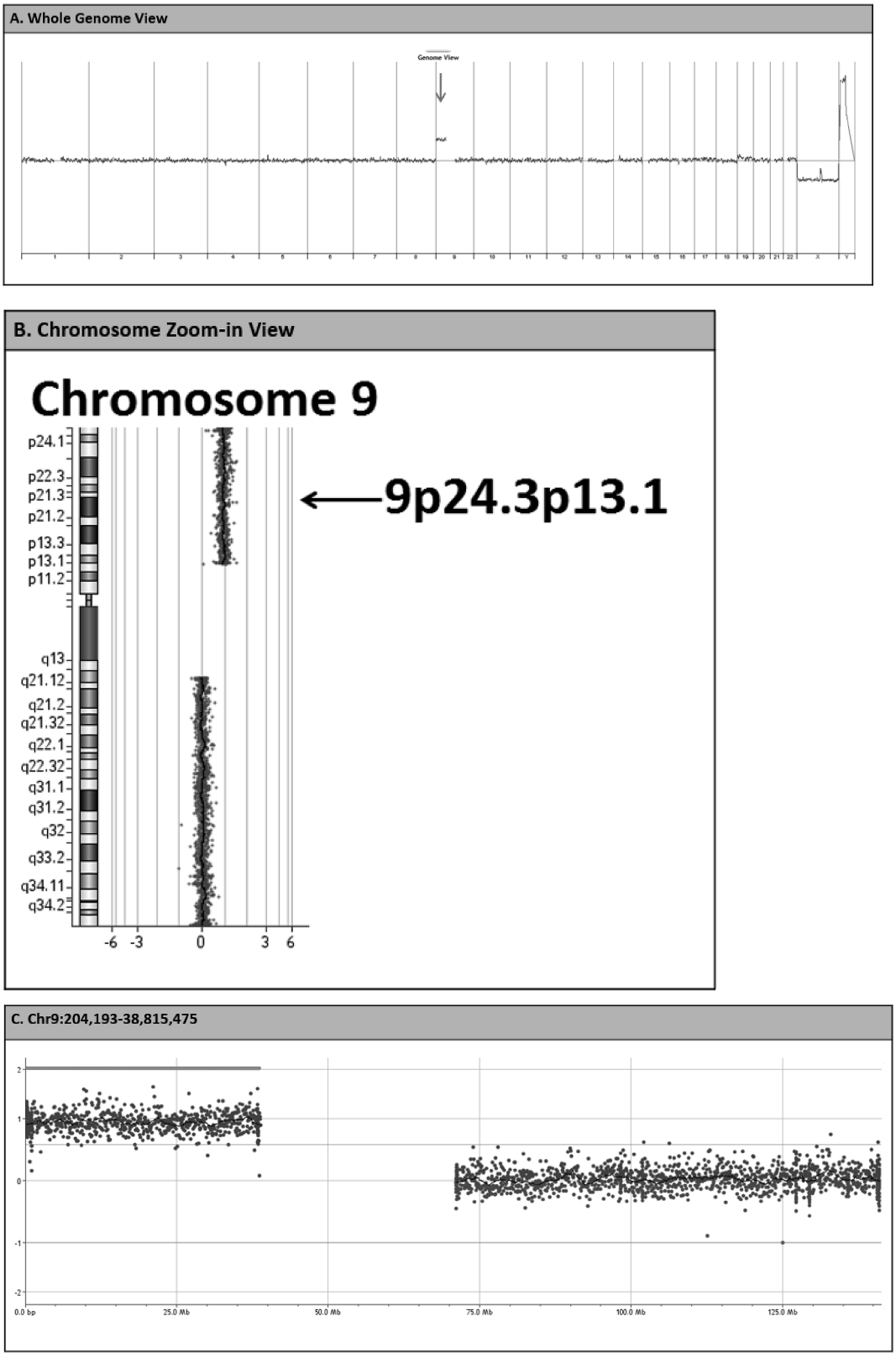

Fig. 1. (A), (B) and (C) Array comparative genomic hybridization on the DNA extracted from placenta using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K Array (Agilent Technologies, Santa Clara, CA, USA) shows the result of arr 9p24.3p23.1 (204,193–38,815,475) × 4.0 [GRCh37].

