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Editorial

Minimally invasive surgery for endometrial cancer: The better choice?

Minimally invasive surgery (MIS) has become one of the best examples due to far-advanced technologies improving the standard of care (SOC) for patients with surgical illnesses, including both benign and malignant diseases [1–4]. The popularity of MIS mainly depends on the much understanding the underlying disease patterns, maturity of surgical skills, far-advanced and continuous improvement of instruments and image systems suitable to MIS [5]. Of course, a large and significant amount of data shows similar surgical or oncological outcomes as well as a significant decrease of surgery-related morbidity, such as the decreased intraoperative complications and fewer postoperative complications compared to laparotomy [6]. After reporting the results of LAP2, a prospective, randomized clinical trial (GOG-2222 or laparoscopic surgery or standard surgery in treating patients with cancer of the uterus) to compare comprehensive surgical staging by laparotomy vs laparoscopy for the treatment of women with stage I to stage IIA endometrial cancer (EC), regarding the completeness of surgical staging, recurrence-free survival, complications, and quality of life (QoL) of laparotomy vs laparoscopy, demonstrating improved QoL and decreased complication in the laparoscopy group without decrement in survival in patients managed with laparoscopy, MIS has been recommended as preferred surgical approach in the management of women with early-stage EC [5–8]. Moreover, laparoscopy-associated superior short-term safety and length-of-stay end points make laparoscopy itself to fulfill the essential component to conduct the enhanced recovery after surgery (ERAS) programs, which significantly cut down the high expense of medical care without compromising the therapeutic effects to reach the target of the better cost-effectiveness [9]. All hint that laparoscopy has become the SOC of surgical treatment for EC.

However, evidence favoring the use of laparoscopy for treating EC faces a big challenge. A report from one of the biggest academic medical centers in Northern Taiwan showed nearly 70% of EC patients were treated with laparotomy [10]. By contrast, in the Central Taiwan, another biggest academic medical cancer significantly favored the treatment of choice for EC, since only 38% patients were treated with laparotomy [7]. In a recent publication from the *Taiwanese Journal of Obstetrics and Gynecology* (*TJOG*), a hospital located in Southern Taiwan reported much lower proportion of EC patients (< one quarter of patients [23.3%]) undergoing conventional laparotomy [11]. This trend from the lowest proportion of using laparoscopy for EC in Northern Taiwan to the highest proportion of using laparoscopy for EC in Southern Taiwan is very interesting, although the aforementioned trend may be biased by different volume of service. In this editorial, we are happy to introduce this report.

Dr. Bing enrolled 133 patients with EC to investigate the outcome and prognostic factors of women with EC who were treated by the local regional hospital in Southern Taiwan [11]. Compared to both medical centers (5-year progression-free survival [PFS] rates of 94.3% and 95.9% respectively and 5-year overall survival [OS] rates of supposed 97.5% [12] and 99.4%, respectively) [7,10], the patients' outcomes (90.3% of 5-year PFS rate and 94.5% of 5-year OS rate) in the low volume of service hospital seemed to be similar, suggesting that the patients with EC can receive the SOC of surgical treatment, regardless where the patients look for service in Taiwan.

Additionally, the authors attempted to identify PFS- or OS-related prognostic factors and showed endometrioid histological type (favorable factor) and lymphovascular space invasion (LVSI) (poor prognostic factor) were associated with PFS (hazard ratio [HR] 0.02 and 9.11, respectively) but in term of factors associated with OS, there were no factors to be identified [11]. There are some uncertainties worthy of discussion.

First, in the current article, Dr. Bing's report only used the conventional histologic classification as type 1 (endometrioid) and type 2 (non-endometrioid) to investigate their contribution to outcome of EC [11]. This is a significant out of date, although this was limited by retrospective in nature and study period (between 2010 and 2020). Since the integration of molecular pathology into conventional histopathological diagnosis becomes popular recently, which was originally from the whole genome project of the Cancer Genome Atlas (TCGA) data and validated by the new FIGO (*International Federation of Gynaecology and Obstetrics*) staging of endometrial cancer: 2023 based on significantly improving the clarity on the diverse biological nature of this collection of EC and their differing prognostic outcomes [8]. In detail, this FIGO staging of endometrial cancer: 2023 recommended that performance of complete molecular classification (*POLEmut*, MMRd [deficient mismatched repair], NSMP [non-specific molecular profile], p53abn [p53 abnormal]) should be added, besides conventional clinical, histological and pathological stage, to offer the powerful accurate prediction for outcomes [8]. High-grade endometrioid-type EC (grade 3 or poor differentiation) may be one of best examples, since this type is originally classified type I EC but plays the worst outcome which shows the distinctive prognostic patterns compared to other type I EC, resulting in inappropriate allocation to a risk group if no molecular classification is integrated [8]. The combination of molecular pathology and conventional histopathology not only clearly distinguishes an excellent prognosis group by *POLEmut* in the early-stage disease from a very poor prognosis group (p53abn) in the initial biopsy/curettage and the final hysterectomy specimen [8], but also offers the bio-markers-guiding

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therapy for patients with EC, such as immune checkpoint inhibitors (ICIs) for deficient MMR EC or bevacizumab for p53abn EC [8,13–15]. If the current study by Dr. Bing can be reviewed by new biological markers as shown above, particularly for those patients having recurrence or dying for diseases. We believe much more informative experiences could be shared with audience.

Second, Dr. Bing indicated that LVSI was a risk factor associated with a lower 5-year PFS rate [11]. Unfortunately, the definition of LVSI is not mentioned in their work. Based on FIGO staging of endometrial cancer: 2023, it is very important to distinguish "substantial" or "extensive" LVSI from "focal" or "no" LVSI [8]. It is easy to mis-interpretate the LVSI, because mimickers, such as a microcystic elongated and fragmented (MELF) pattern of myometrial invasion and retraction artifacts are often found in the routine clinical practice [8]. For staging purpose of EC, $\geq$5 vessels is adopted to distinguish focal (negative LVSI) and extensive/substantial (positive LVSI) for confirmation of presence of LVSI [8].

For predicting oncologic outcome of gynecologic cancers [16–18], FIGO stage plays a key determinant prognostic factor for both OS and PFS. However, it is interesting to find that FIGO stage did not play any role in Dr. Bing's study. If the most critical important risk (or prognostic) factor for survival cannot be reproducible in the study, interpretation of their findings should be in caution because of considering biases not mentioned. Additionally, this concern may be supported, since Dr. Bings study mentioned patients treated with chemotherapy had a worse OS (HR 11.8) [11]. However, no explanation by authors was found. We suppose that the authors have mixed the "product" with "raw materials ("result" with "cause") together. Application of postoperative adjuvant therapy is often based on their own "worse clinico-pathological prognostic factors", such as presence of LVSI, presence of p53abn, advanced stage, presence of lymphadenopathy and many others, which could be found everywhere and every type of cancers [7,8,15–20].

Finally, the finding of favorable outcome in patients after laparoscopic surgery in their study seemed to be over-simplified. So far, compared to laparotomy for treatment of patients with EC, evidence support that laparoscopy can satisfy the aims when EC patients are treated with complete and thorough surgical staging surgery, based on its non-inferior oncological outcome and better intraoperative and short-term postoperative recovery [5–7]. It is hard to claim the oncologic outcome is better in laparoscopy than in laparotomy.

In summary, Dr. Bing's study still showed the important message, which is the use of MIS for EC treatment. Although the argument is always present, we believe that more and more new-generation doctors will proceed this trend in the management of their EC patients.

Conflicts of 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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Editorial

Neoadjuvant chemotherapy is associated with worse prognosis in patients with advanced-stage epithelial ovarian cancer: Is it real?

Epithelial ovarian cancer (EOC) is a highly lethal gynecologic malignancy compared to other two common types of gynecologic cancer, such as cervical cancer or endometrial cancer [1–8]. The diagnosis of EOC is often delayed partly because of non-specific or free of symptoms in the EOC patients and partly because of absence of cost-effective screening strategy, resulting in the majority of patients being diagnosed at the advanced stage [7,8]. Conventionally, primary cytoreductive or debulking surgery (PCS or PDS) and the following platinum-paclitaxel (PT) regimen with/without bevacizumab is believed the standard of care (SOC) for majority of patients with EOC [7,8]. However, due to its anatomic location, and absence of nature cover for defense to block the dissemination or spreading into entire abdominal cavity, management of advanced EOC by PDS may face a big challenge, including difficulty to perform complete resection to no residual tumor status (R0) and high intra- and post-operative complication rates [7,8]. Therefore, some strategies have been developed attempting to overcome the aforementioned PDS-related limitations. Among these, neoadjuvant therapy (NAT), especially for NACT (neoadjuvant chemotherapy) in cancer is an alternative approach for both locally- and far-advanced cancer disease, based on the following hypothesis: decreasing the tumor burden and shrinking large local lesions to make IDS less extensively (fewer organ injuries caused by radical surgeries), and subsequently taking advantages as better cosmetic purposes and better organ preservation or function maintenance to get better quality of life (QoL) of patients [9].

However, some of the aforementioned benefits are in debate. European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group and NCIC Clinical Trials Group conducting a prospective randomized trial to compare the PDS and IDS and additional platinum-based CT in women with advanced EOC (NCT00003636) showed none of the assessment times (EORTC QLQ-C30 (http://groups.eortc.be/qol/questionnaires_qlqc30.htm) and QLQ-Ov28 (http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_ov28.pdf).) were the differences in the QLQ-C30 global health scores significant and the overall test for a treatment effect on global health was not significant [10], suggesting absence of better QoL in patients undergoing IDS. Moreover, a recent cohort study from a Memorial Sloan Kettering Cancer Center Team Ovary study showed, although most procedures were more common during PDS, including bowel surgery (65% of PDS and 33% of IDS), upper abdominal surgery during 72% of PDS and 52% of IDS, more estimated blood loss (median, 500 mL [PDS] vs 300 mL [IDS]), longer operative time (median, 362 min [PDS] vs 267 min [IDS]), higher consultation rates for special surgeons, due to the similar rate of cases achieving complete gross resection between PDS and IDS (76% vs. 71%), the authors still concluded that NACT did not obviate the need for radical surgical resection and emphasized the importance of advanced surgical skills [11]. All suggest that PDS + adjuvant CT is still the standard of care for majority of EOC patients. It is interesting to find a newly published article in the 2024 *Taiwanese Journal of Obstetrics and Gynecology* also explored the potential limitation of NACT (IDS) in the management of patients with advanced EOC, due to higher rate of developing platinum-resistant EOC and shorter period of median progression-free survival (PFS) and overall survival (OS) in IDS (NACT) group than in PDS group [12].

Dr. Yeh's group enrolling 210 patients with advanced EOC aimed to construct a novel predictive nomogram to predict platinum-sensitivity and survival outcomes in these patients [12]. The results identified that NACT (IDS), clear cell (CCC)/mucinous histology and sub-optimal cytoreductive surgery were independent prognostic factors associated with the development of platinum-resistance diseases and worse outcomes, with odd ratio (OR) 2.15 (95% confidence interval [CI] 1.10–4.21), 5.04 (95% CI 2.20–11.54) and 3.37 (95% CI 1.44–7.91), respectively [12]. Moreover, in agreement of the aforementioned findings, the median PFS and OS were also consistently and significantly shorter in the NACT (IDS) group than PDS (10 vs. 23 months and 29 vs. 69 months, with hazard ratio [HR] 1.71, 95% CI 1.19–2.45 and 1.62, 95% CI 1.02–2.56, respectively) [12]. Additionally, other two prognostic factors, such as CCC/mucinous histology (HR 1.74 [95% CI 1.14–2.65] and 3.27 [95% CI 2.01–5.30], respectively) and sub-optimal debulking surgery (HR 1.75 [95% CI 1.08–2.81] and 2.27 [95% CI 1.28–4.01], respectively) were also associated with statistically significantly shorter PFS and OS (3 vs. 15 months [PFS] and 11 vs. 63 months [OS] for CCC/mucinous histology vs. serous histology and 5 vs. 26 months [PFS] and 24 vs. 78 months [OS] for suboptimal debulking surgery vs. R0 status) [12]. All are against the concept to favoring the use of IDS in the management of women with advanced EOC, particularly for those with far-advanced EOC. Their findings are interesting and worthy of discussion.

One of basic hypothesis for NACT (IDS) is in situations such as unresectable disease without access to RT, to enable definite surgical treatment or in presence of resistant tumor cells to kill the majority of cancers and then continue to destroy resistant cells using surgery making the chance of subsequent dissemination less likely, 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, which makes physicians with much understanding the sensitivity of cancers to CT regimen based on the patient's

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response and pathological specimens to better formulate the next treatment strategy, referring the reference to guide the better choice for further treatment [9]. Unfortunately, Dr. Yeh's study seemed to be against the benefits of NACT, because NACT, similar to other two major critical prognostic factors as CCC/mucinous histology and suboptimal debulking surgery was associated with high risk of the development of platinum-resistance status and subsequently shortening PFS and OS [12]. Additionally, the authors put these three factors together using different scores, such as 100 points for CCC or mucinous, 52 points for NACT and 87 points for suboptimal debulking surgery to set up a novel model to estimate the possibility of developing platinum-resistance status after treatment. However, it is still uncertain that this model can work well. As shown by authors, patients with advanced serous-type EOC undergoing PDS without residual tumor and following postoperative adjuvant CT by PT-regimen had an extremely lower risk to develop platinum-resistance status, suggesting this-group patients were guaranteed to have a more than 12 months PFS. By contrast, if the patients with the similar situation (serous type and R0 status after surgery) but were initially treated with NACT, the prognosis may be worse, since this-group patients still had a certain degree of risk to recur within one year. Does it suggest that all patients had better be treated with PDS if they can achieve R0 status, particularly for those patients with CCC/mucinous histology? However, histology of EOC can be made only by surgical approach? Do the authors suggest that all advanced EOC patients have better be evaluated by “biopsy” to confirm its histopathological type before the initiation of therapeutic plan either with PDS or with IDS?

Finally, the authors did not include the role of maintenance therapy for these advanced EOC patients in their novel model, since patients with/without maintenance therapy may be significantly influenced by this factor, particularly for those patients with more severe status, such as IV or those patients with BRCA mutation [13–17]. It is well known that maintenance therapy either by anti-angiogenic agents (bevacizumab) or by poly (ADP-ribose) polymerase (PARP) inhibitors (PARP-i) is correlated with PFS and even though OS in certain subgroups of patients [13–17]. We believe these may play a certain role to establish their model to predict the platinum-resistance status or PFS and OS. Unfortunately, the authors did not mention it.

Although the authors’ novel nomogram model to predict the CT response and outcomes of patients with advanced EOC may be useful and valuable, the baseline difference (tumor behaviors, such as aggressive type) makes us much confusing, and it may result in difficult decision-making in our therapeutic plan in the routine clinical practice. To overcome the aforementioned limitation, the similar strategy to establish a novel nomogram model using the relatively homogenous group patients, such as pure serous type advanced EOC and the same stage of advanced EOC may offer the better clarification to see the impact of NACT on patients with advanced EOC. Without no further data supporting the negative impact of NACT on the development of CT-resistance or worse outcome, the argument between PDS and IDS still exists.

Declaration of competing interest

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Editorial

Primary cytoreductive surgery or interval cytoreductive surgery

Primary cytoreductive (debulking) surgery (PCS or PDS) with following postoperative platinum-paclitaxel-based adjuvant chemotherapy is considered the standard of care therapy for patients with advanced epithelial ovarian cancer (EOC) and many gynecologic oncologists followed this concept [1,2]. However, besides the direct PDS for treating advanced EOC patients, the new update NCCN (National Comprehensive Cancer Network®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 3.2024—July 14, 2024, has another recommendation, based on at least three critical and determined factors [3]. One is clinical stage (IA + IB vs. I ~ IV) plus the request of fertility-preservation [3]. Another is patient's general condition (suitable or unsuitable) plus tumor burden or itself (likely or low likely optimal cytoreduction) [3]. The other is the health structure (facility for feasibility). To manage patients unsuitable immediate surgery or who have little chance to undergo optimal debulking surgery, it needs another treatment strategy to borrow time from heaven to strive for opportunity for establishment of suitability to undergo complete cytoreductive surgery (optimal debulking surgery), and this strategy is called neoadjuvant therapy (NAT), which is frequently based on chemotherapy (called as NACT) [4,5]. This NAT plus (+) interval cytoreductive (debulking) surgery (ICS or IDS) is suggested in those advanced EOC patients who are unlikely to achieve a complete cytoreduction in PCS either due to unresectable metastatic disease or who present unresectability criteria (imaging, laparoscopic and/or by laparotomy) and that have been defined by a gynecologic oncologist and patients with bad performance status and comorbidities according to the criteria of the multidisciplinary team (clinical oncology, gynecologic oncology, radiology, etc.) [6]. Following seminal clinical trials, both PCS and ICS have been positioned as validated alternatives with distinct pros and cons; however, a definite response is still unassessed [7].

In theory, the aforementioned suggestion seems to be very clear and easy to follow, contributing to “possibly high agreement” of gynecologic oncologists in their clinical practice. However, many uncertainties and discrepancies impede the acceptance of NAT + ICS strategy by some gynecologic oncologists [7–9]. Expert consensus for profiling and management of advanced or metastatic EOC recommended that complete PCS is suggested as the initial therapy of choice for patients with advanced or metastatic EOC, which should be ideally be carried out in centers with experience, followed by adjuvant therapy (Recommendation 1.1) [6]. Additionally, Dr. Yeh's research in one of the biggest medical centers in Southern Taiwan indicating that NACT + ICS strategy is strongly associated with higher risk of developing platinum-resistance and subsequently worsening oncologic outcomes by shortening median progression-free survival (PFS) and overall survival (OS) in advanced EOC patients compared to PCS + adjuvant therapy raises the further concern in using the NACT + ICS strategy in the management of advanced EOC patients [8].

NAT is a watch-and-wait (W&W) strategy, although theoretically, many potential benefits may be existed, which, in no doubt, may shift chemo-sensitive strait tumors to chemo-resistant strain and delay the definite surgery with resultant poor oncological outcomes, creating challenges for shared decision-making and in-action [7,10,11]. In fact, OS benefit of NACT remains unconfirmed, including locally- and far-advanced cancer patients, although in certain situations, PCS may be associated with higher morbidity and functional consequences, not least because a transient stoma is required for disseminated digestive system invasion [7,10,11]. Sometimes, the successful down-staging disease or the complete clinical remission makes the complete ICS (without visible residual tumor to R0 status) becomes more possible and frequent. Indeed, cytoreductive surgery represents a cornerstone of multimodal treatment of advanced EOC, nevertheless requiring R0 status to achieve a maximal impact on the OS of patients based on the observation that each 10% increase in the rate of optimal PCS is associated with a 5.5% improvement in OS [7]. Additionally, the best results are observed after complete resection of PCS into R0 status, which has become the mainstay for advanced EOC, a requirement highlighted in all international guidelines and consensus [1–3,6,7], leading to the questions why NACT are not widely used in all advanced EOC patients. However, a higher proportion of patients showing R0 status after NACT + ICS compared to a consistent but lower percentage of patients achieving R0 status after PCS cannot be accurately reflective by better outcome, since outcomes seem to be similar in both.

Updated information of Cochrane systemic review enrolling 1774 women with stage IIIc/IV EOC of randomised clinical trials (RCTs) to investigate the effects of NACT + ICS and PCS for initial treatment in advanced EOC showed little or no difference with regard to PFS (Hazard Ratio [HR] 0.98, 95% CI 0.88–1.08; 1692 participants of four moderate-certainty evidence study) or OS (HR 0.96, 95% confidence interval [CI] 0.86–1.08; 1692 participants of four high-certainty evidence studies) [12]. In probably agreement of clinically meaningful differences in favoring of ICS compared to PCS with regard to overall postoperative serious adverse events (AEs grade 3+) (6% vs. 29%; risk ratio [RR] 0.22, 95% CI 0.13–0.38); the need of stoma formation (5.9% vs. 20.4%; RR 0.29, 95% 0.12–0.74); the need of bowel resection during operation (13% vs. 26.6%; RR 0.49, 95% CI 0.30–0.79); and surgical mortality (0.6% vs. 3.6%; RR 0.16, 95% CI 0.06–0.46), the authors still face the difficulty to conclude their findings, based on only results addressing surgical mortality as high-certainty evidence, suggesting inclusive recommendations in either using PCS or using ICS for treating women with advanced EOC. Subsequently, these results

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remind us the importance of decision-making between patients with gynecologic oncologist multidisciplinary teams to allow treatment to be tailed to the individual, taking into consideration complete resection, tumor behaviors, and patient's global physical or performance status [12]. These debated issues between PCS and ICS are persistently present.

In rationale, NACT + ICS exhibits a high proportion of total resection of EOC compared to PCS and it also has a lower risk to need to do ultra-radical surgery than PCS and all are secondary to the NACT-related down-stage and shrinkage of tumor [7]. Indeed, studies reported an increase in the rate of complete surgery with the use of a NACT, from 19.4% to 17%–51.2% and 39% (EORTC and CHORUS, respectively) [7]. The strongest independent prognostic factor by completeness of surgery to improve OS, particularly for PCS is confirmed by systemic review and network meta-analysis (n = 20,927) which showed the critical importance of completeness of surgery (R0, no visible residual tumors) with a HR for OS of 2.0 (95% CI 1.8–2.2) for <1 cm residual tumor threshold vs. R0 and R0 was associated with prolonged survival across all residual tumor thresholds, leaving R0 as strong predictor to provide longest survival (probability of being best = 99%) [13]. Sensitivity analysis including only those studies that adjusted for extent of disease at PCS also confirmed the benefits of complete and total resection (HR 2.3, 95% CI 1.9–2.6) [13]. Furthermore, after adjustment for experts' opinions, a strong association between the achievement of R0 status and improved OS even after adjustment for publication bias using strong informative priors formed from an expert elicitation exercise remains [14]. However, all aforementioned benefits of complete resection were based on studying PCS.

To reach a R0 status, ultra-radical surgery sometimes may be needed. However, the role of ultra-radical surgery, regardless of either PCS or ICS, for PFS and OS is conflicted, resulting in very low-certainty evidence supporting the positive correlation between ultra-radical surgery and oncological outcome [15]. All hint that standard cytoreductive surgery performed either by PCS or by ICS is still preferred if no further evidence supports the therapeutic effects by using ultra-radical surgery in the management of women with advanced EOC.

The advantages of NACT have been introduced widely, including our previous comments, such as decreasing initial tumor burden to allow distinct benefits as technically easier cytoreductive surgery, fewer sequelae, and the shifting inoperability to operability and reasonably suiting to patients with stage IV diseases and/or poor global performance [4,5,7,10–12]. By contrast, PCS really exhibits notable benefits, including removal of all visible malignancies, favoring the diffusion of subsequent chemotherapy into microscopic residual diseases; blocking neoplastic neoangiogenesis inducing hypoxic zone and intratumoral ischemia which impaired chemotherapy therapeutic efficacy; dramatically cytoreduction of tumor inducing decreasing tumor burden and following reduction of the probability of the emergency of resistant strain formation and further reduction of developing chemo-resistance and the risk of tumor recurrence [7].

Although many RCTs and meta-analyses and even real-world data bringing distinct information have been published [7], as for many "PCS and ICS" dilemmas, distinct advantages should be well discussed between specialists and patients based on similar oncological outcomes between PCS and ICS for advanced EOC patients. So far, international guidelines still have positioned PCS as the preferred option for advanced EOC, unless complete surgery is not considered feasible right from the start and given the current momentum and the need to treat patients in high-volume and expert centers wit standardized and robust surgical procedures, we welcome a high-quality RCT will help us to make a choice between PCS and ICS in the management of patients with advanced EOC.

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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Editorial

Breakthroughs in women's health for treating vasomotor symptoms

Menopause, one of normal physiological changes belonging to ageing process occurs in nearly all women when permanent cease of menstruation [1,2]. Although the underlying pathophysiology of menopause (deficiency of female hormones) is fully understood, the accompanied symptoms or signs (S&S), such as vasomotor symptom (VMS), joint and muscle pains, mood change, sleep disturbance, low libido, and genitourinary symptoms are complex and vary greatly in peri-menopausal and postmenopausal women (PMW), and most of them are not fully explored [3]. Additionally, menopause-associated S&S may result in a troublesome and negative impact on women's daily life. Indeed, more than one quarter of women experience moderate-to-severe S&S, further deteriorating overall quality of life (QoL) of PMW [3,4]. Despite having menopause hormonal therapy (MHT) as standard of care (or gold standard) and possibly the most effective strategy for managing climacteric S&S, particularly useful and valuable to symptomatic women with age <60 years or within 10 years of menopause and absence of contraindications, which include a history of breast cancer (BC), advanced endometrial cancer (EC), cardiovascular accident (CVA, such as coronary heart disease, stroke, myocardial infarction or venous thromboembolism) and many others, concerns regarding a long-term poor and unacceptable safety profile of MHT, such as an increased risk of BC, CVA (stroke, pulmonary embolism) and many others after prescribing the combined estrogen plus progestogen therapy (EPT) are always bothering both physicians and patients [4,5]. The administration of MHT, especially EPT should be consider the benefit-to-risk ratio (B/R) based on potential long-term harms of MHT [4–6].

Traditionally, estrogen alone is considered safe, and it is often prescribed in women without uterus [4]. It is believed that the risk for developing adverse events (AEs) of MHT often relies on the progestin component, particular medroxyprogesterone (MPA); however, to avoid the development of uterine pathology (hyperplasia or cancer), progestin is an essential component of MHT in PMW with an intact uterus [4]. A recent publication from a large-scale randomized trial (RCT, the Women's Health Initiative [WHI]) enrolling more than 16,000 PMW receiving MHT against placebo, found estrogen-alone, versus placebo, significantly increased ovarian cancer incidence (35 cases [0.041%] vs. 17 [0.020%]; hazard ratio [HR] 2.04 [95% confidence interval (CI) 1.14–3.65]) and also significantly increased ovarian cancer mortality after 20-year follow-up [7]. All suggesting the potential risk of using MHT for treating symptomatic PMW cannot be neglected and this relatively low B/R reminds us to urgently needing to search for non-hormonal (including pharmacological and nonpharmacologic) therapies for these symptomatic PMW.

Among menopausal-related S&S, vasomotor symptoms (VMS), the cardinal S&S of menopause consisting of hot flashes (flushes), night sweats and associated sleep disturbances are often considered just a nuisance and also impact many global aspects of PMW's health, such as CV and metabolic problems (CVA, diabetes, insulin resistance, obesity etc.), and resulting in poor QoL of their remaining life [8]. Of most concerns, VMS is very common, affecting up to 80% of women, approximately 25% disruptive and bothersome enough to need treatment, persistent for a median of 7 years, with duration and severity varying by race and ethnicity [8]. Conventionally, the only United States (US) Food and Drug Administration (FDA)-approved nonhormonal treatment for VMS is low dose 7.5 mg paroxetine salt, although the effect is not satisfied to all symptomatic PMW [8]. Other off-label use of antidepressants, gabapentinoids, and clonidine, is substantially less effective than MHT in treating VMS and the intolerable AEs developed [8], hinting us the urgent need to open new chapter to manage this troublesome VMS.

Although use of complementary or alternative therapies for VMS has increased over the past few decades, but concerns regarding their safety and effectiveness persist, partly because of lacking evidence [9]. There are many strategies of complementary and alternative therapies reporting their potential benefits to reduce the severity and frequency of VMA or improve mood and sleep, such as cognitive behavioral therapy, stellate ganglion blockade, trigger avoidance, cooling techniques, dietary modification, exercise, mindfulness-based interventions, acupuncture, electroacupuncture, yoga, traditional Chinese medicine (TCM) and some natural-like supplements (soy foods, S-equol, other soy extracts or derivatives, cannabinoids, herbal medical, as ashwagandha, evening primrose oil); however, the majority of them are defective by lacking of or inclusive evidence, which are frequently secondary to methodological deficiencies, contributing to urgent warranting of larger RCTs to provide more conclusive evidence regarding the B/R in VMS management [9,10].

Due to absence of evidence supporting the B/R of complementary or alternative therapies for VMS, nonhormone pharmacologic agents remain a valuable tool for VMS relief, although not as efficacious as MHT, which include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reupdate inhibitor (SNRIs), gabapentinoids, antimuscarinic agent (oxybutynin), alpha-2 adrenergic agonist (clonidin) and a newer class of medications known as neurokinin-receptor antagonists (fezolinetant) [9]. Except fezolinetant, nearly all aforementioned nonhormonal therapies have been applied on off-labelled use based on their original indication for other diseases. This new chapter for treating vasomotor symptoms has been opened in this editorial comment.

Indeed, breakthroughs in women's health are uncommon; accordingly, it is exciting for me to join a phase 3 RCT of fezolinetant, a selective neurokinin-3 receptor (NK3R) antagonist, confirming its

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safety in the management of moderate to severe VMS among women in East Asia (MOONLIGHT 1 [NCT04234204]), although efficacy was not confirmed [11]. A total of 301 women with moderate to severe VMS were evaluated (150 for 30 mg fezolinetant, and 151 for placebo), and results showed the difference in the least squares mean (SE) change (95% CI) from baseline in the daily frequency of moderate to severe VMS vs. placebo was −0.65 (−1.41~0.12) at Week 4 (W4) and −0.55 (−1.35~0.26) at Week 12 (W12) [11]. The differences in the least SE change from baseline in the VMS severity score vs. placebo were −0.06 (−0.14~0.03) and −0.13 (−0.27~0.01) at W4 and W12, respectively [11], which did not reach the statistically significant difference compared with placebo effects.

Although efficacy of fezolinetant 30 mg did not approve in MOONLIGHT 1, the safety was approved by no increasing serious AEs in participants treated with fezolinetant in W1 to W12 compared to those treated with placebo (0.7% vs. 1.3%) [11]. MOONLIGHT I study only supported the safety profile in using fezolinetant for VMS but conflicted the efficacy in reduction of frequency or severity of VMS in this East-Asia population study [11], compared with the similar trials applied to United States and Europe [12–14]. The aforementioned findings, although interesting, are worthy of our further attention.

In phase 3 RCTs (SKYLIGHT [Study to Find Out How Safe Long-Term Treatment With Fezolinetant is in Women With Hot Flashes Going Through Menopause]), including SKYLIGHT 1 (NCT04003155), SKYLIGHT 2 (NCT04003142) and SKYLIGHGT 4 (NCT04003389), fezolinetant treated PMW with moderate-to-severe VMS had significantly reduced the frequency and severity of moderate-to-severe VMS associated with menopause at W4 and W12, and had a maintaining effect throughout the active treatment extension period up to W52 in women from the United States and Europe [12–14]. In the SKYLIGHT 1 report, fezolinetant 30 mg and fezolinetant 45 mg significantly reduced the frequency of vasomotor symptoms at W4 (difference in change in least squares mean −1.87 [SE 0.42], −2.07 [SE 0.42]) and W12 (−2.39 [SE 0.44], −2.55 [SE 0.43.); and also significantly reduced the severity of vasomotor symptoms at W4 (−0.15 [0.06], −0.19 [0·06]) and W12 (−0.24 [0.08], −0.20 [0.08]), compared with placebo, which indicates the fezolinetant 30 mg and 45 mg once daily were efficacious and well tolerated, supporting the potential use of fezolinetant as a first-in-class nonhormonal treatment option for women with VMS [12].

Additional clinical studies to further definite the safety and efficacy of fezolinetant are demonstrated as the SKYLIGHT 2 report, which was a 40-W active treatment extension [13]. For VMS frequency, W4 least SE reduction vs placebo: fezolinetant 30 mg, −1.82 (0.46); 45 mg, −2.55 (0.46); W12: 30 mg, −1.86 (0.55); 45 mg, −2.53 (0.55) [13]. For VMS severity, W4: 30 mg, −0.15 (0.06); 45 mg, −0.29 (0.06); W12: 30 mg, −0.16 (0.08); 45 mg, −0.29 (0.08) [13]. Th data of SKYLIGHT 2 showed the improvement in VMS frequency and severity by W1 and maintenance through W52, and of most importance, serious treatment-emergent AEs were infrequently, reported by 2%, 1%, and 0% of those receiving fezolinetant 30 mg, 45 mg and placebo, respectively. All data were in agreement with findings of SKYLIGHT 1 showing daily fezolinetant 30 and 45 mg were efficacious and well tolerated for treating moderate to severe VMS [13].

In the SKYLIGHT 4 report focusing on the safety, tolerability and effect of fezolinetant on endometrial health over 52W, treatment-emergent AEs occurred in 64.1% (391/610) of the placebo group, 67.9% (415/611) of the fezolinetant 30-mg group, and 63.9% (389/609) of the fezolinetant 45-mg group, with subsequently leading to discontinuation as similar across groups (placebo, 26/610 [4.3%]; fezolinetant 30 mg, 34/611 [5.6%]; fezolinetant 45 mg, 28/609 [4.6%]) [14]. Regarding the endometrial safety, hepatotoxicity and bone health (bone mineral density and trabecular bone score), results from SKYLIGHT 4 confirm the 52-week safety and tolerability of fezolinetant and support its continued development [14].

Although fezolinetant may be one of breakthroughs in women's health for treating VMS, however, based on AEs reported from SKYLIGHT [12–14], the most common AEs included abdominal pain, diarrhea, headache, nausea, and gastrointestinal disturbances and approximately 2.3% of patients treated with fezolinetant 45 mg experienced transaminase elevations, suggesting regular checking alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is recommended at baseline and every three months when using this medication [9]. However, in MOONLIGHT 3 RCT (W52 safety study) conducted in China, 88.7% of women treated with fezolinetant 30 mg experienced TEAEs, most commonly upper respiratory tract infection (16.0%), dizziness, headache, and proteinuria (10.7% each) [15]. There was no clinically relevant change (mean ± standard deviation [SD]) in endometrial thickness (baseline, 2.95 ± 1.11 mm; W52, 2.94 ± 1.18 mm). ALT and/or AST levels >3 times the upper limit of normal were reported in 1.4% of women; no Hy's Law cases occurred [15]. All suggest the fezolinetant 30 mg-related AEs may be different between United States + Europe and China (East Asia).

Due to aforementioned evidence supporting the use of fezolinetant as nonhormonal treatment of choice for moderate-to-severe VMS of PMW, however, the results of fezolinetant treatment in East Asian symptomatic PMW population (MOONLIGHT) [11] are conflicted to those obtained from SKYLIGHT [12–14]. We hope to find a large-scale RCT to explore the safety and efficacy of fezolinetant for treating moderate-to-severe VMS in Asia PMW and determine whether race and ethnicity may influence the decision of first of choice in using different strategies, such as fezolinetant in the management of PMW with VMS, since evidence or any consensus should be balanced by B/R and race and ethnicity [16].

Conflicts of interest

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Editorial

Antibody–drug conjugates (ADCs) may be a big breakthrough in gynecologic cancer treatment (I)

Clinical outcomes remain suboptimal in advanced, metastatic, persistent, recurrent (AMPR) gynecologic cancers (GC), including endometrial cancer (EC), epithelail ovarian cancer (EOC), and cervical cancer (CC), contributing to a biggest challenge for both patients and physicians, partly due to high heterogeneity of tumors resulting in unpredictable response and subsequent development of resistance to the standard-of-care (SOC) therapies, such as conventional single agent or multi-agent combination chemotherapy (CT, the most common paclitaxel-carboplatin regimen or less frequent use of non-platinum-based therapy), anti-angiogenesis agents (bevacizumab), immunotherapy (IO), targeted therapy by agents or monoclonal antibody (mAb), including poly (ADP-ribose) polymerase (PARP) inhibitors, tyrosine-kinase inhibitor (TKI), and many others, which can be used alone or in combination to act either the front-line therapy (with/without maintenance therapy) or adjuvant therapy as the preferred therapy or rescue therapy [1–6]. However, the aforementioned therapies are not always successful and many of them do not reach the clinical need, resulting in common but troublesome clinical status as AMPR diseases, and final death. Although the advance molecular biology is continuous to provide the better understanding of tumor pathophysiology and underlying associated alternations of tumors, it is still a long way to fight against the cancers. There are many strategies attempting to open a new and promising therapeutic option for this AMPR population [1].

Among these, the biomarker identification has led to the approval or compendium listing of severe therapeutic approaches [1]. There are few successful examples which have been well accepted in clinical practice with dramatical improvement of overall outcomes of patients with GCs. One best example is the use of combination of IO and CT (immune-chemotherapy) with/without bevacizumab in the management of patients with locally- or far-advanced CPS ≧1-CC (evaluating the number of PD-L1 [programmed cell death-ligand 1]–staining cells [tumor cells, lymphocytes, macrophages] relative to all viable tumor cells) with significantly enhanced therapeutic effects and improved overall outcomes reported by KENOTE 826 and KENOTE A18 showing a dramatical improvement of both progression-free survival (PFS) from 8.2 months to 10.5 months (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.47–0.71 for KEYNOTE 826 and HR 0.70, 95% CI 0.55–0.89 for KEYNOTE A18) and overall survival (OS) from 16.5 months to 28.6 months (HR 0.60, 95% CI 0.49–0.74 for KEYNOTE 826) [5,6]. The other example is the use of PARP inhibitors for maintenance therapy of EOC patients with BRCA1/BRCA2 mutations (*BRCA*mut) after the SOC therapy (cytoreductive surgery and paclitaxel-carboplatin with/with bevacizumab therapy), which showed an improvement in PFS over placebo in newly-diagnosed or recurrent OC in the overall population (HR 0.46, 95% CI 0.30–0.71 for newly-diagnosed and HR 0.34, 95% CI 0.29–0.40 for recurrent) and the *BRCA*mut population (HR 0.36, 95%CI 0.29–0.44 for newly-diagnosed and HR 0.24, 95% CI 0.18–0.31 for *BRCA*mut recurrent and HR 0.23, 95% CI 0.18–0.30 for germline *BRCA*mut recurrent) in a recent systematic review and meta-analysis of randomized controlled trials (RCTs) [2,7].

Recently, antibody–drug conjugates (ADCs) stand out as a beacon of innovation for cancer treatment, which are worthy of our attention, because of their functioning as promising and exciting magic bullets to reach the destination site (tumors), offering a multifaceted approach to targeting and treating malignancies with precision and efficacy [8–10]. In this editorial comment part I, we are happy to provide a brief introduction of this brand-new frontier as ADCs for the treatment of GCs.

ADCs are a new class of targeted therapies using the following marvels of biotechnology to produce a strategic fusion containing three critical and essential components: (1) the high specificity of mAb with tumor-surface-receptor-targeting ability serving as the guidance of ADCs, homing in on specific antigens overexpressed on the surface of cancer cells while sparing normal cells; (2) a highly potent cytotoxic molecule payload, encompassing a wide spectrum of agents from traditional chemotherapeutic agents to novel compounds with unique mechanisms of action or enhanced potency (microtubule inhibitors [maytansine derivatives DM1/DM4 and auristatins monomethyl auristatin E/F], DNA-damaging agents [calicheamicin, pyrrolobenzodiazepine analogs (PBDs)], topoisomerase I inhibitors, and RNA polymerase II inhibitors [α-amanitin]) are at the forefront of payload development) and presenting the main firepower of ADCs, capable of delivering a lethal blow to cancer cells on release; and (3) the ideal linker, a specifically designed molecular bridge, which may avoid premature drug release, which could cause systemic toxicity, but labile enough within the tumor cells to release the cytotoxic agent effectively, including two common forms: cleavable (cleavage to release the drug in response to specific tumor microenvironment [TME] condition, such as hydrazone linkers, pH-sensitivity susceptible to acidic condition in cancer cell endosomes and lysosomes; disulfide linkers exploiting the high intracellular glutathione levels in cancer cells for payload release; peptic linkers responsible to specific enzyme cleavage by proteases-cathepsin-B; and beta-glucuronide linkers sensitive to rich beta-glucuronidase in certain-type cancer) and non-cleavable (stability in circulation and requirement of the enzymatic degradation of the entire ADC into the lysosomes to release the payload,

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often resulting in charged amino acids retained on the payload) type to exhibit different properties, which aims to connect the mAb and the payload and to play a pivotal role in the controlled release of the ADCs-related therapeutic fire [1,8–10]. ADCs indeed present a paradigm shift in the fight against malignancy, because of their highly selective binding ability ensuring that cytotoxic payload reaches its intended destination (cancer cells) to minimize collateral damage to the surrounding tissue and reduce unwanted systemic adverse events (AEs) or toxicity, and flexibility of linker allowing for tailored release kinetics, optimizing the therapeutic window of ADCs and maximizing their efficacy [8,11].

Currently (to the end of December 31, 2022), at least 15 ADCs based on different main targets as ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2 for human epidermal growth factor receptor 2: HER2) and TNFRSR8 (CD30), have been approved in management of various kinds of cancers (hematological malignancy, breast cancer, gastric cancer, head and neck squamous cell carcinoma, etc.) and more than one hundred ADC candidates have entered the RCTs for cancer therapy [11]. There are now two Food and Drug Administration (FDA)-approved ADCs for treatment of GC, including (1) mirvetuximab soravtansine-gynx (MIRV) for folate receptor alpha (FRα) positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer with 1–3 prior systemic regimens; (2) and tisotumab vedotin in previously treated recurrent or metastatic CC [12–14].

MIRASOL RCT (NCT04209855) enrolling 453 patients with platinum-resistant, high-grade serous OC (227 for MIRV and 226 for CT) showed the improvement of both PFS and OS in MIRV group compared to those in CT group with median PFS of 5.62 months (95% CI 4.34–5.95) vs. 3.98 months (95% CI 2.86–4.47) and OS of 16.46 months vs. 12.75 months (HR for death 0.67, 95% CI 0.50–0.89) [13]. Additionally, during the treatment period, an objective response rate (ORR) was also better in MIRV group than CT group (42.3% vs. 15.9%, odds ratio [OR] 3.81, 95% CI 2.44–5.94) [13]. Moreover, fewer AEs of ≧ grade 3 occurred with MIRV than with CT (41.7% vs. 54.1%), as did serious AEs of any grade (23.9% vs. 32.9%) and AEs leading to discontinuation (9.2% vs. 15.9%) [13]. All suggested the use of MIRV for treating platinum-resistant, FRα-positive OC demonstrated a significant benefit over CT with respect to PFS, OS and ORR [13].

The innovaTV 301/ENGOT-cx12/GOG-3057 RCT (NCT04697628) enrolling 502 participants with recurrent CC treated with 1–2 prior systemic regimens (223 for TV and 249 for CT) showed the improvement of both PFS and OS in TV group compared to CT group with median PFS of 4.2 (95% CI 4.0–4.4) months vs. 2.9 (95% CI 2.6~3.1) months (HR 0.67, 95% CI 0.54–0.82) and OS of 11.5 (95% CI 9.8–14.9) months vs. 9.5 (95% CI 7.9–10.7) months (HR for death 0.70, 95% CI 0.54–0.89) [14]. Additionally, during the treatment period, an objective response rate (ORR) was also better in TV group than CT group (17.8% vs. 5.2%, OR 4.0, 95% CI 2.1–7.6) [14]. Moreover, fewer AEs of ≧ grade 3 occurred with TV than with CT (52.0% vs. 62.3%) [14]. All suggested the use of second- or third-line TV for treating recurrent CC resulted in significantly greater efficacy than CT with respect to PFS, OS and ORR [14].

Although ADCs seem to be exciting for treating GC patients [12–15], there are many challenges remained on the road to widespread adoption and optimization of ADCs in clinical practice, including fine-tuning antibody specificity and affinity, optimizing linker design for enhanced stability and payload release kinetics, mitigating off-target toxicity, and overcoming mechanisms of resistance [10]. Additionally, ADCs-related AEs, highly dependent on differences in the antibody target and payload with less influence from the linkers, cannot be neglected, such as premature release of cytotoxic payloads into the bloodstream, leading to immune responses resulting in secondary damage [9,16]. Common AEs secondary ADCs are ocular disorders, pneumonitis (interstitial lung disease-ILD), digestive system reactions (diarrhea), and peripheral neuropathy [9]. The possible mechanisms have been proposed by Nguyen et al. including (1) on-target, off-tumor toxicity: expression patterns of target antigen ratio with tumor expression, and not necessarily payload-dependent, (2) off-target, off-tumor toxicity: predominant and related to the payload and the linker, (3) target-independent ADC uptake: non-specific endocytosis and Fc/C-type lectin binding (their non-specific binding with other receptors such as the mannose receptor causes off-target toxicity): immune cells and megakaryocytes [11,17]. In fact, the off-target effect is one of the critical aspects of the ADC mechanism of actions in the "bystander killing" effects, which is particularly beneficial in treating heterogeneous tumors with varying antigen expression when the released cytotoxic payload can successfully diffuse from the tarted tumor cells to neighboring cells, including cancer cells defective expression of the targeted antigen and cell from the surrounding TME [1].

In conclusion, as shown by Cantillo et al. in their publication entitled "Updates in the use of targeted therapies for gynecologic cancers." of the *American Society Clinical Oncology Education Book*, GC patients have had newly approved treatment options and more that are heading toward approval, but these options should be guided by biomarkers-specific to tumor biology and have allowed response and survival to be better than the outcomes based on current SOC or treatment of choice therapy, because there are still treatments that are needed for patients with little response to the current SOC treatments or for those who will progress on these SOC treatments [9]. This editorial summarizes the use of ADCs treatment options and how to tailor ADC-based treatments with mitigation strategies for potential AEs. As the field is continuously changing or altering our SOC or preferred therapies, the benefits and risk ratio (B/R) should be carefully monitored for balance, because any attempt to prioritize which treatments and the mitigation strategies are options for our patients [9].

Conflicts of interest

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Editorial

Antibody–drug conjugates (ADCs) may be a big breakthrough in gynecologic cancer treatment (II): Anti-HER2/*neu*

In the part I, we have reported the recent development of antibody–drug conjugates (ADCs) in the management of many cancers, including the basic structure, mechanisms and treatment-related adverse events (TRAEs) as well as the potential limitations of ADCs (target-specific monoclonal antibody [mAb], linker and payload) for the clinical practice [1]. Additionally, two ADCs (mirvetuximab soravtansine-gynx [MIRV], and tisotumab vedotin [TV]) have been approved by United States Food and Drug Administration (US FDA) based on their safety and efficacy of two common gynecologic cancers (GCs, including epithelial ovarian cancer [EOC], and cervical cancer [CC]) by two randomized controlled trials (RCTs, MIRASOL and innovaTV 301/ENGOT-cx12/GOG-3057) [1]. This ADCs-addressing advance is recognized and sooner [1]. In this part II, the expanding knowledge and evidence related to clinical use of another ADC, which is also recognized and sooner approved by US FDA in the management of various cancer, and GCs (EOC, CC and endometrial cancer [EC] inclusive). Trastuzumab deruxtecan [T-DXd] is designed for treating cancer patients with overexpressed human epidermal growth factor receptor 2 (HER2/neu) or gene amplification or mutation. This editorial is limited to brief summary and focusing on patients with GCs.

With better understanding of immune-oncology (IO) field, antibody-mediated targeted therapy, especially monoclonal antibody (mAb) is the fastest-growing class, opening a brand-new therapeutic window for those patients with advanced, metastatic, persistent, or recurrent (AMPR) cancer status having been treated with the standard-of-care (SOC) therapy but the cancer status is out of control, and additionally, there is very limited selection or even absence of further treatment opinion [2–6]. Besides, mAb targeted programmed cell death 1 or its ligand (anti-PD-1 or anti-PD-L1, often called immune checkpoint inhibitors [ICI]) which has been widely accepted in the management of various complicated AMPR cancers with a dramatical improvement of overall outcomes of the certain-type population, such as CPS $\geqq$1-CC patients (evaluating the number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] relative to all viable tumor cells) [5,6] and deficient DNA mismatch repair (dMMR) EC patients [7], ADCs may provide a better chance to control biodistribution of the payload (powerful cytotoxic agents) to maximize drug delivery to destination site (tumor cells) and minimize cytotoxicity elsewhere, mediated by linker connecting the specific-targeting ability of mAb, producing novel mechanisms of action that can overcome obstacles of the current SOC therapy, with their efficiency rooted in the section of the mAb, epitope, payload, linker, and drug-to-mAb ratio (DAR) [2]. The mAb of ADCs is designed to target complexes located on surface of cancer cells, which play a determinative and key cellular pathway for cellular proliferation, growth and dissemination (metastases) [2]. Among these targeted sites, one such pathway of interest in GCs involves HER2/neu [2].

HER2, protein encoded by the protooncogene *ERBB2* on chromosome 17q12, a 185 kDa,1,225-aminoacid (AA) transmembrane glycoprotein tyrosine kinase (TK) receptor belonging to the epidermal growth factor receptor (EGFR) family, comprises an extracellular domain, a transmembrane lipophilic segment, and an intracellular TK domain [8]. Activation of HER2, an orphan receptor as it does not have a direct ligand, needs dimerization by itself or other HER family, such as the most activator as HER3 to present homodimerization (HER2/HER2) or heterodimerization (HER2/HER3), leading to activation of the intracellular TK function by autophosphorylation which in turn leads to activation of at least three major intracellular signaling cascades, including (1) the mitogen-activated protein kinase (MAPK)/Ras/Raf for regulating cell mitosis; (2) the phosphatidylinositol 3′-kinase (PI3K)/AKT pathway for cell proliferation and apoptosis; and (3) the phospholipase Cγ (PLCγ)/protein kinase C (PKC) pathway [8]. In normal physiology, HER2 expression is restrictedly controlled because it serves a crucial role in stimulating cell proliferation, differentiation, and survival [9]. If overexpression of protein and amplification or mutation of gene in HER2 occur, cell cycle, proliferation, differentiation and survival are de-arranged and dysregulated, resulting in the catastrophic situation as cell overgrowth and malignant transformation [2].

The significance of HER2 stems from the observation of its overexpression, amplification, mutation across various cancer types, including breast, gastric, biliary tract, bladder, pancreatic and GCs, and often associated with a biologically aggressive tumor phenotype, AMPR diseases, an increased risk of development of chemotherapy (CT) resistance, as well as poorer progression-free survival (PFS) and overall survival (OS) [9–11]. HER2-targeted therapy, such as trastuzumab, pertuzumab, and margetuximab, originally was approved in breast, gastric, colorectal and lung cancers [9–11], and the efficacy has mainly depended on overexpression or amplification of HER2, which is a target-driven tissue-agnostic therapy in precision oncology to get the right agent to the right patient with the right genomics. However, defining HER2 positivity is not easy and becomes the biggest challenge as the degree and pattern of HER2 expression vary greatly between different tumor types and different diagnostic criteria, leading to multiple definitions for “HER2-positive” [8]. The typical discrepancy of diagnostic HER2 expression (immunohistochemistry [IHC] staining) is found

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between breast and digestive tract system, based on anatomic location and an incomplete basolateral membrane staining (a relatively uniform and circumferential staining on IHC for breast cancer while lateral and basolateral [U-shaped] staining on IHC for gastric and uterine serous carcinoma) as well as intratumor heterogeneity, and reproducibility of intra- and inter-observer' interpretation (discordance of pathologist's interpretation) [8,12]. The IHC staining is classified as negative (0–1), equivocal (2+), and positive (3+) according to the extent and pattern of membrane staining [8]. When IHC cannot work for identification of HER2 expression, another tool used to evaluate the HER2 amplification can be done by in situ hybridization (ISH) assays on specimens, which calculated the ratio of HER2/*neu* to chromosome enumeration probe 17 (HER2/CEP17) and number of *ERBB2* gene copies per cell, allowing tumor with an IHC 2+ with FISH HER2/CEP17 ratio $\geq$ 2.0 or <2.0 with average HER2 copy number $\geq$ 6 nucleus to be designated as HER2-positive tumors [12]. Furthermore, two major modifications to determine the positivity/negativity of HER2, including new reclassification of HER2-zero (IHC 0) and HER2-low (ICH 1+ or 2+ with negative ISH) labels have been proposed due to poor concordance of HER2 negative to clinical response treated with anti-HER2 drugs [9]. Moreover, alternative tools to determine HER2 amplification by next-generation sequencing (NGS), comprehensive genome sequences, and liquid biopsy to detect *ERBB2* alterations in circulating tumor DNA (ctDNA) as a plasma biomarker have been continuous in development and the recent reports are highly recommended based on their excellent agreement [9,12]. However, these novel technologies are still limited by a small sample size and high cost, which may be too premature to claim their superiority over current testing modalities (IHC and ISH) [12].

The promising advance of ADC anti-HER2 strategy in the management of any HER2-positive AMPR solid cancers (endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and others) having been treated with at least one or more prior standard-of-care (SOC) treatment can be validated by recent phase 2 study (DESTINY-PanTumor02, NCT04482309), which enrolled 249 participants attempting to evaluate the efficacy and safety of T-DXd (Enhertu) for treating these poor-outcome patients without another better choice therapy [13]. In all patients, the objective response rate (ORR) was 37.1% (95% confidence interval [CI] 31.3–43.2), with responses in all cohorts; the median duration of response (DOR) was 11.3 months (95% CI 9.6–17.8); the median PFS was 6.9 months (95% CI 5.6–8.0); and the median OS was 13.4 months (95% CI 11.9–15.5) [13]. The more promising results to improve the overall outcomes can be found in patients with central HER2 IHC 3+ expression with nearly two-fold increase of benefits compared to all cohorts, the ORR was 61.3% (95% CI 49.4–72.4); the median DOR was 22.1 months (95% CI 9.6~not reached [NR]); the median PFS was 11.9 months (95% CI 8.2–13.0); and the median OS was 21.1 months (95% CI 15.3–29.6). In term of evaluation of subgroup for GC patients, the results are particularly exciting and attractive, including ORRs as 57.5% (95% CI 40.9–73.0) for EC, 37.5% (95% CI 22.7–54.2) for CC, and 42.5% (95% CI 27.0–59.1) for OC, respectively; median PFS as 11.1 months (95% CI 7.1~NR) for EC, 7.0 months (95% CI 4.2–11.1) for CC, and 5.9 months (95% CI 4.0–8.3) for OC, respectively; and median OS as 26.0 months (95% CI 12.8~NR) for EC, 13.6 months (95% CI 11.1~NR) for CC, and 13.2 months (95% CI 8.0–17.7) for OC, respectively [13]. All suggest that anti-HER2 ADC by T-DXd as a breakthrough therapeutic approach for AMPR GCs. Moreover, grade $\geq$3 TRAEs were observed in 40.8% of patients; 10.5% experienced adjudicated drug-related interstitial lung disease (ILD), with three deaths in all 249 patients [13]. Therefore, the DESTINY-PanTumor02 results support the durable clinical benefit, meaningful survival outcomes, and safety consistent with the known profile (including ILD) in pretreated patients with HER2-expressing tumors and greatest benefit was observed for the IHC 3+ population after T-DXd treatment [13]. Evidence further favored the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors [13], resulting the US FDA granting and accelerating approval to T-DXd for the tissue-agnostic treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment but have not satisfactory alternative treatment options, making it the first ADC available for the treatment of patients with AMPR cancers presenting HER2 3+ in IHC, and of course, GCs are included [14].

Finally, ADCs-carrying HER2/*neu* targeted therapy showed its efficacy and safety for the treatment for AMPR GCs presenting HER2 overexpression (IHC 3+ or ISH +) which have been exposed by prior SOC therapy. However, there is no doubt that primary treatment (front-line therapy) may be more meaningful for the certain-type cancer population with poor outcomes treated with the current SOC therapy, particularly for those accompanied with overexpression of HER2. Similar to integration of molecular biomarkers into the conventional clinico-pathological staging systems of many cancers altering the treatment of priority [15–17], the concept such as “one shoe fits all” should be reconsidered by its appropriation, since biomarkers-guided therapy has become more and more important, not only for efficacy but also for safety. We are looking forward to seeing the results from more and more current ongoing RCTs to offer the stronger evidence to support their feasibility and better benefit-and-risk ratio for these AMPR cancer patients who may often fail their competition with cancer.

Conflicts of interest

Drs. 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 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

Long-term dienogest treatment in endometriosis: Consensus from Taiwanese experts

A B S T R A C T

Dienogest has been proven effective as long-term therapeutic option for pelvic pain caused by endometriosis. However, in Taiwan, there is a lack of a well-tailored consensus on its long-term administration. To address this gap, Taiwanese experts in collaboration with the Taiwan Endometriosis Society (TES), convened to provide structured recommendations on dienogest treatment and monitoring strategies. Drawing from clinical evidence and collective expertise, the experts formulated individualized treatment strategies based on treatment objectives and the patient's demographics. The experts recommend long-term dienogest administration for endometriosis patients for appropriate symptom control while reducing the risk of disease recurrence. Specifically, they recommend regular ultrasound examinations and relevant blood tests to monitor disease progression and therapeutic response with additional breast screening for patients at high risk for breast cancer. These recommendations aim to provide physicians with comprehensive guidance on the long-term administration of dienogest for endometriosis, ensuring patient safety and optimizing treatment outcomes.

Endometriosis is a chronic gynecological condition characterized by the ectopic presence of endometrial tissue and affects approximately 1 in 10 women of reproductive age [1,2]. Patients with endometriosis experience chronic pelvic pain and infertility, accompanied by several systemic comorbidities such as thyroid disease, dyschesis, immunological dysfunction, and even ovarian cancers. Dienogest, a 4th generation synthetic progestin, has emerged as a promising therapeutic option due to its effectiveness in managing endometriosis symptoms [2–4]. However, in Taiwan, there is a lack of consensus on dienogest administration in treating endometriosis.

To address this issue, 13 Taiwanese experts convened and deliberated on the extended use of dienogest (>2 years) across diverse patient profiles. Before the meeting, a comprehensive survey was conducted to ascertain the current landscape of endometriosis treatment with dienogest. The survey results served as the foundation for discussions during the expert meeting, where specific polling questions were provided to establish consensus on addressing key challenges associated with the long-term use of dienogest and to formulate monitoring strategies during dienogest treatment. The Taiwan Endometriosis Society served as a reviewer during the entire process and approved the consensus recommendations.

Grounding on the pre-meeting survey results, the experts subsequently formulated individualized treatment plans for endometriosis according to age group and their corresponding treatment goals, and the type of endometriosis. Additionally, they provided guidance on monitoring strategies for both the general population and subgroups with specific concerns pertinent to dienogest treatment. These recommendations were specifically tailored for obstetrician-gynecologists or other healthcare providers managing endometriosis patients undergoing extended dienogest treatment.

The pre-meeting survey revealed that ovarian endometriosis (OMA) and adenomyosis, commonly referred to as endometriosis of the uterus, are among the most frequently encountered and treated types of endometriosis. Most experts prescribed dienogest for their patients with a treatment duration extending beyond two years. Notably, clinicians commonly observed that those with adenomyosis and individuals in their 30s–40s, often require longer treatment durations. Based on the experts' collective clinical experience, symptom management and mitigating recurrence emerged as the two most important considerations determining the patient's treatment continuity. Some experts suggested that ovarian function preservation could serve as a motivating factor for patients to continue dienogest treatment.

The experts recommend dienogest as the first-line treatment for symptomatic endometriosis patients unless surgery is required. In cases where patients require surgery, dienogest is recommended to be continued as maintenance hormone therapy post-surgery [4–6]. An observational study found that patients receiving hormonal therapy before and after surgery had significantly lower reoperation rates due to recurrence compared to those receiving hormonal therapy only after their first surgery [5]. Presently, the consensus among Taiwanese experts recommends a minimum of two years of dienogest administration to manage symptoms and

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Table 1
Proposed Management and Monitoring Plan of Patients with Endometriosis undergoing Long-Term Dienogest Therapy.

Age group (years)	Main goal of long-term treatment	Long-term monitoring plan
12–18	Pain management and preservation of normal BMD	Standard monitoring[a]
19–29	Primary goal: Pain management Secondary goal: Preservation of fertility	Standard monitoring[a]
30–40	Preservation of ovarian function in patients planning to conceive	Standard monitoring[a]
>40	Sustained treatment until menopause	Standard monitoring, plus breast cancer screening. For patients <45 years, breast ultrasound is recommended over mammograms

BMD, bone mineral density; E2, estradiol.
[a] Standard monitoring includes ultrasound examinations every 3–6 months; relevant blood test every 6–12 months; and testing for serum E2 levels as necessary to maintain serum E2 levels between 40 and 60 pg/mL.

mitigate recurrence effectively. A comprehensive medical history and appropriate patient counseling are essential, along with early lifestyle modifications and health education on risk factors and preventive measures.

The experts advise a structured approach based on age group and treatment goals. For adolescents (aged12-18), the treatment goal is symptom control, with consideration on the benefit-risk ratio of dienogest 2 mg, particularly regarding risk of bone loss in this population. Given the importance of bone accretion during adolescence, whenever dienogest is prescribed, it should be paired with appropriate exercise and calcium supplementation [7]. For women in their 20s, the primary treatment objective is symptom management, particularly pain control and fertility preservation. On the other hand, for those aged between 30 and 40 years, fertility and reproductive plans should be carefully considered and discussed with the patients. Dienogest may be offered to preserve ovarian function in those not immediately seeking to conceive. Women over 40 years are typically motivated to receive treatment until menopause, warranting a more individualized assessment and monitoring. The strategy includes a comprehensive medical history before drug initiation, followed by regular monitoring. The treatment and the monitoring plan for long-term dienogest therapy are shown in Table 1.

Dienogest is recommended as the first-line medical therapy for all types of endometriosis, including OMA, adenomyosis, and deep infiltrating endometriosis (DIE) [2,4]. Despite its well-substantiated efficacy, the risk of bleeding remains a challenge [8], particularly in patients with adenomyosis. Based on the experts' clinical experience, bleeding usually occurs within the first three months of treatment. For persistent bleeding, hysteroscopy is advised to assess endometrial pathologies. If irregular shedding is observed, combining treatment with Mirena® (levonorgestrel-intrauterine device [IUD]) or a gonadotropin-releasing hormone (GnRH) agonist is advised [9]. Estrogen may be incorporated into the treatment if endometrial atrophy is present. For patients with DIE, medical therapy with dienogest may be initially considered, with surgery being an alternative if medical therapy is inadequate. Overall, a personalized approach, considering the type and severity of endometriosis, and individual patient factors and preferences, is essential for optimizing treatment outcomes.

According to published guidelines, follow-up and psychological support are crucial in women with confirmed endometriosis, especially those with OMA and DIE [10]. The Taiwanese experts recommend a monitoring regimen focused on monitoring disease progression and assessing drug response across all types of endometriosis and patient populations. The recommended monitoring plan includes ultrasound examinations every 3–6 months and relevant blood tests every 6–12 months. Serum estradiol (E2) levels may also be monitored to ensure the patient's reference range remains between 40 and 60 pg/mL. The recommended monitoring strategy and tests for endometriosis patients undergoing long-term dienogest treatment are detailed in Table 1.

The experts highlight that patient perception about the safety of long-term dienogest treatment may pose a significant challenge to extending its use beyond two years. On the contrary, a recent study from the National Taiwan University Hospital [11] found no increased risk of breast cancer with long-term dienogest therapy. Nevertheless, for patients in their 40s or those concerned about breast cancer risk, regular breast cancer screening is recommended following Taiwan's breast cancer prevention guidelines [12]. Additional breast examinations are advised for patients with palpable breast tumors, breast discomfort, or a family history of the disease [11]. Whenever concerns about venous thromboembolism (VTE) risk arise, blood coagulation studies may be conducted every six months during treatment initiation, followed by annual monitoring once the patient's condition stabilizes [13]. Notwithstanding, international guidelines underscored that progestogen-only pills, including dienogest, do not increase the risk of VTE [14]. A study also revealed that coagulation parameters remain within the normal range for patients undergoing dienogest therapy for up to 60 months [8].

Additionally, the experts recommend drug holidays [15] based on the patient's treatment response and desire to continue the therapy. If adequate pain control is not achieved after nine months, a three-month course of GnRH agonist therapy is advised [1], followed by the resumption of dienogest upon symptom improvement. This strategy may improve patient adherence and treatment outcomes. Furthermore, cyclic administration of dienogest is also suggested to manage bleeding during treatment [16].

In summary, the experts propose strategies for the long-term use of dienogest in women with endometriosis and address the associated challenges. They also recommend comprehensive and individualized monitoring tailored to address patients' concerns across different age groups and endometriosis subtypes. This consensus will be updated as new data emerges.

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Review Article

Predictors and outcomes of Mid-urethral sling continence surgeries for stress urinary incontinence among Taiwanese women: What works best?

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A B S T R A C T S

Mid urethral sling (MUS) surgery is a widely accepted and safe procedure performed for stress urinary incontinence (SUI) with excellent cure rate besides its minimal complications. There are various types of MUS which can be offered. In this review we collated published data on MUS surgery performed among Taiwanese women with SUI in search for the best techniques and its outcome. We reviewed 77 articles, searched using PubMed platform related to MUS in USI among Taiwanese women from 1998 to 2023.24 articles, total 2733 participants with at least 12 months follow up after MUS. Objective cure rate for trans-obturator tape (TOT), retropubic sling (TVT, tension vaginal tape), single incision sling (SIS) (Solyx) and SIS (MiniArc) are 80%–92%, 88%–94%, 87%–90% and 87%–91% respectively, while subjective cure is 60%–90% in TOT, 86% in SIS (Solyx) and almost 90% in SIS (MiniArc), Predictors for surgical failure analyzed in 5 papers of 1006 women. Identifiable risk includes low maximal urethral closure pressure, intrinsic sphincter deficiency, previous anti SUI or prolapse surgery, presence of neurogenic disease, constipation, decreased bladder sensation, age >65 years, high pad test, Diabetes, detrusor overactivity, post-menopausal, reduced postoperative urethral mobility and tape percentile. Subsequently we dwell into complications of each type of MUS. This review showed the evolution of MUS and its comparable therapeutic efficacy. However, with certain complication rates and predictors for failure. This will add value in preoperative counselling while taking into accounts patients' factors in choosing the appropriate types of MUS. Future research is needed on long term effectiveness and risk of future recurrence.

Introduction

Stress urinary incontinence (SUI) or activity related incontinence is jointly defined by International Urogynecological Association (IUGA) & International Continence Society (ICS) as involuntary loss of urine on effort or physical exertion [1]. Though isn't life threatening, it's debilitating condition negatively affect the psychosocial, health, hygiene, sexual and quality of life with prevalence of 18% among Taiwanese women [2]. Diagnosis is based on symptoms or observation (clinical SUI) of involuntary leakage from urethra synchronous with exertion or coughing [3], while urodynamic investigations (urodynamic stress incontinence) involves the finding of involuntary leakage during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction. Although conservative management such as

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vaginal cones or pelvic floor muscle therapy may be offered in this group, surgery offer the best objective and subjective cure rate with good safety profile [4].

Modified intravaginal slingplasty because its novelty introduction in 1996 [5] has received numerous alterations and modifications making it a popular choice of treatment for stress urinary incontinence. Other historical procedure includes retropubic urethropexy (RPU), pubovaginal sling (PVS) and previously Kelly plication, needle suspension and periurethral injection [6]. Landmark paper by Wang et al., 1998 showed 84% continence achieved after a vaginal tape surgery, comparable to other invasive surgery [7] has open the way for mid urethral sling surgery (MUS) in Taiwan. High-quality scientific publications and international society has endorsed the safety and effectiveness of MUS [8], this is evidence by noticeable increase in surgical trends and a paradigm shift for female SUI surgery which also entice the older women to seek treatment and undergo surgery [6,9]. With numerous marketed mid urethral sling devices, there must be a way to select one from another. This article aims to review the various types, outcome, possible risk factors contributing to failure of MUS which in turn may assist in MUS selection, and patient counselling during inform consent prior to surgery.

Materials and methods literature search and data synthesis

We conducted a literature search from PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(midurethral%20sling)%20AND%20(women)&filter=years.2010-2023) using search term 'mid-urethral sling women' limited from 1998 to 2023. We included English language, systematic review, RCTs, large prospective studies and retrospective cohort. Case series with less than 15 samples, case reports and associated mesh surgery were excluded. The search yield 2171 results, 98 literatures pertaining to Taiwanese population and after exclusion, 77 articles were included. 24 papers on outcomes after MUS, 13 papers compare different types of MUS, 7 on complication, 5 papers on long term outcome of MUS, 3 discuss on furthermore treatment after MUS failure, 2 articles on different practices in other Asian countries and the evolution of MUS surgery, 2 innovative papers in dealing with urethral obstruction after MUS, management of complication in 3 papers, 5 discuss risk factors associated with MUS failure, remaining 7 papers on tape assessment through ultrasonography, remaining on procedure related, animal studies and important case reports as illustrated in Fig. 1.

The present study collated results on outcome, risk factors/predictors of MUS failure and complications associated with different types of MUS namely, retropubic mid-urethral sling (MUS-r), Trans-obturator tape (TVT-O; TOT (inside-out), TOT (outside in) and single incision sling (SIS). The mid- and long-term outcome reports was summed up and discussed. The intrinsic sphincter deficiency (ISD)/low maximal urethral closure pressure (MUCP), repeated MUS studies were analysed and deliberated.

Several studies provided both objective and subjective success rates while others did not. In the present study, the objective and subjective cure were adopted for analysis, if any. Types of surgery were also illustrated on a bar graph according to the year studied.

Results

Keeping in mind numerous techniques and characteristics of MUS available, the authors analyzed the data according to its different types, however limited to data being presented in the literature. The different types of MUS discussed in this paper includes Transobturator Tape (TOT-outside in) i.e Monarc™ (AMS, Minnetonka, MN, USA), Obtryx™ (Boston Scientific Corporation, Marlborough, MA); TVT-O™ (TOT inside-out) (Gynecare TVT™ Obturator System, USA); Mid-urethral Sling-retropubic (MUS-r), i.e. TVT™ (Gynecare TVT™ System, USA), SPARC™ (Suprapubic Arc Sling, AMS, Minnetonka, MN, USA)); Single Incision Sling (SIS) i.e MiniArc™ (AMS, Minnetonka, MN, USA), Solyx™ (Boston Scientific Corporation, Marlborough, MA), Ajust (C.R. Bard, Covington, GA, USA) or I Stop Mini ™ (CL Medical, Winchester, MA).

We extrapolate 104 cases based on different types of MUS surgery (as illustrated in Fig. 2) from 77 papers that were included for analysis from 1998 to 2023. The bar chart indirectly displays the trend of MUS surgery overtime. TVT was first introduced in 1998, however it regresses after 2010, subsequent studies involves either retrospective study or case reports on its long-term complications. TOT (inside-out) reported from 2006 to 2013. From 2006, TOT (outside-in) was prevalent till current even with introduction of SIS in 2014.

24 papers were available for analyses of 'cure rate' with minimum follow up of 12-month, up to 5 years with 2733 patients. Reliable tools were used to assess cure which include pre- and post-op questionnaire such as UDI-6, IIQ -7 and the use of urodynamic study (UDS). Objective cure rate was defined as no demonstrable involuntary leakage of urine during multichannel UDS and a 1-h pad test weight <2 g. Subjective cure of SUI was based on negative response to UDI-6, question 3 i.e. no urinary leakage on coughing, laughing or sneezing. A score of >1 on this question indicated failure [10–12].

Table 1 reports the objective and subjective cure rate of each type of MUS with minimum 1-year follow up. Objective cure rate for TOT, TVT, SIS (Solyx) and SIS (MiniArc) were 80%–92%, 80%–94%, 87%–90% and 87%–91% respectively, while subjective cure were 60%–90% in TOT, 86% in SIS (Solyx) and almost 90% in SIS (MiniArc). Isolated paper by Long et al. comparing prepubic TVT and TVT (Gynecare) defined 'cure' as patient who felt no more SUI symptoms, 83% vs 80% achieved cure respectively with p0.61 [13]. Women with previous history of vaginal mesh surgery attained 88% significant cure with TVT vs 60% with TOT with p 0.036 [13]. Low cure rate was reported in women with presence of intrinsic sphincter deficiency preoperatively with all types of MUS [12].

Table 2 depicts risk factors associated with failure of MUS surgery. 5 trials with a total of 1006 participants were evaluated. 4 out 5 were in agreement that lower maximum urethral closure pressure (MUCP) is an independent risk factor for failure of MUS, followed by intrinsic sphincter deficiency (ISD), and small cystometric capacity. Other identifiable risk include previous anti SUI surgery, previous prolapse surgery, presence of neurogenic disease, constipation, decreased bladder sensation, age >65 years, high pad test, Diabetes, detrusor overactivity, post-menopausal status, reduced postoperative urethral mobility and tape percentile.

Table 3 shows complications associated to types of MUS surgery.

Discussion

Prevalence of SUI among Taiwanese women were reported to be around 18%–19% [2,15] which is well within the internationally quoted incidence of 4–30% [1,16].

Initial management includes conservative measures to strengthens the pelvic floor and when it fails, surgery will be advised with mid-urethral sling surgery (MUS) being the most popular continent surgery for the last few decades due to its minimally invasive approach, high cure rate, shorter operation and recovery time as compared to other SUI procedures [17]. In Taiwan, the frequency of MUS surgery significantly increased from 27.1% to 52% and became more popular to 75.8% from (1999–2003) to (2004–2008) to (2009–2013), replacing the retropubic urethropexy (13.1%) and injectables (6.7%) during the latter period [6].

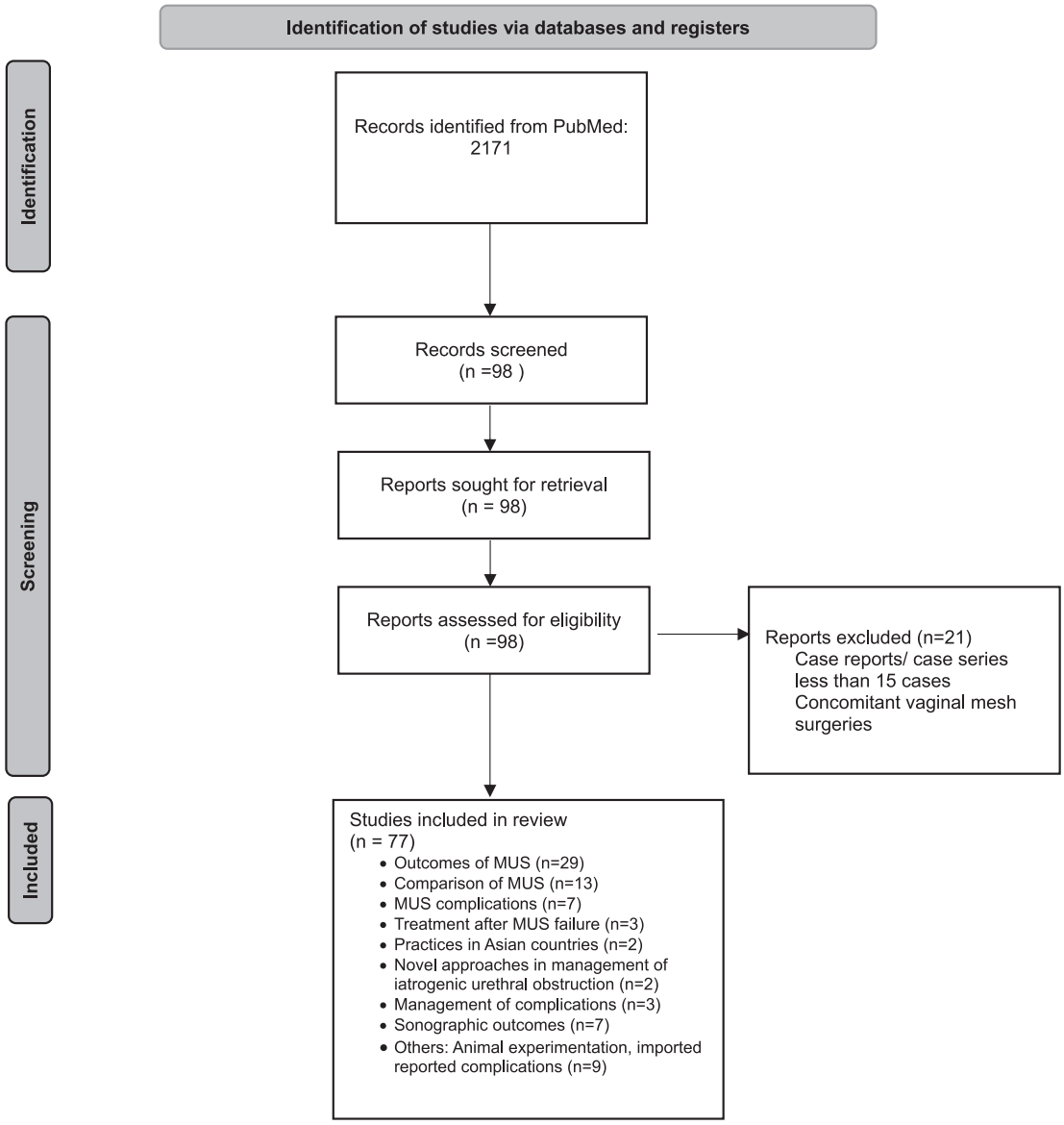


Fig. 1. PRISMA flow diagram
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71.

