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LOCAL DATA & TIPS TO OPTIMISE DIETARY INTAKE

Local Situation

Adults

- 93% adults had intake **below** the Chinese recommended nutrient intake (RNI) level[1] (RNI: 120 mcg/day[6])
- Median iodine intake in adults was **44 mcg/day**[1]

School-aged children, pregnant and lactating women

- The iodine status of school-aged children was classified as **'adequate'**[2]
- The iodine status of pregnant women with iodine supplements (≥ 150 mcg/day) was classified as **'adequate'**[2]
- The iodine status of lactating women was classified as **'insufficient'**[2]

Nutritional Tips

- **Avoid taking too much kelp** as it contains high iodine content **(i.e. ≤ once weekly and in a small amount)**[3]
- Replace non-iodized salt with **iodized salt** and follow WHO recommendation on taking **< 5 g of salt (1 teaspoon) per day** [1,4]
  - ◊ WHO recommends **salt to be iodized with 20 – 40 mg/kg**[5]
- HK DoH recommends pregnant and breastfeeding women to take **prenatal multivitamin and multimineral supplements** daily **(contains iodine ≥ 150 mcg)**[3]
- HK DoH recommends women planning for pregnancy to take **iodine-containing supplements**[3]

References: ***1.*** *Centre for Food Safety. Risk assessment study. Report no. 45. 2011.* ***2.*** *Department of Health. Iodine survey report. 2021.* ***3.*** *Family Health Service. Do you have adequate iodine? https://www.fhs.gov.hk/english/health_info/woman/30146.html. Accessed on 22 Jun 2022.* ***4.*** *WHO. Salt reduction. https://www.who.int/news-room/fact-sheets/detail/salt-reduction. Accessed on 22 Jun 2022.* ***5.*** *WHO. Salt reduction and iodine fortification strategies in public health. https://apps.who.int/iris/bitstream/handle/10665/101509/9789241506694_eng.pdf. Accessed on 22 Jun 2022.* ***6.*** *Chinese Nutrition Society. Chinese dietary reference intakes. 2013.*

HONG KONG JOURNAL

OF

GYNAECOLOGY, OBSTETRICS & MIDWIFERY

July 2022, Volume 22, Number 2

EDITORIAL

OBSTETRICS

GYNAECOLOGY

REVIEW ARTICLE

PERSPECTIVE

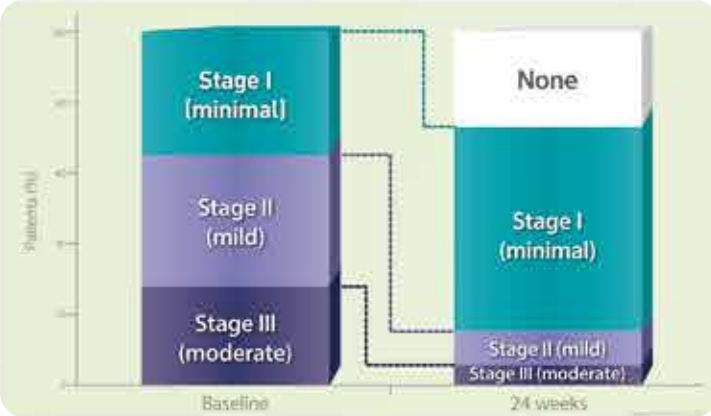
Visanne®
dienogest

5 years of long-term Effectiveness in Reducing Post-operative Recurrence of Endometrioma[1#]

Visanne® dienogest
No reoperation required*

No post-operative medication group:
15 patients required reoperation*

In ~80% of patients, no or only minimal endometriosis was detectable at 24 weeks of Visanne®[2]



The LONG TERM treatment for Endometriosis[1]

There's a way out of the pain

References:
1. Ota Y et al. Long-term administration of dienogest reduces recurrence after excision of endometrioma. J Endometr. 2015;7:63-67.
2. Kohler G et al. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis. Int J Gynaecol Obstet 2010;108:21-25.

Recurrence means lesion previously diagnosed as endometrioma by MRI and ≥6size, 3 months later (on ultrasonography)
^ Cumulative recurrence rates were calculated with the Kaplan-Meier method, and group comparison involved log-rank tests
* Reoperation was performed in patients with endometrioma ≥6 cm who desired it after informed consent

Visanne Abbreviated Prescribing Information
Composition: 2 mg Dienogest per tablet. **Indications:** Treatment of endometriosis. **Dosage and administration:** Oral use. Tablet-taking can be started on any day of the menstrual cycle. One tablet daily. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. Contraindications: Active venous thromboembolic disorder; arterial and cardiovascular disease; present or in history (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease); diabetes mellitus with vascular involvement; presence or history of severe hepatic disease as long as liver function values have not returned to normal; presence or history of liver tumors (benign or malignant); known or suspected sex hormone-dependent malignancies; undiagnosed vaginal bleeding; hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** Before starting Visanne®, pregnancy must be excluded. During treatment, patients are advised to use non-hormonal methods of contraception if contraception is required. Pregnancies that occur among users of progestogen-only preparations used for contraception are more likely to be ectopic than are pregnancies among users of combined oral contraceptives. In women with a history of extrauterine pregnancy or an impairment of tube function, use of Visanne® should be decided on only after carefully weighing the benefits against the risks. Circulatory disorders: From epidemiological studies there is little evidence for an association between progestogen-only preparations and an increased risk of myocardial infarction or cerebral thromboembolism. The risk of cardiovascular and cerebral events is rather related to increasing age, hypertension, and smoking. In women with hypertension the risk of stroke may be slightly enhanced by progestogen-only preparations. Generally recognized risk factors for venous thromboembolism (VTE) include a positive personal or family history, age, obesity, prolonged immobilization, major surgery or major trauma. In case of long-term immobilization it is advisable to discontinue the use of Visanne® (in the case of elective surgery at least four weeks in advance) and not to resume treatment until two weeks after complete remobilization. Increased risk of thromboembolism in the puerperium must be considered. Treatment should be stopped at once if there are symptoms of an arterial or venous thrombotic event or suspicion thereof. Tumors: A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs), mainly estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptives (COC) use. The risk of having breast cancer diagnosed in progestogen-only pill users is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both. In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of hormonal substances such as the one contained in Visanne®. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking Visanne®. Changes in bleeding pattern: Visanne® treatment affects the menstrual bleeding pattern in the majority of women. Uterine bleeding, for example in women with adenomyosis uteri or uterine leiomyomata, may be aggravated with the use of Visanne®. If bleeding is heavy and continuous over time, this may lead to anemia. Discontinuation of Visanne® should be considered in such cases. Osteoporosis: In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed before starting Visanne because endogenous estrogen levels are moderately decreased during treatment with Visanne. Other conditions: Patients who have a history of depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. Visanne® generally does not appear to affect blood pressure in normotensive women. However, if a sustained clinically significant hypertension develops during the use of Visanne®, it is advisable to withdraw Visanne® and treat the hypertension. Recurrence of cholestatic jaundice and/or pruritus which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of Visanne®. Visanne® may have a slight effect on peripheral insulin resistance and glucose tolerance. Diabetic women, especially those with a history of gestational diabetes mellitus, should be carefully observed while taking Visanne®. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking Visanne®. Persistent ovarian follicles (often referred to as functional ovarian cysts) may occur during use of Visanne®. Most of these follicles are asymptomatic, although some may be accompanied by pelvic pain. Lactose: Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should consider the amount contained in Visanne. **Adverse drug reactions:** The most frequently reported undesirable effects during treatment that were considered at least possibly related to Visanne® were headache, breast discomfort, depressed mood, and acne. In addition, the majority of patients treated with Visanne experience changes in their menstrual bleeding pattern. Other common undesirable effects are weight increased, sleep disorder, nervousness, loss of libido, mood altered, migraine, nausea, abdominal pain, flatulence, abdominal distension, vomiting, alopecia, back pain, ovarian cyst, hot flush, uterine/vaginal bleeding including spotting, asthenic conditions, irritability. For a full list of undesirable effects, please refer to the full product insert. **Drug interactions:** Individual enzyme-inducers or inhibitors (CYP3A4) may affect the progestogen drug metabolism. Substances with enzyme-inducing properties can result in increased clearance of sex hormones. Substances with enzyme-inhibiting properties may increase plasma levels of progestogens and result in undesirable effects. A standardized high fat meal did not affect the bioavailability of Visanne®. The use of progestogens may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Please refer to full Prescribing information before prescribing. Dec 2016. Approval number: MA- M_VIS-HK-0002-1

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1. Smith P, Middleton L, Connor M, Clark T. Hysteroscopic morcellation compared with electrical resection of endometrial polyps. Obstet Gynecol. 2014;123(4):745-751.
2. Van Dongen, H., Emanuel M. H., Wolterbeek R., Trimbos J B., Jansen F. W., Hysteroscopic morcellator for removal of intrauterine polyps and myomas. J Minim Invasive Gynecol. Jul-Aug 2008;15(4):466-71.
3. HysteroLux Fluid Management System [instructions for use]. New Haven, CT: Medtronic; 2017. Photo credit: Shutterstock

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適齡時及早預防 有助減低感染風險[1] 請向醫生查詢

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資料來源: 1. CDC. Genital HPV Infection - CDC Fact Sheet, CDC. Available at: https://www.cdc.gov/std/hpv/HPV-FS-July-2017.pdf. Accessed on 8 Apr 2022. 2. American Cancer Society. HPV (Human Papillomavirus). Available at: https://bit.ly/3xvWRPR. Accessed on 14 Apr 2022.

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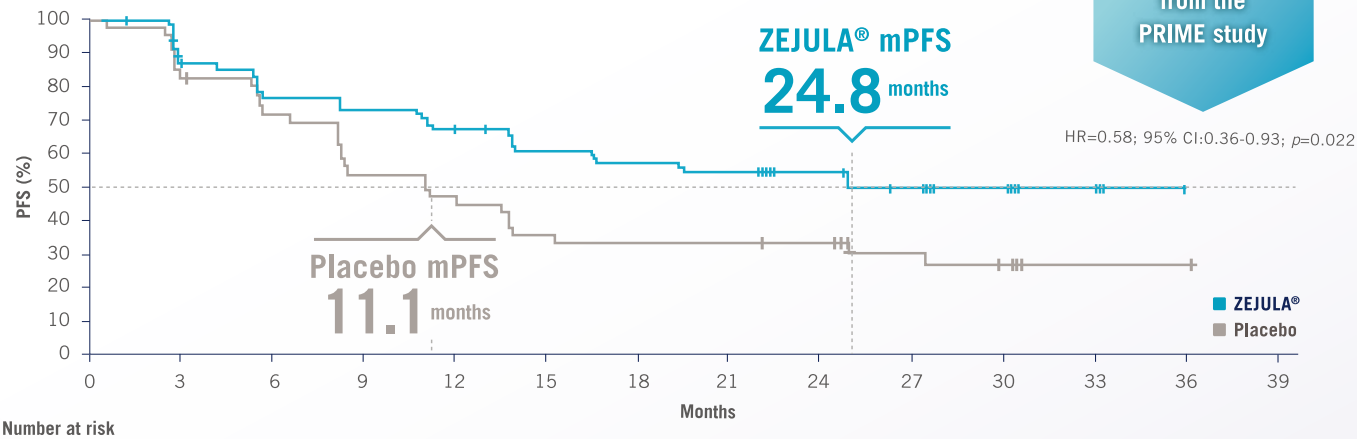
PFS in the BRCAwt, HRd subgroup populations[4]

New data from the PRIME study



Number at risk														
ZEJULA®	85	71	63	60	54	48	45	42	36	25	13	6	0	0
Placebo	47	39	32	24	20	16	15	15	13	8	6	1	1	0

Figure adapted from Li N, 2022.

