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李中遠

SP1

預防子宮頸癌症，HPV 疫苗的選擇與效益分析

李中遠
嘉義長庚醫院

臨床評估是支持疫苗批准的關鍵步驟。鑑於動物模型的局限性，在疫苗可以被廣泛使用之前，必須在人體內進行臨床研究以證明疫苗的安全性和有效性。這些臨床研究的設計和實施對製造商和監管機構來說仍然是一個挑戰。

例如，如果臨床研究的目的是評估疫苗提供針對感染的保護的能力，則通常必須將大量患者納入研究以產生具有統計學意義的足夠數據。當針對疾病的保護不是臨床研究的合適結果時，對疫苗誘發免疫反應的測量可以是另一種方法。然而，這必須基於科學假設來定義，並且在批准後需要確認臨床療效（上市後評估）。

此演說以子宮頸癌疫苗的設計與目前已得到之臨床數據為討論主題，探討疫苗效益評估的核心價值。

詹耀龍

SP2

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守護新生兒遠離百日咳

詹耀龍
林口長庚醫院

母親與寶寶的防護，應從孕產期開始建立。如何才能讓寶寶不易受到病原菌的危害呢？除了合理飲食、充分運動，孕婦還能怎麼做而讓寶寶更健康?孕婦懷孕期間的免疫力及生理產生變化；寶寶剛出生階段，免疫力尚未完整建立，上述種種原因使孕婦、胎兒及出生後新生兒成為易感染的高風險族群。

一些被認為是古老的傳染病似乎有死灰復燃的跡象，但因症狀輕微或不典型等原因，易造成大家的忽視，此演說透過個案分析，與參與聽眾討論－個大家似乎已經陌生，卻依然存在的疾病，並進一步探討如何透過預防注射策略的擬訂，來針對特定疾病提供有效的防護。

施景中
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以模擬訓練來提升產後出血之預防與治療品質

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Postpartum hemorrhage (PPH) is the leading cause of maternal death either worldwide or in Taiwan. Early identifying the risk factors during pregnancy and immediately initiating bleeding control procedures are both crucial to reduce the mortality and morbidity of obstetric patients. During pregnancy, ultrasonic examination helps diagnose high risk factors such as placental abruption, placenta previa, and uterine abnormalities. The preeclampsia can be controlled by monitoring maternal blood pressure, headache index, blood test and urine test before administrating drug. Within 24 hours after fetus delivery, the initiation of active PPH management, regardless of causes, depends on the prompt recognition of excessive bleeding by the obstetric team leader. Although the causes of PPH are commonly categorized as 4 T’ s (i.e. tone, trauma, tissue and thrombin), it can occurs in patients without any known risk factors. Undoubtedly it takes long time to accumulate sufficient clinical experience for medical care providers to correctly response to PPH and provide proper treatment. The patient safety is the first priority to secure no matter how limited the time and resources the obstetric facilities have. Learning and practice are necessary to prepare obstetric teams to overcome this challenge.

Clinical simulation training provides multiple scenarios and accomodate medical teams of different levels to make clinical decisions in a safe environment. It can be implemented repeatedly to increase the obstetric team's accuracy, efficiency and cooperation, meanwhile making up the limited clinical experience of young team members. With the technology advancement, high-end obstetric simulators, ex. SimMom of Laerdal AS, are capable of simulating ultrasonic images with specifically-defined scanning positions, vital sign changes, seizure reactions, electric fetal heart beats, uterine tone, and bleeding from the first to the third labor stage. Various training objectives can thus be fulfilled with the use of high-end obstetric simulator, from enhancing skill proficiency (ex. ultrasonic image/laboratory data interpretation, uterine massage, delivery of placenta, urine catheterization), making appropriate calls (ex. timing of oxytoxin administration, blood transfusion or call for surgery), to rehearsing interdisciplinary teams with established protocols for a special real case or in drills. Intervention made by team members during simulation can be recorded and annotated for after-class review and evaluation.

Not only to improve the PPH care of obstetric teams, running simulations can also help detect system errors of the established obstetric protocol and facilitating optimization. The optimized protocols based on the clinical practice and simulation optimization can in turn enrich local Advanced Life Support of Obstetrics (ALSO) programs, and improve overall maternal/perinatal safety.