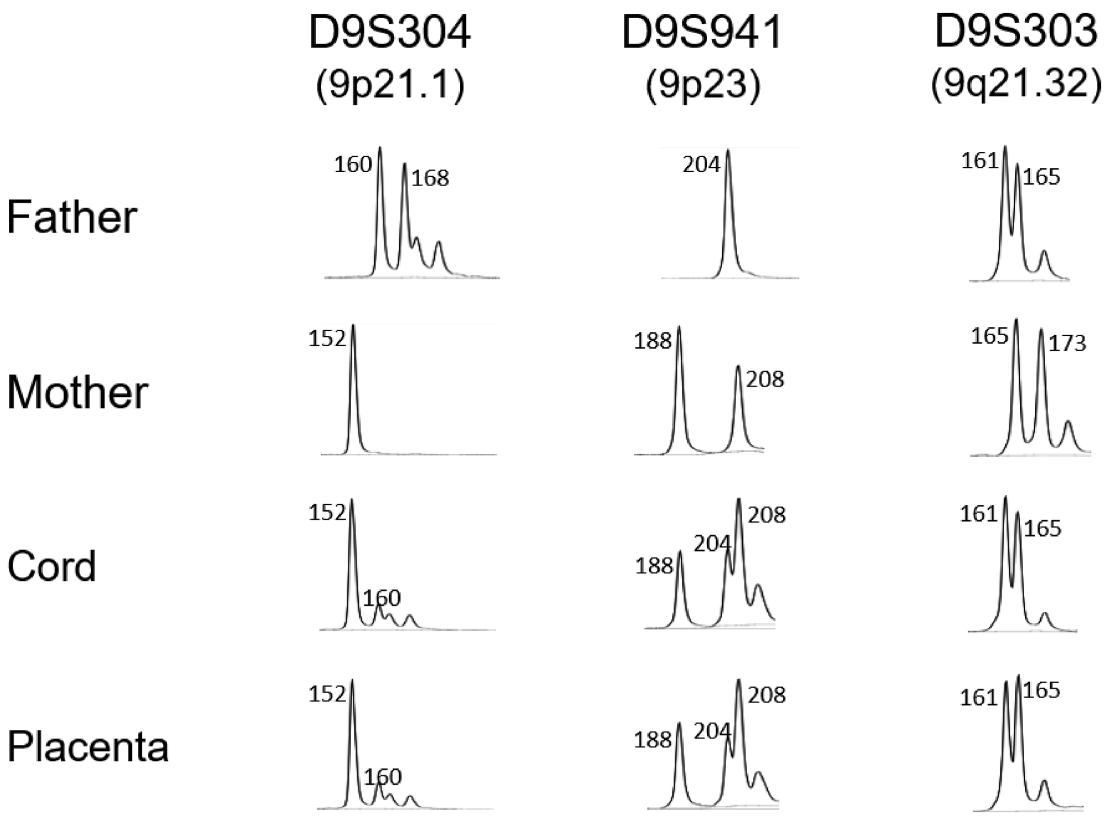

Fig. 2. Quantitative fluorescence polymerase chain reaction analysis of the DNA extracted from parental bloods, umbilical cord and placenta determines maternal origin of the extra i(9p). i = isochromosome.

anomalies in the fetus in case that there is no conventional cytogenetic analysis of the fetus.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Detection of non-mosaic balanced homologous acrocentric rearrangement rea(21q21q) in a young woman with a history of pregnancy loss and a previous pregnancy with positive non-invasive prenatal testing for Down syndrome and rea(21q21q) Down syndrome in the fetus

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Dear Editor,

A 28-year-old woman was referred for genetic counseling because of a history of pregnancy loss and a previous pregnancy with positive non-invasive prenatal testing (NIPT) for Down syndrome and a karyotype of 46,XX,+21,der(21; 21) (q10; q10) in the fetus. Two years previously, she experienced a pregnancy loss because of intrauterine fetal death (IUFD) in the first trimester. Two months previously, she underwent termination of a pregnancy in the second trimester because of an elective NIPT test positive for Down syndrome and a karyotype of 46,XX,+21,der(21; 21) (q10; q10) at amniocentesis. Cytogenetic analysis of the woman revealed a karyotype of 45,XX,der(21; 21) (q10; q10) (Fig. 1) and a karyotype of 46,XY in the husband.

Reports concerning rea(21q21q) such as prenatal diagnosis of rea(21q21q) Down syndrome and its recurrence in subsequent pregnancy [1], detection of mosaic balanced rea(21q21q) in a woman with repeated pregnancy losses [2] and detection of paternal origin of fetal *de novo* rea(21q; 21q) Down syndrome in a pregnancy of a young woman associated with an abnormal first-trimester maternal serum screening result [3] have been well described. Here, an additional case of detection of non-mosaic balanced homologous acrocentric rearrangement rea(21q21q) in a young woman with a history of pregnancy loss and a previous pregnancy with positive NIPT for Down syndrome and rea(21q21q) Down syndrome in the fetus is presented. Positive NIPT for trisomy 21 in a pregnancy with high-level mosaic trisomy 21 at amniocentesis has been previously reported in a young woman of 32 years old who had undergone *in vitro* fertilization [4]. The present case shows that women who have previous pregnancy loss will have the benefit of early diagnosis of rea(21q21q) Down syndrome in the fetus by NIPT. Chen et al. [1] found a frequency of 0.019% for rea(21q21q) Down syndrome at amniocentesis, and *de novo* rea(21q21q) can be associated with recurrence. More than 95% of rea(21q21q) Down syndrome cases arise *de novo* of which the maternally derived cases and paternally derived cases are equal, and most cases are isochromosome 21 [i(21q)] [5]. Kolgeci et al. [6] reported recurrent abortions and Down syndrome in a woman with non-mosaic balanced homologous acrocentric rearrangement rea(21q21q). The rate of recurrence of familial rea(21q21q) Down syndrome in pregnancies of couples in whom one of the partner is a carrier of balanced rea(21q21q) is almost 100% except that both the parents are balanced rea(21q21q) carriers [7]. However, Yan et al. [8] reported birth of a mosaic non–Down syndrome offspring with the karyotype of 46,XX,t(21; 21)[14]/46,XX[86] to a 45,XY,t(21; 21) (q10; q10) homologous Robertsonian translocation carrier father. In