The efficacy with ZEJULA® was observed to be consistent across different patient subgroups, regardless of HRd or BRCA status.[4]

*as monotherapy

Abbreviations: BRCA: Breast cancer susceptibility gene; BRCAwt: Breast cancer susceptibility gene wild type; CI: Confidence interval; HR: Hazard ratio; HRd: Homologous recombination deficient; mPFS: Median progression-free survival; PARP: Poly ADP ribose polymerase; PFS: Progression-free survival

References: 1. ZEJULA® (niraparib). Prescribing information. Zai Lab; Aug 2021. 2. Lynparza® (Olaparib). Summary of Product Characteristics. Jan 2018. 4206580. 3. Rubraca® (Rucaparib). Summary of Product Characteristics. May 2020. 4609275. 4. Li N et al. Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. Presented at: Society of Gynecologic Oncology Annual Meeting on Womens' Cancer 2022; 18-21 March 2022; Phoenix, Arizona, USA.

Zejula Capsules 100 mg – Abbreviated PI

Name of the Medicinal Product: Zejula Capsules 100 mg. Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg niraparib. Therapeutic Indications: Zejula is indicated as monotherapy for the maintenance treatment of adult patients with: • advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy, • platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Posology: *First-line ovarian cancer maintenance treatment*: 200mg once daily. *Recurrent ovarian cancer maintenance treatment*: 300mg once daily. Take the dose at approximately the same time each day. Bedtime administration may potentially help to manage nausea. Continued treatment is recommended until disease progression or toxicity. *Dose adjustments for adverse reactions*: In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, or are not manageable with this strategy of dose interruption and reduction, recommend to discontinue Zejula. Refer to the full prescribing information for detailed recommendations on dosage adjustments for adverse reactions, patients with higher/lower body weight and missed dose. No dose adjustment is needed for patients with mild to moderate renal impairment or mild hepatic impairment. Contraindications: Hypersensitivity. Breast-feeding. Warnings and Precautions: *Haematologic* - Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula. Complete blood counts should be tested according to schedule. Discontinue Zejula if patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption. Anticoagulants and medicinal products known to reduce thrombocyte count should be used with caution. *Myelodysplastic syndrome/acute myeloid leukaemia* - Cases of MDS/AML have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and postmarketing. If MDS and/or AML are confirmed while on treatment with Zejula, treatment should be discontinued and the patient treated appropriately. *Hypertension, including hypertensive crisis* – Hypertension, including hypertensive crisis, has been reported with the use of Zejula. Pre-existing hypertension should be adequately controlled before starting treatment and monitor blood pressure at least weekly for two months, monthly afterwards for the first year and periodically thereafter during treatment. Discontinue Zejula in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy. *Posterior Reversible Encephalopathy Syndrome (PRES)* – PRES has been reported in patients receiving Zejula. In case of PRES, discontinue Zejula and to treat specific symptoms including hypertension. *Hepatic impairment* – Carefully monitor in patients with moderate and severe hepatic impairment. Interaction with other medicinal products and other forms of interaction: Exercise caution when use in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products; when niraparib is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine), and metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline, and ropinirole); when niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate); and when combined with active substances that undergo an uptake transport by OCT1 such as metformin. Fertility, pregnancy and lactation: Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Zejula. Zejula should not be used during pregnancy. Breast-feeding is contraindicated during treatment and for 1 month after receiving the last dose. Undesirable Effects: ADRs of all grades occurring in ≥ 10% of patients in both PRIMA and NOVA trials were: nausea, anaemia, thrombocytopenia, fatigue, constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, decreased appetite, diarrhoea, dyspnoea, hypertension, asthenia, dizziness, neutrophil count decreased, cough, arthralgia, back pain, white blood cell count decreased, and hot flush. The most common serious adverse reactions > 1 % (treatment-emergent frequencies) were thrombocytopenia and anaemia. Please refer to the full prescribing information before prescribing. 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Periodicals

1. Fuchs AR, Fuchs F, Husslein P, et al. Oxytocin receptors in the human uterus during pregnancy and parturition. *Am J Obstet Gynecol* 1984; 150:734-41.

Books edited by other authors of the article

2. Redwine DB, Perez JJ. Pelvic pain syndrome: endometriosis and mid-line dysmenorrhea. In: Arregui MW, Fitzgibbons RJ, Katkhouda N, McKerman JB, Reich H, editors. Principles of Laparoscopic Surgery – Basic and Advanced Techniques. *New York: Springer Verlag*; 1995: 545-58.

Books edited by author

3. Varney H. Nurse Midwifery. *Boston: Blackwell Scientific Publications*; 1987: 23-32.

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Editorial

Taking structured training in obstetrics and gynaecology across the border

The Hong Kong College of Obstetricians and Gynaecologists (HKCOG) was established in 1988 with the insight to oversee specialist training by a local professional body. The Hong Kong Academy of Medicine (HKAM), established in 1993, and its 15 constituent Colleges, including the HKCOG, oversee the maintenance of the standard of specialists practising in Hong Kong.

Back in 2006, the HKAM signed a memorandum of understanding (MOU) with the Mainland Chinese government to assist the Mainland China in developing a registration system for specialists. In 2015, an MOU on standardised specialist training was signed. Subsequently, the HKAM signed an MOU on the training of Shenzhen and Hong Kong specialists with three parties: the Shenzhen Municipal Health Commission, The University of Hong Kong, and The University of Hong Kong-Shenzhen Hospital (HKU-SZH). In 2019, the Shenzhen-Hong Kong Medical Specialist Training Center was established. After much deliberation, the Center adopted a structured specialist programme in the format of '3+4' for all specialties, with 3 years of existing national residency training programme, followed by 4 years of specialist training programme.

Before the formal establishment of the Center, HKU-SZH had already started a pilot obstetrics and gynaecology (O&G) training scheme, taking reference from the HKCOG training programme in general O&G as well as in four subspecialties: maternal and fetal medicine, urogynaecology, reproductive medicine, and gynae-oncology. With the establishment of the Center in 2019, the HKCOG signed an MOU with HKU-SZH to facilitate the development of a structured O&G training programme, and the programme was updated to fit into the agreed '3+4' format rather than the 6 years of specialist training in Hong Kong. The updated programme was one of the first specialist training programmes approved and adopted by the Shenzhen-Hong Kong Medical Specialist Training Center. Currently, five hospitals in the Greater Bay Area have joined this training programme.

This training programme is based on the HKCOG training programme, with completion of logbooks, on-the-job assessments such as objective structured assessment of technical skills and case-based discussions, regular reviews with designated trainers, intermediate assessments such as the structured oral examinations, examinations similar to the Member of the Royal College of Obstetricians and Gynaecologists part 2 and part 3, and a final assessment similar to the HKCOG exit assessment. HKCOG is actively assisting the Shenzhen-Hong Kong Medical Specialist Training Center in providing regular 'train-the-trainer' courses to doctors from different hospitals in Shenzhen. HKCOG also provides assessors for the HKU-SZH trainees. In 2021, HKU-SZH, with assistance from HKCOG, held the first pilot structured oral examinations. In the coming months, HKCOG will assist the Shenzhen-Hong Kong Medical Specialist Training Center in conducting 'train-the-trainer' workshops and in preparing examinations similar to the Member of the Royal College of Obstetricians and Gynaecologists part 2 and part 3.

For more than 30 years, HKCOG has taken up the role of establishing and overseeing structured O&G training in Hong Kong. Most current practising O&G specialists are trained under this programme, which has been proved to be effective and well recognised internationally. We hope that we can bring our experience to the Greater Bay Area and play our part to support the national goal of training medical specialists to international standards.

Karen CHAN
President, Hong Kong College of Obstetricians and Gynaecologists

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Email: kklchan@hku.hk

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Association of pre-pregnancy body mass index and gestational weight gain with pregnancy outcomes

Hoi-Ki CHUNG, MB ChB
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Background: Gestational weight gain (GWG) is a modifiable risk factor for pregnancy outcomes. This study aimed to evaluate the associations of pre-pregnancy body mass index (BMI) and GWG with perinatal and maternal outcomes in Hong Kong women and to identify risk factors for poor perinatal/maternal outcomes.
Methods: Medical records of low-risk women with singleton pregnancy who delivered babies between 1 January 2019 and 28 February 2019 at our hospital were reviewed. Based on pre-pregnancy BMI, women were categorised as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), pre-obesity (25-29.9 kg/m^2), and obesity (>30 kg/m^2). Based on the recommended total GWG by the Institute of Medicine, women were categorised as inadequate, normal, and excessive GWG. The normal group was compared with each of the other groups.
Results: 465 women were included for analysis. Of them, 439 (94.4%) delivered after 37 weeks of gestation and 26 (5.6%) delivered before 37 weeks of gestation. After adjusting for confounders, the risk factors for gestational diabetes were women with pre-obesity (odds ratio [OR]=3.879, p=0.001) and women with obesity (OR=15.118, p<0.001), whereas the risk factor for neonatal ventilator use was women with pre-obesity (OR=5.719, p=0.035) and the risk factor for caesarean section was women with excessive GWG (OR=1.591, p=0.047).
Conclusion: High pre-pregnancy BMI is associated with gestational diabetes and neonatal ventilator use, whereas excessive GWG is associated with caesarean section.

Keywords: Body mass index; Gestational weight gain; National Academies of Science, Engineering, and Medicine, U.S., Health and Medicine Division; Pregnancy outcome

Introduction

The importance of pre-pregnancy nutritional status and gestational weight gain (GWG) is increasingly recognised. Pre-pregnancy underweight is associated with low birth weight and preterm delivery, whereas obesity is associated with gestational diabetes, hypertensive disorder, and macrosomia. Inadequate or excessive GWG has persistent negative impact to offspring on cardiometabolic risks such as childhood adiposity, hypertension, and insulin resistance. Health counselling based on the body mass index (BMI) status is not adequate. GWG is a modifiable risk factor for adverse pregnancy outcomes. Nonetheless, the optimal GWG remains controversial. In 2009, the United States Institute of Medicine proposed a guideline on GWG (Table 1)[1]. Whether this guideline applies to the Chinese population is not known. This study aimed to evaluate the associations of pre-pregnancy BMI and GWG with perinatal and maternal outcomes in Hong Kong women and to identify risk factors for poor perinatal/maternal outcomes.

Materials and Methods

This study was approved by the Kowloon Central Cluster Research Ethics Committee (reference: KC/KE-21-0210/ER-1). Medical records of low-risk healthy Chinese women with singleton pregnancy who were followed up and delivered at Queen Elizabeth Hospital between 1 January 2019 and 28 February 2019 were retrospective reviewed. The hospital is a tertiary public hospital in Hong Kong, with live births around 5000 to 6000 per year.

Exclusion criteria were (1) non-Chinese couples, (2) women with pre-existing medical conditions (diabetes, hypertension, thyroid disease, autoimmune disease, history of malignancy, cardiac disease, epilepsy, liver disease, kidney disease, or other systemic condition), (3) women with a history of substance abuse, (4) smokers, (5) women with negative outcomes in previous pregnancies (low birth weight, macrosomia, intrauterine death, fetal anomaly, placenta pathology, preterm delivery, gestational diabetes, gestational hypertensive disorder, postpartum haemorrhage, severe neonatal complication), (6) women with fetal or placental pathology in the current pregnancy, (7) women with multiple pregnancies or intrauterine death, and (8) women with incomplete follow-up and delivery data.

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Table 1. Total gestational weight gain recommended by the US Institute of Medicine[1]

Body mass index, kg/m^2	Total gestational weight gain recommended, kg
<18.5 (underweight)	12.5-18
18.5-24.9 (normal weight)	11.5-16
25-29.9 (pre-obesity)	7-11.5
>30 (obesity)	5-9

Material characteristics retrieved included maternal age, gravida, parity, previous caesarean section, education level, working status, family history of diabetes mellitus, family history of hypertension, assisted reproductive technology, maternal height, and body weight and BMI before pregnancy, at 20 to 24 weeks of gestation, and at delivery. Early GWG was defined as body weight at 20 to 24 weeks of gestation minus pre-pregnancy body weight. Late GWG was defined as body weight at delivery minus body weight at 20 to 24 weeks of gestation. Total GWG was defined as body weight at delivery minus pre-pregnancy body weight.