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SP4

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非侵入產前染色體/基因篩檢的最新進展與未來趨勢

背景介紹

非侵入性胎兒遺傳篩檢是利用孕婦血液中的胎兒游離DNA篩檢胎兒異常。目前孕婦血液中的胎兒游離DNA主要被用來篩檢三種常見的體染色體異常（三染色體二十一症或稱唐氏症、三染色體十八症、三染色體十三症），染色體顯微缺失症候群（microdeletion syndrome）、以及不常見的體染色體異常（rare autosomal trisomy，RAT）也可能被偵測到，但是準確度稍低，目前也只有少數實驗室能夠提供經過驗證的臨床數據，例如NIFTY PRO，透過增加測序量，針對84項相對常見而且會導致嚴重發育異常的染色體顯微缺失症候群、三種不常見的體染色體異常（九號染色體三體症、十六號染色體三體症、二十二號染色體三體症）進行測試，證實可以比較精確偵測84項染色體顯微缺失症候群以及三種不常見的體染色體三體症。

基因篩檢一般是指一對配偶在沒有罹患特定疾病的情況之下，藉由基因檢查，找到是否帶有基因突變，以預測下一代會罹患特定疾病的機率。傳統基因篩檢的對象，是生殖細胞中的突變（germline mutation），但是不包含雙親體細胞沒有，但是因為個別生殖細胞發生突變，傳給子代的新突變（de novo mutation）。這類突變特別常見於神經發育異常以及骨骼發育異常。雙親，特別是父親的年紀越大，de novo mutation的機會越高。非侵入性胎兒遺傳篩檢未來也將進化到可以篩檢數十種de novo mutation。在高齡化社會這類篩檢有其價值。

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環境有害物質對母胎與生殖健康的影響

背景介紹

數十年來，由於環境的變遷和生活方式的改變，生殖系統和兒童青少年疾病無論在疾病種類、分布、表現形態、盛行率各方面，都有明顯的改變。在婦女疾病方面，子宮平滑肌瘤、子宮腺肌症、子宮內膜異位症、多囊性卵巢、乳癌、子宮內膜癌、流產、不孕症等疾病，都有急遽增加的趨勢。在男性生殖方面，精液品質全世界都有下降的趨勢。在童青少年疾病方面，過敏、氣喘、性早熟、肥胖、神經發展障礙等問題，也有增加的趨勢。

在另外一方面，高齡化及少子化是所有已開發國家都面臨的重大危機。台灣十幾年來的生育率一直在1.0上下徘徊，如何提高生育率是當前刻不容緩的任務。由於孩子生得少，因此更要生得好，生下來之後也要確保兒童可以健康的成長。生殖健康的問題會拖累提振生育率的努力，兒童健康的問題也會影響到長期社會整體健康及生產力。總之維持生育率（人口成長）和婦幼、生殖健康是社會永續發展的基礎。

以上提到的生殖和兒童青少年疾病都與環境污染有關，而且環境污染造成的跨世代健康效應也已經有充分的證據。台灣的環境汙染之中，塑化劑（環境荷爾蒙）跟重金屬都已經累積許多研究資料。塑化劑、重金屬跟子宮平滑肌瘤、子宮腺肌症、子宮內膜異位症、多囊性卵巢、乳癌、子宮內膜癌、流產、男女不孕症，都有關聯性。婦女懷孕時期塑化劑、重金屬的曝露跟子代的神經發育也有關聯。重如何降低塑化劑及的曝露重金屬的曝露是國民健康的重大挑戰。

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The New Shades in the Management of Endometriosis: 3-year Experience of Visanne in Chung Shan Medical University Hospital

Endometriosis is a chronic inflammatory, recurrent disease associated with debilitating pain, infertility and severely reduced quality of life in many affected women. In light of the considerable progress with diagnostic imaging (for example, transvaginal ultrasound and MRI), diagnosis of endometriosis should be based on a structured process involving the combination of patient interviews, clinical examination and imaging. Notably, a diagnosis of endometriosis often leads to immediate surgery. Instead of assessing endometriosis on the day of the diagnosis, gynaecologists should consider the patient' s 'endometriosis life'.

In the absence of a definitive cure, the main management options in endometriosis comprise surgery, hormone therapy, or a combination of these two approaches. Surgical excision of endometriosis lesions provides a rapid alleviation of symptoms, but lesion recurrence rates are high, estimated at 40– 50% at 5 years. For these women, hormone therapy postoperatively can reduce lesion recurrence and extend the pain-free period.