Objective and subjective cure

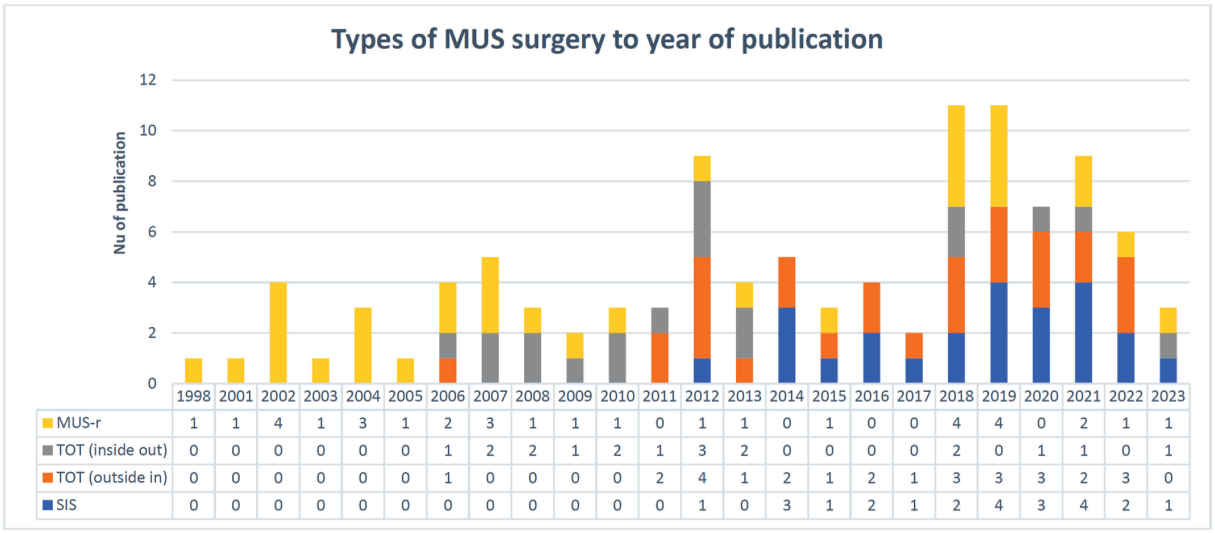
All MUS deliver good outcome, even at 3-year follow up objective and subjective cure rate are close to 90% be it trans-obturator tape or single incision sling. When looking at superiority between the devices, no significant difference were noted between TOT (Monarc or Obtryx [18]), MUS-retropubic/suprapubic (SPARC) (TVT) [19,20], SIS (Solyx [21], MiniArc) [22] or adjustable SIS (Ajust/Istop Mini) [23] in terms of cure rate which is also seen in a prospective study done by White et al. with 3 year follow up [24].While only 1 paper [11] really compare the outcomes of 3 different types of MUS, results from different studies also conquer with similar findings [22,25,26]. However certain risk may reduce its outcome and will be elaborated further.

Positive outcomes of MUS surgery in Taiwan can be detailed out by several reason, firstly the trial and surgery were all conducted in tertiary centre by a specially trained and credential urogynecologist. MUS were performed more by gynecologists than by urologists [6]. Slings except SIS were also subsidised by government health insurance for the patient that increases the number of surgical cases. Besides, Taiwan urogynecology academic training demands the extra 2 years of special training after completing the 4 years of obstetrics & gynecology residency followed by passing of written and oral exam before one is certified to be a urogynecologist.

Failure risk

Detailed preoperative assessment with validated tools (questionnaire) and UDS for triaging, and risk assessment were crucial to prepare patients on the expected outcome.

Identifiable risk associated with MUS failure were history of anti-incontinence surgery-anterior repair, Burch, needle suspension or prior sling surgery [27]. These might be associated with previous scarring, denervation and hypomobility of urethra. Age $\geq$60 years, hypoestrogenism, reduced collagen, which is vital for urethral function make risk of failure 11 times higher [27]. In women with repeat MUS surgery [28], change in cotton swab angle test at rest and straining <30◦ (OR 4.6, 95%CI 2.5–7.9◦), change in



	1998	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
MUS-r	1	1	4	1	3	1	2	3	1	1	1	0	1	1	0	1	0	0	4	4	0	2	1	1
TOT (inside out)	0	0	0	0	0	0	1	2	2	1	2	1	3	2	0	0	0	0	2	0	1	1	0	1
TOT (outside in)	0	0	0	0	0	0	1	0	0	0	0	2	4	1	2	1	2	1	3	3	3	2	3	0
SIS	0	0	0	0	0	0	0	0	0	0	0	0	1	0	3	1	2	1	2	4	3	4	2	1

Fig. 2. Bar Chart Correlation between Types of Surgery and Year of Study Published
MUS-r: MUS- retropubic/Tension free vaginal tape
TOT (inside out): Transobturator vaginal tape (inside-out TOT) TOT (outside in): Transobturator tape (outside-in TOT)
SIS: Single incision sling/mini sling.

inclination angle <30◦, ISD (OR 3.4, 95%CI1.8–6.1) and maximal urethral closure pressure of <60cmH20 (OR 2.9 95%CI 1.5–4.5) negatively impact the success outcome [29]. These data also suggest that patient with hypermobility of urethra have better outcome with MUS surgery [28,30].

Mid-term and long-term outcome

Several long-term studies showed that although there were down going pattern, overall high cure rate was still achieved. At 5-year, TOT maintained high cumulative cure >85%; objective cure being 89.3%, subjective cure 87.5%. Patients with objective treatment failure doesn't even require repeat surgery [31]. While SIS showed declining pattern overtime, possibly from dislocation of its anchoring mechanism, its long term cumulative cure was still >80% [32], Lo et al. demonstrate that 89% maintain continence after TVT at 3-year [33] sonographically. When properly placed at mid urethra, it almost always fixed at its original site to provide dynamic urethral kinking [34]. Similarly, Yang et al. demonstrate that TVT-O tape still maintain its relative position with urethra although it may migrate distally with time, while continue to provide support to bladder neck through rotational urethral descent (also known as urethral knee or dynamic kinking) [35] with good overall cure >80% after 24 months [36].

Publications over years

MUS-retropubic was first introduced in 1990s by Ulmsten & Petros, SPARC (American Medical Systems, Inc., Minnetonka, MN, USA) in 2001. Both had almost comparable positive outcome with high patient satisfaction. These procedures adopted either top down (paraurethrally & retopubically) or upward passage of the trochar claimed to reduce risk of visceral injuries. In 1998 Wang et al. provided local data of its efficiency [7]. Unfortunately, there was sparse publication after 2010 except for retrospective cohort/observational study plausibly due to series of case reports on major complications from blind passage of the needle through retropubic space which halted its usage, among others were bladder perforation, retropubic bleeding, hematoma and voiding dysfunction [37] compared to TOT [38].

In order to minimize such complication, transobturator approach were developed, De Leval-inside-out transobturator, tension free urethral suspension (TVT-O) [39],Delorme-outside in (TOT) [40], Both with equivalent efficacy. After 2006, transobturator tape (inside-out) paved its way in Taiwan, its plus points were high cure rate, no bladder/urethral or vascular injury, but with post-operative gluteal pain and higher incidence of voiding difficulty. TOT in its earlier part was hindered by higher risk of penetration into lateral vaginal fornix and mesh exposure and tape erosion [38], yet it still remains as first choice in the market. Risk of BOO and postop voiding dysfunction was lesser [41]. Example of available TOT kits are Monarc, Kim (Neomedic International, Barcelona, Spain) and Obtryx.

Besides TOT, newer minimally invasive sling surgery, mini-sling or single incision sling gain its spots beginning 2014 and continue until now alongside transobturator tape. Various papers published attest to its efficacy similar to TOT despite its size [26,32,42].

In 2008, US FDA had issued warning against complications of mesh and marketing company were asked to prove their superiority and benefit. This has given a toll to women perception on sling uptake. Hence the static and reducing trend till 2010. Some kits were removed from the market; SPARC (MUS-r), Ajust (SIS) MiniArc (SIS) and Monarc (TOT).

Subgroup: age

Efficacy of MUS surgery in different age group with all three types of MUS were analysed. All types except SIS (MiniArc) provide similar cure, however TVT provide better outcome [43] likely attributed to presence of underlying ISD. Lo et al. described that the outcome reduces with age. 66.7%–80.6% objective cure and 58.3%–77.6% subjective cure was observed in elderly (65- to 74-year-old) and old (≥75 year old) population at 12 months review [11]. A Swedish nationwide register cohort study also in agreement with our local findings that the cure rate significantly reduce in elderly as observed in their data with similar age groups, from 89% to 81%–64% with $p < 0.001$ [44]. Although not demonstrated in earlier study [11], another published data indicate that age >65 and associated ISD [11,12,42,44] which is commonly seen in elderly as a risk factor for higher affinity for failed MUS surgery [45]. Persistent urgency and

Table 1
Outcome of 24 papers on mid-urethral sling surgeries with minimum follow up of 12 months to 5 years.

[a]	Author	Follow Up Period	Outcome (Cure)	Types Of MUS					P Value	Comments
				MUS-r	TOT (inside out)	TOT (outside-in)	SIS	Adjustable SIS		
1	Lo TS et al (2016) [31]	**5-year**				**Monarc**				
			Objective			50/56 (89.3)				
			Subjective			49/56 (87.5)				
2	**Lo TS et al (2018)** [32]	**5-year**					**MiniArc**			
			Objective				72/85 (84.7)			
			Subjective				68/85 (80.0)			
3	**Lo TS, et al (2018)** [50]	**3-year**				**Monarc**	**MiniArc**			
			Objective			72/82 (88.0)	51/56 (91.0)		0.545	
			Subjective			68/82 (83.0)	50/56 (89.0)		0.224	
4	**Lo TS et al (2022)** [42]	**3-year**					**Solyx**			
			Objective				77/88 (88.0)			
			Subjective				75/88 (85.0)			
5	**Su TH et al (2009)** [36]	**2-year**			**TVT-O**					
			Objective		51/67 (76.2)					
			Subjective		56/67 (83.5)					
6	**Liu PE et al (2011)** [47]	**2-year**			**TVT-O**					Population: obese & overweight patients
			Objective		103/129 (80.0)					
			Subjective		79/129 (61.0)					
7	**Tseng HL, et al (2005)** [20]	**2-year**	Objective	**TVT**						Objective cure define as pad test < or = 1 g
				27/31 (87.1)					0.706	
				SPARC						
				25/31 (80.7)						
8	**Wu LY et al (2016)** [22]	**20 months**				**Monarc**	**MiniArc**			Objective failure pad test >2 g Monarc vs Miniarc 10.2% vs 12.9% p 0.77
			Objective			61/68 (89.7)	47/54 (87)			
9	**Sun MJ et al (2016)** [52]	**18 months**					**MiniArc**			Obj cure 18/24 (88.9%), sub cure 79.2% in MUCP <40cmh20, obj. cure assessment at 3 months, subj. cure at 18 months
			Objective				72/88 (81.6)			
			Subjective							
10	**Lo TS et al (2005)** [34]	**18 months**		**TVT-A**						Compare between direction of device application Cure define as pad test <2 g/h without urinary leakage on urethral pressure profilometry (cough profile)
			Cure	40/45 (88.9)					1.000	
				TVT-V						
				41/45 (91.1)						
11	**Lin L et al (2018)** [14]	**18 months**		**TVT**		**TOT**				Population: post transvaginal mesh surgery
			Objective	29/33 (88)		29/43 (60)			0.036	
12	**Wang CA et al (1998)** [7]	**12 months**	Objective	**TVT**						Objective cure defined as pad test <5 g. Subjective cure no urine loss on exercise
				58/70 (83)						
			Subjective	61/70 (87)						
13	**Lo TS et al (2014)** [26]	**12 months**				**Monarc**	**MiniArc**			
			Objective			46/50 (92)	73/80 (91)		0.577	
			Subjective			45/50 (90)	72/80 (90)		0.624	
14	**Long CY et al (2013)** [13]	**12 months**		**TVT**	**PVT-O**					Imbalanced data, with different follow up time 64.2 vs 30.3 months, p < 0.01
			Cure Rate	74/93 (80)	80/97 (83)				0.61	
15	**Lo TS et al (2019)** [21]	**12 months**						**Solyx**		
			Objective					102/113 (90)		
			Subjective					97/113 (86)		

Table 1 (*continued*)

[a]	Author	Follow Up Period	Outcome (Cure)	Types Of MUS					P Value	Comments
				MUS-r	TOT (inside out)	TOT (outside-in)	SIS	Adjustable SIS		
16	**Lo TS et al (2020)** [11]	**12 months**	Objective	**(TVT)** 80/89 (90)		**Monarc** 230/257 (90)	**MiniArc** 191/220 (87) **Solyx** 106/122 (87)			
17	**Lo TS et al (2022)** [12]	**12 months**	Objective Subjective	**MUS-s (TVT)** 3/6 (50) 3/6 (50)		**Monarc** 12/19 (63) 10/19 (53)	**Solyx/MiniArc** 10/23 (44) 10/23 (44)		0.443 0.835	Population: preoperative intrinsic sphincter deficiency (ISD)
18	**Long CY et al (2009)** [37]	**12 months**	Objective Subjective	**TVT** 50/53 (94.3) 49/53 (92.5)	**TVT-O** 25/29 (86.2) 23/29 (79.3)				0.190 0.090	Lack statistical power, not reached optimum sample size
19	**Huang WC et al (2022)** [18]	**12 months**	cure			**Monarc** 126/138 (91.3) **Obtryx** 129/140 (92.1)				Cure/ continence defined as negative cough test and negative response to SUI symptoms
20	**Liang CC et al (2022)** [23]	**12 months**	Objective Subjective				**Solyx** 25/30 (89.3) 27/30 (90)	**Ajust** 25/30 (89.3) 28/30 (93.3)	1.00 0.64	
21	**Lo TS et al (2020)** [10]	**12 months** Preop USI + urgency preop USI + UD DO/ DOI	Objective Objective	**(TVT)** 15/18 (83.3) 9/15 (60)		**TOT** 20/24 (83.3) 13/23 (56.6)	**SIS** 39/48 (81.3) 15/29 (51.7)			Population: mixed urinary incontinence, results with normal UD postop,
22	**Chao WT et al (2023)** [55]	**12 months**	Subjective			**Obtryx** 55/69 (79.7)		**I stop Mini** 54/72 (75)	0.507	Population: severe SUI with ISD. Definition of subjective cure: negative response to (Q3) UDI-6
23	**Chao WT et al (2022)** [56]	**12 months**	Subjective			**Obtryx** 108/127 (85)		**I stop Mini** 156/171 (91.2)	0.097	At 6-month Obtryx vs I stop; 117/132 (89%) vs 167/180 (93%)
24	**Sun MJ et al (2013)** [54]	**12 months**	Objective Subjective		**TVT-O** 31/42 (74.4) 30/42 (71.4)		**MiniArc** 35/43 (81.8) 35/43 (81.8)			Objective cure is negative cough stress test

N = true number of cases in a study. Number in bracket (.) represent %. P < 0.005 regarded as statistically significant.
Definition.
Objective cure: absence of demonstrable leakage of urine on the cough stress test, provocative filling cystometry, and 1-h pad test of a weight <2 g; **Subjective cure**: negative response to Urogenital Distress Inventory Six (UDI-6) (question 3) i.e. no urinary leakage on coughing, laughing or sneezing, unless indicated in comment section.
TVT, tension free vaginal tape; **TOT**, tension free obturator tape, **MUS-r,** midurethral sling-retropubic, **TVT-O,** tension free vaginal obturator tape; **PVTO**, prepubic TVT-Obturator tape; **SIS**, single incision sling; **TVT-A,** craniocaudal TVT; **TVT-V,** conventional caudocranial TVT; **ISD**, intrinsic sphincter deficiency, **MUCP**, maximal urethral cystometric capacity; **UD,** urodynamic study; **SUI**, stress urinary incontinence; **USI**, Urodynamic stress incontinence; **DO**, detrusor overactivity; **DOI**, detrusor overactivity incontinence.
[a] The order on listing was based on the follow up period.

urge incontinence (UI), worst impression of improvement of lower urinary track symptoms [46] and detrusor overactivity were also more pronounced in elderly and old age [11]. Perioperative complications, hospital stay and safety were not different [11,43].

Sub-group: obese

Lower cumulative cure was seen in obese population as compared to normal BMI [47]. This data was further supported by a retrospective cohort study on 688 women, divided according to WHO body mass index classification as normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2) and obese (30 kg/m2 or greater). Women in obese group had worst objective (76%) and subjective cure (70.7%) with all 3 types of MUS except TOT [48]. SIS failure from fixing mechanism and shorter mesh anchorage system [49,50]. Age ≥66 years, menopause, previous prolapse surgery, Diabetes Mellitus were identified as dependant predictors of MUS failure in obese group [48]. No different in complication rate observed.

Sub-group: previous MUS failure, repeated MUS, ISD and low MUCP

Maximal urethral closure pressure (MUCP) represents the intrinsic strength of the urethra at rest. The normal measurement for MUCP was taken as 60 cmH2O based on the study done by Sørensen et al. [51]. Low MUCP were significantly associated with persistent

Table 2
Risk factors/Predictors associated with negative outcome or failure of midurethral sling surgery in 5 trials.

	Author	Type	Definition of negative outcome or MUS failure	Risk factors	Comments
1	Lo TS et al. (2019) [21]	SIS (Solyx) Obj failure: 9.7% (11/113) Subj failure:14.2% (16/113)	Obj failure: presence of USI and/or a pad weight >2 g Subj failure: a score of >1 on UDI-6, question 3. (i.e. no urinary leakage on coughing, laughing or sneezing, indicates failure)	✓ Previous anti- SUI surgery, previous prolapse surgery ✓ Neurogenic disease ✓ Constipation ✓ ISD ✓ MUCP <40cmH_20	Bladder neck hypomoblity and poor urethral function continence surgery itself might have worsened the detrusor instability previously inflicted by the weakened endopelvic fascia or damaged pelvic floor
2	Lo TS et al. (2020) [11]	SIS (Solyx/MiniArc) TOT (Monarc), MUS-r (TVT) in elderly women	Obj failure: presence of USI and/or a pad weight >2 g Subj failure: a score of >1 on UDI-6, question 3. (i.e. no urinary leakage on coughing, laughing or sneezing, indicates failure)	✓ ISD (defined as urine leakage on VLPP <45cmH_2O in a symptomatically full bladder)	
3	Lo TS et al. (2021) [45]	SIS (Solyx, MiniArc), TOT (Monarc), MUS-r (TVT)	MUS failure: presence of USI and/or pad test ≥2 g. De novo urgency: a positive response to question 2 on the UDI-6.	Independent risk factors for DO ✓ age ≥66: (OR, 1.07 [1.01–1.13]) ✓ CC1<150: (OR, 3.80 [1.15–13.1) ✓ MCC<300: (OR, 4.97 [2.01–13.9) ✓ MUCP<40: (OR, 5.20 [1.98–13.1) ✓ Pad test>100 g: (OR, 1.15 [1.05–1.29) Independent risk factors for urgency ✓ age ≥66: (OR, 1.23 [1.05–1.25]) ✓ CC1<150: (OR, 4.18 [2.08–10.78]) ✓ MCC<300: (OR, 5.28 [2.89–10.03]) ✓ MUCP<40: (OR, 2.332 [1.21–4.13]) ✓ Pad test>100 g: (OR, 1.08 [0.96–1.18]) ✓ DM: (OR, 1.32 [1.01–3.03])	Presence of de novo urgency and DO following MUS in patients with USI without urgency
4	Lo TS et al. (2020) [10]	SIS (Solyx/MiniArc) TOT (Monarc) MUS-r (TVT)	SUI: presence of demonstrable involuntary leakage of urine during increased abdominal pressure on filling cystometry and the cough stress test DO: presence of spontaneous or provoked involuntary detrusor contraction during filling cystometry. Subj, persistence of SUI: a positive response to UDI-6 question 3, Urgency: a positive response to UDI-6 question 2	✓ Menopausal ✓ Post hysterectomy ✓ High Pad test (50.3 ± 44.3 g, 95% CI, 33.7–66.8; p = 0.034) ✓ Lower MUCP ✓ Small cystometric capacity (<150 ml) ✓ Presence of DO	Comparison between two groups, USI with urgency and UMI (MUI-UD vs USI and detrusor overactivity [DO]).
5	Lo TS et al. (2022) [12]	SIS (Solyx/MiniArc) TOT (Monarc) MUS-s (TVT)	MUS failure: presence of USI and/or pad test ≥2 g.	✓ reduced postoperative urethral mobility [OR 2.11 (1.24–3.75)] ✓ lower MUCP [OR 1.61 (1.05–3.41)] ✓ tape percentile [OR 3.12 (1.41–8.71)]	Risk factor for MUS surgery failure in women with ISD

SIS, Single incision sling; **TOT** transobturator tape; **MUS-r**, midurethral sling retropubic, **TVT**- Tension free vaginal sling, **Obj**., objective; **Subj**., subjective; **USI**, Urodynamic stress incontinence; **SUI**, stress urinary incontinence; **UDI-6**, Urogenital Distress Inventory-6; **MUS**, mid-urethral sling; **ISD**, Intrinsic sphincter deficiency; **VLPP**, Valsalva leak point pressure; **MUCP (cmH_2O)**, maximum urethral closure pressure; **DO**, detrusor overactivity; **CC1 (ml)**, first sensation of bladder fillingl; **MCC** (ml), maximum cystometric capacity; **UMI**, urodynamic mixed urinary incontinence; **DM**, diabetic mellitus.

SUI which was well observed in few reported papers [10,12,42,45]. In contrast, Sun et al. and Chao et al. founds no significant different in outcome in MUCP <40cmH20, either SIS (MiniArc) [52] and TOT [53,54], as both provides favourable outcomes [55,56]. Besides low MUCP, cotton swab <30◦, change in inclination angle <30◦ measured by ultrasound and ISD also contributes to failure in repeat MUS [29].

TVT was favoured for repeat MUS, also after vaginal mesh repair [14] as it provides better outcome than TOT [57] as most failures were seen in urethral hypomibility plus associated ISD [29,58]. Lo et al. in his study didn't find significant differences in continence rate with various types of MUS [29].

Post operative lower urinary tract symptoms

Women with symptoms of de novo urgency or proven DO 1 year after MUS surgery had poorer cure. Associated risk includes age ≥66 years, smaller bladder capacity, sensitive bladder, low MUCP, greater pad loss (>100 g) and diabetes. Voiding dysfunction was not uncommon. Contributing factors were perioperative abnormal uroflow pattern, maximal flow rate <15 ml/s, presence of vault prolapse or enterocele, concurrent vault suspension surgery and postoperative UTI [59]. Similar results were seen in patients with MUI undergoing MUS [10]. Regardless, QoL improved postoperatively.

Table 3
Complications associated with types of mid urethral slings surgery.

Types of MUS	MUS-r		TOT (inside out)	TOT (outside in)		SIS			
Complication (%)	TVT	SPARC	TVT-O	(Monarc)	(Obtryx)	Solyx	MiniArc	Ajust	I stop Mini
Major complication									
Bladder Injury	0.3–3.8	3.4–12.9	0.2–0.7						
Hematoma	1.9–16.1	3.4–9.7	1.4						
Vaginal Injury	5.7		2.2–0.9	12.9					
Minor complication									
Tape Extrusion	0.7–12.9	3.2	1.5–8.1	1.4–2.2	2.9				
Urinary Retention	9.0–10.0	9.4	2.9	4.4–8.1		6.7	3.7	3.3	
UTI	6.0–15.1	6.3	4.8–17.2	1.4–23.0	5.7–13	3.3	4.5–5.5	3.3	11.1
Voiding Dysfunction	13.2–18	31–40.7	2.2–12.9	5.8–21.7			1.8		
Dyspareunia	5.2		8.1	2.9					1.4
Groin Pain	3.3–4.4		0.5–2.4	4.3–12.9	1.4–20.3				18.1
Denovo Urgency	5.6–8.6	10.3–47.2	1.1–5.9	9.7–13.1	40.9		4.7–11.1		27.8
Frequency	9.7	16.1–24.1		7.3–12.9			3.7		

Complication presented in (%) of incidence.
MUS, mid-urethral sling**; SIS**, Single incision sling; **TOT** transobturator tape; **MUS-r**, midurethral sling retropubic, **TVT**- Tension free vaginal sling; **SPARC**, Suprapubic arc sling; **TVT-O** Tension free vaginal sling obturator; **UTI**, urinary tract infection.

Managing voiding dysfunction

Some techniques have been developed and reported on managing issues associated with immediate voiding dysfunction postoperatively. Tension-releasing suture (TRS) and lateral excision [60] of the tape can be performed to relieve iatrogenic urethral obstruction. A published data has shown that TRS was well tolerated by patient without compromising the continence effect at 1 year follow up [61].

In patient with recurrent SUI after TVT surgery, shortening pre implanted tape was shown to be effective. This minimally invasive approach was published by Lo et al. It is a relatively easy procedure, small incision avoiding the need for major reoperation [62].

Complication related to MUS

MUS-r (TVT) carries higher risk of perioperative complication-such as bladder perforation, hemorrhage, hematoma, which is related to the passage of trocars between the vagina and abdomen. Postoperative-Urinary retention and de novo urgency [63]. Isolated case reports on atypical immediate presentation such as vulvar edema resulting from bladder perforation, mid-term complication of retropubic abscess [64], bladder injury associated late tape migration was reported 4 and 11 years after sling surgery [65,66]. More cases resurfaced making it less popular after 2010.

TOT and SIS avoided this passage hence lowered the risk of bladder injury. Vaginal injuries were more common; at fornices, during trochar insertion which can be dealt with and repaired intraoperatively. Risk of lower urinary tract symptoms and infections after TOT was linked with preoperative RU > 100 cc. Cystoscopy after every MUS surgery is best practiced to ensure lower urinary tract patency, early recognition and management of immediate intraoperative complication.

Immediate urinary retention and voiding dysfunction can be treated by early recognition and tape release [67]. Huang et al. founds that complications such as voiding dysfunction, de novo urgency and UTI didn't impair post operative QoL scores [68] likely attributed by the women's satisfaction of feeling dry.

Tape erosion was seen in 0.7–12.9% after TVT, while up to 8.1% with TOT (inside-out), Chen et al. reported DM and use of Type III multi-filamentous polypropylene sling (intravaginal slingplasty) as risk factors for mesh erosion [69]. Type I monofilament polypropylene sling has larger pore size (75 μm) that allow microphages, fibroblasts, white cells and collagen to pass through, which is important for mesh incorporation and reduces infection. Eroded mesh can be trimmed or conservatively managed with estrogen cream [69].

In Asia however, complications were not frequently reported [70]. This data is in agreement with IUGA position statement on MUS for SUI, 2014- "Nevertheless, the results of a recent large multi-centre trial have confirmed excellent outcomes and a low rate of complications to be expected after treatment with MUS" [71].

Strength and limitations

Limitations of this observation review is (1) this is not a meta-analysis as there is only few randomized trials and most studies are of level 2 (prospective) to level 3 (retrospective) evidences. (2) There is possible biases and confounding factors that may have influenced the results. The different types of MUS were studied in different cohort of patients and timeline and may not represent the true or optimal outcomes. (3) It is not possible to replete all kind of heterogeneity and biases due to types of studies and difference in characteristics, and (4) most of the included data have short follow up period of 12–18 months and maximum being 5-years.

In conclusions, MUS is a gold standard treatment for SUI with the best cure outcome, improvement in patient symptoms and quality of life supported and endorsed internationally- IUGA Society [71], FIGO [8]. It has evolved in its technique, kit and application from retropubic approach to trans obturator and mini-sling or single incision sling.

To answer 'Which works best?' There's still lack of data on head-to-head comparison. As previously described, all MUS deliver comparable good outcome in terms of efficacy and cure rate. Each carries its own benefit and risk, TVT has longest data and proven beneficial for repeat MUS or with concomitant PRS however had highest complication rate compared to TOT and mini-slings. Perioperative counselling is crucial, all options should be discussed and treatment should be individualized as there is 'no one-size fits all'.

Nevertheless, continuous training, monitoring of outcomes, reporting and longer-term data is still crucial to provide clearer depiction of MUS efficiency, and long-term effect. This procedure has high acceptance rate not just in Taiwan with promising outcome.

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Author contributions section

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

M Kamarudin: Manuscript writing Data collection and Data analysis.

MJ Sun: Data analysis,

TH Su: Manuscript editing.

Declaration of interest

All authors have no competing interest to disclose.

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Original Article

Prenatal genetic investigation in pregnancies with oligohydramnios: Results from a single referral medical center

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ABSTRACT

Objective: The aim of this study was to investigate the value of genetic testing using exome sequencing (ES) in oligohydramnios pregnancies with or without other structural abnormalities.

Materials and methods: A total of 110 singleton pregnancies complicated by oligohydramnios were enrolled, including 52 of isolated oligohydramnios and 58 of non-isolated oligohydramnios. All fetal samples were first tested by quantitative fluorescent polymerase chain reaction (QF-PCR) and followed by chromosomal microarray analysis (CMA). Those with normal CMA were informed of the option of trio ES.

Results: QF-PCR detected chromosomal abnormality in 4 cases (4/110, 3.6%), including 1 of XXY, 1 of XYY and 2 of triploidy. The remaining 106 cases were tested by CMA, with pathogenic copy number variations (CNVs) detected in 5 cases (5/106, 4.7%), and uniparental disomy (UPD) in 2 cases (2/106, 1.9%). As an option for cases with a normal CMA, ES was accepted by 12 non-isolated cases, and pathogenic or likely pathogenic variants were detected in 5, involving the following genes: *PBX1*, *FREM2*, *PKHD1* and *BBS2*, with a 41.7% (5/12) diagnostic rate.

Conclusion: We provided further evidence of using advanced genetic approaches for oligohydramnios pregnancy. Non-isolated oligohydramnios increases the risk of having monogenetic conditions.

Introduction

A normal amount of amniotic fluid is essential for healthy pregnancy. It cushions the body and promotes the development and expansion of fetal lungs. The volume of amniotic fluid is the result of a balance between fluid production and clearance in the gestational sac. For example, fetal genitourinary abnormalities can lead to oligohydramnios after 16–20 weeks gestation, including bladder outlet obstruction, dysplastic kidneys, and renal agenesis. Diagnosis of oligohydramnios during the second trimester is more likely to be associated with fetal or maternal anomalies, whereas diagnosis in the third trimester is more likely to be of unexplained origin [1]. In cases of oligohydramnios diagnosed in the second trimester, pulmonary hypoplasia is the most significant predictor of fetal mortality. An early study recommends the use of fetal chromosome analysis in every pregnancy complicated oligohydramnios as 13.8% of fetuses with oligohydramnios and congenital malformations had a chromosomal aberration [2]. A recent study found that the 2% risk for clinically significant chromosomal microarray analysis (CMA) finding in pregnancies with oligohydramnios did not differ from the control population with normal ultrasound, not supporting invasive prenatal testing in pregnancies with isolated oligohydramnios [3]. In this study, we report the results of genetic testing with CMA and exome sequencing (ES) in the prenatal diagnosis of oligohydramnios, with the aim to provide further evidence of using advanced genetic approaches for oligohydramnios pregnancies.

Materials and methods

Patients and sample preparation

The retrospective study reviewed consecutive prenatal cases of oligohydramnios that accompanied with or without other sonographic abnormalities diagnosed at the Guangzhou Women and Children's Medical Center during the period 2012–2021. A maximum vertical pocket (MVP) < 2 cm was diagnosed as

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oligohydramnios, excluding maternal complications such as chronic hypertension or other chronic maternal comorbidity and premature rupture of membranes. Clinical data from these cases were reviewed, including maternal demographics, indications for invasive testing, results of CMA and ES, and pregnancy outcomes. Only cases with prenatal genetic results were included. Fetal samples are collected by using amniocentesis or cordocentesis. A total of 110 singleton pregnancies complicated by oligohydramnios were enrolled, and the demographic characteristics of these pregnancies are presented in Supplementary Table S1. According to the results of ultrasonography, 110 cases were further classified into isolated oligohydramnios (n = 52) and non-isolated oligohydramnios (n = 58) groups. Isolated cases were defined as oligohydramnios without any other fetal structural anomalies including fetal growth restriction (FGR). Written informed consent for invasive procedures and genetic tests was obtained in all cases. The study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Centre.

Genetic testing

In this study, all fetal samples were first tested by quantitative fluorescent polymerase chain reaction (QF-PCR) for the detection of common aneuploidies and triploidy and excluding maternal contamination. The CMA was conducted with CytoScan 750K array (Affymetrix, USA) with an average resolution of 100 kb. Those with normal CMA results were informed of the option of trio ES. The library preparation process is carried out according to the routine operation. The average sequencing depth was 90 × and the 20 × depth of coverage was achieved for 98% of targets. Agilent SureSelect All Exon V6 kits were used to do exome capture , and then the library were sequenced on Illumina HiSeq2500 Analyzers (Illumina, San Diego) platform with 150 base pair sequencing. Paired-end reads were aligned to the GRCh37/hg19 human reference sequence. BAM and VCF files were generated by NextGENe software (SoftGenetics, State College, PA). All SNVs and indels were filtered and estimated via multiple databases, including NCBI dbSNP, 1000 Genomes Project, Exome Aggregation Consortium (ExAC), Exome Sequencing Project (ESP), Genome Aggregation Database (gnomAD), Online Mendelian Inheritance in Man (OMIM), ClinVar, Human Gene Mutation Database (HGMD) and local database.

Statistical analysis

Statistical analysis was performed using the Pearson chi-square test with SPSS software, version 26.0 (SPSS Inc, Chicago, IL, USA). A p value < 0.05 was considered to be statistically significant.

Results

During the study period, 110 singleton pregnancies of oligohydramnios with or without other ultrasound abnormalities were screened for genetic conditions (Supplementary Figure S1). The mean maternal age was 29.2 (range, 19–41) years old. The mean gestational age at diagnosis of oligohydramnios was 24.1 (range, 15–28) weeks. QF-PCR detected chromosomal abnormality in 4 cases (4/110, 3.6%), including 1 of XXY, 1 of XYY and 2 of triploidy. The case of XXY presented with isolated oligohydramnios, while cases of XYY and triploidy had non-isolated oligohydramnios phenotypes. The remaining 106 cases were tested by CMA, with CNVs detected in 5 cases (5/106, 4.7%), and uniparental disomy (UPD) in 2 cases (2/106, 1.9%). All of the 7 abnormal CMA results were detected in non-isolated group (Table 1), and none in isolated group. One of the 2 UPDs was confirmed to be maternal origin, and included the 14q31.3q32.33 region. The maternal UPD for 14q31.3q32.33 results in Temple syndrome. Therefore, the overall diagnostic yield of CMA was 6.6% (7/106) in total oligohydramnios pregnancies, and 12.1% (7/58) in non-isolated pregnancies (Supplementary Table S2) after QF-PCR testing.

As an option for cases with a normal CMA, ES was accepted by 12 non-isolated cases. Through trio ES analysis, pathogenic or likely pathogenic variants were detected in 5 cases (Table 2), involving the following genes: *PBX1*, *FREM2*, *PKHD1* and *BBS2*. Except for the variant of *PBX1*, which is de novo and autosomal dominant, the remaining variants are autosomal recessive, and inherited from parents. All of the 5 positive cases came from non-isolated group, with a 41.7% (5/12) diagnostic rate of ES.

In this study, all pregnancies with non-isolated oligohydramnios were terminated by the requests of parents. In the 52 isolated cases,

Table 1
Fetal chromosomal abnormalities of 11 pregnancies with oligohydramnios.

Case	MA (yr)	GA (wk)	MVP (mm)	Ultrasound findings	Chromosomal results	Size (Mb)	Pregnancy Outcome
1	28	18	19	Normal	47, XXY	–	TOP
2	29	27	14	FGR	47, XYY	–	TOP
3	35	25	18	Left polycystic kidney, right diaphragmatic hernia, non-visualization of gastric bubble, left kidney and bladder	Triploid	–	TOP
4	24	17	19	Body asymmetry with relative macrocephaly, hydrocephalus	Triploid	–	TOP
5	32	24	0	Bilateral renal dysplasia, pulmonary hypoplasia, congenital cystic adenomatoid malformation of the lung	arr17q12(34,822,465–36,418,529) × 1	1.6	TOP
6	25	19	14	Pulmonary stenosis, hypoplasia of left lung, non-visualization of left kidney and bladder	arr16q13q24.3(56,713,490–90,155,062) × 3	33.4	TOP
7	28	24	19	Bilateral renal dysplasia, FGR	arr4p16.3p16.1(68,345–6,033,676) × 1	5.97	TOP
8	26	24	15	Bilateral renal dysplasia, pulmonary hypoplasia, right aortic arch, aberrant left subclavian artery	arr10q23.33q24.32(96,066,675–103,742,345) × 1	7.68	TOP
9	39	26	19	Ventricular septal defect	arr9p24.3p11.2(258,491–44,900,526) × 3 arr9q13q21.32(66,837,485–86,009,559) × 3	44.6 19.2	TOP
10	28	18	19	FGR	arr14q31.3q32.33(86,088,056 –105,996,119) × 2hmz	19.9	TOP
11	32	22	19	Single umbilical artery, aberrant right subclavian artery; FGR	arr2p25.3q37.3(15,702–242,775,910) × 2hmz	243.76	TOP

FGR, fetal growth restriction; GA, gestational age; MA, maternal age; MVP, maximal vertical pocket; TOP; termination of pregnancy.

Table 2
Exome sequencing results of 12 cases of non-isolated oligohydramnios.

Case	MA (yr)	GA (wk)	MVP (mm)	Ultrasound findings	Sequencing results	Inheritance	Associated syndrome	Outcome
1	30	26	17	Bilateral renal dysplasia, pulmonary hypoplasia	*PBX1*(NM_002585.3) c.973_974delTC, p.(S325AfsX14), de novo, P	AD	Congenital renal and urinary tract syndrome	TOP
2	32	21	11	Bilateral renal agenesis	*FREM2*(NM_207361.5) c.4396C > T, p.(R1466X) (pat), P c.8347A > T, p(I2783L) (mat), VUS	AR	FRASER syndrome	TOP
3	23	23	16	Bilateral polycystic kidneys	*PKHD1*(NM_138694) c.6091delG (p. Ala2031LfsX2) (pat), P c. 9290C > A, p.(A3097E) (mat), LP	AR	Polycystic kidney disease type IV	TOP
4	29	27	17	Bilateral polycystic kidneys	*PKHD1*(NM_138694) c.2891T > A, p.(V964D) (pat), LP c.3629G > A, p.(G1210E) (mat), LP	AR	Polycystic kidney disease type IV	TOP
5	32	23	18	Bilateral polycystic kidneys	*BBS2*(NM_031885) c.2107C > T, p.(R703X) (pat), P c.534+1G > T(mat), LP	AR	Bardet-Biedl syndrome	TOP
6	23	28	11	Bilateral polycystic kidneys	Normal	/	/	TOP
7	30	17	18	Bilateral polycystic kidneys	Normal	/	/	TOP
8	33	21	18	Bilateral renal agenesis	Normal	/	/	TOP
9	31	23	12	Hydrops fetalis, ventricular septal defect	Normal	/	/	TOP
10	32	26	19	Single umbilical artery, aberrant right subclavian artery, FGR	Normal	/	/	TOP
11	29	24	14	Pericardial effusion, right clubfoot, FGR	Normal	/	/	TOP
12	25	24	18	FGR	Normal	/	/	TOP

AD, autosomal dominant; AR, autosomal recessive; FGR, fetal growth restriction; GA, gestational age; MA, maternal age; MVP: maximal vertical pocket; LP, likely pathogenic; P, pathogenic; TOP, termination of pregnancy, VUS, variant of unknown significance.

27 pregnancies ended with live births, and 25 pregnancies were terminated, including 17 with anhydramnios and 8 with a diagnosis at early gestation (<24 weeks).

Discussion

An adequate amniotic fluid volume is necessary for normal fetal limb and lung development and for cushioning the body and umbilical cord from uterine compression. Pregnancies complicated by midtrimester oligohydramnios from any cause are at risk for pulmonary hypoplasia, fetal deformation, and umbilical cord compression. Therefore, reduced fluid volume is associated with an increased risk for adverse pregnancy outcomes which are either related to the underlying causes or the sequalae of oligohydramnios, or both [4]. One of the factors that determine the prognosis is genetic syndromes. We found only one case (1.9%, 1/52) of chromosomal abnormality in isolated oligohydramnios. This case was diagnosed at 24 weeks and was showed to have the XXY karyotype by fetal blood sampling. Our results also support a previous study that concluded that if no fetal anomalies are detected, the risk of genetic abnormalities does not appear to be increased above the baseline risk [3]. However, genetic testing may be offered to these patients as part of standard obstetric care because of the possibility of undetected anomalies. The sonographic examination of fetuses is generally compromised because oligohydramnios subjectively degrades image resolution, and adequate visualization of some fetal anatomies is difficult [5].

We detected 1 case of sex chromosomal aneuploidy and 2 cases of triploidy in the non-isolated series. Oligohydramnios is seen in most fetuses with triploidy as early as the first trimester [6,7]. We reported a XYY karyotype in a fetus with oligohydramnios and FGR diagnosed at 26 weeks' gestation. No other structural anomalies were demonstrated. The pregnancy was terminated and did not undergo further investigation. Another study also reported a case of oligohydramnios syndrome found to have an XYY karyotype [8]. Other sex chromosomal aneuploidies associated with oligohydramnios included XXY and 45,X [9,10]. All of these associations were case reports without monogenetic testing, and therefore could not exclude an incident finding. Indeed, abnormalities of sex chromosomes are identified in approximately 1% of all pregnancies that undergo a prenatal karyotype [11].

We achieved a 12.1% diagnostic yield in non-isolated oligohydramnios using CMA. If only small fragments (<10 MB) are considered, which are assumed to be missed by routine karyotyping, the additional yield was 5.2% (3/58). This finding is expected since CMA can detect an additional 5.2%–10% of clinically significant aberrations compared to conventional karyotyping in structurally anomalous fetuses [12,13]. Notably, we detected two UPD cases. One was maternal UPD for14q31.3q32.33. The fetus presented with FGR and oligohydramnios at 23 weeks. Chromosome 14 harbors an imprinted locus at 14q32. Maternal UPD of 14q32 causes an imprinting disorder, called Temple syndrome [14]. The most frequent phenotypic manifestations are prenatal and postnatal growth failure, hypotonia, developmental delay, small hands/feet, precocious puberty, and truncal obesity. Sometimes the clinical characteristics of Temple syndrome overlaps with other imprinting disorders such as Silver-Russell or Prader–Willi syndromes [15]. The other UPD case with non-isolated oligohydramnios was UPD (2). The fetus was found at 22 weeks to have oligohydramnios combined with FGR, single umbilical artery and aberrant right subclavian artery. As there have not been any imprinted genes found on chromosome 2, an attempt was not made to identify the UPD parental origin. The mother declined ES and opted for termination of pregnancy. Uniparental disomy of a non-imprinted chromosome can cause an autosomal recessive condition if a disease-causing recessive variant presents in the involved chromosomes [16]. In the seven cases with non-isolated oligohydramnios and positive CMA findings, the CMA abnormalities are more likely response for the associated structural anomalies or FGR, and oligohydramnios might result from the abnormal fetuses and placentae.

Recent systematic review reported that prenatal ES increases a diagnostic yield of 6.2%–80% depending on different inclusion criteria and trio versus singleton approaches [17]. In our series, 5 (41.7%, 5/12) cases were detected to have monogenetic conditions by ES in non-isolated group, caused by variants of *PKHD1*, *BBS2*,

PBX1 and *FREM2* genes. Two fetuses with bilateral polycystic kidneys and oligohydramnios diagnosed at 23 and 27 weeks respectively were revealed to have *PKHD1* variants. The *PKHD1* is the most common gene implicated in autosomal recessive polycystic kidney disease [18]**.** Renal anomalies with oligohydramnios were an important clinical sign for diagnosis in utero, and pulmonary hypoplasia, oligo/anhydramnios, and kidney enlargement were associated with a significantly worse neonatal prognosis. One fetus complicated by bilateral polycystic kidneys and oligohydramnios at 23 weeks had compound heterozygous *BBS2* variants associated with Bardet-Biedl syndrome with mainly an autosomal recessive inheritance [19]. This syndrome is an emblematic ciliopathy characterized by retinal dystrophy, obesity, postaxial polydactyly, learning disabilities, hypogonadism and renal dysfunction. Before birth, enlarged/cystic kidneys as well as polydactyly are the hallmark signs of Bardet-Biedl syndrome to consider in absence of familial history [20]. Until now, there are at least 21 genes (*BBS1-21*) in which variants are known to lead to the development of Bardet-Biedl syndrome. One fetus presented with bilateral renal dysplasia, pulmonary hypoplasia and oligohydramnios at 26 weeks, and was detected to have a de novo pathogenic *PBX1* variant. It has been showed that PBX1 is essential for normal kidney formation, and variants of *PBX1* cause congenital abnormalities of the kidney and urinary (CAKUT syndrome) [21]. Kidney phenotypes comprise uni- and bilateral renal hypoplasia with or without hyperechogenicity, horseshoe kidneys, renal pelvis dilatation, dilated or duplex ureters, renal ectopia and, more rarely, renal agenesis. Defects of *PBX1* should be suspicious in fetuses with bilateral renal hypoplasia, oligohydramnios and FGR [22]. Two variants of *FREM2* were detected in a 21-week fetus with bilateral renal agenesis and oligohydramnios. The *FREM2* aberrations have been found to cause Fraser syndrome [23]. This genetic syndrome is an autosomal recessive multiple malformation syndrome whose major manifestations are cryptophthalmos, syndactyly, laryngeal atresia and urogenital defects. Non-visualization of the kidneys and oligohydramnios were usually sonographic markers leading to the prenatal detection of this rare disorder [24]. In this case, only one pathogenic allele c.4396C > T, p.(R1466X) was detected, and the other allele c.8347A > T, p(I2783L) was classed as a variant of uncertain significance (VUS). Considering that the genotype is consistent with the phenotype in the fetus, we believe that the two variants are likely to be the cause of the disease.

In this series, the mean gestation age at diagnosis was 22.6 weeks for the 14 cases with positive genetic testing, which was significantly earlier than that (24.3 weeks) for those with negative results ($p = 0.032$). This finding indicates that an early-onset oligohydramnios is more likely indicative for genetic etiologies. We also found that all of the 5 positive ES cases had genetic conditions which are associated with kidney phenotypes, indicating that the oligohydramnios was the result of renal dysfunction. It seems that oligohydramnios resulting from reduced fluid production is at high risk for a genetic aberration, compared to other causes such as placental dysfunction. This information might be used as a pre-test counseling consideration.

In conclusion, we report the genetic testing results of pregnancies complicated by oligohydramnios. We found a low risk of genetic findings in fetuses with isolated oligohydramnios, but a considerably increased yield in fetuses with non-isolated oligohydramnios by both CMA and ES. Despite the facts that there are some limitations such as a retrospective design, a small sample size and absence of long-term follow-up for survivals, this study is the first one in which ES was used for investigating the underlying causes of oligohydramnios pregnancies. Accurate genetic diagnosis is important to provide information for reproductive decision making, including pregnancy and perinatal management. Although oligohydramnios itself can warrant a pregnancy termination, identification of a genetic defect allows counselling about recurrence risks and can help preparation for prenatal testing or preimplantation genetic diagnosis in future pregnancies. Even de novo variants or negative results may provide some relief to the parents in the light of a decreased risk of recurrence.

Declaration of competing interest

The author declares that has no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2024.08.002.

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Original Article

Human chorionic gonadotropin of pituitary origin in Chinese postmenopausal women: A single-center retrospective study

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ABSTRACT

Objective: We analyze the characteristics and related factors of human chorionic gonadotropin (hCG) of pituitary origin to establish the reference interval to resolve clinical confusion and avoid harmful therapy to Chinese postmenopausal women with "positive" hCG.
Materials and methods: This retrospective cohort study identified individuals who underwent hCG measurements at an academic hospital. Three gonadotropins (hCG, follicle stimulating hormone (FSH), and luteinizing hormone (LH)) was drawn from medical records. The age-stratified analyses were performed first. Then the correlations of hCG and FSH, LH as well as age were analysed. Finally, characteristics and associations of hCG, LH, and FSH were evaluated to identify pituitary hCG in postmenopausal women in clinical settings.
Results: In total, 9796 cases from 11172 records met inclusion criteria and contributed 9796 hCG, 7541 FSH, and 7536 LH values. The upper reference interval for our cohorts was 5.3 IU/L. HCG, FSH, and LH concentration had no significant correlations with age. HCG moderately correlated with FSH ($r = 0.47$) and LH level ($r = 0.53$). However, it was FSH but not LH that manifested good clinical applicability.
Conclusion: The prevalence of hCG≥5.0 IU/L and 5.3 IU/L in women ≥55 years is 2.8% and 2.3% in the study population from China. The level of hCG 5.3 IU/L was suggested to be the positive threshold for postmenopausal women. FSH≥40IU/L helps to distinguish the pituitary source of hCG in postmenopausal women whose serum hCG concentrations were between 5.3 and 16 IU/L.

Introduction

Low-level human chorionic gonadotropin (hCG) detected in healthy aged women is generally considered as the presence of hCG from the pituitary [1,2]. It results from the incidental potent action of gonadotropin-releasing hormone (GnRH) on the group of eight CGBs (encoding hCG β) and the parallel single LHB (encoding LH β) on chromosome 19 [3]. So, in women of childbearing age, pulses of pituitary hCG are detected paralleling with LH levels in the menstrual cycle [4,5]. When the ovary fails to provide estrogen and progesterone to negative feedback to the hypothalamus-pituitary-ovarian axis, hCG increases in parallel with follicle stimulating hormone (FSH) and luteinizing hormone (LH) production. So, in peri- or post-menopause women, LH and FSH are high, and pituitary hCG increases too [2,6]. Generally, pituitary hCG showed very low concentrations in childbearing women (<3IU/L) [5] and peri- or post-menopause (<14 IU/L) [2,6].

However, diagnosing the underlying cause of hCG elevation can be challenging if a pituitary source, which remains largely under-recognized, is not considered. It would create clinical confusion and even lead to harmful therapies such as chemotherapy and inappropriate surgery [7]. On the other hand, no clinical data of pituitary hCG is available in China yet. Thus, the traits and correlations with FSH/LH as well as other related factors of pituitary hCG were retrospectively analyzed based on a large sample from China in an age-related manner.

Methods

Study population

This retrospective study was performed at Women's Hospital, School of Medicine, Zhejiang University, and approved by the ethics committees of our facility (IRB-20200078-R). We extracted

Abbreviations: hCG, human chorionic gonadotropin; FSH, follicle stimulating hormone; LH, luteinizing hormone; GnRH, Gonadotropin-releasing hormone.

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electronic 11172 records of women aged 55 years and greater who had undergone hCG testing in our hospital from January 21, 2008, to January 21, 2020. Most of these tests are routine preoperative examinations for inpatients, some for differential diagnosis and others for health checkups. A medical record review was performed on all cases. For multiple measurements of an individual within one year, only the largest one is counted, and the measurement over one year was counted as an independent case. Individuals were excluded if a patient had no chart available for review, if a patient had a history of gestational trophoblastic disease or cancer, if a patient suffered primary hypogonadism, if a patient had other conditions that were currently known to have an impact on detection based on antibody response such as vaccination, celiac disease or immunoglobulin A deficiency. The cases who had received therapeutic antibody administration or hormone replacement therapy were excluded too.

Measurement of hCG, FSH, and LH

All measurements were performed on the Roche cobas® e601 modular analyzer (Roche Diagnostics, Mannheim, Germany) by electrochemiluminescence immunoassay (ECLIA). Serum concentrations of hCG, FSH, and LH were measured with the Elecsys HCG+β (Roche Diagnostics, Mannheim, Germany), Elecsys FSH (Roche Diagnostics, Mannheim, Germany) and Elecsys LH (Roche Diagnostics, Mannheim, Germany) respectively. Elecsys HCG+β is intended for the in vitro quantitative determination of the sum of hCG plus the hCG β subunit in human serum and plasma based on 2-site (sandwich) immunoassays the monoclonal antibodies included were both mouse origin. All the detections complied with the manufacturer's instructions. The lower detection limit of the reagents of hCG, FSH, and LH was 0.1 IU/L.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Values that were below the sensitivity were used as reported by the instrument. Substitution with half the detection limit has reasonable properties under specific conditions [8]. Firstly, nonparametric percentile estimations were used as a basis for the reference intervals. Descriptive statistics were used to sum up the features of hCG, LH, and FSH in the entire population. In addition, age-stratified analyses were performed with 55–64, 65–74 and, 75–90 years subgroups. Secondly, hCG was treated as a continuous variable, and its correlations with FSH, LH, and age were performed by Spearman rank correlation. Thirdly, chi-square analyses were performed to evaluate differences in frequencies between all age groups. For all of the tests, statistical significance was set at 5%.

Results

Study population

In total, 9796 cases from 11172 records met inclusion criteria and contributed a total of 9796 hCG values, 7541 FSH values, and 7536 LH values. The age of all populations was between 55 and 90 and the mean was 61.2 ± 5.7 years. Age was considered as a categorical variable and groups were defined as 55–64 (n = 7437), 65–74 (n = 2064), and 75–90 years (n = 313). The age per cohort was 58.6 ± 2.9, 68 ± 2.6, and 78.2 ± 3.1 years respectively. The respective percentage of measurable hCG (≥0.1 IU/L) was 92.7% (6891/7347), 96.0% (1964/2046), and 97.1% (304/313) for 55–64, 65–74, 75–90 years groups, and 93.5% (9159/9796) for all individuals. The highest hCG was 15.31 IU/L and the average was 1.50 IU/L for the total population. The highest ones observed in each age group were: 55–64 years maximum 15.31 IU/L, 65–74 years maximum 10.50 IU/L, 75–90 years maximum 10.30 IU/L and the averages were 1.44, 1.657, 2.06IU/L respectively. At the same time, the corresponding medians were 1.20, 1.10, 1.30, and 1.63 IU/L (Table 1).

Characteristics and association of hCG, LH, and FSH in postmenopausal women

The hCG concentration and the upper limits of 97.5 percentile with 95% (CI) [9] for all populations and three age cohorts were 5.30 IU/L, 5.20 IU/L, 5.60 IU/L, 8.11 IU/L respectively (Table 1). So, the hCG concentration of 5.30 IU/L was adopted as "positive" in the present population. Under this context, the prevalence for "positive" hCG was 2.3% (221/9796) in entire populations and the respective percentages were 2.0% (147/7438), 2.8% (57/2046), and 5.4% (17/313) in subgroups ($p = 0.000$) (Table 1). Also, HCG level was significantly different between every two age groups ($p = 0.000$) (Table 1). In total, there were 9575 cases with the hCG <5.30 IU/L and 221 cases ≥5.30 IU/L. The mean ages of these two populations were 61.2 ± 5.6 and 62.9 ± 6.6 years ($p = 0.000$, Table 2). The highest levels of hCG (15.30 IU/L), FSH (196.80 IU/L), and LH (105.40 IU/L) were from women aged 57, 68, and 57 respectively. Years of age, FSH, and LH concentrations were significantly higher in women with hCG concentrations≥5.30 IU/L than in individuals whose hCG concentrations<5.30 IU/L ($p = 0.000$) (Table 2). On the other hand, in clinical practice, 5.0 IU/L has been accepted as a normal reference range for distinguishing pregnancy and monitoring ectopic pregnancy, gestational trophoblastic diseases and hCG-secreting tumors, *etc* [10]. So, the prevalence of ≥5.0 IU/L was also calculated (2.8%, 269/9796) for comparison with the other studies. This prevalence was very different from earlier reports (8.0%) [11] and lower than the other one (6.7%) [12]. The proportions of the three sub-cohorts were 2.5% (182/7437), 3.4% (70/2046), and 5.4% (17/313) respectively. The concentration of hCG increased with age and substantial differences were observed between three subgroups classified by years of age (Table 1). However, no correlation was revealed between hCG and age in the present population (Table 3 and SFig. 1). The minimum FSH and LH concentrations in women with hCG ≥5.3 IU/L were 42.6 IU/L and 17.95 IU/L, and the maximums were 168.20 IU/L and 98.45IU/L respectively. Also, neither LH nor FSH indicated a significant correlation with age (SFig. 2). On the contrary, hCG concentrations moderately correlated with FSH levels in entire populations ($r = 0.47$), which was consistent with the previous study [12]. Similar results were observed in three cohorts: 55–64 years ($r = 0.48$), 65–74 years ($r = 0.48$) and ≥75 years ($r = 0.51$) respectively. The same applied to the LH level and the r values were 0.53, 0.55, 0.57, and 0.59 respectively (Table 3). When hCG was greater than 5.0 or 5.3IU/L, however, both FSH and LH didn't show significant correlations with hCG concentrations (Fig. 1).

Discussion

Post menopause has been situationally defined as ≥50 years of age with a mean of 55 years in women [7,12,13]. In our study, the subjects aged 55 years or greater were included and defined as menopausal women. We investigated the hCG of postmenopausal women with a large cohort by retrospectively analyzing data from 9796 cases in an academic hospital. A maximum of 15.31 IU/L was observed and different from data from the USA hCG reference service (39.0 IU/L from menopausal women aged 45 years who experiencing amenorrhea) [14]. The differences might lie in ethnic origins, sample size, reagent, and age of populations. Although the upper reference of the whole population and three sub-cohorts could be calculated, no correlation between hCG concentrations and age was unexpectedly found in the population (Table 3 and

Table 1
Characteristics of hCG in aged women.

Age group (yr)	Case (*n*)	hCG (IU/L)								
		mean[a]	SD	median	minimum	maximum	97.5 Centile	95% CI	≥5.3 (*n*, %)[b]	≥5.0 (*n*, %)[b]
55–64	7437	1.44	1.31	1.10	<0.10	15.31	4.90	4.69–5.20	147 (2.0%)	182 (2.5%)
65–74	2046	1.66	1.34	1.30	<0.10	10.50	5.32	5.02–5.60	57 (2.8%)	70 (3.4%)
75–90	313	2.06	1.68	1.63	<0.10	10.30	6.80	6.00–8.11	17 (5.4%)	17 (5.4%)
Total	9796	1.50	1.33	1.20	<0.10	15.31	5.13	4.90–5.30	221 (2.3%)	269 (2.8%)

CI, Confidence Interval; SD: Standard deviation.
[a] $p = 0.000$, significant difference was founded between every two age groups.
[b] Chi–Square test, $p < 0.05$.

Table 2
The comparison of age, FSH and LH level between aged women with hCG≥5.3 IU/L and <5.3 IU/L.

hCG	age (year)				FSH(IU/L)				LH(IU/L)			
	n	mean	SD	median	*n*	mean	SD	median	*n*	mean	SD	median
<5.3IU/L	9575	61.2[a]	5.6	60.0	7412	62.52[a]	23.44	60.32	7407	29.58[a]	11.39	28.39
≥5.3IU/L	221	62.9	6.6	61.0	129	90.67	27.62	87.57	129	47.09	13.44	45.57

SD: Standard deviation.
[a] $p < 0.05$, age, FSH and LH were all significantly different.

Table 3
Spearman correlation analysis of pituitary hCG (IU/L) with FSH(IU/L), LH(IU/L) and age (yr).

Age group (yr)	FSH			LH			Age		
	r	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*
55–64	0.49	0.000	5618	0.55	0.000	5613	0.16	0.000	7347
65–74	0.48	0.000	1685	0.57	0.000	1685	−0.03	0.174	2046
75–90	0.51	0.000	238	0.59	0.000	238	−0.03	0.588	313
Total	0.47	0.000	7541	0.54	0.000	7536	0.17	0.000	9796

SFig. 1), which was confirmed in the previous report [11]. The highest HCG values for three age sub-cohorts, *i.e.* 55-64 years maximum 15.31 IU/L, 65–74 years maximum 10.50 IU/L, 75–90 years maximum 10.30 IU/L, might be an exact reflection of this pattern. Therefore, age-specific reference for hCG would not be suggested in women 55 years of age or greater. Reference ranges can be established directly from the 2.5th and 97.5th percentile of the measurements in the reference group [9]. In the present research, the 97.5 percentile with 95% (CI) for whole cohorts was 5.3 IU/L. Thus, we suggested 5.3 IU/L, instead of the traditional 5.0 IU/L, to be used as the positive threshold for postmenopausal women, which will reduce the psychological burden of these individuals and avoid costly diagnostic testing. In previous reports, 14 IU/L [12] and 16 IU/L [2] have been set as upper limits of normal serum hCG for menopausal women. Likewise, by rounding the highest serum hCG (15.3 IU/L) to the nearest whole number that would include all individuals in the cohort, we recommend a serum hCG of 16.0 IU/L as the upper limit for healthy postmenopausal women.

Surely, suppression of pituitary hCG production with estrogen-progesterone hormone therapy is a reliable alternative to identify pituitary hCG. If hCG does not suppress, other sources of hCG should be investigated. However, this method is not useful in emergent situations when pregnancy or pregnancy-related diseases must be ruled out quickly before diagnostic procedures or treatment. Also, estrogen-progesterone hormone therapy doesn't work when one encounters contradictions. Therefore, it is

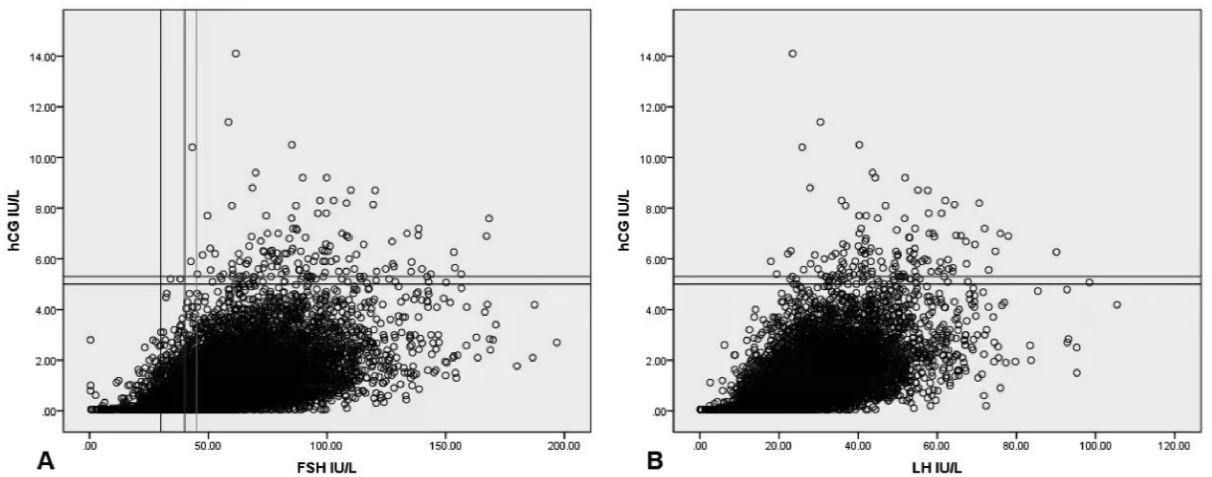

Fig. 1. HCG concentrations positively correlated with FSH (A) and LH (B) content. However, when hCG increased to 5.0 or 5.3 IU/L, the relationships could not be observed. Red line represents a hCG level of 5.3 IU/L and black one is 5.0 IU/L. The red, black and blue vertical lines represent cutoff of 30, 40 and 45 IU/L respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

particularly important to confirm pituitary hCG through integrative analysis of other variables, such as age, FSH, and LH. In the present study, a meaningful correlation between FSH and hCG determinations is observed ($r = 0.47–0.51$, Table 3) and the r values are higher compared with a previous small cohort ($n = 80$, $r = 0.385$) [13], but it did not consist with Khushbu's finding [11]. Meanwhile, the ratio of hCG to FSH was between 3.37% and 24.06%. At the same time, hCG and LH showed a moderate correlation ($r = 0.53–0.59$, Table 3) as well and the ratio of hCG to LH ranged from 5.15 to 60.10%. A previous study [2] including 28 referred cases revealed serum hCG levels ranging from 2.7 to 19.0% of LH levels, but there was no significant correlation, which was different from our data. Another research [15] indicated that urinary hCG could be detected at the time of the LH peak in 84% of cases, and a correlation ($r^2 = 0.97$) was observed. It was very interesting that markedly strong correlations were observed between serum pituitary HCG and FSH ($r = 0.665$) or LH ($r = 0.698$) in the men who underwent androgen deprivation therapy by luteinizing-hormone releasing hormone agonist treatment for prostate cancer [16]. However, it was worth noting that when hCG was more than 5.0 or 5.3IU/L, neither FSH nor LH significantly correlated with the concentration determinant of hCG (Fig. 1). This same association between hCG and FSH was revealed in the past [11], but the relationship between hCG and LH has not been reported yet.

As described above, increased serum FSH indicates a lack of sufficient steroid feedback to the hypothalamus and indicates a rise in pituitary hCG [12]. So, a simple test for reflex FSH has empirically been used to diagnose pituitary hCG in peri- and postmenopausal women. FSH concentrations of 30, 40, and 45IU/L have been used to assist in determining pituitary hCG in the previous studies [12,14,17]. We recommend 40 IU/L of FSH to assist in identifying pituitary hCG in postmenopausal Chinese women based on their characteristics. All cases with hCG levels below 5.3 IU/L can be distinguished by FSH levels below 40 IU/L in the present study and have good clinical applicability. The diagnostic utility of LH concentrations in diagnosing hCG of pituitary origin in women who are menopausal was evaluated as well. Regretfully, LH doesn't show clinical feasibility at all and it might lie in its high degree of inter-individual variability, whether LH itself [18] or the ratio of hCG (5.15–60.10%). So, when one encounters positive hCG during the postmenopausal period, serum hCG below 5.3 IU/L is considered completely normal. If the serum hCG is between 5.3 and 16.0 IU/L, reflex FSH testing should be suggested and when FSH is equal to or more than 40 IU/L, the possibility of pituitary hCG will be considered. If the FSH concentration is below 40 IU/L or the hCG level is still high, hormone therapy may be initiated or other sources of hCG may be investigated.

Our study is a retrospective analysis, and some effective techniques for eliminating false positives, such as excluding heterophilic antibodies through urine hCG test, cannot be implemented. So, firstly, a systematic review of medical records was taken to exclude the pathological conditions that can produce hCG and/or affect the survey of hCG. The second consideration is the prevalence of interference antibodies, including heterophilic antibodies and human anti-mouse antibodies (HAMA). Very few studies have evaluated the prevalence of these antibodies in the determination of hCG. Thus, the precise frequency of individuals who are positive for anti-mouse antibodies is not known. A study involving 10,000 blood donors indicated that the incidence of HAMA was 0.72% [19]. Another research [20] focused on investigations requested by physicians because of the suspected heterophilic antibody interference revealed the frequency was 2.9% (2/68) utilizing the same reagent (Roche Elecsys HCG+β immunoassay) to us. It was worthy of notice that this ratio might be elevated for the study including only the suspected cases. Although it cannot be completely ruled out, its impact should be very small, particularly in the context of our large sample. The third is technical consideration that the pre-incubation with serum of antibody-derived animal included in blocking reagent can minimize this effect, which is routinely used in the modern 2-site hCG test. The fourth issue is the cross-interactions with LH and FSH. Early hCG radioimmunoassay has exhibited some cross-reactions with LH. However, neither LH nor its β subunit is currently a problem with sandwich immunometric assays, which use 2 different monoclonal antibodies against specific epitopes of the hCG molecule [21]. As a matter of fact, the cross-reactivity provided by manufactures is rare: LH, not detectable; FSH, 0.1; TSH, not detectable.

Conclusions

These findings reveal that the threshold of FSH 40 IU/L and hCG 16 IU/L is suitable for identifying pituitary hormones in Chinese menopausal women. It's important to note that the data is exclusively gathered from elderly women who have had hCG tests done for health checkups, preoperative examinations, or differential diagnosis. The conclusion is only applicable in specific circumstances and should not be overly interpreted. If the elevated hCG level and high menopausal FSH levels are not enough to determine a pituitary source of hCG, hormone therapy will be necessary. The strength of this retrospective research lies in the fact that conclusions are drawn from a large population sample. Potential limitations should also be considered, such as age as the sole criterion for determining menopause and the inherent shortage of retrospective design. The other weakness is that certain individuals experience benign gynecological diseases, although they are currently known and do not affect the hCG content. These variables need to be carefully considered for future studies.

Author contributions

Yonghong Tian and Yimin Zhu did the conceptualization, investigation, and resources. Long Zhang did the methodology, validation and data collection. Jingping Li did the data analysis. Yonghong Tian did the writing (original draft preparation). Huijuan Gao and Yimin Zhu did the writing (review and editing) and supervision.

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Ethical approval

This study was approved by the Medical Ethics Committees of Women's Hospital, School of medicine, Zhejiang University (IRB-20200078-R).

Conflicts of interest

None reported.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2024.06.011.

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Original Article

Impact of colposcopy-guided carbon dioxide laser vaporization therapy on peripheral cervical intraepithelial neoplasia lesions

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ABSTRACT

Objective: Laser vaporization is less invasive than conization for cervical intraepithelial neoplasia (CIN). The outcome of laser vaporization for CIN is empirically known to depend on the colposcopic findings, especially localization of the lesion. In this study, we sought to identify factors involved in the outcome of laser vaporization.
Materials and methods: We retrospectively investigated 290 cases of CIN (CIN2, n = 180; CIN3, n = 110) treated with laser evaporation at Nishikawa Women's Health Clinic between 2018 and 2021. All treatments were performed using a carbon dioxide laser under either colposcopic vision (n = 172) or direct vision using a vaginal speculum (n = 118). Risk factors were statistically examined for cure rate after treatment.
Results: Multivariate analysis using a logistic regression model identified independent factors affecting the success of treatment to be high-risk human papillomavirus infection status preoperatively, CIN grade, presence of CIN lesions at the periphery of the cervix, and the surgical method used. Colposcopy-guided laser vaporization reduced the risk of treatment failure by 84% (odds ratio 0.16, 95% confidence interval 0.06–0.46; p = 0.001) compared with direct vision using a vaginal speculum. For lesions at the periphery of the cervix, most of the treatment failures were in the group that was not guided by colposcopy (p = 0.031).
Conclusion: The presence of a peripheral CIN lesion was suggested to be a risk factor for treatment failure. Laser vaporization under colposcopic vision is recommended for treatment of peripheral CIN lesions.

Introduction

Cervical cancer is the second most common cause of cancer-related mortality in women of reproductive age. Cervical intraepithelial neoplasia (CIN) is a precancerous cervical lesion, and fertility preservation may be difficult if it progresses to invasive cancer [1]. Cervical cancer can develop at a young age, but fertility can be preserved if CIN is detected early by human papillomavirus (HPV) and cytological screening with early therapeutic intervention [2,3]. The fertility-preserving treatment for CIN with the highest cure rate is cervical conization, but perinatal outcomes are affected by shortening of the cervix, with increased miscarriage and preterm delivery rates [4]. Nevertheless, cervical conization as a treatment for CIN has an almost 100% cure rate [5,6]. Less invasive treatments for CIN include cryotherapy, loop electrosurgical excision, large loop excision of the transformation zone using a wire loop heated by an electric current, and laser vaporization. These treatments have been shown to have similar cure rates in the range of 85.2%–94.7% [7] and to have less of an effect than cervical conization on perinatal outcomes. Laser vaporization appears to be even less invasive than these other treatments, with meta-analyses showing no increased risk of preterm delivery [4,8]. Carbon dioxide lasers are commonly used for laser vaporization therapy. However, other types of lasers such as semiconductor lasers have also been developed, and no significant differences in treatment outcomes have been shown using these devices [5,9].

As is widely known, the more extensive the area of CIN, the lower the success rate of laser vaporization therapy [10]. A good cervical field of view at the time of vaporization is desirable for large CIN lesions, and carbon dioxide laser vaporization using a

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colposcope has been described [11]. The Australian Cancer Council guidelines recommend that all treatments for CIN other than cold-knife conization should be performed under colposcopic vision [12]. Furthermore, the International Agency for Research on Cancer suggests that the excisional procedure should be performed under colposcopic vision to minimize the extent of resection. However, when performing ablation therapy, colposcopic vision is only indicated when the transformation zone is large [13]. The situation in the European Union continues to be inconsistent. For example, while there has been improvement as a result of establishment of guidelines and quality indicators, evaluation by colposcopy was not conducted before or during CIN treatment in France until 2015. Moreover, biopsies are not consistently performed before treatment of CIN in Germany. Therefore, there is still a significant degree of variation in the treatment of CIN between countries [14,15]. In Japan, there is no published recommendation or guideline for use of surgical colposcopy in the treatment of CIN, and not all institutions have introduced colposcopes for use in surgery in addition to examination. Laser vaporization under colposcopic vision is expected to be more radical and less invasive than the conventional technique of direct visualization of the cervix using a vaginal speculum. We have been using a colposcopy-guided laser manipulation system for laser vaporization and conization since December 2019.

In this study, we examined the clinical impact of size of a CIN lesion and colposcopic findings on treatment and the effect of implementing a colposcopy-guided laser manipulation system at time of carbon dioxide laser vaporization.

Materials and methods

Ethics approval and consent to participate

This retrospective clinical investigation of laser vaporization as a treatment for CIN was approved by the Ethics Committee of Sapporo Medical University. Informed consent was obtained via the opt-out route on the Nishikawa Women's Health Clinic and Sapporo Medical University websites.