Pregnancy and neonatal outcomes retrieved included low birth weight, macrosomia, preterm birth, modes of delivery, primary postpartum haemorrhage, gestational diabetes, gestational hypertensive disorder, maternal peripartum fever, neonatal intensive care unit admission, neonatal sepsis, need for neonatal resuscitation, neonatal respiratory distress syndrome, transient tachypnoea of the newborn, need for ventilator support, neonatal jaundice, neonatal necrotising enterocolitis, hypoxic-ischemic encephalopathy, neonatal seizure, meconium-stained liquor, and obstetric anal sphincter injury.

Analyses were performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant. Based on pre-pregnancy BMI, women were categorised as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), pre-obesity (25-29.9 kg/m^2), and obesity (>30 kg/m^2). Based on the recommended total GWG by the Institute of Medicine, women were categorised as inadequate, normal, and excessive GWG. The normal group was compared with each of the other groups using the unpaired sample t-tests or ANOVA for continuous data and the Chi-square test or Fisher exact test for categorical data. Multivariate analysis was used to adjust the effect of confounders on adverse maternal and neonatal outcomes.

Results

Of 916 women followed up and delivered during the 2-month study period, 451 were excluded based on the exclusion criteria and 465 were included for analysis. Of them, 439 (94.4%) delivered after 37 weeks of gestation and 26 (5.6%) delivered before 37 weeks of gestation. In terms of pre-pregnancy BMI, 61 (13.1%) women were underweight, 329 (70.8%) women were normal weight, 60 (12.9%) women were pre-obese, and 15 (3.2%) women were obese. In terms of total GWG, 157 (33.8%) women were inadequate, 194 (41.7%) women were normal, and 114 (24.5%) women were excessive.

Association of maternal demographics with pre-pregnancy BMI

Compared with women with normal weight, women with underweight were younger (29.33 vs 30.28, p=0.020), and women with obesity were older (31.60 vs 30.28, p=0.005), and women with pre-obesity had a higher parity (0.55 vs 0.35, p=0.009) and more caesarean sections (0.17 vs 0.05, p=0.048) [Table 2]. Women with normal weight had the highest percentage of tertiary education, compared with women with underweight, pre-obesity, or obesity (72.3% vs 55.7% vs 51.7% vs 40%, p=0.016 to p=0.001), and had higher percentage of being employed, compared with women with obesity (53.5% vs 82.7%, p=0.01).

Association of pre-pregnancy BMI with GWG

Compared with women with normal weight, women with pre-obesity had a lower percentage of normal GWG (26.7% vs 42.6%, p=0.021), whereas women with underweight had a lower percentage of excessive GWG (9.8% vs 23.1%, p=0.020) and women with pre-obesity had a higher percentage of excessive GWG (46.7% vs 23.1%, p<0.001) [Table 2].

Association of maternal demographics with GWG

Compared with women with normal GWG, women with excessive GWG were younger (29.43 vs 30.29 years, p=0.013), had a lower percentage of tertiary education (57% vs 71.6%, p=0.009) and had a higher pre-pregnancy BMI (22.817 vs 21.195 kg/m^2, p<0.001) [Table 3].

Association of pre-pregnancy BMI with pregnancy outcomes

The percentage of gestational diabetes was highest in women with obesity (46.7%), followed by women with pre-obesity (18.3%), compared with women with normal weight (5.5%) [p<0.001 and p=0.002, respectively]. Gestational diabetes was associated with a

Table 2. Maternal characteristics and pregnancy outcomes among women with normal weight, underweight, pre-obesity, or obesity

Characteristic	Normal weight (n=329)*	Underweight (n=61)*	p Value	Pre-obesity (n=60)*	p Value	Obesity (n=15)*	p Value
Age, y	30.28±2.901	29.33±3.048	**0.020**	30.33±2.660	0.900	31.60±1.502	**0.005**
Parity	0.35±0.554	0.38±0.610	0.697	0.55±0.565	**0.009**	0.53±0.516	0.201
Gravida	1.71±0.954	1.72±0.933	0.903	1.95±0.964	0.069	2.07±1.223	0.157
Previous caesarean section	0.05±0.228	0.10±0.351	0.213	0.17±0.418	**0.048**	0.13±0.352	0.405
Maternal height, cm	159.4±5.7	159.7±4.9	0.679	158.6±5.2	0.296	159.2±5.5	0.888
Tertiary education	238 (72.3)	34 (55.7)	**0.010**	31 (51.7)	**0.001**	6 (40.0)	**0.016**
Employment	272 (82.7)	44 (72.1)	0.054	44 (73.3)	0.088	8 (53.3)	**0.010**
Assisted reproductive technology	12 (3.6)	1 (1.6)	0.701	1 (1.7)	0.701	2 (13.3)	0.119
Family history of diabetes mellitus	56 (17.0)	14 (23.0)	0.268	19 (31.7)	0.008	3 (20.0)	0.728
Family history of hypertension	114 (34.7)	22 (36.1)	0.831	26 (43.3)	0.198	3 (20.0)	0.241
Gestational weight gain							
Inadequate	113 (34.3)	25 (41.0)	0.319	16 (26.7)	0.245	3 (20.0)	0.250
Normal	140 (42.6)	30 (49.2)	0.338	16 (26.7)	**0.021**	8 (53.3)	0.410
Excessive	76 (23.1)	6 (9.8)	**0.020**	28 (46.7)	**<0.001**	4 (26.7)	0.757
Outcome							
Preterm birth	15 (4.6)	5 (8.2)	0.218	6 (10.0)	0.113	0 (0)	1.000
Caesarean section	74 (22.5)	17 (27.9)	0.410	14 (23.3)	0.886	5 (33.3)	0.349
Maternal complication							
Gestational diabetes	18 (5.5)	3 (7.7)	1.000	11 (18.3)	**0.002**	7 (46.7)	**<0.001**
Gestational hypertensive disorder	9 (2.7)	0 (0)	0.365	2 (3.3)	0.681	0 (0)	1.000
Postpartum haemorrhage	16 (4.9)	2 (3.3)	0.750	4 (6.7)	0.526	0 (0)	1.000
Peripartum fever	25 (7.6)	6 (9.8)	0.605	5 (8.3)	0.795	1 (6.7)	1.000
Neonatal complications							
Low birth weight	16 (4.9)	5 (8.2)	0.348	1 (1.7)	0.489	0 (0)	1.000
Macrosomia	4 (1.2)	1 (1.6)	0.575	1 (1.7)	0.569	1 (6.7)	0.201
Neonatal sepsis	18 (5.5)	4 (6.6)	0.762	3 (5.0)	1.000	1 (6.7)	0.581
Neonatal intensive care unit admission	70 (21.3)	13 (21.3)	0.995	12 (20.0)	0.824	3 (20.0)	1.000
Need of resuscitation	3 (0.9)	0 (0)	1.000	0 (0)	1.000	0 (0)	1.000
Respiratory distress syndrome	7 (2.1)	1 (1.6)	1.000	4 (6.7)	0.073	1 (6.7)	0.303
Transient tachypnoea of the newborn	20 (6.1)	1 (1.6)	0.222	2 (3.3)	0.551	0 (0)	1.000
Need of ventilator support	3 (0.9)	1 (1.6)	0.495	3 (5.0)	**0.018**	0 (0)	1.000
Respiratory complication	24 (7.3)	2 (3.3)	0.400	7 (11.7)	0.296	1 (6.7)	1.000
Neonatal jaundice	131 (39.8)	29 (47.5)	0.260	32 (53.3)	0.051	7 (46.7)	0.597
Meconium stained liquor	31 (9.4)	9 (14.8)	0.207	6 (10.0)	0.888	1 (6.7)	1.000

* Data are presented as mean ± standard deviation or No. (%) of participants

Table 3. Maternal characteristics and pregnancy outcomes among women with normal gestational weight gain (GWG), inadequate GWG, or excessive GWG

Characteristic	Normal GWG (n=194)	Inadequate GWG (n=157)	p Value	Excessive GWG (n=114)	p Value
Age, y	30.29±2.89	30.66±2.69	0.222	29.43±2.96	**0.013**
Parity	0.37±0 .54	0.46±0.61	0.111	0.30±0.51	0.282
Gravida	1.65±0.88	1.82±0.96	0.094	1.83±1.08	0.106
Previous caesarean section	0.08±0.29	0.09±0.30	0.835	0.05±0.22	0.350
Maternal height, cm	159.550±5.24	158.775±5.93	0.195	159.761±5.27	0.735
Tertiary education	139 (71.6)	105 (66.9)	0.334	65 (57.0)	**0.009**
Employment	152 (78.4)	128 (81.5)	0.461	88 (77.2)	0.813
Assisted reproductive technology	8 (4.1)	7 (4.5)	0.877	1 (0.9)	0.162
Family history of diabetes mellitus	40 (20.6)	27 (17.2)	0.417	25 (21.9)	0.785
Family history of hypertension	69 (35.6)	55 (35.0)	0.917	41 (36.0)	0.944
Pre-pregnancy body mass index, kg/m^2	21.195±3.4236	21.493±3.5690	0.426	22.817±4.161	**<0.001**
Preterm birth	7 (3.6)	11 (7.0)	0.151	8 (7.0)	0.180
Caesarean section	45 (23.2)	28 (17.8)	0.218	37 (32.5)	**0.048**
Maternal complications					
Gestational diabetes	15 (7.7)	14 (8.9)	0.688	10 (8.8)	0.747
Gestational hypertensive disorder	4 (2.1)	3 (1.9)	1.000	4 (3.5)	0.474
Postpartum haemorrhage	6 (3.1)	11 (7.0)	0.140	5 (4.4)	0.543
Peripartum fever	16 (8.2)	10 (6.4)	0.504	11 (9.6)	0.674
Neonatal complications					
Low birth weight	7 (3.6)	13 (8.3)	**0.048**	2 (1.8)	0.493
Macrosomia	3 (1.5)	1 (0.6)	0.631	3 (2.6)	0.674
Neonatal sepsis	11 (5.7)	7 (4.5)	0.609	8 (7.0)	0.635
Neonatal intensive care unit admission	40 (20.6)	28 (17.8)	0.512	30 (26.3)	0.249
Need of resuscitation	3 (1.5)	0 (0)	0.256	0 (0)	0.298
Respiratory distress syndrome	6 (3.1)	2 (1.3)	0.305	5 (4.4)	0.543
Transient tachypnoea of the newborn	9 (4.6)	8 (5.1)	0.843	6 (5.3)	0.806
Need of ventilator support	5 (2.6)	1 (0.6)	0.230	1 (0.9)	0.418
Respiratory complication	15 (7.7)	10 (6.4)	0.662	9 (7.9)	0.959
Neonatal jaundice	82 (42.3)	59 (37.6)	0.373	58 (50.9)	0.143
Meconium-stained liquor	21 (10.8)	15 (9.6)	0.696	11 (9.6)	0.744

* Data are presented as mean ± standard deviation or No. (%) of participants

family history of diabetes mellitus (odds ratio [OR]=5.78, p<0.001), early GWG (OR=1.13, p=0.048), and late GWG (OR=0.78, p<0.001) but not total GWG. After adjusting for confounders, gestational diabetes was associated with women with pre-obesity (OR=3.879, p=0.001) and women with obesity (OR=15.118, p<0.001) [Table 4].