Medical treatment is the first-line therapeutic option for patients with pelvic pain and no desire for immediate pregnancy. The clinical study programs performed in Europe and Asia showed that dienogest at a 2 mg daily dose provided pain relief in endometriosis significantly superior to placebo and equivalent to the GnRHa, with safety advantages over GnRHa related to its milder hypoestrogenic effects. Long-term clinical studies of up to 15 months' duration demonstrated that dienogest 2 mg provides continued effective lesion reduction and pain relief, associated with improvements in quality of life.

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SP7

60 Years of the Pill – Benefits Beyond Contraception
Why We Have to Recommend Branded OCs to Women?

T The oral contraceptives (OCs), often referred to as the birth control pill or colloquially as "the pill", is a type of birth control that is designed to be taken orally by women. It has been recognized for over 50 years that OCs are also capable of offering health benefits beyond contraception through the treatment and prevention of several gynaecological and medical disorders.

Acne is a common disorder affecting the majority of adolescents and often extends into adulthood. Drospirenone (DRSP) is a unique progestin structurally related to spironolactone with progestogenic, antimineralocorticoid, and antiandrogenic properties. These preparations are bereft of the fluid retentional side effects typical of other progestins and their safety has been demonstrated in large epidemiological studies in which no increased risk of vascular thromboembolic disease or arrhythmias was observed.

The first OC was approved for contraceptive use in the United States in 1960. Most OCs are no longer patent protected and are available for the development of generic pharmaceutical copies. The U.S. Food and Drug Administration considers generic and brand name OC products clinically equivalent and interchangeable. The American College of Obstetricians and Gynecologists (ACOG) supports patient or clinician requests for branded OCs or continuation of the same generic or branded OCs if the request is based on clinical experience or concerns regarding packaging or compliance, or if the branded product is considered a better choice for that individual patient.

張家銘

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Clinical applications of next generation sequencing based techniques -whole exome sequencing

Omics technologies, such array CGH, SNP array and NGS have developed rapidly these years and bring considerable advancement of medicine to us. These techniques can examine entire chromosomes as well as genome in a short time with a relative low cost, which makes the prenatal diagnosis more and more accurate and accessible. In comparison with conventional karyotyping, array CGH and SNP array can detect subtle chromosomal aberrations, providing much more important information for precise prenatal or postnatal diagnosis than ever.

Most of all, NGS can sequence entire human genome within a single day, and many NGS based techniques have been developed and translated into routine clinical practice. One commonly utilized NGS based techniques is NIPT, it is a safe non-invasive prenatal test offering screening for aneuploidies with >99% accuracy. Furthermore, clinical genome sequencing can examine all genetic variants in human genome. It has been shown to be a feasible and powerful tool to detect genetic aberrations associated with congenital malformations, such as epilepsy, inborn errors of metabolism, or developmental retardation. Among 29 congenital malformations analyzed by exome or whole genome sequencing at our laboratory, the detection rate is 65.5%. In addition to congenital malformations, clinical genome sequencing can also be applied to premarital genetic testing or normal population for purpose of preventive medicine. We will introduce these emerging NGS based techniques and share our experience of clinical genome sequencing.

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SP9

The implementation of SNP-array and next generation sequence in clinical practice

The new molecular cytogenomic technologies such as chromosomal microarray analysis (CMA) and next-generation sequencing (NGS) have advanced dramatically in the past few decades, and theirs application and use in caring for and counseling pregnant women and infertility couples have been transformational in the realm of prenatal diagnosis and preimplantation genetic screening (PGS). CMA detects imbalances in the kilobase range, referred as copy number variants (CNVs), readily demonstrates its superiority over standard karyotyping which is limited to imbalances greater than 5– 10 million bases. There are two CMA techniques used in identifying submicroscopic imbalances: comparative genomic hybridization (CGH) and single nucleotide polymorphisms (SNP). In addition to detecting CNVs, other clinical information may be extracted from the genotype plots generated from the SNPs. This includes uniparental disomy (UPD), mosaicism, zygosity, maternal cell contamination, parent of origin and consanguinity. Lastly, triploidy which cannot be detected by array-CGH(aCGH), can easily be identi fi ed by assessing the SNP allele patterns on the array.