Patients and study design

We investigated the risk factors for treatment failure and the utility of a colposcopy-guided laser vaporization system for treatment of CIN2 and CIN3. Women with CIN2 or CIN3 treated at Nishikawa Women's Health Clinic between November 2018 and February 2021 were recruited. Of 301 patients treated during the study period, 290 were eligible for inclusion in the study (Fig. 1). Laser vaporization was performed for CIN2 and CIN3 when there was no discrepancy between the Papanicolaou test and punch biopsy. If discrepancy was detected in pre-operative testing, conization was recommended and laser vaporization was not performed. Additionally, cases suspected of malignancy or less common cell types on Papanicolaou test were also initially excluded from consideration for laser vaporization treatment. All colposcopic images were reviewed by two gynecologic oncologists to determine the type of transformation zone (1 or 2), area of the CIN lesion in the cervix (1/3, 1/3 to 2/3, or >2/3; Fig. 2A–C), presence or absence of peripheral CIN lesions (Fig. 2D–G), and major (grade 2) changes in accordance with the 2011 International Federation for Cervical Pathology and Colposcopy (IFCPC) terminology [16]. We defined a CIN lesion located at the outermost periphery of the cervix, adjacent to the vaginal fornix, under colposcopic view with acetic acid staining as a “peripheral CIN lesion”, without consideration of the extent of the lesion. Peripheral lesions included both widespread CIN lesions (Fig. 2D–F) and lesions only outside the broad squamocolumnar junction (Fig. 2E–G). If endocervical disease was suspected on colposcopy, endocervical curettage was added to rule out an endocervical lesion. All punch biopsies under colposcopy were performed by highly skilled colposcopists. Laser vaporization was not performed when a lesion was not visible under colposcopy. All patients were followed up after treatment using Papanicolaou and HPV tests. At least two follow-up visits were made at 2 and 5 months after treatment. Eight patients who did not attend for these follow-up visits were excluded. A further patient who had persistently abnormal cytology (atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion) at 5 months after treatment and changed to another hospital was also excluded. If abnormal cytology was detected during

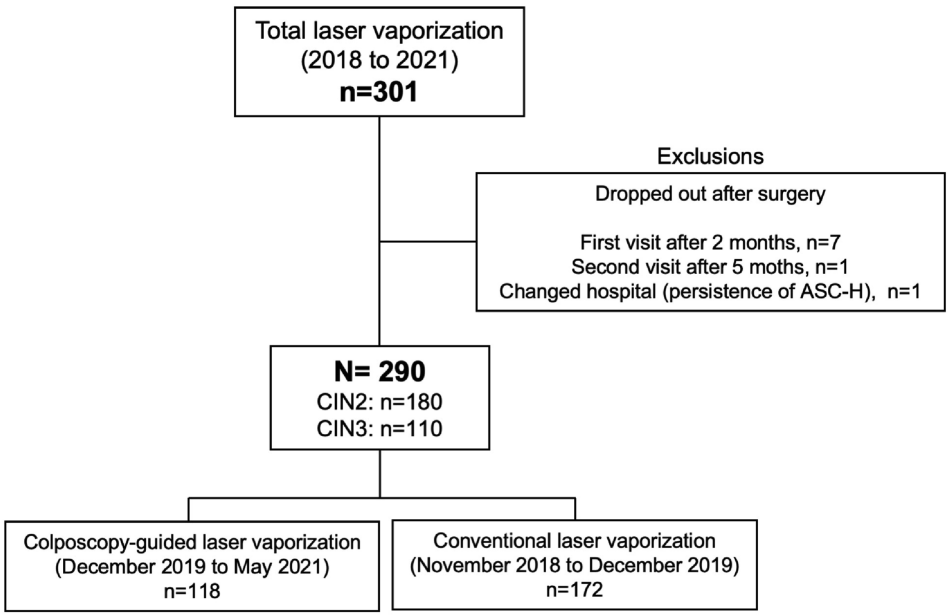

Fig. 1. Flow chart showing the patient selection process. ASC-H, atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

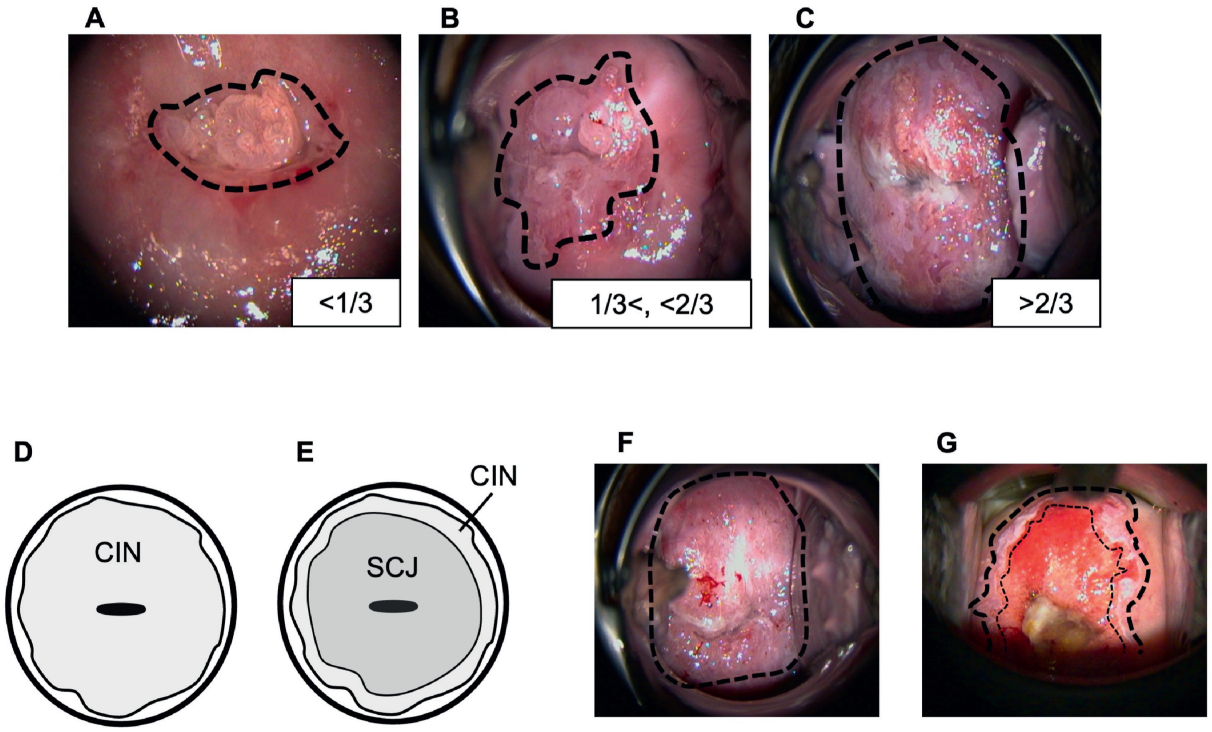

Fig. 2. Colposcopic images and classification for analysis. A–C. Examples of classifications according to lesion area (**A**, 1/3; **B**, 1/3 to 2/3; **C**, >2/3). **D, E.** Schematic illustrations of peripheral CIN lesions; D is an example of an extensive CIN throughout cervix, while E shows a CIN lesion around a wide SCJ. **F, G.** Colposcopic view in which F corresponds to schema D and G corresponds to schema E. The dotted line points to the CIN lesion and the thin inner dotted line points to the SCJ. CIN, cervical intraepithelial neoplasia; SCJ, squamocolumnar junction.

follow-up, a colposcopy test and, if necessary, a punch biopsy under colposcopic guidance were performed within two weeks of diagnosis as a mandatory procedure.

Treatment failure was defined as CIN2 or CIN3 on biopsy. Persistence of CIN1 after vaporization was not included in treatment failure in this study but was investigated separately. Continued HPV infection was defined as detection of HPV at 2 or 5 months after treatment in patients found to be HPV-positive preoperatively. Regarding additional treatment after treatment failure, decisions were made on a case-by-case basis based on colposcopic findings, cytological findings, and the persistence of HPV infection.

Surgical procedure

Carbon dioxide laser vaporization was performed using a Bel Laser system (Takara Belmont, Osaka, Japan) under direct vision with a vaginal speculum in patients treated from November 2018 to March 2020 and an AcuPulse system (Lumenis Be Japan K.K.) in those treated from April 2020 to February 2021. We used a laser adaptor device (ColpoSlad; Lumenis Be Japan K.K.) with the AcuPulse for colposcopy-guided vaporization. The cervix was stained with 3% acetic acid and the lesion was visualized before treatment. Vaporization was performed with free margins of 3–5 mm from the lesion and a depth of at least 6 mm with the guidance of laser spot diameter set in 3 mm.

HPV genotyping

We used the Megben kit (MBL, Tokyo, Japan) for HPV genotyping in patients with CIN2, which is covered by insurance for HPV testing in Japan. The Megben kit uses the PCR-rSSO method and can detect 13 HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). The PapiPlex test (GeneticLab, Sapporo, Japan) was used for HPV genotyping in patients with CIN3, as described elsewhere [5,17]. The PapiPlex test uses multiplex PCR and can detect 16 HPV genotypes (6, 11, 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66).

Because of the differences in HPV genotypes detected by each test and the high number of genotypes requiring statistical processing, we grouped the HPV genotyping results (Table 1). The groups were combined further into three groups for logistic regression analysis (Table 2).

Statistical analysis

The chi-squared test was used to determine the significance of differences in demographic characteristics between patients in whom surgery was performed using the conventional method and those in whom it was performed using the colposcopy-guided method. We also analyzed the treatment failure and HPV persistence rates based on the presence of peripheral lesions using the chi-squared test. A logistic regression model was used for multivariate analysis to determine the adjusted risk ratio and independent significance of treatment failure and HPV persistence. The statistical analysis was performed using SPSS for Windows (version 27; IBM Corp., Armonk, NY). A p-value of <0.05 was considered statistically significant. GraphPad Prism (version 8.4; GraphPad Software Inc., San Diego, CA) was used to plot the bar graphs.

Results

Clinical features and treatment outcome according to surgical method used

Table 1 shows the patient demographics according to type of surgical method used. Although there were almost no significant differences between surgical methods in background

Table 1
Patient demographics and treatment outcomes according to surgical method used.

Factor		Guided vaporization n = 118	Conventional vaporization n = 172	Total (or mean ± SD) N = 290	p-value (chi-squared test)
Age, years		32.4 ± 6.5	33.5 ± 7.1	33.1 ± 6.8	0.154
Parity		0.51 ± 0.86	0.67 ± 1.1	0.60 ± 0.99	0.612
Smoking		13	29	42	0.165
HPV status					**0.02***
	Not tested	0	2	2	
	Negative	0	**11***	11	
	HPV16	14	24	38	
	HPV18	6	6	12	
	Other hrHPV	80	108	188	
	16 + other hrHPV	17	14	31	
	18 + other hrHPV	1	7	8	
CIN grade					0.953
	2	73	107	180	
	3	45	65	110	
Colposcopic findings	Transition zone				0.698
	TZ1	113	163	276	
	TZ2	5	9	14	
	CIN area				0.363
	<1/3	27	35	62	
	1/3 to 2/3	74	101	175	
	>2/3	17	36	53	
	Peripheral lesion present	41	60	101	0.981
	Major change	47	65	112	0.726
Treatment outcome	Cured	**111***	139	250	**0.001****
	Failed	7	33	40	
	Disappearance of HPV	60	90	150	0.34
	Persistence of HPV	58	69	127	

*p < 0.05 and **p < 0.01, statistically significant. CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; OR, odds ratio; TZ, transition zone.

characteristics, there were significantly more negative HPV tests preoperatively in the conventional vaporization group (0% vs 6.4%; p = 0.02). The cure rate was significantly better in the guided vaporization group than in the conventional vaporization group (94.1% vs. 80.8%; p < 0.001) but there was no significant difference in the HPV disappearance rate (56.6% vs 50.8%; p = 0.34).

Risk factors for treatment failure and HPV persistence

Multivariate analysis of risk factors for treatment failure and HPV persistence was performed using a logistic regression model. Negative preoperative HPV infection status (p = 0.032) and a lower CIN grade (p = 0.001) were independent predictors of treatment

Table 2
Multivariate analysis for treatment outcomes using logistic regression model.

Factor			Treatment failure OR	95% CI			p-value	HPV persistence OR	95% CI			p-value
Age			1.00	0.93	to	1.08	0.90	0.96	0.92	to	1.00	0.05
Parous			1.21	0.74	to	1.99	0.45	0.90	0.66	to	1.24	0.51
Smoking			0.82	0.27	to	2.47	0.72	0.82	0.40	to	1.68	0.59
Infected HPV	Negative		ref				**0.032***	–				–
	HPV16/18 (± other hrHPV)		7.82	0.61	to	100.56	0.11	ref				**0.004****
	Other hrHPV		2.53	0.21	to	30.11	0.46	0.44	0.25	to	0.77	
CIN grade		2	ref				**0.001****	ref				0.73
		3	6.09	2.13	to	17.45		1.11	0.61	to	2.03	
Colposcopic findings	Transformation zone	1	ref				0.43	ref				0.25
		2	0.36	0.03	to	4.49		2.11	0.59	to	7.62	
	Area of abnormal findings	<1/3	ref				0.11	ref				0.36
		1/3 to 2/3	3.22	0.38	to	27.55	0.29	0.61	0.31	to	1.20	0.15
		>2/3	7.36	0.76	to	71.02	0.08	0.64	0.24	to	1.69	0.37
	Presence of peripheral lesion		4.75	1.82	to	12.35	**0.001****	2.02	1.10	to	3.70	**0.023***
	Major findings		0.93	0.32	to	2.71	0.89	1.31	0.69	to	2.50	0.41
Surgical method	Conventional vaporization		ref				**0.001****					0.46
	Guided vaporization		0.16	0.06	to	0.46		1.22	0.73	to	2.04	

*p < 0.05 and **p < 0.01, statistically significant. CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; OR, odds ratio.

success in multivariate analysis (Table 2). HPV infection involving the 16 and/or 18 genotype was an independent risk factor for persistence of HPV when compared with other high-risk HPV genotypes ($p = 0.004$). The only colposcopic finding identified to be an independent risk factor for treatment failure was a peripheral CIN lesion (odds ratio [OR] 4.75, 95% confidence interval [CI] 1.82–12.35; $p = 0.001$), which was also an independent risk factor for HPV persistence after vaporization (OR 2.02, 95% CI 1.10–3.70; $p = 0.023$). Interestingly, although guided vaporization was associated with an 84% lower risk of treatment failure than conventional vaporization (OR 0.16, 95% CI 0.06–0.46; $p = 0.001$), there was no statistically significant difference in risk of HPV ($p = 0.46$).

A colposcopic finding of peripheral CIN lesion status was an independent risk factor for treatment failure and was examined in further detail. There were more treatment failures in the group with peripheral lesions than in the group with no peripheral lesions (Fig. 3A; $p < 0.001$). HPV persistence after treatment was also affected by the presence of peripheral lesions (Fig. 3B; $p = 0.011$), and the HPV persistence rate was higher in the group with peripheral lesions than in the group without peripheral lesions. Comparison according to the surgical method used showed that most of the failed cases with peripheral lesions were treated by conventional vaporization (Fig. 3C; $p = 0.031$). This finding suggests that colposcopy-guided vaporization may be preferable for peripheral CIN lesions.

In total, there were 40 unsuccessful cases in which a CIN2 grade persisted postoperatively. Furthermore, there were 14 cases in which additional treatment was not required but in which CIN1 was detected postoperatively. The course of all cases is shown in Fig. 4. Twenty-five cases required repeat vaporization, including one case that was refractory to treatment and required additional conization. Ten patients underwent additional conization and two underwent hysterectomy. Thirty-five of 40 patients were cured, but five are still under follow-up because of persistence of mildly atypical cells without a detectable CIN lesion. None of the cases developed to invasive cancer during the study period.

Discussion

There are few reports on the risk of treatment failure in laser vaporization for CIN. However, scar tissue from previous treatment and insufficient vaporization depth have been reported to be risk factors [18]. Glandular involvement, age over 40 years, and high body mass index have been shown to be associated with the risk of recurrence after laser vaporization [19]. Margin involvement is widely recognized as a risk factor for failure of excisional treatment of CIN, and it is presumed that a missed non-vaporized lesion is the most important reason for treatment failure and recurrence after laser vaporization [20]. It is important to note that persistence of HPV infection suggests treatment failure or early recurrence, even if the cytological findings have normalized [21]. In the present study, the risk of treatment failure was found to depend on peripheral CIN status and the treatment procedure used, in addition to high-risk HPV infection and CIN histological grade. Our data clearly show the usefulness of colposcopy-guided laser vaporization, especially in patients with peripheral cervical lesions. However, an improved outcome of laser vaporization under colposcopic vision has not been reported previously. A CIN lesion in need of vaporization is clearly visible with acetic acid staining, which seems adequate for confirmation of extension of the lesion even under direct vision using a vaginal speculum. However, in the present study, laser vaporization under colposcopic vision markedly improved the cure rate for peripheral CIN lesions, which had a relatively higher treatment failure rate when performed under direct vision using a vaginal speculum. Therefore, direct vision with a vaginal speculum may not be sufficient to examine peripheral CIN lesions, and an improved view of the vaporization region under colposcopic vision would be desirable. A limitation of this study is the time frame of the research period, which spans from 2018 to 2021, somewhat predating the submission of this paper. This delay was due to the time needed for the publication process after the results were summarized. However, there have been no significant changes in treatment guidelines for CIN2 and CIN3 during this time. In Japan, clinical practice guidelines for treatment with laser vaporization have been updated every 3 years since 2017, but no significant changes affecting treatment decisions have been observed. Another limitation is that the choice of vaporization method was not randomized, and the comparison was made before and after the introduction of the device (AcuPulse system and ColpoSlad, Lumenis Be Japan K.K.). And another important limitation is that this study only includes short-term follow-up data up to 5 months after vaporization. As a result, we cannot confirm the recurrence of CIN lesions or the development of invasive cancer over a long-term observation period. However, our study provided significant insights into the persistence of post-vaporization HPV infection, which is an established clinical marker for incomplete CIN treatment or recurrence prediction [20,22]. Specifically, the presence of peripheral CIN lesions was identified as an independent risk factor for persistent HPV infection after treatment (Table 2). This result

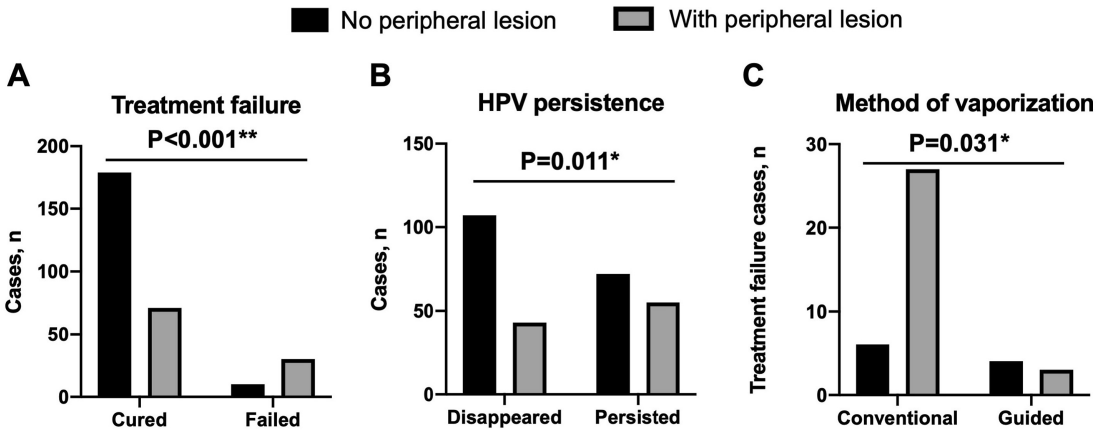

Fig. 3. Differences in treatment outcomes according to peripheral CIN lesion status. A, B Relationship between treatment failure or HPV persistence and presence of a peripheral CIN lesion. **C.** Relationship between presence of a peripheral CIN lesion and treatment failure according to the laser vaporization method used. *$p < 0.05$ and **$p < 0.01$, chi-squared test. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

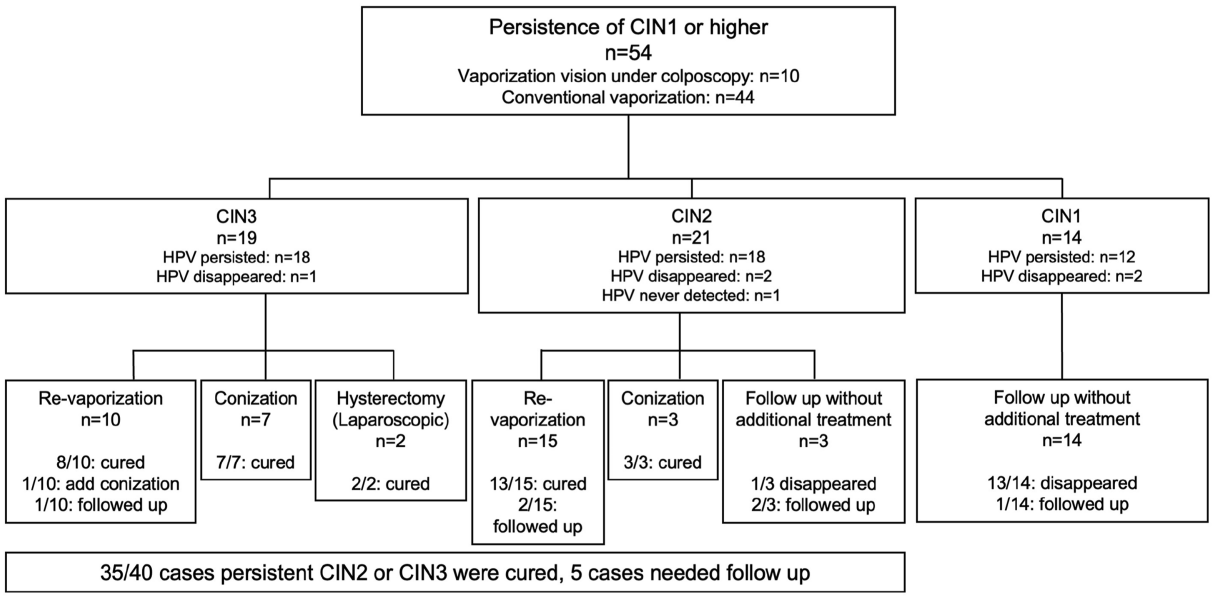

Fig. 4. Tree chart showing the clinical course after treatment failure and persistent cases of CIN1. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

suggests that accurate lesion visualization using intraoperative colposcopy can also impact the long-term outcomes of laser vaporization.

We believe that preoperative colposcopic evaluation is even more important than intraoperative colposcopic guidance. In this study, we found no difference in cure rates when minor or major colposcopic findings were compared based on IFCPC 2011 terminology [16] This finding does not mean that grading by colposcopy is unnecessary but may indicate that laser vaporization is sufficiently curative for CIN2 and CIN3. However, the efficacy of laser vaporization for invasive cervical cancer has not been established. In our study, no cases of invasive cancer were observed during the clinical course, and even among the unsuccessful treatments, no cases developed into invasive cancer as shown in Fig. 4. However, it should be noted that in some cases, lesions previously diagnosed as CIN by biopsy may actually contain invasive cancer [23]. Therefore, favorable clinical outcomes with laser vaporization are dependent on appropriate previous evaluation of a lesion by colposcopic examination and accurate selection of the biopsy site. There have been many studies on the concordance rate of colposcopic diagnosis using the IFCPC 2011 terminology, particularly the detailed study by Zhang et al. of the concordance between minor/major colposcopic findings and low-risk/high-risk squamous intraepithelial lesions [24]. They indicated that evaluation of acetowhite epithelium thickness is especially important for grading. Other morphological findings such as mosaic and punctation, although lacking high sensitivity, have at least 90% specificity for CIN. A systematic review by Qin et al. that included 15 articles found that colposcopic examination using the 2021 IFCPC terminology had a specificity of 93% for lesions with CIN3 or higher, suggesting that colposcopy is essential for exclusion of invasive cancer [25]. In a study that compared the concordance rate between colposcopic and histological diagnosis, colposcopists with more than 10 years of experience had the highest concordance rate for lesions that were high-risk squamous intraepithelial lesions or higher, with a 12.5% difference in sensitivity for lesion detection in comparison with colposcopists who had 0–5 years of experience [26]. Therefore, precise preoperative diagnosis is essential for laser vaporization, and colposcopic evaluation by experts both before and during the treatment procedure is recommended.

Conclusion

The presence of a peripheral lesion was strongly associated with treatment failure of laser vaporization for CIN. Choosing a device that can perform fine laser vaporization under colposcopic vision is expected to increase the cure rate.

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Author contributions

Akira Nishikawa: Conceptualization, Methodology. Tasuku Mariya: Visualization, Investigation, Software, Writing – Original draft preparation. Mina Umemoto and Shiori Ogawa: Data collection and analysis. Tsuyoshi Saito: Supervision.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest

All authors report no conflicts of interest.

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Original Article

Progesterone receptor isoform B in the stroma of squamous cervical carcinoma: An independent favorable prognostic marker correlating with hematogenous metastasis

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ABSTRACT

Objectives: To ascertain the prognostic role of the expression levels of estrogen receptor (ER) and progesterone receptor (PR) within the stroma microenvironment of cervical cancer and explore their correlation with clinical parameters.
Materials and methods: This retrospective cohort study involved patients with cervical cancer diagnosed and treated at Hualien Tzu Chi Hospital between 2000 and 2010. ERα, PRB, and PR (A + B) expression levels in 169 cervical carcinoma samples, including both the tumor and stromal components, were independently scored by two pathologists, and survival and clinicopathological parameters were analyzed.
Results: ERα or PRs were predominantly expressed in the stromal compartment rather than within cervical cancer cells. Their expression was observed comprehensively within the intra- and peritumor stroma cells. A stromal PRB expression significantly correlated with a lower 5-year mortality because of cervical cancer ($p = 0.011$). Particularly, levels of both stromal ERα and PRB expressions correlated with lower hematogenous distant metastase rates ($p = 0.013$ and $p = 0.011$, respectively). In the multivariable logistic regression analyses, stromal PRB independently conferred a lower risk of 5-year mortality ($p = 0.022$), regardless of age, histology, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor differentiation, lymphovascular space invasion, and lymphatic and hematogenous metastases. Moreover, the incorporation of stromal PR (A + B) and PRB expression in the FIGO stage significantly enhanced the accuracy of survival prediction.
Conclusion: Stromal PRB expression emerges as an independent and favorable prognostic marker for cervical squamous cell carcinoma and correlated with a low risk of hematogenous metastases. The findings imply that incorporating this marker into the FIGO stage better predicts the survival for cervical cancer.

Introduction

Cervical cancer is the fourth most prevalent cancer in women worldwide, with a disproportionately higher incidence and mortality rate in less developed and developing countries [1]. Epidemiological and preclinical studies have reported that sex hormones play essential roles in cervical carcinogenesis [2–4]. Clinical studies investigating the prognostic role of estrogen receptor (ER) and progesterone receptor (PR) in cervical cancer have predominantly focused on the carcinoma component, with limited

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attention to the stromal aspect [5–8]. Moreover, most were small-sample studies and revealed inconclusive prognostic value [6–9].

ER and PR are normally expressed in the basal and suprabasal layers of the normal cervical epithelium, and their expression levels decrease in cervical intraepithelial neoplasia and progressively decrease in high-grade dysplasia, carcinoma in situ, and invasive cervical carcinoma. These receptors are rarely detected in invasive squamous cell carcinoma [10]. Very few studies have examined the ER and PR expression in the cervical stroma [5,6,8,9]. The crosstalk between cancer cells and neoplastic stromal cells [11] facilitates tumor invasion, angiogenesis, and metastasis [12,13]. However, the roles of ER and PR expression in tumor stromal cells during cervical cancer development remain unclear. An important breakthrough in this area was the development of K14-HPV E6/E7 transgenic mouse model of cervical carcinogenesis where estrogen and ERα (ER isoform expressed in the uterus) are the absolute requirement for the development of human papillomavirus (HPV)-associated cervical cancer. In the selective transgenic knockout study, ERα deletion in the tumor stroma promoted the regression of cervical neoplasia and abrogated the transformation of epithelial cells [14–18]. In contrast, in this cervical carcinogenesis model, progesterone and PR appeared to function as tumor suppressors. Yoo et al. showed that medroxyprogesterone acetate promoted the regression of cancers and precancerous lesions in these mice [19]. Another study on genetic knockout of *Pgr* confirmed that PR mediated this regression effect [20].

The current classification and staging systems for cervical cancer are largely based on clinical and pathological findings. The roles of ER and PR in the cervical carcinoma stroma during invasion or metastasis are also barely known. Our previous study revealed that ERα and PRB expressions in the cervical stroma were independent favorable prognostic factors in squamous cell carcinoma [21], indicating the potential involvement of stromal ER/PR in invasion or metastasis of cervical cancer. However, further clinicopathological analysis was limited by the small number of patients.

In this study, we examined the epithelial (carcinoma) and peritumor stromal expressions of ERα, PR (A + B), and PRB and further extended the scale and follow-up duration of the previous cohort for thorough clinicopathological analyses. In this study, stromal PRB expression was found to be an independent and favorable prognostic marker for cervical cancer, correlating with a low risk of hematogenous metastases. These biomarkers could be used to indicate disease severity and predict outcomes.

Materials and methods

Patient samples and clinical data

This study enrolled 169 patients who had been diagnosed with invasive cervical carcinoma and treated at Hualien Tzu Chi Hospital, Taiwan, between 2000 and 2010. Among these patients, 149 had squamous cell carcinoma (SCC) (88.17%), whereas 20 had non-SCC tumors (11.83%), consisting of 16 adenocarcinomas and 4 neuroendocrine carcinomas. This study was approved by the Institutional Review Board of Hualien Tzu Chi Hospital, Taiwan (IRB103-139-A & IRB104-100-A).

Formalin-fixed paraffin-embedded (FFPE) blocks of cervical carcinoma were taken from radical hysterectomies or cervical biopsies. The cervical cancer stage was based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria [22]. Clinical and histopathological characteristics, including lymph node and/or distant metastasis upon diagnosis, and follow-up outcomes were extracted from clinical and pathology records of the hospital and the Taiwan National Cancer Registry (TNCR) [23,24]. In particular, metastasis to distant organs such as the lung, liver, and bones were categorized as hematogenous distant metastasis, whereas metastases to paraaortic, supraclavicular, and inguinal lymph node deposits were regarded as lymphatic distant metastases. Patients were followed up for a minimum of 5 years or until their demise. Clinical data and the cause and date of death were confirmed based on information from the TNCR.

Immunohistochemistry (IHC) staining

IHC staining was conducted on FFPE primary cervical cancer tissues to assess the expression of ERα, PR (A + B), and PRB. Initially, 5-μm sections were prepared from all specimens and mounted on slides. Subsequently, sections were deparaffinized using xylene, and slides were rehydrated through a graded alcohol series and placed in running water. For immunohistochemical detection, the Novolink Polymer Detection System (Novocastra Laboratories, Newcastle, UK) was used. For antigen retrieval, the slides were subjected to heat treatment in 10 mM citrate buffer (pH 6.0). Then, a peroxidase block was applied to neutralize the endogenous peroxidase activity. The tissue slides were then incubated with the following antibodies: anti-ERα monoclonal antibody (dilution, 1:250) (EPR4097, ab108398; Abcam, Cambridge, MA, USA), anti-PR (A + B) antibody (dilution, 1:100; NCL-L-PGR-312; PGR-312-L-F; Leica Biosystems, Newcastle, UK) [25,26], or anti-PRB antibody (dilution, 1:100; YR85, ab32085; Abcam) [22] for 30 min. Subsequently, the slides were incubated with a Novolink polymer and then exposed to a 3,3′-biaminobenzidine chromogen solution to induce peroxidase activity for visualization.

Evaluation of IHC staining

IHC staining was conducted independently by two experienced gynecological histopathologists from different hospitals, both unaware of the clinicopathological outcomes. The IHC staining of ERα, PR (A + B), and PRB was assessed in tumor and intra- and peritumor stromal cells. To minimize the effect of polymorphonuclear (PMN) cell infiltration, low PMN infiltration areas were prioritized for evaluation. The IHC results were assessed and scored using the immunoreactive score (IRS) system in tissue IHC research [27,28]. The IRS is considered the "gold standard" scoring system, widely used for various malignant gynecological tumors [29–31], and recommended by leading organizations [32,33]. Positively stained cells were scored as 0 (0%), 1 (1%–10%), 2 (11%–50%), 3 (51%–80%), or 4 (>80%). Staining intensity was graded 0 (none), 1 (weak), 2 (moderate), or 3 (strong). The multiplication of these two scores resulted in an IRS ranging from 0 to 12. For comparison, expression was stratified into no expression (IRS $\leq$0.5) and positive expression including low expression (IRS >0.5 to <6.0), and high expression (IRS $\geq$6.0–12.0).

Statistical analyses

To detect mean differences among groups, various statistical tests were employed depending on data normality. Specifically, independent two-sample t-tests, the Wilcoxon rank-sum test, one-way analysis of variance, and the Kruskal–Wallis test were utilized. Categorical variables were compared using either the chi-square test or Fisher's exact probability test as appropriate. To assess underlying trends, the Cochran–Armitage trend test was employed. Survival analysis, focusing on 5-year mortality risk among all patients with SCC, was conducted using Kaplan–Meier curves and Cox proportional hazard models. These models were adjusted for demographic and clinical covariates. Significance was defined as a p value < 0.05. All statistical analyses were performed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

This study enrolled a total of 169 patients (Table 1). Among these patients, 87 (51.5%) had FIGO tumor stage IIA or earlier, and 58 (65.9%) of these patients underwent radical or modified radical hysterectomy according to NCCN guidelines®. Among patients who had undergone surgery, 28 received concurrent chemo-radiotherapy (CCRT) with weekly cisplatin (40 mg/m^2) during external radiation therapy with or without brachytherapy. Most patients with advanced tumors (37/65, 56.9%) received CCRT, and some (28/65, 43.1%) received radiotherapy and/or chemotherapy depending on their medical conditions. Of the 25 patients with stage IV cervical cancer, 17 (68%) received hospice care. No differences in age, parity, FIGO stage, 5-year mortality rate due to cervical cancer, tumor differentiation, distant metastasis, lymphovascular space invasion (LVSI), or expressions of ERα, PR (A + B), and PRB were found between the SCC and non-SCC histological groups.

Once expressed, ER or PR is comprehensively found within both peri- and intratumor stromal cells

In this study, sex hormone receptors were mainly expressed in the nuclei of stromal cells adjacent to and within the cervical carcinoma (Fig. 1A, B, 1C). ERα, PR (A + B), and PRB were expressed in tumor cells in 24.7%, 3.2%, and 3.6% of the patients (Table 1), whereas their expression the intra- or peri-tumor stroma was recorded in 73.7%, 58.9%, and 67.1% of the patients, respectively. Expressed ones were comprehensively seen in the intratumor nests (Fig. 1C and D) and peritumor stroma (Fig. 1E and F) up to 3 mm from the margin. The IRS of both PRB and PR (A + B) decreased with aging ($r = 0.159$, $p = 0.060$; $r = 0.205$, $p = 0.015$, respectively) (Figs. S1A and S1B); however, this phenomenon was not observed in ERα (Fig. S1C).

Stromal PRs correlated with low 5-year mortality, but only stromal ERα and PRB expressions correlated with less hematogenous metastases

Cervical cancer patients with ERα and PRB expressions in the tumor stroma had a lower distant metastasis rate than patients without such expressions (7.0% vs. 19.5%, $p = 0.034$; and 6.6% vs. 17.3%, $p = 0.036$, respectively) (Table 2). On the contrary, stromal expressions of PRB and PR (A + B), but not ERα, were associated with lower 5-year mortality rates. More importantly, on hematogenous metastases (excluding metastases to paraaortic and other distant lymph nodes), the stromal expression of ERα and PRB remarkably correlated with a lower hematogenous metastasis rate (4.6% vs. 18.4%, $p = 0.013$; and 4.0% vs. 16.0%, $p = 0.011$, respectively). In contrast, the presence of ER/PR in tumor cells (carcinomas) did not relate to mortality rate or metastases (Table S1).

The stromal expression of PRB is an independent predictor of favorable prognosis

In multivariable logistic regression analysis, mortality showed association with the FIGO stage [crude hazard ratio (cHR) = 16.02, 95% CI 7.46–34.39, $p < 0.001$ at stage IV vs stage I], lymph node metastasis (cHR = 4.62, 95% CI 2.53–8.44 $p < 0.001$),

Table 1
Demographics, histopathology, and expression of sex hormone receptors in the stroma and carcinoma of patients with cervical cancer.

Characteristics	Overall		Non-SCC		SCC		p value
							SCC vs non-SCC
Number	169		20		149		
Age	58.7 ± 15.1		57.0 ± 13.9		58.9 ± 15.2		0.581
Parity	3.9 ± 2.1		3.3 ± 1.8		4.0 ± 2.1		0.179
FIGO stage at diagnosis							0.684
I	66 (39.3%)		9 (45.0%)		57 (38.5%)		
II	50 (29.8%)		4 (20.0%)		46 (31.1%)		
III	27 (16.1%)		3 (15.0%)		24 (16.2%)		
IV	25 (14.9%)		4 (20.0%)		21 (14.2%)		
Extrafascial hysterectomy	6 (3.55%)		1		5		0.067
Radical or modified radical hysterectomy	58 (34.32%)		2		56		0.756
Concurrent chemoradiotherapy	28 (16.57%)		2		26		0.508
Radiotherapy and or chemotherapy	28 (16.57%)		4		24		0.316
Hospice care	17 (10.06%)		2		15		0.487
Tumor differentiation							0.771
Grade 1	52 (33.1%)		6 (30.0%)		46 (33.6%)		
Grade 2	75 (47.8%)		9 (45.0%)		66 (48.2%)		
Grade 3	30 (19.1%)		5 (25.0%)		25 (18.2%)		
Lymphovascular space invasion	55 (36.4%)		11 (55.0%)		44 (33.6%)		0.064
Overall lymph node metastasis	35 (25.9%)		6 (31.6%)		29 (25.0%)		0.576
Overall distant metastasis	17 (10.1%)		2 (10.0%)		15 (10.1%)		1.000
Follow-up time (year)	6.8 ± 5.6		7.5 ± 5.6		6.7 ± 5.6		0.536
5-year death due to cervical cancer	64 (37.9%)		7 (35.0%)		57 (38.3%)		0.778
	Positive IHC	**IRS**	Positive IHC	**IRS**	Positive IHC	**IRS**	
Stroma ERα positive	115/156 (73.7%)	3.0 (6.0)	15/19 (78.9%)	3.0 (5.0)	100/137 (73.0%)	3.0 (6.0)	0.695
Stroma PR (A + B) positive	93/158 (58.9%)	1.0 (4.0)	11/19 (57.9%)	1.0 (4.0)	82/139 (59.0%)	1.0 (4.0)	0.759
Stroma PRB positive	106/158 (67.1%)	2.0 (5.0)	15/19 (78.9%)	3.0 (4.0)	91/139 (65.5%)	2.0 (5.0)	0.516
Carcinoma ERα positive	40/162 (24.7%)	0.0 (1.0)	3/20 (15.0%)	0.0 (0.0)	37/142 (26.1%)	0.0 (1.0)	0.152
Carcinoma PR (A + B) positive	5/157 (3.2%)	0.0 (0.0)	1/19 (5.3%)	0.0 (0.0)	4/138 (2.9%)	0.0 (0.0)	0.839
Carcinoma PRB positive	6/165 (3.6%)	0.0 (0.0)	0/20 (0.0%)	0.0 (0.0)	6/145 (4.1%)	0.0 (0.0)	0.226

ERα, estrogen receptor isoform α; PR(A + B), progesterone receptor isoforms A and B; FIGO, International Federation of Gynecology and Obstetrics (2009 criteria); IHC, immunohistochemistry staining; IRS, immunoreactive score = (intensity × percentage) of IHC stain. PRB, progesterone receptor isoform B; SCC, squamous cell carcinoma; Vs.: versus Data are presented as number/total number (percentage) or mean ± standard deviation or median (IQR). *SCC Vs. Non-SCC.

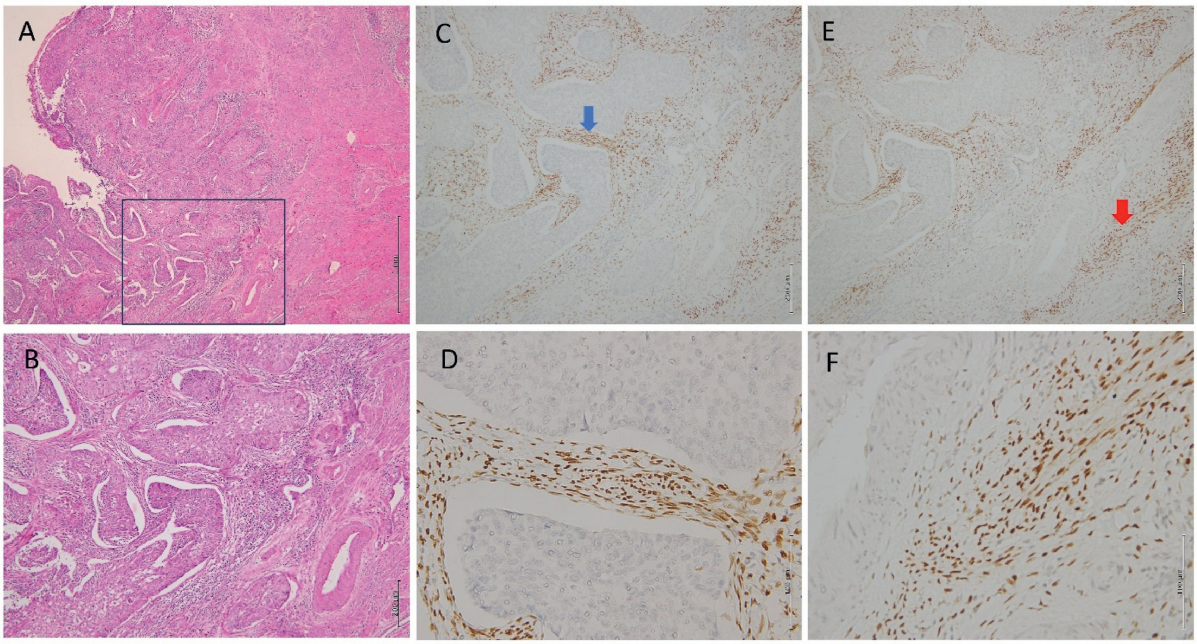

Fig. 1. Comprehensive expression of ERα and PRB expression in the stroma of intra- and peri-tumor. (A, B) Hematoxylin and eosin (H&E) staining of squamous cervical carcinoma, (B) low middle panel inset in figure A, magnification: 100X. (C, D) High expression level of ERα at intra-tumor stroma with (C) magnification: 100X and (D) magnification: 400X (blue long arrow site in figure C), with IRS score of 12 (positive stained cells was categorized as 4 (>80%) and staining intensity was graded as 3 (strong); (E, F) High expression level of PRB at peri-tumor stroma with (E) magnification: 100X and (F) magnification:400X (red short arrow site in figure E), with IRS score of 12 (positive stained cells was categorized as 4 (>80%) and staining intensity was graded as 3 (strong).

Table 2
Relation of the stromal ER/PR expression to clinicopathological parameters, lymphatic, or hematogeneous metastasis and 5-year mortality rate.

Parameters	Stroma ERα expression (n = 156)			Stroma PR (A + B) expression (n = 158)			Stroma PRB expression (n = 158)		
	No	Yes	p value*	No	Yes	p value*	No	Yes	p value*
Number	41	115		65	93		52	106	
Age	57.1 ± 15.0	60.0 ± 15.0	0.298	62.1 ± 15.0	56.6 ± 15.1	0.024†	61.7 ± 14.9	57.7 ± 15.0	0.123
Parity	3.8 ± 2.4	4.0 ± 2.0	0.560	4.1 ± 2.3	3.7 ± 2.0	0.314	4.0 ± 2.4	3.8 ± 2.0	0.710
FIGO stage			0.014†			0.059†			0.104†
I	11 (18.0%)	50 (82.0%)		18 (29.5%)	43 (70.5%)		15 (23.8%)	48 (76.2%)	
II	13 (28.9%)	32 (71.1%)		24 (50.0%)	24 (50.0%)		19 (42.2%)	26 (57.8%)	
III	3 (12.5%)	21 (87.5%)		9 (37.5%)	15 (62.5%)		5 (20.8%)	19 (79.2%)	
IV	13 (52.0%)	12 (48.0%)	0.001‡	13 (54.2%)	11 (45.8%)	0.148‡	12 (48.0%)	13 (52.0%)	0.071‡
Tumor differentiation			0.046†			0.651†			0.278†
Grade 1	12 (25.5%)	35 (74.5%)		27 (55.1%)	22 (44.9%)		18 (38.3%)	29 (61.7%)	
Grade 2	15 (20.5%)	58 (79.5%)		19 (25.7%)	55 (74.3%)		16 (21.6%)	58 (78.4%)	
Grade 3	14 (51.9%)	13 (48.1%)	0.002§	16 (59.3%)	11 (40.7%)	0.037§	16 (57.1%)	12 (42.9%)	0.003§
Lymph node metastasis (vs. no LN Meta.)	11/35 (31.4%)	23/91 (25.3%)	0.486	13/43 (30.2%)	21/84 (25.0%)	0.529	12/40 (30.0%)	22/88 (25.0%)	0.553
Distant metastasis (Vs. no distant Meta.)	8/41 (19.5%)	8/115 (7.0%)	0.034	8/65 (12.3%)	8/93 (8.7%)	0.447	9/52 (17.3%)	7/106 (6.6%)	0.036
Lymphatic‖	3/41 (7.3%)	4/115 (3.5%)	0.380	3/65 (4.6%)	4/93 (4.3%)	1.000	2/52 (3.8%)	5/106 (4.7%)	1.000
Hematogeneous¶	7/38 (18.4%)	5/109 (4.6%)	0.013	5/57 (8.8%)	6/91 (6.6%)	0.750	8/50 (16.0%)	4/99 (4.0%)	0.011
LVSI	11/40 (27.5%)	41/102 (40.2%)	0.158	14/59 (23.7%)	38/85 (44.7%)	0.010	11/49 (22.4%)	42/95 (44.2%)	0.010
5-year mortality rate due to cervical cancer (Vs. alive)	19 (46.3%)	38 (33.0%)	0.129	35 (53.8%)	25 (26.9%)	0.001	26 (50.0%)	31 (29.2%)	0.011

ERα: estrogen receptor isoform α; FIGO: International Federation of Gynecology and Obstetrics (2009 criteria). Data are presented as number/ratio (percentage) or mean ± standard deviation.

* P for independent t test or chi-squared test.

† P for the Cochran–Armitage trend test.

‡ Stage I/II/III vs. IV.

§ Grade 1/2 vs. grade 3.

‖ Paraaortic and other distant -lymph node metastasis; LN Meta., lymph node metastasis; LVSI, lymphovascular space invasion; PR (A + B), progesterone receptor isoforms A and B; PRB, progesterone receptor isoform B; vs, versus.

¶ Distant organs metastasis, e.g., lung, bone, and liver.

hematogenous metastasis (cHR = 7.53, 95% CI 3.83–14.80, p < 0.001), and stromal expression of PR (A + B) and PRB (cHR = 0.37, 95% CI 0.22–0.62, p < 0.001; cHR = 0.47, 95% CI 0.28–0.80, p = 0.005). After considering age, histology, FIGO stage, tumor differentiation, LVSI, and lymphatic and hematogenous metastases, only stromal PR (A + B) and PRB were associated with a lower 5-year mortality [adjusted HR (aHR) = 0.42, 95% CI 0.19–0.96, p = 0.04 and aHR = 0.39, 95% CI 0.18–0.87, p = 0.022, respectively) (Table 3).

The stratification of the FIGO stage with stromal PRB significantly improves survival prediction, particulalry for patients with advanced stage

In the Kaplan–Meier disease-specific survival analysis, for stromal ERα, only the high expression (IRS ≥6.0) group showed good survival (log-rank test, p = 0.006) (Fig. 2A). For the correponding group with stromal expression of PR (A + B) and PRB (Fig. 2B and C), either low- or high expression positive groups, both showed significantly better survival than the group without such expressions (log-rank test, p < 0.001 and p = 0.004, respectively). Furthermore, when stromal ERα, PR (A + B), and PRB were incorporated accordingly to the FIGO staging 2009 criteria [22], stratified by early (I/II) and advanced stages (III/IV), remarkable divergence of survival curves was found between the positive and non-expressing groups (log-rank test, p < 0.001), particularly for the stromal PRB(+) group in advanced stages (III/IV) (Fig. 2F). Considering age, histology, tumor differentiation, LVSI, and lymphatic and hematogenous metastases, when compared with the stage I,II/ERα(+) group, the aHRs of the 5-year mortality for stage I,II/ERα(−), stage III,IV/ERα(+), and stage III,IV/ERα(−) groups were 1.46 (95% CI 0.42–5.10), 5.78 (95% CI 2.01–16.63), and 12.45 (95% CI 3.65–42.48), respectively. In the same stratification and model for PRB, higher aHRs were found: 2.15 (95% CI 0.67–6.90), 7.28 (95% CI of 2.28–23.19), 16.33 (95% CI of 4.52–59.01) (Table S2). The prognostic power of stromal PRB appeared to be the best among them (Fig. 2D–F), particularly in the prediction of prognosis of patients with advanced disease stages; it was even better than that of the current four-tier FIGO staging (Fig. 2G).

Discussion

In this study, PRB expression in the tumor stroma significantly correlated with a favorable 5-year survival in patients with cervical SCC, irrespective of age, histology, FIGO stage, tumor differentiation, LVSI, and lymphatic and hematogenous metastases. To the best of our knowledge, it is the first time in the literature that the expression levels of PRB and ERα in the tumor stroma are associated with low hematogenous metastasis rates is reported.

Table 3
Hazard ratio of 5-year mortality according to different prognostic factors and stromal ER/PR expressions.

	Number*(%)	Crude HR (95% CI)	p value	Multivariant-ERα‡		Multivariant-PR (A + B)‡		Multivariant-PRB‡	
				Adjusted HR (95% CI)†	p value	Adjusted HR (95% CI)[b]	p value	Adjusted HR (95% CI)[b]	p value
Age group									
<50 y/o	18 (31.6%)	1.00		1.00		1.00		1.00	
≧50 y/o	46 (41.4%)	1.44 (0.83, 2.48)	0.193	1.73 (0.75, 4.01)	0.200	1.23 (0.54, 2.78)	0.625	1.38 (0.61, 3.13)	0.437
Histology									
Non-SCC	7 (35.0%)	1.00		1.00		1.00		1.00	
SCC	57 (38.3%)	1.15 (0.53, 2.53)	0.725	1.66 (0.58, 4.77)	0.344	1.74 (0.59, 5.07)	0.314	1.55 (0.54, 4.44)	0.410
FIGO Stage									
I	10 (15.2%)	1.00		1.00		1.00		1.00	
II	15 (30.0%)	2.17 (0.98, 4.83)	0.058	1.28 (0.40, 4.12)	0.681	1.14 (0.38, 3.39)	0.819	1.31 (0.42, 4.05)	0.638
III	17 (63.0%)	5.61 (2.54, 12.40)	<0.001	5.38 (1.61, 17.97)	0.006	4.48 (1.41, 14.25)	0.011	6.21 (1.86, 20.77)	0.003
IV	22 (88.0%)	16.02 (7.46, 34.39)	<0.001	12.89 (3.47, 47.92)	<0.001	15.01 (4.00, 56.38)	<0.001	21.26 (5.23, 86.35)	<0.001
Tumor differentiation									
Grade 1	24 (46.2%)	1.00		1.00		1.00		1.00	
Grade 2	19 (25.3%)	0.45 (0.25, 0.82)	0.009	0.51 (0.21, 1.24)	0.136	0.60 (0.25, 1.46)	0.263	0.56 (0.24,1.32)	0.181
Grade 3	15 (50.0%)	1.00 (0.52, 1.93)	1.000	0.57 (0.23, 1.39)	0.215	0.63 (0.26, 1.58)	0.327	0.68 (0.28, 1.65)	0.398
LVSI									
No	32 (33.3%)	1.00		1.00		1.00		1.00	
Yes	24 (43.6%)	1.33 (0.78, 2.27)	0.289	1.40 (0.61, 3.22)	0.430	1.36 (0.59, 3.14)	0.474	1.62 (0.69,3.81)	0.266
Lymph node metastasis									
No	21 (21.0%)	1.00		1.00		1.00		1.00	
Yes	23 (65.7%)	4.62 (2.53, 8.44)	<0.001	0.90 (0.30, 2.76)	0.859	0.98 (0.35, 2.81)	0.975	0.63 (0.20,2.03)	0.439
Hematogenous metastasis									
No	45 (31.3%)	1.00		1.00		1.00		1.00	
Yes	11 (91.7%)	7.53 (3.83, 14.80)	<0.001	2.27 (0.73, 7.09)	0.159	1.85 (0.57, 5.94)	0.304	1.78 (0.54,5.92)	0.346
Stroma ERα expression									
No	19 (46.3%)	1.00		1.00					
Yes	38 (33.0%)	0.60 (0.34, 1.04)	0.066	0.63 (0.27, 1.48)	0.290				
Stroma PR (A + B) expression									
No	35 (53.8%)	1.00				1.00			
Yes	25 (26.9%)	0.37 (0.22, 0.62)	<0.001			0.42 (0.19, 0.96)	0.040		
Stroma PRB expression									
No	26 (50.0%)	1.00						1.00	
Yes	31 (29.2%)	0.47 (0.28, 0.80)	0.005					0.39 (0.18,0.87)	0.022

ERα, estrogen receptor isoform α; PR(A + B), progesterone receptor isoforms A and B; PRB, progesterone receptor isoform B; SCC, squamous cell carcinoma; HR hazard ratio; CI, confidence interval.
LVSI, lymphovascular space invasion. Data are presented as number (percentage) or HR (95% CI).
* Missing values for any predictor were excluded from the analysis.
† Cox's proportional hazards model.
‡ Multivariant analysis considering age, histology, FIGO stage, tumor differentiation, lymphatic and hematogeneous metastasis, and stromal expression of ERα or PR (A + B) or PRB.

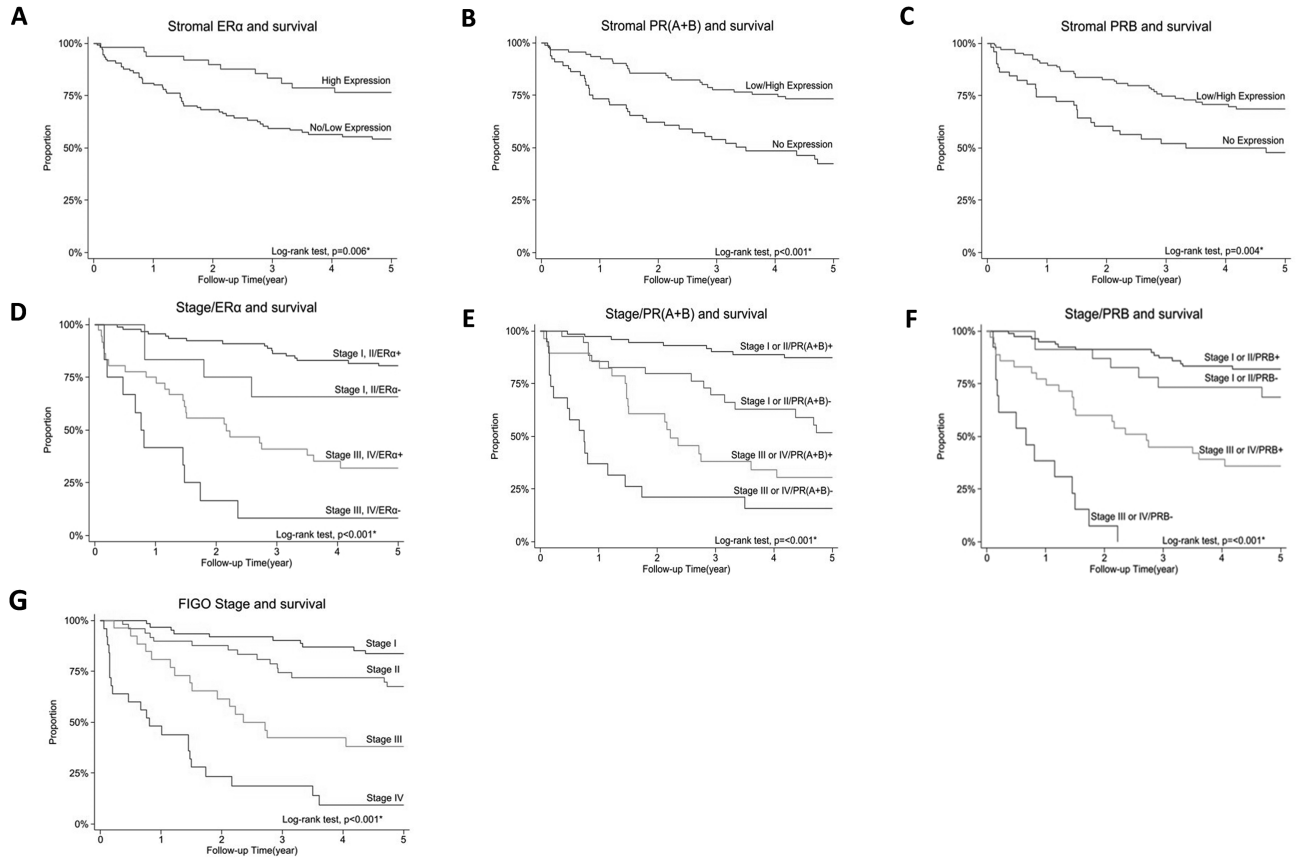

Fig. 2. Kaplan–Meier disease-specific survival plots by (A) stromal ERα: no and low expression versus high expression. (B, C). Stromal PR (A + B) or PRB: positive expression versus no expression. (D–F) Incorporation of FIGO stage I/II or stage III/IV with the presence or absence of stromal ERα or PR (A + B) or PRB. (G) FIGO stage alone.

In an HPV oncogene-expressing transgenic mouse model of cervical carcinogenesis, Park Y et al. recently uncovered a tumor-suppressive role of the *PGR* gene [34]. In their analysis of The Cancer Genome Atlas data, the same research team also established a link between low expression of PGR mRNA in tumor tissue and poor prognosis in patients with cervical cancer, particularly those aged <50 (hazard ratio, 0.203) [25]. Consistently, this study identified a correlation between reduced stromal PRB expression and an increased risk of hematogenous metastasis, and identified PR protein primarily expressed in the tumor stroma. The precise mechanism by which stromal PR exerts a protective influence on hematogenous metastasis is still unclear. In this context, the HPV's role appears to be limited because the expression of sex hormone receptors in the tumor stroma did not correlate with the HPV infection status [21].

Physiologically, PR expression in the female genital tract is highly dependent on the priming of estrogen [35,36] because E2-bound ERα transactivates *PGR* expression [37]. This notion was verified by Pearson's correlation analysis between the expression of ER and PRs, and the results revealed that stromal PRB expression highly correlated with ERα (Figs. S1D–S1F). In addition, primary stromal cells from the normal and cancerous cervix were preliminarily treated with estradiol. In the presence of fetal bovine serum, which contains high amounts of progesterone, PRs in both cells were downregulated because of ligand binding, as reported in other cell systems [38,39]. Under the serum-free culture, estradiol upregulated the PRB and PR (A + B) expression in stromal cells from both normal and cancerous cervix (Fig. S3). Consequently, the collaboration between ERα and PRB positively plays a pivotal role within the stromal environment, offering protection against hematogenous metastasis. We hypothesized that the PRB serves as the principal effector responsible for safeguarding against hematogenous metastasis, with ERα potentially exerting an indirect influence by facilitating of PRB expression.

In this study, cervical carcinomas exhibited similar ERα expression levels across different age groups. However, stromal PRB expression consistently declined with increasing age at diagnosis. This observation could explain why Park et al. found a favorable prognostic association between high PGR expression and young patients, but not for older patients [34]. The loss of stromal PGR expression in older individuals aligns with the earlier finding that advanced age is an independent poor prognostic factor even after accounting for FIGO stage, histological type, and race [40]. To investigate whether the age-related inferior prognosis is linked to decreased stromal ERα expression, Kaplan–Meyer survival analysis of stromal PRB in cervical cancer cases was performed across different age groups (<50, 50–60, and >65 years). As shown in Figs. S2A, S2B, S2C, stromal PRB demonstrated stronger prognostic significance in patients aged >65 and < 50 years than in those aged 50–65 years, but for stromal PR (A + B) prognostic significance only seen in those aged <50 years (Figs. S2D–S2F). This outcome may be attributed to a notable trend of distant metastasis in patients aged >65 (10/58 or 11.4%) and <50 (4/57 or 7.02%) years as opposed to those aged 50–65 years (2/44 or 4.55%) ($p = 0.07$). Consequently, the age-associated decline in stromal PR expression likely presents as a factor of the poorer prognosis observed in older patients with cervical cancer.

This study was conducted meticulously, with several notable strengths. First, all available FFPE primary cervical cancer tissues from patients diagnosed and treated at our hospital were analyzed,

minimizing selection bias. Second, the diagnosis and adequacy of the tissue specimens were reconfirmed. Third, IHC staining was independently assessed by two experienced gynecological histopathologists from different hospitals. In addition, disease characteristics, diagnosis dates, and death causes were cross-verified with high-quality data from the TNCR [23].

However, this study has limitations. The single-center setting may affect the generalizability of the results to broader populations. In addition, PRA and PRB are two isoforms of the *PGR* gene [41], and they are different only by a shortage of a N-terminal segment in PRA. Currently available peptide-specific antibodies cannot exclusively distinguish PRA in immunohistochemistry; they can only stain both PR isoforms. Therefore, in the absence of a conformation-specific antibody, we are currently limited to detecting PR (A + B) as a whole and PRB using an N-terminal-specific antibody in FFPE [25]. Alternatively, PRA can be identified by extracting proteins from the stroma and analyzing them by Western blotting; however, this method is not practical for clinical applications. The impact of stromal PRA expression on prognosis is expected to be minimal, as the multivariate analysis indicates that PRB, rather than PR(A+B), is significantly associated with 5-year mortality. It is likely that PRA serves as a byproduct of PGR gene transcription, with PRB being the primary effective product. From a clinical perspective, it seems logical to treat advancing cervical cancer with a PR antagonist by selecting patients who lack PR expression in the stroma.

Conclusions

This study demonstrated that stromal PRB expression predicts a more favorable prognosis and correlated with lower hematogenous metastasis rates. The incorporation of stromal PRB expression with FIGO stage significantly improved survival prediction in patients with SCC, particulary for those with advanced disease stages.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2024.07.017.

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Original Article

Three-dimensional ultrasound for evaluation of residual placental volume after conservative management of placenta accreta spectrum in a single tertiary center

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ABSTRACT

Objective: To evaluate the residual placental volume and correlated factors using three-dimensional ultrasound (3D) in patients with placenta accreta spectrum (PAS) after conservative management.
Materials and methods: From January 2005 to December 2023, we retrospectively reviewed patients with PAS who underwent prophylactic transcatheter arterial embolization and retained the placenta in situ. The residual placental volume was assessed using 3D ultrasound equipped with virtual organ computer-aided analysis. We determined the resorption rate of the residual placenta (RRRP) and analyzed correlated factors.
Results: Eighteen patients with PAS were included. The mean RRRP was 152.64 ± 147.97 cm^3/month. The median natural resorption time was 5.5 months. According to Spearman's correlation, only the initial placental volume was significantly associated with RRRP ($p = 0.001$, correlation coefficient = 0.701). Initial placental volume was not associated with postpartum hemorrhage, postpartum infection, resume of menstruation, subsequent pregnancy, or mean white blood cell count.
Conclusion: 3D ultrasound is useful for measuring the volume of residual placenta. A larger initial placental volume was associated with a higher RRRP.

Introduction

Placenta accreta spectrum (PAS) is a disorder characterized by the abnormal invasion of trophoblastic tissue through the myometrium, or penetration of the serosa into adjacent organs, such as the bladder. According to the current definition of the depth of invasion in PAS, it is classified as placenta accreta, increta, or percreta [1,2]. The prevalence rate of PAS increases with the rising rate of cesarean sections. Having undergone more than three cesarean deliveries with placenta previa significantly increases the risk of PAS [3]. In addition to a previous cesarean delivery, the common risk factors for PAS include maternal age, parity, placenta previa, prior uterine surgery, infertility procedures and abnormal placental biomarkers [4,5]. Given the high perinatal morbidity and mortality associated with severe forms of PAS, prenatal diagnostic imaging tools play a crucial role in detection and differentiation. Among these tools, prenatal ultrasound examination is paramount for evaluating and screening cases with risk factors. These factors include vascular lacunae, interrupted surface between the uterine serosa and bladder, abnormalities of the retroplacental clear zone, and bridging vessels penetrating through the myometrium to the bladder [6–9]. When prenatal diagnosis is established by ultrasound, magnetic resonance imaging (MRI) plays a complementary role in providing informative images for surgical planning. MRI allows for a more accurate review of the extent of myometrial invasion and involvement of adjacent organs [10]. Three-dimensional (3D) Doppler ultrasound has also been utilized in diagnosing PAS from placenta previa, identified by the presence of numerous coherent vessels in basal and lateral views, with a sensitivity of 97% and a specificity of 92% [11].

To date, there is still no consensus on the management of PAS, and the optimal approach depends on factors such as hospital equipment, multidisciplinary teams, and fertility considerations.

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Current guidelines recommend total hysterectomy without extirpation of the placenta following cesarean delivery, rather than conservative management with leaving the placenta in situ (LPIS) or partial excision of invaded myometrium. Prophylactic pelvic arterial embolization may help reduce blood loss during surgery, but sufficient evidence supporting its efficacy is still lacking [12]. However, we opted for conservative management with leaving the placenta in situ for selected cases where fertility preservation was strongly desired. Among those undergoing conservative management, the rates of infection (57%) and postpartum hemorrhage (PPH) (19%) remained higher due to the presence of residual placenta [13]. The use of 3D ultrasound for volume measurements of residual placentas was first reported in 2015 [14]. Compared with traditional two-dimensional (2D) ultrasound, 3D ultrasound, equipped with calculation software, can provide more accurate volume measurements [15]. To monitor postpartum conditions related to residual placenta, measuring its volume may aid clinical physicians in evaluating the placenta's resorption rate. Currently, no study has analyzed the resorption rate of residual placentas or its correlated factors. The purpose of our study is to measure the volume of residual placenta using 3D ultrasound, determine the resorption rate, and analyze correlated factors.

Material and methods

Study design and participants

In this retrospective study, patients diagnosed with PAS were conservatively managed with prophylactic transcatheter arterial embolization (TAE) and leaving the placenta in situ (LPIS) at Kaohsiung Chang Gung Memorial Hospital in Taiwan between January 2005 and December 2023. The volume of the residual placenta was measured using 3D ultrasound at each clinical visit. Approval for this study was obtained from the institutional review board (number: 202400065B0). Patients' profiles, complications, and laboratory data were thoroughly reviewed.

Conservative management with interventional radiology

MRI was arranged for individuals at high risk of PAS, who had been screened by 2D ultrasound, at 30–32 weeks of gestation. Diagnostic criteria for PAS on MRI were determined based on placental heterogeneity and abnormal intraplacental vascularity [16]. The surgical plan was thoroughly discussed with patients and their families before planned conservative management, including potential postpartum complications and the possibility of hysterectomy. Prior to general anesthesia, a femoral arterial sheath was inserted into the femoral artery by the interventional radiologist. A classical uterine incision was then made, followed by neonatal delivery. Any active bleeders on the uterus were clamped using hemostatic forceps. The bilateral internal iliac and uterine arteries were embolized, and radiologists ensured there was no additional extravasation of contrast media from pelvic vessels. Following prophylactic TAE, the classical uterine wound was sutured. The placenta was left in situ without extirpation or partial resection. After cesarean delivery, prophylactic broad-spectrum intravenous antibiotics, including aminoglycosides and clindamycin, were prescribed for 7 days [13].

Postpartum clinical visits and 3D ultrasound measurements

During the postpartum period, patients were followed up monthly at clinics, with regular monitoring of white blood cell (WBC) count to assess maternal infection status. Three-dimensional (3D) ultrasound examinations were scheduled for the first week after cesarean delivery and every 1–2 months during the postpartum period. Due to limited availability of our technician to operate the 3D ultrasound, not every visit could accommodate the examination. The 3D ultrasound device used for measuring the residual placental volume was equipped with a 3D convex volume transducer (1.5–5.5 MHz, Voluson 730; GE Medical Systems). Volume measurements were consistently performed by the same technician. The process for measuring placental volume involved several steps: first, the 3D convex volume transducer was used to assess the placental location and acquire comprehensive views containing longitudinal, transversal, and horizontal planes (see Fig. 1). Automatic contour detection of the placental margin in each plane and estimated volume calculations were performed by the VOCAL program. In the second step, the rotation angle was set to 30°, resulting in a total of six tracing planes ($180°/30° = 6$). To minimize automatic measurement errors, the technician manually traced the yellow contour of the placental margin on each tracing plane. Finally, the placental volume after manual tracing was determined by the VOCAL program (see Fig. 2).

Factors possibly associated with the resorption rate of the residual placenta

The maternal profiles were comprehensively reviewed, including maternal age, gravidity, parity, gestational age at delivery, number of previous cesarean sections and history of surgical abortion. Additionally, postoperative conditions and laboratory data were assessed, including surgical blood loss, PPH (blood loss exceeds 500 ml), postpartum infection, hysterectomy, surgical evacuation, resume of menstruation, future pregnancy, and average white blood cell (WBC) count. Patients presenting symptoms indicative of infection, such as fever, abdominal pain, vaginal bleeding, or purulent endocervical discharge, upon admission were classified as having postpartum infection. The initial measurement of placental volume, obtained within the first week after cesarean delivery, was designated as the initial volume. The resorption rate of the residual placenta (RRRP) was calculated by subtracting the final measured placental volume from the initial volume and dividing by the number of months, as depicted in Fig. 3. If the placenta underwent natural resorption without requiring surgical evacuation or hysterectomy, and ultrasound examination revealed a clear uterine cavity, the final volume was defined as zero.

Statistical methods

The statistical analysis was conducted using SPSS version 22 (SPSS, Chicago, IL, USA). Maternal profile data, laboratory data, and resorption rate were described using mean ± standard deviation (interquartile range: Q1, Q2, Q3), median (minimum, maximum), or number (percentage), as appropriate. The associations between resorption rate of the residual placenta (RRRP) and various factors were assessed using Spearman's correlation due to the data not meeting the assumptions of normal distribution. Statistical significance was defined as a p-value <0.05.

Results

From January 2005 to December 2023, our study included eighteen patients diagnosed with PAS. All patients underwent conservative treatment with prophylactic TAE and LPIS. Initially, twenty-eight patients were enrolled; however, ten were subsequently excluded as their residual placenta was measured solely using 2D ultrasound. Therefore, the remaining eighteen patients were included and analyzed in our study. The patient profiles, postpartum conditions, residual placental volume, and laboratory

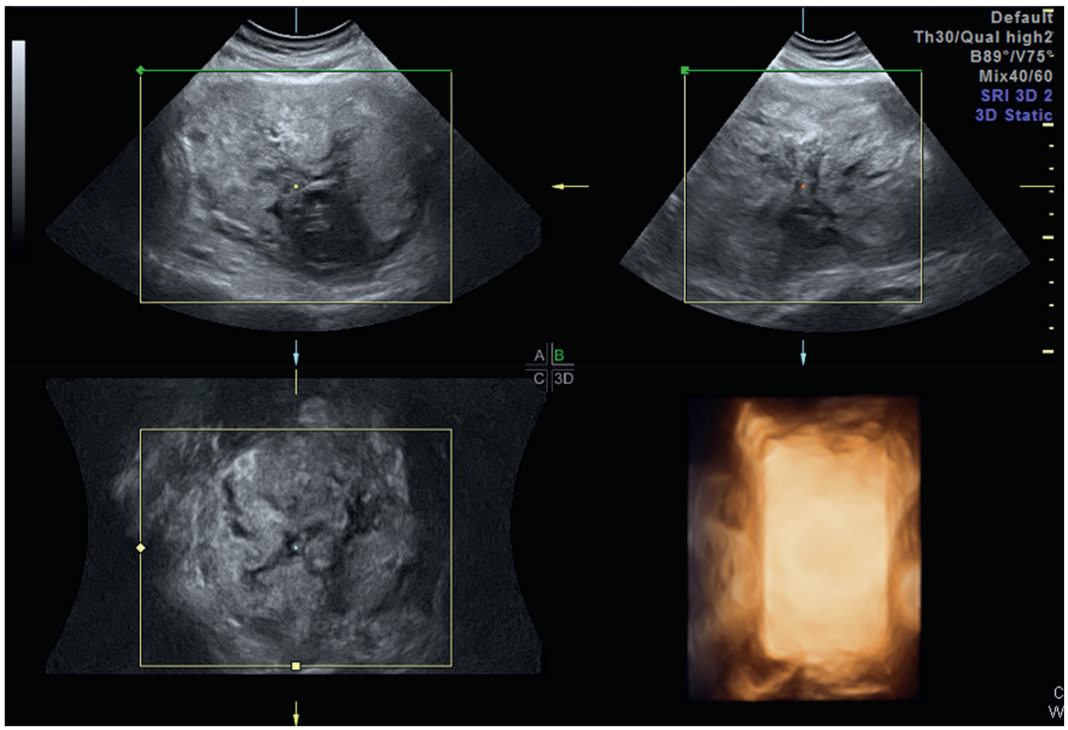

Fig. 1. Longitudinal, transverse, and horizontal planes of the residual placenta. The whole placenta must be under the window of a 3-D convex volume transducer.

data are illustrated in Table 1. The mean maternal age (years old) was 34.78 ± 5.44, median gravidity was 3, median parity was 1.5, median number of previous cesarean section (C/S) was 1.5, 9 patients (50%) had more than 2 times of C/S, 4 patients (22.22%) had more than 3 times of C/S, median gestational age during delivery (weeks) was 36, 22.22% patients had previous history of surgical abortion, mean surgical blood loss (ml) was 744.44 ± 417.59, and the mean WBC count (/μL) was 9680.94 ± 1720. Regarding postpartum conditions and residual placental volume, 4 patients (22.22%) had PPH, 10 patients (55.56%) had postpartum infection, 4

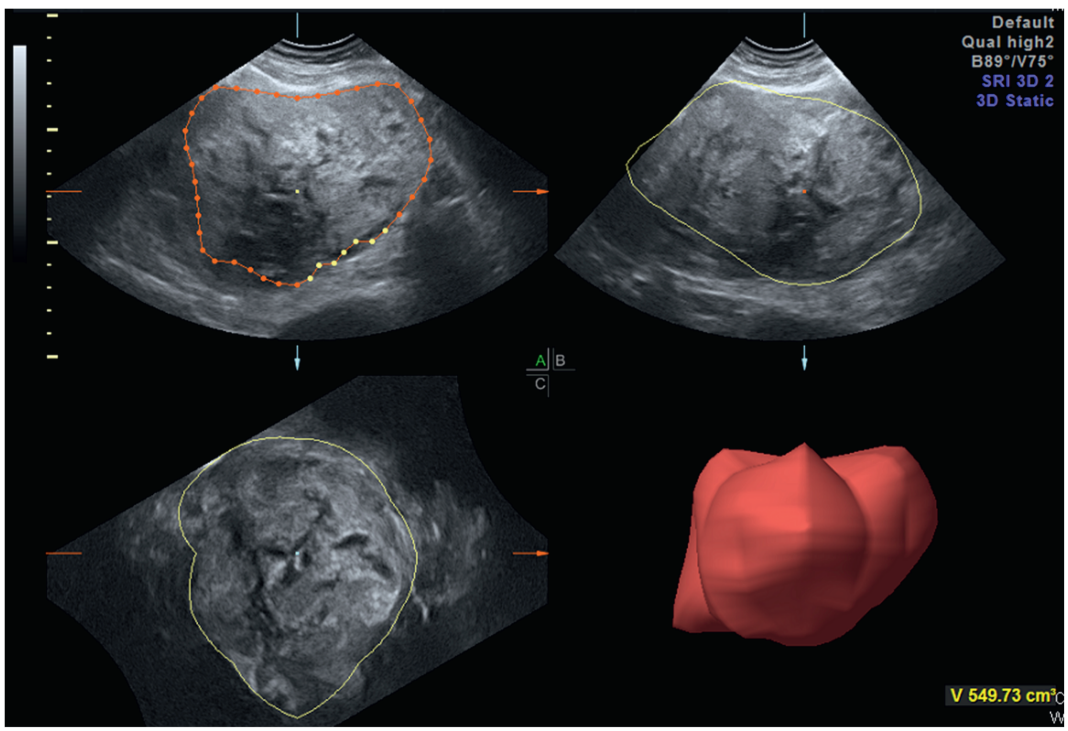

Fig. 2. Each of the contours on the placental margin was manually traced to minimize the error of automatic detection. The yellow contours could be manually traced and shifted into red contours after adjustment.

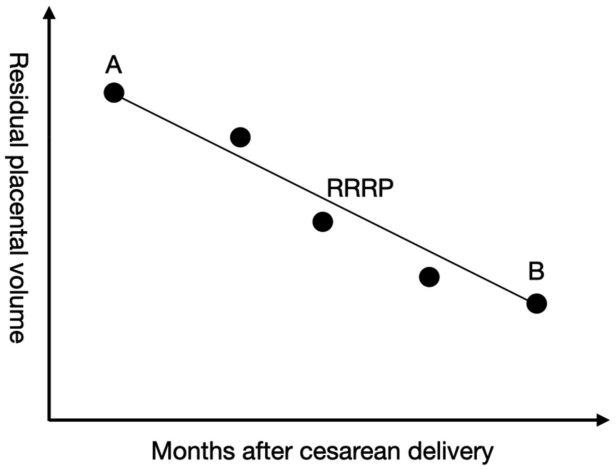

Fig. 3. The volume of the residual placenta was measured during clinical visits. A represents the initial volume of the placenta within the first week after cesarean delivery, while B represents the final volume of the residual placenta. The resorption rate of the residual placenta was calculated by subtracting the final measured placental volume from the initial volume and dividing by the number of months.

patients (22.22%) received surgical evacuation, 3 patients (16.67%) failed conservative treatment and had hysterectomy, 15 patients (83.33%) had resume of menstruation, only one patient (5.56%) had subsequent pregnancy, the initial placenta volume (cm^3) was 556.78 ± 401.49, mean RRRP (cm^3/month) was 152.64 ± 147.97, and the median natural resorption time (month) was 5.5.