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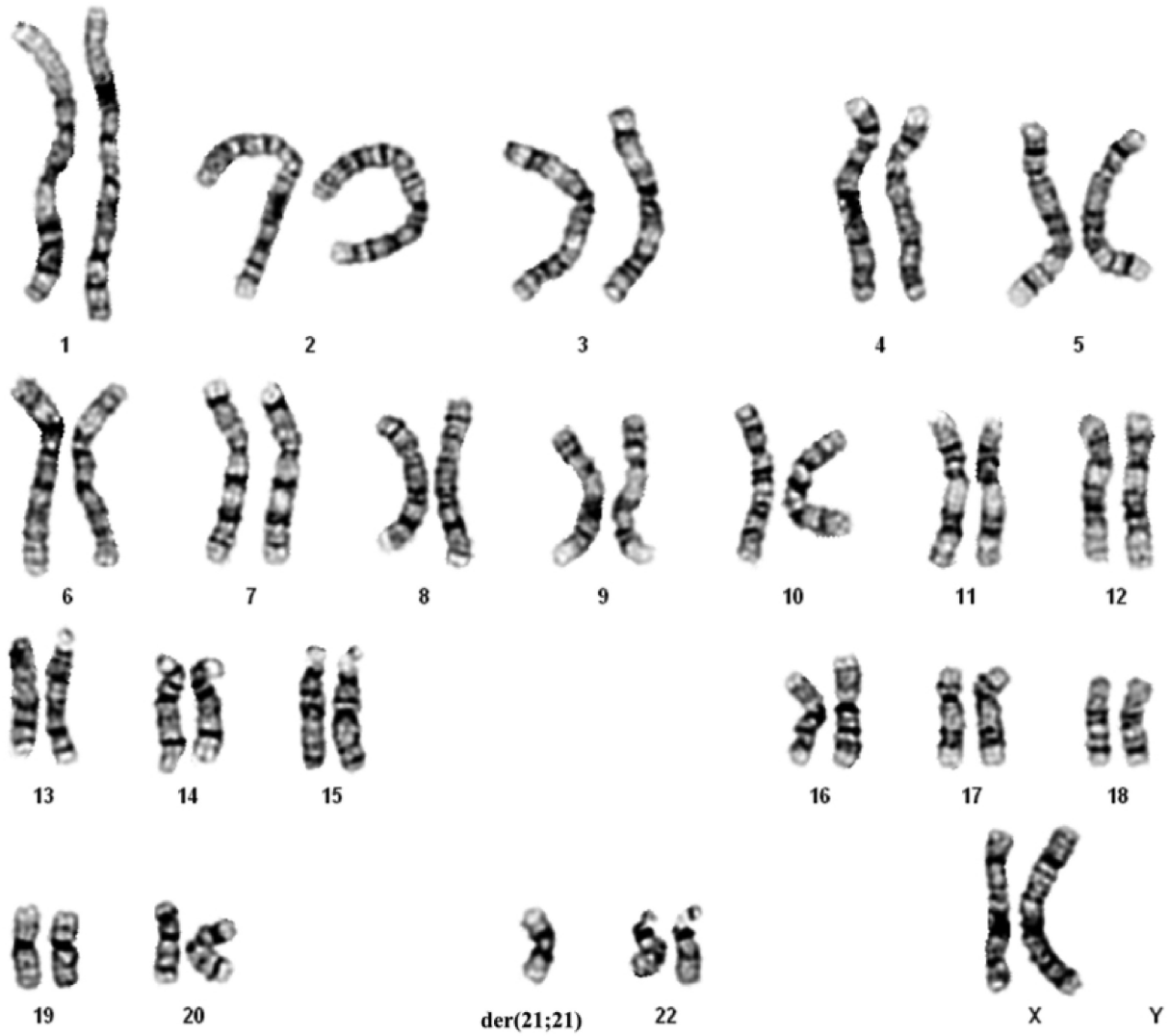

Fig. 1. A karyotype of 45,XX,der(21; 21) (q10; q10). der = derivative.

the present case, genetic counseling should include refraining from further pregnancies, and the use of normal donor ova under the circumstance of a female carrier of balanced rea(21q21q).

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Research Letter

Molecular cytogenetic analysis of mosaic 45,X/46,X,r(X) at amniocentesis in a fetus with hydrops fetalis

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Dear Editor,

A 34-year-old gravid 2, para 0, woman underwent chorionic villus sampling (CVS) at 13 weeks of gestation because of increased nuchal translucency (NT) thickness of 3.7 mm. CVS revealed a karyotype of 45,X[21]/46,X,add(X) (p22.3)[20]. Array comparative genomic hybridization (aCGH) analysis on chorionic villi revealed arr [GRCh 37] Xp22.33p21.1 × 1–2, Xp21.1q28 × 1–2. The pregnancy was conceived by *in vitro* fertilization and embryo transfer. The parental karyotypes were normal. Level II ultrasound showed hydrops fetalis, nuchal edema, hypoplastic left heart syndrome and pericardial effusion. Amniocentesis at 21 weeks of gestation revealed a karyotype of 45,X[20]/46,X,r(X) [1] (Figs. 1 and 2). aCGH analysis on the DNA extracted from uncultured amniocytes revealed the result of arr (1–22) × 2, X × 1.1–1.3,Y × 0, consistent with 70% mosaicism for a 57.862-Mb deletion of Xp (Xp22.33-p11.21) and 90% mosaicism for a 93.277-Mb deletion of Xq (Xq11.1-q28) (Fig. 3). The pregnancy was subsequently terminated, and a dead hydropic fetus was delivered.