The percentage of neonates needing ventilator support was higher in women with pre-obesity, compared with women with normal weight (5.0% vs 0.9%, p=0.018). After adjusting for confounders, the need for neonatal ventilator support was associated with women with pre-obesity (OR=5.71, p=0.035) [Table 4].

Table 4. Multivariate analysis for the association of pre-pregnancy body mass index with gestational diabetes and need for neonatal ventilator support

	Adjusted odds ratio (95% confidential interval)		
	Underweight vs normal weight	Pre-obesity vs normal weight	Obesity vs normal weight
Gestational diabetes*	0.894 (0.255-3.132)	3.879 (1.728-8.704)	15.118 (4.932-46.341)
p Value	0.861	0.001	<0.001
Need for neonatal ventilator support†	1.811 (0.185-17.704)	5.719 (1.126-29.041)	-
p Value	0.610	0.035	

* Adjusted for family history of diabetes and early and total gestational weight gain
† Adjusted for maternal age, preterm birth, and late gestational weight gain

Table 5. Multivariate analysis for the association of gestational weight gain (GWG) with caesarean section and low birth weight

	Adjusted odds ratio (95% confidential interval)	
	Underweight vs normal weight	Obesity vs normal weight
Caesarean section*	0.719 (0.424-1.218)	1.591 (1.241-3.012)
p Value	0.220	0.047
Low birth weight†	2.412 (0.938-6.200)	0.477 (0.097-2.337)
p Value	0.068	0.361

* Adjusted for parity, gravida, number of previous caesarean sections, and maternal height
† Adjusted for maternal height and parity

Association of GWG with pregnancy outcomes

Compared with women with normal GWG, women with excessive GWG had a higher percentage of caesarean section (32.5% vs 23.2%, p=0.048). After adjusting for confounders, excessive GWG was associated with a higher rate of caesarean section (OR=1.591, p=0.047, Table 5).

Compared with women with normal GWG, women with inadequate GWG had a higher percentage of low birth weight babies (8.3% vs 3.6%, p=0.048, Table 3). After adjusting for confounders, the association became not significant (Table 5).

Discussion

Age and education level were associated with pre-pregnancy BMI and total GWG. Age may affect the metabolic rate. Women with higher education levels may have higher awareness of the consequences of an abnormal BMI and GWG and thus had better diet control[2].

The percentage of inadequate GWG was highest in underweight women, whereas the percentage of excessive GWG was highest in pre-obesity women. These findings are consistent with those in previous studies[3,4]. Inadequate and excessive GWG can be associated with diet. The diet quality score was highest in women with normal GWG, and the association between GWG adherence and prenatal diet quality was dependent on pre-pregnancy BMI[4]. This suggests that antenatal interventions such as nutrition counselling may improve diet quality and GWG, particularly in women with pre-obesity or obesity[3-6].

Women with pre-obesity or obesity had higher risk of gestational diabetes. Pre-pregnancy BMI is associated with gestational diabetes[14,15], probably owing to the difference in adipose tissue influences insulin resistance[12,13]. In women with obesity, adipocytes can act as an endocrine factor, releasing adipokines, which can affect oocyte differentiation and maturation[2]. In addition, implantation and reproductive functions are also impaired in women with obesity. Higher early GWG is associated with a higher risk of gestational diabetes[16,17]. Advice for optimal BMI should be provided in pre-conception and antenatal counselling, as high BMI increases the risk of developing type 2 diabetes mellitus. Thus, diet modification and physical activities during and beyond pregnancy are important[14-18].

Women with excessive GWG had a higher rate of caesarean section, whereas women with pre-obesity had a higher rate of neonatal ventilator support. Women with higher GWG have been reported to have a higher risk of emergency caesarean sections and instrumental deliveries[7-11].

The total GWG recommended by the US Institute of Medicine was associated with the mode of delivery only.

An increase in adverse pregnancy outcomes in women with excessive GWG can be due to effects of oxidative stress, pro-inflammatory status, altered placental function, and impaired insulin sensitivity. However, the present study failed to demonstrate such associations, as did other studies[19,20]. The reasons can be due to socioeconomic, medical, cultural, and nutritional differences or the small sample size. The prevalence of obesity is higher in Western countries. Strict inclusion criteria might have eliminated many risk factors of maternal and perinatal complications. Active smokers have a higher risk of preterm delivery, low birth weight, and neonatal respiratory distress syndrome[21]. Advanced maternal age is associated with operative vaginal delivery, caesarean section, preterm birth, low birth weight, and neonatal death[22]. A multicentre study with a larger population is required to verify the applicability of the Institute of Medicine recommendations in Hong Kong Chinese populations. A specialised electronic obstetric system is needed to facilitate data collection and analysis across various hospitals[23].

The present study has limitations. The sample size was too small to determine the optimal GWG range. The number of women with obesity was small. Pre-pregnancy body weight was self-reported. Women with delivery during 24 to 41 weeks of gestation were included; GWG partly depends on the pregnancy duration. Smaller GWG occurs in extreme preterm birth, and smaller babies have more neonatal complications. The reason for including preterm births was to compare the effect of GWG on the risk of preterm delivery. GWG per week was not examined owing to the retrospective nature. The rate of GWG through trimesters may be more accurate. The oral glucose tolerance test is not universally performed in Hong Kong; the prevalence of gestational diabetes may be underestimated. Long-term outcomes of the newborn and mother were not studied.

Conclusion

High pre-pregnancy BMI is associated with gestational diabetes and neonatal ventilator use, whereas excessive GWG is associated with caesarean deliveries.

Contributors

The author designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The author has disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central Cluster Research Ethics Committee (reference: KC/KE-21-0210/ER-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Experience and confidence in vaginal twin/breech delivery among trainees and junior specialists in Hong Kong public hospitals

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Objectives: To evaluate the perceived experience and confidence in providing vaginal twin delivery and vaginal breech delivery among obstetric trainees and junior specialists in Hong Kong, and to determine the correlations between the perceived experience and confidence and the numbers of vaginal twin/breech deliveries, forceps deliveries, and rotational operative deliveries performed.

Methods: An anonymous online questionnaire was developed to assess experience and confidence in vaginal twin/breech delivery among trainees and junior specialists in public hospitals. Respondents were asked about the numbers of vaginal twin/breech deliveries, forceps deliveries, and rotational operative deliveries performed. They were asked if they intended to offer vaginal twin/breech delivery in practice. Those who reported insufficient confidence in performing such deliveries were asked for their reasons.

Results: Of 141 eligible respondents, 58 (41.1%) responded. Of them, 52 (40 trainees and 12 junior specialists) were included for analysis. For vaginal twin delivery, the number of procedures performed was correlated with the perceived sufficient experience (r=0.612, p<0.01) and confidence (r=0.586, p<0.01). 12 (23%) respondents reported no sufficient confidence in performing vaginal twin delivery. Reasons provided were lack of training or experience (n=12) and concern about medical legal issues (n=5). 69.2% of respondents intended to offer vaginal twin delivery in practice; the percentage of those with confidence was not correlated with that of those with intention to offer it in practice (r=0.212, p=0.132). For vaginal breech delivery, the number of procedures performed was correlated with perceived sufficient experience (r=0.307, p=0.027) and confidence (r=0.659, p<0.01). 15 (29%) respondents reported no sufficient confidence in performing vaginal breech delivery. Reasons provided were lack of training and experience (n=14) and concern about medical legal issues (n=7). Only 25% of respondents intended to offer vagina breech delivery in practice; the percentage of those with confidence was not correlated with that of those with intention to offer it in practice (r=0.11, p=0.438).

Conclusion: Most respondents did not perceive themselves having sufficient experience and confidence in vaginal twin/breech delivery. The perceived sufficient experience and confidence in vaginal twin/breech delivery was positively correlated to actual clinical experiences. Training of vaginal twin/breech delivery should be provided before these techniques become obsolete.

Keywords: Breech presentation; Delivery, obstetric; Pregnancy, twin

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Introduction

Vaginal twin delivery and vaginal breech delivery are essential skills of obstetricians. According to the audit by the Hong Kong College of Obstetricians and Gynaecologists, the overall incidence of vaginal breech delivery was 0.2% over the 10-year period between 2004 and 2014, whereas the rate of spontaneous vaginal delivery of twin pregnancy declined from 0.5% in 2004 to 0.3% in 2014. Lack of clinical exposure by Hong Kong obstetricians may affect their performance of these procedures and willingness to offer them in daily practice.

For twin pregnancies reaching 32 weeks of gestation with cephalic presentation, there is no evidence to show that planned caesarean delivery is superior to planned vaginal delivery in terms of neonatal outcome[1]. The National Institute for Health and Care Excellence guideline suggests that planned vaginal delivery is a safe option for suitable candidates[2]. Although the Term Breech Trial reported that perinatal mortality and morbidity were significantly lower for planned caesarean delivery than vaginal birth[3], vaginal breech delivery remains a feasible option and should be offered in selected cases by those with expertise[4-7].

Forceps can be used to deliver the after-coming head in vaginal breech delivery, whereas ventose extraction and forceps can be used in delivering the second twin vaginally[8,9].

This study aims to evaluate the perceived experience and confidence in vaginal twin delivery and vaginal breech delivery among obstetric trainees and junior specialists in Hong Kong, and to determine the correlations between the perceived experience and confidence and the numbers of vaginal twin/breech deliveries, forceps deliveries, and rotational operative deliveries performed.

Methods

This study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECEREC-2021-046), Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-01-0146/ER-3), Kowloon West Cluster Research Ethics Committee (reference: KW/FR-21-029(156-11)), New Territories West Cluster Research Ethics Committee (reference: NTWC/REC/21041), Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference: UW 21-394), and Joint Chinese University of Hong Kong – New Territories East Clinical Research Ethics Committee (reference: 2021.340).

Based on previous survey studies[10,11], an anonymous online questionnaire (Appendix) was developed to assess experience and confidence in vaginal twin/breech delivery among trainees and junior specialists (who attained fellowship within the past 5 years) in public hospitals. The questionnaire was refined after a pilot testing in five trainees who provided feedback on the questions and logistics of completing the questionnaire online. In September 2021, each trainee and junior specialist received an email via the Hospital Authority system, with a link to the online questionnaire. A reminder email was sent 3 weeks later. Respondents were asked about the numbers of vaginal twin/breech deliveries, forceps deliveries, and rotational operative deliveries performed. They were asked if they intended to offer vaginal twin/breech delivery in practice. Those who reported no sufficient confidence in performing such deliveries were asked for their reasons. Those who stated no interest in practising obstetrics in future were excluded from analysis.

Statistical analysis was performed using the SPSS (Macintosh version 28; IBM Corp, Armonk [NY], US). The Chi-squared test and Fisher exact test were used to compare differences between those perceived to have sufficient experience/confidence and those perceived to have not. The correlations between the perceived experience and confidence and the numbers of vaginal twin/breech deliveries, forceps deliveries, and rotational operative deliveries performed were assessed using the Spearman correlation analysis.

Results

Of 141 eligible respondents in Hong Kong public hospitals, 58 (41.1%) responded. Of them, six (10.3%) stated no interest in practising obstetrics and were excluded and the remaining 52 (40 trainees and 12 junior specialists) were included for analysis.