According to the Spearman's correlation, the maternal age (p = 0.514, correlation coefficient(c.c.) = -0.165), gravidity (p = 0.675, c.c. = 0.106), parity (p = 0.581, c.c. = 0.139), history of previous C/S (p = 0.388, c.c. = 0.217), history of surgical abortion (p = 0.412, c.c. = -0.206), gestational age during delivery (p = 0.816, c.c. = -0.059), surgical blood loss (p = 0.077, c.c. = 0.427), PPH (p = 0.355, c.c. = 0.232), postpartum infection (p = 0.550, c.c. = -0.151), resume of menstruation (p = 0.609, c.c. = -0.129), subsequent pregnancy (p = 0.927, c.c. = -0.023), and mean WBC count (p = 0.240, c.c. = 0.301) were not significantly associated with RRRP. Only the initial placental volume was significantly associated with RRRP (p = 0.001, c.c. = 0.701). Besides, the initial placental volume was not associated with postpartum condition, including PPH (p = 0.355, c.c. = 0.232), postpartum infection (p = 0.609, c.c. = 0.129), resume of menstruation (p = 0.085, c.c. = -0.417), subsequent pregnancy (p = 0.154, c.c. = -0.351), and mean WBC count (p = 0.993, c.c. = -0.002). These results are shown in Table 2.

Table 1
Patients' profiles, postpartum conditions, residual placental volume, and laboratory data (n = 18).

Maternal Profile	
Mean maternal age (years old)[a]	34.78 ± 5.44 (32.25, 34, 38.25)
Median gravidity[b]	3 (2, 5)
Median parity[b]	1.5 (1, 3)
Median number of previous C/S[b]	1.5 (1, 2.25)
≥2 times of previous C/S[c]	9 (50%)
≥3 times of previous C/S[c]	4 (22.22%)
Median gestational age during delivery[b]	36 (34.75, 37)
Previous surgical abortion[c]	4 (22.22%)
Mean surgical blood loss (ml)[a]	744.44 ± 417.59 (387.5, 650, 1000)
Laboratory data	
Mean WBC count (/μL)[a]	9680.94 ± 1720 (8934.5, 9700, 10,933)
Postpartum conditions	
Postpartum hemorrhage[c]	4 (22.22%)
Postpartum infection[c]	10 (55.56%)
Surgical evacuation[c]	4 (22.22%)
Hysterectomy[c]	3 (16.67%)
Resume of menstruation[c]	15 (83.33%)
Future pregnancy[c]	1 (5.56%)
Initial placental volume[a]	556.78 ± 401.49 (253, 430.5, 714)
Mean RRRP (cm^3/month)[a]	152.64 ± 147.97 (48.38, 107.15, 204.88)
Median natural resorption time (month)[b,d]	5.5 (2, 8), n = 11

C/S: cesarean section; WBC: white blood cell; RRRP: resorption rate of residual placenta.
[a] Values are presented as mean ± SD (interquartile range: Q1, Q2, Q3).
[b] Values are presented as median (minimum, maximum).
[c] Values are presented as case number (percentage).
[d] Natural resorption time: the residual placentas were not intervened with surgical evacuation or hysterectomy after cesarean section.

Discussion

The main findings of our study indicate a significant correlation between the initial placental volume and the RRRP. Pathological analysis of retained placentas following surgical evacuation revealed prominent features of infarction and necrosis. It is noteworthy that uterine infarction and necrosis have been documented following interventional radiology procedures, with pathology demonstrating these effects approximately three weeks post-procedure [17]. It has been reported that patients with large submucosal fibroids may develop septic uterine necrosis following arterial embolization [18,19]. Residual placenta within the uterine cavity, akin to submucosal fibroids, can transform into a source of infection rich in pathogens subsequent to uterine infarction. This necrotic manifestation resulting from infarction and subsequent infection is characterized by liquefactive necrosis, wherein dissolution of cellular organelles occurs due to hydrolytic enzymes or lysosomal hydrolytic enzymes released from bacteria or neutrophils [20]. There have been limited studies analyzing the decomposition process of residual placenta. We hypothesize that this process resembles human putrefaction. The placenta primarily consists of 87% water, with the remaining 13% composed of protein, fat, and ash [21]. Lou et al. reported that a larger volume of hematoma in the brain following spontaneous intracranial hemorrhage correlates with a higher rate of resorption [22]. From the perspective of human decomposition, putrefaction is accelerated by microorganisms, leading to the catabolism of bodies into smaller molecules [23]. Therefore, a larger volume of residual placenta may experience a greater rate of resorption, accelerated by microorganisms from the genitourinary tract.

The tools for volume assessment of soft tissue includes ultrasound [24], computed tomography (CT) [25] and MRI [26].

Table 2
Associated factors with resorption rate of residual placenta and initial placental volume, analyzed by Spearman's correlation.

Associated factors	RRRP	Initial placental volume
Age	p = 0.514, c.c. = -0.165	
Gravidity	p = 0.675, c.c. = 0.106	
Parity	p = 0.581, c.c. = 0.139	
Hx of previous C/S	p = 0.388, c.c. = 0.217	
Hx of surgical abortion	p = 0.412, c.c. = -0.206	
Gestational age	p = 0.816, c.c. = -0.059	
Surgical blood loss	p = 0.077, c.c. = 0.427	
Initial placental volume	[a]**p = 0.001, c.c. = 0.701**	c.c. = 1.0
Postpartum hemorrhage	p = 0.355, c.c. = 0.232	p = 0.355, c.c. = 0.232
Postpartum infection	p = 0.550, c.c. = -0.151	p = 0.609, c.c. = 0.129
Resume of menstruation	p = 0.609, c.c. = -0.129	p = 0.085, c.c. = -0.417
Subsequent pregnancy	p = 0.927, c.c. = -0.023	p = 0.154, c.c. = -0.351
Mean WBC count	p = 0.240, c.c. = 0.301	p = 0.993, c.c. = -0.002

RRRP: resorption rate of residual placenta; Hx: history; C/S: cesarean section; WBC: white blood cell; c.c.: correlation coefficient.
[a] Statistical significance was considered when the p value was <0.05.

Compared to CT and MRI, ultrasound offers advantages such as lower cost, greater availability, and nonionizing radiation. 3D power Doppler ultrasound represents a recent technological advancement, with the VOCAL program for volume calculation introduced since 2007. In measuring irregularly shaped masses, 3D ultrasound is considered more precise than traditional 2D ultrasound [27]. Although our findings indicate a significant correlation between RRRP and the initial volume, we did not identify factors predicting the total length of resorption time or postpartum complications. However, we believe that 3D ultrasound remains a promising tool for evaluating residual placenta and exploring potential factors. Further studies with larger sample sizes or improved designs are warranted to elucidate this matter.

According to our literature review, 3D ultrasound is considered an optimal tool for prenatal diagnoses and evaluations of the severity of invasive placentas [11,28]. Monitoring residual placentas is crucial following conservative management due to the potential risk of severe postpartum complications. However, due to factors such as the small population size, rare incidence, heterogeneous results, and limited conservative management of PAS, few studies have specifically examined the resorption rate of residual placental volume and its correlated factors. Roulot A. et al. [14] reported on 7 patients with PAS who underwent conservative management from 2007 to 2009. They initially employed 3D power Doppler ultrasound monthly to monitor parameters such as residual placental volume, vascularization, flow, and perfusion indexes. Their findings revealed a mean time of 280 days for complete elimination of the placenta, with the vascularization of the placental mass disappearing before complete resorption. In comparison, our finding was approximately 165 days, which was shorter than 280 days and compatible with the results of this retrospective study in that the median delay for placental resorption in the embolization group was significantly shorter than that in the non-embolization group [29].

The major strength of our study is that we are the first to analyze factors correlated with RRRP and the second study to utilize 3D ultrasound in evaluating residual placenta. Despite the limitation of a small case number for analyzing resorption rate and factors correlated with RRRP, our study's aim is both innovative and promising. However, several limitations should be acknowledged. Firstly, the retrospective nature of the study may introduce biases. Secondly, the small case number is attributed to the rare incidence of PAS in a single tertiary center. Lastly, the lack of assessment of vascularization of the residual placenta using power Doppler prevents the evaluation of its relationship with RRRP.

In conclusion, our study demonstrates that the volume of residual placenta following conservative management can be effectively evaluated using 3D ultrasound. Furthermore, we observed that a larger initial placental volume was associated with a higher resorption rate of the residual placenta.

Details of ethics approval

Ethical approval was obtained from Chang Gung Memorial Hospital Institutional Review Board (number: 202400065B0) on 2024/02/07.

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Author's Contribution

T-YH, and K-LH designed this study and interpreted the data. K-LH wrote the first draft of the paper and carried out statistical analysis under the supervision of Biostatistics Center, Kaohsiung Chang Gung Memorial Hospital. C-CT, H-HC, Y-JL reviewed charts and collected data. K-LH, C-CT, H-HC, and P-FL illustrated figures and tables. All authors contributed to the revising of this manuscript and approved the final submission.

Declaration of competing interest

None declared.

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Original Article

The trend and factors associated with severe maternal morbidity among delivery and postpartum hospitalizations in Taiwan: A nationwide study, 2011–2021

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ABSTRACT

Objective: To investigate the prevalence and longitudinal trend of severe maternal morbidity (SMM) at nationwide level in Taiwan. The associated maternal factors contributing to SMM were also analyzed.
Materials and methods: A population-based secondary analysis using administrative datasets released by Ministry of Health and Welfare of Taiwan from 2011 to 2021 was carried out. SMM was defined from ICD-9 or10-CM diagnosis and procedure codes previously released by CDC. The existence of any SMM indicators identified by delivery and postpartum hospitalizations between ≧20 weeks of gestational age and within 42 days after childbirth was retrieved for analysis. Kendall Tau-b correlation was applied for trend test. Logistic regression was used to investigate the associated maternal factors for SMM. All the data were analyzed using SAS statistical software version 9.4. Statistical significance was defined as P value < 0.05.
Results: A total of 2,054,010 delivery hospitalization records were identified during the study period. 6961 subjects met the SMM indicators, yielding an average SMM rate of 3.4 per 1000 deliveries. The pure transfusion rate was 2.33%. The overall SMM rate including transfusion reached 26.7 per thousand deliveries. The trend of SMM including and excluding transfusion demonstrated significantly increasing. Extreme maternal age and cesarean delivery were two main maternal associated factors for SMM.
Conclusion: Our findings demonstrated the steadily increasing trend of SMM in the past decade from nationwide study in Taiwan. The sharply growing rates of blood transfusion made the prevention of obstetric hemorrhage imperative. Health policies should be focused on the encourage of early childbearing and avoidance of unnecessary cesarean delivery to reduce the maternal risks associated with SMM. Continuous surveillance of SMM is required to improve obstetric care and reduce severe maternal complications.

Introduction

Nowadays, maternal mortality is still a major health concern worldwide which is defined as the maternal death during pregnancy, childbirth or 42 days postpartum.

Between 1990 and 2015, the global maternal mortality ratio decreased from 385 to 216 maternal deaths per 100,000 live births [1]. For most high-income countries, maternal deaths are relatively rare events with the rate between 3 and 12 per 100,000 births [2]. But in many low-resource areas, the maternal mortality rates remain high which range from 70 to 319 per 100,000 births with an average of 55 [3]. The Sustainable Development Goal for 2030 sets the goal to reduce global maternal mortality ratio to 70 per 100,000 live births and no country exceeds double the ratio.

As maternal death is a relatively rare event, the small case numbers often limits most countries to investigate and analyze the associated factors resulting in mortality.

Besides maternal mortality, there are more pregnant women suffering from severe pregnancy-related complications which

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might lead to maternal death if there are no adequate interventions provided. For identification of the life-threatening events, severe maternal morbidity (SMM) is conceptualized [4–6]. SMM can also be considered as maternal near miss (MNM). Delay in identification and adequate management usually result in maternal mortality [6,7].

Stone proposed SMM as an indicator to assess quality of maternal care in 1991 [8]. Severe maternal morbidity and maternal death share similar characteristics. It's reported that SMM is 50 times more common than maternal mortality. Modification of delivery care in women with SMM might reduce maternal deaths [5]. Therefore, SMM is globally used for surveillance and gathering more information during perinatal period. In addition, it is worldwide accepted as an indicator for the quality of obstetric care [4].

In 2009, the WHO working group defined maternal near miss as 'a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy' [9]. For identification of women who experienced SMM from administrative data, the Center for Disease Control and Prevention (CDC) of US has released the definition based on 25 indicators retrieved from diagnosis and procedure codes by ICD-9-CM and then revised to 21 indicators by ICD-10-CM in 2015 [10]. In US, it was estimated that around 60,000 women suffered from SMM each year [5]. The systemic review by Tunçalp et al. demonstrated that the rates of SMM/MNM in high-income countries were relatively lower, ranging from 0.79% in Europe to 1.38% in North America. However, in low- and middle-income countries of Asia and Africa, SMM rates significantly increased from 5.07% to 14.98%, respectively [11]. For improving the quality of perinatal care and reducing maternal mortality rate, the Department of Health Resource and Services Administration in U.S. starts putting more efforts to decrease the rate of SMM [12].

In many countries, the characteristics of pregnant women have been changed for period of time, such as increasing percentage of advanced maternal age, pre-pregnancy obesity, chronic diseases and cesarean delivery [13–18]. Pregnant women in Taiwan carry similar characteristics as well. These changes might have negative impact on maternal and neonatal outcomes, with increases in morbidity and even mortality during perinatal period. For the past decade, the maternal mortality ratio in Taiwan gradually increased from 5 in 2011 to 14 in 2021 with the peak reaching 16 in 2019 per 100,000 live births. Surveillance of severe maternal morbidity thus becomes an important issue for monitoring adverse pregnancy related outcomes and declines in maternal mortality. It's also imperative to understand the associated maternal factors contributing to severe maternal morbidity. Currently, the study related to SMM from large population in Taiwan is still lacking. The purpose of this study aimed to investigate the prevalence and longitudinal trend of SMM at population level in Taiwan during the period between 2011 and 2021. The associated maternal factors contributing to SMM were analyzed as well. We hypothesized that the delayed childbearing age and persistent high cesarean delivery rate were associated with the prevalence of SMM in Taiwan.

Materials and methods

This was a nationwide population-based secondary analysis study using administrative datasets released by Ministry of Health and Welfare of Taiwan. In Taiwan, national health insurance (NHI) coverage reaches over 99.9% of the population. Childbirths and delivery hospitalizations almost occurred in hospitals or maternity clinics held by obstetrics and gynecology specialists. For reimbursement, the childbirths associated diagnoses and managements were required to submit using the coding system of International Classification of Disease 9 or 10 (ICD-9 or10). As such, population-based information on severe maternal morbidity was available and also reliable from hospital discharge records at national level.

The delivery hospitalization was identified by the current procedure terminology (CPT) codes related to vaginal and cesarean delivery. The main exposure was the existence of any SMM indicators identified by delivery and postpartum hospitalizations between ≧20 weeks of gestational age and within 42 days after childbirth during the period of 2011–2021. For 2021, deliveries from January to October were included to meet the SMM definition. Only who aged ≧18 years were included. The ICD-9/10-CM coded during hospitalization included primary diagnosis and up to 4 additional diagnoses as well as up to 5 procedure codes for reimbursement. The coding system was shifted from ICD-9-CM to ICD-10-CM in July, 2016 in Taiwan. To reduce the bias for SMM trend analysis, only 21 SMM indicators were used in ICD-9-CM during the period between 2011 and June, 2016. Indicators of SMM were selected from ICD-9/10-CM diagnosis and procedure codes previously released by CDC of US [10]. For identification of more additional appropriate SMM cases, admission to intensive care unit (ICU) during hospitalization was also included [19]. Administrative data from delivery hospitalizations was linked to infant birth certificates for identification of gestational age. To further investigate the role of blood transfusion on SMM, we presented the rates both with and without blood transfusion. The SMM rates over the study period were stratified into those with at least one SMM indicators without code for transfusion and those with a code for transfusion but without any other SMM indicators.

The prevalence of severe maternal morbidity was defined as the number of women who met at least one of severe maternal morbidity indicators per 1000 deliveries.

The SMM rates were tabulated by personal and hospital characteristics which were available in the datasets. To test whether the rate of severe maternal morbidity had changed over the 11-year period, Kendall Tau-b correlation for trend was used. We divided age into five groups: <25, ≧25 < 30, ≧30 < 35, ≧35 < 40, ≧40 years old. For hospital characteristics, hospital levels were classified as medical center, regional hospital, district hospital and maternity clinics. Additionally, the hospitals were divided into quartile according to their annual delivery volume using the cut-off value of 600, 1200, 2400, respectively. Logistic regression was used to examine the effect of age and method of delivery on the rates of severe maternal morbidity. The study was approved by the research ethics committee of National Taiwan University (202303HM025). All the data were analyzed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as P value < 0.05.

Results

A total of 2,054,010 delivery hospitalization records were identified between 2011 and 2021 (97.5% of live birth records) and included in this study. 6961 subjects met at least one of the SMM indicators excluding blood transfusion, yielding an average SMM rate of 3.4 per 1000 deliveries. In addition, there were also another 46,520 hospitalization records identified with a code for transfusion but without any other SMM indicators. The pure transfusion rate during delivery hospitalization was 23.3 per 1000 deliveries. The overall SMM rate reached 26.7 per 1000 deliveries during delivery and postpartum hospitalizations.

The cesarean delivery rate yielded an average of 35.2% during the study period. The mean age of childbirth was 31.2 years with twenty-five percent who delivered after 35 years old (Table 1). The most common SMM diagnosis indicators included eclampsia (0.4/1000), disseminated intravascular coagulation (DIC) (0.3/1000), shock (0.2/1000), pulmonary edema or acute heart failure (0.2/

Table 1
Sociodemographic and maternal comorbidity information, 2011–2021.

Variable	n (%)
Total deliveries	2,054,010
Vaginal delivery	13,303,54 (64.8)
Cesarean delivery	7,236,56 (35.2)
Previous cesarean delivery	296,412 (14.4)
Placenta previa	27,436 (1.3)
Maternal age	
<25	201,755 (9.82)
≧25,<30	516,650 (25.15)
≧30,<35	812,720 (39.57)
≧35,<40	443,234 (21.58)
≧40	79,651 (3.88)
Calendar year	
2011	193,403 (9.4)
2012	228,297 (11.1)
2013	190,789 (9.3)
2014	206,237 (10.0)
2015	207,985 (10.1)
2016	202,949 (9.9)
2017	190,403 (9.3)
2018	176,520 (8.6)
2019	171,006 (8.3)
2020	158,783 (7.7)
2021[a]	127,638 (6.2)

[a] Deliveries from Jan to Oct, 2021 were enrolled.

1000), and sepsis (0.2/1000) (Table 2). Blood transfusion was identified among 24% of delivery hospitalizations which became the most common procedure of SMM. The other commonly performed procedures included ventilation (1/1000) and ICU admission (1.7/1000) (Table 2).

The rates of SMM without transfusion significantly increased from 2.8 in 2011 to 4 in 2021 per 1000 deliveries ($T = 0.67$, $P = 0.0047$). The rates of blood transfusion without any other SMM indicators demonstrated steadily elevated from 14.8 to 32 per 1000 deliveries between 2011 and 2021 ($T = 1$, $P < 00.0001$). The overall SMM rates including transfusion doubly increased from 17.6 in 2011 to 36 in 2021 per 1000 ($T = 1$, $P < 00.0001$) (Fig. 1). For the maternal age at delivery, the mean value gradually elevated from 30.4 to 31.7 years old ($P < 00.0001$) (Fig. 2). For the method of delivery, SMM was over five times greater among cesarean delivery (5.39%) in comparison with vaginal delivery (1.05%). The cesarean delivery rates significantly decreased from 35.4% in 2011 to 34.6% in 2016 ($P = 0.038$). However, the cesarean delivery rates steadily elevated from 34.4% to 36.9% during the period of 2017–2021($P = 0.014$) (Fig. 3). Further analysis demonstrated that the cesarean delivery rates remained stable among different levels of hospitals but significantly increased from 35% to 42% at maternity clinics ($T = 0.91$, $P = 0.0002$) (Fig. 4).

Logistic regression analysis demonstrated that deliveries at extreme age increased the odds for severe maternal complications (OR 1.4, CI 1.35–1.44 for age<25; OR 1.45, CI 1.40–1.51 for age≧40, $p < 0.0001$). Delivery by cesarean section was also a significantly contributing factor for SMM (OR 5.63, CI 5.51–5.75, $p < 0.0001$) (Table 3).

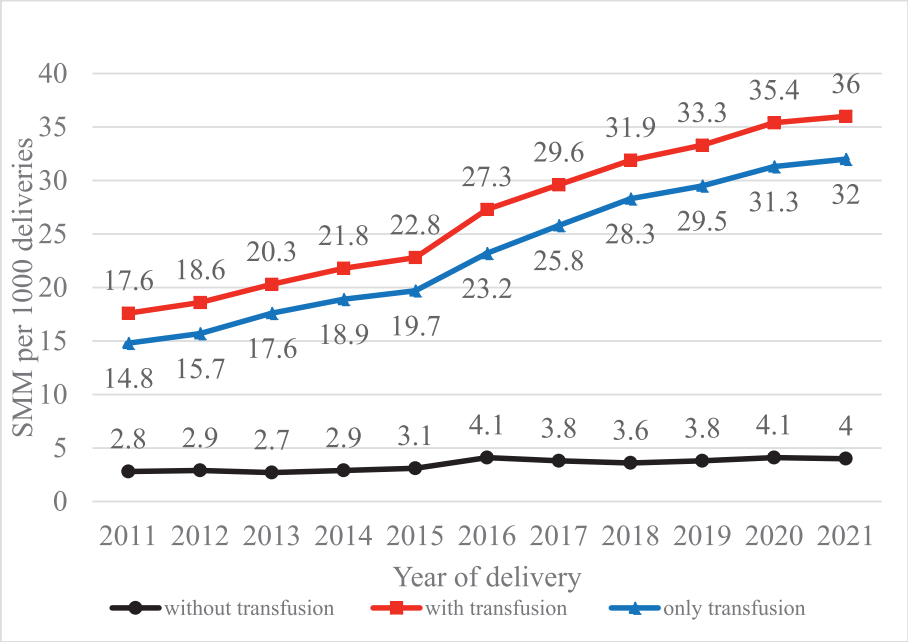
Discussion

In this study, we've applied the indicators released by CDC [10] to investigate the trend and associated factors of severe maternal morbidity at nationwide level. Our results demonstrated the escalating trend of SMM from 2.8 to 4.1 per thousand deliveries between 2011 and 2021 in Taiwan. The sharply increasing blood transfusion rate made the prevalence doubled (17.6–38 per 1000) when transfusion was included as one of SMM indicators. Moreover, advanced maternal age and cesarean delivery were maternal characteristics associated with the occurrence of severe morbidity.

According to previous studies in the US, the prevalence of SMM ranged from 2.9 to 15.8 per 1000 [4,5,20,21]. Dzakpasu also reported the SMM rate between 4.1 and 6.2 per thousand in Canada during the period of 2003–2016 [22]. The prevalence of SMM in England and Australia was 5 and 8.2 per 1,000, respectively [21]. The report from the other high-income, rapidly developing country in Middle East, the United Arab Emirates demonstrated the SMM to birth ratio of 7.5/1000 deliveries [23]. In our results, the average rate of SMM ranged from 2.8 to 4.1 with an average of 3.4 per thousand deliveries. This was similar and even lower than these high-income countries. The possible explanation might be the contributing of national health insurance in Taiwan. The universal coverage by NHI enhances the availability of medical services. Timely intervention and management may interrupt the continuum of maternal disease severity proposed by Geller [24], thus preventing these pregnancy-related adverse events from

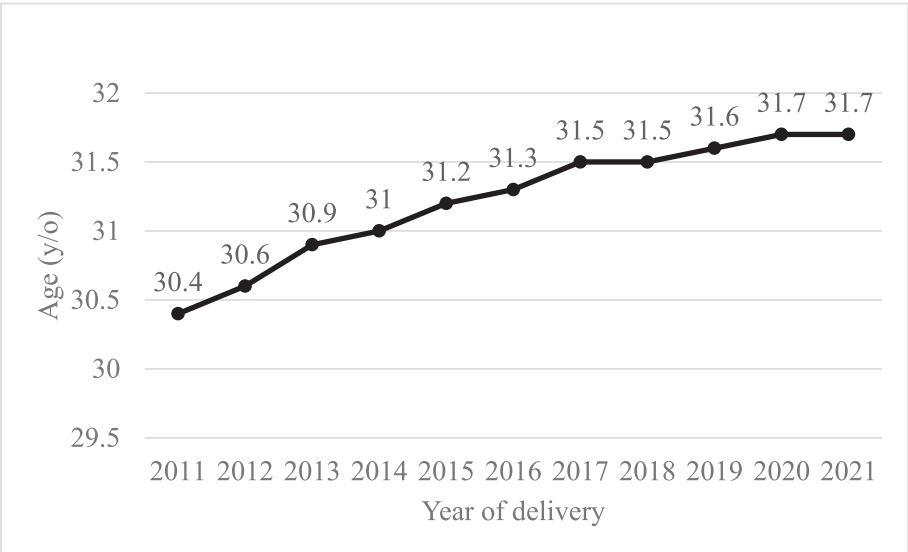
Table 2
Severe maternal morbidity during delivery and postpartum hospitalization using CDC criteria, 2011–2021.

SMM indicator	n	Rate per 1000 deliveries
Acute myocardial infarction	8	0
Aneurysm	13	0.01
Acute renal failure	140	0.07
Adult respiratory distress syndrome	213	0.10
Amniotic fluid embolism	141	0.07
Cardiac arrest or ventricular fibrillation	35	0.02
Disseminated intravascular coagulation	710	0.35
Eclampsia	838	0.41
Heart failure or arrest during surgery or procedure	0	0
Puerperal cerebrovascular disorders	286	0.14
Pulmonary edema or acute heart failure	491	0.24
Severe anesthesia complications	91	0.04
Sepsis	430	0.21
Shock	502	0.24
Sickle cell disease with crisis	0	0
Air and thrombotic embolism	160	0.08
Conversion of cardiac rhythm	284	0.14
Blood products transfusion	50,075	24.38
Hysterectomy	899	0.44
Temporary tracheostomy	10	0
Ventilation	2057	1.00
ICU admission	3422	1.67



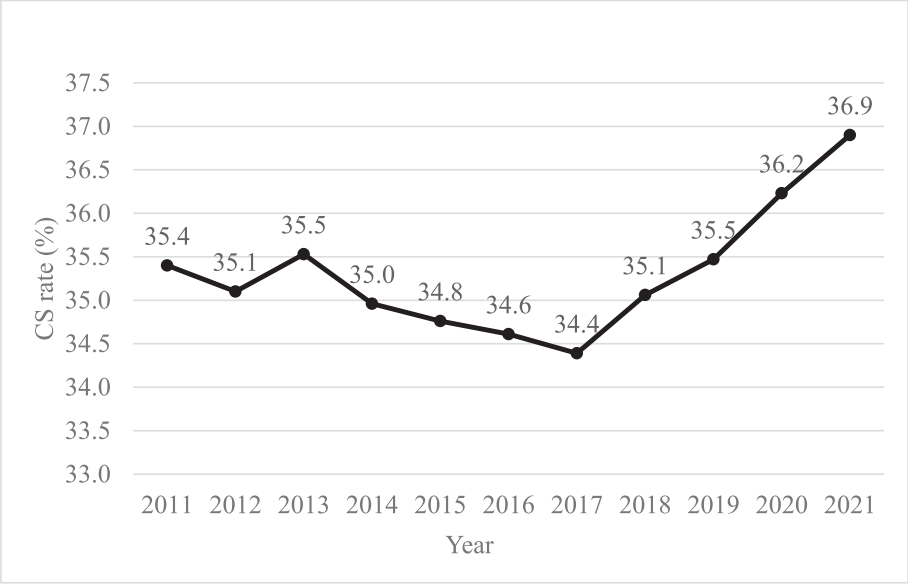
Kendall Tau-b correlation:
without transfusion: T=0.67, P=0.0047
with transfusion: T=1, P<.0001
only transfusion: T=1, P<.0001

Fig. 1. Severe maternal morbidity with and without transfusion by year, 2011–2021.



Kendall Tau-b correlation:
T=1, P<.0001

Fig. 2. Mean maternal age at delivery by year, 2011–2021.



Kendall Tau-b correlation:
2011-2016: T= -0.73, P=0.038
2017-2021: T=0.867, P=0.014

Fig. 3. Rate of cesarean delivery by year, 2011–2021.

progression to severe morbidity and even mortality. Unlike the nearly doubly increased rates in US [4,25], the trend escalated from 2.8 to 4.1 per thousand with an increasing ratio of 46% during the study period. This might be the other evidence of the benefit from NHI.

Eclampsia was the most common disease identified among severe morbidities in our study. The prevalence (0.4/1000) was consistent with the recent reports in England (0.4/1000) and Australia (0.6/1000) [21]. The systemic review and meta-analysis of SMM also yielded eclampsia the second common event in the Asia Pacific countries [26]. As our results, the childbearing age in Taiwan significantly delayed over the past decade. Women may carry more comorbidities during perinatal period as advanced maternal age, most commonly hypertension and diabetes. Many studies also demonstrated that hypertensive disorders were the important etiology of SMM [5,21,23,27]. Poorly controlled hypertension increases the risk of eclampsia and pre-eclampsia. Adequate management of hypertensive disorders prior to pregnancy and close surveillance during pre- and perinatal period to prevent from disease progression into life-threatening events become paramount.

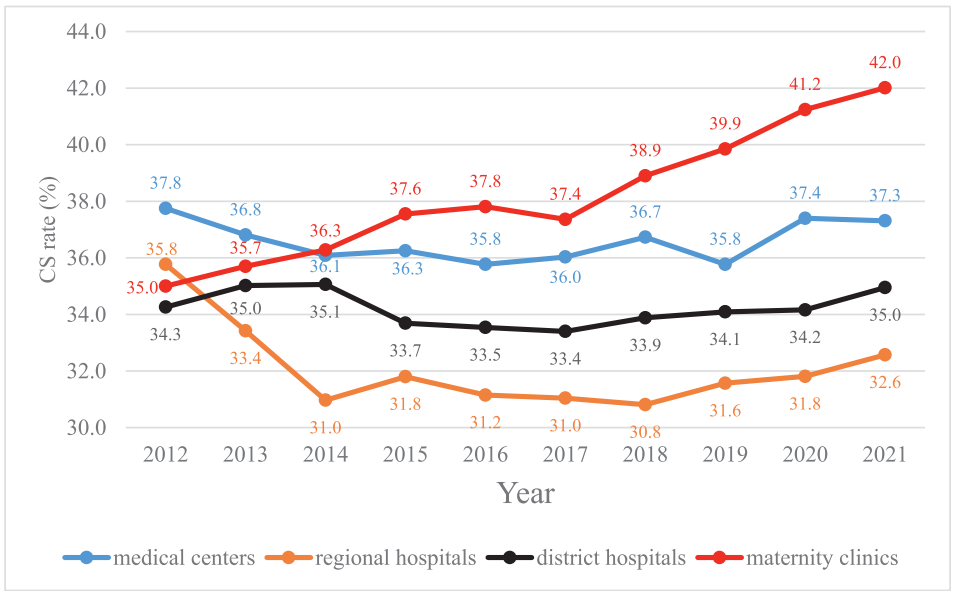


Fig. 4. Rate of cesarean delivery by different types of hospitals.

Table 3
Logistic regression analysis of severe maternal morbidity.

Variable	aOR[a]	95% CI	P value
Maternal characteristics			
Age (years)			
<25	1.40	1.35–1.44	<0.0001
≧25, <30	0.99	0.96–1.02	<0.0001
≧30, <35	1		
≧35, <40	1.19	1.17–1.23	0.53
≧40	1.45	1.40–1.51	<0.0001
Cesarean delivery			
Yes	5.63	5.51–5.75	<0.0001
No	1		
Insurance status			
Category 1	1		<0.0001
Category 2	1.10	1.07–1.13	<0.0001
Category 3	1.31	1.25–1.38	0.0007
Category 5	2.39	2.22–2.57	<0.0001
Category 6	1.59	1.55–1.64	<0.0001
Hospital characteristics			
Level			
Medical centers	1		
Regional hospitals	0.89	0.87–0.92	<0.0001
District hospitals	0.45	0.43–0.46	<0.0001
Maternity clinics	0.18	0.18–0.19	<0.0001
Annual deliveries quartile			
Q1 (<600)	1		<0.0001
Q2 (≧600,<1200)	1.13	1.09–1.16	<0.0001
Q3 (≧1200,<2400)	0.85	0.82–0.87	<0.0001
Q4 (≧2400)	0.68	0.66–0.71	<0.0001

Adjusted for insurance status, hospital level, annual delivery volume.
[a] aOR, adjusted odds ratio.

Blood transfusion was the major procedure among SMM indicators with an average rate over 2.4% in our study. The sharply increasing trend from 1.48 to 3.2% resulted in the SMM ratio doubled during the study period. Obstetric hemorrhage was proven the important leading cause of SMM in many studies [4,6,21,23,26–28]. Despite the similar blood transfusion rate (2.46%) in Australia, Lipkind found the trend became stable over time [21]. The reported maternal transfusion in the US was also high reaching a rate of 2.2% and remained elevated [21], but the growing ratio was slower than in Taiwan. Moreover, the hemorrhage-related diagnosis such as shock and DIC reached around 0.2–0.3 per thousand in our results. More attention should be paid on the dramatically elevated transfusion rate and pregnancy related hemorrhage, even though we lacked of the information on the volume of blood transfusion using administrative data. Prevention and management of peri-partum hemorrhage has to be regularly delivered in continuous medical education for physicians.

The cesarean delivery rate was high reaching over 30% for decades in Taiwan. In our results, the trend of cesarean rate temporally decreased from 35.4% to 34.6% between 2011 and 2016. But thereafter, the rate continuously elevated to 36.9% in 2021. Cesarean delivery was well known an important risk for SMM [29]. Our study also revealed the significantly increased odds (5.6) of cesarean delivery compared with vaginal delivery for SMM. Previous cesarean delivery also increased the risk of placental previa or accreta which may lead to severe obstetric hemorrhage and blood transfusion requirement. According to our analysis, the persistently elevated cesarean delivery rate from 35 to 42% at maternity clinics mainly contributed to the increasing trend of high cesarean rate in Taiwan. Regular surveillance of cesarean indication in maternity clinics is recommended in the future to avoid unnecessary surgery and reduce the risk of SMM.

Our study has several strengths. To our knowledge, this was the first large population-based study related to SMM in Taiwan. Deliveries almost occurred in hospitals and maternity clinics. The nearly universal coverage of NHI made the evaluation of severe maternal morbidity by using nationwide administrative hospitalization data more reliable. 97.5% of delivery hospitalization was retrieved in comparison with live birth records in our study. This also made the results more representative. Inclusion of ICU admission in our study can also enhance the accuracy in identification of SMM cases and reduce the bias from coding errors [19]. Additionally, the long-term study period covering eleven years could help us to well investigate the trend of these severe maternal complications for further policy-making. We also acknowledged some limitations. First, the cases with severe maternal morbidity were defined based on ICD-9 or 10-CM codes from delivery hospitalization records in our study. Administrative data may be inaccurate in identification of severe pregnancy or delivery related complications. For example, some diagnosis may not be properly coded. Fortunately, the SMM related diagnosis indicators are major diseases for delivery hospitalization. To gain more reimbursement from increased case mixed index, coders will prevent from missing these important diagnosis codes as possible. Additionally, we identified SMM related procedures from CPT codes to reduce the potential coding bias. Second, even the transfusion was identified from CPT codes, the information related to the volume of blood transfusion was also lacking. As many other studies, the severity of hemorrhage and anemia could not be well differentiated. Moreover, the sociodemographic details, such as obesity or parity were not available from administrative data. Some obstetrical risk factors were failed to well evaluate.

In conclusion, we presented the trend of severe maternal morbidity in Taiwan from nationwide perspective. Our findings demonstrated the steadily increase in severe maternal complications during delivery and postpartum hospitalization in the past decade. The sharply growing rates of blood transfusion made the prevention of obstetric hemorrhage imperative. The increasing trend of SMM was also paralleled by the advancing childbirth age and elevating cesarean delivery rate. Health policies should be focused on the encourage of early childbearing and prevention from unnecessary cesarean delivery. Continuous surveillance of severe maternal morbidity becomes an emerging issue for improving obstetric care to reduce severe maternal complications and even mortality in Taiwan.

Conflicts of interest

The authors have no conflicts of interest.

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Original Article

Clinical and sonographic risk factors for developing pre-eclampsia refractory to aspirin prophylaxis

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ABSTRACT

Objective: Identify risk factors for development of preeclampsia refractory to aspirin prophylaxis in women at high-risk of preeclampsia.
Material and methods: A retrospective cohort study analyzed 206 women identified as high-risk for preeclampsia through first-trimester screening and prescribed aspirin prophylaxis. We compared maternal characteristics, medical history, biochemical markers, and uterine artery Doppler indices between those with and without preeclampsia.
Results: Women with preeclampsia had significantly higher rates of chronic hypertension (54.3% vs. 8.2%), higher first-trimester mean arterial pressure (MAP, 109.6 vs. 95.4 mmHg), and higher body mass index (BMI, 27.6 vs. 24.9) compared to controls. Second-trimester MAP and mean uterine artery pulsatility index (UtA-PI) were also significantly elevated in the preeclampsia group (103.3 mmHg and 1.39, respectively) compared to controls (89.7 mmHg and 1.05). ROC curve analysis identified an optimal second trimester UtA-PI cut-off of 1.36 for predicting preeclampsia, with sensitivity of 49% and specificity of 87.1%. When using a cut-off value of 0.77 for the second-to-first trimester UtA-PI ratio, the sensitivity and specificity were 60% and 90.6%, respectively.
Conclusion: Chronic hypertension, high first and second trimester MAP, higher BMI, and elevated second trimester UtA-PI are associated with preeclampsia despite aspirin prophylaxis. Evaluating second trimester UtA-PI or the ratio of second to first trimester UtA-PI may be a promising tool for identifying women who do not respond to aspirin.

Introduction

Preeclampsia, a major cause of maternal and perinatal morbidity and mortality, accounts for 2–8% of all pregnancies worldwide [1,2]. Therefore, the identification of women at a high risk of developing preeclampsia, followed by timely therapeutic interventions, is crucial [3,4]. Various screening programs and prediction models for preeclampsia have been proposed, with the most common first-trimester screening method currently relying on an algorithm based on Bayes' theorem [4–6]. This screening program utilizes multivariate logistic regression analysis to integrate maternal characteristics, mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI), serum pregnancy-associated plasma protein-A (PAPP-A), and placental growth factor (PlGF) at 11–13^{+6} weeks of gestation, providing an individual risk assessment for the development of preeclampsia. At a false-positive rate of 10%, the screening method could detect 90% of early-onset preeclampsia, 75% of preterm preeclampsia, and 41% of term preeclampsia cases [6].

Predicting subsequent preeclampsia development may be achieved solely by examining longitudinal changes in Doppler indices, particularly mean UtA-PI, without including other maternal or biochemical markers [7]. In a cohort study involving 870 singleton pregnancies, sequential changes in uterine artery waveform were examined at 11–14 weeks and 19–22 weeks. The study reported that persistent abnormal mean UtA-PI is associated with the highest risk of adverse perinatal outcomes [8]. Another study reported that an increasing gap between the first and second trimester UtA-PI, indicative of abnormal spiral artery transformation, can accurately predict early and preterm preeclampsia [9].

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The pathophysiology of preeclampsia is not fully elucidated. It is widely accepted that the development of preeclampsia involves inadequate trophoblast invasion, resulting in increased oxidative stress and systemic endothelial dysfunction, which subsequently manifests as the clinical features of preeclampsia [10]. Additionally, preeclampsia is associated with increased platelet turnover and the excessive production of platelet-derived thromboxane, a vasoconstrictor that contributes to both vasoconstriction and platelet aggregation, key features of preeclampsia [11]. Hence, antiplatelet therapy, particularly aspirin, has been proposed to reduce the risk of developing preeclampsia. Over the past decades, studies have demonstrated the benefits of low-dose aspirin (ranging from 50 to 150 mg per day) in preventing preeclampsia. Initiating low-dose aspirin at the 16th week of gestation or earlier has been shown to reduce the incidence of severe preeclampsia [12,13]. In the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial, women at high risk for preterm preeclampsia, identified based on the maternal factors and biomarkers mentioned above, were prescribed aspirin at a dose of 150 mg per day from 11 to 14 weeks of gestation until 36 weeks of gestation. This protocol resulted in a 62% reduction in the incidence of preterm preeclampsia [14].

Professional associations have begun recommending the use of prophylactic low-dose aspirin in pregnant women at high risk for preeclampsia. Despite these recommendations, the benefits of prophylactic aspirin may not be evident in certain groups of pregnant women, and the etiology remains unknown [15]. Therefore, the identification of high-risk women who do not respond to aspirin has become clinically important. This study aims to evaluate maternal characteristics, medical history, serum biochemical markers, and uterine artery Doppler to identify possible risk factors associated with the development of preeclampsia refractory to aspirin prophylaxis.

Material and methods

This was a retrospective cohort study of pregnancies at high risk of preeclampsia identified through first-trimester screening and received aspirin for prophylaxis, collected from Mackay Memorial Hospital in Taiwan between November 2017 and February 2022. The exclusion criteria included multiple gestation, loss to follow-up/inadequate data collection (not delivering at our hospital or not receiving second-trimester UtA-PI measurements), major fetal anomalies (structural anomalies, aneuploidy, or identified genetic syndromes), intrauterine fetal demise unrelated to preeclampsia, or non-compliance with regular Aspirin intake. This study was approved by the Institutional Review Board of Mackay Memorial Hospital (#21MMHIS191e). All personal information were de-identified prior to analysis.

Gestational age was determined based on the estimated date of conception and corrected by the measurement of fetal crown-rump length in the first trimester. Between 11 and 13 + 6 weeks of gestation, preeclampsia risk was assessed using the fetal medicine foundation (FMF) first-trimester competing-risk algorithm, which incorporated maternal factors, including demographic characteristics, medical and obstetric history, as well as measurements of MAP, mean UtA-PI, serum PAPP-A, and serum PlGF. Sonographic measurements were obtained using either the GE Voluson E8 or E10 ultrasound machine (GE Healthcare Technologies, Milwaukee, MI, USA) with a 2–5 MHz transabdominal transducer, performed by operators (CYC, YYC, LKW) with certification of competence in preeclampsia risk assessment from the FMF. MAP was measured using a validated automated device under a standardized protocol. Biochemical factors, including serum concentrations of PAPP-A and PlGF, were measured using an automated device (BRAHMS Kryptor Analyzer, Thermo Fisher Scientific, Germany) and presented as multiples of the median (MoM) values. In women at a preeclampsia risk exceeding 1 in 200, aspirin 100 mg was initiated nightly from before 16 weeks of gestation until 36 weeks or delivery, whichever occurred earlier. Adherence to aspirin prophylaxis was assessed by reviewing medication records, including prescriptions at each prenatal visit. Maternal weight, fetal body weight, MAP, and mean UtA-PI were subsequently measured at 20–24 weeks of gestation using the same methods mentioned above.

The main outcome was preeclampsia, diagnosed by the new onset of hypertension accompanied by proteinuria after 20 weeks of gestation in previously normotensive women. Hypertension was defined as repeated measurements of systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg on at least two occasions 4 h apart. Proteinuria was defined as $\geq$ 0.3g in a 24-h collection or at least 2+ in urine dipstick analysis. In women with chronic hypertension (defined as a history before conception or the onset of hypertension before 20 weeks of gestation), preeclampsia is characterized by the development of proteinuria (as defined above) after 20 weeks of gestation. Perinatal outcomes included preterm delivery, small for gestational age (SGA), and NICU admission.

Statistical analysis was performed using SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Data were presented as mean ± SD or n (%). Categorical variables were compared using the Chi-square test and reported as proportions. Fisher's exact test was employed for correction in cases of small sample sizes. Quantitative variables between the two groups were compared using Student's t-test, with the significance level set at 0.05. The association between preeclampsia and adverse events, including perinatal outcomes, was reported as odds ratios (OR) with 95% confidence intervals (CIs). The predictive performance of mean UtA-PI in detecting preeclampsia development was evaluated using the area under the receiver operating characteristic curve (AUC).

Results

During the study period, a total of 3904 pregnant women underwent first-trimester preeclampsia screening. Among them, 373 (9.5%) were identified as high risk for preeclampsia, and subsequently, low-dose aspirin (100 mg/day at night) was prescribed. 167 (44.8%) pregnancies were excluded for various reasons, including twins (n = 16), loss to follow-up (n = 36), fetal anomalies (n = 7), intrauterine fetal demise (n = 8), inadequate data collection (n = 78), and irregular aspirin intake (n = 22). Loss to follow-up indicates cases where delivery did not occur at our hospital. Additionally, due to the optional and non-reimbursed nature of second trimester UtA-PI measurements, those who did not receive the second trimester UtA-PI assessment are classified as having inadequate data. The remaining 206 women were included, and among them, 35 developed preeclampsia during pregnancy (Fig. 1).

The characteristics of the study population are presented in Table 1. In the preeclampsia group, 19 (54.3%) women had chronic hypertension, compared to 14 (8.2%) in the control (no preeclampsia) group ($p < 0.0001$). Among these women with chronic hypertension, all but four were taking anti-hypertensive medication before conception. Notably, two of these who did not take medication later developed preeclampsia, initially presenting with high MAP (103 mmHg and 108 mmHg). In the preeclampsia group, the first trimester MAP was 109.6 ± 15.4 mmHg, significantly higher compared to the control group (95.4 ± 11.7 mmHg, $p < 0.0001$). Additionally, the pregestational BMI was higher in the preeclampsia group than in the control group (27.6 ± 6.3 vs. 24.9 ± 5.0, $p = 0.006$). There was no statistically significant

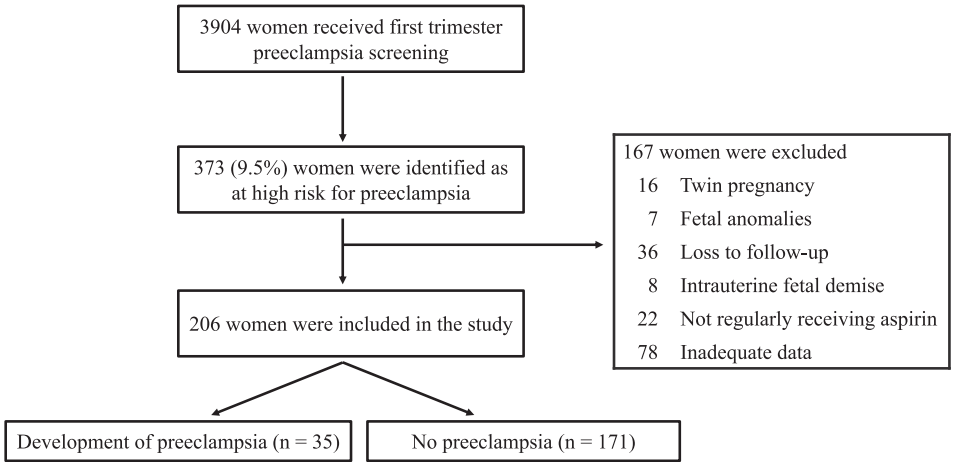

Fig. 1. Flow diagram showing the study population.

Table 1
Clinical characteristic of the participants.

Variable	Preeclampsia (n = 35)	Control (n = 171)	*p* value
Age	35.4 ± 5.3	35.4 ± 5.0	0.987
Pre-gestational BMI	27.6 ± 6.3	24.9 ± 5.0	0.006*
Gravida	1.9 ± 1.1	1.8 ± 1.0	0.296
Parity	0.3 ± 0.5	0.3 ± 0.5	0.684
ART	7 (20)	33 (19.4)	0.747
Chronic hypertension	19 (54.3)	14 (8.2)	<0.0001*
DM	1 (2.9)	3 (1.8)	0.667
Smoker	0	0	NA
Mean arterial pressure (mmHg)	109.6 ± 15.4	95.4 ± 11.7	<0.0001*
Mean first trimester UtA-PI	1.72 ± 0.54	1.86 ± 0.45	0.095
PAPP-A (MoM)	0.95 ± 0.48	1.13 ± 0.62	0.106
PlGF (MoM)	0.55 ± 0.36	0.62 ± 0.31	0.272
GA of aspirin started	14.9 ± 1.10	14.9 ± 0.96	0.799

Data are presented as mean ± standard deviation or number (percentage).
ART: assisted reproductive technology; UtA-PI: uterine artery pulsatility index; PAPP-A: pregnancy associated plasma protein-A; PlGF: placental growth factor; MoM: multiple of median; GA: Gestational age.
*$p < 0.05$.

difference in other maternal characteristics (age, parity, DM history), first-trimester UtA-PI, PAPP-A, or PlGF between the two groups.

Table 2 compares specific physical and sonographic measurements obtained in the second trimester between the preeclampsia and control groups. The preeclampsia group exhibited a significantly higher MAP (103.3 ± 15.2 mmHg) compared to the control group (89.7 ± 10.6 mmHg; $p < 0.0001$). Additionally, women with preeclampsia had a significantly higher mean UtA-PI in the second trimester than the control group (1.39 ± 0.60 vs. 1.05 ± 0.33, $p < 0.0001$). There was no difference in maternal weight gain or the incidence of small for gestational age between the two groups.

The receiver-operating characteristic (ROC) curves, comparing the predictive performance of second trimester mean UtA-PI alone and its ratio to the first trimester mean UtA-PI for subsequent preeclampsia development, were shown in Fig. 2. An ROC curve analysis (AUC = 0.683, 95% CI: 0.565–0.820, p = 0.002) identified an optimal cut-off value of 1.36 for the second trimester mean UtA-PI in identifying women at risk of subsequent preeclampsia. Using this cut-off, with mean UtA-PI above 1.36, the model achieved a sensitivity of 49% and a specificity of 87.1% for predicting preeclampsia. Moreover, when using the ratio of the second to the first trimester mean UtA-PI with the cut-off value of 0.77, the sensitivity rate and specificity rate were 60% and 90.6%, respectively.

Table 2
Second trimester measurements of the participants.

Variable	Preeclampsia (n = 35)	Control (n = 171)	*p* value
Mean arterial pressure	103.3 ± 15.2	89.7 ± 10.6	<0.0001*
Weight gain (%)	5.5 ± 5.9	6.6 ± 6.1	0.345
Weight gain (Kg)	3.6 ± 4.4	3.8 ± 3.7	0.687
SGA	1 (2.9%)	2 (1.2%)	0.448
Mean UtA-PI	1.39 ± 0.60	1.05 ± 0.33	<0.0001*

Data are presented as mean ± standard deviation or number (percentage).
SGA: small for gestational age; UtA-PI: uterine artery pulsatility index.
*$p < 0.05$.

The perinatal outcomes, presented as odds ratios with 95% confidence intervals, were shown in Table 3. Preterm delivery (defined as delivery before 37 weeks of gestation) was significantly more prevalent in the preeclampsia group (15 cases, 42.9%) compared to the control group (28 cases, 16.4%), with an odds ratio of 2.83 (95% CI [1.75–8.38], $p < 0.0001$). Similarly, small for gestational age (SGA), defined as birth weight below the 10th percentile using national singleton birth weight percentiles in Taiwan [16], was significantly more prevalent in the preeclampsia group (15 cases, 42.9%) compared to the control group (31 cases, 18.1%), with an odds ratio of 3.39 (95% CI [1.56–7.35], $p = 0.001$). The rate of Neonatal Intensive Care Unit (NICU) admission was higher in the preeclampsia group (n = 11, 31.4%) compared to the control group (n = 10, 5.8%), with $p < 0.0001$ (95% CI [2.83–19.2], OR = 7.37). Details of adverse events during NICU admission are also presented in Table 3.

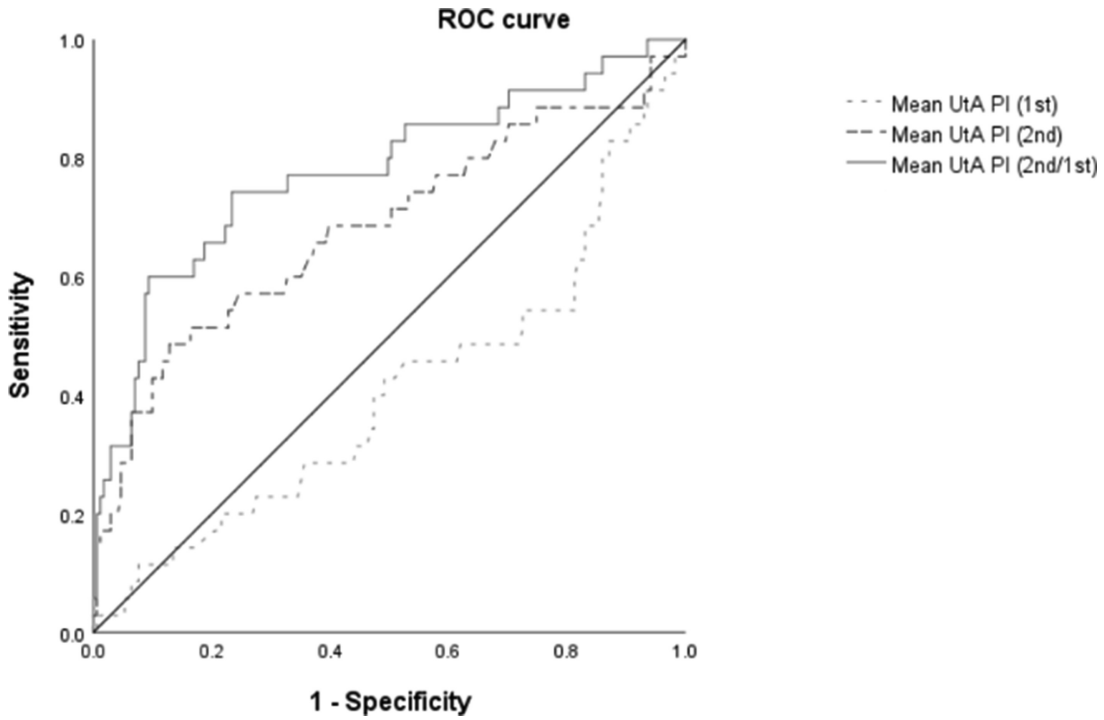

Fig. 2. Receiver-operating characteristic curves for predicting subsequent preeclampsia development using second trimester uterine artery pulsatility index measurements.

Table 3
Perinatal outcomes.

	Preeclampsia (n = 35)	Control (n = 171)	Odds Ratio (95% CI)	*p* value
Preterm delivery	15 (42.9%)	28 (16.4%)	2.83 (1.75–8.38)	<0.0001*
GA of delivery (weeks)	35.9 ± 3.1	38.2 ± 2.2		
SGA	15 (42.9%)	31 (18.1%)	3.39 (1.56–7.35)	0.001*
NICU admission	11 (31.4%)	10 (5.8%)	7.37 (2.83–19.2)	<0.0001*
Prematurity	11	7		
Very low birth weight	7	6		
TTN	10	7		
Clinical sepsis	3	5		
Hypoglycemia	4	4		
Hyperbilirubinemia	8	5		
GI bleeding	2	1		

Data are presented as mean ± standard deviation or number (percentage).
Very low birth weight: birth weight ≤1500g.
CI: confidence interval; NICU: neonatal intensive care unit; TTN: transient tachypnea of the newborn.
*$p < 0.05$.

Discussion

The current study investigated maternal characteristics, medical history, serum biomarkers and sonographic findings in pregnant women at high risk of preeclampsia receiving aspirin prophylaxis. Our findings indicate that high-risk women who develop pre-eclampsia despite aspirin treatment demonstrate significantly higher second trimester UtA-PI compared to those who do not develop preeclampsia. This observation, to the best of our knowledge, has not been reported in the literature before. Furthermore, individuals who developed pre-eclampsia despite aspirin treatment exhibited higher MAP during the first and second trimesters compared to those who did not develop the condition.

Aspirin prophylaxis has gained wide acceptance for pregnancies at high risk of preeclampsia in recent years. Nevertheless, some pregnant women at high risk of preeclampsia show refractoriness to aspirin prophylaxis, and the identification of this subgroup of women appears clinically important. Recently, the application of the soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio has been recommended for predicting late-onset pre-eclampsia and adverse perinatal outcomes [17]. An elevated sFlt-1/PlGF ratio indicates placental disease, while a ratio of 38 or lower can be considered indicative of the short-term absence of pre-eclampsia. Mendoza et al. further discovered that the sFlt-1/PlGF ratio at 24–28 weeks of gestation could serve as an indicator for discontinuing aspirin in pregnant individuals at high risk of pre-eclampsia [18]. However, the cost of sFlt-1/PlGF and its lack of reimbursement by health insurance may limit its clinical application.

The examination of uterine artery Doppler is regarded as a potential tool for screening the development of preeclampsia, fetal growth restriction and stillbirth by indirectly assessing uteroplacental circulation [7,19]. Throughout pregnancy, the mean UtA-PI gradually declines, reflecting the adaptation of the uterine artery to a state of high capacity and low resistance. An abnormal high UtA-PI is considered to result from impaired trophoblastic invasion, which is one of the possible pathophysiological causes of

preeclampsia [19]. In addition, the sequential changes in uterine artery blood flow pattern from the first to the second trimester is associated with the subsequent development of preeclampsia. Previous studies have shown that aspirin initiated in the first trimester is associated with a significant decrease in UtA-PI compared to a placebo [13,20]. However, these studies did not compare the difference in mean UtA-PI between pregnancies under aspirin that eventually developed preeclampsia and those that did not. The present study revealed a significant elevation in UtA-PI during the second trimester among individuals in the preeclampsia group compared to the control group. Employing a uterine artery PI cutoff value of 1.36, the sensitivity and specificity were found to be 49% and 87.1%, respectively. Notably, the ratio of the mean UtA-PI in the first and second trimesters emerged as a superior indicator for the detection of preeclampsia when compared to relying solely on the mean UtA-PI value in the second trimester (AUC 0.777 vs. 0.683). While the mechanism underlying aspirin resistance in some pregnant women requires further investigation, these findings indicate that the absence of a progressive decrease in UtA-PI is associated with the subsequent development of preeclampsia in high-risk women under aspirin prophylaxis. These results also suggest that examining second-trimester UtA-PI could serve as a promising tool for identifying the subgroup of high-risk women who do not respond to aspirin prophylaxis.

In terms of clinical risk factors for the development of preeclampsia despite aspirin prophylaxis, consistent with previous studies [21,22], the present study confirmed the association between a history of chronic hypertension, elevated first trimester blood pressure, and the development of preeclampsia. Block-Abraham et al. demonstrated that women who develop preeclampsia under aspirin prophylaxis are more like to have chronic hypertension and elevated first-trimester blood pressure [21]. Similarly, Shen L et al. identified chronic hypertension as a risk factor for development of preterm preeclampsia despite aspirin prophylaxis in a secondary analysis of ASPRE trail [22]. In addition, our study found that women under aspirin prophylaxis who develop preeclampsia exhibit a significantly higher second-trimester MAP than controls. Consistent with this finding, Baschat AA et al. demonstrated that in women treated with prophylactic aspirin, those who develop preeclampsia have consistently and significantly higher blood pressure throughout pregnancy compared to those who do not develop preeclampsia [23]. Regardless of the underlying mechanism behind why women with chronic hypertension or elevated first-trimester blood pressure tend to development preeclampsia, these observations highlight the importance of continued blood pressure monitoring and potentially more intensive management strategies for high-risk women, despite preventive measures. Furthermore, women who subsequently developed preeclampsia in our study exhibited a significantly higher pre-gestational BMI. This finding is consistent with a previous study indicating that this subgroup of women is more likely to have obesity. In contrast, there was no association between maternal BMI and the development of preeclampsia in the secondary analysis of the ASPRE trial. This difference may be attributed to the fact that our cohort consists exclusively of Taiwanese women, with Asians generally adhering to stricter BMI requirements for health [24]. Finally, pregestational diabetes and serum biochemical markers, such as PAPP-A and PlGF, are not associated with the development of preeclampsia despite aspirin prophylaxis in our study.

Our study has several limitations. Firstly, the relatively small sample size is attributed to the single-center nature of this study. Unlike previous studies that exclusively focused on preterm preeclampsia, our investigation included women who developed preeclampsia, encompassing both preterm and term cases. Despite this limitation, our findings hold clinical significance as perinatal outcomes were observed to be significantly worse in the preeclampsia groups. Secondly, we did not conduct examinations on intra- or inter-observer variability; however, we assumed that the variability is minimal because all sonographers hold licenses from the FMF, which requires an annual audit. Thirdly, since our study comprised participants from Taiwan, the findings may not directly translate to other populations without further research.

In conclusion, our study demonstrates that in pregnancies at high risk of preeclampsia identified by first-trimester screening, chronic hypertension, high first and second trimester MAP, higher BMI and elevated second-trimester UtA-PI are associated with the development of preeclampsia despite prophylactic aspirin. An increased UtA-PI value in the second trimester and an inadequate decrease between the first and second trimester (the ratio of second to first trimester UtA-PI) may predict the development of preeclampsia, with the cut-off values of 1.36 and 0.77, respectively. The findings suggest that women at a high risk of preeclampsia, undergoing aspirin prophylaxis with an elevated second-trimester UtA-PI or an increased second-to-first trimester UtA-PI, require additional clinical investigation and care.

Conflict of interest

The authors declare no conflict of interest.

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Original Article

The risks of emergency C-section, infant health conditions and postpartum complications in Taiwanese primiparous women with gestational diabetes mellitus: A propensity matched cohort study

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ABSTRACT

Objective: Gestational diabetes mellitus (GDM) is a disorder that can occur during the second trimester of pregnancy. Our main objective was to perform a retrospective propensity-score matched analysis of a general population and to examine commonly occurring adverse maternal and infant outcomes in Taiwanese primiparous women with GDM.

Materials and methods: We conducted a nationwide population-based, retrospective propensity-score matched cohort study using the claims data from the Taiwan's National Health Insurance program between 2000 and 2015. A 1:4 propensity matched cohort of women who aged 18 years or older with GDM (n = 5981) were compared with women without GDM (n = 23,924). Propensity score was calculated based on women's age, residential urbanicity, delivery mode, antepartum comorbidity, and index year of delivery.

Results: The GDM group had a significantly higher risk of overall emergency caesarean section, infant health conditions, and postpartum complications than the comparison group. Women in the GDM group were more likely to undergo emergency C-section for fetal distress, uterine atony, obstructed labor, delayed delivery, failed induction of labor, and umbilical cord prolapse. Infants of women with GDM were also more likely to encounter pregnancy complications of malpresentation, pre-maturity and post-maturity. Being the most common infant conditions, roughly one-third (36.41%) of all infant were affected by jaundice, particularly in women with GDM than those without GDM (45.96% vs 34.02%). There were also significant differences in perinatal period infection, congenital anomalies, transitory tachypnea, fetal distress and asphyxia, respiratory distress, and birth injury between the groups. Women with GDM were associated with increased risks of developing postpartum complications in perineum laceration, mastitis, postpartum hemorrhage, and subinvolution of uterus.

Conclusion: The present study suggests that GDM is associated with increased risks of adverse maternal and infant outcome in primiparous women without pre-existing mental diseases.

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Introduction

Gestational diabetes mellitus (GDM) is considered to be one of the most common complications of childbirth that can affect both mothers and their children [1]. According to a recent meta-analysis, GDM affects roughly one in every six women with childbirth with a pooled age-standardized global prevalence of 14.0% [2]. The GDM prevalence of 20.8% in South-East Asian countries is nearly two-fold higher than the prevalence of 7.1%–7.8% in North America, Caribbean and Europe [2]. In Taiwan, the prevalence of GDM was 13.4% in 2015 [3]. There has been an increasing focus on the maternal and infant outcomes that can occur in women with GDM [4]. This complication if left untreated can lead to pregnancy-associated high blood pressure (preeclampsia), premature delivery of the baby and shoulder dystocia [5,6]. Infants whose mother with GDM are also at an increased risk for dangerously low blood sugar levels immediately after childbirth. These babies also tend to increase in birthweight, and can cause complications during delivery. Despite the recognized increased risks between GDM and adverse pregnancy outcomes, the treatment of GDM is currently based on consensus and expert opinion [4]. Due to a lack of a universal consensus in treatment, the optimal treatment of GDM remains uncertain, but the overall aim is to lower the blood sugar level to that of women without GDM during pregnancy [7].

A careful review of the literature indicates that the risks for developing adverse pregnancy outcomes in women with GDM may differ substantially under different health-care systems, lifestyle factors and ethnicity [8]. To devise a suitable treatment for Taiwanese women, further understanding of the population risks of maternal and infant outcomes with GDM is therefore critical. Using the claims data from the Taiwan's National Health Insurance (NHI) program, we can create similar groups of women with or without GDM for comparison of various maternal and infant outcomes using propensity-score analysis. The NHI is an universal single-payer health insurance program that has been available to all civilian residents in Taiwan since 1995 [9]. All women have similar access to the free prenatal care visits during pregnancy under the NHI program in Taiwan. Using the nationwide population-based National Health Insurance claim data, our main objective was to perform a retrospective propensity-score matched analysis of a general population and to examine commonly occurring adverse maternal and infant outcomes in Taiwanese primiparous women with GDM.

Materials and methods

Study design and data source

We conducted a nationwide population-based, retrospective propensity-score matched cohort study of all beneficiaries with childbirth in Taiwan. The main data source was the longitudinal health insurance database of two million randomly selected beneficiaries, representing approximately 10% of all enrollees covered under the NHI Program. The NHI is a single-payer insurance program with an enrollment rate of more than 99% of Taiwan's civilian residents in 2011 [9]. For this study, we utilized the 2000–2016 NHI inpatient admission files, NHI outpatient visit files, NHI enrollment files, and death registry. This comprehensive healthcare database includes patient's basic sociodemographic information (age, gender, birth date, area zip code of enrollment location), mortality information (date of death, place of death, underlying cause of death), and medical claims (outpatient visits and inpatient admissions). One primary and up to four secondary codes (based on the International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM), are provided for disease diagnosis and surgical/diagnostic/therapeutic procedures for each inpatient admission claims. Three disease diagnosis codes (based on ICD-9-CM) are provided for each outpatient visit claims. To ensure the confidentiality of enrollees, the dataset was received as de-identified data from the Health and Welfare Data Science Center (HWDC), and allowed only on-site analyses in the Yangming branch office of the Collaboration Center of Health Information Application (CCHIA). The CCHIA is supervised by Office of Statistics, Ministry of Health and Welfare (MOHW), which aims to unify available MOHW health data and promote quality of public health-related decisions, related academic research, and the research and innovation of medical health insurance services in Taiwan [10]. Approval for this study was obtained from the Institutional Review Board and Ethical Committees of MacKay Memorial Hospital in Taiwan (No. 18MMHIS144).

Study population

Incident cases of childbirth (n = 120,070) were retrospectively identified from the inpatient admission claims using the procedure codes for vaginal and (72, 73) and C-section (74.0, 74.1, 74.2, 74.4) birth between 2003 and 2015. The index birth was defined as the date of childbirth on the inpatient admission claims. All women were divided into two groups according to their GDM status at index admission: (i) GDM (disease code 648.8) and (ii) non-GDM comparison group. The exclusion criteria applied to both groups were: (1) women aged less than 18 years (n = 1205); (2) disease code for pre-existing diabetes mellitus (250) prior or within the same inpatient admission claims or outpatient visit claims to promote homogeneity in disease severity (n = 1749); (3) disease codes for all symptoms and disorders related to mental health (290–319) within three years before the index admission (n = 27,626); (4) procedure codes for vaginal birth (72, 73) and C-section birth (74.0, 74.1, 74.2, 74.4), disease codes associated with GDM (648.8), pregnancy-related conditions, emergency caesarean section (emergency C-section), infant health conditions, and postpartum outcomes (n = 23,563) ten months before the index admission to rule out the possibility of multigravid women; and (5) women with incomplete information or missing information on independent variables of interests (n = 22). To reduce bias due to baseline differences in observed covariates between the GDM and the non-GDM comparison groups at baseline, a propensity score matched cohort analysis was carried out to reduce selection bias between the groups [11,12]. Each woman was assigned a propensity score generated from logistic models, i.e., the likelihood that a woman would be diagnosed of GDM based on women's age at delivery, residential urbanicity, delivery mode, antepartum comorbidity, and index year of delivery. A total of 5981 women aged 18 years or older with were included in the final GDM group. A total of 23,924 primiparous women with the least within-pair difference in propensity score were selected randomly without replacement from the remaining women (n = 59,952) in the non-GDM comparison group using the 8-to-1 greedy matching logarithm on a 1:4 ratio (Table 1) [11].

Covariates

Covariates included in the study were age, residential urbanicity, delivery mode, antepartum comorbidity, and index year of delivery. Women's residential area were classified into urban (cluster 1), suburban (clusters 2–4), and rural (clusters 5–7) according to the seven urbanization stratification clusters (1, most urbanized; 7, least urbanized) as defined by Liu et al. [13]. Antepartum comorbidities were considered as antenatal and peri-natal

Table 1
Propensity-score matched (1:4 ratio) characteristics by GDM and non-GDM comparison groups in women with childbirth.

Independent Variables	GDM[b]	Non-GDM[b] (Comparison Group)					
		Unmatched		Matched (1:4)			
	(n = 5981; 9.1%)	(n = 59,952; 90.9%)	*P*[a]	(n = 23,924)	*P*[a]	Pre-Mat SMD (%)	Post-Mat SMD (%)
Propensity score	0.10 ± 0.02			0.10 ± 0.02	0.964		
Age (y)							
18-34	5041 (84.28)	52,582 (87.71)	<0.001***	20,178 (84.34)	0.911	9.88	0.16
≧35	940 (15.72)	7370 (12.29)		3746 (15.66)			
Residential urbanicity							
Urban	2508 (41.93)	20,143 (33.60)	<0.001***	10,032 (41.93)	1.000	16.54	<0.01
Suburban	3468 (57.98)	39,376 (65.68)		13,872 (57.98)			
Rural	5 (0.08)	433 (0.72)		20 (0.08)			
Delivery mode[c]							
Vaginal birth	3697 (61.81)	38,050 (63.47)	0.011*	14,787 (61.81)	0.995	3.42	0.01
C-section birth	2284 (38.19)	21,902 (36.53)		9137 (38.19)			
Antepartum comorbidity							
No	3161 (52.85)	35,686 (59.52)	<0.001***	12,637 (52.82)	0.968	13.48	0.06
Yes	2820 (47.15)	24,266 (40.48)		11,287 (47.18)			
Index year of delivery							
2003	615 (10.28)	7945 (13.25)	<0.001***	2460 (10.28)	1.000	14.84	5.21
2004	535 (8.94)	6563 (10.95)		2140 (8.94)			
2005	511 (8.54)	5421 (9.04)		2045 (8.55)			
2006	493 (8.24)	5133 (8.56)		1965 (8.21)			
2007	505 (8.44)	4805 (8.01)		2046 (8.55)			
2008	486 (8.13)	4267 (7.12)		1930 (8.07)			
2009	497 (8.31)	3980 (6.64)		1980 (8.28)			
2010	382 (6.39)	3223 (5.38)		1520 (6.35)			
2011	427 (7.14)	3658 (6.10)		1708 (7.14)			
2012	494 (8.26)	4250 (7.09)		1987 (8.31)			
2013	362 (6.05)	3557 (5.93)		1447 (6.05)			
2014	367 (6.14)	3575 (5.96)		1468 (6.14)			
2015	307 (5.13)	3575 (5.96)		1228 (5.13)			

C-section, caesarean section; GDM, gestational diabetes mellitus; Pre-Mat, pre-matched; Post-Mat, post-matched; SMD, standardized mean difference.
Data are n (%) unless otherwise indicated.
[a] Unadjusted *P*-value (Chi-square test).
[b] Disease code [GDM (ICD-9-CM: 648.8)].
[c] Operative procedure code [Vaginal delivery (ICD-9-CM: 72, 73); Cesarean delivery (ICD-9-CM: 74.0, 74.1, 74.2, 74.4)].

conditions within 10 months before childbirth using diseases codes based on at least one inpatient or outpatient claim: genital herpes (054.1), condyloma accuminata (078.11), syphilis and other venereal diseases (090–099), myoma uterine or benign uterine tumor (218.9, 219.9), epilepsy (345), asthma (493), placenta previa (641.0, 641.1), premature separation of placenta (641.2), eclampsia or pre-eclampsia (642.4, 642.5, 642.6), hypertension-complicated pregnancy (642.9), early delivery onset (644), unspecified renal disease in pregnancy (646.2), diabetes mellitus complicating pregnancy (648.0 + 250), thyroid dysfunction in pregnancy (648.1 + 246.9), cardiovascular diseases in pregnancy (648.6), abnormality of organs and soft tissues of pelvis (654), pregnancy and myoma of uterus (654.13 + 218.9), and other known or suspected fetal abnormality (655.8).

Outcomes

Adverse maternal and infant outcomes of interest included emergency C-section, infant health conditions, postpartum complications and other pregnancy related conditions [14,15]. All outcomes were based on at least one inpatient or outpatient claims measures during childbirth. Emergency C-section were considered for C-section due to disproportion (653), fetal distress (656.3), delayed delivery after spontaneous or unspecified rupture of membranes (658.2), failed induction of labor or dystocia (659.0, 659.1), obstructed labor (660), uterine atony (661), long labor (662.1), and umbilical cord prolapse (663.0). Infant health conditions were considered for infants with any congenital anomalies (740–759), slow of fetal growth and malnutrition (764), birth injury (767), fetal distress and asphyxia (768, 769), respiratory distress syndrome (768.9), meconium aspiration syndrome (770.1), congenital pneumonia (770.0), transitory tachypnea of newborn (770.6), perinatal period infection (771), and fetal jaundice (773, 774). Postpartum complications were considered for postpartum hemorrhage (666.0, 666.1, 666.2), major puerperal infection (670), subinvolution of uterus (621.1), urinary tract infection (599.0), mastitis (611.0), perineum laceration (664.1, 664.2, 664.3, 664.4, 666.0), disruption or dehiscence of cesarean wound (674.1), disruption or dehiscence of perineum wound (674.2), and infection of cesarean section or perineum wound (674.43). Other pregnancy related conditions included malpresentation of fetus (652.2–652.4, 652.9), pre-mature infant (765.0, 765.1), and post-mature infant (766.0, 766.1, 766.2).

Statistical analysis

The dissimilarities in categorical variables for baseline characteristics before matching and outcomes of interest after matching between the GDM and non-GDM comparison groups were compared using the Pearson's chi-squared (χ^2) test, whereas the overall propensity score before and after matching were compared using the student's *t*-test. To examine the balance of covariates between the GDM and non-GDM comparison groups before and after propensity-score matching, standardized mean difference (SMD) was computed for each covariate. SMD was calculated by the difference in the means between the two groups divided by pooled

standard deviation. A SMD value of greater than 10% suggested an imbalance between the matched groups. All statistical analyses were performed using the software package SAS (Statistical Analysis System) for Windows® (release 9.4; SAS Institute Inc., Cary, NC, USA). All reported *P*-values of less than 0.05 (or 5%) were considered statistically significant.

Results

Baseline characteristics

A total of 5981 women aged 18 years or older were diagnosed with GDM during pregnancy between January 2003 and December 2015. Table 1 compares the covariates of the GDM and non-GDM comparison groups before and after propensity-score matching ratio of 1:4. In general, women in the GDM group were more likely to be 35 years or older (15.72% vs 12.29%), had a higher prevalence of antepartum comorbidities (47.15% vs 40.48%), resided in urban cities (41.93% vs 33.60%), and underwent C-section birth (38.19% vs 36.53%) than those in the unmatched non-GDM group (*P*-values <0.05 for all). There was also significant difference in the index year of delivery between the groups. After propensity score matching, the SMD value of less than 10% and the lack of significant differences between the covariates suggested that the two groups were comparable in those characteristics.

Propensity-score matched analysis

A total of 29,905 women were included in the analysis (5981 in the GDM group and the 23,924 in the non-GDM comparison group). The GDM group had a significantly higher risk of overall emergency C-section (Table 2), infant health conditions (Table 3), and postpartum complications (Table 4) than the non-GDM comparison group. Women in the GDM group were more likely to undergo emergency C-section for fetal distress, uterine atony, obstructed labor, delayed delivery, failed induction of labor, and umbilical cord prolapse (Table 2). In contrast, there was no increased risk of disproportion and long labor between the two groups. On the other hand, infants of women with GDM were also more likely to encounter pregnancy complications of malpresentation, prematurity and post-maturity (Table 3). Being the most common infant conditions, roughly one-third (36.41%) of all infant were affected by jaundice, particularly in women with GDM than those without GDM (45.96% vs 34.02%). There were also significant differences in perinatal period infection, congenital anomalies, transitory tachypnea, fetal distress and asphyxia, respiratory distress, and birth injury between the groups. Women with GDM were associated with increased risks of developing postpartum complications in perineum laceration, mastitis, postpartum hemorrhage, and subinvolution of uterus (Table 4). In contrast, women without GDM were more likely to suffer from an infection of cesarean section or perineum wound and major puerperal infection. There were no statistical differences between urinary tract infection, disruption or dehiscence of perineum wound, and disruption or dehiscence of cesarean wound.