Cases with 45,X/46,X,r(X) with phenotypic abnormalities have been well described [1–9]. In the present case, most of the cells were 45,X, only a very small portion of the cells was 46,X,r(X), and the r(X) contained Xp22.33-p11.21 and Xq11.1-q28. In the present case, the r(X) contains the *XIST* gene (OMIM 314670) which is located at Xq13.2. *XIST* gene is responsible for inactivation of X chromosome. In case of lacking the *XIST* locus, there will be severe phenotype of physical and mental defects due to a functional disomy caused by the ring X chromosome lacking the *XIST* locus [10–12]. The present case does not belong to the tiny ring X syndrome. However, the present case presented severe hydrops fetalis because of high-level mosaicism for 45,X.

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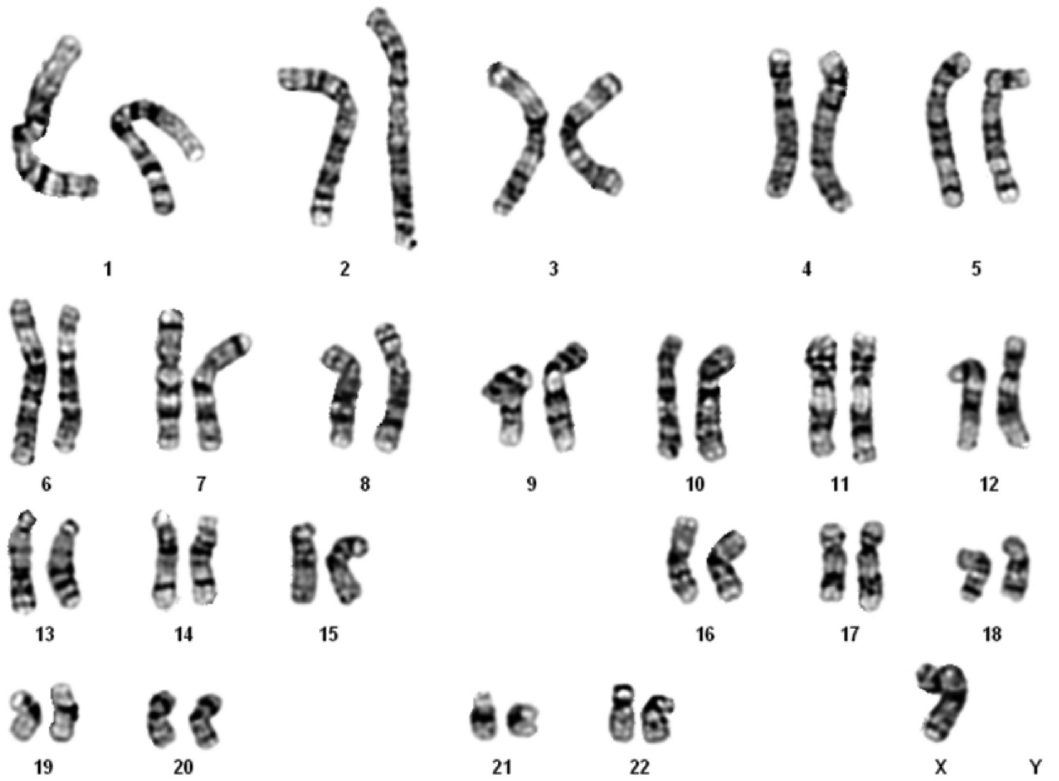

Fig. 1. A karyotype of 45,X.