For vaginal twin delivery, more junior specialists than trainees perceived to have sufficient experience (91% vs 35%, $p<0.001$), but the percentage related to confidence was similar (91% vs 72.5%, $p=0.253$). The number of procedures performed was correlated with the perceived sufficient experience ($r=0.612$, $p<0.01$) and confidence ($r=0.586$, $p<0.01$) [Table 1]. In respondents who had performed <6 procedures, only 31% perceived to have sufficient experience. The percentage increased to 92% in those who had performed >10 procedures. In those who had performed <6 procedures, 56% and 14% perceived to be confident with and without supervision, respectively. The percentage increased to 100% and 69%,

Table 1. Perceived sufficient experience and confidence of trainees and junior specialists in relation to the number of vaginal twin/breech deliveries performed

Perceived sufficient experience and confidence	No. of vaginal twin/breech deliveries performed*			Spearman's coefficient	p Value
	0-5	6-10	>10		
Perceived sufficient experience					
Vaginal breech delivery				0.307	0.027
Yes (n=15)	7 (19)	2 (40)	6 (60)		
No (n=37)	30 (71)	3 (60)	4 (40)		
Vaginal twin delivery				0.612	<0.01
Yes (n=25)	11 (31)	2 (50)	12 (92)		
No (n=27)	24 (69)	2 (50)	1 (8)		
Perceived sufficient confidence					
Vaginal breech delivery				0.659	<0.01
Yes without supervision (n=10)	1 (3)	1 (17)	8 (89)		
Yes with supervision (n=27)	23 (62)	3 (50)	1 (11)		
No (n=15)	13 (35)	2 (33)	0		
Vaginal twin delivery				0.586	<0.01
Yes without supervision (n=15)	5 (14)	1 (33)	9 (69)		
Yes with supervision (n=25)	20 (56)	1 (33)	4 (31)		
No (n=12)	11 (30)	1 (33)	0		

* Data are presented as No. (%) of respondents

respectively, in those who had performed >10 procedures. 12 (23%) respondents reported no sufficient confidence in performing vaginal twin delivery. Reasons provided were lack of training or experience (n=12) and concern about medical legal issues (n=5). They suggested that supervision (n=12) and simulation training (n=7) could improve their confidence. 26 respondents reported to have experienced, witnessed, or learned about adverse events of vaginal twin delivery; the most common was failed vaginal delivery requiring caesarean section (n=23) followed by primary postpartum haemorrhage (n=18). 69.2% of respondents intended to offer vaginal twin delivery in practice; the percentage of those with confidence was not correlated with that of those with intention to offer it in practice (r=0.212, p=0.132).

For vaginal breech delivery, more (but not significantly) junior specialists than trainees perceived to have sufficient experience (50% vs 22.5%, p=0.81) and confidence (91% vs 64%, p=0.143). The number of procedures performed was correlated with perceived sufficient experience (r=0.307, p=0.027) and confidence (r=0.659, p<0.01) [Table 1]. The percentage of respondents who perceived to have sufficient experience increased from 19% in those with <6 procedures to 60% in those with >10 procedures. In those with <6 procedures, only 3% perceived to be confident to perform vaginal breech delivery without supervision. The percentage increased to 89% in those with >10 procedures. 15 (29%) respondents reported no sufficient confidence in performing vaginal breech delivery. Reasons provided were lack of training and experience (n=14) and concern about medical legal issues (n=7). They suggested that supervision (n=14) and simulation training (n=9) could improve their confidence. 19 respondents reported to have experienced, witnessed, or learned about adverse events of vaginal breech delivery; the most common was entrapment of after coming head (n=16) followed by birth asphyxia (n=9). Only 25% of respondents intended to offer vagina breech delivery in practice; the percentage of those with confidence was not correlated with that of those with intention to offer it in practice (r=0.11, p=0.438).

Perceived sufficient experience and confidence in vaginal twin delivery and vaginal breech delivery were all correlated with the number of forceps deliveries performed (Table 2) and the number of rotational operative deliveries performed (Table 3).

Discussion

Vaginal twin delivery and vaginal breech delivery are essential skills in obstetrics but have fallen out of favour

Table 2. Perceived sufficient experience and confidence of trainees and junior specialists in relation to the number of forceps deliveries performed

Perceived sufficient experience and confidence	No. of forceps deliveries performed*							Spearman's coefficient	P Value
	0	1-10	11-20	21-30	31-40	41-50	>50		
Received sufficient experience									
Vaginal breech delivery								0.302	0.029
Yes (n=15)	1 (11)	3 (17)	2 (33)	4 (57)	3 (43)	0	2 (40)		
No (n=37)	8 (89)	15 (83)	4 (67)	3 (43)	4 (57)	0	3 (60)		
Vaginal twin delivery								0.364	<0.01
Yes (n=25)	1 (11)	9 (50)	2 (33)	4 (57)	5 (71)	0	4 (80)		
No (n=27)	8 (89)	9 (50)	4 (67)	3 (43)	2 (29)	0	1 (20)		
Perceived sufficient confidence									
Vaginal breech delivery								0.620	<0.01
Yes without supervision (n=10)	0	0	1 (17)	3 (43)	4 (57)	0	2 (40)		
Yes with supervision (n=27)	1 (11)	14 (78)	4 (66)	3 (43)	2 (29)	0	3 (60)		
No (n=15)	8 (89)	4 (22)	1 (17)	1 (14)	1 (14)	0	0		
Vaginal twin delivery								0.514	<0.01
Yes without supervision (n=15)	0	2 (11)	2 (33)	3 (43)	4 (57)	0	4 (80)		
Yes with supervision (n=25)	3 (33)	14 (78)	3 (50)	3 (43)	2 (29)	0	0		
No (n=12)	6 (67)	2 (11)	1 (17)	1 (14)	1 (14)	0	1 (20)		

* Data are presented as No. (%) of respondents

in recent year. This renders obstetric trainees lacking such clinical experience. There is a paradigm shift from vaginal to caesarean delivery for breech presentation since the Term Breech Trial in 2000[12].

For vaginal twin delivery, cephalic/breech presentation should not be the contraindication. There is about 20% chance for the second twin to change the presentation[13]. Vaginal breech extraction and internal podalic version for the second twin is the key technique to achieve successful and safe vaginal twin delivery[14]. These techniques can be learned indirectly during caesarean section. For vaginal breech delivery, techniques such as the Løvset or Bickenbach manoeuvres (to reduce nuchal arms) and the Mauriceau-Smellie-Veit manoeuvre or Piper forceps (to deliver the after-coming head) can also be learned during caesarean section[15].

Most trainees perceived themselves lacking experience in both procedures, whereas half of junior specialists perceived themselves lacking experienced in vaginal breech delivery. Junior specialists were not more likely than trainees to be confident in both procedures. 69.2% of respondents intended to offer vaginal twin delivery in practice, whereas only 25% of respondents intended to offer vagina breech delivery in practice. This finding is consistent with the 87.3% and 32.7%, respectively, reported in trainees and new specialists in Australia and New Zealnd[10].

The numbers of forceps deliveries and rotational operative deliveries performed were correlated with the perceived sufficient experience and confidence in vaginal twin/breech delivery. Some skills in vaginal twin/breech delivery overlap those in forceps/rotational operative deliveries. Experience in these complex techniques may indirectly boost respondent confidence in practising vaginal twin/breech delivery.

In Hong Kong, all obstetricians receive training in public hospitals. With an increasing rate of caesarean section worldwide[16], techniques of vaginal twin/breech delivery may be less practised. Trainers have less hands-on experience as well[17]. Thus, the Hong Kong College of Obstetricians and Gynaecologists should review up-to-date evidence on vaginal twin/breech delivery and provide guidance for frontline obstetricians on counselling. Education to public should be provided to clear

Table 3. Perceived sufficient experience and confidence of trainees and junior specialists in relation to the number of rotational operative deliveries performed

Perceived sufficient experience and confidence	No. of rotational operative deliveries performed*							Spearman's coefficient	p Value
	0	1-10	11-20	21-30	31-40	41-50	>50		
Received sufficient experience									
Vaginal breech delivery								0.330	0.017
Yes (n=15)	0	4 (25)	1 (20)	3 (50)	2 (50)	3 (100)	2 (25)		
No (n=37)	10 (100)	12 (75)	4 (80)	3 (50)	2 (50)	0	6 (75)		
Vaginal twin delivery								0.351	0.011
Yes (n=25)	4 (40)	4 (25)	1 (20)	5 (83)	2 (50)	3 (100)	6 (75)		
No (n=27)	6 (60)	12 (25)	4 (80)	1 (17)	2 (50)	0	2 (25)		
Perceived sufficient confidence									
Vaginal breech delivery								0.609	<0.01
Yes without supervision (n=10)	0	1 (6)	0	3 (50)	1 (25)	2 (67)	3 (38)		
Yes with supervision (n=27)	3 (30)	8 (50)	5 (100)	3 (50)	2 (50)	1 (33)	5 (62)		
No (n=15)	7 (70)	7 (46)	0	0	1 (25)	0	0		
Vaginal twin delivery								0.619	<0.01
Yes without supervision (n=15)	0	1 (6)	0	5 (83)	1 (25)	2 (67)	6 (75)		
Yes with supervision (n=25)	6 (60)	8 (50)	5 (100)	1 (17)	2 (50)	1 (33)	2 (25)		
No (n=12)	4 (40)	7 (44)	0	0	1 (25)	0	0		

* Data are presented as No. (%) of respondents

misconception towards these procedures. Careful selection of suitable patients for counselling on vaginal twin/breech delivery may enable trainers and trainees to gain experience in teaching and learning. Regular simulation training should be provided to maintain proficiency of skills so as to improve patient outcomes, quality, and safety[18].

The perceived confidence was not correlated with intention to offer vaginal twin/breech delivery. Medico-legal consideration plays a role in the decision-making process of clinical practice[19]. In addition to adequate training and practice, medicolegal support should be provided to obstetricians to encourage them to offer vaginal twin/breech delivery to suitable patients. Private obstetricians have additional concerns about insurance.

There are limitations to the present study. The nature of questionnaire survey has a built-in recall bias. The response rate is low (41.1%), which is similar to the 31.7% to 65% reported in other studies[10,11]. Web-based survey is prone to low response rate[20]. The long questionnaire may further reduce the incentive to complete the questionnaire. To improve the response rate, using shorter questionnaire, offering incentives, and providing mail options can be considered[21]. The rates of vaginal deliveries and caesarean sections of twin and breech pregnancies in the respondents' units are associated with the individual respondents' practice[22]. The level of confidence was not measured objectively.

Conclusion

Most respondents did not perceive themselves having sufficient experience and confidence in vaginal twin/breech delivery. The perceived sufficient experience and confidence in vaginal twin/breech delivery was positively correlated to actual clinical experiences. Training of vaginal twin/breech delivery should be provided before these techniques become obsolete.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

This study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECEREC-2021-046), Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-01-0146/ER-3), Kowloon West Cluster Research Ethics Committee (reference: KW/FR-21-029(156-11)), New Territories West Cluster Research Ethics Committee (reference: NTWC/REC/21041), Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster (reference: UW 21-394), and Joint Chinese University of Hong Kong – New Territories East Clinical Research Ethics Committee (reference: 2021.340).