We intended to study the prevalence of CNVs in prenatal samples using a single SNP-array platform stratified by indication. Of 10,377 cases, 689 had ultrasound abnormalities and 9688 were ascertained to have other indications. The overall prevalence of CNVs was 2.1% (n = 223/10 377, 95% confidence interval [CI] 1.9-2.4), but the prevalence was 4.4% (95% CI 3.0-6.1) for cases referred with abnormal ultrasound findings and 2.0% (95% CI 1.7-2.3) for other indications. With an indication of advanced maternal age but normal ultrasound scans, the prevalence of pathogenic CNVs was 0.4% and that of susceptibility CNV 0.7%. Thus, this study provides further evidence that CMA should be available for all women who wish to receive diagnostic testing, as this risk is above the cut-off of 1:300 for Down syndrome, leading to the suggestion of invasive testing.

The massively parallel sequencing technology known as NGS has revolutionized the biological sciences. NGS is the newest platform for PGS, which performs high throughput and high resolution sequencing by synthesis. NGS can identify and screen for embryos with reduced viability such as mosaic embryos and those with partial aneuploidies or triploidy. PGS using NGS significantly improves pregnancy outcomes versus PGS using aCGH in single thawed euploid embryo transfer cycles.

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From Minimally Invasive Surgery to Non-invasive Surgery, HIFU is Revolutionary and Disruptive

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High Intensity Focused Ultrasound (HIFU) paves the way for Minimally Invasive Surgery (MIS) to Non Invasive Surgery, in my personal experience. My lecture on the use of HIFU for treatment of uterine fibroids and adenomyosis will document the turning point in my career as a surgeon trained in open and MIS, to that of a HIFU surgeon. A transformation of using a blood stained knife to a bloodless virtual knife is a pinnacle in surgery. HIFU will be disruptive and revolutionary to Obstetrics and Gynaecology.

I will relate my initial scepticism of HIFU, changing to that of a believer, then becoming a follower. All these, after an in depth study and handling of HIFU, the virtual knife and learning the art of HIFU.

The first reason that struck me was that, it was a very different machine than the one I knew before. This is a ultrasound guided HIFU and not a MRI-guided HIFU. The technology is similar using high intensity ultrasound energy, but the mode of delivery and the operator is different. In MRI-guided HIFU, the operator is often a radiologist, but in US-guided HIFU, the operator is the gynaecologist or surgeon. Real time ultrasound scanning is employed during the whole HIFU process.

The second reason, that impressed me was the high level systems and features built into the machine to ensure safety and avoidance of complications. The safety protocol involves home preparation a week before HIFU, the pre-operation preparation in hospital, the nursing care during HIFU and the post-operation recovery period. All these help to minimise complications many times over compared to conventional surgery. Its smart systems give it a better ablation effectiveness and better results compared to MRI-guided HIFU.

The third point and perharps the most important is that patient recovery is fast and hospitalisation is usually one day. Downtime is just a few days to a week. Hospitalisation costs are much lower and hospital beds can be freed for other needy patients.

Colleagues who are not comfortable or not trained in conventional surgeries may now have a chance to perform non-invasive surgeries e.g the maternal fetal specialists. Surgeons who are unable to stand for long hours on their feet can now be in HIFU surgery sitting comfortably in front of the console table.

Chongqing HAIFU hospital does not rest on its laurels. It continues in its research to improve on energy delivery, safety and realtime imaging.

There are preceptorship programmes to suit the learning gynaecologist. This preceptorship training can even be continued after acquisition of the machine to an overseas site.

Many research and scientific papers have been written on this US-guided HIFU. About 120,000 patients have been treated by US-guided HIFU at the end of 2018 compared to about 4,000 cases worldwide by MRI-guided HIFU. Results have been reportedly good by many centres. Complication rates were low. Pregnancies were achieved with no HIFU related side effects. In July 2019, NICE of UK accepted US-guided HIFU as an alternative for treatment of uterine fibroids and uterine adenomyosis.

US-guided HIFU adds another dimension to surgery for the treatment of fibroids and adenomyosis. But it will never replace conventional surgery. It offers patients an alternative choice to be treated. US-guided HIFU revolutionises the art of surgery and is a new disruption in the world of medicine.

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Calm Before the Storm: Managing Threatened Miscarriage and Those At-Risk – What Works?

Progesterone is a steroid hormone vital to human pregnancy. It helps to sustain decidualization, control uterine contractility and is a pivotal mediator in progesterone-dependent immunomodulation towards the fetal semi-allograft. Low maternal serum progesterone level has been linked to increased risk of first trimester miscarriage and third trimester adverse outcomes such as low birth weight and preterm birth. In the presence of progesterone, lymphocytes and decidual cells synthesize Progesterone-induced blocking factor (PIBF), which has several anti-abortive effects in vivo and is a pivotal mediator in progesterone-dependent immunomodulation for pregnancy maintenance.