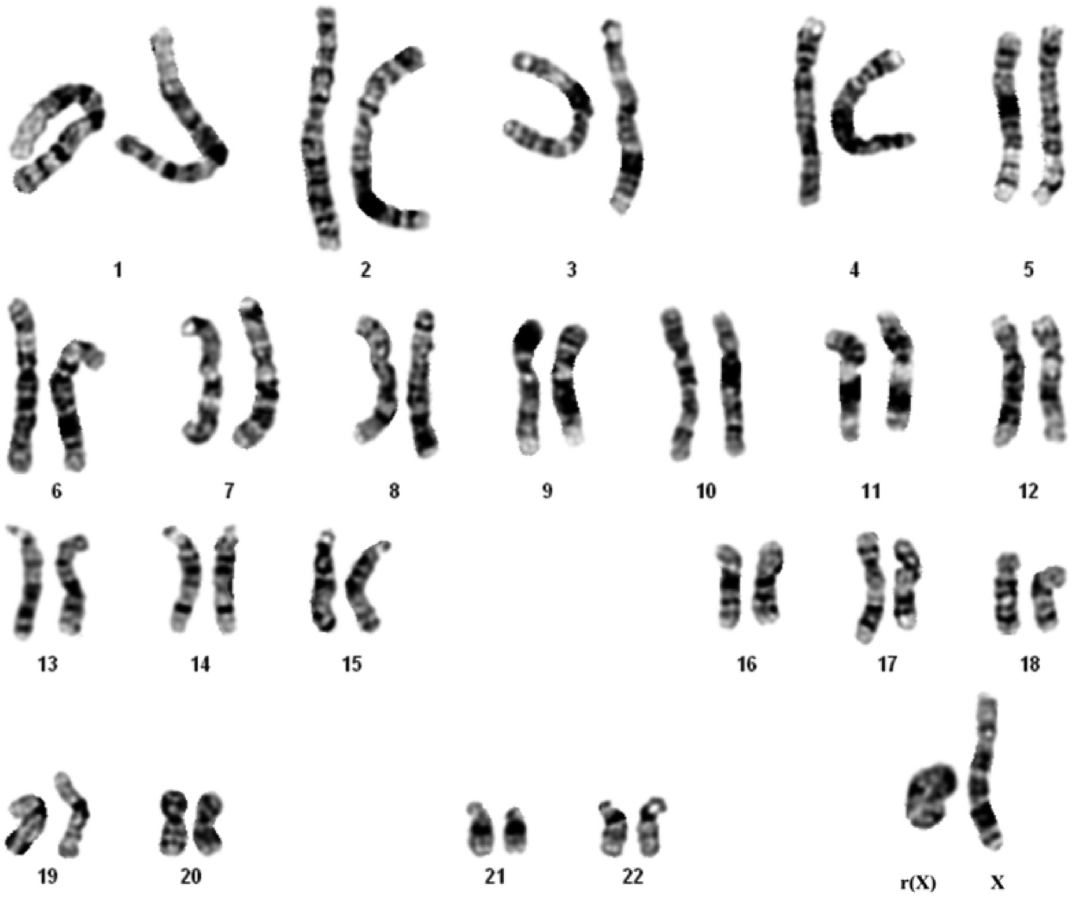

Fig. 2. A karyotype of 46,X,r(X). r = ring.

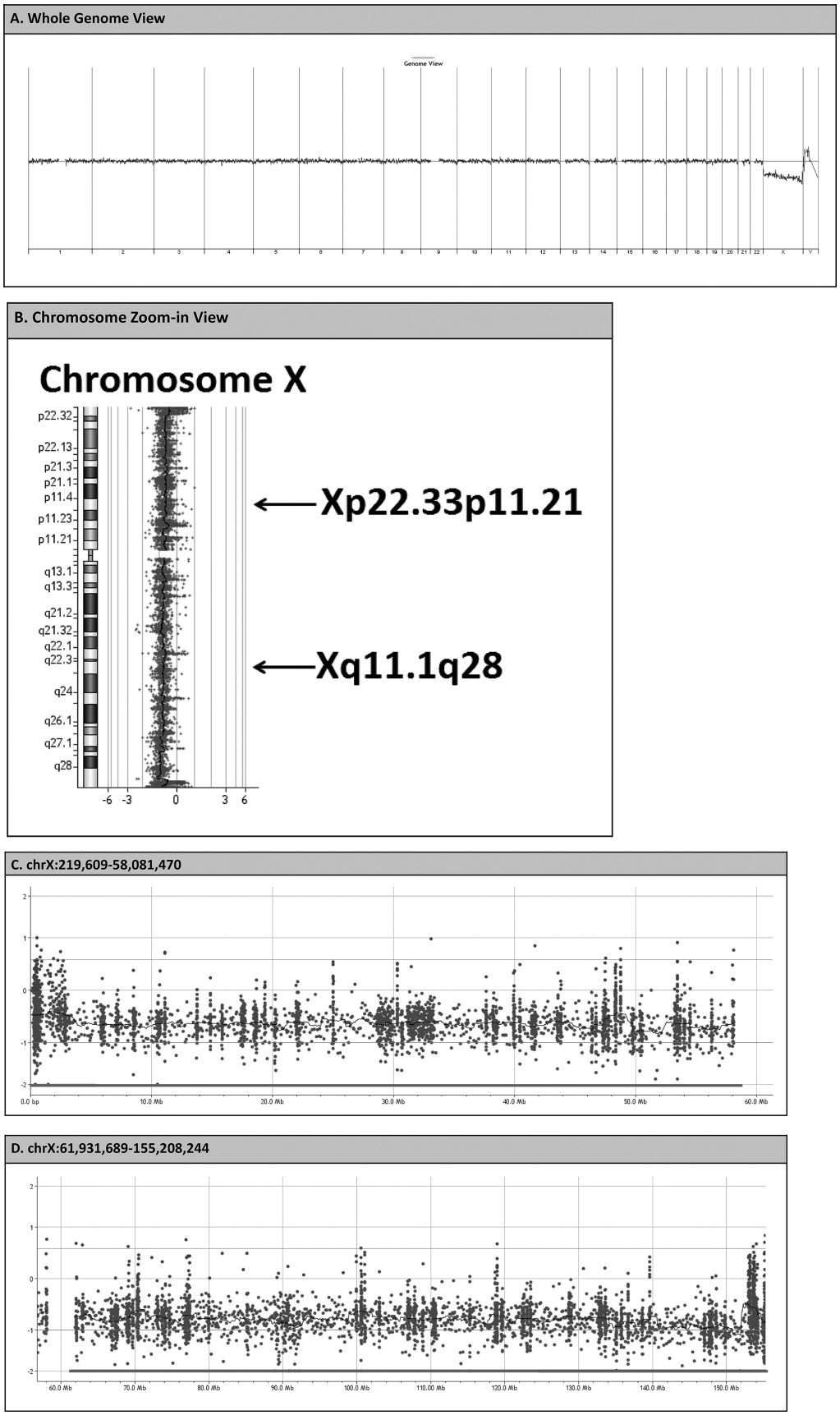

Fig. 3. (A), (B) and (C) Array comparative genomic hybridization (aCGH) analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from uncultured amniocytes shows the result of arr (1–22) × 2, X × 1.1–1.3,Y × 0, consistent with 70% mosaicism for a deletion of Xp (Xp22.33-p11.21) and 90% mosaicism for a deletion of Xq (Xq11.1-q28).