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Appendix. Questionnaire

Demographics

1. What is your level of training?
   - Basic trainee
   - Higher trainee
   - Junior specialists (year 1-5 post fellowship)
2. If you are a trainee, which level of professional examinations have you already achieved?
   - MRCOG part 1
   - SOE
   - MRCOG part 2
   - MRCOG part 3
3. If you are a specialist, what is your current career pathway?
   - Not related to maternal-fetal medicine (MFM)
   - MFM trainee
   - MFM sub-specialist
4. What is your gender?
   - Male
   - Female
5. What is your age group (years)?
   - 18-24
   - 25-34
   - 35-44
   - ≥45
6. Do you intend to practise obstetrics in your future career as specialist?
   - Yes
   - No
   - Not sure

Vaginal breech delivery

7. How many singleton vaginal breech deliveries have you conducted?

Live birth	IUD
• None	• None
• 1	• 1
• 2	• 2
• 3	• 3
• 4	• 4
• 5	• 5
• 6	• 6
• 7	• 7
• 8	• 8
• 9	• 9
• 10	• 10
• >10	• >10

8. Have your ever personally experienced, witnessed, or learned about any adverse event during vaginal breech delivery?
   - Yes
   - No

   If your answer to question 8 is "No", please go to question 11.
9. What is/are the type of adverse event(s)?
   - Cord prolapse
   - Birth asphyxia
   - Entrapment of after coming head
   - Birth trauma
   - Failed vaginal breech delivery requiring caesarean section
   - Major genital trauma
   - Primary postpartum haemorrhage
   - Others: _____
10. Your personal experience with adverse event(s) during virginal delivery. (Can choose multiple options as appropriate.)
    - I experienced it myself.
    - I witnessed it.
    - I learned about it.
11. Do you feel you have received sufficient experience to perform vaginal breech deliveries?
    - Yes
    - No
12. Do you feel confident in performing vaginal breech deliveries?
    - Yes (Unsupervised)
    - Yes (Supervised with a senior present)
    - No

    If your answer is "Yes" to question 12, please go to question 15
13. What is the reason making you feel not confident enough in performing vaginal breech delivery?
    - Lack of training or experience
    - Lack of support from senior obstetrician
    - Lack of support from other specialties such as anaesthesiologists/paediatricians
    - Worry about medico-legal consequences in case of complications
    - Others: _____
14. What would make you feel more confident in offering vaginal breech delivery?
    - Simulation training
    - Lectures
    - Performing vaginal breech deliveries under supervision
    - Adequate support from other specialties
    - Adequate medico-legal support
    - Others: _____
15. Do you intend to offer vaginal breech delivery in your practice?
    - Yes
    - No
    - Not sure

Appendix. (cont'd)

Vaginal twin delivery

16. How many vaginal twin deliveries have you conducted?

Live birth	IUD in one twin or both twins
• None	• None
• 1	• 1
• 2	• 2
• 3	• 3
• 4	• 4
• 5	• 5
• 6	• 6
• 7	• 7
• 8	• 8
• 9	• 9
• 10	• 10
• >10	• >10

17. Have your ever personally experienced, witnessed, or learned about any adverse event during vaginal twin delivery?
    - Yes
    - No

    If your answer is "No" to question 17, please go to question 20
18. What is/are the type of adverse event(s)?
    - Cord prolapse
    - Birth asphyxia
    - Entrapment of after coming head
    - Birth trauma
    - Failed vaginal twin delivery requiring caesarean section
    - Major genital trauma
    - Primary postpartum haemorrhage
    - Others: _____
19. Your personal experience with adverse event(s) during virginal delivery. (Can choose multiple options as appropriate.)
    - I experienced it myself.
    - I witnessed it.
    - I learned about it.
20. Do you feel you have received sufficient experience to perform vaginal twin delivery?
    - Yes
    - No
21. Do you feel confident in performing vaginal twin delivery?
    - Yes (Unsupervised)
    - Yes (Supervised with a senior present)
    - No

    If your answer is yes to question 21, please go to question 24
22. What is the reason making you feel not confident enough in performing vaginal twin delivery?
    - Lack of training or experience
    - Lack of support from senior obstetrician
    - Lack of support from other specialties such as anaesthesiologists/paediatricians
    - Worry about medico-legal consequences in case of complications
    - Others: _____
23. What would make you feel more confident in offering vaginal twin delivery?
    - Simulation training
    - Lectures
    - Performing vaginal twin deliveries under supervision
    - Adequate support from other specialties
    - Adequate medico-legal support
    - Others: _____
24. Do you intend to offer vaginal twin delivery in your practice?
    - Yes
    - No
    - Not sure

Complex vaginal delivery

25. How many forceps deliveries have you performed?
    - None
    - 1-10
    - 11-20
    - 21-30
    - 31-40
    - 41-50
    - >50
26. How many rotational operative deliveries have your performed?
    - None
    - 1-10
    - 11-20
    - 21-30
    - 31-40
    - 41-50
    - >50
27. Do you feel confident in performing forceps delivery?
    - Yes
    - No
28. Do you feel confident in performing rotational operative delivery?
    - Yes
    - No
29. Any other comments:

    _____

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Predictors for outcome of induction of labour with double balloon catheter as second-line method after dinoprostone

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Objectives: To determine the predictors for outcome of induction of labour (IOL) with double balloon catheter (DBC) as the second-line method after dinoprostone.
Methods: Medical records of patients who underwent IOL with DBC as the second-line method after dinoprostone between October 2016 and December 2019 at Pamela Youde Nethersole Eastern Hospital in Hong Kong were retrospectively reviewed. Inclusion criteria were singleton pregnancy, vertex presentation, gestational age of ≥36 weeks, unfavourable cervix (Bishop score <6) after initial priming by dinoprostone, intact membranes, and no contraindication for vaginal delivery. The primary outcomes were the success and failure rates of IOL, which were defined as the rates of vaginal delivery and caesarean delivery, respectively.
Results: 88 patients were included for analysis. The most common indications for IOL were gestational diabetes (23.86%) and past term pregnancy (19.32%). 79 (91.86%) patients had successful cervical ripening after DBC insertion, with a median improvement in Bishop score of 3. However, only 32 (36.36%) patients achieved vaginal birth, whereas 56 patients had caesarean birth. The most common indication for caesarean birth was failed IOL (40.91%). An occiput-anterior position of the fetal head at delivery was predictive of a vaginal birth/successful IOL (odds ratio=0.211, p=0.036), whereas a heavier birth weight was a risk factor for a caesarean birth/failed IOL (odds ratio=1.002, p=0.027).
Conclusion: The success rate of IOL with DBC as a second-line method was only 36.36%. The Bishop score before DBC insertion was not predictive of a successful IOL. Earlier consideration of caesarean section is suggested in patients with unsatisfactory response to dinoprostone as well as non-occiput-anterior position of the fetal head and heavier fetal weight.

Keywords: Dinoprostone; Labour, induced

Introduction

Induction of labour (IOL) is commonly used to shorten the duration of pregnancy. In developed countries, as high as 20% to 25% of term pregnancies are delivered following IOL[1]. IOL is performed when the risks of waiting for spontaneous onset of labour are deemed greater than those associated with IOL[2]. The Bishop score is used to assess the likelihood of a successful IOL[3]. A Bishop score of <6 is defined as an unfavourable cervix to achieve vaginal delivery. Dinoprostone is commonly used to ripen an unfavourable cervix. When pharmacological agents are contraindicated or ineffective, mechanical devices such as a double balloon catheter (DBC) is an alternative[4,5]. DBC is similarly efficacious and safer[6-8] and more cost-effective than dinoprostone[7,9]. However, the use of DBC remains unconventional in some obstetric units. This study aims to determine the predictors for outcome of IOL with DBC as the second-line method after dinoprostone.

Methods

This study was approved by the Hong Kong East Cluster Research Ethics Committee (Reference: HKECREC-2021-090). Medical records of patients who underwent IOL with DBC (Cook Cervical Ripening Balloon; Cook Medical, Bloomington [IN], US) as the second-line method after dinoprostone between October 2016 and December 2019 at Pamela Youde Nethersole Eastern Hospital in Hong Kong were retrospectively reviewed through the Clinical Management System. The hospital conducted 2300 to 2700 deliveries per year from 2016 to 2019.

Inclusion criteria were singleton pregnancy, vertex presentation, gestational age of ≥36 weeks, unfavourable cervix (Bishop score <6) after initial priming by dinoprostone, intact membranes, and no contraindication for vaginal delivery. Exclusion criteria were any contraindication for vaginal delivery and maternal request to terminate IOL.

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Patients indicated for IOL were admitted for in-patient care. IOL was offered at 41 weeks of gestation for post-term or at 40 weeks for gestational diabetes so as to achieve birth no later than 40 weeks plus 6 days as per recommendations of the National Institute of Health and Care Excellence[5,10]. The cervical status was assessed using the Bishop score, and a 30-minute cardiotocography was performed to rule out fetal distress. If the Bishop score was <6, the first-line method was to administer non-sustained released dinoprostone vaginal tablets once per day and up to two separate doses 24 hours apart. If dinoprostone tablets were deemed unsuitable (eg scarred uterus) or ineffective (the cervix remains unfavourable), the patient was counselled for DBC insertion. The DBC was inserted 36 hours after the last dose of dinoprostone to allow adequate weaning of its medical effect. The vaginal and uterine balloons were each inflated with a minimum of 40 mL of normal saline. Each balloon can hold a maximum of 80 mL of saline. Another 30-minute cardiotocography was performed to ensure fetal well-being. In patients with positive Group B Streptococcus screening, antibiotic prophylaxis was initiated immediately after insertion of the DBC. If a spontaneous pre-labour rupture of membrane occurred during cervical ripening, the DBC was removed and augmentation by syntocinon infusion was used to complete the IOL. The DBC was also removed in the event of an emergency such as severe vaginal bleeding, suspected fetal distress, or suspected scar rupture. Otherwise, the DBC was removed up to 12 hours after insertion. The cervical status was assessed again using the Bishop score. If the cervix was ripened (Bishop score ≥6), artificial rupture of membrane with syntocinon augmentation was performed. If the Bishop score remained <6, either Caesarean section or continuation with IOL was offered.

The primary outcomes were the success and failure rates of IOL, which were defined as the rates of vaginal delivery and caesarean delivery, respectively. The secondary outcomes were maternal and fetal complications, including pain intolerance, uterine hyperstimulation, uterine rupture, intrauterine infection, placental abruption, umbilical cord prolapse, low Apgar score, and admission to the neonatal intensive care unit.

Statistical analysis was performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant. Comparisons between successful IOL (vaginal delivery) and failed IOL (caesarean delivery) were made using the Chi-squared test for categorical variables and binary logistic regression for continuous variables. Significant variables in univariate analysis were included in logistic regression analysis to determine the predictors for outcome of IOL with DBC as the second-line method.

Results

Of 129 women who underwent IOL with DBC as the second-line method after dinoprostone, 41 were excluded according to the exclusion criteria and the remaining 88 were included for analysis (Table 1). The most common indications for IOL were gestational diabetes (23.86%) and past term pregnancy (19.32%). 79 (91.86%) patients had successful cervical ripening after DBC insertion, with a median improvement in Bishop score of 3. However, only 32 (36.36%) patients achieved vaginal birth, whereas 56 patients had caesarean birth. The most common indication for caesarean birth was failed IOL (40.91%).

There were eight maternal complications associated with the DBC. Five patients had intolerable vaginal pain, which was resolved by reducing the amount of fluid in the balloons. One patient had umbilical cord prolapse upon artificial rupture of membranes and underwent category 1 caesarean section. The patient was nulliparous and was induced at 41 weeks for post-term. She was transferred to the labour room for artificial rupture of membrane 20 minutes after removal of the DBC. The fetal head was stationed at -3, but there was no definite disengagement or palpable cord before artificial rupture of membrane. The fetal outcome was satisfactory. One patient had severe antepartum haemorrhage necessitating immediate removal of the DBC and emergency caesarean section. Nonetheless, maternal and fetal outcomes were good.

In logistic regression analysis, an occiput-anterior position of the fetal head at delivery was predictive of a vaginal birth/successful IOL (odds ratio=0.211, p=0.036), whereas a heavier birth weight was a risk factor for a caesarean birth/failed IOL (odds ratio=1.002, p=0.027) [Table 2]. The Bishop score before DBC insertion was not predictive of a successful IOL.