Discussion

From a clinical perspective, postpartum follow-up of women with GDM and their neonates are as important as the early detection of GDM during prenatal visit [16–20]. GDM creates an adverse hyperglycemic or hyper insulinemic environment that can potentially alter epigenetics in the placenta of mother and her offspring. The effects are complex and can have a continuous effect on fetal growth and organ functions. Possible sequelae of GDM, including metabolic and cardiovascular diseases and neuropsychiatric outcomes are more likely to develop in the latter life of infants [21]. When compared with women without GDM during pregnancy, our population-based propensity-score matched analysis demonstrated that a significantly higher risk of adverse maternal and infant outcomes in Taiwanese primiparous women with GDM without pre-existing mental diseases. In other words, higher levels of adverse maternal and infant outcomes suggest a longer postnatal care of the mother and newborn, including longer hospital stay and longer duration required for the mother to resume the baseline activities of daily livings.

Most studies did not eliminate women with previous diagnoses of mental diseases from their study cohorts [5,22]. Pre-existing mental diseases are associated with adverse birth outcomes such as preterm births and neonates small for gestational age as described in studies by Sūdžiūtė et al. [23], Edvardsson et al. [24], and Abdelhafez et al. [25] Our previous investigation on postpartum depression had approximately 9% of women with past history of mental illness prior childbirth [14]. In this study, we observed a much higher proportion of women (23%) with prior history of mental illness, possibly due to the different time periods used in exclusion (1995–1999 vs 2000–2002 this study, both using the NHI database). This finding suggests that the proportion of pre-existing mental diseases range from a minimal of roughly 10% to as much as 20% in women during pregnancy. We intentionally excluded women with pre-existing mental diseases from our study cohort. This was done to accurately account for the contributions of GDM on maternal and infant outcomes without the overlay of past psychiatric history. Consequently, the resulting matched study cohort in our study allows better comparison of maternal and infant outcomes between women with or without GDM.

Approximately 4–6% of women experience post-traumatic stress disorder (PTSD) following childbirth [26,27]. In our

Table 2
Incidence of emergency C-section in GDM and matched non-GDM comparison group (1:4 ratio) from 2003 to 2015 in Taiwan.

Independent Variables	GDM	Non-GDM	*P*[a]
	(*n* = 5981)	(*n* = 23,924)	
Fetal distress	487 (8.14)	1646 (6.88)	<0.001***
Uterine atony	385 (6.44)	1369 (5.72)	0.036*
Disproportion	303 (5.07)	1179 (4.93)	0.665
Long labor	217 (3.63)	824 (3.44)	0.478
Obstructed labor	184 (3.08)	463 (1.94)	<0.001***
Delayed delivery after spontaneous or unspecified rupture of membranes	104 (1.74)	329 (1.38)	0.039*
Failed induction of labor or dystocia	44 (0.74)	121 (0.51)	0.040*
Umbilical cord prolapse	8 (0.13)	11 (0.05)	0.038*

GDM, gestational diabetes mellitus; C-section, caesarean section.
Data are n (%) unless otherwise indicated.
[a] Chi-square test (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

Table 3
Incidence of infant health conditions in GDM and matched non-GDM comparison group (1:4 ratio) from 2003 to 2015 in Taiwan.

Independent Variables	GDM ($n = 5981$)	Non-GDM ($n = 23,924$)	P^a
Malpresentation of fetus	1122 (18.76)	3953 (16.52)	<0.001***
Pre-mature infant	292 (4.88)	1005 (4.20)	0.023*
Post-mature infant	37 (0.62)	36 (0.15)	<0.001***
Infant health conditions			
Fetal jaundice	2749 (45.96)	8140 (34.02)	<0.001***
Perinatal period infection	835 (13.96)	2511 (10.50)	<0.001***
Infants with any congenital anomalies	541 (9.05)	1677 (7.01)	<0.001***
Transitory tachypnea of newborn	215 (3.59)	623 (2.60)	<0.001***
Fetal distress and asphyxia	161 (2.69)	507 (2.12)	0.008**
Respiratory distress syndrome	119 (1.99)	373 (1.56)	0.023*
Slow of fetal growth and malnutrition	90 (1.50)	308 (1.29)	0.186
Meconium aspiration syndrome	75 (1.25)	258 (1.08)	0.242
Birth injury	79 (1.32)	186 (0.78)	<0.001***
Congenital pneumonia	56 (0.94)	171 (0.71)	0.080

GDM, gestational diabetes mellitus.
Data are n (%) unless otherwise indicated.
[a] Chi-square test (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

Table 4
Incidence of postpartum complications in GDM and matched non-GDM comparison group (1:4 ratio) from 2003 to 2015 in Taiwan.

Independent Variables	GDM ($n = 5981$)	non-GDM ($n = 23,924$)	P^a
Urinary tract infection	1566 (26.18)	6251 (26.13)	0.934
Perineum Laceration	870 (14.55)	2709 (11.32)	<0.001***
Mastitis	686 (11.47)	2512 (10.50)	0.031*
Infection of cesarean section or perineum wound	328 (5.48)	1879 (7.85)	<0.001***
Postpartum hemorrhage	436 (7.29)	1392 (5.82)	<0.001***
Subinvolution of uterus	109 (1.82)	269 (1.12)	<0.001***
Disruption or dehiscence of perineum wound	31 (0.52)	139 (0.58)	0.631
Major puerperal infection	19 (0.32)	129 (0.54)	0.030*
Disruption or dehiscence of cesarean wound	20 (0.33)	56 (0.23)	0.195

GDM, gestational diabetes mellitus.
Data are n (%) unless otherwise indicated.
[a] Chi-square test (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

propensity-score matched cohort, women with GDM experience an overall higher incidences of emergency C-section. Compared with a planned C-Section, the unexpected nature of an emergency C-section is a precipitating factor for both PTSD and post-partum depression (PPD) [28–30]. A recent study suggested that unplanned emergency C-section was indirectly associated with the development of PPD through the mechanism of PTSD [31]. Among women with PTSD, more than half of them were also latter diagnosed with PPD [32]. The prevalence rate of PTSD at 6 months postpartum was roughly 1.5% [32]. With C-sections representing 37% of all Taiwan's deliveries in 2016, in Taiwan with 138,986 births in 2022, these numbers would imply that annually, at least 12,342 to 25,713 women may suffer from PTSD as a consequence of delivery [33,34]. PTSD symptoms among primiparous women can include feelings of rejection, avoidance, lack or loss of control, and lack of support by medical staff [28,35]. PTSD is a serious psychiatric illness that currently lacks serious attention by the healthcare provides. Further researches in relationship with GDM and PTSD require our immediate attention. We suggest that women with GDM should be provided with increased support from health practitioners and carefully monitor their childbirth experience for any possible psychiatric symptoms.

Our population-based study has several strengths. First, the current study uses a population-based registry containing claims data regarding all births in Taiwan during the study period, enhancing the validity of our study. Second, the propensity-score matched cohort between GDM and non-GDM comparison groups for women with childbirth minimized confounders and further enhanced the validity of our findings. Third, to maintain a homogeneity in prognosis, we excluded a total of 27,626 (23.1%) women with disease diagnosis of mental diseases prior to inpatient admission. Fourth, being a single-provider insurance system, the misclassification bias of status of the emergency C-section, infant health conditions, and postpartum complications associated with pregnancy is minimal. The present study should also be interpreted with the inherent limitations of health claims data. First, it lacks sociodemographic variables such as socioeconomic status, maternal BMI, and education, as well as clinical variables such as parity, family history of DM, assisted reproductive technique, and birth numbers (singleton or multiple birth), which may confound our results. Asian population has been shown to have a much higher risk of GDM at lower BMI than non-Asian ethnic groups, i.e., prevalence of GDM at BMI 22–24 (10.1% Asian, 2.3% Non-Hispanic White, 3.9% Hispanic, 1.8% African American) [36]. Although BMI is considered an important risk factor for adverse pregnancy outcomes, the overall lower BMI in women with GDM in the Asian population contributes to minor confounding effect. Second, since propensity score-matching analysis controls only for covariates used to calculate the propensity score, unknown confounders that are not included in the calculation may introduce bias. To reduce bias, all variables used for the calculation of propensity score were based on the literature, and were associated with both the GDM and non-GDM comparison group assignment and the outcomes of interest.

Conclusions

The present study suggests that GDM is associated with increased risks of adverse maternal and infant outcome in primiparous women without pre-existing mental diseases. Women with GDM were more likely to undergo emergency C-section than vaginal delivery for various adverse outcomes, particularly fetal distress and obstructed labor, as well as pregnancy complications of malpresentation. These women were also more likely to develop postpartum complications in perineum laceration and postpartum hemorrhage than those without GDM. Although no randomized clinical study has yet been designed to investigate a suitable management in healthy women diagnosed with GDM during pregnancy, obstetricians are encouraged to develop a systematic way and intervene with appropriate treatments for women with GDM on an as-needed basis. In a meta-analytic study, Mitanchez and colleagues suggested that dietary treatment plus exercise is the best maternal lifestyle intervention with the least number of obstetric complications [6]. Other studies have investigated treatment with insulin, metformin, or other oral hypoglycemic agents to normalize blood sugar level [37]. Given the association with increased risk of postpartum psychiatric illness, in addition to medical consultation, we advocate that a discussion of mental health concern pregnancy should be an integral part of routine antenatal service for all pregnant women. This information is essential to inform obstetricians and women with GDM regarding adverse pregnancy outcomes and their potential association with postpartum psychiatric illness.

Financial conflict

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Conflict of interest

The authors declared no conflict of interest.

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Original Article

Factors associated with insufficient cervical ripening in a controlled-release dinoprostone vaginal delivery system: A single perinatal center retrospective study

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ABSTRACT

Objective: In this study, we aimed to evaluate the factors associated with insufficient cervical ripening in a controlled-release dinoprostone vaginal delivery system (Propess).
Materials and methods: This retrospective cohort study included 103 pregnant women who used Propess for labor induction. The outcomes were the factors associated with insufficient cervical ripening, defined as a Bishop score ≤6 on the morning after Propess administration.
Results: Forty-nine participants had insufficient cervical ripening, and 54 had sufficient cervical ripening. Univariate analysis of these two groups showed that maternal age ≥35 years, early-term delivery (gestational age between 37 and 38 weeks), and Bishop scores at insertion ≤1 were significantly higher in the insufficient cervical ripening group. Multivariate logistic analysis showed that maternal age ≥35 years (adjusted odds ratio: 3.08, 95% confidence interval: 1.29–7.36, p = 0.011) and early-term delivery (adjusted odds ratio: 3.17, 95% confidence interval: 1.23–8.20, p = 0.017) were independent factors associated with poor Propess efficacy. Parity, pre-pregnancy body mass index, body mass index at delivery, and indications for labor induction were not associated with insufficient cervical ripening.
Conclusions: In our study, older maternal age and early-term delivery were independent predictors of insufficient cervical ripening with Propess. More effective delivery management can be achieved by considering induction protocols tailored to individual maternal factors for patients with factors associated with poor Propess efficacy.

Introduction

Patients with unfavorable cervical conditions require cervical ripening before labor induction to increase the likelihood of vaginal delivery and reduce the duration of induction [1]. This procedure is performed using pharmacological methods, such as prostaglandin administration, or mechanical methods, such as inserting a balloon catheter [2].

Dinoprostone is a slow-release vaginal insert (Propess®, Ferring, Saint-Prex, Switzerland) containing 10 mg of prostaglandin E2 that promotes cervical ripening and uterine contraction. It is relatively easy to adjust, since the retrieval system allows the device to be easily removed at the onset of labor or when complications arise [3]. Thus, it is often used to induce labor. Some factors favoring the efficacy of Propess are multiparity and a high Bishop score before insertion [4,5]. However, in some cases, insufficient cervical ripening occurs with Propess administration, and few reports have investigated the factors behind poor efficacy. More effective cervical ripening procedures can be considered by identifying the characteristics of pregnant women less likely to respond to Propess treatment. Therefore, in this study, we aimed to assess the factors associated with ineffective cervical ripening when using Propess.

Materials and methods

Study design, participants, and ethics

This retrospective cohort study was conducted at a single perinatal medical center between September 2021 and January 2023. Clinical data on maternal characteristics and delivery outcomes

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were obtained from hospital records. The study was approved by the Ethics Committee of Nippon Medical School Musashi Kosugi Hospital, and informed consent was obtained from all participants prior to their inclusion in the study (approval number: 693-5-3, June 9, 2023).

The inclusion criteria for this study were patients with (i) singleton pregnancy, (ii) cephalic position of the fetus, (iii) gestational age between 37 and 41 weeks, and (iv) Bishop score at the beginning of induction ≤6. The exclusion criteria were (i) hypersensitivity to dinoprostone or its components, (ii) cases in which nonreassuring fetal heart rate (NRFHR) or uterine hyperstimulation (defined as more than five contractions in 10 min averaged over a 30-min period) required Propess extraction prior to successful cervical ripening, and (iii) patients with symptoms of possible side effects of Propess.

Data collection and definitions

The following maternal data and primary reason for induction were compiled from each patient's clinical records: gestational age at delivery, maternal age, body mass index (BMI) at pre-pregnancy and delivery, parity, and maternal perinatal complications such as hypertensive disorder of pregnancy (HDP), gestational diabetes mellitus, fetal growth restriction (FGR), and oligohydramnios. HDP was characterized by elevated blood pressure ≥140/90 mmHg in pregnant women. FGR was operationally defined as a condition in which the estimated fetal weight falls below 1.5 standard deviations of the mean.

Labor induction protocol

The labor induction protocol was implemented according to the following procedure. Upon admission, medical professionals in the delivery room conducted internal examinations to evaluate each patient's Bishop score. Physicians recommended Propess as a suitable intervention when a Bishop score ≤6 was observed during the examination. After obtaining the patient's consent, the medication was inserted into the posterior vaginal fornix at approximately 10:00 a.m. The duration for which Propess was left in place ranged between 9 and 12 h unless unforeseen circumstances necessitated its removal. The patients were reevaluated using internal examinations at 8 a.m. the following morning if no signs of labor onset occurred overnight. Alternative methods such as oxytocin administration and instrumental cervical dilatation were considered for additional induction measures if labor and sufficient cervical ripening failed to be initiated by that point. Additionally, cases involving NRFHR, labor initiation, uterine tachysystole, hypersensitivity reaction, or spontaneous rupture of membranes prompted Propess removal.

For cases in which cervical ripening did not progress, a Bishop score ≤6 on the morning after Propess administration was classified as insufficient cervical ripening. On the other hand, a Bishop score >6 was classified as sufficient cervical ripening. Patients who went into labor and had a vaginal delivery by the morning of the next day were also defined as having sufficient cervical ripening. Deliveries were classified based on the gestational week as early-term (37–38 weeks), full-term (39–40 weeks), or late-term (≥41 weeks) for comparison. Bishop scores were classified into two groups for comparison: Bishop scores ≤1 and ≥ 2. The outcomes were factors associated with insufficient cervical ripening.

Statistical analysis

Quantitative data were evaluated for normal distribution (Shapiro–Wilk test). The age was compared using Student's t-test in two groups, and BMI was compared using the Mann–Whitney U test. Qualitative data were analyzed using the chi-squared test, and p-values <0.05 were considered statistically significant. Multivariate logistic regression analysis was performed using variables that were significantly different in the univariate analysis. All data were analyzed using SPSS (version 29.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics and clinical background

There were 1352 deliveries during the study period, 114 of them involved labor induction with Propess. A total of 103 patients were included in the final analysis after excluding 11 patients with NRFHR (n = 7), uterine tachycardia (n = 3), and symptoms of possible Propess side effects (n = 1). The patients were all females and managed according to our protocol. The average insertion time was 10.3 h, and the average post-extraction time was 12.4 h. Forty-nine females met the definition of insufficient cervical ripening, and 54 were in the sufficient cervical ripening group. Analyses were performed for both groups (Fig. 1).

The most common indication for induction was post-term pregnancy (21.4%), followed by pregestational/gestational diabetes (17.5%), oligohydramnios (15.5%), HDP (14.6%), and premature membrane rupture (12.6%). Other indications included FGR (8.7%) and the patient's wishes. Propess was removed in 49 patients (47%) due to labor onset (n = 33), spontaneous rupture of the membranes (n = 10), and spontaneous dropout (n = 6).

Factors predicting insufficient cervical ripening with Propess

Table 1 shows that the factors associated with increased insufficient cervical ripening were maternal age ≥35 years, early-term delivery, and Bishop scores at insertion ≤1 ($p = 0.001$, $p < 0.002$, and $p = 0.035$, respectively). No significant differences in parity and BMI at pre-pregnancy or delivery were observed. Multivariate logistic regression identified maternal age ≥35 years (adjusted OR: 3.08, 95% CI: 1.29–7.36 $p = 0.011$) and early-term delivery (adjusted OR: 3.17, 95% CI: 1.23–8.20, $p = 0.017$) as independent predictors of insufficient cervical ripening (Table 2).

Delivery outcomes in the two groups

The delivery outcomes are shown in Supplemental Table 1. The insufficient group had significantly more cesarean sections than the sufficient group ($p < 0.001$).

Discussion

This study showed that early-term delivery (gestational age between 37 and 38 weeks) and maternal age ≥35 years were independent factors associated with poor Propess efficacy. Multiparity and Bishop scores ≤1 were not associated with poor Propess efficacy.

This study found that maternal age ≥35 years was associated with poor Propess efficacy. One previous study reported that maternal age ≥30 years, nulliparity, and maternal obesity were factors associated with insufficient cervical ripening after administering prostaglandin E2 vaginal tablets [6]. Another previous study examining labor induction and maternal age reported increased cesarean sections when the maternal age was ≥35 years for nulliparous females and ≥40 years for term women [7]. The present study showed that the effectiveness of Propess for cervical ripening may not be fully realized in older pregnancies because of

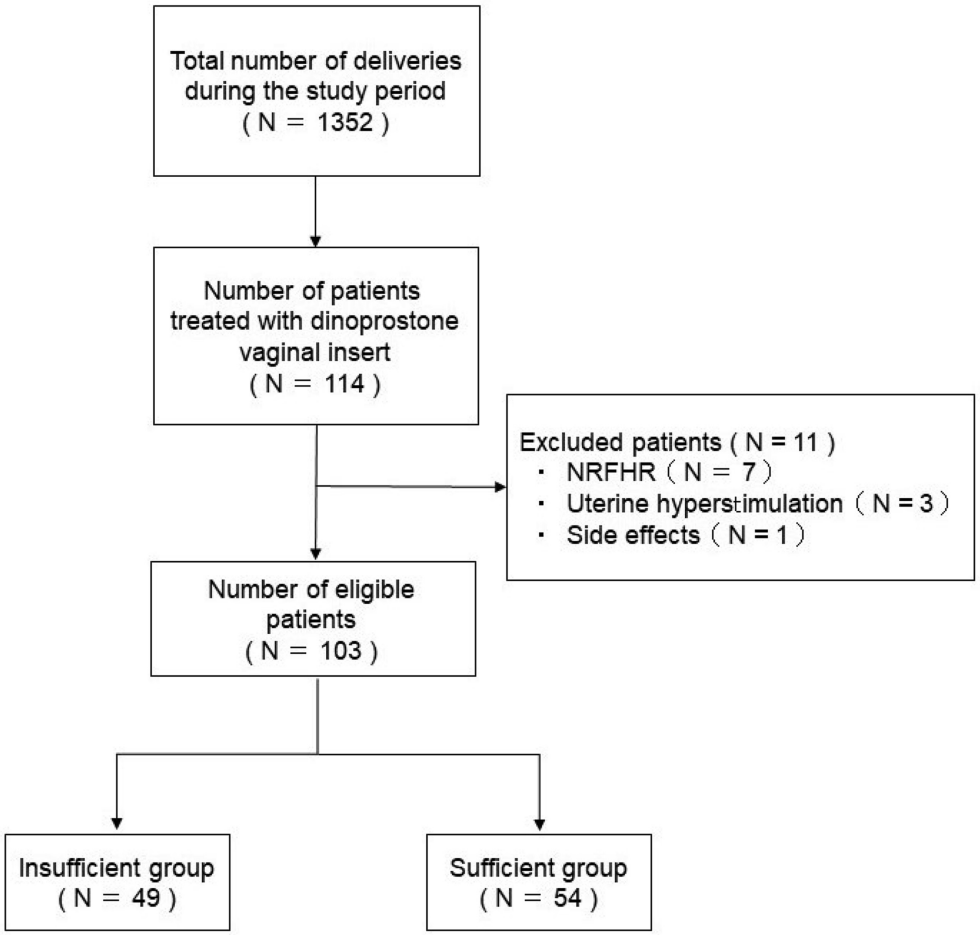

Fig. 1. Study flow chart.

Table 1
Characteristics of the study groups.

		Insufficient group (N = 49)	Sufficient group (N = 54)	Total, N	p-value
Maternal age (years), mean ± SD		35.4 ± 4.64	32.5 ± 4.64		**0.002**
Maternal age ≥35 years, N (%)		30 (61.2)	16 (29.6)	46 (44.7)	**0.001**
BMI at pre-pregnancy, medians [interquartile ranges]		21.6 [20.3–23.6]	21 [19.2–23.3]		0.197
BMI at deliverly, medians [interquartile ranges]		25.9 [24.0–28.1]	24.9 [23.4–27.8]		0.216
Multiparity, N (%)		11 (22.4)	12 (22.2)	23 (22.3)	0.978
Gestational age at induction, N (%)	Early-term	25 (51.0)	10 (18.5)	35 (34.0)	**<0.001**
	Full-term	15 (30.6)	31 (57.4)	46 (44.7)	0.006
	Late-term	9 (18.4)	13 (24.1)	22 (21.4)	0.48
Primary reason for induction, N (%)	GDM	12 (24.5)	6 (11.1)	18 (17.5)	0.074
	Oligohydramnios	6 (12.2)	10 (18.5)	16 (15.5)	0.38
	HDP	10 (20.4)	5 (9.3)	15 (14.6)	0.109
	Premature rupture of membranes	3 (6.1%)	10 (18.5%)	13 (12.6)	0.059
	Fetal growth restriction	7 (14.3%)	2 (3.7%)	9 (8.7)	0.082
Bishop score at insertion ≤1, N (%)		17 (34.7%)	9 (16.7%)	26 (25.2)	**0.035**

BMI: body mass index, Early-term: 37 0/7–38 6/7 weeks of gestation, Full-term: 39 0/7–40 6/7 weeks of gestation, Late-term: 41 0/7–42 6/7 weeks of gestation, GDM: gestational diabetes mellitus, HDP: hypertensive disorders of pregnancy, SD: standard deviation.
Bold values represent $p < 0.05$.

Table 2
Multivariate analysis for insufficient cervical ripening by Propess.

	Adjusted odds ratio (95% CI)	p-value
Maternal age ≥35 years	3.082 (1.291–7.358)	**0.011**
Early-term	3.169 (1.225–8.200)	**0.017**
Bishop score at insertion ≤1	1.969 (0.702–5.523)	0.198

Bold values represent $p < 0.05$.
CI, confidence interval.

the association between advanced maternal age and ineffective cervical ripening.

Furthermore, this study showed that early-term delivery between 37 and 38 weeks contributed to poor Propess efficacy. Word et al. reported that biochemical events progressively accelerate cervical ripening depending on the gestational age [8]. They suggested that cytological changes occurred even before the Bishop score changed; this supported the possibility that gestational age was a stronger factor associated with cervical ripening [8].

Multiparity was not associated with poor Propess efficacy in the present study. While some previous studies indicate that multiparity favors the cervical ripening effect of Propess [4,9], it has also been reported to be negatively correlated with Propess efficacy [10]. Although the success rate of vaginal delivery after labor onset was significantly higher in multiparous women [11], no significant difference in the rate of progression was observed during the latent period of labor [12]. While it is plausible that serum prostaglandin levels in nulliparous women could be a contributing factor compared to those in multiparous women [13], the precise impact of parity on cervical ripening remains incompletely understood. Therefore, future research is required on the association between parity and poor Propess efficacy.

Interestingly, the Bishop score was not a statistically significant variable in the multivariate analysis in the present study. One previous study demonstrated that unfavorable Bishop scores at admission in nulliparous women at term with a singleton pregnancy indicated an increased risk of cesarean delivery during medical and elective labor induction [14]. It is reasonable to infer that a higher Bishop score at admission is linked to the natural biochemical and structural changes in the cervix that occur before the spontaneous onset of delivery. Therefore, increasing the Bishop score enhances the likelihood of successful cervical ripening. Previous reports on internal examination findings before Propess device insertion have not provided criteria for consistent Bishop scores. For example, Hiersch et al. found that increased cervical dilation was associated with successful cervical ripening of Propess, but their study compared the closure of the cervix to that of others [10]. In contrast, Daykan et al. reported that the Bishop score on admission did not predict successful maturation. They utilized a protocol in which Propess was inserted for up to 24 h [4]. The present study examined Bishop scores at admission $\leq$1, which suggests a lack of sufficient cervical ripening. Consequently, the univariate analysis showed a significant difference, but the multivariate analysis results showed that it was not an independent factor. These results suggest that gestational and maternal age are strong risk factors for cervical ripening.

Considering these points mentioned above, induction methods appropriate for the maternal background could allow for more effective delivery management. In addition to prostaglandins, other methods of inducing labor include mechanical dilation, uterine contractions, and artificial rupture of membranes. The factors related to poor efficacy identified in this study are often cited as failure factors not only for Propess but also for mechanical cervical dilation and labor induction with other agents [7,15]. Therefore, patients with these factors may also often experience difficulty with other induction methods. Tonouchi et al. found no difference in the rate of vaginal delivery during early-term induction compared with mechanical dilation [16]. However, the study showed that more deliveries occurred within 24 h in the Propess group [16]. Additionally, a clinical trial comparing the effect of instrumental cervical dilation and Propess on cervical ripening in cases of poor cervical ripening showed that instrumental cervical dilation was more effective when the cervical opening was 1–3 cm, while Propess was more effective when the opening was 3–6 cm [17]. This method may need to be modified for women with factors associated with poor Propess efficacy. Imai et al. reported that vaginal bleeding at the time of insertion potentiates the effect of cervical ripening. They considered that changes in vaginal pH due to bleeding might increase the release of dinoprostone, contributing to the successful cervical ripening after Propess administration [5]. Therefore, the utilization of mechanical dilation before a Propess procedure in cases with maternal factors, such as insufficient cervical ripening in early-term delivery and older patients, might be beneficial. A future prospective intervention trial in women with poor Propess efficacy would be helpful.

Regarding delivery outcomes, there was a significant difference in cesarean section rates between the insufficient and sufficient groups. It was suggested that unsuccessful cervical ripening with Propess leads to cesarean section. An anteroposterior cohort study demonstrated that the success rate of induced delivery depends on the status of cervical ripening, and poor cervical ripening increases the cesarean section rate [18]. In this light, the results of this study are valid. In other words, understanding the factors that contribute to poor cervical ripening will ultimately lead to more successful labor induction.

This study had two limitations. First, this was a single-center retrospective study, which means that the number of cases was limited, and the study was subject to bias. However, all women were managed using the same criteria because a structured protocol was used to induce labor with Propess; this attenuated bias due to different management approaches. A future prospective study examining methods of inducing labor in women with factors related to poor Propess efficacy, for example, by comparing Propess with other methods of labor induction, such as mechanical cervical ripening, should be considered. Second, this study covered labor induction for various indications. A previous study on oligohydramnios reported a difference in the success rate of cervical ripening based on maternal age and Bishop scores [19]. Another study on FGR reported significantly more successful vaginal deliveries in multiparity and high Bishop scores [20]. Although each indication needs to be separately examined, this is the first report examining factors associated with poor Propess efficacy in all Japanese cases with indications for Propess administration.

In conclusion, this study clearly showed that maternal age $\geq$35 years and early-term delivery are independent factors associated with insufficient cervical ripening. These findings suggest that more effective delivery management might be achieved by considering induction protocols tailored to the maternal background if the maternal background predicts poor Propess efficacy.

Conflicts of interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjog.2024.05.026.

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Original Article

Noninvasive prenatal testing (NIPT) results are less accurate the later applied during pregnancy

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ABSTRACT

Objective: Noninvasive prenatal testing (NIPT) has been introduced in prenatal genetics, recently. Even though it is connected with biological, technical, medical and ethical issues also reviewed here, it is meanwhile applied as a standard screening test. One of the obvious, but yet not further reviewed peculiarities of NIPT is that the reported false positives rates are variant, specifically in European, compared with Chinese publications.

Materials and methods: Here the only 15 suited studies on >600,000 cases were identified in which at least average pregnancy age was reported for the time NIPT was done.

Results and conclusion: It could be shown, that NIPT is done in China in later weeks of gestation, than in other countries. Besides, here for the first time it is highlighted that false positive NIPT results are less frequent, the earlier the screening is performed. Most likely this is related to two biological phenomena: loss of trisomic pregnancies and preferential survival of fetuses which underwent trisomic rescue, however, with major trisomic populations in placenta. This yet not considered aspect needs to be kept in mind especially in late stage high risk pregnancies.

Introduction

Noninvasive prenatal testing (NIPT) has been implemented as a new prenatal screening tool during the last 10–15 years worldwide [1,2]. Together with ultrasound imaging [3], NIPT promises risk-free information on the well-being and genetics of an unborn child. Even though the risk of invasive diagnostics dropped to 0.01–0.05% [1], NIPT became widely applied, not considering its principal problems.

The latter are of biological, technical, medical and ethical nature, as summarized recently [1,4].

The most important biological issue is to understand that in NIPT no "free fetal DNA = cffDNA" is studied, but the in literature falsie labelled cffDNA is indeed derived from placenta [1]. Furthermore, in a certain part of pregnancies there is a feto-placental discordance concerning genetics of both tissues. Thus, if a placenta has a trisomy 21 (T21) the fetus can have only normal cells with 46 chromosomes, because a so-called trisomic rescue took place in the blastocyst stage. This kind of event is not the only, but the most frequent reason for a false positive NIPT-result. Other possibilities or a false positive NIPT can be e.g. a vanishing twin or a maternal malignancy [1,4].

Other biological issues influencing the NIPT result are the fact that 'cffDNA' concentration may be too low in serum of an adipose pregnant women, leading to a no-call result, or that instead of a sex chromosome aberration (SCA) of the placenta NIPT indeed detects an SCA of the pregnant woman herself [1,4].

Technical issues to be considered are that NIPT is based on next generation sequencing (NGS), and can be able to detect a triploidy if the single nucleotide polymorphisms (SNP) based NGS platform is used. However, it is very difficult for the medical doctor or the reader of scientific literature to distinguish which NIPT platform was used, and in many cases besides which copy number variants were accessed by the individual tests. Most scientific papers just refer in title and abstract that NIPT was done, and technical details are scarce, and/or NIPT-target regions are only mentioned in the text of the publication [1,4].

Medical challenges of offering an NIPT start with the problem how to make sure that an informed consent has been achieved with the pregnant woman or couple, due to complexity of the approach, and the low probability to obtain a positive NIPT result. NIPT guidelines request the medical doctor to offer pre- and post-NIPT genetic counselling [5]. However, practical experiences of patients [6] suggest that such informed counselling may easily fail, due to different reasons.

With the latter point already ethical issues of NIPT are touched, as how can a test be offered without being sure the couple

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understood all implications and what a positive or negative NIPT result really means [7]? In addition, ethical issues raised in connection with NIPT are coming from patient support groups [8].

In a previous work [4] a meta-analyses was done on >750,000 NIPT results, were relatively high false positive rates were summarized from 25 studies. 15 of the 25 studies were from China, while the remainder were performed in USA, Europe, Korea and Japan. Already then, a discrepancy concerning false positive rates of NIPT results in Chinese papers and reports from other countries were noticed, but not further followed up. Here 15 suited publications on >600,000 cases from China, Italy, Japan, Netherlands, and Russia were (re-)reviewed [9–23]. Their closer analysis revealed that there is an influence on false positive rates of the time when NIPT is performed during course of pregnancy. These results are presented here.

Materials and methods

A search in Pubmed was done for "NIPT" and "noninvasive prenatal testing"; of the >1200 retrieved papers, only publications were included, which fulfilled following criteria:

- Data provided on the average week of gestation when NIPT was performed,
- Article available in English,
- NIPT done in >5000 cases peer publication,
- Trisomy 13 (T13), 18 (T18) and 21 (T21) were tested, and
- If RATs (= rare autosomal trisomies) and SCAs were additionally tested, also this data was included.

In Table 1, 15 studies fulfilling these criteria are listed: nine came from China [14–17,19–23], two from Japan [11,12] and the

Table 1
Included are publications (Ref. = references), which fulfilled following criteria: NIPT done in >5000 cases; Trisomy 13 (T13), 18 (T18) and 21 (T21) are tested - if RATs (= rare autosomal trisomies) and SCAs (sex chromosome aberrations) are tested, also this data is welcome; numbers are given for NIPT-positive cases verified with a second approach; average number is given for week of gestation (w.o.g.); article available in English.

Ref. Country	w.o.g.	T13		T18		T21		SCA		RAT		NIPT cases	NIPT + cases	NIPT + cases checked	NIPT + cases verified
		all +	real +	all +	real +	all +	real +	all +	real +	all +	real +				
9. Netherlands	11.9	55	31	49	48	239	230	n.d.	n.d.	101	10	73,239	444	444	135
10. Italy	12.25	27	22	62	56	247	245	117	99	n.d.	n.d.	36,456	501	453	422
11. Japan	13.2	55	29	37	19	717	708	n.d.	n.d.	n.d.	n.d.	43,133	809	809	755
12. Japan	13.4	44	28	128	106	289	279	n.d.	n.d.	n.d.	n.d.	30,613	545	461	413
13. Russia	14	12	7	40	38	126	124	40	19	24	3	12,345	258	254	198
14. China	15.5	21	7	29	19	74	60	137	80	n.d.	n.d.	42,894	261	261	162
15. China	16	18	5	53	36	123	112	n.d.	n.d.	n.d.	n.d.	22,343	237	194	152
16. China	16.3	38	7	70	25	164	107	360	113	288	54	68,763	920	920	564
17. China	16.3	28	6	61	19	196	125	316	68	90	5	41,819	609	439	223
18. Italy	16.5	3	2	7	5	62	58	13	8	n.d.	n.d.	7108	85	85	73
19. China	16.5	33	15	76	50	276	250	410	266	n.d.	n.d.	89,366	795	556	342
20. China	16.83	5	5	12	9	49	46	42	18	15	2	14,574	123	123	77
21. China	17.3	41	8	101	66	327	262	295	79	92	1	57,204	856	669	416
22. China	18	15	7	36	25	113	95	143	61	n.d.	n.d.	31,515	434	307	188
23. China	19	28	4	27	13	125	105	218	76	n.d.	n.d.	40,311	468	398	198
Overall	-	**423**	**183**	**788**	**534**	**3127**	**2806**	**2091**	**887**	**610**	**75**	**611,683**	**7345**	**6373**	**4318**

Table 2
This table summarized the 15 studies from Table 1 according to pregnancy age. Data from this Table is used to set up Fig. 1.

Ref.	w.o.g.	T13		T18		T21		SCA		RAT		NIPT cases	NIPT + cases	NIPT + cases checked	NIPT + cases verified
		all +	real +	all +	real +	all +	real +	all +	real +	all +	real +				
9–10	12	82	53	111	104	486	475	117	99	101	10	109,695	945	897	557
11–12	13.3	99	57	165	125	1006	987	0	0	0	0	73,746	1354	1270	1168
13	14	12	7	40	38	126	124	40	19	24	3	12,345	258	254	198
14	15.5	21	7	29	19	74	60	137	80	n.d.	n.d.	42,894	261	261	162
15–19	16.3	120	35	267	135	821	652	1099	455	378	59	229,399	2646	2194	1354
20–21	17	46	13	113	75	376	308	337	97	107	3	71,778	979	792	493
22	18	15	7	36	25	113	95	143	61	n.d.	n.d.	31,515	434	307	188
23	19	28	4	27	13	125	105	218	76	n.d.	n.d.	40,311	468	398	198
Overall	-	**423**	**183**	**788**	**534**	**3127**	**2806**	**2091**	**887**	**610**	**75**	**611,683**	**7345**	**6373**	**4318**

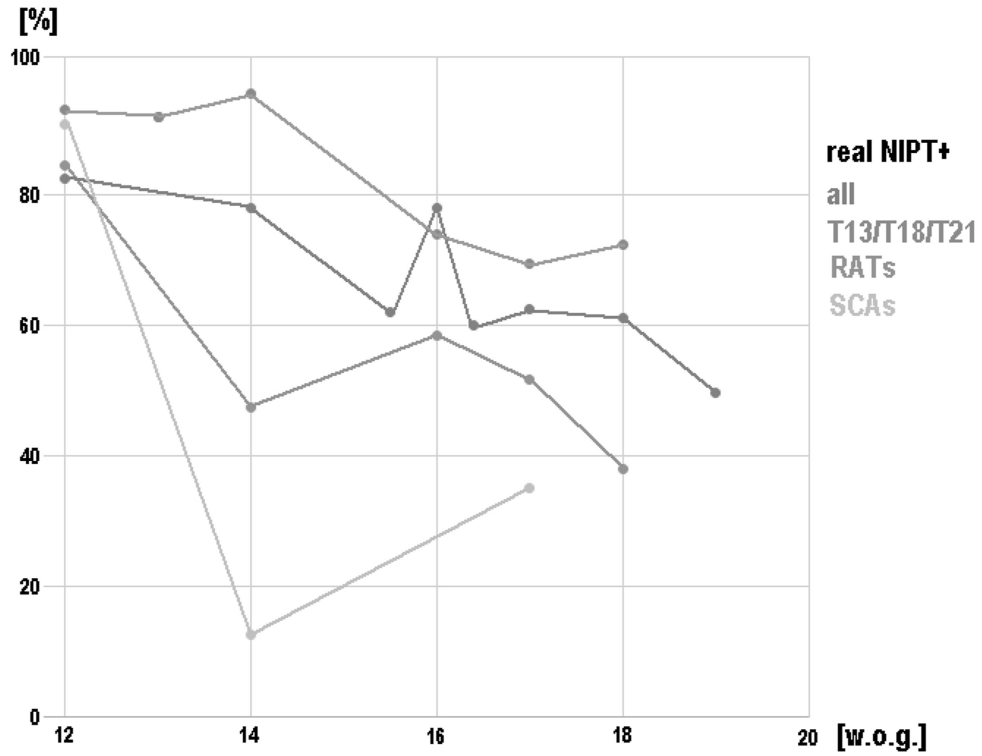

Fig. 1. The relation of real NIPT positive (NIPT+) cases to all by a second approach tested NIPT + cases from Table 2 is shown here: with respect to the pregnancy age. In early (~12th) weeks of gestation (w.o.g.) the false positive rate is only around 8–18% while it is up to over 60% in 17th w. o.g.

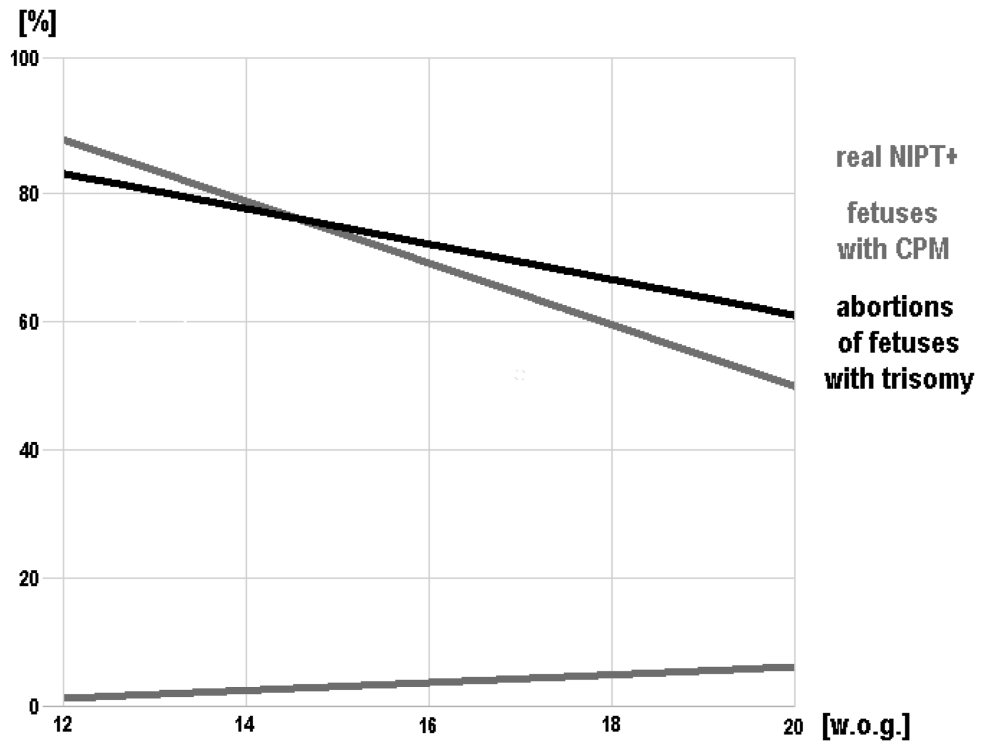

Fig. 2. Here the overall tendency of decreasing real NIPT + cases between 12th and 20th w. o.g. is shown in red. It is put in relation to the loss of trisomies between 12th and 20th w. o.g. according to Cavadino and Morris [24] shown as black line. The grey line is showing the fetuses with confined placental mosaic, which tend to get more in relation to the fetuses with trisomy (in both, fetus and placenta).

remainder four from Europe (Netherlands [9], Italy [10,18] and Russia [13]). Overall, 611,683 cases were collected, and 7345 cases were NIPT positive for one of the tested conditions. Overall, only 6373 of those cases (86.8%) were confirmed by a second test, in contracts to what is recommended in NIPT-guidelines [5]. Thereof only 4318 = 67.8% were real-positive and the remainder one third was false positive (Tables 1 and 2).

Results

False positive NIPTs are less frequent, the earlier the screening is performed. In Table 2, the data from Table 1 was cumulated according to the average gestational week the NIPT screening was performed, and the results are visualized in Fig. 1. Overall, there is a clear tendency that NIPT done around 12th w.o.g. has with ~8%–~18% the lowest false positive rates for T13, T18 and T21, SCAs and RATs. The further the pregnancy proceeds, the less reliable the test is: then the false positive rate rises to 25% to >60% after 17th w.o.g. The values being not on line with the general tendencies (like those for RATs and SCAs in w.o.g. 14 or for "all" in w.o.g. 16) are most likely due to low case numbers.

Biologically this yet not considered observation can be explained by following facts (see Fig. 2): in early pregnancies trisomies of placenta, as detected by NIPT are in most cases also present in the corresponding fetuses. The later the stage of pregnancies the more likely is a survival of only those fetuses with a rescued trisomy. As shown schematically in Fig. 2, the number of real positive NIPT results decreases while the number of cases with a normal chromosome content in the fetus and still an abnormal one in placenta increases relatively with pregnancy age. At the same time the surviving fetuses with a chromosomal imbalance decreases [24].

Discussion

The presented data highlights for the first time that false positive rates of NIPT screening are dependent from pregnancy age. In addition, an explanation for this observation is provided. This data needs to be considered when NIPT is offered. Especially in late stage high risk pregnancies the usefulness of NIPT is unclear.

Ethical background to this study

This is a study based on published data. So no ethical board statement was necessary.

Conflicts of interest

No COI to declare.

Funding statement

No funding received for this study.

Data availability statement

All data is included in this paper or in References referred to.

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Original Article

Evaluation of atherogenic indices in patients with endometrioma: A case-control study

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ABSTRACT

Objective: To evaluate the cardiovascular risk status of patients with endometriosis using serum lipid parameters and atherogenic indices.
Materials and methods: The study was retrospective, single-centric, case-control study, involving a total of 190 women, including 95 cases and 95 control groups. Blood parameters, inflammatory markers as serum pan-immune-inflammation value, systemic immune-inflammation index, systemical inflammation-response index, and the atherogenic indices as Atherogenic Index of Plasma (AIP), Castelli Risk Index I and II (CRI-I and II), and the Atherogenic Coefficient (AC) were calculated.
Results: Triglyceride (TG) levels among serum lipid parameters (103.09 ± 54.17 vs 77.52 ± 23.37, $p < 0.001$) and Atherogenic Index of Plasma (AIP) values (0.25 ± 0.24 vs −0.13 ± 0.19, $p < 0.001$) were significantly higher in endometriosis patients than in the control group. Patients with endometriosis had 2.31 times higher high-risk AIP values (1.23–4.33, $p = 0.008$).
Conclusion: Our study indicates that patients with endometriosis are at a heightened risk for developing a proatherogenic lipid profile and an elevated atherogenic index of plasma (AIP). Given the often delayed diagnosis of endometriosis and the extended period of chronic exposure to the disease, patients should be evaluated for atherosclerotic cardiovascular diseases during clinical follow-ups.

Introduction

Endometriosis (EM) is a chronic, inflammatory, benign disease characterized by the presence of endometrial glands and stroma outside the uterine cavity. Clinically, it is associated with dysmenorrhea, dyspareunia, pelvic pain, and infertility, and is commonly seen in women of reproductive age. Although it most frequently occurs in the ovaries, it can also be found less commonly outside the pelvis, such as in the intestines, diaphragm, and pleural cavity. It is an estrogen-dependent disease that affects the hormonal structure during premenarchal, reproductive, and postmenopausal periods [1,2].

Epidemiologically, endometriosis (EM) affects 10–15% of women of reproductive age and is associated with 70% of women experiencing chronic pelvic pain [3]. A recent self-reported study conducted in Turkey, involving 15,673 women aged 18–50, reported an EM prevalence of 18.3% [4]. A multicenter study involving 1418 premenopausal women aged 18–45 from 10 countries indicated that the average duration from the onset of EM symptoms to a surgical diagnosis was 6.7 years, with the majority of this delay occurring at the primary care level. Additionally, the study found that EM significantly impacts quality of life, resulting in an average weekly loss of 10.8 h of work per woman and associated costs reaching up to $456 [5].

The development of endometriosis (EM) involves the interaction of ethnic, genetic, epigenetic, immunoregulatory, hormonal, and environmental factors. Various theories such as direct implantation, retrograde menstruation, indirect implantation, genetic basis, and in-situ transformation attempt to explain the disease's development [2]. Early menarche, short menstrual cycles, tall stature, alcohol consumption, and caffeine intake are reported to increase the risk [3].

Several recent studies have explored the relationships between various diseases associated with chronic inflammation, and atherogenic indices which are derived from serum lipids and used to estimate the risk of cardiovascular events developing based on atherosclerosis. The investigated atherogenic indices include the Atherogenic Index of Plasma (AIP), Castelli Risk Index I and II (CRI-I

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and II), and the Atherogenic Coefficient (AC) [6,7]. A meta-analysis involving 20,833 patients found that individuals with high AIP had a 1.63 times greater risk of developing coronary artery disease compared to those with low AIP. Another meta-analysis investigating the relationship between AIP and coronary artery disease indicated that, overall, AIP increased the risk by 2.10 times, with high AIP compared to low AIP increasing the risk by 2.35 times [8]. Both meta-analyses emphasized that AIP is an independent risk factor for coronary artery disease [8]. [9].

The literature includes several studies suggesting that endometriosis increases the risk of developing atherosclerosis, new-onset coronary artery disease, and cardiovascular events [10,11]. However, to our knowledge, no studies have examined the relationship between endometriosis and atherogenic indices—such as the Atherogenic Index of Plasma (AIP), Castelli Risk Index I and II (CRI-I and II), and the Atherogenic Coefficient (AC)—which are considered independent risk factors for coronary artery disease in many studies. This study aims to evaluate the activity of these atherogenic indices and serum lipid parameters as a whole, and consequently, the risk of cardiovascular events between individuals with and without endometriosis.

Materials and methods

This retrospective case control study was conducted in patients with and without endometriosis who visited a tertiary care hospital's gynecology and obstetrics clinic between September 2019 and February 2024. The study was approved by the Hospital's Ethics Committee (E2-24-6628) and included a total of 190 participants, comprising 95 cases and 95 controls, with no significant age and body mass indexes (BMI) difference between the groups. Patients over 18 years of age and diagnosed with ovarian endometriosis by clinical findings and ultrasonography were included in the study group, regardless of endometrioma size. Patients with any additional diseases were excluded from the study. Patients who are pregnant or postmenopausal, had to take any kind of medication (oral contraceptives, hormone therapy, lipid-lowering treatment exc.), were addicted to drugs, or consumed alcohol or tobacco were also excluded.

Data collection and study parameters

The demographic and laboratory data of the patients were obtained from the healthcare center's database. The laboratory values at diagnosis include serum hemoglobin (g/dL), serum leukocytes (10^9/L), neutrophils (1 0^9/L), lymphocytes (10^9/L), monocyte s (10^9/L), serum cholesterol (mg/dL), serum triglycerides (mg/dL), serum high-density lipoprotein cholesterol (HDLc) (mg/dL), and serum low-density lipoprotein cholesterol (LDLc) (mg/dL). For the diagnosis of anemia, a serum hemoglobin value below 12 g/dL for women was used as the cut-off [12]. To assess inflammation, the study utilized PIV (pan-immune-inflammation value), SII (systemic immune-inflammation index), and SIRI (systemic inflammation-response index), which are regarded as inflammatory markers in recent studies [13]. The calculation of these indices is as follows:

PIV = [neutrophil count ($\times 10^9$/L) $\times$ platelet count ($\times 10^9$/L) $\times$ monocyte count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L)]

SII = [neutrophil count ($\times 10^9$/L) $\times$ platelet count ($\times 10^9$/L)/ lymphocyte count ($\times 10^9$/L)],

SIRI = [neutrophil count ($\times 10^9$/L) $\times$ monocyte count ($\times 10^9$/L)/ lymphocyte count ($\times 10^9$/L)]

To assess cardiovascular risk levels, the atherogenic indices were calculated using the obtained serum lipid values. The atherogenic indices in our study were calculated using the following formulas:

AIP = Log (serum triglyceride/serum HDLc)

CRI-I = Serum total cholesterol/serum HDLc; CRI-II = Serum LDL cholesterol/serum HDLc, AC = NHC /serum HDLc

NHC = Serum total cholesterol-serum HDLc.

To assess cardiovascular risk, the cutoff values for atherogenic indices were determined based on previous studies. An AIP value of <0.1 was considered low risk, and a value of ≥0.1 was considered high risk. CRI-I < 4, CRI-II < 3, and AC < 2 were considered low risk [7,14].

Statistical analysis

The data in this study were analyzed using SPSS 20 (Statistical Package for Social Sciences). Descriptive statistics were presented as numbers, percentages, means, and standard deviations. The t-test was used to evaluate the significance of continuous variables between the case and control groups. The chi-square test was used for categorical variables, and risk estimates were calculated with odds ratios and 95% confidence intervals (CIs). Power analysis was performed using G*Power 3.1 [15]. With a two-tailed test, an effect size of 0.5, a type I error (α) value of 0.05, and 95 participants in both the case and control groups, the power of the study was calculated to be 92.9%. A p-value of <0.05 was considered statistically significant.

Results

A total of 190 individuals participated in this study, consisting of 95 cases and 95 controls. The case and control groups were matched in terms of age, with no significant difference between them. The characteristics of the study population are presented in Table 1.

The serum parameters of the case and control groups are shown in Table 2. There were no significant differences in serum hemogram parameters, including hemoglobin, leukocytes, neutrophils, lymphocytes, and monocytes. However, there was a statistically significant difference among serum lipid parameters. Specifically, the serum triglyceride level (103.09 ± 54.17 vs. 77.52 ± 23.37, p < 0.001) was higher in patients with endometriosis compared to the control group.

Table 3 presents the findings of atherogenic and inflammatory indices in the case and control groups. The most commonly evaluated atherogenic risk index, Atherogenic Index of Plasma (AIP), was significantly higher in patients with endometriosis compared to the control group (0.25 ± 0.24 vs. −0.13 ± 0.19, p < 0.001).

Table 1
Characteristics of the case and control groups.

Characteristics	Case	Control	p
Number of participants	95	95	
Age (year) (mean ± SD)	33.19 ± 7.57	32.95 ± 6.53	0.814
Anemia status [n (%)]			
Yes	22 (23.2)	22 (23.2)	>0.05
No	73 (76.8)	73 (76.8)	
BMI (kg/m^2) (mean ± SD)	22.50 ± 1.40	22.13 ± 1.49	0.079
Endometrioma size (mm) (mean ± SD)	55.38 ± 34.40		

SD: Standard Deviation; BMI: Body Mass Index.

Table 2
Comparison of the serum parameters between case and control groups.

Parametre	Case (mean ± SD)	Control (mean ± SD)	p
Hemoglobin (g/dL)	12.97 ± 3.02	12.64 ± 1.71	0.322
Leukocytes (10^9/L)	6.94 ± 1.51	7.14 ± 1.52	0.382
Neutrophils (10^9/L)	4.23 ± 1.23	4.28 ± 1.42	0.791
Lymphocytes (10^9/L)	2.11 ± 0.50	2.15 ± 0.57	0.642
Monocytes (10^9/L)	0.42 ± 0.47	0.38 ± 0.13	0.476
Triglycerides (mg/dl)	103.09 ± 54.17	77.52 ± 23.37	**<0.001***
Total cholesterol (mg/dl)	171.71 ± 33.18	169.30 ± 30.01	0.600
HDL (mg/dl)	52.89 ± 13.35	55.15 ± 13.04	0.239
LDL (mg/dl)	98.26 ± 27.05	98.15 ± 27.05	0.979
NHC (mg/dl)	118.82 ± 30.34	114.14 ± 28.83	0.278

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NHC: Non-high density lipoprotein cholesterol; SD: Standard deviation.
* Significant.

Table 3
Comparison of the atherogenic risk and inflammatory indices between case and control groups.

Parametre	Case (mean ± SD)	Control (mean ± SD)	P
AIP	0.25 ± 0.24	0.13 ± 0.19	**<0.001**[a,*]
CRI-I	3.39 ± 0.90	3.20 ± 0.80	0.125[a]
CRI-II	1.95 ± 0.64	1.87 ± 0.73	0.444[a]
AC	2.39 ± 0.90	2.20 ± 0.80	0.125[a]
PIV	248.70 ± 221.86	299.91 ± 468.11	0.759[b]
SII	594.13 ± 231.95	751.67 ± 1402.72	0.579[b]
SIRI	0.85 ± 0.71	0.86 ± 0.66	0.795[b]

AIP: Atherogenic index of plasma; CRI-I and II: Castelli Risk Index I and II; AC: Atherogenic coefficient; PIV: Pan Immun Inflammation Value; SII: Systemic Immune Inflammation Index; SIRI: Systemic Inflammation Response Index; SD: Standard deviation.
[a] T Test.
[b] Mann-Whitney U Test.
* Significant.

However, there were no significant differences in other atherogenic indices or inflammatory indices such as PIV, SII, and SIRI.

According to the accepted cutoff values, atherogenic index values were categorized as high and low risk, and the difference between the case and control groups is presented in Table 4. In the chi-square analysis, it was found that patients with endometriosis were significantly more likely to be in the high-risk group for AIP. Having endometriosis increased the risk of being in the high-risk group for AIP by 2.31 times (95% CI: 1.23–4.33; $p = 0.008$).

Discussion

As a result of delay in diagnosis, endometriosis which is a chronic inflammatory gynecological condition, can seriously affect the health and quality of life of women of reproductive age. The atherogenic lipid profile is associated with serious immune-mediated events associated with increased oxidative stress and systemic inflammation. Both atherosclerosis and endometriosis involve inflammatory tissue macrophages exposed to lipoproteins [16]. Endometriotic lesions outside the endometrial tissue form a dynamic structure associated with pro-inflammatory, pro-angiogenic, and endocrine signaling. Through various pathways, including B and T lymphocytes, neutrophils, macrophages, natural killer cells, dendritic cells, and pro-inflammatory cytokines such as TNF-alpha, IL-6, and IL-1 beta, they trigger humoral and cellular immunity, leading to chronic systemic inflammation [1]. This chronic systemic inflammatory state increases lipoprotein lipase activity in the endothelial wall, resulting in an increase in LDLc levels. The resultant dyslipidemic proatherogenic lipid profile contributes to the development of cardiovascular diseases stemming from atherosclerosis [17].

In our study, the case and control groups were similar in terms of age and anemia status. Upon examination of serum parameters, triglycerides were found to be significantly higher in the EM group. Although total cholesterol, LDL cholesterol, and non-HDL cholesterol were elevated in individuals with endometriosis, the differences were not statistically significant. Similarly, previous studies in the literature have highlighted the significant elevation of triglyceride levels among endometriosis patients. In a national registry-based cross-sectional study involving a total of 2389 participants investigating the relationship between endometriosis and metabolic syndrome, serum triglyceride levels were found to be higher in individuals with endometriosis compared to those without, and it was noted to be the only significant indicator in the regression model. In the study, close monitoring of serum lipid levels in patients with endometriosis was recommended [18]. In another study on endometriosis, while there was no significant difference in serum HDLc and LDLc values between the case and control groups, it was found that serum triglyceride levels were significantly higher in patients with endometriosis [19]. In a study investigating the relationship between endometriosis and subclinical atherosclerosis in 643 women, it was found that serum triglyceride, total cholesterol, and LDL cholesterol levels were significantly higher in patients with endometriosis. It was stated that endometriosis is a sex-specific cardiovascular risk factor [20].

In our study, atherogenic indices, considered as cardiovascular risk factors, were analyzed. To ensure that the inflammatory status of both groups did not act as a confounding factor in the comparison of atherogenic indices, values of inflammatory indices such as PIV, SII, and SIRI were calculated, and no significant difference was observed between the two groups. According to our results, among atherogenic indices, the Atherogenic Index of Plasma (AIP) value was found to be significantly higher in patients with endometriosis compared to those without ($p < 0.001$). When the study sample was categorized into high and low-risk categories for developing cardiovascular diseases using cut-off values previously used for these indices, endometriosis was found to significantly increase the risk of being in the high-risk group for AIP by 2.31 times. While there is limited literature directly addressing the relationship between endometriosis and atherogenic indices, studies examining its association with coronary artery disease exist. In a national-based cohort study with a 12-year follow-up involving a total of 13,988 newly diagnosed endometriosis patients, the incidence of new-onset coronary artery disease was significantly higher among endometriosis patients, with endometriosis increasing the risk by 1.52 times. In the same study, it was noted that individuals aged 20–39 years were 1.73 times more likely to develop new-onset coronary artery disease compared to other age groups [11]. Similarly, in a retrospective population-based cohort study with a total

Table 4
The relationship between atherogenic risk indices and endometrioma.

Parametre	Case n (%)	Control n (%)	p	OR	95% CI
AIP					
High	73 (76.8)	56 (58.9)	**0.008***	2.311	1.233–4.330
Low	22 (23.2)	39 (41.1)			
CRI-I					
High	23 (24.2)	18 (18.9)	0.378	1.367	0.682–2.739
Low	72 (75.8)	77 (81.1)			
CRI-II					
High	5 (5.3)	9 (9.5)	0.267	0.531	0.171–1.647
Low	90 (94.7)	86 (90.5)			
AC					
High	57 (60.0)	55 (57.9)	0.768	1.091	0.612–1.945
Low	38 (40.0)	40 (42.1)			

AIP: Atherogenic index of plasma; CRI-I and II: Castelli Risk Index I and II; AC: Atherogenic coefficient; OR:Odds Ratio; CI:Confidence Interval.
* Significant.

of 19,454 endometriosis patients and 77,816 controls with a median follow-up period of 7 years over a 12-year period, the incidence of coronary artery disease was significantly higher among endometriosis patients, with a 1.34 times increased risk [10]. In a prospective cohort study, the Nurses' Health Study, involving 116,430 women over a 20-year follow-up period, it was found that endometriosis patients were 1.52 times more likely to develop myocardial infarction, 1.91 times more likely to develop angiographically confirmed angina, and 1.62 times more likely to develop any coronary heart disease compared to those without endometriosis [21]. Although limited, some studies in the literature report similar risk of endometriosis patients for atherogenic cardiovascular diseases as the general population. In a case-control study measuring intima media thickness and distensibility coefficient in the common carotid artery, no significant difference was observed between groups, suggesting that endometriosis patients have a similar risk to the general population for developing subclinical atherosclerosis [22].

To the best of our knowledge in the literature, our study is the first to demonstrate that Atherogenic Index of Plasma (AIP) levels, considered as an independent risk factor for atherosclerotic heart disease in numerous studies, are elevated in patients with endometriosis. Consequently, patients with endometriosis are at risk of developing atherosclerotic heart disease. Additionally, since AIP is calculated from serum lipid parameters, clinicians can easily determine the risk group of endometriosis patients in clinical practice and organize the patient's treatment and follow-up accordingly. In this respect, our study proposes a more practical tool, unlike other studies that invasively detect the increased risk of atherosclerotic heart disease in endometriosis patients.

The limitations of the study include its single-center design, retrospective nature based on patient records, and relatively small sample size. Although, due to lack of data in patient records, the insulin resistance status of the participants, which is a factor that may affect the atherosclerosis status, is unknown.

In conclusion, our study demonstrates that patients with endometriosis are prone to dyslipidemia, with elevated triglyceride levels and a high risk level of Atherogenic Index of Plasma (AIP), which is considered an independent risk factor for atherosclerotic heart disease. Patients with endometriosis face a high risk of developing cardiovascular diseases associated with atherosclerosis. To prevent morbidity and mortality related to cardiovascular diseases, it is recommended that dyslipidemic status and AIP be considered in the clinical follow-up of patients exposed to endometriosis over a long period, and that those at risk be evaluated by a cardiologist.

Consent to participate (ethics)

Approval of the Ankara Bilkent City Hospital ethics committee (E2-24-6628).

Author contribution

Gamze Yilmaz: Hypothesis of the research, Design the method to achieve results, Data collecting and processing, Literature scan, Article writing, Critical examination.

Onur Acar: Design the method to achieve results, Organizing the execution of the work, Monitor its progress and take responsibility, Literature scan, Article writing, Critical examination.

Conflicts of interest

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

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Retrospective evaluation of obstetric processes in patients with Familial Mediterranean Fever's disease: The three years experience of a tertiary rheumatology clinic

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ABSTRACT

Objectives: Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease affecting both genders in reproductive age. In this study, we aimed to investigate the relation between FMF and pregnancy on both maternal and fetal aspects.
Material and methods: In this retrospective, single-center, descriptive study we analysed total of 95 pregnancies of 40 FMF patients. Clinical and demographic data were obtained from patients' records. To prevent recall bias, only the last pregnancy of each patient was evaluated for disease activity and use or revision of medications during pregnancy.
Results: The median age of the patients at diagnosis was 22 and the first pregnancy age was 26 years. The median duration of FMF at last pregnancy was 8 (0–23) years. Eight (20%) patients had at least 1 pregnancy via assisted reproductive techniques (IVF), while 34 (85%) patients had at least 1 spontaneous pregnancy. While 32 patients were in remission (80%) before pregnancy, 8 were clinically active (20%). Improvement in clinical course and attack frequency during pregnancy was observed in 23 patients (57.5%), stable course in 10 (25.0%), and worsening in 7 (17.5%). The rate of live birth was 70.0%, abortus was 28.9%, preterm labor was 8.1%, pre-eclampsia was 5.0%, and only 1 achondroplasia as congenital fetal abnormality was observed.
Conclusion: FMF did not constitute a contraindication for pregnancy. The most important obstetric problems, complications, and negative fetal outcomes in the course of pregnancy are increased IVF requirement, abortion, and cesarean rates. There is no increase in the risk of congenital malformations due to FMF itself or use of colchicine.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disease inherited with an autosomal recessive pattern and particularly affects Turkish, Arabic, Armenian, and Jewish populations [1]. Recurrent fever, serositis, arthritis-arthralgia, erysipelas-like erythema, and myalgia are the main symptoms [1]. While elevated acute phase values are expected as an indicator of the inflammatory response during the attack period, uncontrolled attacks lead to serious complications, especially amyloidosis, in the long term [2]. Clinical findings start in childhood and mostly affect patients of reproductive age.

In this study, we aimed to investigate the course, maternal and fetal outcomes of pregnant patients followed with FMF, in which our country is one of the endemic regions.

Materials and methods

In this retrospective, single-center, descriptive study the records of the patients who were diagnosed with FMF according to Tel

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Hashomer criteria [3] between 01.06.2020 and 31.03.2023 in our clinic and followed up with at least one completed or continuing pregnancy were reviewed, retrospectively. We screened the data of 1080 female FMF patients and analyzed a total of 95 pregnancies of 40 FMF patients. The demographic, clinical, and obstetric data were recorded by using a standard data form. Diagnosis and gestational age, duration of disease before pregnancy, clinical findings, treatments received, obstetric history, clinical findings during pregnancy, treatment changes before and during pregnancy, obstetric and fetal complications, and pregnancy outcomes were analyzed. To avoid repeating data and recall errors, clinical findings during pregnancy, agents used in treatment and treatment revisions were analyzed only on the last or current pregnancy. Patients with insufficient data were excluded from the study.

The study protocol was approved by the Institutional Research Ethics Committee (file number 05.05.2023/685) and no informed consent was needed according to the nature of this retrospective record-based study. No funding was received for the study.

Statistical analysis

Since only patient group data were defined, median and range values were given for quantitative data and frequencies for qualitative variables. Statistical analyses were performed using SPSS Statistics for Windows, version 28.0 (SPSS Inc., Chicago, Ill., USA).

Results

The data of a total of 95 pregnancies of 40 patients with a median age of 29 years (22–42), with at least 1 pregnancy detected during our follow-up were analyzed. The median age of symptom onset was 11 (5–30), the median age of diagnosis was 22 (5–37), and the median age at first pregnancy was 26 (19–41) years. The median duration of FMF at last pregnancy was 8 (0–23) years. While 57.7% of the patients had at least 1 FMF patient in their family, the comorbidities of the patients were as; 1 systemic lupus erythematosus, 1 chronic renal failure, 1 atypical HUS, 1 amyloidosis, 1 hypothyroidism, 1 previous cerebrovascular disease, 1 asthma, 1 epilepsy, 1 ulcerative colitis, 1 ankylosing spondylitis, 1 factor V leiden mutation carrier, 1 idiopathic thrombocytopenic purpura and 2 hypertension.

The disease and attack characteristics of the patients were given in Table 1. The attack was defined as the one or more of acute onset fever, serositis presented as abdominal pain, pleural pain, pericardial pain, arthritis, and erysypelas like erythema, lasting at least 24 h and up to 5 days. The remission state was defined as the decrease in attack frequency during pregnancy and 2 or less attack during 6 months. Stable state was defined as the similar attack frequency before and during pregnancy period. Wosening was defined as the increase in attack frequency during pregnancy and 3 or more attack during 6 months. Clinically active patients were defined as 3 or more attack in 6 months before pregnancy indicating uncontrolled FMF disease activity. While 32 patients were in remission (80%) before pregnancy, 8 patients were clinically active (20%) at the last pre-pregnancy visit. Improvement in clinical course and attack frequency during pregnancy was observed in 23 patients (57.5%), stable course in 10 patients (25.0%), and worsening in 7 patients (17.5%). The number of patients who had at least 1 attack during pregnancy was 14 (35%), and the median number of attacks during pregnancy was 2 [1–10]. Three of nine patients who were not under any colchicine during pregnancy had at least one attack (33.3), while 11 of 31 patients who used any colchicine during pregnancy had at least one attack (35.5%). The treatments received by the patients during the overall follow-up period before the last pregnancy and at the last visit before the last pregnancy were given in Table 2. Treatment revision was required in one patient during pregnancy and anakinra was added to colchicina lirca due to the high attack frequency as 9 attacks during pregnancy under 2 mg per day of colchicina lirca. She had history of one successful pregnancy and 1 abortus. The last pregnancy was completed at 38th week of gestation via cesarean section. Her comorbidities were chronic renal failure, atypical hemolytic uremic syndrome and previous attack of HELLP. The baby had no congenital abnomality or malformation.

Table-1
Clinical findings and attack characteristics of the patients during all follow-up.

Variable (n = 40)	Frequency n, %
Attack frequency (n = 35)	
2 per month	5/35 (14.3)
1 per month	9/35 (25.7)
6 per year	4/35 (11.4)
4 per year	3/35 (8.6)
3 per year	1/35 (2.8)
2 per year	3/35 (8.6)
1 per year	10/35 (28.6)
Attack duration, median, day	3 (2–7)
Fever	29 (72.5)
Peritonitis	37 (92.5)
Pleuritis	16/40 (40.0)
Pericarditis	1/40 (2.5)
Pelvic attack	9/40 (22.5)
Erysipelas like erythema	6/40 (15.0)
Artralgia/Arthritis	24/40 (60.0)
Prolonged febrile myalgia	1/40 (2.5)
Neurologic symptoms	0
Proteinuria	2/40 (5.0)
Amyloidosis	1/40 (2.5)

The obstetric histories of the patients, and maternal and fetal complications during pregnancy were given in Table 3. Eight (20%) patients had at least 1 pregnancy via assisted reproductive techniques (IVF-in vitro fertilization), while 34 (85%) patients had at least 1 spontaneous pregnancy history. According to declaration of patients, none of them underwent any surgical intervention to relieve pelvis adhesions during infertility work-up of IVF process.

Among patients who continued to use any kind of colchicine before the last pre-pregnancy visit and during pregnancy a total of 74 pregnancies of 31 patients were recorded, while a totally of 21 pregnancies of 9 patients were recorded among patients who is not under any kind of colchicine before pregnancy. Among those 9 patients, only one of them has not used colchicine in every time. Considering the extremely small size of these subgroups no comparison was performed for maternal and fetal outcomes.

While 5 out of 95 pregnancies were ongoing, 63 of 90 completed pregnancies resulted in live births (70.0%). In our study, preterm labor that occurred before 37 weeks of gestation was found with a frequency of 8.1% in 4 of the last completed pregnancies. All of these patients had used any type of colchicine during pregnancy. While at least 1 FMF attack was detected during pregnancy in three of them, the course of the disease worsened during pregnancy in two. Perinatal mortality was not detected as a result of pregnancies with or without treatment. Achondroplasia, unassociated with FMF and treatment, with FGF3 mutation in only 1 infant was found, and no other congenital anomalies were observed. Other maternal and fetal complications and detailed obstetric history are given in Table 3.

Discussion

The clinical findings of FMF are usually manifested by recurrent fever, serositis, and joint findings in childhood and pubertal period,

Table-2
Treatments received during all follow-up and last pre-pregnancy visits of the patients.

Treatment (n = 40)	Overall n, (%)	Last visit before pregnancy n, (%)
Not receiving colchicine or alternative therapy	1 (2.5)	9 (22.5)
Native colchicine (dispert)	39 (97.5)	23 (57.5)
Imported colchicine (colchicina lirca, colchicine opocalcium or colchicine seid)	9 (22.5)	8 (20.0)
Corticosteroid	0 (0)	0 (0)
Anakinra	1 (5.6)	1 (2.5)
Canakinumab	0 (0)	0

considering that attacks tend to go into remission after the fifth decade. Therefore, it is seen that the affected female patient group consists of fertile-age women [4]. The data showing that infertility and oligomenorrhea increase in FMF patients had been reported especially in the era when the number of untreated patients was high, and it was thought that there was a tendency to ovulatory dysfunction with an unclear pathogenesis in addition to intra-abdominal adhesions occurs via inflammatory reactions during attacks [5,6].

Colchicine has become the main treatment agent in not only the prevention and control of attacks but also complications, namely amyloidosis and related end-stage renal disease, with its introduction in treatment since in 1972. In particular, pelvic adhesions due to inflammation and serositis decrease with the regular use of colchicine, and it improves reproductive capacity, also [6–9]. Interleukin-1 blockade is additionally used effectively with an increasing frequency in case of resistance or inadequate response to colchicine [10,11]. Although there is safety and usage data for the use of colchicine and IL-1 blockade during pregnancy and lactation, still there is a concern about their use by rheumatology and gynecology practice [2,10,12]. Especially, considering the anti-mitotic effect of colchicine, its effect on pregnancy and fetal outcomes is still a hot topic [13].

On the other hand, uncontrolled disease activity results in many complications, especially peritoneal adhesions, amyloidosis, and end-stage renal disease [14]. Therefore, effective attack prophylaxis and treatment, prevention of unplanned pregnancies during an active stage of FMF, and giving close follow-up during pregnancy are important issues.

The duration of the disease at pregnancy, which is one of the factors that can affect the disease activity, is around 7 years in the literature, and it was similar to our data [15]. While the number of patients with at least 1 attack during pregnancy was 35% in our study, clinical improvement was found in 57.5% of the patients and clinical worsening was found in 17.5% of the patients. Quite similar to previous studies, Bodur et al. showed no attacks were detected during pregnancy in 61.4% of the patients [15]. Again, Akar et al. examined a total of 73 pregnancies and no attack was found in 62.5% of the patients, and the disease course worsened in 17.5% of the patients [16]. The median frequency of attacks during pregnancy was 2 in our study, which was similar to the literature [15]. In our study, the frequency of at least one attack was similar in pregnancies with and without colchicine, while İskender et al. found that patients who received colchicine treatment had more frequent attacks than those who did not (59.5% vs 18.2%, p = 0.012) [17].

Obstetric history was similar to previous cohort analyses and the rate of live births was reported about 65–70% in almost all studies [15,18]. The most important obstetric complications and fetal adverse outcomes in the course of pregnancy were increased IVF requirement, abortion, and cesarean section rates. There is no risk of congenital malformations from the use of FMF or colchicine. FMF itself has been associated with pelvic adhesions, subfertility, and oligomenorrhea, and the frequency of IVF is increasing in FMF patients, similar to our cohort [13].

In our study, the increase in the frequency of abortion and cesarean section was found to be higher in the FMF group compared to healthy pregnant women in previous studies. When healthy pregnant women and pregnant women with FMF disease were compared, a 15–20% increase in abortion frequency was observed in the FMF group compared to healthy pregnant women in previous studies [15,19]. While the frequency of cesarean section was found to be quite high as 63.5% in our study, it is around 15–40% even though it is found to be higher than healthy pregnant women in the literature [18,19].

The data on preterm birth are contradictory, and it was found with a frequency of 8.1% in our study. In previous studies, the presence of FMF was shown as an independent risk factor for preterm birth and was found to be 7% in the general FMF group and 59% in the colchicine group [15,18–20].

The frequency of preeclampsia was found to be similar to the literature in our study, and it did not increase in the FMF group compared to healthy individuals [18]. No evidence has been shown that FMF poses a risk for perinatal mortality and congenital fetal anomalies, and similar to our study, polyhydramnios, oligohydramnios, congenital malformations, and placental anomalies

Table-3
Obstetric history, maternal and fetal complications of the patients.

Total pregnancies, (n, %)[a]	95
Ongoing pregnancy	5
Total live births	63/90 (70.0)
Normal vaginal delivery	*23 (36.5)*
Cesarean section	*40 (63.5)*
Abortion	26/90 (28.9)
Curettage	0/90 (0)
Ectopic pregnancy	2/95 (2.1)
In vitro fertilization	8/40 (20)
Multiple pregnancies	27/40 (67.5)
Week of birth, median (range)	39 (29–41)
Maternal complications, n (%)[b]	
Threatened abortion	6/40 (15.0)
Bleeding before 20 weeks gestation	3/40 (7.5)
Placenta abruptia	0
Placenta previa	1/40 (2.5)
Preeclampsia/HELLP	2/40 (5.0)
Ovarian torsion	0 (0)
Fetal complications, n (%)	
Preterm birth[c]	4/37 (8.1)
Oligohydramnios	1/90 (2.22)
Polyhydramnios	0 (0)
Fetal chylothorax	0 (0)
Fetal distress	1/90 (1.11)
IUGR	1/90 (1.11)
Congenital anomaly (achondroplasia)	1/90 (1.11)
Perinatal mortality	0

[a] Calculation was made based on terminated pregnancies. Gravida was entered as 1 because one fetus of twin pregnancy of 1 patient was born and one fetus was terminated with abortion.

[b] Calculated over the number of patients since preeclampsia and miscarriage threat recur in recurrent pregnancies.

[c] Complications are calculated based on patients the last terminated pregnancy of 37 patients, remaining 3 had their first pregnancy which still ongoing.

were found to be around 4–5% and similar to the healthy population [17,19].