Declaration of competing interest

The author has no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Complete cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes is common in mosaic trisomy 20 at amniocentesis with positive conventional cytogenetic analysis and negative chromosomal microarray analysis

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Dear Editor,

A 36-year-old, gravida 4, para 1, woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+20 [4]/46,XY [7] (36.4% mosaicism for trisomy 20) in cultured amniocytes. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed no genomic imbalance. Prenatal ultrasound was unremarkable. She was referred for genetic counseling at 21 weeks of gestation, and non-invasive prenatal testing (NIPT) was negative for trisomy 20. A 3620-g healthy baby was delivered at 38 weeks of gestation without any phenotypic abnormality. At the age of 1½ years, the neonate was normal in phenotype and development. His peripheral blood had a karyotype of 46,XY. The parental karyotypes were normal.

The present case and the seven consecutive cases of mosaic trisomy 20 at prenatal diagnosis reported by Chen et al. [1–7] provide evidence that complete cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes is common in mosaic trisomy 20 at amniocentesis, with mosaic trisomy 20 by conventional cytogenetic analysis and no genomic imbalance by chromosomal microarray analysis (CMA). The present case also had negative NIPT for trisomy 20 which has been observed in the previous report [4]. These reported cases had normal karyotype in the neonates after birth, and no uniparental disomy (UPD) 20 could be found. Jin et al. [8] reported the discrepancy finding in a case of mosaic trisomy 20 at amniocentesis with trisomy 20 in the cultured amniocytes and normal CMA in the uncultured amniocytes. This indicates that mosaic trisomy 20 at amniocentesis in case of complete cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, with positive conventional cytogenetic analysis and negative CMA, is likely caused by laboratory amniocyte culture procedures. We suggest that it is a benign condition and can be associated with a favorable fetal outcome.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Research Letter

Application of quantitative fluorescent polymerase chain reaction on the DNA extracted from cultured amniocytes for rapid exclusion of uniparental disomy 20 in case of mosaic trisomy 20 at amniocentesis

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Dear Editor,

A 36-year-old, gravida 2, para 1, woman underwent amniocentesis at 16 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 47,XY,+20 [2]/46,XY[44]. Prenatal ultrasound was unremarkable. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis applied on the DNAs extracted from parental bloods and cultured amniocytes using the informative markers of D20S482 and D20S438 showed biparental inheritance and thus excluded uniparental disomy (UPD) 20 (Fig. 1). At 39 weeks of gestation, a 2760-g phenotypically normal baby was delivered. Cytogenetic analysis of the cultured tissue cells from cord blood, umbilical cord and placenta revealed the karyotype of 46,XY in all sampling tissues.

Prenatal diagnosis of mosaic trisomy 20 by amniocentesis should include a differential diagnosis of UPD 20. Maternal UPD 20 is associated with Mulchandani-Bhoj-Conlin syndrome (OMIM 617352) which is characterized by perinatal growth restriction, severe short stature, prominent feeding difficulty failure to thrive and the Silver-Russell syndrome-like phenotype [1]. Paternal UPD 20 is associated with autosomal dominant pseudohypoparathyroidism type 1 B (PHP1B; OMIM 603233) which is characterized by hypocalcemia, hyperphosphatemia, osteitis fibrosa cystica with resistance to parathyroid hormone and abnormally high levels of parathyroid hormone [1].

Maternal UPD 20 has been reported in cases of mosaic trisomy 20 at amniocentesis. Velissariou et al. [2], first reported maternal uniparental isodisomy 20 in a fetus with trisomy 20 mosaicism. In their case, trisomy 20 mosaicism was originally detected in amniotic fluid (98%) and was confirmed in the term placenta (100%), neonate's blood (10%) and urine sediment (100%). There were intrauterine and postnatal growth retardation. At the age of nine months, the child manifested moderate psychomotor retardation, central hypotonia, peripheral hypertonia, marked kyphosis, extensive Mongolian spots and numerous minor morphogenetic variants. The diploid blood cells had maternal UPD 20. Qin et al. [3] reported the result of maternal UPD 20 in uncultured amniocytes and 47,XY,+20[45]/46,XY[5] at amniocentesis at 20 weeks of

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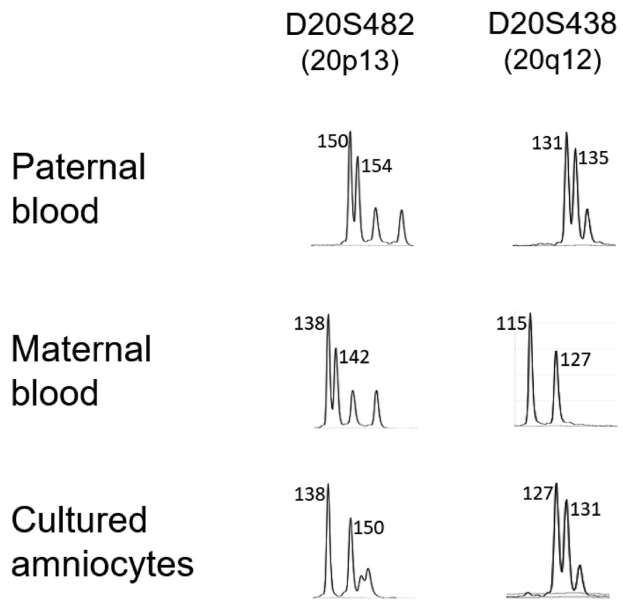

Fig. 1. Quantitative fluorescent polymerase chain reaction analysis on the DNAs extracted from cultured amniocytes and parental bloods using the informative markers of D20S482 and D20S438 shows biparental inheritance and thus excludes uniparental disomy 20.

gestation in a 35-year-old pregnant woman because of an abnormal maternal serum screening result. In their case, none of the trisomy 20 cells were detected in uncultured amniocytes by chromosome microarray analysis and copy number variation (CNV) sequencing analysis. The fetus had adverse pregnancy outcome of intrauterine growth restriction, and the pregnancy was terminated.