Discussion

The successful cervical ripening rate was 91.86% and the median improvement in Bishop score was 3, but the vaginal birth/successful IOL rate was only 36.36%. These findings are comparable with the 88% successful cervical ripening rate, the mean of 3.8 improvement in Bishop score[11], and the 55% to 68.6% vaginal delivery rate in 24 hours[6,7,11] reported in other studies. The lower vaginal delivery rate in our patients could be attributed

Table 1. Baseline characteristics, indications and outcomes of induction of labour (IOL) with double balloon catheter (DBC), and maternal and fetal complications of 88 patients

Parameter	Value*
Maternal age, y	32 (30-35)
Maternal body mass index, kg/m^2	23.89 (21.58-26.67)
Nulliparous	80 (90.91)
Multiparous	8 (9.09)
Indications of IOL	
Gestational diabetes	21 (23.86)
Past term	17 (19.32)
Hypertensive disorders (pregnancy-induced hypertension, pre-eclampsia)	13 (14.77)
Reduced fetal movement	9 (10.23)
Small for date fetus	8 (9.09)
Large for date fetus	5 (5.68)
Oligohydramnios	5 (5.68)
Prolonged latent phase	4 (4.55)
Maternal choice	2 (2.27)
Non-reassuring cardiotocography	2 (2.27)
Bad obstetric history	1 (1.14)
Polyhydramnios	1 (1.14)
Bishop score before insertion of DBC	
≤3	23 (26.14)
4-5	65 (73.86)
Bishop score after insertion of DBC (n=86)	
<6	7 (7.95)
6-7	71 (80.68)
>7	8 (9.09)
Improvement in Bishop score after DBC	3 (2-3)
Duration of DBC in place, min	660 (614.50-686.25)
Caesarean birth	56 (63.64)
Failed induction	36 (40.91)
Cephalo-pelvic disproportion	7 (7.95)
Abnormal cardiotocography	6 (6.82)
Obstructed labour due to persistent occiput-posterior position	4 (4.55)
Umbilical cord prolapse	1 (1.14)
Severe antepartum haemorrhage	1 (1.14)
Suspected intrauterine infection	1 (1.14)
Vaginal birth	32 (36.36)
Spontaneous vaginal birth	28 (31.82)
Forceps delivery	3 (3.41)
Vacuum extraction	1 (1.14)
Fetal head position at delivery	
Occiput-anterior	65 (73.86)
Non-occiput-anterior	23 (26.13)
Birth weight, g	3262.5 (2906.25-3502.5)
Material complication	
Intolerance secondary to vaginal pain	5 (5.68)
Umbilical cord prolapse	1 (1.14)
Severe antepartum haemorrhage	1 (1.14)
Intrauterine infection	1 (1.14)
Hyperstimulation	0
Neonatal complication	
1-min Apgar score <7	2 (2.27)
5-min Apgar score <7	0
Neonatal intensive care unit admission	1 (1.14)

* Data are presented as median (interquartile range) or No. (%) of participants

to patient selection, as only patients with failed IOL after dinoprostone were included.

An occiput-anterior position of the fetal head was predictive of a vaginal birth/successful IOL. An occiput-posterior position is well-recognised risk factor for caesarean delivery[12-15]. However, the fetal head position can only be ascertained at the time of delivery and thus it may be of limited predictive value. As the fetal head position changes dynamically as labour progresses, it is worthwhile to evaluate whether the head position at the initiation of IOL or before delivery predicts labour outcome.

A heavier birth weight was a risk factor for caesarean birth/failed IOL. Some studies reported comparable findings[16,17], but others reported no significant association[18-20]. Similar to fetal head position, birth weight can only be accurately measured after delivery and thus it may be of limited predictive value. Ultrasound scan to estimate fetal weight near labour is prone to measurement errors and can only achieve accurate estimates (±10% of the actual birth weight) in approximately 70% of patients[21-23].

Multi-parity has been reported as a predictor for successful IOL[16-18,24]. However, it was not predictive of IOL outcome in the present study. This may be explained by the

Table 2. Logistic regression analysis for predictors of outcome of induction of labour with double balloon catheter

Variable	Odds ratio (95% confidence interval)	p Value
Maternal age	1.114 (0.973-1.274)	0.117
Maternal body mass index	1.093 (0.956-1.250)	0.194
Multiparity	0.218 (0.036-1.336)	0.100
Gestational age at induction of labour	0.9099 (0.528-1.566)	0.732
Duration of double balloon catheter in place	1.001 (0.996-1.006)	0.789
Bishop score before insertion		
≤3	3.201 (0.683-14.996)	0.140
4-5	-	
Bishop score after insertion		
<7	2.624 (0.199-34.657)	0.464
≥7	-	
Improvement in Bishop score		
<3	1.092 (0.290-4.114)	0.896
≥3	-	-
Occiput-anterior position of the fetal head	0.211 (0.049-0.905)	0.036
Birth weight	1.002 (1.000-1.004)	0.027

limited number of multiparous patients (n=8); only half of them were able to achieve vaginal delivery, compared with 35% in the nulliparous patients.

Bishop score is a well-recognised predictor for IOL outcome[18-20,25-27]. However, it was not predictive of IOL outcome in the present study. The extent of improvement in the Bishop score was also not correlated to the IOL outcome, which is consistent with other studies[24,28]. Thus, the Bishop score should not be used solely to predict IOL outcome. Other parameters including maternal age, body mass index, gestational age at IOL, and duration of DBC in place were also not predictive of IOL outcome.

Maternal and neonatal complications of DBC insertion were uncommon. Although the rate of umbilical cord prolapse (1.14%) was higher than that in the general population (0.16%-0.18%)[29-31], the association lacks robust evidence[32,33]. Nevertheless, obstetricians should be aware of clinical signs such as an unengaged or highly stationed fetal head after removal of the DBC and should consider performing a controlled amniotomy or converting to caesarean delivery as indicated.

Because of the low success rate (36.36%) of IOL with DBC, it is reasonable to consider resolving to caesarean section earlier if the response to dinoprostone has not been satisfactory in patients with other unfavourable factors such as a heavier fetal weight or a need for prompt delivery (in case of severe pre-eclampsia).

There are limitations to the present study. The sample size was too small to produce analyses for indications of IOL and safety of the DBC. The sample was recruited in one centre; outcomes may be influenced by local obstetric practice and patient characteristics in this locality. Only patients who had IOL with DBC as the second-line method were included. A prospective study with a larger sample size from multiple centres that includes patients who use DBC as the first-line method may generate more useful findings.

Conclusion

The success rate of IOL with DBC as a second-line method was only 36.36%. The Bishop score before DBC insertion was not predictive of a successful IOL. Earlier consideration of caesarean section is suggested in patients with unsatisfactory response to dinoprostone as well as non-occiput-anterior position of the fetal head and heavier fetal weight.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically

revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Hong Kong East Cluster Research Ethics Committee (Reference: HKECREC-2021-090). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Pregnancies with positive non-invasive prenatal testing result for sex chromosome abnormalities in a tertiary hospital in Hong Kong

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Objective: To review medical records of pregnant women with positive non-invasive prenatal testing (NIPT) results for sex chromosome abnormalities who attended Tuen Mun hospital between 2015 and 2021. Patient decision after prenatal diagnosis, confirmatory diagnostic testing results, and pregnancy/neonatal outcomes were summarised.
Methods: Medical records of women with abnormal NIPT results for sex chromosome abnormalities who attended Tuen Mun Hospital between January 2015 and December 2021 were retrospectively reviewed.
Results: 56 Chinese women attended our prenatal diagnostic clinic with abnormal NIPT results for sex chromosome abnormalities involving 45,X (n=17), 47,XXY (n=10), 47,XXX (n=6), 47,XYY (n=8), disproportionate level of sex chromosomes (n=9), copy number variants of sex chromosomes (n=3), and suspected maternal sex chromosome imbalance (n=3). 53 had singleton pregnancies and three had dichorionic-diamniotic twin pregnancies. 58.9% had conventional combined Down syndrome screening; 15.2% of them were at high risk for trisomy 21. 33 (58.9%) of the patients opted for invasive diagnostic test: amniocentesis (n=29), chorionic villus sampling (n=3), and chorionic villus sampling followed by amniocentesis (n=1). Confirmatory cytogenetic test results (including postnatal results) were available in 35 cases. The overall positive predictive value of NIPT to detect fetal sex chromosome aneuploidies was 71.4%; the value was 42.9% for detecting 45,X, 100% for detecting 47,XXY, 80% for detecting 47,XXX, and 83.3% for detecting 47,XYY. False positive results were observed in three cases of confined placental mosaicism and three cases of vanishing twin pregnancies. Two women with 47,XXX and one woman with mosaic 45,X/46,XX were also incidentally discovered.
Conclusion: Positive NIPT results for sex chromosome abnormalities can be caused by true fetal sex chromosome abnormalities, confined placental mosaicism/placental mosaicism, vanishing twins, and maternal X chromosome abnormalities. Multidisciplinary management can help prenatal counselling and genetic diagnosis. Follow-up confirmatory cytogenetic analysis prenatally and/or postnatally is useful to characterise the numeric or structural fetal sex chromosome abnormalities and their mosaic patterns, and can maximise the benefits of prenatal genetic screening in obtaining more genetic information to support pregnancy management and clinical care of affected unborn child.

Keywords: Genetic testing; Noninvasive prenatal testing; Prenatal diagnosis; Sex chromosome aberrations

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Introduction

With the discovery of the presence of circulating cell-free fetal DNA in maternal plasma[1] and the development of high throughput next-generation sequencing, non-invasive prenatal testing (NIPT) for common fetal aneuploidies was introduced in 2011[2]. Compared with traditional prenatal screening, NIPT is superior in detecting fetal trisomies 21, 18, and 13 and reduces the need for invasive diagnostic procedures[3-8]. Since then, NIPT has been implemented as first-tier or second-tier prenatal screening worldwide, using techniques of massively parallel sequencing (shotgun or target) and single nucleotide polymorphism[9]. Since December 2019 in Hong Kong public hospitals, NIPT has been used as second-tier screening for high-risk women with positive traditional prenatal screening result.

Cell-free fetal DNA testing can identify fetal sex and fetal sex chromosome aneuploidies (SCAs)[10], which is one group of sex chromosome abnormalities. The most common SCAs are 45,X, 47,XXY, 47,XXX, 47,XYY, and their various forms of sex chromosome mosaicisms[11]. Collectively, SCAs are the most common chromosomal condition, with estimated prevalence of 1/400 births[11]. Individuals with SCAs display wide spectrum of phenotypes from asymptomatic to serious physical, reproductive, and behavioural presentations[12]. The unpredictability and variable clinical manifestations of SCAs make genetic counselling and parental decision-making towards SCA-affected pregnancy very difficult.

Expanded use of NIPT for SCAs remains a controversy. Nonetheless, NIPT for SCAs has been readily available in the private sector. In a survey in Hong Kong, 98.50% of women preferred to be informed when NIPT results were suspicious of SCAs, and 33% of whom would consider prenatal diagnosis[13]. Post-test counselling by genetic specialists for those with prenatal diagnosis of SCAs may facilitate continuation of pregnancy[14]. There is a need for clinicians to interpret results and provide counselling to those facing unexpected positive results for sex chromosome abnormalities.

We reviewed medical records of pregnant women with positive NIPT results for sex chromosome abnormalities who attended Tuen Mun hospital between 2015 and 2021. Patient decision after prenatal diagnosis, confirmatory diagnostic testing results, and pregnancy/neonatal outcomes were summarised.

Methods

This study was approved by the Central Institutional Review Board of Hospital Authority (reference: CIRB-2021-011-3). Medical records of women with abnormal NIPT results for sex chromosome abnormalities who attended Tuen Mun Hospital between January 2015 and December 2021 were retrospectively reviewed.

In July 2010, publicly funded first- or second-trimester screening tests for Down syndrome were provided in Hong Kong. In December 2019, publicly funded second-tier NIPT or a conventional diagnostic test was offered for those screened positive for Down syndrome (with a term risk of ≥1:250). The publicly funded NIPT is restricted to reporting trisomies 21, 18, and 13 only. Our unit also receives referrals of cases of abnormal NIPT results from private obstetric care providers and provides genetic counselling by maternal-fetal medicine specialists (Figure).