Although colchicine is a mitotic inhibitor and shows transplacental transmission, it is an agent that is used safely during pregnancy [13,20–22]. In amniocentesis studies, it has been shown that there is no increase in chromosomal anomalies or miscarriages in pregnancies that occur under the colchicine use of any of the partners [23]. Again, in patients using colchicine for any indication, live birth (around 91%), miscarriage, ectopic pregnancy, major anomaly frequencies, and postpartum growth and development retardation were found to be similar compared to healthy individuals [13,20,24]. However, preterm birth was found to be 15%, and cesarean section 24.4% more frequently than the healthy group [20]. Therefore, untreated patients seem to be at higher risk than the use of colchicine and it was thought that routine amniocentesis is not required [13].

While 22.5% of our patients were followed without any treatment during pregnancy, this rate varies between 11 and 85% in previous studies [15,16,19,20]. The data on the use of anti-IL-1 agents in pregnancy is increasing with their use in FMF and other autoinflammatory diseases, and the number of patients who are using IL-1 blockage, namely anakinra or canakinumab during an attack or in insufficient response to colchicine is increasing [10,11,25]. In our study, anakinra was used in addition to colchicine in one patient due to the increased frequency of attacks, and no maternal or fetal complications were observed.

The limitations of the study were the small sample size, restriction in a single center, and the reliability of data regarding the number of attacks and clinical findings which were based on patient statements with risk of recall bias.

Conclusion

In conclusion, in our study, it was thought that FMF did not constitute a contraindication for pregnancy. The most important obstetric problems, complications and negative fetal outcomes in the course of pregnancy are increased IVF requirement, abortion, and cesarean rates. FMF or the use of colchicine was not associated with an increase in the risk of congenital malformations. It seems important to have a planned pregnancy after achieving disease remission, if possible, and to reduce maternal and fetal risks frequent and close follow-up of pregnant patients should be advised.

Ethics committee approval

The study protocol was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (no: 03.03.2023–404).

Financial disclosure

The authors reported that they have received no financial support.

Informed consent

This is a retrospective study and informed consent was not needed.

Data availability statement

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request and all authors have access the all data.

Declaration of competing interest

No conflict of interest was declared by the authors and the study has not been presented in any platform before.

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Original Article

The clinical experience of fetoscopic repair of myelomeningocele in Taiwan: The dilemma in prenatal decision-making and first successful case

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ABSTRACT

Objective: Objective: Myelomeningocele (MMC) is the most severe type of spina bifida, with an incidence of 1.87 per 10,000 live births in Taiwan. Exposure of the lesion to amniotic fluid exacerbates neurological outcomes, while fetal surgery for MMC repair, now a routine practice, improves postnatal outcomes. However, Asian women and their families often find it difficult to accept prenatal defects, leading nearly all pregnancies with fetal MMC to opt for termination without considering fetal surgery.
Materials and methods: In Taiwan's first approved trial of fetoscopic MMC repair, we prospectively recruited 15 cases from 2020 to 2023. Final diagnoses were confirmed using MRI and ultrasound. The medical team provided non-direct consultations to discuss possible outcomes of fetal surgery with family members. For those opting for fetal surgery, we offered total percutaneous fetoscopic MMC repair.
Results: Over 30 months, 14 of 15 cases (93%) chose to terminate their pregnancies between 18 and 26 weeks of gestational age. Decision factors included potential disabilities, morbidities, economic, social, and psychological aspects. Despite supportive groups in the country, the termination rate remained high among the Chinese population. One out of the 15 cases underwent fetal surgery successfully, resulting in a 30-month-old child without motor function delays, able to walk and run naturally.
Conclusion: We initiated the first fetoscopic MMC repair in Taiwan with promising outcomes, though we faced a high termination rate here and similar situation in other Asian countries. Continuous social education through media could play a crucial role in changing perceptions and increasing acceptance of fetal surgery.

Introduction

Open spina bifida (OSB) is the most common of congenital anomalies with the prevalence of 3.4 per 10,000 live births in United States and 2.51 per 10,000 live births in Taiwan [1,2]. Myelomeningocele (MMC) is the most severe and common type of spina bifida with the incidence of 1 in 2900 live births, and also affects 1.87 per 10,000 live births in Taiwan [2,3]. MMC is characterized by protrusion of the spinal cord to the spinal canal, and it is known to cause lifelong motor and neurodevelopmental complications. This includes bowel and urinary dysfunction, hindbrain herniation, hydrocephalus, sensory and motor neurological defects [4–6]. The surgical history of spina bifida could trace from 17th century, but the surgical outcome was resulting in mortality due to immature surgical skill and lack of aseptic surgical concept. The surgical procedure was relative mature since early 20th, there are various methods of closure including primary repair, rotation and flap.

The exposure of lesion to the amniotic fluid would worsen the neurological outcome, and the fetal surgery for MMC repair improves the postnatal outcome as the routine practice nowadays

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[1,7–10]. In 2011, the Management of Myelomeningocele Study (MOMS) clinical trial was published by Adzick et al. and first proved that prenatal surgery of OSB has advantages over postnatal surgery, such as reduced need for shunting and improved motor outcomes [1]. Several studies over 10 years following were published and indicate open fetal surgery for fetal MMC closure had the improvement of neurologic outcome and long-term physical functioning benefits [3,5,7,10–13]. Later in 2017, Belfort et al. reviewed the fetoscopic applied in open neural tube defect repair and showed the fetoscopic approach was not inferior to open surgery [5,14]. Fetoscopic surgery for MMC seems to be the trend in recent years, and large scale of studies are needed to compare the outcome between prenatal open surgery and fetoscopic surgery.

Owing to the significantly benefits of prenatal surgery for MMC, our center getting the technological transfer and license of prenatal surgery of MMC from Brazil. Therefore, we began a clinical trial to recruit the fetus diagnosed as MMC referred to provide the complete decision-making to their parents. In this study, we will present the results of these parents after decision-making and first fetoscopic repair of MMC in Taiwan.

Material and methods

Participants recruitment and selection

This study was prospective design and the trial was approved by Chang Gung Medical Foundation Institutional Review Board (201800470A0) and approved by TFDA. Participants were recruited at Chang Gung Memorial Hospital between July 2020 and January 2023. The patients were diagnosed with ultrasound and MRI and consulted by our multidisciplinary team composed of fetal therapy specialist, pediatric neurosurgeon, neonatologist, and obstetrician, for the complete decision-making. Parents were eligible for the study if they met the inclusion criteria, including 20 years of age or older, open spina bifida with the upper boundaries located between T1 and S1, a gestational age of 19–28 weeks at randomization, a normal karyotype and singleton pregnancy without any combined anomalies (Fig. 1).

The exclusion criteria include multiple gestation, kyphosis >30°, cervical length <2 cm, low-lying placenta, placental abruption, history of preterm birth <37 weeks, history of incompetent cervix, alloimmunization, positive serology (HIV, hepatitis B and C), large uterine fibroids, body mass index >35 kg/m2, maternal diabetes and hypertension (or high risk of preeclampsia: first trimester screening or maternal history).

The baseline characteristic will be recorded including maternal age, gestational age of diagnosis and intervention (fetoscopic repair or termination), defect type (open or closed).

Surgery techniques and post-operative protocol

In this study, we performed fetoscopic repair using the technique from Brazil team [15]. We also granted the technological transfer via multiple live demonstrations. Surgery will be performed under general maternal–fetal anesthesia. Two 11F vascular introducers (Terumo, Tokyo, Japan) and one 5-mm balloon-tipped laparoscopic trocar (Applied Medical, Rancho Santa Margarita, CA, USA) will be placed. Partial amniotic CO2 insufflation will be performed [15]. The fetus will be positioned using standard 3.0-mm laparoscopic instruments and 5.0 mm zero-degree endoscope (Karl Storz, Tüttlingen, Germany). The neural placode will be released at the transition zone, and the skin will be further undermined to allow easy closure at the midline. The placode will be covered with a biocellulose patch (Bionext, Paraná, Brazil). The skin will be closed over the patch using a 2-0 monofilament (Quill SRS; Angiotech, Reading, PA, USA). No uterine closure devices will be placed to seal the puncture sites. Patients will be allowed to early intake after the first postoperative day and will be discharged one week later. Preoperative, postoperative, and postnatal magnetic resonance imaging will be performed to assess hindbrain herniation. Neurodevelopmental evaluation will be accessed before discharge, at 3, 6 and 12months.

Outcome measures

The primary outcome is the decision-making of the patients, including operation rate and termination rate of the patients after consultation by our team. The secondary outcomes include fetal and neonatal condition, rate of PPROM, preterm birth rate, maternal birth complication, neonatal motor function, shunt percentage, and bladder function after birth.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Categorical variables were compared using the Chi-square or Fisher exact test as appropriate. A p value (2-tailed) $\leq$0.05 was considered statistically significant.

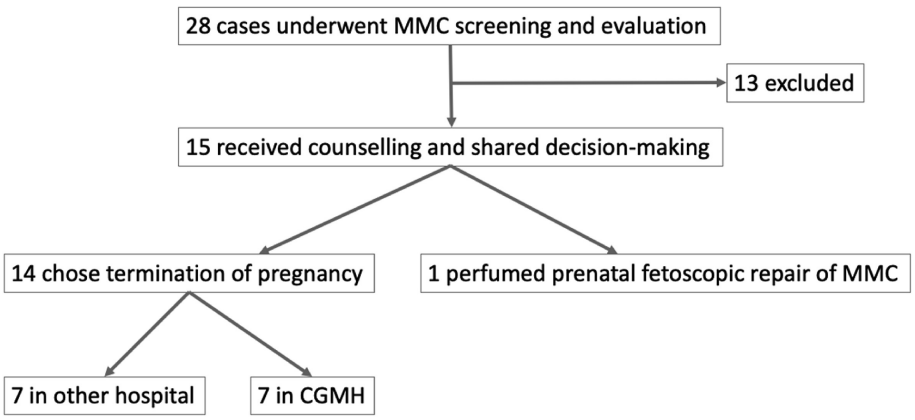

Fig. 1. Routine screening, diagnosis, and enrollment of MMC in the study. CGMH: Chang Gung Memorial Hospital.

Results

During the 30 months period, 14 out of 15 MMC cases (93%) decided to terminate the pregnancy from 18 to 26 weeks of gestational age (Fig. 1). Initially 28 case were highly suspected of prenatal MMC, but thirteen cases were excluded due to lack of definite diagnosis or close type spina bifida. All the termination cases were via vaginal delivery and half of them were done in our hospital. There are some reasons for the parents chose to termination of pregnancy. Several factors affected the decision were disabilities, morbidities, economic, social and psychological aspects. The leading concerns for parents were no-cure guarantee after birth, cost for medical care of the child, pressure from other family members, lack of similar case experience.

The first case was referred to our center at 23 weeks of gestational age due to suspected MMC. Fetal MRI and ultrasound confirmed the diagnosis. After consultation with the team including fetal medicine specialist, neural surgeon and pediatricians, they decided to having the fetoscopic repair. The surgery was performed at 27 weeks of gestational age using 3 trocars as described above (Figs. 2 and 3). The surgical time was 126 min with minimal blood loss. Postoperative antibiotics and tocolytic agents were given. She discharged 4 days after surgery without major complication. At 32 weeks for gestational age, she came to delivery room due to low abdominal pain. Emergent Cesarean section was arranged due to non-reassuring fetal heartbeat. A female baby weight 2295 gm was delivered smoothly with Apgar score 8 and 9 at 1 min and 5 min. One uterine scar can be seen during the Cesarean section due to main trocar (5 mm) insertion with spontaneously healing (Fig. 4). This girl is now 30-month-old without moto-function delay and she can walk and run naturally.

Discussion

Myelomeningocele is the most severe type of spinal bifida and it affects 1.87 per 10,000 live births in Taiwan and 3.5 per 10,000 live births in America [2], Diagnosing fetal MMC is performed by ultrasound at 18–20 weeks of gestation during the routine prenatal examination or [16], fetal magnetic resonance imaging (MRI) [17]. The infants with MMC may have lifelong motor and neurodevelopmental complications such as bowel and urinary dysfunction, hindbrain herniation, hydrocephalus, sensory and motor neurological defects [4–6]. The management of MMC had a significantly changed after the MOMS Trial. It was demonstrated

Fig. 3. Demonstration the surgical theme for fetoscopic repair of MMC.

that prenatal surgery can significantly improve the fetal outcomes, including decreasing the risk of fetal death, the need for shunting by 12 months of age, reducing the degree of hindbrain herniation associated with Chiari II malformation and improving motor function and the likelihood of independent walking compared with postnatal surgery [1]. Prenatal myelomeningocele repair can be performed by using either open or fetoscopic surgery. Joyeux et al. and Kabagambe et al. further compared the outcomes and complications between these two surgical options of myelomeningocele [18,19]. They concluded that fetoscopic repair has a lower risk of uterine thinning or dehiscence but with higher risk of preterm labor and needs of additional postnatal procedures [18,19]. Although the prenatal surgery had lots of benefits on fetal outcomes, it still had some risk of complications including chorioamniotic membrane separation, oligohydramnios, placental abruption, spontaneous rupture of membranes, and preterm delivery [20,21]. Despite prenatal surgery provides better outcomes for the patients, this method was not provided in every center considering that it is more technically demanding [22]. Except the medical problems, the families also consider several non-medical factors [23]. Ravindra et al. proposed a shared decision-making approach discussing prenatal counseling for MMC and stated that multiple legitimate treatment options should be provided, including termination, postnatal repair and prenatal surgery [24].

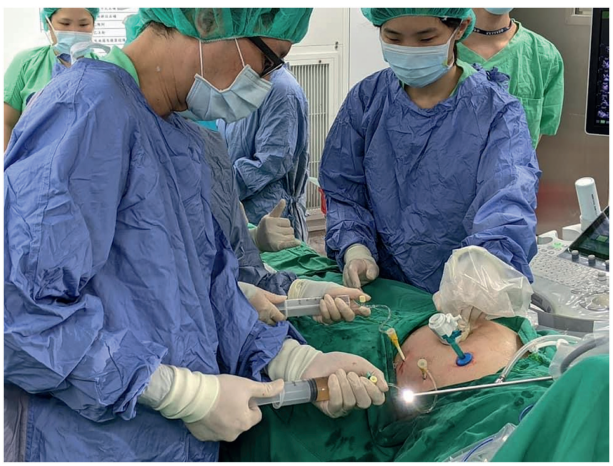

Fig. 2. Three trocars including one major 5 mm trocar (green).

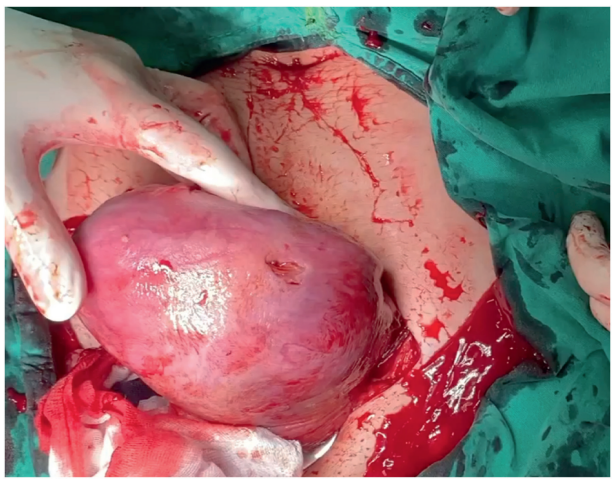

Fig. 4. A uterine scar fund during Cesarean section.

Previous studies have discussed numerous influencing factors of decision making for parents with MMC babies and the rate of prenatal surgery, postnatal surgery or termination was various due to different consideration [23,25–27]. These included maternal risks, childs' quality of life, financial conditions, religious beliefs, family values, cultural and social values, support system, socio-demographic characteristics, and medical accessibility. It is challenging to find a balance between risks and benefits of the different options. Boyd. et al. surveyed the termination rate of prenatal diagnosis of neural tube defects in Europe. Except some countries where the termination of prenatal fetal abnormally was illegal, the termination rate was ranged from 40% to 92% [28]. AlRefai et al. mentioned between the MOMS trial and their MMC surgery program, fifty one percent of the eligible patients for fetal repair chose to terminate the pregnancy. The termination rate amongst ineligible cases was sixty percent in USA [29].

Our study revealed the obstacles of low acceptance rate for prenatal surgery of MMC in Asian society. We inferred some several possible impacting factors for the current decision-making situation according to the previous studies reviewed included Asian and our clinical experience. Previous systemic review in 2018 from Blencowe et al. revealed the termination rate was three times much more in east Asia then the worldwide [30]. The result was similar with our data in Taiwan and the reasons could be the following things. First, our center had the ability for either prenatal or postnatal treatment of MMC. Although the outcome would improve after the treatment, the patients still had more residual disabilities and morbidities than unaffected individual. And these problems lead more medical, economic, social, and psychological costs [26,31]. Second, Taiwan and some other Asian societies had the severe phenomenon of sub-replacement fertility with low fertility rates. This phenomenon could cause lower acceptability for uncertainties regarding the future of their unborn child. Third, the society still consisted the discrimination and lacked of sound policies for these patients with disability in Taiwan. Last but not the least, these patients were lack of family support due to the socio-cultural values in traditional Asian families. Decisions-making can be affected by the eldership in the family, and the elder membership usually consider the children with disability as a burden. All of the reasons may complicate the counseling process and make it more difficult to promote new treatment options such as fetoscopic surgeries in Taiwan even with better outcomes.

To our knowledge, there were no previous studies reviewed the factors impacting the decision making of MMC in Asia. More and more cases were diagnosed prenatally due to high resolution ultrasound scan is routinely practice. Our data showed more than 90% of MMC cases diagnosed prenatally was terminated. Continuous social education for general people from media could be the important step. There were several limitations in our study, such as small sample size, lack of the quantified questionnaire, and the short duration of patient collected. Further large scale of studies should be performed.

In conclusion, we started the first fetoscopic repair of MMC in Taiwan with promising outcome, but we faced the high termination rate in Chinese population. Continuous social education for general people from media could be the important step in the future to help recruit more patients.

Funding

There is no funding regarding this study.

Conflicts of interest

All authors declare no conflicts of interest regarding this study.

Acknowledgements

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Case Report

First-trimester application of expanded non-invasive prenatal testing in the genetic investigation of fetal 1p36 deletion syndrome associated with a familial unbalanced reciprocal translocation of 46,XX,der(1)t(1;2) (p36.2;q37.3)dmat

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Translocation

ABSTRACT

Objective: We present first-trimester application of expanded non-invasive prenatal testing (NIPT) in the genetic investigation of fetal 1p36 deletion syndrome associated with a familial unbalanced reciprocal translocation of 46,XX,der(1)t(1;2) (p36.2;q37.3)dmat.
Case report: A 37-year-old, gravida 2, para 0, woman underwent expanded NIPT at 13 weeks of gestation because of advanced maternal age and the fear of complications of invasive procedures of prenatal diagnosis. She had experienced one spontaneous abortion. The pregnancy was conceived by *in vitro* fertilization and embryo transfer (IVF-ET) because of tubal occlusion. NIPT was positive for 1p36 deletion. At 17 weeks of gestation, she underwent amniocentesis but intrauterine fetal death occurred after amniocentesis and the pregnancy was terminated. Amniocentesis revealed a derivative chromosome 1 with an aberrant short arm terminal segment of chromosome 1. Subsequent cytogenetic analysis of parental bloods showed a karyotype of 46,XY in the father and a karyotype of 46,XX,t(1;2) (p36.2;q37.3) in the mother. The karyotype of amniocytes was 46,XX,der(1)t(1;2) (p36.2;q37.3)dmat, consistent with partial monosomy 1p (1p36.2→pter) and partial trisomy 2q (2q37.3→qter). Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed the result of arr 1p36.33p36.22 (852,863–11,303,452) × 1.0 and arr 2q37.3 (242,785,405–243,068,396) × 3.0 [GRCh 37] with a 10.451-Mb deletion of 1p36.33-p36.22 encompassing 116 OMIM genes including *RERE* and a 283-kb duplication of 2q37.3 encompassing one OMIM gene of *PDCD1*.
Conclusion: Expanded NIPT has the advantage of early detection of familial unbalanced reciprocal translocation in the fetus.

Introduction

We previously reported prenatal diagnosis of chromosome 1p36 deletion in a fetus with ventriculomegaly, ventricular septal defect and midface hypoplasia on fetal ultrasound at 20 weeks of gestation and subsequent amniocentesis revealed a karyotype of 46,XX,der(1)t(1;20) (p36.23;p12.1)dn with partial monosomy 1p

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(1p36.23→pter) and partial trisomy 20p (20p12.1→pter) [1]. Here, we present an additional case of first-trimester application of expanded non-invasive prenatal testing (NIPT) in genetic investigation of fetal 1p36 deletion syndrome associated with a familial unbalanced reciprocal translocation of 46,XX,der(1)t(1;2)(p36.2;q37.3)dmat.

Case report

A 37-year-old, gravida 2, para 0, woman underwent expanded NIPT at 13 weeks of gestation because of advanced maternal age and the fear of complications of invasive procedures of prenatal diagnosis. She had experienced one spontaneous abortion. The

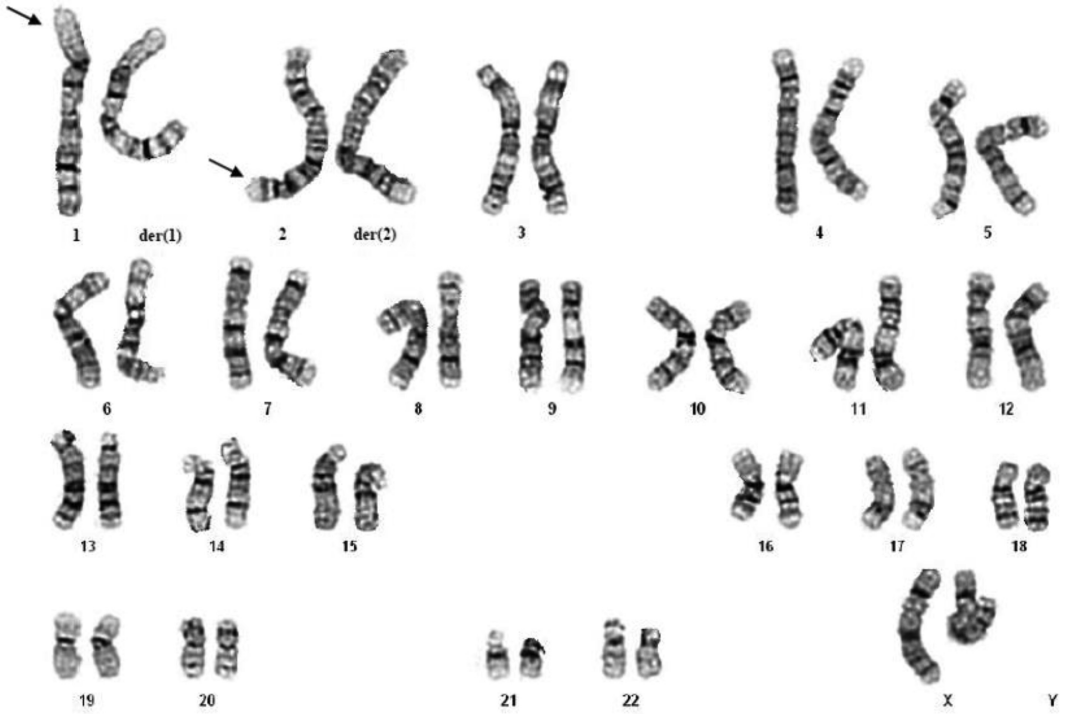

Fig. 1. A karyotype of 46,XX,t(1;2)(p36.2;q37.3) in the mother. The arrows indicate the break points.

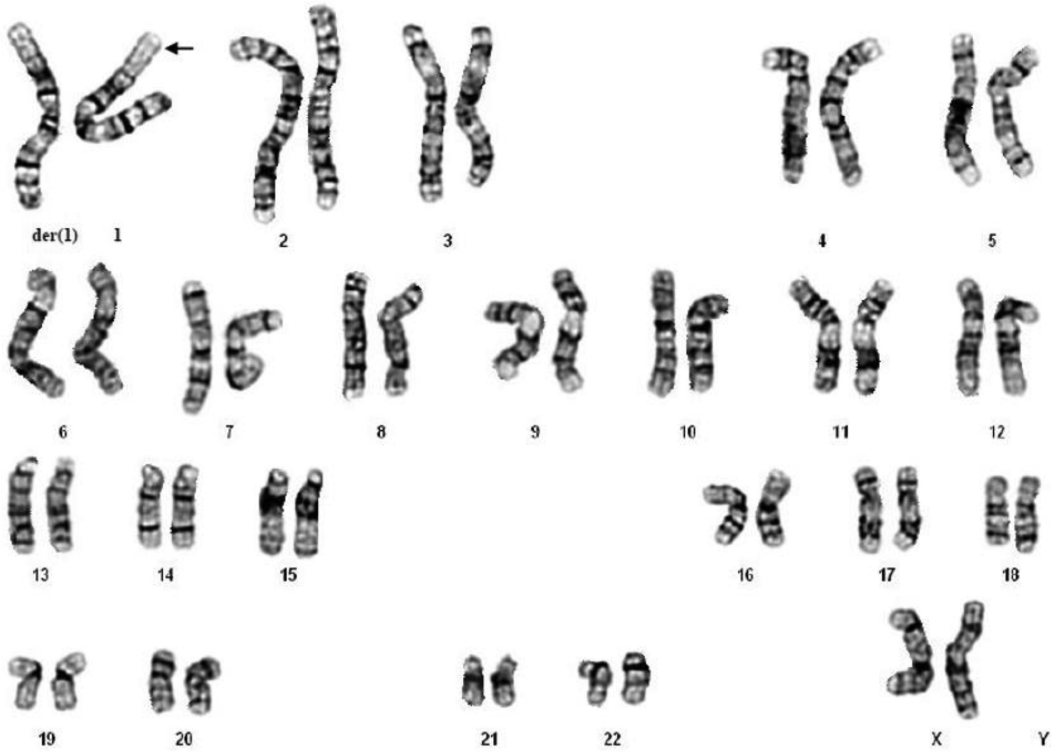

Fig. 2. A karyotype of 46,XX,der(1)t(1;2)(p36.2;q37.3)dmat in the fetus. dmat = derived from maternal origin. The arrow indicates the break point.

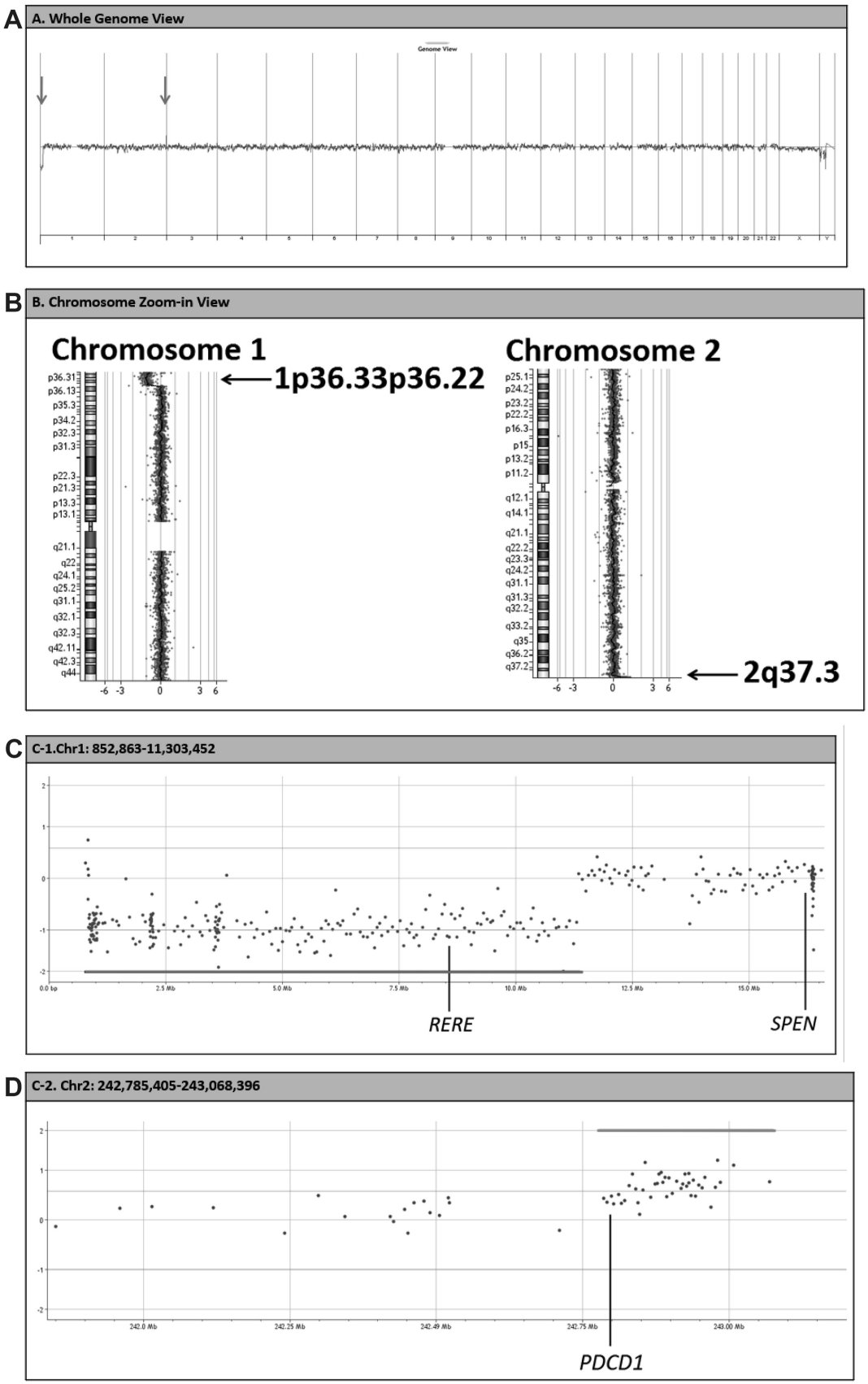

Fig. 3. (A), (B), (C) and (D) Array comparative genomic hybridization (aCGH) analysis using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) on the DNA extracted from cultured amniocytes shows the result of 1p36.33p36.22 (852,863–11,303,452) × 1.0 and arr 2q37.3 (242,785,405–243,068,396) × 3.0 [GRCh 37] with a 10.451-Mb deletion of 1p36.33-p36.22 encompassing *RERE* and a 283-kb duplication of 2q37.3 encompassing *PDCD1*.

pregnancy was conceived by *in vitro* fertilization and embryo transfer (IVF-ET) because of tubal occlusion. NIPT revealed was positive for 1p36 deletion. At 17 weeks of gestation, she underwent amniocentesis but intrauterine fetal death occurred after amniocentesis and the pregnancy was terminated. Amniocentesis revealed a derivative chromosome 1 with an aberrant short arm terminal segment of chromosome 1. Subsequent cytogenetic analysis of parental bloods showed a karyotype of 46,XY in the father and a karyotype of 46,XX,t(1;2)(p36.2;q37.3) in the mother (Fig. 1). The karyotype of amniocytes was 46,XX,der(1)t(1;2)(p36.2;q37.3)dmat (Fig. 2), consistent with partial monosomy 1p (1p36.2→pter) and partial trisomy 2q (2q37.3→qter). Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed the result of arr 1p36.33p36.22 (852,863–11,303,452) × 1.0 and arr 2q37.3 (242,785,405–243,068,396) × 3.0 [GRCh 37] with a 10.451-Mb deletion of 1p36.33-p36.22 encompassing 116 OMIM genes including *RERE* and a 283-kb duplication of 2q37.3 encompassing one OMIM gene of *PDCD1* (Fig. 3).

Discussion

Chromosome 1p36 deletion syndrome, either distal (OMIM 607862) or proximal (OMIM 619343), is the most common subtelomeric terminal deletion syndrome, and is characterized by typical craniofacial features developmental delay, intellectual disability, hypotonia, epilepsy, cardiomyopathy, congenital heart defect, brain abnormalities, hearing loss, eyes and vision problem, and short stature [1–6]. Chromosome 1p36 deletion syndrome has an estimated frequency of 1 in 5000 live births [3].

The present case had a 10.451-Mb deletion of 1p36.33-p36.22 encompassing *RERE* but no *SPEN*. *RERE* (OMIM 605226) is located at 1p36.23 which encodes a nuclear receptor co-regulator that positively regulates retinoic acid signaling [7]. Heterozygous mutations in the *RERE* have been reported to be associated with autosomal dominant neurodevelopmental disorder with or without anomalies of the brain, eye, or heart (NEDBEH) (OMIM 616975) [7,8]. *SPEN* (OMIM 613484) is located at 1p36.21-p36.13, and heterozygous mutations in the *SPEN* have been reported to be associated with autosomal dominant Radio-Tartaglia syndrome (RATARS) (OMIM 619312) which is characterized by global developmental delay with impaired intellectual development, speech delay, and variable behavioral abnormalities [9].

The peculiar aspect of the present case is the application of expanded NIPT for early detection of 1q36 deletion syndrome. Wapner et al. [10] reported a 100% (1/1) detection rate of 1p36 deletion and no false positive rate (0/422) by single-nucleotide polymorphism (SNP)-based NIPT. Petersen et al. [11] found a 14% (1/7) PPV for 1p36 deletion syndrome in expanded NIPT of which there were one true positive case and six false positive cases. Martin et al. [12] reported the use of SNP-based NIPT for the detection of one case of 1p36 deletion with a true positive NIPT result. Yang et al. [13] reported a case of false negative NIPT for 1p deletion syndrome of which the case had an abnormal first-trimester combined screening test and a normal NIPT result. However, subsequent amniocentesis showed the result of 46,XX,del(1)(p36). Shi et al. [14] reported the PPV of 20%–30% for 1p36 deletion syndrome in their nation-wide study of 219 Chinese laboratories.

The present case adds to the list of first-trimester application of expanded NIPT in the diagnosis of fetal 1p36 deletion. The preset case provides evidence that expanded NIPT has the advantage of early detection of familial unbalanced reciprocal translocation in the fetus.

Declaration of competing interest

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

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Case Report

Prenatal diagnosis of a 14-Mb 11p11.2-p13 deletion by chromosome microarray analysis in a pregnancy with fetal recombinant chromosome 11 syndrome of rec(11)del(11)(p11.2p13) ins(11)(q21p11.2p13) and maternal intrachromosomal insertion of ins(11)(q21p11.2p13)

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ABSTRACT

Objective: We present prenatal diagnosis of a 14-Mb 11p11.2-p13 deletion by chromosome microarray analysis (CMA) in a pregnancy with fetal recombinant chromosome 11 syndrome of rec(11)del(11)(p11.2p13)ins(11)(q21p11.2p13) and maternal intrachromosomal insertion of ins(11)(q21p11.2p13).
Case Report: A 25-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of a family history of psychiatric disorders in her two brothers and one maternal uncle. Array comparative genomic hybridization (aCGH) analysis of amniocentesis revealed a 14-Mb 11p13p11.2 deletion. The pregnancy was terminated at 19 weeks of gestation, and a 252-g fetus was delivered. Cytogenetic analysis of the parental bloods and cord blood revealed a karyotype of 46,XX,ins(11)(q21p11.2p13) in the mother, 46,XY in the father and 46,XY,rec(11)del(11)(p11.2p13)ins(11)(q21p11.2p13) in the fetus. aCGH analysis on the DNA extracted from cord blood revealed the result of arr 11p13q11.2 (32,697,424–46,712,173) × 1.0 [GRCh37] with a 14-Mb deletion of 11p13-p11.2 encompassing 54 OMIM genes including *PHF21A*, *ALX4*, *EXT2* and *SLC1A2*. Polymorphic DNA marker analysis showed a maternal origin of the 11p deletion. The present case had an 11p13-p11.2 deletion encompassing 11p12-p11.3 which is associated with Potocki-Shaffer syndrome (PSS) or chromosome 11p11.2 deletion syndrome.
Conclusion: CMA is useful for prenatal detection of fetal genomic imbalance in case of familial intrachromosomal insertion.

Introduction

We previously reported prenatal diagnosis and molecular cytogenetic characterization of rec(10)dup(10p)inv(10)(p11.2q26.3) in a fetus associated with paternal pericentric inversion [1]. Here, we present an additional case of prenatal diagnosis of 11p11.2-p13 deletion in the recombinant chromosome 11 [rec(11)] associated with maternal intrachromosomal insertion of ins(11).

Case Report

A 25-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of a family history of psychiatric

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disorders in her two brothers and one maternal uncle. Array comparative genomic hybridization (aCGH) analysis of amniocentesis revealed a 14-Mb 11p13p11.2 deletion. The pregnancy was terminated at 19 weeks of gestation, and a 252-g fetus was delivered (Fig. 1). Cytogenetic analysis of the parental bloods and cord blood revealed a karyotype of 46,XX, ins(11)(q21p11.2p13) (Fig. 2) in the mother, 46,XY in the father and 46,XY,rec(11) del(11)(p11.2p13) ins(11)(q21p11.2p13) (Fig. 3) in the fetus. aCGH analysis on the DNA extracted from cord blood revealed the result of arr 11p13q11.2 (32,697,424–46,712,173) × 1.0 [GRCh37] with a 14-Mb deletion of 11p13-p11.2 encompassing 54 OMIM genes including *PHF21A*, *ALX4*, *EXT2* and *SLC1A2* (Fig. 4). Polymorphic DNA marker analysis showed a maternal origin of the 11p deletion (Fig. 5).

Discussion

The present case was associated with a 14-Mb 11p13-p11.2 deletion of with haploinsufficiency of the genes of *PHF21A*, *ALX4*, *EXT2* and *SLC1A2* but without involving *PAX6*. *PHF21A* (OMIM

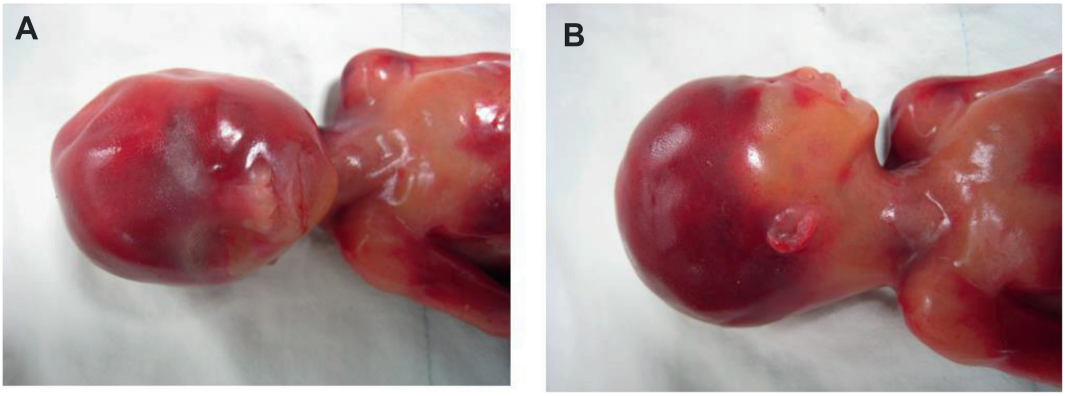

Fig. 1. (A) and (B) The craniofacial dysmorphism of the fetus at birth.

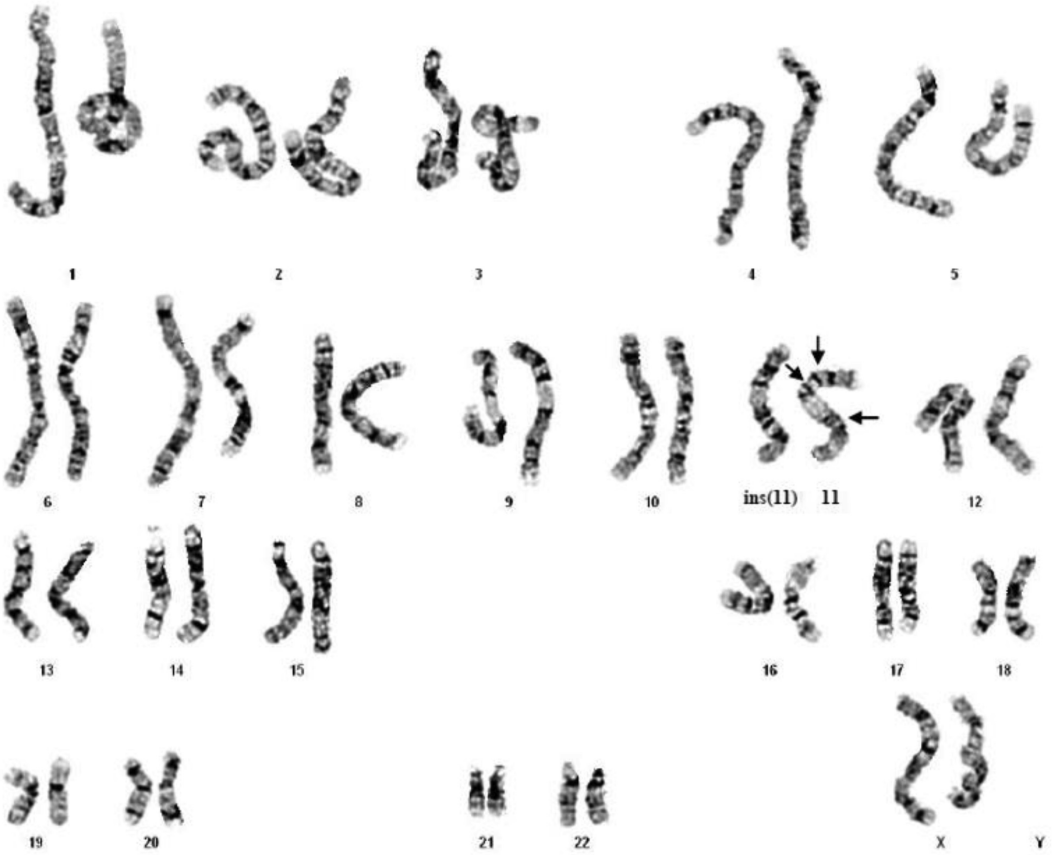

Fig. 2. A karyotype of 46,XX, ins(11)(q21p11.2p13) in the mother. The arrows indicate the breakpoints of intrachromosomal insertion. The segment of 11p11.2-p13 is inserted into 11q21 in the aberrant chromosome ins(11). ins = insertion.

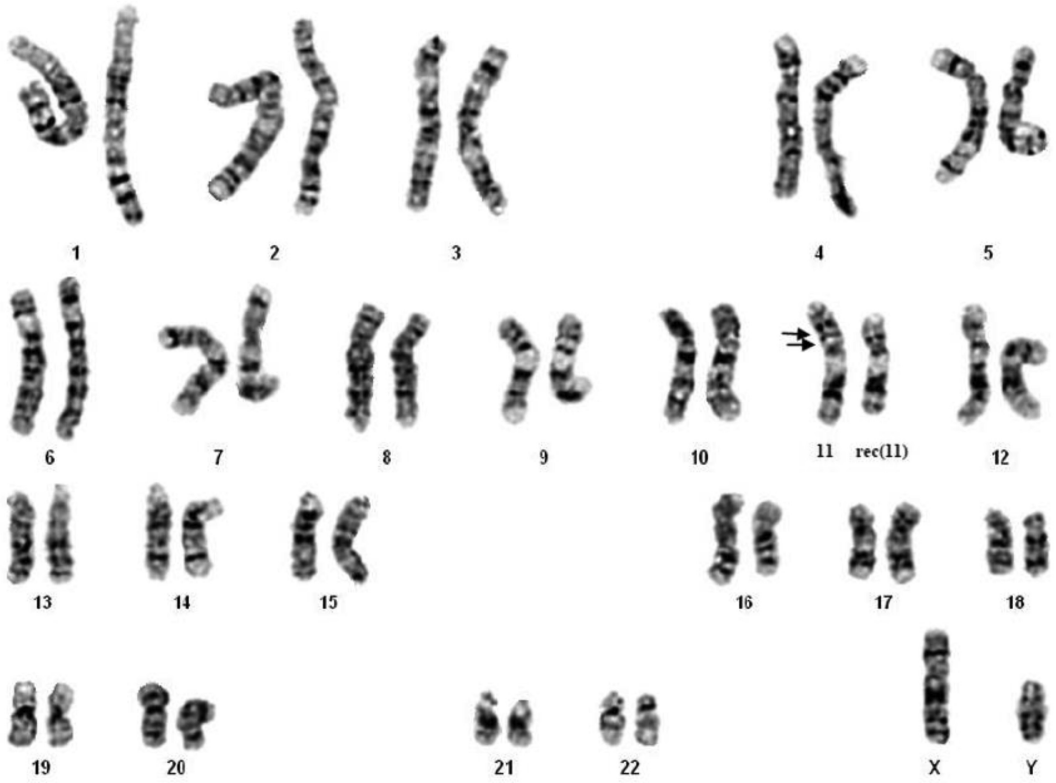

Fig. 3. A karyotype of 46,XY,rec(11)del(11)(p11.2p13)ins(11)(q21p11.2p13) in the fetus. The arrows indicate the breakpoints. The recombinant chromosome contains an interstitial deletion of 11p11.2-p13. rec = recombinant, ins = insertion.

608325) is located at 11p11.2, and deletion and mutation of *PHF21A* are associated with autosomal dominant intellectual developmental disorder with behavioral abnormalities and craniofacial dysmorphism with or without seizures (IDDBCS) (OMIM 618725) characterized by impaired intellectual development, developmental delay of varying severity with impaired motor skills, language delay, macrocephaly, obesity, overgrowth and seizures, and neurobehavioral disorders including autism in half of the patients [2,3]. *ALX4* (OMIM 605420) is located at 11p11.2, and deletion and mutation of *ALX4* are associated with autosomal dominant parietal foramina 2 (PFM2) (OMIM 609597) and craniosynostosis 5 (OMIM 615529) characterized by bilateral parietal foramina in skull, frontonasal dysplasia, hypertelorism and nose abnormalities [4]. *EXT2* (OMIM 608210) is located at 11p11.2, and deletion and mutation of *EXT2* are associated with autosomal dominant multiple exostoses type 2 (OMIM 133701) [5]. *SLC1A2* (OMIM 600300) is located at 11p13, and deletion and mutation of *SLC1A2* are associated with autosomal dominant developmental and epileptic encephalopathy 41 (DEE41) (OMIM 617105) characterized by neurologic disorder of early onset of seizures in the early life, impaired psychomotor development, hypotonia, spasticity, lack of speech, poor visual fixation, feeding difficulties, poor growth, microcephaly and contractures [6]. The present case had an 11p11.2-p13 deletion outside *PAX6* (OMIM 607108) which is susceptible for many autosomal dominant eye disorders of aniridia, cataract, keratitis, optic nerve hypoplasia and foveal hypoplasia.

The present case had an 11p13-p11.2 deletion encompassing 11p12-p11.3 which is associated with Potocki-Shaffer syndrome (PSS) (OMIM 601224), or chromosome 11p11.2 deletion syndrome, or proximal 11p deletion syndrome or defect 11 syndrome. PSS is an autosomal dominant contiguous gene deletion syndrome due to haploinsufficiency of the 11p12-p11.2 region and is characterized by craniofacial abnormalities, developmental delay, intellectual disability, multiple exostoses and biparietal foramina [7].

The risk of having an abnormal recombinant child from an intrachromosomal insertion carrier parent is estimated to be 15% [8]. Gardner and Amor [9] suggested a risk of 0~50% of which the risk is likely higher (30~40%) if one of the involved segments is small and the other one is long, and the risk is likely lower (<10%) if both segments are short. The present case had one short segment of 11q21 and one long segment (14 Mb) of 11p11.2-p13. Therefore, the risk of recurrence in the present case is high (30~40%). In the present case, the affected offspring can be either 11p11.2-p13 deletion or 11p11.2-p13 duplication. Gardner and Amor [9] reported a similar intrachromosomal insertion of ins(11)(q23.1p11.2p12) in the carriers in a family with a 2 Mb length in the inserted segment. In their report, the affected probands in the family had either rec(11)del(11) (p11.2p12) ins(11)(q23.1p11.2p12) with PSS or rec(11)dup(11)(p11.2p12) ins(11)(q23.11p11.2p12). In the second generation of seven children in their report, two had balanced insertion 11, two (2/7 = 28.6%) were affected including one deletion 11p and one duplication 11p, and three had normal chromosome 11. In the third generation of the offspring of two carrier parents in their report, 1/4 (25%) were an affected including one deletion 11p with PSS.

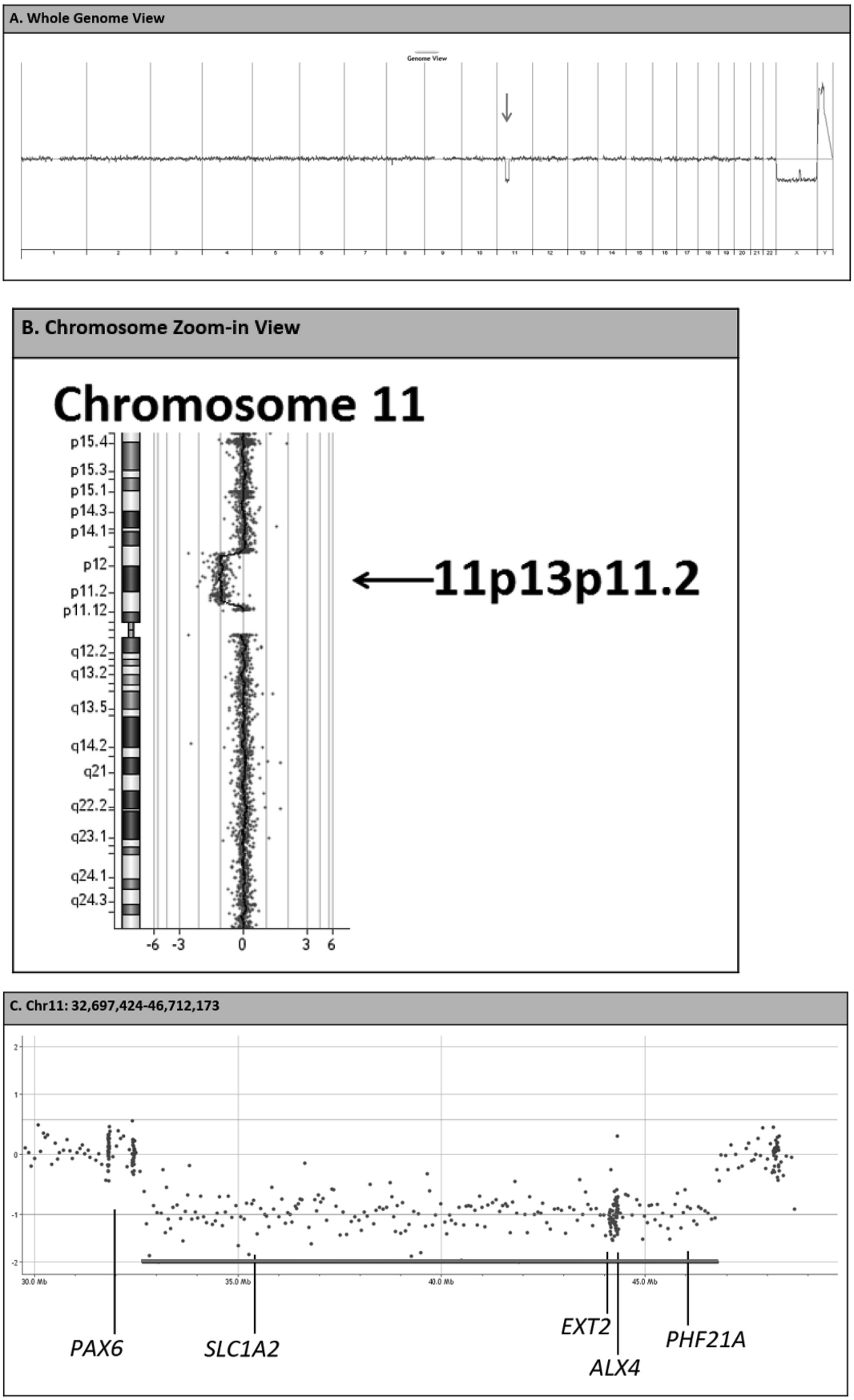

Fig. 4. (A), (B) and (C) Array comparative genomic hybridization analysis on the DNA extracted from the cord blood using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K Array (Agilent Technologies, Santa Clara, CA, USA) shows the result of arr 11p13q11.2 (32,697,424–46,712,173) × 1.0 [GRCh37] with a 14-Mb deletion of 11p13-p11.2 encompassing 54 OMIM genes including *PHF21A*, *ALX4*, *EXT2* and *SLC1A2* but without involving *PAX6*.

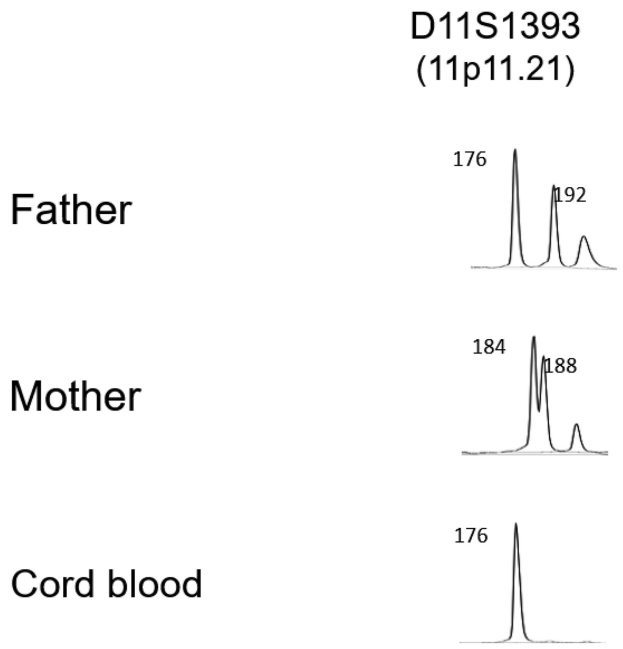

Fig. 5. Quantitative fluorescent polymerase chain reaction analysis on the DNA extracted from parental bloods and cord blood shows a maternal origin of the 11p11.21 deletion. In the informative marker of D11S1393, only one paternal allele is noted, indicating a maternal origin of the deletion.

In summary, we present prenatal diagnosis of a 14-Mb 11p11.2-p13 deletion by CMA in a pregnancy with fetal recombinant chromosome 11 syndrome of rec(11)del(11)(p11.2p13) ins(11)(q21p11.2p13) and maternal intrachromosomal insertion of ins(11)(q21p11.2p13). CMA is useful for prenatal detection of fetal genomic imbalance in case of familial intrachromosomal insertion.

Declaration of competing interest

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

Acknowledgements

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Case Report

Detection of chromosome 5q interstitial deletion of 5q14.3-q31.1 by chromosome microarray analysis in a second-trimester fetus with multiple congenital anomalies and a literature review of chromosome 5q interstitial deletion syndrome

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Congenital anomalies

ABSTRACT

Objective: We present application of chromosome microarray analysis (CMA) in the detection of chromosome 5q interstitial deletion of 5q14.3-q31.1 in a second-trimester fetus with multiple congenital anomalies on fetal ultrasound.
Case Report: A 30-year-old, gravida 2, para 1, woman was found to have multiple anomalies in the fetus at 14 weeks of gestation by prenatal ultrasound screening. The fetal anomalies included echogenic bowel, a left neck cyst, hypoplastic left heart, single umbilical artery and bilateral clubfeet. The pregnancy was subsequently terminated, and a 64-g malformed fetus was delivered. CMA by array comparative genomic hybridization (aCGH) analysis on the DNA extracted from umbilical cord revealed the result of arr 5q14.3q31.1 (83,557,042–130,841,093) × 1.0 [GRCh37] with a 47.3-Mb 5q14.3-q31.1 deletion encompassing 95 OMIM genes including *NR2F1*, *MEF2C*, *APC*, *KCNN2* and *FBN2*. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from parental bloods and umbilical cord using the informative markers of D5S2496 (5q21.3) and D5S818 (5q23.2) showed that the fetus inherited only one maternal allele, indicating a paternal origin of the interstitial 5q deletion in the fetus.
Conclusion: CMA is useful for genetic investigation of unknown congenital anomalies detected by fetal ultrasound.

Introduction

We previously reported prenatal diagnosis of microdeletion of 5q35.2-q35.3 [1], familial 5q13.2 microdeletion [2] and 5q11.2-q14 deletion [3]. Here, we present application of chromosome microarray analysis (CMA) in the detection of chromosome 5q interstitial deletion of 5q14.3-q31.1 in a second-trimester fetus with multiple congenital anomalies on fetal ultrasound. We also review the literature of chromosome 5q interstitial deletion syndrome.

Case Report

A 30-year-old, gravida 2, para 1, woman was found to have multiple anomalies in the fetus at 14 weeks of gestation by prenatal ultrasound screening. The fetal anomalies included echogenic bowel, a left neck cyst, hypoplastic left heart, single umbilical artery and bilateral clubfeet. The pregnancy was subsequently terminated, and a 64-g malformed fetus was delivered. CMA by array

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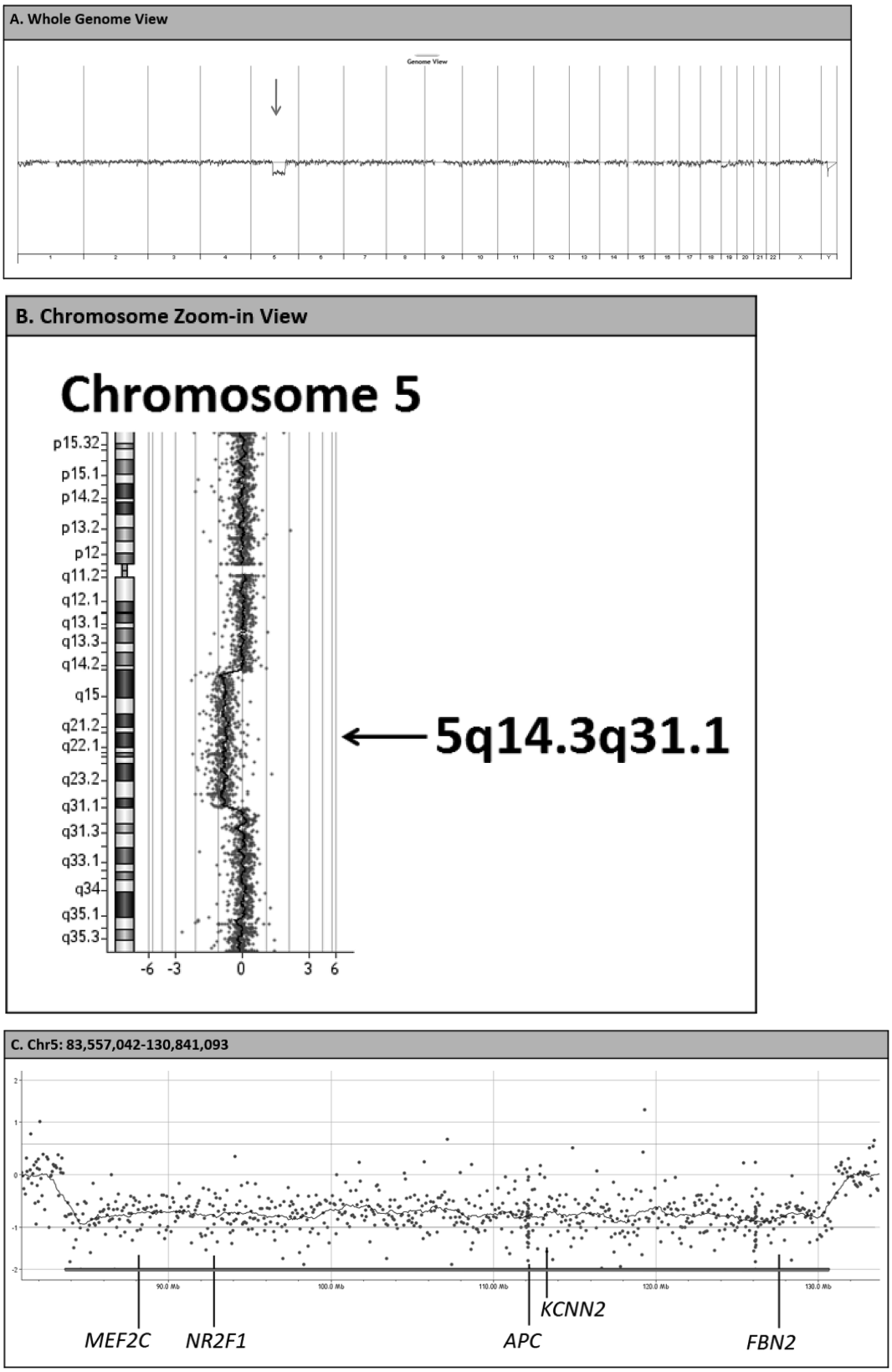

Fig. 1. (A), (B) and (C) Array comparative genomic hybridization analysis on the DNA extracted from umbilical cord by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, CA, USA) shows arr 5q14.3q31.1 (83,557,042–130,841,093) × 1.0 [GRCh37] with a 47.3-Mb 5q14.3-q31.1 deletion encompassing *NR2F1*, *MEF2C*, *APC*, *KCNN2* and *FBN2*.

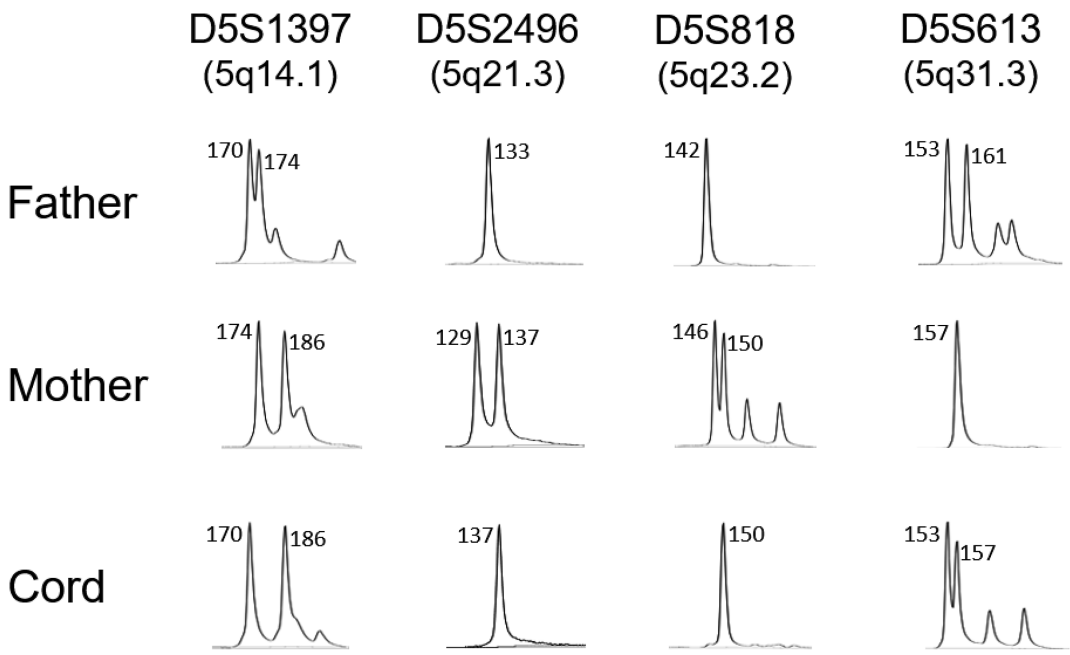

Fig. 2. Quantitative fluorescent polymerase chain reaction analysis on the DNA extracted from parental bloods and umbilical cord using the informative markers of D5S2496 (5q21.3) and D5S818 (5q23.2) shows that the fetus inherited only one maternal allele, indicating a paternal origin of the interstitial 5q deletion in the fetus.

comparative genomic hybridization (aCGH) analysis on the DNA extracted from umbilical cord revealed the result of arr 5q14.3q31.1 (83,557,042–130,841,093) × 1.0 [GRCh37] with a 47.3-Mb 5q14.3-q31.1 deletion encompassing 95 OMIM genes including *NR2F1*, *MEF2C*, *APC*, *KCNN2* and *FBN2* (Fig. 1). Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from parental bloods and umbilical cord using the informative markers of D5S2496 (5q21.3) and D5S818 (5q23.2) showed that the fetus inherited only one maternal allele, indicating a paternal origin of the interstitial 5q deletion in the fetus (Fig. 2).

Discussion

The present case had a 47.3-Mb 5q14.3-q31.1 deletion encompassing *NR2F1*, *MEF2C*, *APC*, *KCNN2* and *FBN2*. Distal chromosome 5q14.3 deletion syndrome (OMIM 612881) encompassing 5q14.3-q15 is characterized by severe mental retardation, epilepsy, bilateral periventricular heterotopia, hypotonia, delayed motor development, no speech acquisition and minor dysmorphic features [4–8]. *NR2F1* haploinsufficiency and *MEF2C* haploinsufficiency have been reported to be associated with distal chromosome 5q14.3 deletion syndrome [4,7,8]. Malan et al. [9] reported prenatal diagnosis of 5q15-q21.3 deletion in a fetus with dysmorphic features, thin limbs and renal abnormalities. Sobreira et al. [6] reported interstitial deletion 5q14.3-q21 associated with iris coloboma, hearing loss, dental anomaly, moderate intellectual disability, and attention deficit and hyperactivity disorder in an 11-year-old boy. *NR2F1* (OMIM 132890) is located at 5q15, and deletion and mutation of *NR2F1* are associated with autosomal dominant Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS) (OMIM 615722) characterized by delayed development, moderately impaired intellectual development and optic atrophy [10]. *MEF2C* (OMIM 600662) is located at 5q14.3, and deletion and mutation of *MEF2C* are associated with autosomal dominant chromosome 5q14.3 deletion syndrome and neurodevelopmental disorder with hypotonia, stereotypic hand movements and impaired language [7].

APC (OMIM 611731) is located at 5q22.3. Privitera et al. [11] reported *APC*-related phenotypes and intellectual disability in 5q interstitial deletions and suggested that *KCNN2* (5q22.3) as the most likely candidate gene contributing to the neurologic phenotype of 5q22.1-q23.1 deletion. *KCNN2* (OMIM 605879) is located at 5q22.3, and deletion and mutation of *KCNN2* are associated with autosomal dominant neurodevelopmental disorder with or without variable movement or behavioral abnormalities (NEDMAB) (OMIM 619725) [12].

Tzschach et al. [13] reported a 2-year-old boy with 5q23.3-q31.2 interstitial deletion encompassing *FBN2* and the phenotype of failure to thrive, psychomotor retardation, mid-facial dysmorphic features and long and slender fingers and toes, and suggested that deletion of *FBN2* might be responsible for the phenotype. *FBN2* (OMIM 612570) is located at 5q23.3, and deletion and mutation of *FBN2* are associated with autosomal dominant congenital contractural arachnodactyly (CCA) (OMIM 121050) [14–17] and autosomal dominant early-onset macular degeneration (OMIM 616118) [18].

In summary, we present application of CMA in the detection of chromosome 5q interstitial deletion of 5q14.3-q31.1 in a second-trimester fetus with multiple congenital anomalies on fetal ultrasound. CMA is useful for genetic investigation of unknown congenital anomalies detected by fetal ultrasound.

Declaration of competing interest

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

Acknowledgements

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Case Report

Prenatal diagnosis of Jacobsen syndrome associated with a distal 11q deletion and a distal 8q duplication by chromosome microarray analysis in a fetus with a *de novo* unbalanced translocation of 46,XX,der(11)t(8;11)(q24.13;q23.3) and multiple congenital anomalies on fetal ultrasound

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ABSTRACT

Objective: We present prenatal diagnosis of Jacobsen syndrome associated with a distal 11q deletion and a distal 8q duplication by chromosome microarray analysis (CMA) in a fetus with multiple congenital anomalies on fetal ultrasound.
Case Report: A 41-year-old, gravida 2, para 1, woman underwent amniocentesis at 25 weeks of gestation because of intrauterine growth restriction, endocardial cushion defect, clenched hands, arthrogryposis, rocker bottom feet and craniosynostosis on fetal ultrasound. Amniocentesis revealed a karyotype of 46,XX,add(11)(q23.3). Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from the uncultured amniocytes revealed the result of arr 8q24.13q24.3 × 3, 11q23.3q25 × 1. Analysis of *FGFR2* revealed no mutation. The karyotype was 46,XX,der(11)t(8;11)(q24.13;q23.3). The parental karyotypes were normal. The pregnancy was subsequently terminated, and a dead malformed fetus was delivered with craniofacial dysmorphism of low-set malformed ears, depressed nasal bridge, hypertelorism, small mouth, clenched hands and rocker bottom feet. Cytogenetic analysis of the placenta revealed a karyotype of 46,XX,der(11)t(8;11)(q24.13;q23.3). aCGH analysis of the DNA extracted from the umbilical cord showed the result of arr 8q24.13q24.3 (126,302,369–146,280,020) × 3.0, arr 11q23.3q25 (120,469,928–134,868,407) × 1.0 [GRCh37] with a 19.978-Mb duplication of 8q24.13-q24.3 and a 14.398-Mb deletion of 11q23.3-q25 encompassing the genes of *BSX*, *ETS1*, *FLI1* and *ARHGAP32*.
Conclusion: CMA is useful for detection of *de novo* chromosomal rearrangement in the fetus with multiple congenital anomalies on fetal ultrasound.

Introduction

We previously reported perinatal diagnosis of Jacobsen syndrome (JBS) associated with pure distal 11q deletion [1–4] and concomitant distal 11q deletion due to unbalanced reciprocal translocation [5–9]. Here, we present an additional case of prenatal diagnosis of JBS associated with a distal 11q (11q23.3-q25) deletion

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and a distal 8q (8q24.13-q24.3) duplication in a fetus with a *de novo* unbalanced translocation of 46,XX,der(11)t(8;11)(q24.13;q23.3) and multiple congenital anomalies on fetal ultrasound.

Case Report

A 41-year-old, gravida 2, para 1, woman underwent amniocentesis at 25 weeks of gestation because of intrauterine growth restriction (IUGR), endocardial cushion defect, clenched hands, arthrogryposis, rocker bottom feet and craniosynostosis on fetal ultrasound. Amniocentesis revealed a karyotype of 46,XX,add(11)(q23.3). Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from the uncultured amniocytes revealed the result of arr 8q24.13q24.3 × 3, 11q23.3q25 × 1. Analysis of *FGFR2* revealed no mutation. The karyotype was 46,XX,der(11)t(8;11)(q24.13;q23.3). The parental karyotypes were normal. The pregnancy was subsequently terminated, and a dead malformed fetus was delivered with craniofacial dysmorphism of low-set malformed ears, depressed nasal bridge, hypertelorism, micrognathia, small mouth, clenched hands and rocker bottom feet (Figs. 1–3). Cytogenetic analysis of the placenta revealed a karyotype of or 46,XX,der(11)t(8;11)(q24.13;q23.3) (Fig. 4). aCGH analysis of the DNA extracted from the umbilical cord showed the result of arr 8q24.13q24.3 (126,302,369–146,280,020) × 3.0, arr 11q23.3q25 (120,469,928–134,868,407) × 1.0 [GRCh37] with a 19.978-Mb duplication of 8q24.13-q24.3 and a 14.398-Mb deletion of 11q23.3-q25 encompassing the genes of *BSX*, *ETS1*, *FLI1* and *ARHGAP32* (Fig. 5).

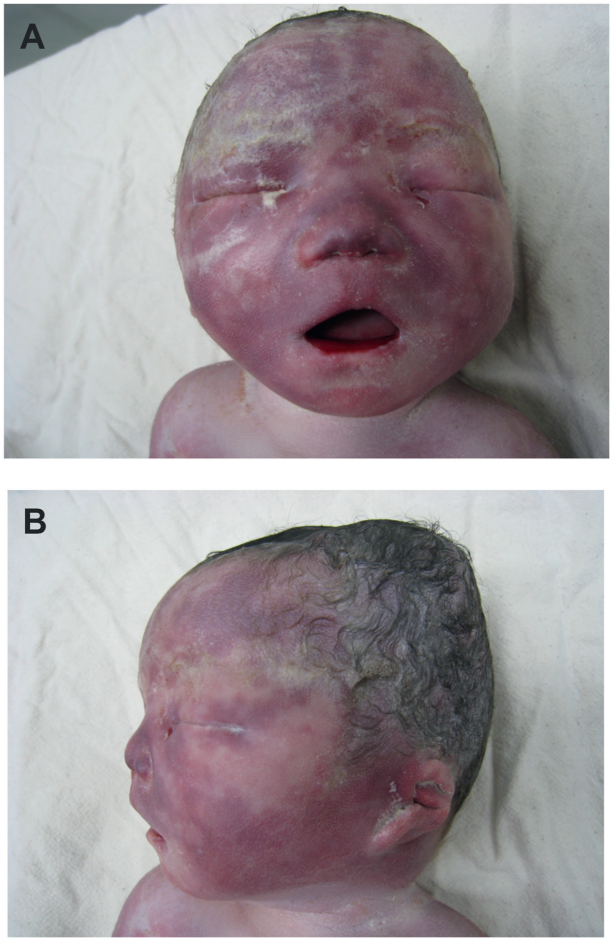

Fig. 1. Craniofacial appearance of the fetus at birth shows hypertelorism, depressed nasal bridge, micrognathia and a small mouth.

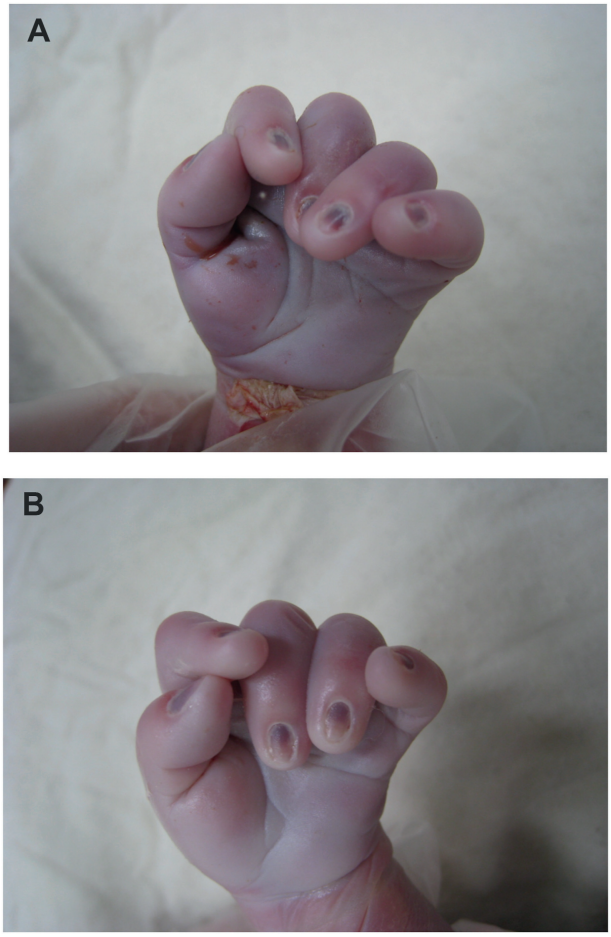

Fig. 2. Clenched hands.

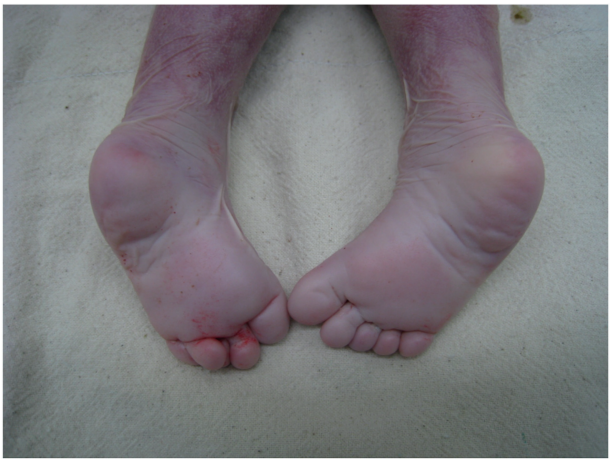

Fig. 3. Rocker bottom feet.