The present case demonstrates the usefulness of application of QF-PCR on the DNA extracted from cultured amniocytes for rapid exclusion of UPD 20 in case of mosaic trisomy 20 at amniocentesis.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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Correspondence

Glycosylation of FSH and cancer

Dear Editor

Last September 2023, the Yang et al. team published a review called "The role of sialylation in gynecologic cancers" [1]. Elegantly, the authors clearly explain the role of this group of sugars in various gynecological cancers. Within the wide variety of possible mechanisms, they identified four ways in which sialylation promoted various events present in cancer: evasion of the immune system, evasion of cell death, invasion, and extravasation from the systemic circulation. However, in the entire article, there is no mention of Follicle -stimulating hormone (FSH), which is related to gynecological cancers, and its activity also depends directly on its glycosylation pattern, particularly its sialylation.

This hormone is a peptide type and is made up of two subunits; the first is alpha, which is expected of other hormones such as TSH, hCG, and LH and which has a glycosylation site. The second subunit, called beta, is specific for FSH and has two glycosylation sites. Since each site can carry different sugar complexes, FSH is secreted as a mixture of different variants of glycoforms, which do not differ in their protein structure but in their carbohydrates. Changes in the carbohydrate structure of the protein can alter its tertiary or quaternary structure, affecting pharmacokinetics, pharmacodynamics, and biological response [2]. Specifically, hyperglycosylated isoforms of FSH show a lower half-life but higher FSH receptor (FSHR) binding activity and biological activity compared to hyperglycosylated isoforms [3].

The role of FSH in gynecological cancers has been reported in vitro on many occasions by promoting or inhibiting specific cell processes, which results in cancer progression. It is reported that FSH promotes the inhibition of apoptosis, cell survival, and metastasis induction by activating the Notch pathway [4]. Furthermore, FSH measurement on blood samples could be used as a marker for granulosa cell cancer. These tumours have a low incidence and represent only 1–2% of ovarian tumours, but their heterogeneity makes them challenging to diagnose. It has been showed that FSH levels are valuable markers for the differential preoperative diagnosis of this pathology; for women in menopause, a cut-off level of 2.0 IU/L, and for post-menopause, the cut-off level of 1.8 IU/L during the follicular phase improves the assertiveness of the diagnosis [5].

In conclusion, FSH should not be ruled out when incorporating its role in the incidence of ovarian cancer, specifically in the granulosa cell type, where the effect of glycosylation (or sialylation) on hormonal function and its effect has been shown to date. Considering the pulsatile secretion pattern of FSH, a direct link between a specific sialylated isoform and granulosa cell cancer will be challenging for researchers in the field.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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"The role of probiotics in women's health: An update narrative review."

Dear Editor,

I read the article by Wu LY et al. [1] with interest. The authors listed "Clinical studis of probiotics in obstetric conditions" in table 3. Preterm labor with 21 RCTs. Main results and findings of Probiotic vs. placebo: <34 weeks birth, RR 1.03 (95% CI 0.29–3.64); <37 weeks birth, RR 1.08 (95% CI 0.71–1.63). Level of evidence listed "None". Why the level of evidence is none?

The reference is #50, that is a systemic review and meta-analysis. We all known that A systematic review is a comprehensive summary of all available evidence that meets predefined eligibility criteria to address a specific clinical question or a range of questions. Meta-analysis is commonly included in systematic reviews, and is a statistical method that quantitatively combines the results from different studies. It is commonly used to provide an overall pooled estimate of the benefit or harm of an intervention [2]. Therefore, the level of evidence is strong, isn't it?

Declaration of competing interest

None.

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Common on “craniorachischisis in a stillbirth associated with maternal smoking”

Dear Editor,

I read the article by Chen CP [1] with great interest. In the present case, the pregnant woman was a heavy smoker and smoked 10 cigarettes per day. It is likely that there is a correlation of maternal smoking with fetal craniorachischisis and intrauterine fetal death in this case.

In the USA estimated that 480,000 deaths annually are attributed to cigarette smoking, including secondhand smoke exposure. Smoking during pregnancy can increase the risk of various adverse pregnancy outcomes, such as miscarriage and congenital anomalies, as well as complications in the offspring, including sudden infant death syndrome and impaired lung function in childhood [2]. Asian culture believes that good women should not smoke. There is a saying in Northeast China that women smoking is considered one of the three monsters in Northeast China. Of course, the harm of men smoking and secondhand smoke should not be underestimated.