Recent evidence has shown the efficacy of progestogen treatment in the management of threatened miscarriage and recurrent miscarriage. However, further studies need to be conducted to more accurately define high-risk patient populations that will allow for better risk stratification as well as define the role and efficacy of progestogen treatment in these patients. This session summarizes current opinions and trials on progestogen use in threatened miscarriage and recurrent miscarriage. After the session, clinicians would better understand the selective use of progestogens and pregnancy outcomes.

Keywords: Progestogens, Miscarriage, Progesterone

Highlights

- Low serum progesterone levels have been associated with first trimester miscarriages.
- Prophylactic treatment for asymptomatic women has no benefit on reducing spontaneous miscarriage rate.
- Progestogen treatment of patients presenting with threatened miscarriage has a significant reduction in the rate of spontaneous miscarriage.

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SP12

HPV Vaccination in Adult Women, Women with LEEP and MEN

Since the licensure of the first-generation human papillomavirus (HPV) vaccines in 2006, primary prevention of the majority of cervical cancer cases is possible. Meanwhile, we are aware that a substantial fraction of vulvar and vaginal cancers, most anal cancers and possibly other neoplasms affecting women and men such as oral cancers can be prevented.

On population level, HPV vaccination is most effective when vaccination is administered early in life and should be given as early as possible in agreement with national guidelines and programs. But with increasing age, the chance of infection persistence is higher. Persistent high-risk HPV infection was a major risk factor for CIN1 progression to CIN2+. High-grade cervical intraepithelial neoplasia (CIN2– 3) bears a risk of developing invasive carcinoma if left untreated. Electrosurgical excision procedure (LEEP) is a diagnostic as well as therapeutic procedure that can effectively eradicate CIN2– 3 .However, residual/recurrent rate after a LEEP varies between 5% and 30%, requiring follow-up and retreatment once lesions have been identified. Due to increasing risk of other HPV related disease and cancer for patients with LEEP, vaccination can be offered on an individual basis.

HPV can also cause genital warts in men, just as in women and increase a man's risk of getting genital cancers, although these cancers are not common. For vaccination programs aiming solely at girls, the protection of men is dependent on the vaccination status of their female partners, and they leave men who have sex with men unprotected. Current girls-only vaccination programs vary by country. In more developed countries, 34% of the females aged 10– 20 years received all three doses of HPV vaccine, compared with only 3% of the females in the less developed regions. Such low vaccination coverage will not provide adequate cancer control or HPV-disease elimination. Gender-neutral vaccination approach can provide benefits to both males and females, particularly in settings where female vaccination rates are low to 99-100%.

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SP13

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HPV Vaccine Durability and Post-Vaccination Ecology

Cervical cancer is the fourth most frequent cancer in women with an estimated 570,000 new cases in 2018 representing 6.6% of all female cancers. Almost all cervical cancer cases (99%) are linked to infection with high-risk human papillomaviruses (HPV), an extremely common virus transmitted through sexual contact. Two HPV types (16 and 18) cause 70% of cervical cancers and pre-cancerous cervical lesions, but other types seems have difference prevalence in the Asia area, especial the types of 52, 58. Whatever nearly All HPV-Related Cancers and Diseases are Caused by 9 HPV types (HPV 6,11,16,18,31,33,45,52,58).

The ultimate goal of HPV vaccination is the eradication of high-risk (hr) HPVs. In the past few years, we saw the prevalence of HPV16 and HPV18 reduce significantly due to massive vaccination programs around the world. It is predicted that Seventy-five percent coverage gender-neutral vaccination of early adolescents will rapidly eradicate HPV16 from the general population. After HPV vaccine launched over 10 years, we could see the changes in post vaccination ecology.

In 2019 Eurogin, there were systematic reviews showing HPV type replacement, especially in some non-vaccine high risk types in young girl population. It is possibile that other HPV types may emerge to fill the vacated ecological niche following a reduction in vaccine-targeted types among vaccinated populations.

In this presentation, we would like to look at the durability of efficacy of quadrivalent and nanovalent HPV vaccines and the changes of HPV ecology after long term systematic vaccination programs.