Discussion

JBS (OMIM 147791) or chromosome 11q deletion syndrome or partial 11q monosomy syndrome is a contiguous gene deletion

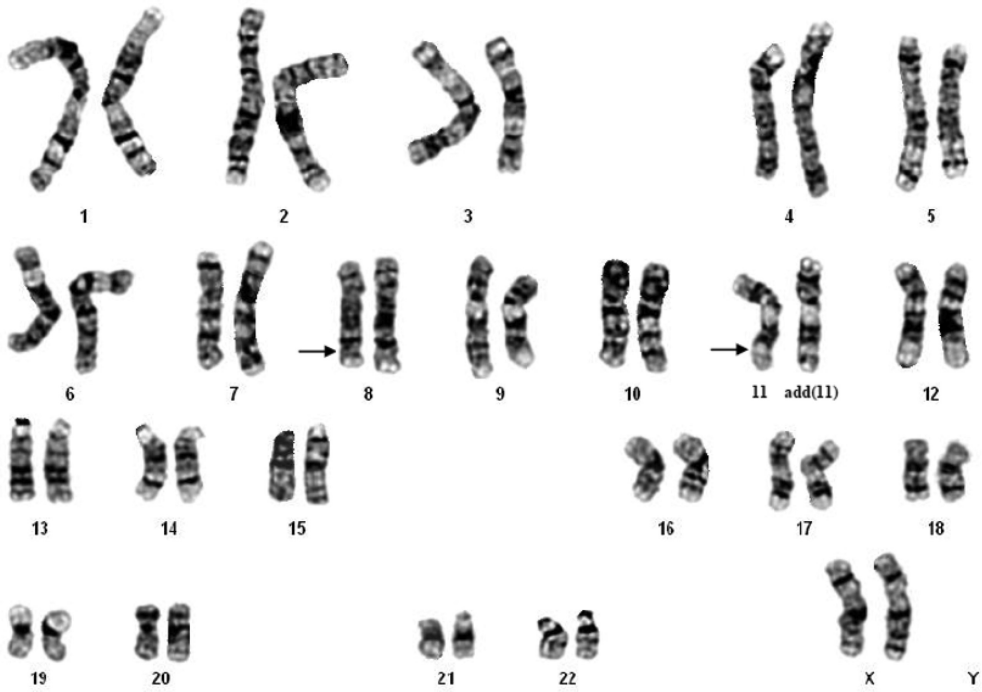

Fig. 4. A karyotype of 46,XX,add(11)(q23.3) or 46,XX,der(11)t(8;11)(q24.13;q23.3). The arrows indicate the break and reunion regions on the normal chromosomes. add = additional material on the chromosome, der = derivative chromosome.

syndrome with major clinical features of growth retardation, psychomotor retardation, trigonocephaly, divergent intermittent strabismus, epicanthus, telecanthus, broad nasal bridge, short nose with anteverted nostrils, carp-shaped upper lip, retrognathia, low-set dysmorphic ears, bilateral camptodactyly, hammertoes and isoimmune thrombocytopenia [10,11]. JBS is also associated with abnormal platelet function, thrombocytopenia, pancytopenia, congenital malformations of the heart, kidney, gastrointestinal tract, genitalia, central nervous system and skeleton, and less common features of eyes, hearing, immune system and endocrine problems [12]. JBS has a prevalence of 1/100,000 births, a female: male ratio of 2:1, a *de novo* occurrence in 85% of the reported cases, and an occurrence resulting from an unbalanced segregation of a familial balanced translocation or from other chromosome rearrangements in the other 15% of the cases [12].

The present case was diagnosed because of multiple anomalies such as IUGR, endocardial cushion defect, clenched hands, arthrogryposis, rocker bottom feet and craniosynostosis on fetal ultrasound. Chen [5] and Chen et al. [6,7] reported recurrent omphalocele in three consecutive siblings with der(11)t(3;11)(q21;q23)pat. Chen et al. [8] reported prenatal diagnosis of 46,XX,der(11)t(3;11)(q21;q23)pat by amniocentesis in a fetus with Dandy-Walker variant and trigonocephaly. Chen et al. [2] reported prenatal diagnosis of 46,XY,del(11)(q24.2)dn by amniocentesis in a fetus with short femurs and overlapping of the toes because of high maternal serum α-fetoprotein. Chen et al. [2] reported prenatal diagnosis of 46,XX,del(11)(q24.1)dn by amniocentesis in a fetus with no ultrasound findings because of advanced maternal age. Boehm et al. [13] reported prenatal diagnosis of 46,XX,del(11)(q23) by amniocentesis in a fetus with oligohydramnios and dilated cerebral ventricles. Foley et al. [14] reported prenatal diagnosis of 46,XY,del(11)(q23) by amniocentesis in a fetus with abnormal sonographic findings of hypoplastic left heart syndrome (HLHS) and hydronephrosis. The mother had a karyotype of 46,XX,t(11;15)(q24.2;q26.3). The karyotype of the fetus was likely 46,XY,der(11)t(11;15)(q24.2;q26.3). Valduga et al. [15] reported prenatal diagnosis of 46,XY [16]/46,XY,del(11)(q23) [3] by amniocentesis in a fetus with no obvious abnormalities. Chen et al. [9] reported prenatal diagnosis of 46,XX,der(11)t(3;11)(q21;q23)pat by amniocentesis in a fetus with abnormal sonographic findings of holoprosencephaly, orofacial clefts, pyelectasis and a unilateral duplex renal system. Xu et al. [16] reported detection of 46,XX,del(11)(q23.3)dn in a fetus with abnormal sonographic findings of congenital heart defect (CHD) with single ventricle, single atrium and common atrioventricular valve at 24 weeks of gestation. Lo et al. [17] reported detection of JBS by noninvasive prenatal testing (NIPT) at 14 weeks of gestation and the karyotype of 46,XX,del(11)(q23.3)dn by cord blood at birth in the fetus with second-trimester ultrasound findings of cardiomegaly, ascites, hydrops fetalis, double-outlet right ventricle and single umbilical artery. Chen et al. [4] reported prenatal diagnosis of JBS with 11q23.3-q25 deletion in a fetus with double outlet right ventricle, HLHS and ductus venosus agenesis on fetal ultrasound. Guo et al. [18] reported prenatal diagnosis of JBS in a fetus carried by a pregnant woman with intellectual disability and the karyotype of 46,XX,del(11) (q24) in the mother. Chen et al. [19] reported the prenatal sonographic findings of interventricular septal defect, dilation of the left renal pelvis and single umbilical artery in a fetus with JBS and 46,XX,del(11)(q23). Zhong et al. [20] reported prenatal sonographic findings in four cases of JBS with CHD and IUGR in 3/4 cases, and ventriculomegaly, shortened femur length and pyelectasis in 2/4 cases.

The present case had a 14.398-Mb deletion of 11q23.3-q25 encompassing the genes of *BSX*, *ETS1*, *FLI1* and *ARHGAP32*. Favier et al. [21] suggested a genotype-phenotype correlation of *ETS1* with CHD and immunodeficiency, *FLI1* with Paris-Trousseau syndrome (PTS) of thrombocytopenia and platelet dysfunction, *BSX* with intellectual disability and *ARHGAP32* with autism spectrum disorder (ASD), respectively. *ETS1* (OMIM 164720) is located at 11q24.3 and has been suggested to be the critical gene responsible for HLHS and

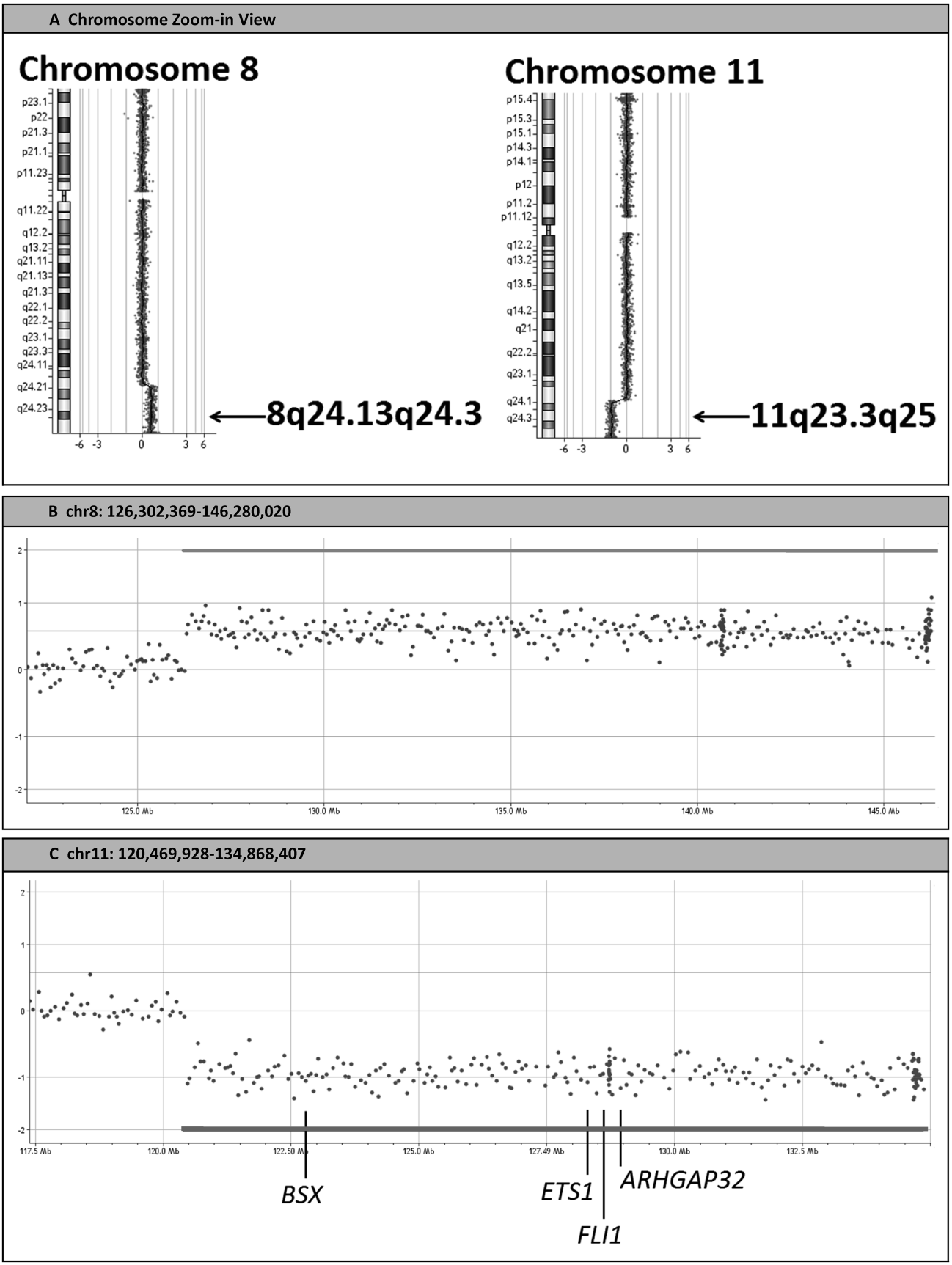

Fig. 5. (A), (B) and (C) Array comparative genomic hybridization analysis on the DNA extracted from umbilical cord by SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, CA, USA) shows the result of arr 8q24.13q24.3 (126,302,369-146,280,020) × 3.0, arr 11q23.3q25 (120,469,928-134,868,407) × 1.0 [GRCh37] with a 19.978-Mb duplication of 8q24.13-q24.3 and a 14.398-Mb deletion of 11q23.3-q25 encompassing the genes of *BSX*, *ETS1*, *FLI1* and *ARHGAP32*.

CHD in JBS [22–29], for kidney disease in JBS [30] and for immunodeficiency in JBS [31–33]. *FLI1* (OMIM 193067) is located at 11q24.3. Deletion and mutation of *FLI1* are associated with autosomal dominant and recessive bleeding disorder, platelet-type 21 (OMIM 617443) [25,34,35]. The present case had a 19.978-Mb duplication of 8q24.13-q24.3. Duplications of 8q22.2–24.3 [36], 8q24.11q24.3 [37] and 8q24.12-q24.3 [38] have been reported to be associated with non-specific mild phenotype.

In summary, we present prenatal diagnosis of Jacobsen syndrome associated with a distal 11q deletion and a distal 8q duplication by CMA in a fetus with multiple congenital anomalies on fetal ultrasound. CMA is useful for detection of *de novo* chromosomal rearrangement in the fetus with multiple congenital anomalies on fetal ultrasound.

Declaration of competing interest

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

Acknowledgements

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Case Report

Low-level mosaic trisomy 21 at amniocentesis and cordocentesis in a pregnancy associated with a favorable fetal outcome and perinatal progressive decrease of the trisomy 21 cell line

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ABSTRACT

Objective: We present low-level mosaic trisomy 21 at amniocentesis and cordocentesis in a pregnancy associated with a favorable fetal outcome and perinatal progressive decrease of the trisomy 21 cell line.
Case Report: A 36-year-old, primigravid woman underwent amniocentesis at 16 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,XY,+21 [3]/46,XY [17] (15% mosaicism) and simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr (21) × 2~3 (X,Y) × 1, consistent with 24.5% mosaicism for trisomy 21. Cordocentesis performed at 21 weeks of gestation revealed a karyotype of 47,XY,+21 [3]/46,XY [37] (6% mosaicism). She was referred for genetic counseling at 31 weeks of gestation, and continuing the pregnancy was advised. The parental karyotypes and prenatal ultrasound were normal. At 37 weeks of gestation, a phenotypically normal baby was delivered with a body weight of 2900-g. The karyotypes of cord blood, umbilical cord and placenta were 47,XY,+21 [1]/46,XY [39] (2.5% mosaicism), 47,XY,+21 [10]/46,XY [30] (25% mosaicism) and 47,XY,+21 [22]/46,XY [18] (55% mosaicism), respectively. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from umbilical cord and parental bloods excluded uniparental disomy (UPD) 21 and revealed a maternal origin of the extra chromosome 21. When follow-up at the age of 2 months, the neonate was normal in phenotype and development. The peripheral blood had a karyotype of 47,XY,+21 [1]/46,XY [39] (2.5% mosaicism), and interphase fluorescence *in situ* hybridization (FISH) analysis on uncultured buccal mucosal cells revealed 4.7% (5/105 cells) mosaicism for trisomy 21, compared with 0% (5/100 cells) in the normal control.
Conclusion: Low-level mosaic trisomy 21 at amniocentesis and cordocentesis can be associated with favorable fetal outcome and perinatal progressive decrease of the trisomy 21 cell line.

Introduction

We previously reported prenatal diagnosis of low-level mosaic trisomy 21 by amniocentesis in 11 consecutive cases with favorable fetal outcomes of which two cases was associated with uniparental disomy (UPD) 21 [1–12]. Here, we present an additional case. This case adds to the list of mosaic trisomy 21 at amniocentesis with favorable fetal outcomes. The information provided in this case

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along with our previous reports is very 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 36-year-old, primigravid woman underwent amniocentesis at 16 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,XY,+21 [3]/46,XY [17] (15% mosaicism) and simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr (21) × 2~3 (X,Y) × 1, consistent with 24.5% mosaicism for trisomy 21. Cordocentesis performed at 21 weeks of gestation revealed a karyotype of 47,XY,+21 [3]/46,XY [37] (6% mosaicism). She was referred for genetic counseling at 31 weeks of gestation, and continuing the pregnancy was advised. The parental karyotypes and prenatal ultrasound were normal. At 37 weeks of gestation, a phenotypically normal baby was delivered with a body weight of 2900-g. The karyotypes of cord blood, umbilical cord and placenta were 47,XY,+21 [1]/46,XY[39] (2.5% mosaicism), 47,XY,+21 [10]/46,XY [30] (25% mosaicism) and 47,XY,+21 [22]/46,XY[18] (55% mosaicism), respectively (Figs. 1 and 2). Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from umbilical cord and parental bloods excluded uniparental disomy (UPD) 21 and revealed a maternal origin of the extra chromosome 21. When follow-up at the age of two months, the neonate was normal in phenotype and development. The peripheral blood had a karyotype of 47,XY,+21[1]/46,XY[39] (2.5% mosaicism), and interphase fluorescence *in situ* hybridization (FISH) analysis on buccal mucosal cells revealed 4.7% (5/105 cells) mosaicism for trisomy 21 (Fig. 3), compared with 0% (5/100 cells) in the normal control.

Discussion

In accordance with our previous reports [1–12], the present case provides evidence for perinatal progressive decrease of the trisomy 21 cell line in case of mosaic trisomy 21 at amniocentesis and cordocentesis. In the present case, amniocentesis at 16 weeks of gestation revealed 15% (3/20 colonies) mosaicism for trisomy 21 in cultured amniocytes by conventional cytogenetic analysis and 24.5% mosaicism for trisomy 21 in uncultured amniocytes by aCGH analysis. Cordocentesis at 21 weeks of gestation revealed 6% (3/50 cells) mosaicism for trisomy 21 and at birth and at the age of two months, the cord blood and peripheral blood revealed 2.5% (1/40 cells) mosaicism for trisomy 21. At the age of two months, the neonate's buccal mucosal cells had 4.7% (5/105 cells) mosaicism for trisomy 21 by FISH analysis.

The present case had cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes (15% vs. 24.5% for mosaicism of trisomy 21, respectively). It is likely that the DNA extracted from uncultured amniocytes may contain dead trisomy 21 cells. Therefore, during repeat amniocentesis, conventional cytogenetic analysis should be included. The present case also had cytogenetic discrepancy among cord blood, umbilical cord and placenta (2.5% vs. 25% vs. 55% for mosaicism of trisomy 21, respectively). It is likely that this case is caused by a successful trisomy 21 rescue in the fetus himself, and the placenta remained a higher level of mosaicism for trisomy 21.

In summary, we present low-level mosaic trisomy 21 at amniocentesis and cordocentesis in a pregnancy associated with a favorable fetal outcome and perinatal progressive decrease of the trisomy 21 cell line. Low-level mosaic trisomy 21 at amniocentesis

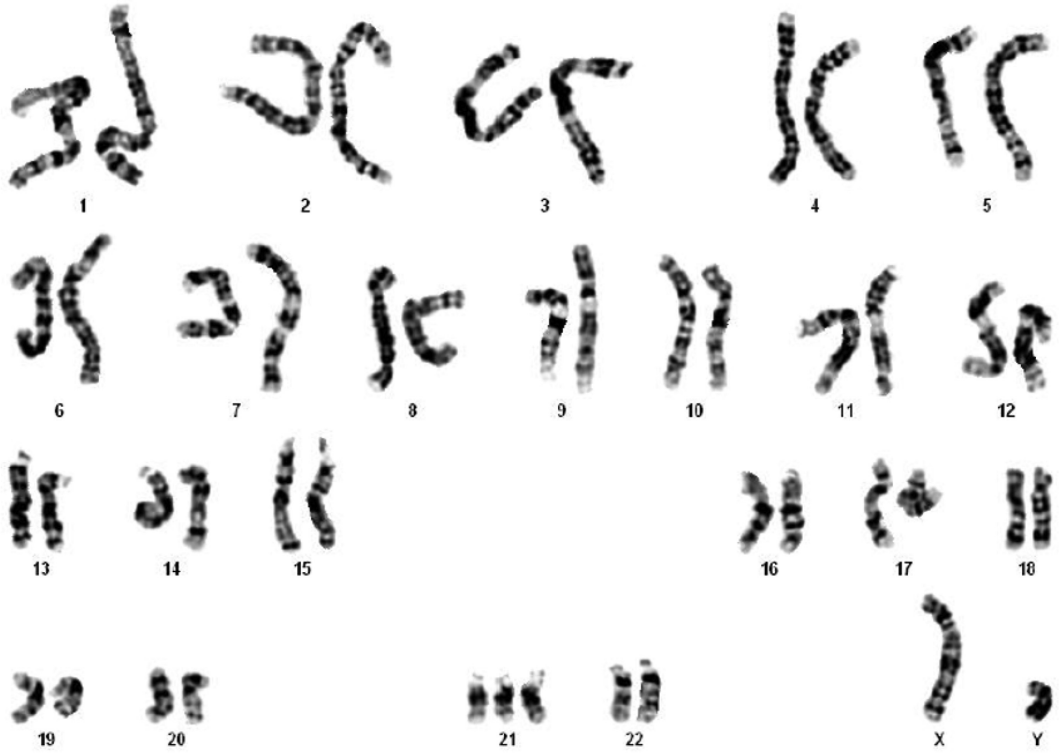

Fig. 1. A karyotype of 47,XY,+21.

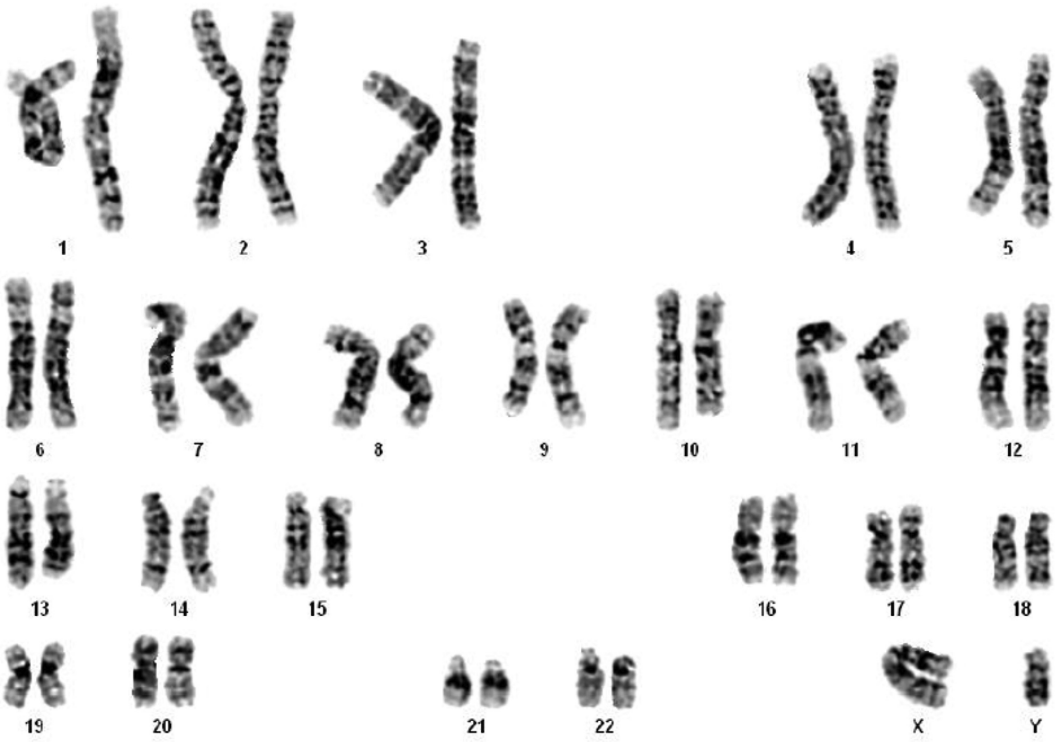

Fig. 2. A karyotype of 46,XY.

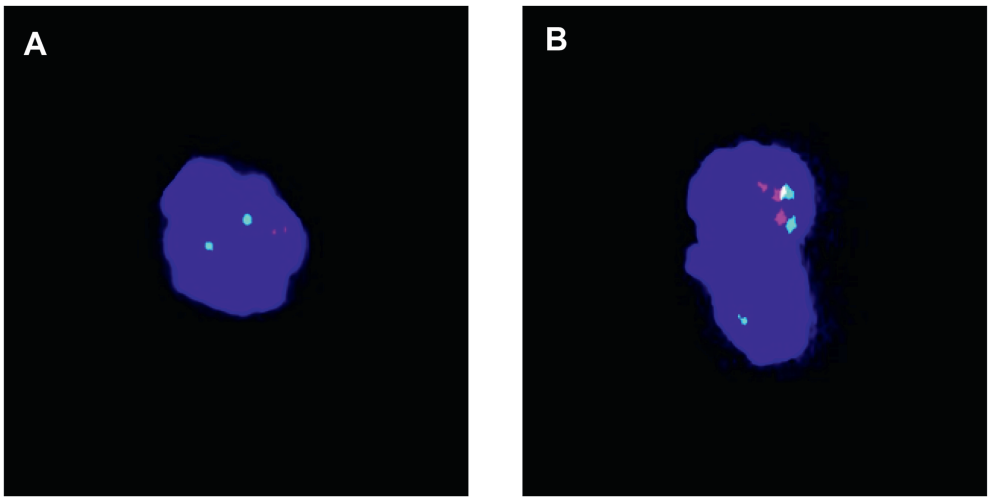

Fig. 3. Interphase fluorescence *in situ* hybridization (FISH) analysis on 105 buccal mucosal cells using bacterial artificial chromosome (BAC) probes of RP11-138O15 [21q11.2; fluorescein isothiocyanate (FITC), spectrum green] and RP11-345F15 (21q22.3; Texas Red, spectrum red) shows (A) a normal disomy 21 cell with two green signals and two red signals and (B) a trisomy 21 cell with three green signals and three red signals.

and cordocentesis can be associated with favorable fetal outcome and perinatal progressive decrease of the trisomy 21 cell line.

Declaration of competing interest

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

Acknowledgements

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Case Report

Low-level mosaic trisomy 21 due to mosaic unbalanced Robertsonian translocation of 46,XX,+21,der(21;21) (q10;q10)/46,XX at amniocentesis in a pregnancy associated with a favorable fetal outcome, cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, cytogenetic discrepancy among various tissues and perinatal progressive decrease of the trisomy 21 cell line

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ABSTRACT

Objective: We present prenatal diagnosis of mosaic trisomy 21 at amniocentesis associated with unbalanced Robertsonian translocation in the fetus and a favorable fetal outcome.
Case Report: A 41-year-old, primigravid woman underwent amniocentesis at 17 weeks of gestation because of advanced maternal age. Her husband was 41 years old. Amniocentesis revealed a karyotype of 46,XX,+21,der(21;21) (q10;q10)[8]/46,XX[18], consistent with 30.8% (8/26 colonies) mosaicism for trisomy 21. 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. Repeat amniocentesis at 21 weeks of gestation revealed a karyotype of 46,XX,+21,der(21;21) (q10;q10)[2]/46,XX [25], consistent with 7.4% (2/27 colonies) mosaicism for trisomy 21. Cord blood sampling revealed the result of 46,XX and rsa X(P095) × 2, 13,18,21(P095) × 2. Prenatal ultrasound findings were normal. At 23 weeks of gestation, she underwent cord blood sampling which revealed a karyotype of 46,XX. At 26 weeks of gestation, she was referred for genetic counseling. No repeat amniocentesis and continuing the pregnancy were advised. The mother had a karyotype of 46,XX, and the father had a karyotype of 46,XY. At 38 weeks of gestation, a 3476-g, phenotypically normal baby was delivered. The cord blood had a karyotype of 46,XX,+21,der(21;21) (q10;q10)[1]/46,XX[39] (2.5% mosaicism). The placenta had a karyotype of 46,XX,+21,der(21;21) (q10;q10) (40/40 cells). 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 resulted no genomic imbalance.
Conclusion: Low-level mosaic trisomy 21 at amniocentesis due to mosaic unbalanced Robertsonian translocation with a normal cell line can be associated with a favorable fetal outcome, cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, cytogenetic discrepancy among various tissues and perinatal progressive decrease of the trisomy 21 cell line.

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Discussion

Unbalanced Robertsonian translocation mosaicism with a normal cell line at amniocentesis has been reported to be associated with a normal fetus and/or a favorable fetal outcome. For examples, Chen et al. [13] 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, and the karyotype of 45,XY,der(15;22) (q10;q10) in the peripheral blood and normal buccal mucosal cells by fluorescence *in situ* hybridization (FISH) analysis at age seven months. Long et al. [14] and Hsu et al. [15] 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. Hsu et al. [15] 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. Worton and Stern [16] and Hsu et al. [15] 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. Yan et al. [17] 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]. However, unbalanced Robertsonian translocation mosaicism with a normal cell line at amniocentesis has occasionally been reported to be associated with fetal abnormality. For example, Lambert et al. [18] and Hsu et al. [15] 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 mosaicism was found in fetal skin (12.9%), ovary (32%) and kidney (4%). The present case provides evidence that low-level mosaic trisomy 21 at amniocentesis due to mosaic unbalanced Robertsonian translocation with a normal cell line can be associated with a favorable fetal outcome.

The peculiar aspect of the present case is complete cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, cytogenetic discrepancy among various tissues and perinatal progressive decrease of the aneuploid cell line. In the present case, amniocentesis at 17 weeks of gestation revealed 30.8% (8/26 colonies) mosaicism for trisomy 21 in the cultured amniocytes, whereas, there was no genomic imbalance in the uncultured amniocytes, and cord blood sampling at 21 weeks and 23 weeks of gestation revealed a normal karyotype. At 21 weeks of gestation, repeat amniocentesis revealed 7.4% (2/27 colonies) mosaicism for trisomy 21. At birth, the cord blood had 2.5% mosaicism for trisomy 21, and the placenta had complete trisomy 21. 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 resulted no genomic imbalance. This indicates that in case of mosaic trisomy 21 at amniocentesis, repeat amniocentesis for confirmation should always include conventional cytogenetic analysis of cultured amniocytes, even though cord blood sampling and molecular cytogenetic analysis can provide quicker results.

In the present case, the placenta had the karyotype of 46,XX,+21,der(21;21) (q10;q10), and both the amniocytes and the cord blood at birth had the karyotype of 46,XX,+21,der(21;21) (q10;q10)/46,XX. It is likely that the low-level mosaic trisomy associated with mosaic unbalanced Robertsonian translocation of 46,XX,+21,der(21;21) (q10;q10) at amniocentesis could be caused by a trisomy rescue. The zygote formed the embryonic cells with 46,XX,+21,der(21;21) (q10;q10), and during subsequent mitosis, the homologous Robertsonian translocation chromosome der(21;21) (q10;q10) separated into two independent chromosomes, and one of the three independent chromosomes 21 might be lost due to anaphase lag to form a normal karyotype of 46,XX with disomy 21. Another possible mechanism might be the condition that the zygote formed the embryonic cells with 46,XX,+21,der(21;21) (q10;q10), and the cell, during subsequent mitosis, separated into two independent chromosomes 21 and two independent Robertsonian translocation chromosomes der(21;21) (q10;q10), and resulted in one cell with 46,XX carrying two identical chromosomes 21 and one cell with tetrasomy 21q of 46,XX,+i(21q),i(21q) carrying the i(21q) which could not survive.

In summary, we present prenatal diagnosis of mosaic trisomy 21 at amniocentesis associated with unbalanced Robertsonian translocation in the fetus and a favorable fetal outcome. Low-level mosaic trisomy 21 at amniocentesis due to mosaic unbalanced Robertsonian translocation with a normal cell line can be associated with a favorable fetal outcome, cytogenetic discrepancy between cultured amniocytes and uncultured amniocytes, cytogenetic discrepancy among various tissues and perinatal progressive decrease of the trisomy 21 cell line.

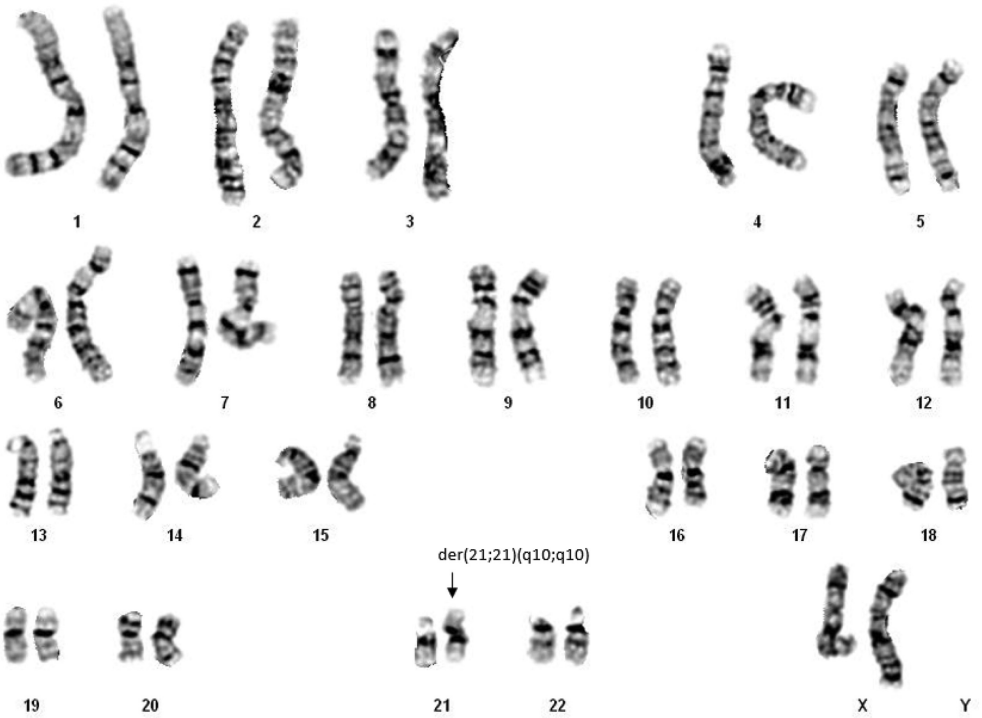

Fig. 1. A karyotype of 46,XX,+21,der(21;21) (q10;q10). der = derivative chromosome.

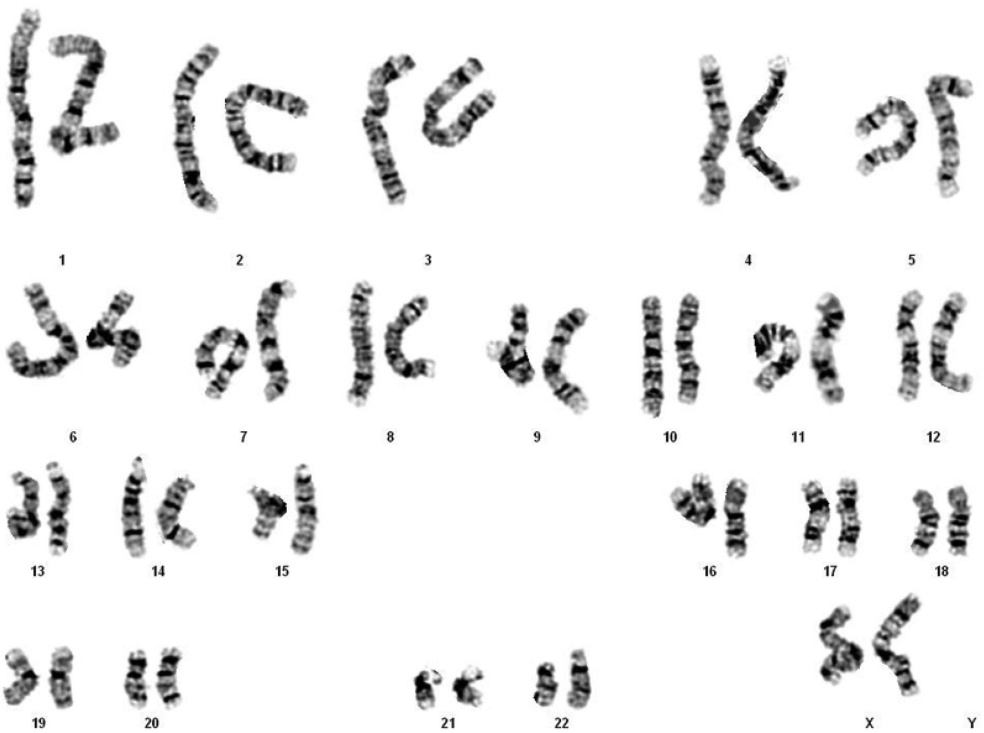

Fig. 2. A karyotype of 46,XX.

Declaration of competing interest

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

Acknowledgements

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Case Report

A case of Fitz-Hugh-Curtis syndrome diagnosed by noninvasive metagenomic next-generation sequencing

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ABSTRACT

Objective: Fitz-Hugh-Curtis Syndrome (FHCS) is an inflammation of the liver capsule as a complication of pelvic inflammatory disease (PID) in sexually active women, mostly associated with *Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae*. Classically presenting as sharp right upper quadrant pain, usually accompanied salpingitis and ascites. With nonspecific clinical presentation and poor specificity, definitive diagnosis needs tissue biopsy and culture by laparoscopy.
Case report: We report the case of a 22-year-old female with a 2-month history of abdominal pain and distention. Symptomatic relief when supportive treatments were given, with the ultrasound and PET-CT suggested advanced bilateral ovarian cancer. After metagenomic next-generation sequencing (mNGS) detected *C. trachomatis* in ascitic fluid. Following anti-infective medication, clinical improvement was satisfactory and the patient was discharged.
Conclusion: FHCS with distention was rare and challenging to diagnose. The mNGS would be a potent, non-invasive pathogen detection method with significant sensitivity and specificity.

Introduction

Fitz-Hugh-Curtis syndrome (FHCS) is occasionally identified in females with malignant gynecological oncology, which manifests as abdominal pain, distension, and ascites. With an incidence rate ranging from 4 % to 27 %, FHCS is considered a relatively uncommon form of pelvic inflammatory disease (PID). It is also known as inflammation of the liver capsule concurrent with pelvic inflammation without hepatic parenchymal damage [1–3]. The prevalence of FHCS is higher among women under 25 years old who recently underwent intrauterine device (IUD) insertion, particularly following vaginal lavage. Teenagers are particularly vulnerable due to the structural characteristics of their genitourinary tract and poor resistance. This vulnerability arises from exposure of the cervix's transitional zone to antigens. *Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae* are the most frequently implicated pathogens causing FHCS. These bacteria often affect sexually active individuals as they pass through the fallopian tube from the vaginal tract to paracolic gutters [4]. According to Nielsen et al., peritoneal fluid rolls from the pelvis to the diaphragm before being typically absorbed on the right side of the upper abdomen. Bacteria flow to the liver capsule, where it forms perihepatic "violin string" fibrinous strands during breathing. The spread of FHCS through blood circulation is rare; infections primarily occur within the abdominal cavity despite lymph nodes existing in retroperitoneal areas. Considering anatomical factors, bacterial infection via lymphatic system involvement remains unlikely.

Acute pain in the right upper quadrant, which may start many days following pelvic pain or may start simultaneously [5], is a common sign of FHCS. Additional symptoms encompass fever, abdominal pain, and vaginal discharge. Nausea, vomiting, and even ileus can also be experienced by individuals [2]. The presence of acute inflammatory exudations circulating within ascitic fluid in the abdominal and pelvic cavities may eventually lead to adhesion formation and potential intestinal obstruction. Consequently, diagnosing FHCS can pose challenges as atypical symptoms could be misinterpreted as cholecystitis, cholangitis, pleuritis, hepatitis, pulmonary embolism, herpes zoster infection or appendicitis.

FHCS diagnosis and particular treatment are consistently delayed due to the lack of precise clinical and laboratory characteristics. Neutrophils and white blood cells may show a slight

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increase or remain within normal range in FHCS patients. Occasionally, an elevated CA-125 level may account for peritoneal irritation. Cultures for *C. trachomatis*, *N. gonorrhoeae*, or PCR for *C. trachomatis* can be used to identify the pathogen, with samples taken from the vagina, urine, and cervix; however, these tests have limited specificity and sensitivity. While radiographic tests are not sufficiently sensitive for accurate diagnosis, they can help rule out other potential diseases such as ectopic pregnancy, tubo-ovarian abscesses, hydrosalpinx, and pyosalpinx endometritis. Key diagnostic criteria for FHCS include obvious adhesions between the liver capsule and abdominal wall observed during laparoscopic examination as well as culture results from lesions [6–9]. Increased perihepatic enhancement in the arterial phase of a computerized tomography (CT) scan is recommended as it can reveal perihepatic "violin string" fibrinous strands in FHCS patients—a powerful diagnostic indicator [3,10–13].

Despite the urgency of early diagnosis, the identification of FHCS remains challenging due to its rarity and nonspecific presentation, heavily relying on surgical intervention and tissue culture. The limited ability to culture vaginal discharge samples leads to prolonged pathogen detection time. Misdiagnosis can result in severe abdominal and pelvic adhesions, leading to ectopic pregnancies and infertility [8]. To safeguard the fertility of young women, it is imperative to enhance diagnostic accuracy promptly with minimal invasiveness. Considering these factors, mNGS may serve as a valuable non-invasive diagnostic method offering high specificity, efficiency, and sensitivity.

Sequencing is an attractive and promising technique for pathogen detection due to the fact that almost all diseases possess genomes composed of either DNA or RNA. By directly extracting nucleic acids from clinical specimens, mNGS represents a high-throughput sequencing technology capable of identifying pathogens without the need for culture. This method relies on nucleic acid levels for sequence detection and can identify not only live pathogens but also bacteria, fungi, viruses, and other pathogenic microorganisms. Moreover, it overcomes limitations imposed by different types of pathogens and provides unbiased, comprehensive coverage of tens of thousands of pathogens. In addition to these advantages, mNGS has gradually emerged as a pivotal tool in the field of clinical microbiology, particularly for rapid response to emerging infectious diseases caused by novel pathogens; consequently reducing the detection time from conventional 2–5 days to just 24 h.

Case report

A 22-year-old woman with no significant medical history visited the emergency room complaining of vaginal discharge for three days and genital bleeding the next day. Little intrauterine effusion was showed on ultrasound. Following a week of taking estradiol valerate tablets for hemostasis, she experienced abdominal pain, distension, anorexia with flatulence, and feces. Due to acute persistent upper abdominal discomfort, high temperature, nausea, vomiting, and sweating that persisted for several days thereafter, she revisited the emergency room. Physical examination indicated stable hemodynamics and the auscultation of the lungs and heart was normal. Palpation revealed soft depressible tenderness on superficial palpation and mild lower abdominal pain. Hepatobiliary-pancreatic-splenic ultrasound as well as urinary system ultrasound showed no abnormalities. She was admitted to the hospital where intestinal obstruction was diagnosed. Blood routine test results displayed an increased white blood cell count of 9.94*109/L along with a high NEUT% of 80.5 %. Gastroenterological endoscopy revealed chronic superficial gastritis accompanied by bile reflux. The abdominal CT scan revealed aerenterectasia, mesenteric lymph node hyperplasia, abdominal and pelvic effusion, and a few small exudations surrounding the pancreas. She underwent supportive treatment including fasting, acid suppression, spasmolytic administration, and parenteral nutrition for one month. However, imaging studies indicated potential malignancy in oncology. Gynecological ultrasound showed left salpingitis and mass seroperitoneum. Pelvic CT scan suggested left ovarian cancer while excluding inflammation, mass ascites, and enlarged lymph nodes. Subsequently, a PET/CT scan was conducted (Fig. 1), which identified an active mass on both adnexa that was likely indicative of ovarian cancer as well as active lymph node hyperplasia at the cardiophrenic angle and retroperitoneal space suggesting metastasis. The scan also revealed thickened peritoneum in the pelvis and abdomen with increased metabolic activity along with significant pelvic and abdominal effusion.

Considering these diagnoses, she was transferred to our hospital in October with a chief complaint of abdominal pain and distension accompanied by irregular menstruation for 2 months. A physical examination revealed abdominal distension and positive shifting dullness. During the gynecological examination, cervical contact bleeding was observed, the posterior fornix appeared full, and a 4*3 cm mass was identified on bilateral adnexa. This mass exhibited slight tenderness but no rebound tenderness. Examination of the leukorrhea suggested *Candida glabrata* infection. Regarding fallopian tube cancer, a gynecological ultrasound revealed a duct-like tumor measuring 41 mm*20 mm adjacent to the left ovary and a mass measuring 40 mm*24 mm next to the right ovary (Fig. 2A and B). She underwent peritonrocentesis; however, ascites culture yielded negative results with no evidence of cancer cells.

Despite imaging tests suggesting bilateral ovarian/fallopian tubal carcinoma based on her age, family history, and current symptoms, she was suspected of having a benign gynecological disease. However, enhanced CT on admission indicated Fitz-Hugh Curtis syndrome. To identify the causative pathogens, metagenomic next-generation sequencing (mNGS) was recommended to detect ascites, which revealed positive *C. trachomatis* within 24 h (Fig. 3). Subsequently, PCR was performed to detect the presence of *C. trachomatis* in both cervical secretions and ascites, with positive results obtained after 3 days. Considering the patient's clinical manifestations and mNGS findings, a diagnosis of *C. trachomatis*-induced Fitz-Hugh-Curtis syndrome (FHCS) was established. Due to *Candida glabrata* infection identified through leucorrhea culture, anti-infective treatment comprising Azithromycin 0.5g qd and Itraconazole 100 mg qd for 5 days was initiated on the following day (Fig. 4). Following this intervention, there was a significant reduction in ascites volume; however, bilateral tubal masses remained unchanged based on gynecological ultrasound assessment. The CA-125 level decreased to 625.6 U/ml, indicating treatment efficacy. Considering potential drug resistance issues, the anti-infective therapy regimen was switched to moxifloxacin 0.4g qd and itraconazole 100 mg qd for an additional duration of 7 days. Subsequently, ultrasonography findings were unremarkable (Fig. 2C–F), and the CA-125 level decreased to 480.5 U/ml, leading to the patient's discharge on the following day. The comprehensive summary of admission details and significant laboratory results before and after treatment is presented in Table 1.

Follow up

She has achieved complete recovery, exhibiting no further symptoms of abdominal pain or bloating. All supplementary tests yielded negative results (Fig. 2G and H).

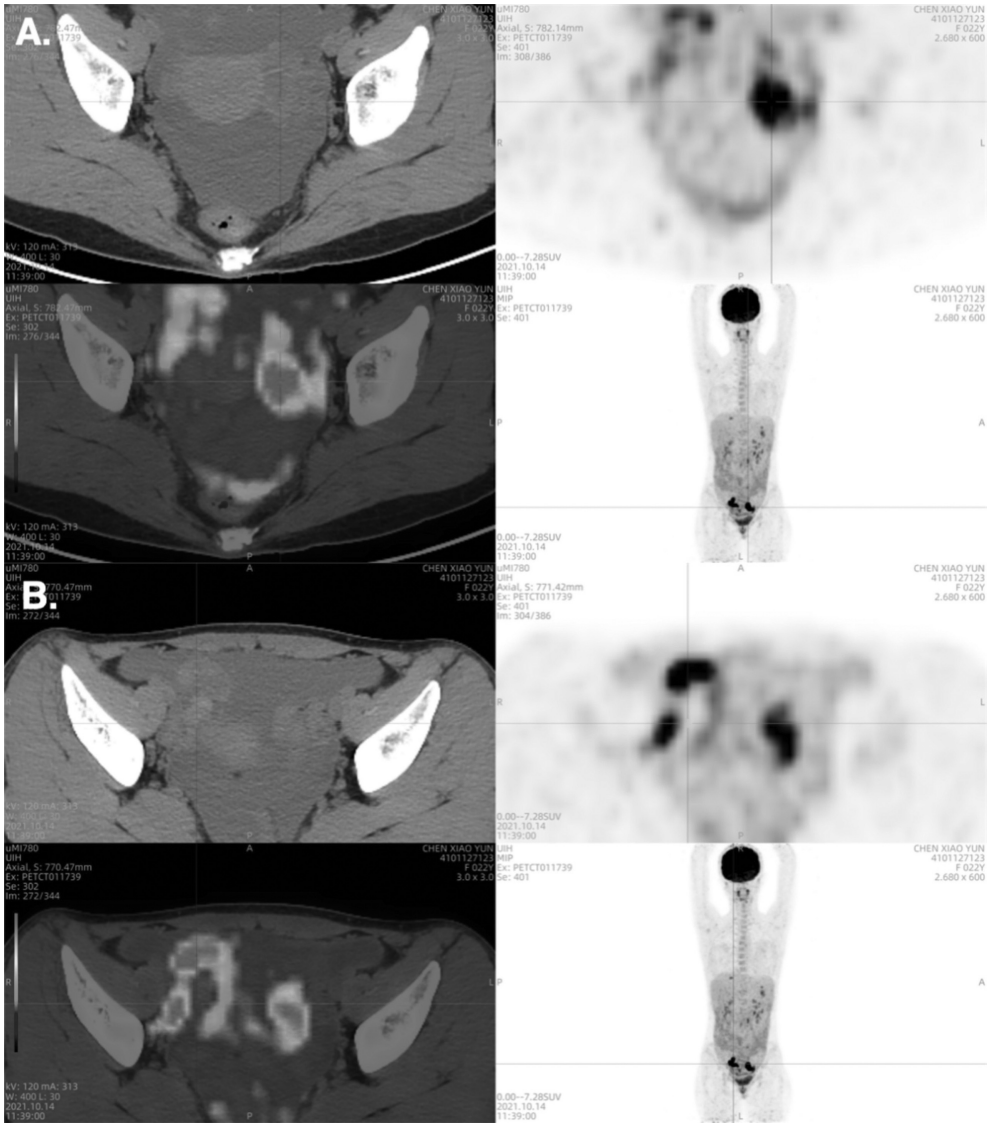

Fig. 1. Picture of PET-CT. (**A**) Left side of left adnexa. (**B**). Right side of adnexa. Both side of adnexa showed a mass, 4.8containing solid and cystic components with obscure boundary. FDG uptake increased uneven, SUVmax 18.0, delayed imaging SUVmax 18.3.

Discussion

FHCS is a rare inflammation of the liver capsule associated with genital tract infection, commonly caused by *N. gonorrhoeae*, *C. trachomatis*, and *Mycobacterium tuberculosis*, particularly *C. trachomatis* [14]. Sexually active women are susceptible to FHCS. Common symptoms include right upper abdominal pain, fever (>38.3 °C), and hypoactive bowel movements. In addition, some females may also present with intestinal obstruction and significant pelvic and abdominal effusion. Visible signs during a gynecological examination include vaginal discharge, cervical contact bleeding, cervical motion pain, and adnexal soreness. Furthermore, non-specific laboratory testing reveals that 50 % of patients may exhibit normal or elevated neutrophil and white blood cell counts [14]. An increased CA-125 tumor marker level could be attributed to peritoneal irritation. Radiographic examination results indicate the presence of endometritis, tubo-ovarian abscess, hydrosalpinx, and pyosalpinx. PET-CT suggests the existence of significant pelvic and abdominal effusion, an adnexal malignant tumor with abundant blood supply, as well as retroperitoneal lymphadenopathy. Laparoscopy and biopsy, the two most crucial diagnostic tools, can identify perihepatic “violin string” fibrinous strands between the liver capsule and abdominal wall. Even though enhanced CT imaging may suggest FHCS [3], it is essential to utilize laparoscopy and biopsy for accurate diagnosis. The DNA probe of *C. trachomatis* and genital pathogen culture can provide supportive evidence for diagnosing FHCS, however, their sensitivity is relatively low. Identifying FHCS can be challenging due to its resemblance in physical characteristics with other disorders causing discomfort in the right upper abdomen, such as cholelithiasis, cholecystitis, pleurisy, and pyelonephritis.

The 22-year-old patient initially presented with acute abdominal discomfort, fever, and symptoms suggestive of bowel obstruction. Despite receiving symptomatic treatment for approximately one month, radiography revealed bilateral tubal carcinoma. However, the lesion remained uncontrolled and these interventions did not aid in confirming the diagnosis. Upon admission to our hospital, she was diagnosed with advanced ovarian

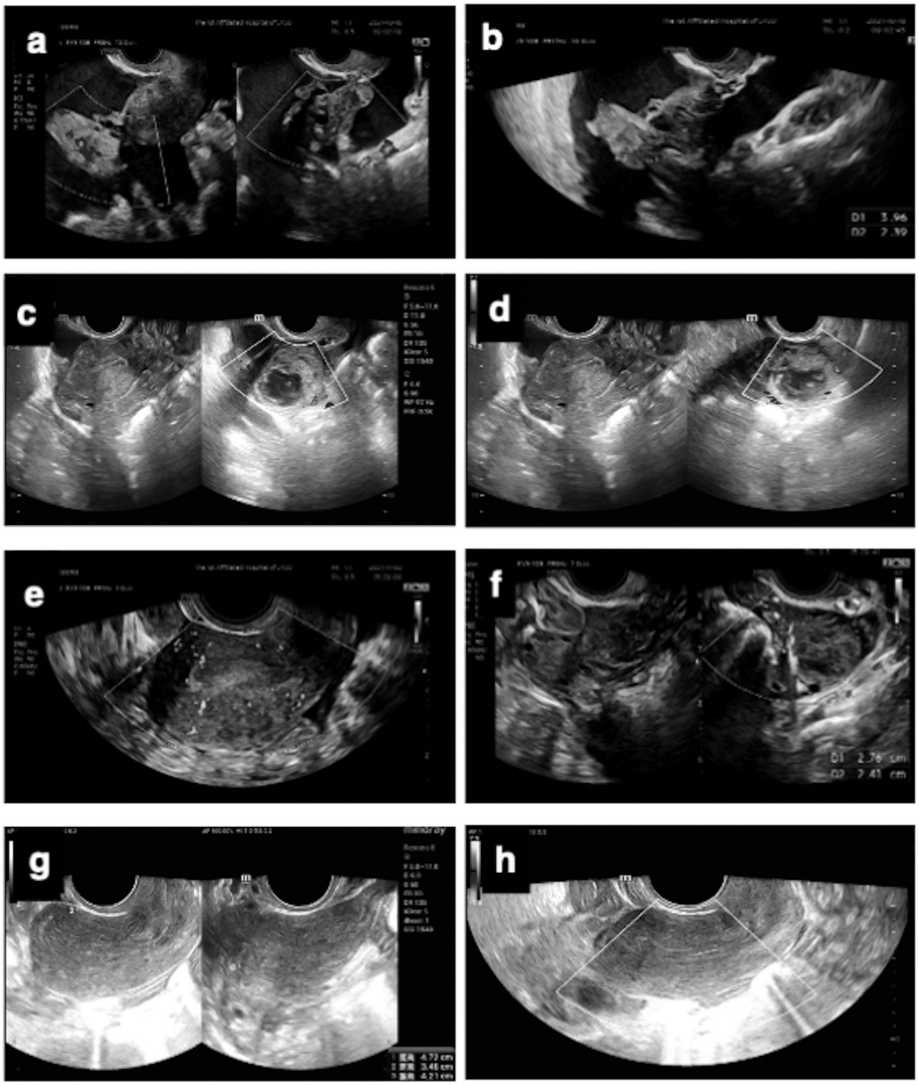

Fig. 2. Gynecological ultrasound.
Fig. 2A–B (2021.10.18) Ultrasound images. (A) A duct-like mass was 41mm × 20 mm beside left ovary, (B) another duct-like mass beside right ovary was 40 mm × 24 mm. Both of mass has irregular appearance with has obscure boundary. The solid part of the mass had rich blood supply. The max diameter of echo free area in pelvic was 79 mm. Considered fallopian cancer.
Fig. 2C–D (2021.10.27) Ultrasound images. Left ovarian cyst was 36 mm × 39 mm with clear boundary and cloudy mixed echo. The blood flow was abundant around the mass. (C) A duct-like mass on the left side of uterus was 50 mm × 14 mm, (D) another duct-like mass was 35 mm × 14 mm. Both of mass has irregular appearance with has obscure boundary. The solid part of the mass had rich blood supply. The max diameter of echo free area in pelvic was 30 mm.
Fig. 2E–F (2021.11.2) Ultrasound images. (F) The duct-like mass was 28 mm × 24 mm with clear boundary. The solid part of the mass had rich blood supply, and reticular high echo in it. Considered hemorrhagic corpus luteum. (E) No abnormal findings in the right adnexa.
Fig. 2G and H (2021.11.11) Ultrasound images No abnormal findings in the pelvic.

cancer. In this clinical scenario, she would undergo cytoreductive surgery followed by 6–8 cycles of chemotherapy. It is important to note that she may experience long-term postoperative pain and potential loss of fertility. Chronic stomach and pelvic pain, ectopic pregnancy, and infertility can all result from this operation. However, we disregarded benign conditions for the following reasons. Firstly, she initially presented with symptoms consistent with pelvic inflammatory disease (PID), including a high fever, abdominal pain, and vaginal discharge. Secondly, considering her young age within the reproductive years, PID was more likely to be the cause rather than ovarian or tubal cancer. Bilateral tubal carcinoma is particularly rare as tubal cancer itself is uncommon; typically occurring in individuals over 50 years old. Thirdly, there was no family history of cancer. Lastly, the rapid progression observed in her case made it unlikely to be cancerous; while it takes a month for a unilateral tumor to develop into bilateral involvement, her condition progressed bilaterally within just three days. Cervical and vaginal specimens were cultured, taking into consideration these factors, revealing the presence of candida glabrata. An abdominocentesis was performed to detect cancer cells, however, no cells were found and pathogen culture yielded negative results. Ascites examination using metagenomic next-generation sequencing (mNGS) suggested *C. trachomatis* infection, confirming the presence of the pathogen. Treatment was initiated based on these findings with Itraconazole 100 mg qd and Zithromax 0.5g qd for 5 days. Upon admission, gynecological ultrasound showed a significant reduction in ascites volume compared to previous measurements but bilateral tubal masses remained unchanged. CA-125 levels decreased by more than 50 %. Following successful treatment, the patient received a course of anti-infective therapy consisting of

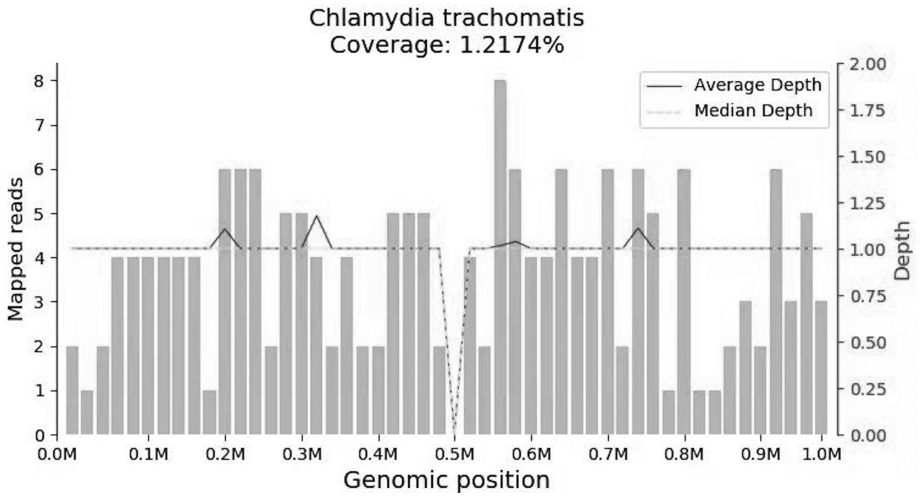

Fig. 3. The mNGS result. 212 specific *Chlamydia trachomatis* sequences that covered 1.2174 % of the total *Chlamydia trachomatis* genome were detected by mNGS in the ascitic fluid sample of the patient.

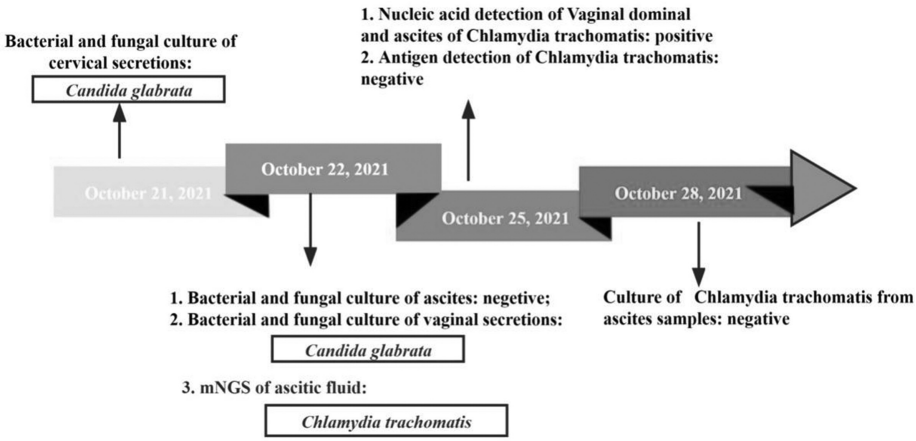

Fig. 4. The process of pathogen detection.

Table 1

Laboratory Parameters	On Admission	After Treatment	Normal Range
WBC	7.08	NA	4.00–10.00
NEUT%	70.1	47.2	0.46–0.75
NEUT	4.97	4.8	1.80–6.40
CRP	4.91	0.32	0.00–10.00
CA125	1104.4	40.8	0.00–35.00
Chlamydial Trachomatis	+	–	–

moxifloxacin 0.4g qd and itraconazole 100 mg qd for seven days. Subsequently, CA-125 levels significantly decreased and an ultrasound revealed no abnormalities were present. Ultimately, the patient retained her reproductive capacity while avoiding surgical intervention or chemotherapy.

The critical stage in the diagnosis of FHCS is the identification of the pathogen; however, culturing genital secretions has limitations due to potential interference from other microbes, which can impact the sensitivity and specificity of this test. Moreover, detecting *N. gonorrhoeae* or *C. trachomatis* in ascites fluid poses challenges, with reporting results taking three to five days. In some cases, continuous culture is necessary, leading to significant delays in patient diagnosis and treatment as well as increased economic burden. Conversely, although a biopsy serves as the gold standard for diagnosing FHCS, it presents several drawbacks including invasiveness during laparoscopic exploration. On the second, Sensitive antibiotics are the most effective treatment for the acute phase of pelvic inflammatory disease (PID), while surgical intervention is effective for single lesions but not recommended for pelvioperitonitis. However, surgery may exacerbate the condition by causing pelvic adhesions, ileus, pelvic discomfort, infertility, and ectopic pregnancy. Moreover, surgical procedures can result in increased costs. In comparison to traditional auxiliary examination assays, metagenomic next-generation sequencing (mNGS) based on nucleic acid levels enables testing of various pathogen types and provides unbiased and comprehensive coverage of tens of thousands of pathogens simultaneously. Therefore, mNGS has gradually emerged as an important tool in clinical microbiology, particularly for rapid response to emerging infectious diseases caused by novel pathogens with detection time shortened from conventional 2–5 days to 24 h.

The mNGS technique enables noninvasive identification of the precise pathogen within 24 h, using easily obtainable specimens. Hence, mNGS is particularly suitable for patients presenting with high fever and unexplained infections, when routine test results yield negative findings.

Conclusion

FHCS is a complicated PID that is challenging to diagnose. Laparoscopic investigation is invasive and costly while tissue culture lacks sensitivity and specificity. mNGS may provide a more accurate, specific, and noninvasive diagnostic approach.

Authors' contributions

Professor Mian He made a significant contribution for this report. She was attending doctor of this patient. She took charge of oversight and leadership responsibility for the research activity planning and execution. Chengcheng Ding wrote the manuscript and performed data curation. Run chen performed data curation, editing and review. Peng Guo performed editing and review. Juhua Yang performed illustration and polish the manuscript.

Declaration of competing interest

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

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Case Report

Erosive stitches of cervical cerclage as a factor of abnormal uterine bleeding: A report of two cases

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ABSTRACT

Objective: Abnormal uterine bleeding (AUB) is a prevalent condition in reproductive-aged women that significantly decreases the quality of life. A thorough history is necessary to determine the causes of AUB, which were categorized by the AUB System 2 (PALM-COEIN). AUB has been associated with retained intrauterine objects. However, studies regarding AUB caused by retained stitches of the cervical cerclage were limited.
Case Report: We present two cases of AUB caused by retained stitches of the cervical cerclage. Both cases were successfully treated by removing the retained stitches by hysteroscopy.
Conclusion: A comprehensive history is crucial to AUB evaluation, especially a previous history of iatrogenic processes, such as intrauterine device placement, retained cerclage stitches, or other foreign bodies.

Introduction

Abnormal uterine bleeding (AUB) is a prevalent condition in reproductive-aged women that can significantly decrease the quality of life and increase medical expenses [1]. The prevalence of AUB was approximately 35% [2], and the symptoms can vary from each individual but may include heavy bleeding, prolonged bleeding, bleeding between periods, or irregular periods. The effect of AUB depends on its severity, duration, and underlying disease and may result in iron-deficiency anemia, pain, fertility problems, and disruption to a woman's daily life and activities, thereby causing stress, anxiety, and mental illness.

A variety of factors, including hormonal imbalances, uterine fibroids or polyps, malignancy, pregnancy complications, thyroid dysfunction, and certain medications, can cause AUB. Comprehensive history, sonography, official hysteroscopy, and endometrial sampling may identify the causes of AUB. The International Federation of Gynecology and Obstetrics first developed an AUB classification system, named Polyps, Adenomyosis, Leiomyoma, Malignancy and Hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not yet classified (PALM-COEIN), to categorize AUB based on the underlying causes in 2011 and revised AUB System 2 in 2018 [3]. This system enables a more comprehensive AUB evaluation and helps guide appropriate diagnostic and treatment options. An intrauterine foreign body may contribute to the AUB [4]. Hysteroscopy stands out as a precise tool for assessing the underlying causes of AUB. In this context, we highlight two cases of AUB resulting from erosive stitches of the cervical cerclage, both effectively addressed through hysteroscopic removal.

Case Report

Case 1

A 53-year-old female patient experienced failed Macdonald cervical cerclage because of the short cervix, which caused a previable preterm delivery at 21 weeks of gestation in 2003, followed by abdominal cerclage placement with tape during the next pregnancy at 18 weeks of gestation in 2005. Unfortunately, preterm prelabor rupture of membranes with fetal death occurred after 6 weeks, and a subsequent classical cesarean delivery was performed. The Mersilene tape was left in place for furthermore pregnancies. However, she did not get pregnant in the following time.

In 2022, after 16 years, she presented to our gynecologic department with complaints of intermenstrual bleeding that was

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unresponsive to medical treatments. Transvaginal ultrasound confirmed the existence of a foreign body in the endocervix. Hysteroscopy revealed a suture tape with a knot in the endocervix, which was successfully removed (Fig. 1a–c).

Case 2

A 40-year-old female patient, gravida 3, para 2, presented to our gynecologic outpatient department with prolonged bleeding. Cervical insufficiency (CI) was diagnosed with a history of previable abortion at 18 weeks of gestation. She then received two surgeries of McDonald's cerclages in 2015 and 2018, respectively, followed by two successful term pregnancies. The patient stated both cerclages were removed postpartum.

She had received conservative treatment, including nonsteroidal anti-inflammatory agents and hormonal management, but intermenstrual bleeding persisted. Transvaginal ultrasound revealed intrauterine high echogenicity that mimicked an intrauterine device. We removed the residual cerclage tape by hysteroscopy thereafter (Fig. 1 d–f).

Discussion

CI is one of the causes of preterm birth. It affects approximately 1% of pregnant women, half of whom may require a cervical cerclage placement based on their medical history or clinical conditions. Indications for cervical cerclage include a history of previous second-trimester pregnancy losses or preterm birth with the sonographic finding of short cervical length. The two most commonly used techniques for cervical cerclage were the transvaginal McDonald and Shirodkar procedures. The McDonald procedure involves a purse-string stitch insertion around the upper portion of the vaginal cervix and provides relative ease of cerclage placement and removal. A transabdominal cervical cerclage is performed when transvaginal procedures fail. Intrauterine infection, bleeding, suture displacement, incomplete suture removal, and vesicocervical fistula or erosion into the bladder are complications following a cervical cerclage placement [5–9].

Considering these risks, the American College of Obstetricians and Gynecologists recommended the complete removal of the cerclage in patients between 36 and 37 weeks of gestation or during delivery for those who choose a cesarean delivery. A transabdominal cervical cerclage might be retained in place for subsequent pregnancies. Cerclage was performed with nonabsorbable sutures to maintain a closed cervix and prolong pregnancies. The suture should be removed after their childbirths are completed. Some sutures may be difficult to remove, or they may have been incompletely removed during late pregnancy. The residual suture may migrate into surrounding tissue, including the bladder, endocervical, or uterine cavity, because of the effect of pressure. The erosive suture caused infection and bleeding.

The patients may not undergo this procedure according to the practice during stitch removal at different institutions despite the importance of cervical cerclage removal. A previous study reported the theoretical risk of forgetting to remove the stitches for patients choosing elective cesarean sections. Furthermore, patients in Taiwan were more likely to leave their districts to acquire prenatal care in large hospitals, thus they may not receive subsequent follow-up at the same institution during the postpartum period [10]. Once the patient does not undergo surgery for removal at the previous institution, it becomes more difficult to address this problem unless a thorough history is obtained. Consistent with a previous report, a patient presented with AUB was observed to have an intrauterine foreign body initially [11]. The patient revealed a history of receiving a cervical cerclage 23 years ago during her second pregnancy after obtaining a detailed history.

Regarding the causes of AUB, the "I" that represented "iatrogenic causes" in the PALM-COEIN system usually include intrauterine systems or devices and systemic pharmacotherapy with hormone therapy or anticoagulants. Our two cases presented with AUB caused by migrating stitches of cervical cerclage in the intrauterine cavity, which was rarely mentioned in the iatrogenic causes of AUB and reported in previous literature [12]. Regarding intrauterine

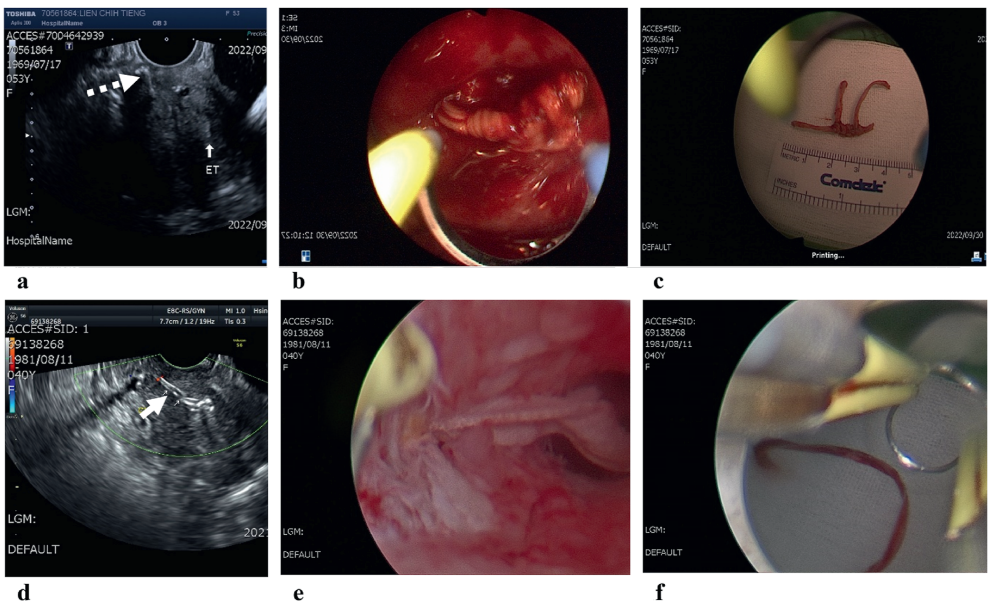

Fig. 1a. Transvaginal ultrasound showing a linear hyperechoic content (dashed arrow) at the endocervix. b) Hysteroscopy revealing a suture tape with a knot in the endocervix. c) Suture (Mersilene tape) removal by means of hysteroscopy. d) Transvaginal ultrasound showing a linear hyperechoic content (white arrow) at the endocervix. e) Hysteroscopy revealing a suture tape in the endocervix. f) Suture (Mersilene tape) removal by means of hysteroscopy.

foreign bodies other than retained stitches that cause AUB, previous literature reported fetal bones and forgotten parts of intrauterine contraceptive devices [5,13]. Therefore, taking both obstetric and gynecologic histories thoroughly, especially a previous history of iatrogenic processes, such as placement of intrauterine devices, retained stitches of cerclage, or other foreign bodies, which are classified in the "I" of the PALM-COEIN classification system for patients with AUB. Additionally, cerclage removal is necessary during the postpartum follow-up periods if the patient does not have future reproductive plans because of the possibility of stitch migration and erosion, causing AUB and infection according to the site of migration in the future. Foreign body in the uterine cavity is the cause of AUB and is consider to be removed.

Conclusion

A comprehensive history is crucial to AUB evaluation. Taking both obstetric and gynecologic history thoroughly, especially a previous history of iatrogenic processes, such as intrauterine device placement or retained cerclage stitches, is important. Additionally, cerclage removal during the postpartum follow-up periods is mandated if the patient does not have future reproductive plans to reduce the AUB or infection because of the possibility of stitch migration and erosion in the future. The migration of cerclage Mersilene tape can induce AUB, and hysteroscopy proves to be an accurate method for identifying and removing the tape.

Declaration of competing interest

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

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Case Report

Drug-induced thrombotic microangiopathy after adjuvant chemotherapy in malignant ovarian germ cell tumor: A case report and literature review

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ABSTRACT

Objective: We presented a rare case of drug-induced thrombotic microangiopathy (DI-TMA) following chemotherapy with the regimen of bleomycin, etoposide, and cisplatin (BEP) in a patient with malignant ovarian germ cell tumor (MOGCT). The objective is to highlight the difficulty in diagnosing and treating DI-TMA associated with BEP chemotherapy.
Case report: A 21-year-old woman presented with a pelvic mass. Fertility-sparing staging surgery was performed, and a diagnosis of endodermal sinus tumor was confirmed. The patient received the first course of adjuvant chemotherapy with BEP regimen, but she developed symptoms of anemia, thrombocytopenia, and acute kidney injury. DI-TMA was diagnosed after thorough examinations, and she improved gradually by three courses of plasma exchange. Adjuvant chemotherapy was discontinued due to DI-TMA, and she kept disease-free for 17 months after the operation.
Conclusion: DI-TMA, a rare lethal complication in MOGCT patients receiving the BEP regimen, requires prompt diagnosis and appropriate treatments.

Introduction

Malignant ovarian germ-cell tumors (MOGCTs) account for approximately 1–2% of ovarian cancer, commonly in adolescents and children. Endodermal sinus tumor (EST), also known as yolk sac tumor, account for 20% of MOGCTs. Due to the favorable prognosis and prevalent in women of reproductive age, fertility-sparing staging surgery and adjuvant chemotherapy using regimen of bleomycin, etoposide and cisplatin (BEP) have widely accepted [1]. Common side effects of BEP regimen include myelosuppression, gastrointestinal symptoms and alopecia. Drug-induced thrombotic microangiopathy (DI-TMA) is a rare fatal complication, and only few cases of DI-TMA related to BEP treatments had been published in the literature [2,3]. Here, we reported one case of DI-TMA after chemotherapy with BEP regimen in one patient of MOGCT. The difficulty regarding diagnosis and treatment of BEP-related TMA was also illustrated.

Case presentation

It was approved by the ethics committee of the institutional review board of our hospital, and the patient provided written informed consent. A 21-year-old, G0P0, woman presented to our hospital for a pelvic mass. The initial complaints were lower abdominal dull pain and abdominal distension for one month, while she denied poor appetite, body weight change, abnormal vaginal bleeding, bowel habit change, or lower urinary tract symptoms. Her medical history included dilated cardiomyopathy with decompensated heart failure status post orthotopic heart transplantation at 14-year-old, using Everolimus and Tacrolimus for 7 years. She had no family history of cancer.

Physical examinations revealed one movable hard mass occupying in the pelvis with the size about 13~14 cm. The sonography showed one large solid pelvic mass with strong vascular flow

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signals (resistive index 0.36, with malignancy feature of IOTA rule: irregular solid tumor and strong flow, simple rule risk estimated risk of malignancy = 97.6%) (Fig. 1A). The results of computed tomography scan were compatible to the sonographic findings, while no regional nodal metastasis or distant metastasis was noted (Fig. 1B). Serum CA-125 was 257.0 U/mL, and alpha-fetoprotein was 3166.15 ng/ml. Fertility-sparing staging laparotomy was performed, including left salpingo-oophorectomy, left pelvic lymph node sampling and omentum biopsy (Fig. 1C). The pathology report revealed endodermal sinus tumor of the left ovary, which the tumor cells had oval nuclei, conspicuous nucleoli, and scanty clear cytoplasm, while frequent hyaline globules were noted (Fig. 1D). The IHC stain showed positivity for glypican-3 in most tumor cells and negativity for CD30 (Fig. 1E). There was no malignant cell in the lymph node, omentum and peritoneal washing cytology. The International Federation of Gynecology and Obstetrics (FIGO) stage IA was assigned based on tumor limited to left ovary.

The adjuvant chemotherapy with BEP regimen for a total 3 courses were planned, and she received the first course of adjuvant chemotherapy smoothly. However, profuse vaginal bleeding, exertional dyspnea, dizziness, poor appetite and general malaise were noted 1 week after chemotherapy. She was brought to emergency department where physical examination revealed tachycardia (110 beats per minute). Significant laboratory findings were hemoglobin of 4.4 g/dL and hematocrit of 13.2%, platelet 7000/μL, lactic acid 5.45 mmol/L, serum creatinine (Cre) 5.6 mg/dL. Chemotherapy related anemia and thrombocytopenia with pre-renal acute kidney injury were impressed, and she was admitted for supportive care.