The harm of smoking is well-known, and I would like to add a mechanism that smoking causes fetal neural tube defects and congenital heart disease. The impact on embryonic development is influenced by the severity and duration of the hypoxic event, as well as the timing of hypoxia during organogenesis. The vascular endothelium of recently formed arteries in the embryo is especially susceptible to damage from reactive oxygen species. Endothelial injury may result in vascular disruption, hemorrhaging, and irregular development of organs that rely on the affected artery for proper blood supply [3].

Declaration of competing interest

None.

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Correspondence

Comment on "Loeys-Dietz syndrome with a novel in-frame SMAD3 deletion diagnosed as a result of postpartum aortic dissection"

Dear Editor,

We appreciate the unique case study by Nagao et al. [1], reporting the first-ever case report on pregnancy in women with Loeys-Dietz syndrome (LDS) with a novel in-frame SMAD3 deletion, who was also diagnosed with aortic dissection in the postpartum period, which was successfully managed and treated in their institute. Given the high-risk nature of the disease, with aortic regurgitation already diagnosed in the patient and a significant aortic root dilation, and a strong family history of aortic aneurysm which was likely a connective tissue disorder, We are very interested to know if prenatal genetic counseling, diagnostic testing, and the fetal echo were performed in the fetus?

Maternal echocardiography which was performed at 31 weeks of gestation revealed an aortic root measuring 49 mm in diameter, which belongs to the WHO-4 cardiovascular risk classification which has an extremely high risk of maternal morbidity and mortality [2], was cardiologist involved in the management and was repeat echo performed in the patient later during follow up? Patients with aortic root dilation warrant a repeat echo 6 weekly up to the postpartum period [3]. The team should be commended for their great efforts in the management of the patient, We are interested in knowing why was elective cesarean not planned in this patient with aortic root dilation of more than 45 mm [2], rather a vacuum was utilized at an later stage and the indication also being prolonged second stage of labor? and also cutting short the second stage of labor would have prevented this drastic complication.

Furthermore, clarity is needed regarding the post-partum blood pressure values since the patient had developed a sudden episode of aortic dissection and information is lacking regarding the anti hypertensives if any administered to the patient in the postpartum period and also for long-term blood pressure control.

However, we are also interested in interrogating the contraceptive counseling offered to the patient and the contraceptive decision made for a such high-risk patient who had already developed an aortic dissection in the postpartum.

Since Loeys Dietz syndrome has an autosomal dominant pattern of inheritance, the offspring have a 50% chance of developing the disorder, no mention was made regarding the follow-up of the baby postnatally. Comments could have been made regarding evidence of any postnatal features of LDS in the baby. The literature describes neonatal LDS present with features like skeletal and facial abnormalities, including eyes, palate malformations, and aortic involvement [4]. We would also like to know if the SMAD3 deletion was detected in the neonate too.

The great efforts taken by the team Nagao et al. are highly commendable. It creates an opportunity for researchers all over the globe to manage such high-risk cases.

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Declaration of competing interest

None declared.

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Reply to “the role of probiotics in women's health: An update narrative review”

Dear Dr. Tsai,

Thank you for your comments regarding our use of the term “None” in the “Level of evidence” category in Table 3. We concur with Dr. Tsai that data derived from multiple randomized controlled trials or meta-analyses consistently produce high-quality and robust evidence. However, when reporting the level of evidence, it is recommended to use a standardized scale such as level A to E or 1 to 5, rather than terms like “strong” or “weak”. Level A (or 1) represents the highest quality of evidence, typically derived from numerous studies with multiway sensitivity analyses, as demonstrated in reference #50 that we cited [1,2]. Therefore, the term “none” in Table 3 is intended to indicate that probiotics have no effect on preventing preterm labor based on level A or 1 evidence. We apologize for any confusion caused by our lack of clarity in this description.

Declaration of competing interest

None.

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Reply to “glycosylation of FSH and cancer”

Dear Editor,

We appreciated Dr. Orellana-Walden for the interest in our previously review article entitled “The role of sialylation in gynecologic cancers”, which has been published in 2023 issue of the *Taiwanese Journal of Obstetrics and Gynecology* [1]. We totally agree with Dr. Orellana-Walden's opinion addressing the important role of follicle-stimulating hormone (FSH) either on the pathogenesis or prognostic prediction of ovarian cancers as well as adult ovarian granulosa cell carcinoma as shown by Dr. Orellana-Walden [2] and Dr. Richards [3]. However, all gonadotropin, s subset of glycoprotein hormones, not only FSH but also luteinizing hormone (LH) may have a significant but not fully clear role for the development and/or progression of ovarian cancer, which are involved in ovarian cancer progression by means of enhancing cell proliferation, evading apoptosis, and promoting invasion/adhesion/angiogenesis [4]. Apart from gonadotropins, these hormones-related receptors, such as FSH receptors (FSHR) and LH receptors (LHR) were associated with pathophysiology of ovarian cancer. However, how these gonadotropin/gonadotropin pathway work on the development/progression of ovarian cancer remains uncertain [4,5]. Sialylation modulation by the addition of sialic acid residues to glycoproteins is an important regulatory mechanism, controlling the biological activity of FSH and LH including half-lives and binding activities; thereby affecting their stability and interactions with receptors [6–8]. That is why we express our gratitude to Dr. Orellana-Walden for bringing this insightful perspective on the sialylation of ovarian cancer.

Declaration of competing interest

Dr. Peng-Hui Wang and Dr. Szu-Ting Yang, editorial board members at Taiwanese Journal of Obstetrics and Gynecology, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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