However, the patient's hemostasis, renal functions and general symptoms showed limited improvement under blood transfusions and conservative treatments (Fig. 2). Medical doctors were consulted for inadequate recovery of renal functions and anemia. Immune profiles, including immunoglobulins, complements and auto-antibodies, were checked and all showed normal results. No active viral or bacterial infection was noted according to lab data and clinical manifestation. The additional lab data showed lactate dehydrogenase (LDH) 2258 U/L, haptoglobin <29.00 mg/dL, total bilirubin (T-bil) 0.75 mg/dL, direct bilirubin (D-bil) 0.13 mg/dL, indirect bilirubin 0.62 mg/dL, and negative indirect Coomb's test. Peripheral blood smear showed schistocytes 8–10/HPF. ADAMTS13 activity was within normal limit (0.79985 IU/Ml; 76%) which excluded thrombotic thrombocytopenic purpura. No pathogenic mutation was found in gene sequencing analysis related to atypical hemolytic uremic syndrome (aHUS) by MGIEasy Exome Kit on the DNBSEQ-G400 Genetic Sequencer, including *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR5, DGKE, ADAMTS13, C2, C3AR1, C4BPA, CFD, CFHR2, CFHR3, CFHR4, MASP2, MMACHC, PLG, WT1, C5: p. Arg885, VWF, CR1* and *MASP1.* Thus, TMA syndrome was impressed, and the renal biopsy showed segmental sclerosis accompanying mild endocapillary, mesangial hypercellularity and mild matrix expansion of the renal glomeruli. The tubules reveal focal injury with some isometric vacuolization of the tubular cytoplasm. The included muscular arteries show moderate arteriosclerosis with intimal fibrosis, which were compatible with TMA with arteriosclerosis and segmental glomerulosclerosis (Fig. 3.) BEP induced TMA with severe microangiopathic hemolytic anemia and acute kidney injury were diagnosed. She received 3 courses of plasma exchange and conservative supportive treatments. LDH decreased to 365 U/L, and hemogram and renal functions improved gradually. The levels of total bilirubin, direct bilirubin and indirect bilirubin remained within normal limits in the course. Adjuvant chemotherapy was discontinued due to TMA syndrome, and she was disease free 17 months after the operation.

Discussion

Thrombotic microangiopathy (TMA) is a broad spectrum of disorders that cause occlusive microvascular or macrovascular

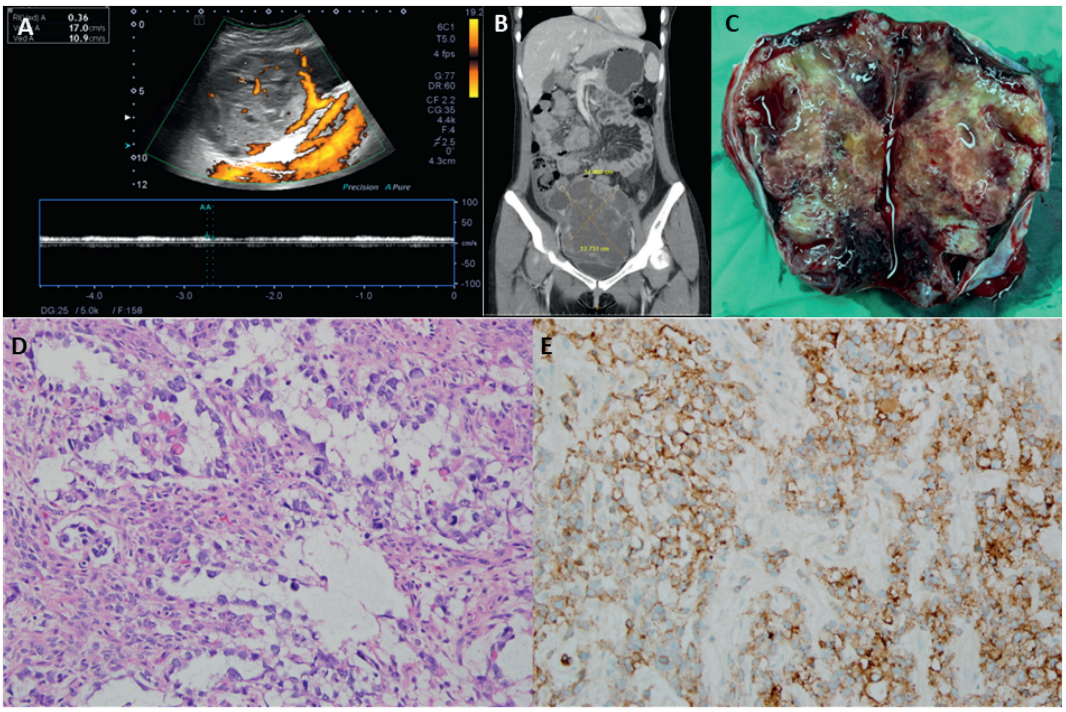
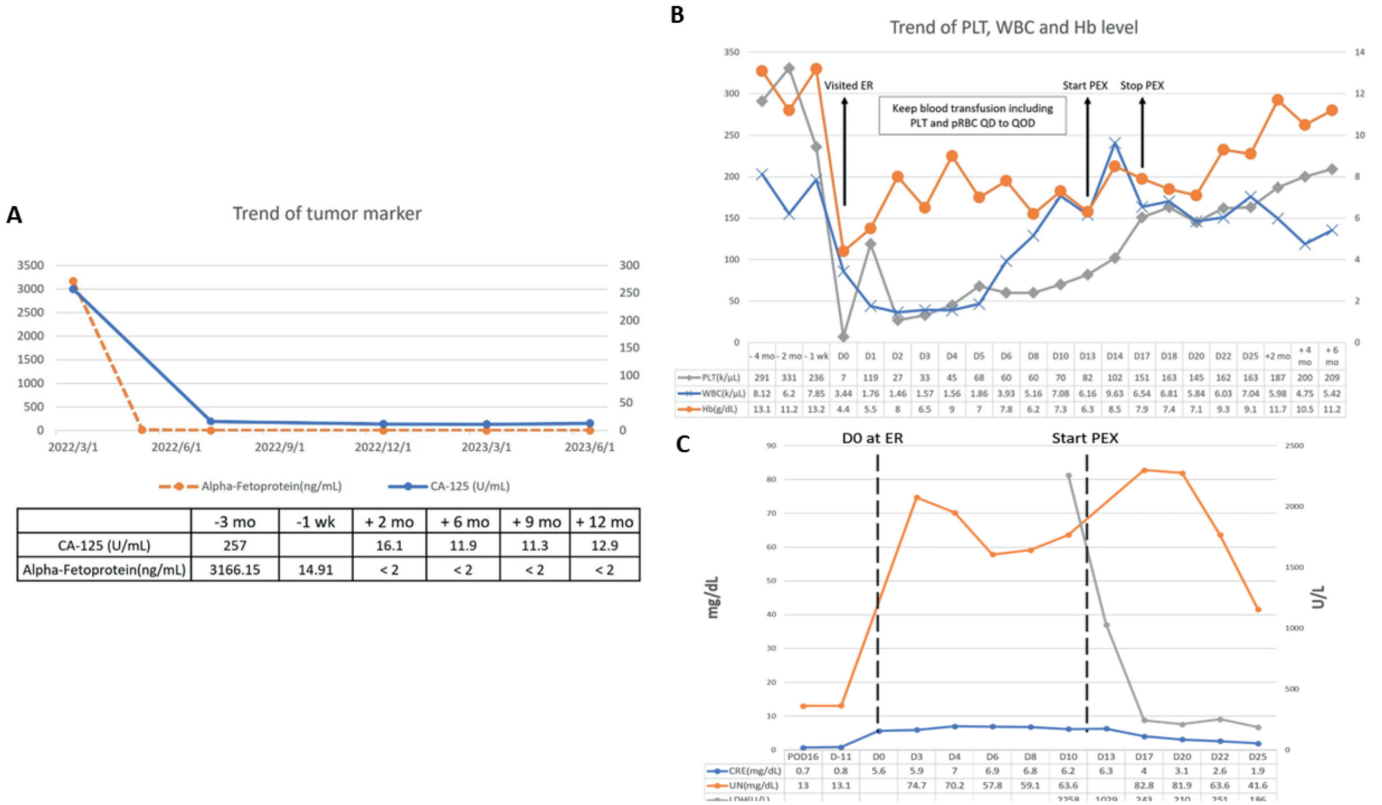


Fig. 1. Clinical and pathological characteristics of the patient. (A) Transabdominal sonography showed one huge solid pelvic tumor with 97.6% of IOTA simple rule risk estimated risk of malignancy. (B) Computed tomography revealed a large tumor with complex components in the pelvis, up to 14 cm. (C) Operation finding showed one 15cm × 8.5 cm x 8.5 cm solid tumor. (D) The left ovary shows yolk sac tumor arranged in reticular, cystic, and papillary patterns. The tumor cells have oval nuclei, conspicuous nucleoli, and scanty clear cytoplasm. (E) Most tumor cells are positive for glypican-3.



	-3 mo	-1 wk	+ 2 mo	+ 6 mo	+ 9 mo	+ 12 mo
CA-125 (U/mL)	257		16.1	11.9	11.3	12.9
Alpha-Fetoprotein(ng/mL)	3166.15	14.91	< 2	< 2	< 2	< 2

Fig. 2. The changes of the blood tests in the course. (A) The trends of tumor markers. (B) The trends of PLT, WBC and Hb level in the course. (C) Elevated levels of Cre and blood urea nitrogen were observed in the initial 10 days following the patient's visit to our emergency department, despite receiving appropriate supportive care. Following three sessions of plasma exchange, the levels of Cre and LDH decreased. Consequently, the patient was discharged on the 25th day of hospitalization.

thrombosis. Diagnosis is made by demonstrating evidence of microangiopathic hemolytic anemia (MAHA), non-immune thrombocytopenia and/or end-organ ischemia (e.g., brain, heart, kidneys), often associated with high morbidity or mortality. MAHA could be classically characterized elevation of lactate dehydrogenase, indirect bilirubin, and reticulocytes while haptoglobin might be decreased. Peripheral blood smear could give more information of hemolytic anemia if schistocytes is found [4]. All types of diseases share similar pathologic features such as vascular damage that manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall. In addition to this triad, other characteristic symptoms and signs are non-specific, such as unexplained severe hypertension and neurologic manifestations [5].

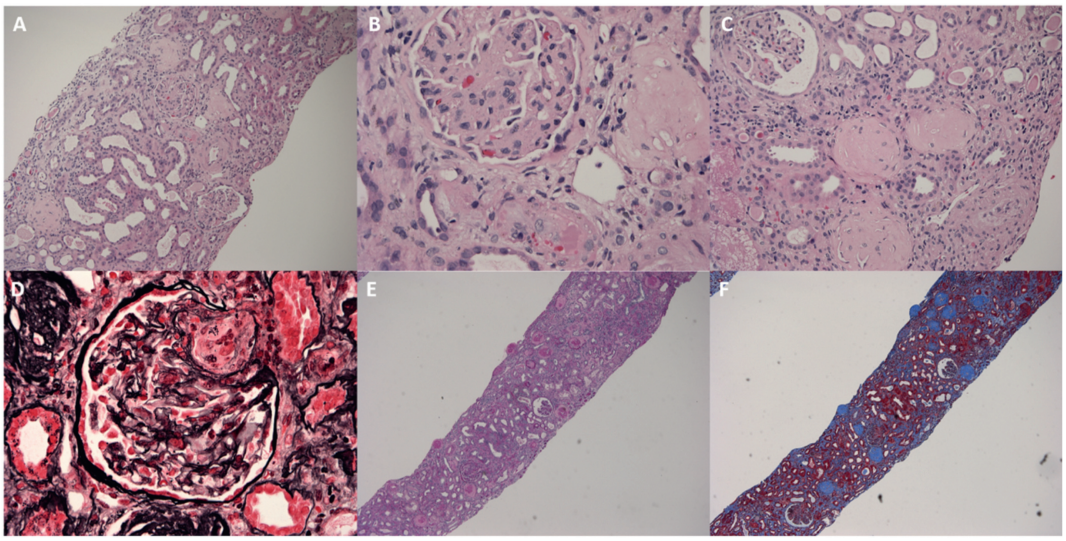


Fig. 3. Pathology section of kidney biopsy. (A, B) The H&E stain of glomeruli shows mild shrinkage change with segmental sclerosis accompanying mild endocapillary and mesangial hypercellularity and mild matrix expansion. The interstitium discloses mild inflammatory cell infiltration (20~25%). (C) The included muscular arteries show moderate arteriosclerosis with intimal fibrosis. (D) CSM stain reveals mild double contour of glomerular capillary walls. (E) PAS stain discloses mild tubular atrophy (10~15%). (F) Masson trichrome stain discloses mild interstitial fibrosis (20~25%). It is compatible with TMA with arteriosclerosis and segmental glomerulosclerosis.

Table 1
Summary of previous published cases of ovarian germ cell tumor with thrombotic microangiopathy.

Case	Author year	Cancer type	FIGO stage	C/T regimen	Cycles before TMA	Clinical Presentation	Renal Biopsy	Treatment	Outcome
1	Ogunleye, Dele A, 2004	Endodermal sinus tumor	1C	Bleomycin, etoposide, and cisplatin for 5 days every 3 weeks	3	Anemia, thrombocytopenia, HTN,↑LDH, AST, ALT, Cre	Yes	Nitroglycerin, 3 courses of plasmapheresis, Hemodialysis	Resolved without Sequelae
2	Kuang-Yen Lee, 2023	Endodermal sinus tumor	IA	Bleomycin, etoposide and cisplatin for 5 days every 3 weeks	1	Anemia, thrombocytopenia, leukopenia, ↑LDH, Cre, lactic acid	Yes	Blood transfusion, 3 courses of plasma exchange	Resolved without Sequelae

C/T, chemotherapy; TMA, thrombotic microangiopathy; HTN, hypertension, LDH, lactic dehydrogenase; AST, aspartate aminotransferase; ALT, alanine transaminase; Cre, creatine.

Over the past two decades, the TMA classification has evolved significantly, leading to variations in how it's described in different literature sources. In 2014, J.N. George et al. identified nine primary TMA types, encompassing conditions like thrombotic thrombocytopenic purpura (TTP, associated with ADAMTS13 deficiency-mediated TMA), hemolytic uremic syndrome (HUS, related to Shiga toxin-mediated TMA), complement-mediated TMA, and drug-induced TMA [6]. However, in 2021, F. Fakhouri et al. categorized DI-TMA as a subgroup of secondary TMA, further dividing it into immune-related and toxic dose-related types [7]. In immune-related type of DI-TMA, antibiotics are usually dependent on presence of drug or its metabolites. The most common associated cancer therapy agents include gemcitabine and oxaliplatin. The initial presentation is a sudden onset of severe systemic symptoms with anuric acute kidney injury [8]. Regarding the non-immune mechanism in toxic dose-related type of DI-TMA, the toxic drug effect may directly affect endothelium, causing endothelial dysfunction, increased platelet aggregation, or excess activation of complement protein or clotting factors. Gradual onset of renal failure may occur over weeks or months [5].

For BEP related DI-TMA, only limited bleomycin-related cases have been described [9] and only one case report is about ovarian germ cell tumor (Table 1.) [2]. Cisplatin was considered to have the potential to enhance the vascular damage induced by bleomycin, resulting in the accumulation of activated von Willebrand factor multimers, the aggregation of platelets, and the deposition of fibrin which was similar to non-immune mechanism [10]. It is commonly observed that the patients frequently presented with co-occurring TMA and acute lung fibrosis, yet the underlying etiology linking endothelial injury to both renal and pulmonary manifestations remain indeterminate. The differentiation between DI-TMA and other subtypes of TMA is challenging, and checking ADAMTS13 activity, aHUS related-genes sequencing, autoimmune status, infection profiles help to figure out possible etiology in the spectrums of TMA [11]. Tumor induced TMA (Ti-TMA) may be another possible differential diagnosis, and it is more likely to happen in patients with systemic microvascular metastases or bone marrow metastases. In one cohort of 168 cases of presumed Ti-TMA showed metastases in 91.8% cases and bone marrow infiltration in 81.1% of the evaluable cases [12]. Thus, for our patient with normal immune profile, normal ADAMST-13 activity, no pathogenic mutation in aHUS related-genes, and no evidence of infection, DI-TMA is the preferred diagnosis.

Treatment for DI-TMA primarily involves supportive care and avoidance of the offending drug [5,13]. The role of plasma exchange (PEX) in drug-associated TMA was indetermined, and some previous reports considered that PEX may not be so effective in the occasions which the potential toxic drugs cause direct endothelium injury [14,15]. However, the favorable outcomes in our patient indicated that PEX may be one treatment choice for bleomycin-related DI-TMA. Sofiane Salhi et al. had reported one 56-year-old male patient who developed TMA following administration of bleomycin, cisplatin and etoposide, and he was refractory to PEX. Eculizumab, a kind of complement C5 inhibition, was used as salvage therapy leading to complete remission of TMA, which may be another potential choice for bleomycin-related DI-TMA [9].

In conclusion, DI-TMA is a rare side effect associated with certain chemotherapeutic agents. The diagnosis could be challenging, but it should be considered in patients receiving BEP chemotherapy who present with intractable anemia, thrombocytopenia, and acute kidney injury. It requires prompt diagnosis and appropriate treatments for the rare but lethal complication.

Conflict of interest

The authors declare that they have no conflict of interest.

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Case Report

Prenatal diagnosis of 9q34.3 microdeletion-associated Kleefstra syndrome in a pregnancy complicated by polyhydramnios: A case report and literature review

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ABSTRACT

Objective: Kleefstra Syndrome (KS) is a rare genetic disorder caused by a deletion at 9q34.3. Studies showed that various heart defects are observed in 41–43% of patients and abnormal features on brain imaging in 58–63%. To date, the prenatal phenotype in KS has yet to be defined.
Case report: We present the first prenatal diagnosis and chromosomal microarray analysis (CMA) of a case of 9q34.3 microdeletion in a fetus with increased amniotic fluid, supported by abnormal prenatal ultrasound findings, and confirmed via autopsy. CMA revealed a 2.1 Mb 9q34.3 microdeletion encompassing an OMIM gene of EHMT1, which is consistent with the diagnosis of Kleefstra syndrome and 9q subtelomeric deletion syndrome.
Conclusion: When a fetus with normal karyotype presents with polyhydramnios or abnormalities noted during second-trimester prenatal ultrasound screening, CMA analysis can be considered as the next step to rule out or confirm the diagnosis of chromosomal or other genetic aberrations.

Introduction

Kleefstra Syndrome (OMIM# 610253) is a rare genetic disorder caused by a deletion at 9q34.3 or presence of pathogenic variants in the EHMT1 gene, inherited in an autosomal dominant manner. Almost all cases reported to date have been de novo. Kleefstra syndrome (KS) is characterized by intellectual disability, autistic-like features, childhood hypotonia, and distinctive facial features (GeneReviews®, Last Update: March 21, 2019, Accessed on 3/1/2020).

Polyhydramnios is defined as an excess accumulation of amniotic fluid, and the reported prevalence of polyhydramnios ranges from 0.2 to 1.6 % in all pregnancies [1]. The diagnosis is obtained by ultrasound evaluation [2]. Common causes of polyhydramnios include gestational diabetes, fetal anomalies resulting in disturbed fetal swallowing of amniotic fluid, and fetal infections [3,4]. Previous studies have reported that fetuses with polyhydramnios have an increased prevalence of chromosomal or genetic diseases [1,5,6]. However, polyhydramnios has not been recognized as a consistent pathological feature in KS.

Studies showed that various heart defects are observed in 41–43% of patients and abnormal features on brain imaging in 58–63% [7,8]. However, the prenatal phenotype in KS has yet to be defined. The objective of the present study was to contribute to the identification of KS phenotype by reporting a new case and reviewing the past literatures. Here, we reported a chance prenatal diagnosis concerning a pregnant woman with idiopathic polyhydramnios who carried a fetus with 9q34.3 microdeletions-associated KS.

Case presentation

A 29-year-old woman, gravida-3-para-1, was referred to the Department of Medical Genetics at National Taiwan University Hospital for second opinion counseling at 28 weeks and 2 days of gestation. She had no family history of chromosomal abnormalities, congenital anomalies, metabolic disorders or drug exposure before or during this pregnancy. She had an uncomplicated vaginal delivery of a normal male infant 13 years ago. A total of 60 metaphases (GTC-banding) were analyzed for fetal karyotyping, showing 46,

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XX, a normal female karyotyping result. Oral glucose tolerances test and serological investigations regarding TORCH infections were normal. She was referred to our center this time due to fetal abnormalities noted on prenatal screening ultrasound. Detailed ultrasound exam revealed ventricular septal defect (VSD) (Fig. 1(A)), coarctation of aorta (Fig. 1(B)), absence of stomach (Fig. 1(C)), and polyhydramnios. The amniotic fluid index (AFI) measurement, the deepest amniotic pocket in each of the four quadrants is measured vertically and the values added together, was more than 34 cm (Fig. 1(D)). An amniocentesis was performed at 15th week at a local clinic. Additionally, an amnio-drain for symptom relief was performed at the 29th gestational weeks due to preterm uterine contraction. During this time, amniotic fluid and blood samples of both parents were went for chromosomal microarray analysis (CMA) to further identify CNVs for both fetus and parents. One de novo microdeletion segment was confirmed by single nucleotide polymorphism (SNP)-based Affymetrix 750 K microarray analysis: 2.10-Mb deletion in 9q34.3 (chr9: 138,915,822–141,018,648) (Fig. 1(E)). The array comparative genomic hybridization profile, revealing a 9q34.3 deletion.). After genetic counseling, the pregnancy was therapeutically terminated at 32 nd week. The aborted female fetus showed somatic measurements corresponding to 32

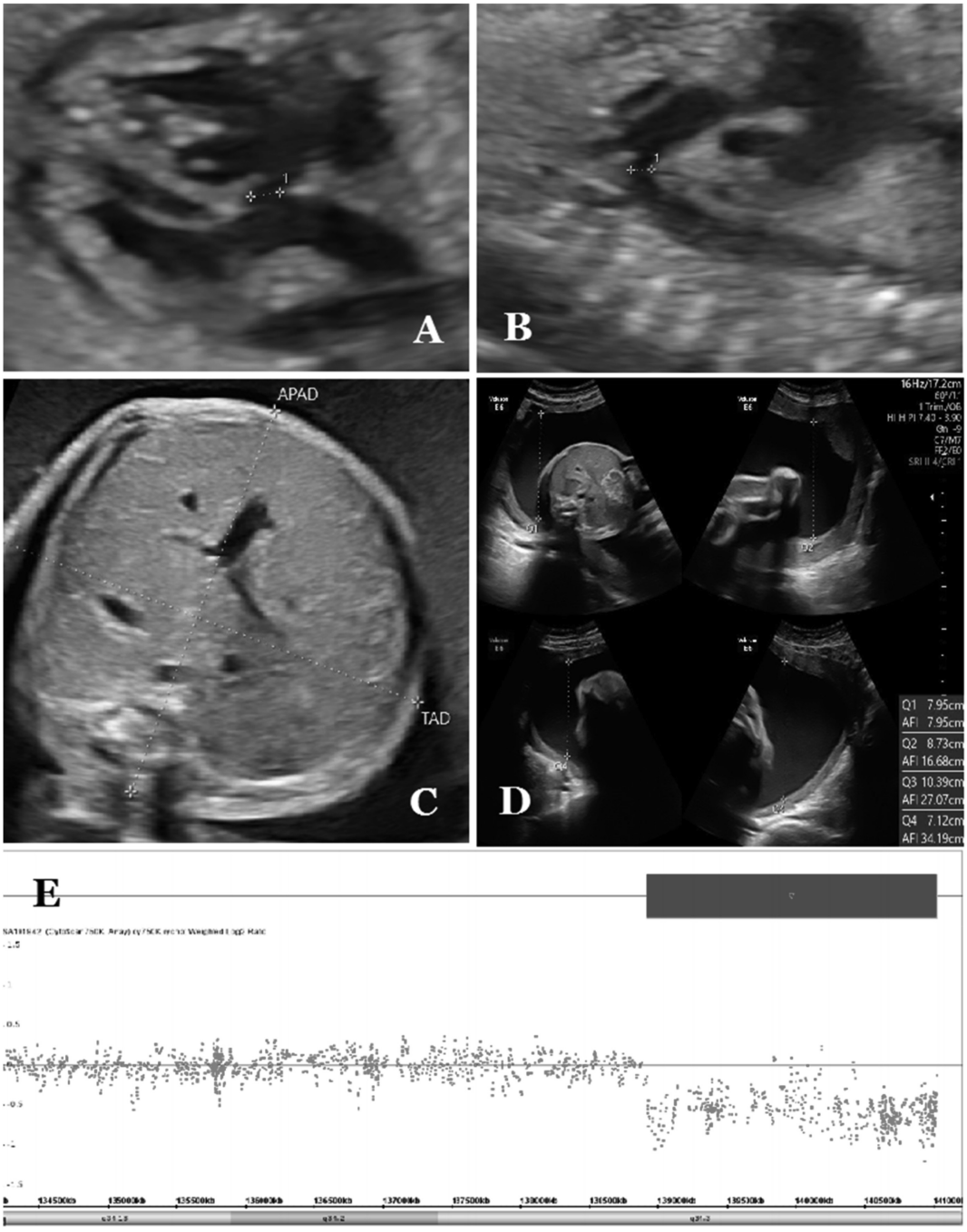

Fig. 1. Ultrasound imaging of the fetus at 28th week of gestation (A) ventricular septal defect (yellow star) (B) coarctation (yellow star) (C) absence of stomach (D) polyhydramnios (E) Chromosome microarray analysis result showing array plot for the 9q34.3 region in the fetus. DNA copy number change is represented by the positive log 2 ratio above baseline. The deletion encompasses approximately 2.1 Mb, extending from 138,915,822 proximally to 141,018,648 distally, arr [hg19]9q34.3 (138,915,822_141,018,648)*x*1.

weeks. Fetal necropsy revealed slight craniofacial dysmorphisms, including arched eyebrows, hypertelorism, midface retrusion, thickened ear helices, short nose with anteverted nares, and tented upper lip (Fig. 2(A) Craniofacial appearance of the fetus at birth). Brachydactyly of the left middle finger was observed. Autopsy of the fetus confirmed the diagnosis of preductal coarctation of aorta (Fig. 2(B)) and ventricular septal defect (Fig. 2(C)). A distended ileal loop (84–112 cm from ligament of Treitz with presence of ganglion cells) was discernible, which could be associated with polyhydramnios (Fig. 2(D)).

Discussion

We present prenatal diagnosis and molecular cytogenetic characterization of 9q34.3 microdeletion in a pregnancy with fetal ultrasound abnormalities including polyhydraminos. To date, few studies were published regarding prenatal diagnosis of KS resulted from deletions at 9q34.3. In our case, absence of stomach, coarctation of aorta, ventricular septal defect (VSD), and polyhydraminos were the abnormal ultrasound features documented at 28 weeks of gestation. Previous clinical studies (Table 1) revealed prenatal ultrasound findings of cardiac anomaly, including hypoplasic pulmonary artery, coarctation of the aorta, and VSD in more than half of the cases of KS [9–11]. Abnormal ultrasound findings in corpus callosum (CC) were shown in the two previously published cases [9,11]. In the case with a mosaic ring chromosome 9 (with deletion of the chromosome's short and long arm) and a chromosome 9 monosomy, only ambiguous genitalia were described [12]. Penacho et al. [11] also reported a case with homogeneous ring chromosome 9 and an ultrasound assessment revealed fetal growth retardation, hypoplastic pulmonary artery, single umbilical artery, retrognathism, hypoplastic nasal bone, CC agenesis, hyperechogenic bowel and subcutaneous thoracic edema. Various abnormal ultrasound findings were described in the three cases with an additional chromosome imbalance [10–12]. Only two prenatally diagnosed cases (our case and one previous case [9]) featured 'pure' deletions, in which only the 9q34.3 region was involved. Coarctation of the aorta in the prenatal ultrasound was recognized in both cases. Short and thick CC was noted in the previous case with pure 9q34.3 deletion. However, the corpus callosum structure in our case was found to be normal by the autopsy. While several abnormal ultrasound findings are associated with KS, polyhydramnios has not been recognized as a consistent feature with 9q34.3 microdeletion. More cases with confirmed diagnosis of KS need to be collected, and the results of their prenatal ultrasound exam should be reviewed, in order to make conclusions about any uniform appearance under prenatal ultrasonography.

The peculiar aspect of the present case is the association with polyhydramnios. Previous studies have reported that fetuses with polyhydramnios have an increased prevalence of chromosomal or genetic diseases [5,6]. The anomaly detection rate in pregnancies with polyhydramnios was nearly 80% and aneuploidy was present in 10% of fetuses with sonographic anomalies [1]. Our results confirm existing evidence that pregnancies with polyhydramnios have an increased prevalence of major fetal structural defects detectable on obstetric ultrasound. Furthermore, studies revealed decreased elimination of amniotic fluid, either from structural anomalies (eg, choanal atresia, esophageal atresia, tracheoesophageal fistula, and duodenal or intestinal atresia) or as a result of reduced swallowing ability (central nervous system anomalies), can all result in polyhydramnios [13]. In the present case, the ultrasound examination revealed absence of stomach, so esophageal atresia or tracheoesophageal fistula was suspected. The fetal necropsy showed no anomaly in stomach, trachea, and esophagus. The

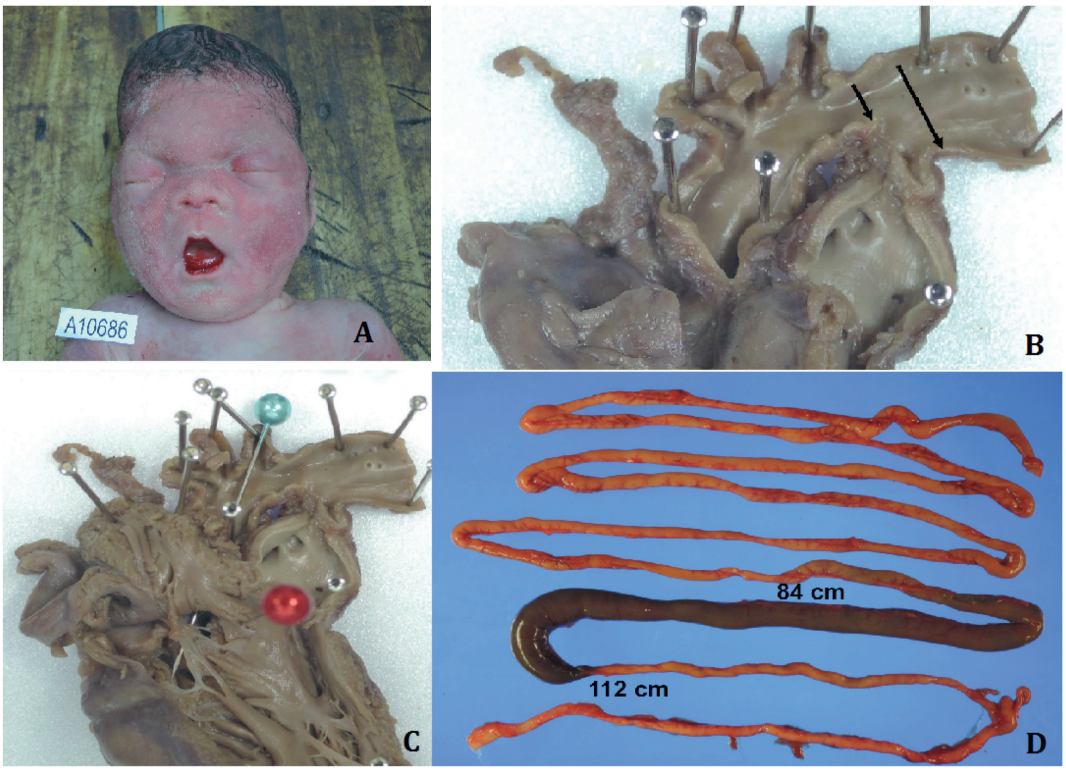

Fig. 2. Image of the female fetus after therapeutic termination of pregnancy in the 32 nd week (A) Craniofacial appearance of the fetus at birth, including arched eyebrows, hypertelorism, midface retrusion, thickened ear helices, short nose with anteverted nares, and tented upper lip (B) Preductal coarctation of aorta (short black arrow) and normal aorta (long black arrow) (C) ventricular septal defect (blue pin) (D) A distended ileal loop (84–112 cm from ligament of Treitz).

Table 1
Summary of literature reports of prenatal diagnosis of Kleefstra syndrome (KS) and clinical comparison of the patients in the present study and typical KS images of ultrasound findings.

First author	ultrasound findings			Chromosome formula	aCGH findings	Microdeletion size	Outcome	Autopsy
	Cardiac	Cerebral	Other features					
Present case	Coarctation of the aorta, VSD		absence of stomach, polyhydraminos	46, XY	arr [hg19] 9q34.3 (138,915,822_141,018,648) *x*1	2.1 Mb	TOP	+
Guterman S [9]	Coarctation of the aorta	Short, thick corpus callosum		46, XY	arr [hg19]9q34.3 (140 083 938–140 958 088) *x*1	0.9 Mb	TOP	–
Chen [12]			Ambiguous genitalia	Mos 45XY, −9/46, XY,r (9) (p24q34.4)			TOP	–
Chen [10]	VSD		Omphalocele	46, XX, der (9) t (3; 9) (q26.31; q34.3)	arr [hg19]3q26.31q29 (171 287 090 −197 897 268) × 3, 9q34.3 (140 047 349–141 019 600) *x*1	2.6 Mb	TOP	–
Penacho [11]	Hypoplasic pulmonary artery	Corpus callosum agenesis	Fetal growth restriction, single umbilical artery, retrognathism, hyperechogenic bowel, subcutaneous edema	46, XX, r (9) (p24q34)	arr [hg19] 9pterp24.2 (163 131–2 729 722) *x*1, 9p24 (5 090 443–5 235 765) *x*1, 9q34.3qter (138 523 302–141 122 055) *x*1	3.6 Mb	TOP	–

distended ileal loop (84–112 cm from ligament of Treitz with presence of ganglion cells) found in the autopsy was likely associated with polyhydramnios. However, gastrointestinal tract myotonia was rarely recognized as a consistent feature in either EHMT1 mutations or 9q34.3 microdeletion-associated KS. Future studies are needed to determine the association of polyhydramnios in fetus with KS.

Karyotyping is the mainstay for prenatal diagnosis. However, diagnostic discrepancy between karyotyping and CMA was noted in the present case. Fetal abnormalities were not apparent at the time of initial amniocentesis at 15th week, and the karyotyping result was unremarkable. Subsequent ultrasound anomalies detected at 28 weeks led to CNV investigations of the fetus and parents, which found one deleted segment in 9q34.3 via microarray analysis. The rate at which CMA can detect clinically significant copy number alterations in fetuses with sonographic anomalies ranges from 2% to 16% [14]. In our previous study of fetuses with major sonographic anomalies and normal metaphase karyotypes, the abnormality detection rate of CMA was 10.5% in fetuses with a single anomaly, and 15.4% in fetuses with anomalies involving two or more organ systems [15]. It is recommended that fetuses with normal karyotypes and abnormal ultrasonographic reports should undergo CMA analysis.

Ethical approval

No ethical committee approval was necessary for this case report.

Funding statement

No external funding was received for this work.

Declaration of competing interest

The authors declare no conflicts of interest in connection with this article.

Acknowledgements

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Research Letter

Rapid confirmation of maternal origin of trisomy 21 by quantitative fluorescent polymerase chain reaction in a fetus associated with increased nuchal translucency, abnormal first-trimester maternal serum screening result and positive non-invasive prenatal testing for trisomy 21

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Dear Editor,

A 36-year-old, primigravid woman underwent first-trimester maternal serum screening at 12 weeks of gestation and received an abnormal result of adjusted risk of 1:9 for trisomy 21 calculated from an increased nuchal translucency (NT) thickness of 4.3 mm, normal maternal serum free β-hCG (human chorionic gonadotropin) [1.038 multiples of the median (MoM)], low PAPP-A (pregnancy-associated plasma protein A) (0.272 MoM) and low PlGF (placental growth factor) (0.284 MoM). She underwent non-invasive prenatal testing (NIPT) at 13 weeks of gestation, and the result was positive for trisomy 21. She underwent amniocentesis at 16 weeks of gestation, which revealed a karyotype of 47,XY+21 in conventional cytogenetic analysis and arr [GRCh37] (X,Y) × 1, (21) × 3 by array comparative genomic hybridization (aCGH). The pregnancy was subsequently terminated at 18 weeks of gestation, and a malformed male fetus was delivered with characteristic facial features of Down syndrome. Quantitative fluorescent polymerase chain reaction (QF-PCR) analysis on the DNA extracted from parental bloods, umbilical cord and placenta revealed a maternal origin of trisomy 21, consistent with maternal meiosis I non-disjunction (Fig. 1).

The present case was associated with first maternal meiotic division [meiotic I (MI)] error. More than 90% of the cases of trisomy 21 are caused by chromosomal non-disjunction during maternal meiotic division and occur more frequently in the maternal MI than the second maternal meiotic division [meiotic II (MII)] [1–6]. Vraneković et al. [7] found that the majority of Down syndrome was maternal origin (93%), followed by paternal origin (5%) and mitotic origin (2%), and the frequencies of MI error and MII error in maternal origin were 86% and 14%, respectively.

QF-PCR has been shown to have the advantage of rapid detection of the parental origin in fetal trisomy 21 at prenatal diagnosis [8,9]. The information acquired is very helpful for genetic counseling under such a circumstance.

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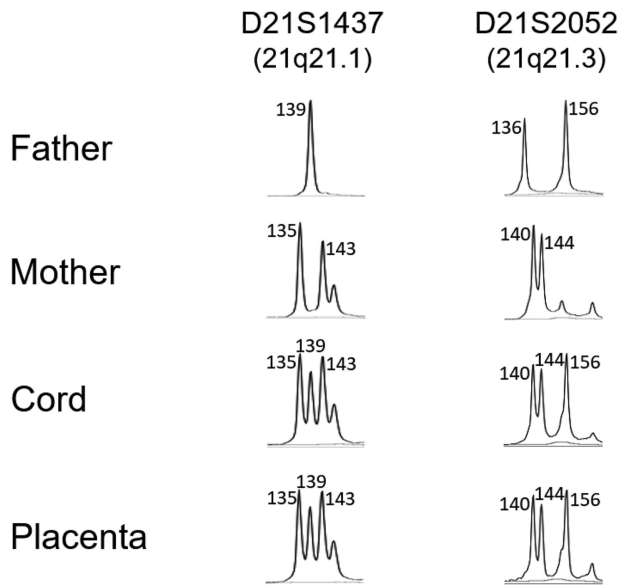

Fig. 1. Quantitative fluorescent polymerase chain reaction assays using the DNA extracted from the parental bloods, umbilical cord and placenta show three equal peaks on the informative markers of D21S1435 and D21S2052 in the umbilical cord and placenta with two different maternal alleles and one paternal allele, consistent with maternal meiosis I non-disjunction of trisomy 21.

Declaration of competing interest

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

Acknowledgements

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Research Letter

Detection of a heterozygous *de novo* pathogenic variant in the *PTPN11* gene (c.1505 C > T, p.S502L) in a fetus associated with cystic hygroma and congenital heart defects

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Dear Editor,

A 38-year-old, gravida 2, para 1, woman underwent amniocentesis at 16 weeks of gestation because of nuchal cystic hygroma in the fetus. Amniocentesis revealed a karyotype of 46,XY and a heterozygous *de novo* pathogenic variant of c.1505 C > T, p.S502L in the *PTPN11* gene by next-generation sequencing (NGS). Level II ultrasound at 21 weeks of gestation showed cystic hygroma with skin edema over the head and face, atrioventricular septal defects (AVSD), pericardial effusion and hydrops fetalis. The pregnancy was subsequently terminated, and an 882-g male fetus was delivered with characteristic facial features of a board forehead, hypertelorism, down-slanting palpebral fissures, low-set ears and webbed neck (Figs. 1 and 2). Molecular analysis of the DNA extracted from umbilical cord revealed a heterozygous c.1505 C > T, p.S502L mutation in the *PTPN11* gene (Fig. 3).

The present case was associated with Noonan syndrome (NS), euploid increased nuchal translucency (NT), cystic hygroma and congenital heart defects. Prenatal diagnosis of increased NT, cystic hygroma and pleural effusion should raise a suspicion of chromosomal abnormalities and genetic disorders of RASopathy and NS [1–6].

NS1 (OMIM 163950) is an autosomal dominant disorder caused by heterozygous mutation in the *PTPN11* gene (OMIM 176876) and is characterized by short stature, congenital heart defects such as pulmonic stenosis and hypertrophic cardiomyopathy, facial dysmorphism of a broad forehead, hypertelorism, downslanting palpebral fissures, a high-arched palate and low-set ears, and other abnormalities including skeletal defects of chest and spine, webbed neck, mental retardation and cryptorchidism [2]. NS1 caused by *PTPN11* gene accounts for about half of the patients with NS. The present case was associated with a pathogenic variant of c.1505 C > T, p.S502L [7,8]. Cao et al. [7] reported a fetus with nuchal edema, pleural effusion, pulmonary stenosis, agenesis of the ductus venosus, polyhydramnios and ventriculomegaly on ultrasound at 21 weeks of gestation, a karyotype of 46,XY, arr (1–22) × 2, (X, Y) × 1 on array comparative genomic hybridization (aCGH) analysis and a *de novo PTPN11* mutation of c.1505 C > T, p.S502L. The pregnancy was subsequently terminated, and a fetus was delivered with increased NT, pleural effusion and pulmonary stenosis. Wagner et al. [8] reported a fetus with thickened nuchal fold (10 mm), hydronephrosis, absent ductus venosus, wide inferior vena cava (IVC), aberrant vessel between IVC and umbilical vein on ultrasound at 26 weeks of gestation, NS and a *de novo PTPN11* mutation of c.1505 C > T, p.S502L. The pregnancy was subsequently terminated.

This presentation suggests that prenatal diagnosis of euploid cystic hygroma should make a differential diagnosis of Noonan syndrome and include NGS of the *PTPN11* gene.

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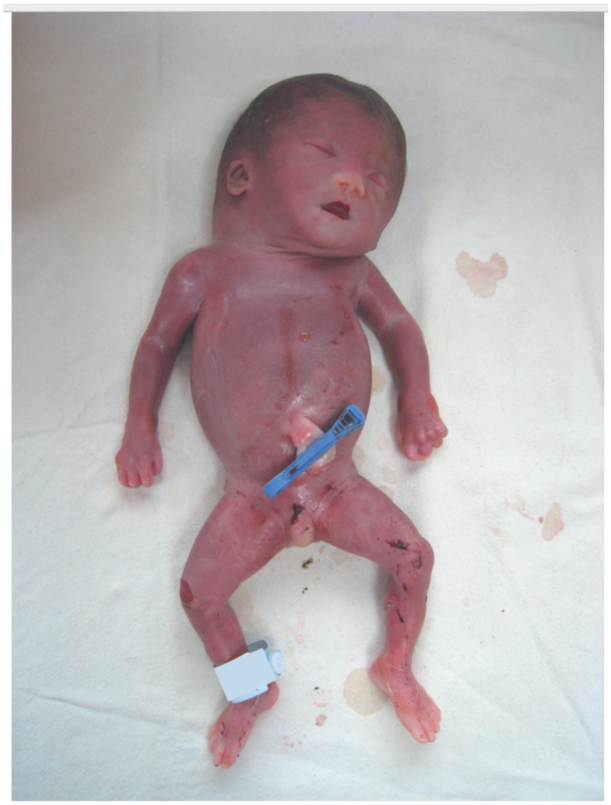

Fig. 1. Whole body view of the fetus at birth.

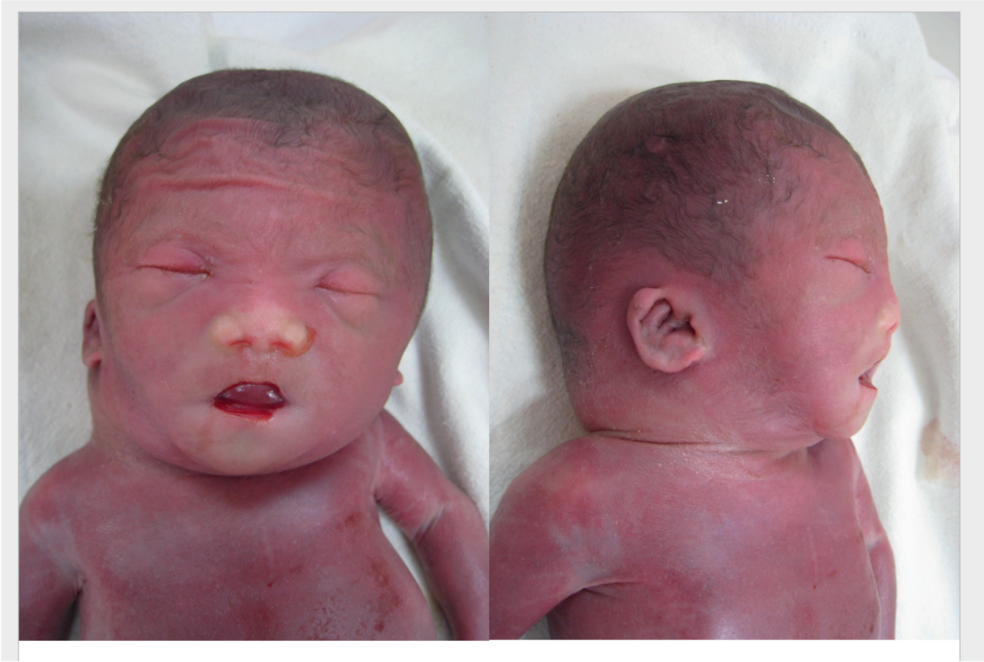

Fig. 2. The craniofacial appearance of the fetus.

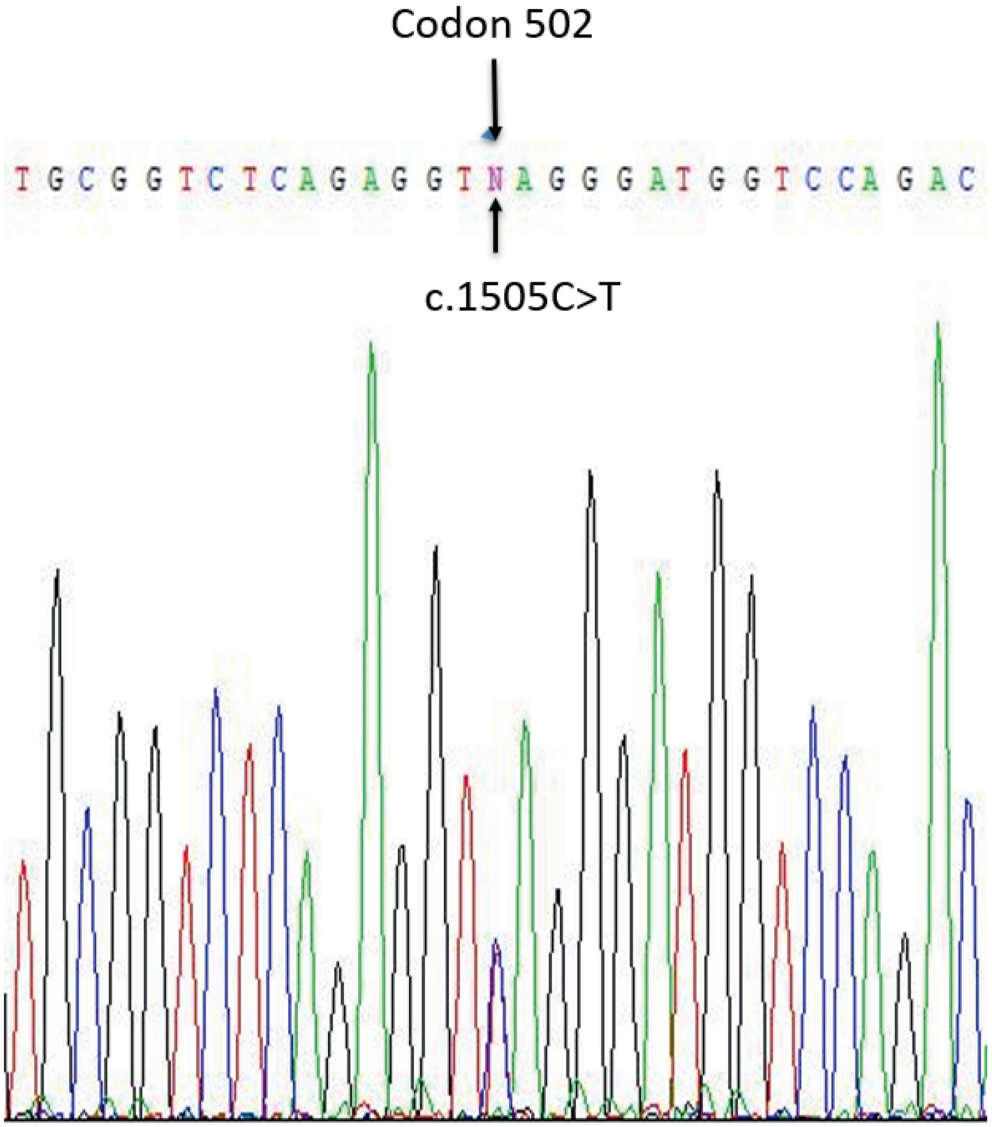

Fig. 3. Molecular analysis of the DNA extracted from umbilical cord shows a heterozygous c.1505 C > T, p.S502L mutation in the *PTPN11* gene.

Declaration of competing interest

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

Acknowledgements

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Research Letter

Mosaicism for r(20) or 46,XY,r(20)(p13q13.3)/46,XY at amniocentesis in a pregnancy with a favorable outcome and no prominent perinatal decrease of the r(20) cell line with no genomic imbalance

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Dear Editor,

A 40-year-old, primigravid woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype of 46,XY,r(20)(p13q13.3)[12]/46,XY[23] (Figs. 1 and 2), consistent with 34.3% (12/35 colonies) mosaicism for r(20). The parental karyotypes were normal. Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cultured amniocytes revealed the result of arr (1–22) × 2, (X,Y) × 1 with no genomic imbalance. Prenatal ultrasound findings were unremarkable. She was advised to continue the pregnancy, and a healthy 2822-g male baby was delivered at 39 weeks of gestation with no phenotypic abnormality. aCGH analysis on the DNA extracted from cord blood revealed the result of arr (1–22) × 2, (X, Y) × 1 with no genomic imbalance. The karyotypes of umbilical cord and placenta were 46,XY,r(20)(p13q13.3)[14]/46,XY[26] (35% mosaicism) and 46,XY,r(20)(p13q13.3) [1]/46,XY[39] (2.5% mosaicism), respectively. When follow-up at the age of three months, the peripheral blood had a karyotype of 46,XY,r(20)(p13q13.3)[17]/46,XY[23], consistent with 42% mosaicism for r(20).

In the present case, amniocentesis at 18 weeks of gestation revealed 34.3% (12/35 colonies) mosaicism for r(20). The umbilical cord had 35% (14/40 cells) mosaicism for r(20), and the peripheral blood at the age of three months had 42% (17/40 cells) mosaicism for r(20). aCGH analysis on cultured amniocytes and cord blood revealed no genomic imbalance. The present case, in accordance with the previous reports presented by Chen [1–3], provides evidence that there will be no perinatal decrease of the mosaic cell line with no genomic imbalance as well as 47,XXY. The cell line of 46,XY,r(20)(p13q13.3) in this case as well as the cell line of 45,XY,der(13;21)(q10;q10) in the report of Chen [1], the cell line of 47,XXY in the report of Chen [2] and the cell line of 46,XY,t(4;10)(q12;p12.32) in the report of Chen [3] are as strong as the euploid cell lines of 46,XY and are completely different from those aneuploid cell lines at amniocentesis such as trisomy, deletion and duplication which are weaker and less competitive than the normal euploid cell line.

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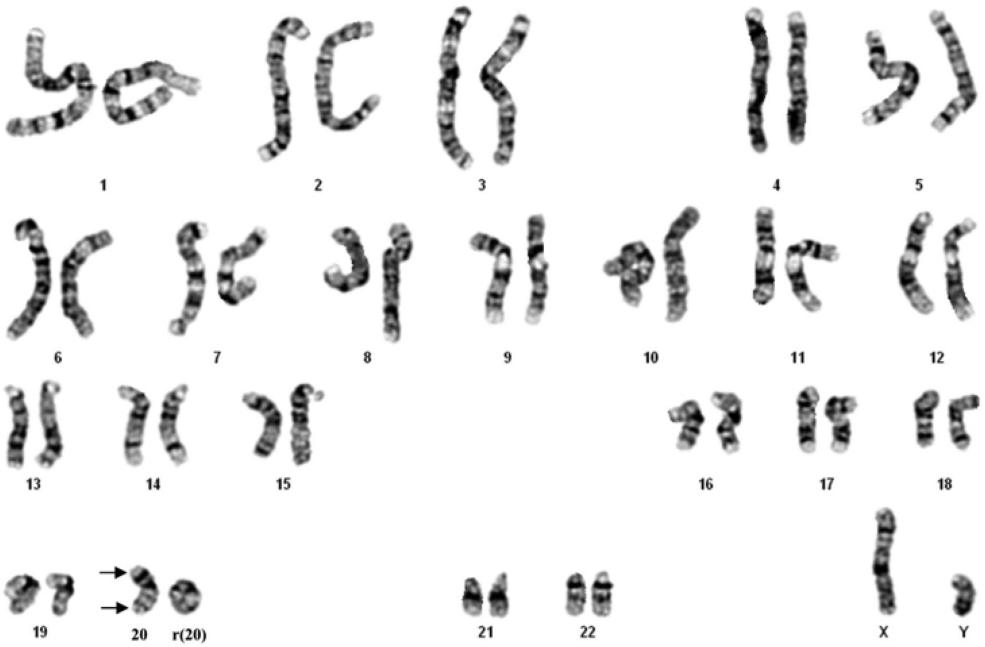

Fig. 1. A karyotype of 46,XY,r(20)(p13q13.3). The arrows indicate the breakage and reunion. r = ring.

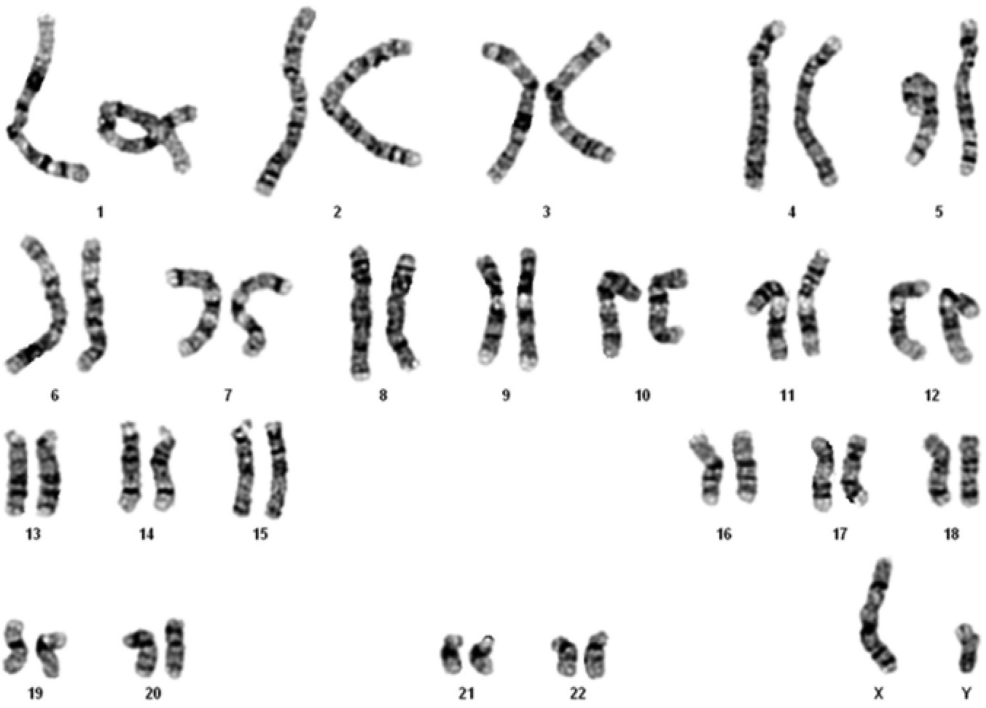

Fig. 2. A karyotype of 46,XY.

Declaration of competing interest

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

Acknowledgements

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Research Letter

Prenatal diagnosis of 22q11.2 distal deletion syndrome in a fetus associated with perinatal growth restriction but no structural abnormalities

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Dear Editor,

A 31-year-old, primigravid woman underwent elective amniocentesis at 17 weeks of gestation. Amniocentesis revealed a karyotype of 46,XY. Simultaneous array comparative genomic hybridization (aCGH) analysis on the DNA extracted from uncultured amniocytes revealed the result of arr 22q11.21 [GRCh37] (20,659,547–21,540,347) × 1dn. The parents did not have such a deletion. Prenatal ultrasound revealed no structural abnormalities. The deletion encompassed 12 OMIM genes including *ZNF74*, *SCARF2*, *KLHL22*, *MED15*, *PI4KA*, *SERPIND1*, *SNAP29*, *CRKL*, *LZTR1*, *THAP7*, *SLC7A4* and *BCRP2*. The pregnancy was carried to 39 weeks of gestation, and a 2396-g phenotypically normal baby was delivered. The cord blood had a 751-kb 22q11.21 deletion (Fig. 1). When follow-up at the age of 2½ months, his body length was 56 cm (<3rd centile), and his body weight was 4.5 Kg (<3rd centile). When follow-up at the age of seven months, the neonate had only growth restriction with the body length of 73 cm, body weight was 6.4 Kg, and head circumference of 40.6 cm (all <3rd centile), but manifested no dysmorphism and no central nervous system (CNS) abnormalities by magnetic resonance imaging (MRI) examinations.

The present case had a 22q11.2 distal deletion outside the critical region of *UFD1L*, *TBX1*, *COMT* and *TOP3B* but was not associated with gross structural abnormalities. Mutation or deletion of *TBX1* (OMIM 602054) is associated with DiGeorge syndrome (DGS) (OMIM 188400), velocardiofacial syndrome (VCFS) (OMIM 192430), conotruncal heart malformations (CTHM) (OMIM 217095) and tetralogy of Fallot (TOF) (OMIM 187500). Prenatal diagnosis of 22q11.2 deletion involving *TBX1* with congenital heart defects and other major anomalies have been well described [1–7]. *COMT* (OMIM 116790) is associated with susceptibility to schizophrenia (OMIM 181500) and panic disorder (OMIM 167870). *UFD1L* (*UFD1*) (OMIM 601754) polymorphism is associated with schizophrenia [8]. *MED15* (OMIM 607372) polymorphism is associated with schizophrenia [9–11]. *TOP3B* (OMIM 603582) deletion is reported to be associated with neurodevelopmental disorders such as schizophrenia and cognitive impairment [12].

Distal 22q11.2 deletion syndrome (OMIM 611867) is distinct from DGS and VCFS [13]. Tan et al. [14] reported inter- and intrafamilial phenotypic variability of distal 22q11.2 copy number abnormalities. Mikhail et al. [15] reported that the recurrent distal 22q11.2 microdeletions are often *de novo* and do not represent a single clinical entity. The present case adds to the list of prenatal diagnosis of distal 22q11.21 deletion syndrome.

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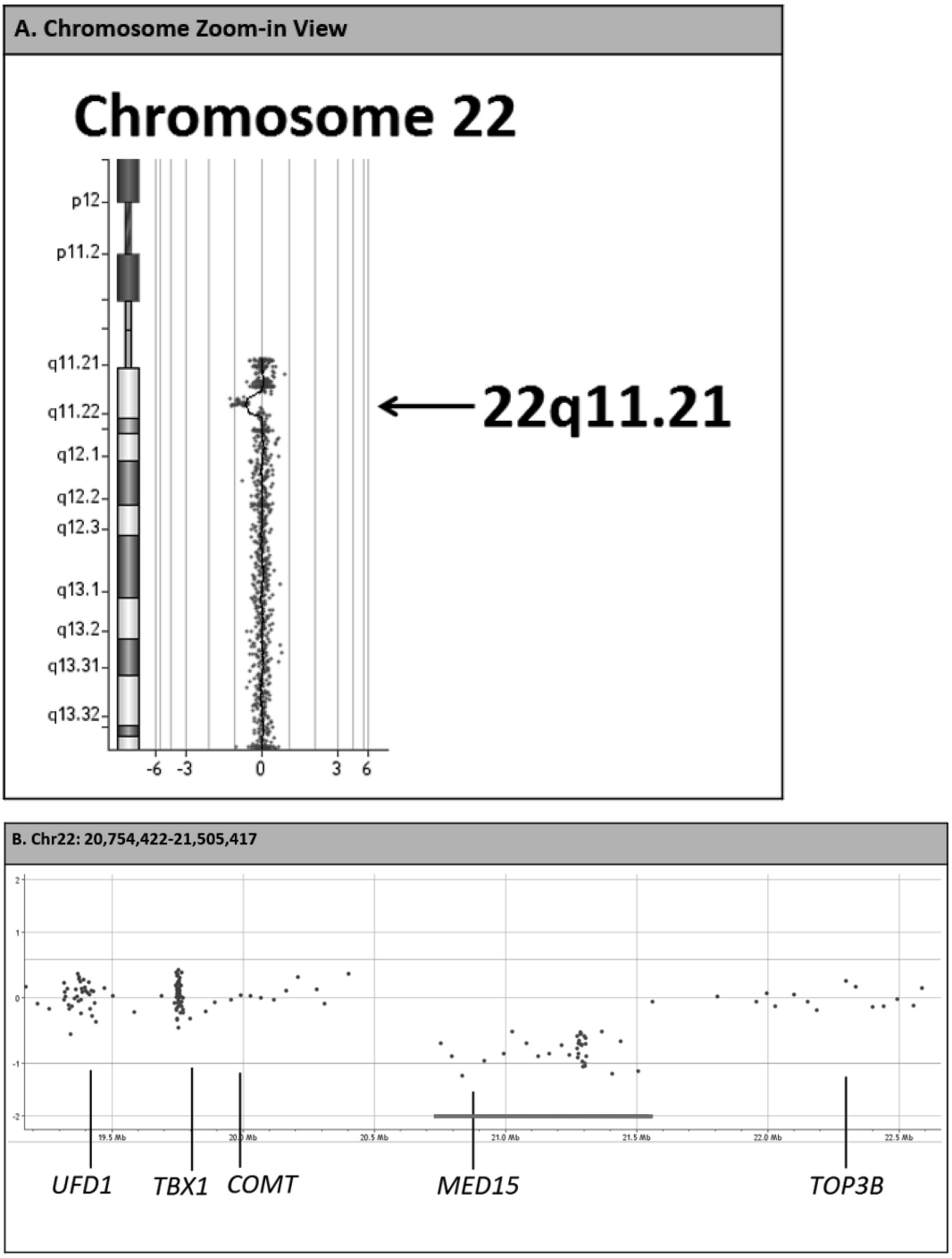

Fig. 1. (A) and (B) Array comparative genomic hybridization (aCGH) analysis on the DNA extracted from cord blood using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60 K (Agilent Technologies, CA, USA) shows the result of arr 22q11.21 [GRCh37] (20,754,422–21,505,417) × 1.0 with a 751-kb 22q11.21 deletion encompassing *ZNF74*, *SCARF2*, *KLHL22*, *MED15*, *PI4KA*, *SERPIND1*, *SNAP29*, *CRKL*, *LZTR1*, *THAP7*, *SLC7A4* and *BCRP2*. The microdeletion is outside the critical region of *UFD1L*, *TBX1*, *COMT* and *TOP3B* but contains the gene of *MED15*.

Declaration of competing interest

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

Acknowledgements

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Research Letter

Prenatal diagnosis and genetic counselling of a rare paternally inherited chromosome 2p21 microdeletion in a Chinese family

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Dear Editor,

Copy number variants (CNVs) are an important source of normal and pathogenic genomic variation. Unbalanced chromosome abnormalities (UBCA) are either gains or losses or large genomic regions, but the affected individual has no or minimal clinical impact. CNVs and UBCA identified in prenatal cases need careful consideration and correct interpretation if those are harmless or harmful variants from the norm [1,2]. Here we report the prenatal diagnosis and genetic counselling of a rare paternally inherited chromosome 2p21 microdeletion in a Chinese family using ultrasound examination, chromosome G-banding and chromosomal microarray analysis (CMA).

In 2021, a 31-year-old, gravida 2, para 0, woman underwent amniocentesis because the ultrasound scan revealed the absence of the foetus' right kidney. There was no family history of birth defects or genetic diseases. Cytogenetic analysis of the cultured amniocytes revealed a normal karyotype of 46,XY. CMA on uncultured amniocytes was performed using the Affymetrix CytoScan 750 K chip, which includes 550 k non-polymorphic markers and 200 k single nucleotide polymorphism (SNP) markers [3,4]. CMA detected a 257.6-Kb chromosomal microdeletion in the region of 2p21(arr [GRCh37]2p21(42,994,484_43,252,109)x1) (Fig. 1). The clinical significance of this microdeletion is unclear at the present time. We then performed both CMA and conventional karyotyping on the parents' peripheral blood samples. Their karyotypes were normal. The CMA results showed that the father had the same microdeletion as the fetus. SNP markers in the Affymetrix CytoScan 750 K chip confirmed a paternal origin of the 2p21 microdeletion. We performed a comprehensive physical examination of the parents to identify anything abnormal. After genetic counselling, the parents decided to continue the pregnancy. At 30 weeks of gestation, the ultrasound scan showed no intrauterine growth restriction (IUGR) or malformations (except for an absent right kidney) in the fetus.

At 40^{+} weeks of gestation, the expectant mother gave birth vaginally to a male baby. The baby's growth parameters at birth were in the normal range. The baby received a complete physical examination and the results were normal (except for the absence of the right kidney). At 24-month checkup, the baby was developing normally.

This study identified a 257.6-Kb chromosomal microdeletion of chromosome 2p21 (Chr2: 42,994,484_43,252,109), which contains a RefSeq(Reference Sequence) protein-coding gene, *HAAO* (OMIM ID: 604521). The translation product of *HAAO* gene is 3-hydroxyanthranilate 3,4-dioxygenase. 3-hydroxyanthranilate 3,4-dioxygenase is a monomeric cytosolic protein belonging to the family of intramolecular dioxygenases containing nonheme ferrous iron. It is widely distributed in peripheral organs, such as the liver and kidneys, and is also present in low amounts in the central nervous system. *HAAO* catalyzes the synthesis of quinolinic acid (QUIN) from 3-hydroxyanthranilic acid. QUIN is an excitotoxin whose toxicity is mediated by its ability to activate glutamate N-methyl-D-aspartate receptors. Increased cerebral levels of QUIN may participate in the pathogenesis of neurological and inflammatory disorders. *HAAO* has been suggested to play a role in disorders associated with altered tissue levels of QUIN [5].

Homozygous mutation of this gene is associated with autosomal recessive disorders of vertebral, cardiac, renal and limb defects

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Fig. 1. CMA detected a 257.6-Kb chromosomal microdeletion in the region of 2p21(arr[GRCh37]2p21(42,994,484_43,252,109)x1).

syndrome 1, and its clinical phenotypes include short stature, microcephaly, sensorineural hearing impairment, mental retardation, general developmental delay, atrial septal defect, spinal canal insufficiency, etc. In the ClinGen database, there is no evidence of haploinsufficient pathogenicity of this segment or gene. No similar fragment deletion causing phenotypic abnormalities has been reported [6,7].

In this case, the father carries the same microdeletion and has a normal phenotype. During pregnancy, there were no dysmorphisms (except for an absent right kidney) or IUGR in the fetus. At the 2-year follow-up, the baby did not have an abnormal phenotype and exhibited no evidence of developmental delay.

To summarize, we present a rare case of paternally inherited microdeletion of chromosome 2p21. Our case can be helpful for prenatal diagnosis and genetic counselling. When counselling CNVs, we should consult the database and the latest literature to provide patients with the latest genotype-phenotype correlation information.

Chromosomal microdeletions and microduplications are difficult to detect by conventional cytogenetics. Non-invasive prenatal testing (NIPT) is widely used in the screening of common fetal chromosomal aneuploidies, but NIPT cannot detect a small dose(less than 1 Mb) change of fetal (placental) fraction. Combination of NIPT, prenatal ultrasound, karyotype analysis, CMA and genetic counselling is helpful for the prenatal diagnosis of CNVs [8].

Ethics approval and consent to participate

The research was approved by the Ethics Committee of Wuhan City College. All patient guardians gave informed consent to the study.

Funding

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Consent for publication

All patient guardians gave informed consent to the publication of this study.

Availability of data and materials

Please contact the corresponding author for data requests.

Declaration of competing interest

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

Acknowledgments

We thanked all the participants and the families in this study for their cooperation.

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Correspondence

Which one occurs first?Telomere length (TL) shortening or PCOS?

Dear Editor,

After reviewing the article, Function of the granulosa cells (GCs) in women with polycystic ovary syndrome (PCOS) [1], that is published in Volume 63 Issue 2, March 2024, Pages 141-143.

I want to present my few different thoughts.

Author Szu-Ting Yang showed below two viewpoints,

1 PCOS will result in a heavy socio-economic burden.
2 PCOS will result in a shorter telomere length (TL) of CCs.

From my point of view and my clinical experience and literature searching [2], a heavy socio-economic burden on normal women without PCOS may result in heavy mental stress and then PCOS, and then PCOS aggravates this burden again. Why do I think so ? Because, if my patients try to lower their burden, the PCOS can be improved, or even be cured. So, I think that a socio-economic burden may be a cause and a result at the same time.

The same questions occur between a shorter TL and PCOS when we find PCOS and shorter TL exist on one patient at the same time.

Which one occurs first ? A shorter TL or PCOS ?

Or they both proceed almost simultaneously [3,4].

Besides, there is a contradiction about **increase** or **decrease** of androgen receptor (AR) in granulosa cells of PCOS patients in this article.

From Line 4 to 7 of Section 3,

"and found that the expression of LHR and AR of CCs in PCOS patients were statistically significantly **lower**."

From Line 2 to 5 of Section 5,

"It is in long term believed that AR expression may be **increased** in various organs of PCOS women, and this may be also apparent in women reproductive organs."

Abbreviation summary:

abbreviation	Full text
PCOS, PCOD	Polycystic ovarian syndrome
IR	Insulin resistance
HPO	Hypothalamus-pituitary-ovary
AMH	anti-Mullerian hormone
GCs	Granulosa cells
CCs	Cumulus cells of mature oocyste
COC	Cumulus oocyte complex
TL	Telomere length
LHR	Luteinizing hormone receptor
AR	Androgen receptor
FSH-R	Follicle-stimulating hormone receptor

Funding

As this is a correspondence, no funding was required.

Declaration of competing interest

The author has nothing to disclose.

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Chronic endometritis **63**:336
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Coccidiomycosis **63**:242
Colchicine **63**:900
Colposcopy-guided laser vaporization **63**:846
Complete septate uterus **63**:402
Complex adnexal mass **63**:557
Complication **63**:741
Compound heterozygosity **63**:771
Congenital anomalies **63**:918
Congenital dacryocystocele **63**:717
Congenital heart disease **63**:238
Congenital malformation **63**:700
Conservative management **63**:861
Continence surgery **63**:826
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Cordocentesis **63**:927
COX-2 **63**:178
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Cumulus cells **63**:205

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D

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Delayed postpartum hemorrhage **63**:768
Deletion **63**:628
Delivery complications **63**:350
DeSanto-Shinawi syndrome **63**:545
Dienogest **63**:532
Differentially expressed genes **63**:297
Dinoprostone vaginal insert **63**:887
Distal 10q deletion **63**:398
Distal 11q deletion **63**:922
Distal 3p deletion **63**:561
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Dual-stained cytology **63**:192
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Early catheter removal **63**:451
Early diagnosis **63**:935
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Endometrial cancer **63**:369, 500, 679
Endometrial carcinoma **63**:741
Endometrial neoplasms **63**:98
Endometrial polyps **63**:57
Endometriosis **63**:178, 350, 532, 896
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Epithelial ovarian cancer **63**:10
Epstein-Barr virus **63**:161
Etanercept **63**:405
Etoposide and cisplatin (BEP) regimen **63**:944
Exome sequencing **63**:836
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Familial Mediterranean Fever **63**:900
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Favorable outcome **63**:394, 755, 927
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Fertility sparing treatment **63**:90
Fertility-sparing **63**:95
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Fetal macrosomia **63**:64
Fetal megacystis **63**:17, 19
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Fetal pleural effusion **63**:168
Fetal surgery **63**:904
Fetal venous anomaly **63**:700
Fetoscopy **63**:904
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Flare **63**:161
Follicle stimulating hormone **63**:841
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Foreign body **63**:941
Frozen–thawed embryo transfer **63**:57
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G

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Galectin-3 **63**:37
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GATA3 **63**:745
Gaucher's disease **63**:771
GDM **63**:880
Genetic counseling **63**:293
Gestational diabetes mellitus **63**:341
Gestational hypertension **63**:552
Gestational trophoblastic disease **63**:73
Gestational weight gain **63**:220
Gonadotropin-releasing hormone **63**:492
Gonadotropin-releasing hormone agonist **63**:57
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Great obstetrical syndrome **63**:341
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Gynecologic conditions **63**:29
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H

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Heavy menstrual bleeding **63**:506
Hematogenous metastasis **63**:853
Hematological change **63**:381
Hemoglobin **63**:381
Hemoperitoneum **63**:768
High-intensity focused ultrasound ablation **63**:492
HNF1B **63**:77
HPV **63**:192
Human chorionic gonadotropin **63**:841
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Hydrops fetalis **63**:771
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I

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Intrauterine adhesion **63**:312
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Intrinsic sphincteric deficiency **63**:685
In-vitro fertilisation **63**:341
Isthmocele **63**:459
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J

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K

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L

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Lactobacillus-based vaccine **63**:22
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Laparoscopy **63**:557, 777
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Liquid biopsy **63**:745
Live birth rate **63**:57
Locally advanced cervical cancer (LACC) **63**:651
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Lower limb lymphedema **63**:500
Lower urinary tract symptoms **63**:518
Lumbar vein **63**:98
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Lymph node invasion **63**:679
Lymphadenectomy **63**:500
Lymphatic metastasis **63**:369
Lymphocele **63**:741
Lymphocyte DNA **63**:536
Lymphovascular space invasion **63**:679
Lysosome storage disorder **63**:771

M

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Malignant tumors of the reproductive system **63**:154
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Maternal near miss **63**:867
Maternal uniparental disomy 15 **63**:81
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Menorrhagia **63**:506
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Mortality-to-incidence ratio **63**:527
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Mosaic trisomy 15 **63**:81
Mosaic trisomy 21 **63**:391, 394, 927, 931
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Mosaic unbalanced translocation **63**:750
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N

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Neovagina **63**:737
Neurologic manifestations **63**:234
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Noninvasive prenatal testing (NIPT) **63**:892

O

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Obstetric morbidity **63**:867
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Oocyte maturation **63**:307
Ophira **63**:685
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Oregovomab **63**:10
Outcome **63**:717
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Ovarian epithelial carcinoma **63**:601
Ovarian neoplasms **63**:601
Ovary **63**:722
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P

10p12-p11 deletion syndrome **63**:545
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1p36 deletion **63**:909
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Para-aortic lymphadenectomy **63**:741
Paracervical block **63**:186
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Placenta accreta spectrum **63**:861
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Pregnancy complication **63**:867
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Pregnant **63**:350
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Protective factor **63**:665
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Q

17q12 microdeletion **63**:77
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R

Radiation-free multimodality treatment **63**:651
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S

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Severe maternal morbidity **63**:867
Sexually transmitted diseases **63**:935
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Spontaneous conception **63**:350
Stress incontinence **63**:826
Stress urinary incontinence **63**:692
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T

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Transneovaginal oocyte retrieval **63**:737
Transvaginal cerclage **63**:731
Transvaginal surgery **63**:451
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U

Ultrasonography **63**:759
Ultrasound **63**:229, 717
Ultrasound-guided induced abortion **63**:214
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Uniparental disomy **63**:418
UPD 7 **63**:549
Ureter **63**:777
Urethral diverticulum **63**:781
Urinary retention **63**:451
Urinary stress incontinence **63**:685
Urinary tract infection **63**:451
Urodynamic stress incontinence **63**:685
Uterine artery Doppler **63**:874
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V

Vaccination **63**:320
Vaginal agenesis **63**:737
Vaginal health **63**:29
Vaginal microbiome **63**:610
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Vascular malformations **63**:98
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Vertebral artery tortuosity **63**:225
Vesicoureteral reflux **63**:777
Vitamin D **63**:673
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W

WAC **63**:545
Well-being **63**:486
White blood cell **63**:381
Whole exon sequencing **63**:771
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Y

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