Patients were explained that NIPT was only a screening test, with varying performance for SCA detection and other limitations. The variable and unpredictable phenotypic expressions of SCA and available intervention strategies were discussed. Baseline ultrasound examination was offered to evaluate the number of fetuses, presence of a vanishing twin, fetal sex, and obvious fetal structural anomalies such as cystic hygroma. An invasive diagnostic test by chorionic villus sampling and/or amniocentesis were also offered; the procedure-related risk of miscarriage is about 0.5%. Compared with chorionic villus sampling, amniocentesis provides more definitive fetal genetic information because of possible confined placental mosaicisms. Before June 2019, rapid screening of common aneuploidies of chromosomes 21, 18, 13, X, and Y was by quantitative fluorescence– polymerase chain reaction (QF-PCR) and then conventional karyotyping. After June 2019, chromosomal microarray is performed if QF-PCR shows normal results. Both chromosomal microarray and conventional karyotyping are performed in those with abnormal QF-PCR for sex chromosomes. For abnormal genetic findings, karyotyping of parental blood samples is offered to establish inheritance. For discordant NIPT results for SCA, maternal karyotyping is performed for biological explanations of the false positive results. All samples are sent to the prenatal diagnostic laboratory of Tsan Yuk Hospital for genetic analysis. Some patients are referred to the clinical genetic service of the Department of Health for further genetic counselling before or after invasive procedures, depending on the NIPT/diagnostic test results and specialists' discretion or patients' preference.

Patients with abnormal diagnostic test results are counselled by maternal-fetal medicine specialists and/or

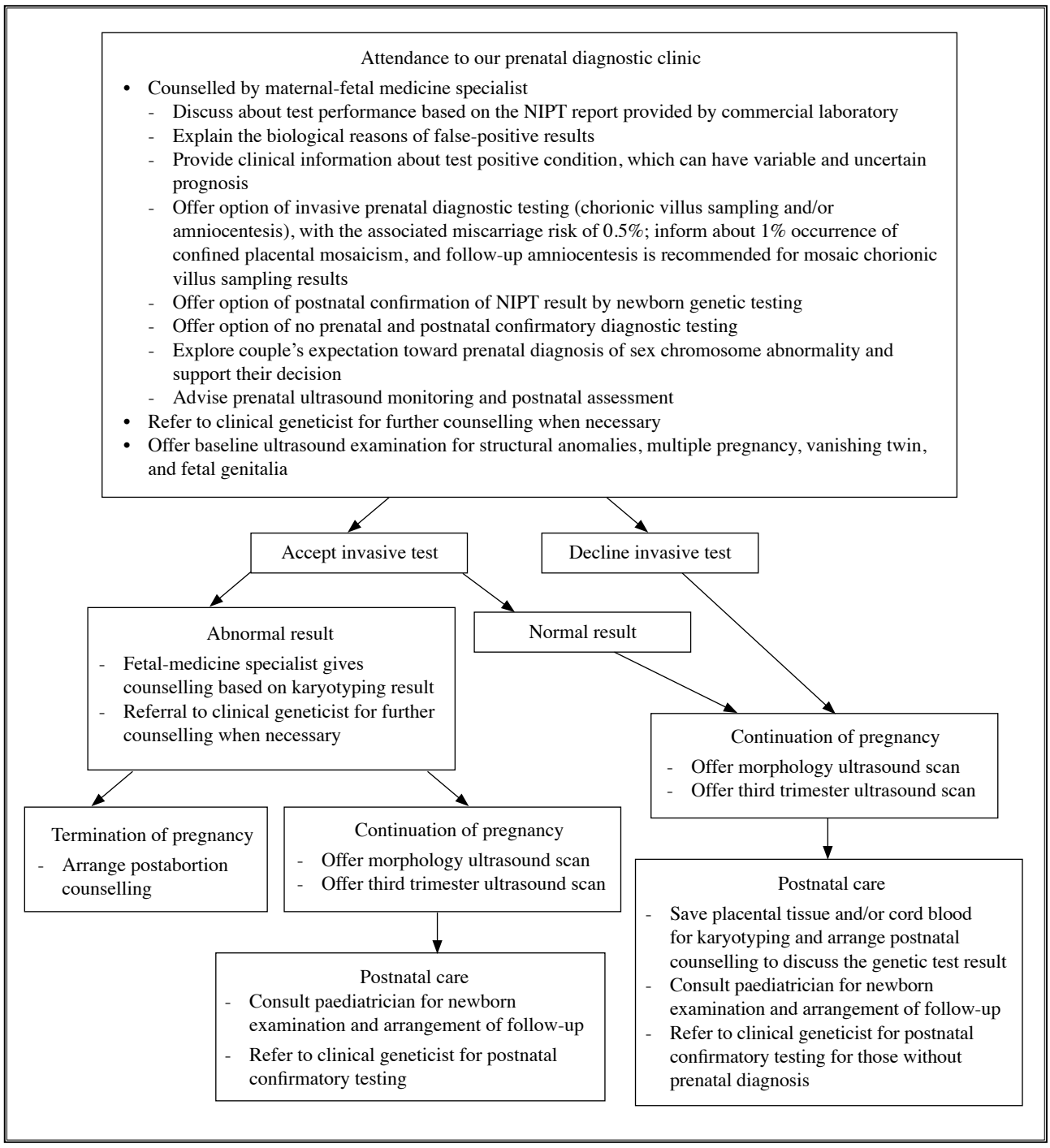

Figure. Workflow for patients with abnormal non-invasive prenatal testing (NIPT) result for sex chromosome abnormalities

clinical geneticist regarding the prognosis and pregnancy management. The option of termination or continuation of pregnancy is provided. The legal limit of termination of pregnancy is 24 weeks in Hong Kong. Those who opt for continuation of pregnancy are offered detailed fetal anomaly ultrasound scan and third trimester ultrasound scan. Anomaly ultrasound scan is used to detect any SCA-associated fetal structural abnormalities (such as cardiovascular and renal anomalies in fetuses with 45,X) and other coincidental anomalies. Third trimester ultrasound scan is used to detect any fetal growth restriction related to SCAs and their mosaicism as well as any late presentation of SCA-associated findings. For example, fetuses with 45,X can develop non-immune hydrops fetalis, and ventricular or vascular disproportion (indicating coarctation of aorta) may become more clinically evident in the third trimester. In addition, renal hypoplasia in fetuses with 47,XXX may only be diagnosed in advanced gestation.

Those with normal diagnostic test results are offered further testing after delivery. Karyotyping for the placenta tissue can detect possible placental mosaicism leading to inconsistent findings. For those who declined diagnostic test, both anomaly and growth ultrasound scans are suggested, and their placental tissue or cord/neonatal blood are saved for karyotyping after delivery. All newborns with abnormal NIPT results for sex chromosome abnormalities are examined by our paediatric team in postnatal ward.

Data retrieved included patient demographics, NIPT results, genetic counselling personnel, diagnostic test results, ultrasound findings, karyotyping results, and pregnancy and neonatal outcomes. Small for gestational age is defined as a birthweight below the 10th percentile for the gestational age.

Statistical tests were performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US). The positive predictive value of NIPT in detecting SCAs was calculated as the number of true positive test results confirmed by amniocentesis or neonatal karyotyping divided by the total number of positive NIPT results.

Results

Between January 2015 and December 2021, 56 Chinese women attended our prenatal diagnostic clinic with abnormal NIPT results for sex chromosome abnormalities involving 45,X (n=17), 47,XXY (n=10), 47,XXX (n=6), 47,XYY (n=8), disproportionate level of sex chromosomes (n=9), copy number variants of sex chromosomes (n=3), and suspected maternal sex chromosome imbalance (n=3) [Table 1]. The median maternal age was 33.5 years; 39.3% were at an advanced maternal age (≥35 years). 53 had singleton pregnancies and three had dichorionic-diamniotic twin pregnancies. The median gestational age at NIPT was 12.5 weeks. 58.9% had conventional combined Down syndrome screening; 15.2% of them were at high risk for trisomy 21.

The median gestational age at first prenatal diagnostic clinic attendance was 15.6 (range, 12.3-29) weeks. 33 (58.9%) of the patients opted for invasive diagnostic test: amniocentesis (n=29), chorionic villus sampling (n=3), and chorionic villus sampling followed by amniocentesis (n=1) [Table 2]. 36 (64.3%) of the patients received prenatal counselling by clinical geneticists. Confirmatory cytogenetic test results (including postnatal results) were available in 35 cases. The overall positive predictive value of NIPT to detect fetal SCAs was 71.4%; the value was 42.9% for detecting 45,X, 100% for detecting 47,XXY, 80% for detecting 47,XXX, and 83.3% for detecting 47,XYY (Table 3).

Table 1. Clinical characteristics of 56 patients with abnormal non-invasive prenatal testing (NIPT) results for sex chromosome abnormalities

Characteristics	Value*
Chinese ethnicity	56 (100)
No. of fetuses	
Singleton	53 (94.6)
Twin	3 (5.4)
Conception	
Natural	50 (89.3)
Assisted	6 (10.7)
Maternal age, y	33.5 (23-48)
<35	34 (60.7)
≥35	22 (39.3)
Nulliparity	35 (62.5)
Conventional Down syndrome screening test results	
Done	33 (58.9)
High risk (≥ 1 in 250)	5 (15.2)
Low risk (< 1 in 250)	28 (84.8)
Not done	23 (41.1)
Gestational age at NIPT, weeks	12.5 (10-22)
10+0 to 13+6	39 (69.6)
14+0 to 15+6	10 (17.9)
16+0 to 20+6	4 (7.1)
≥21	3 (5.4)
NIPT platform	
Massively parallel sequencing	55 (98.2)
Single nucleotide polymorphism	1 (1.8)
Gestational age at prenatal diagnostic clinic attendance, weeks	15.6 (12.3-29)
10+0 to 13+6	11 (19.6)
14+0 to 15+6	18 (32.1)
16+0 to 20+6	19 (33.9)
21+0 to 23+6	5 (8.9)
≥24	3 (5.4)

* Data are presented as median (range) or No. (%) of patients

17 patients had positive NIPT results for 45,X (Table 4). Four of them had abnormal ultrasound findings. Patients 1 and 2 had findings of hydrops fetalis; chorionic villus sampling confirmed the abnormal karyotype, and they opted for termination of pregnancy. Patient 3 had

Table 2. Options of invasive diagnostic testing among 56 patients with positive non-invasive prenatal testing (NIPT) results for sex chromosome abnormalities

Abnormal NIPT result	No. (%) of patients who declined invasive diagnostic testing	No. (%) of patients who accepted invasive diagnostic testing	No. of patients who had invasive diagnostic testing		
			Chorionic villus sampling	Amniocentesis	Chorionic villus sampling followed by amniocentesis
45,X (n=17)	6 (35.3)	11 (64.7)	2	8	1
47,XXY (n=10)	5 (50.0)	5 (50.0)	0	5	0
47,XXX (n=6)	4 (66.7)	2 (33.3)	1	1	0
47,XYY (n=8)	4 (50.0)	4 (50.0)	0	4	0
Others (n=15) [disproportionate level of sex chromosomes (n=9), copy number variants of sex chromosomes (n=3) and suspected maternal sex chromosome imbalance (n=3)]	4 (26.7)	11 (73.3)	0	11	0
Total (n=56)	**23 (41.1)**	**33 (58.9)**	**3**	**29**	**1**

Table 3. Performance of non-invasive prenatal testing (NIPT) in detecting fetal sex chromosome aneuploidy

Sex chromosome aneuploidy	No. of patients with					No. of true positive / No. of confirmed karyotype, %
	NIPT positive	Karyotype confirmed	True positive	False positive	Karyotype not confirmed	
45,X	17	14	6	8	3	6/14, 42.9%
47,XXY	10	10	10	0	0	10/10, 100%
47,XXX	6	5	4	1	1	4/5, 80%
47,XYY	8	6	5	1	2	5/6, 83.3%
Total	**41**	**35**	**25**	**10**	**6**	**25/35, 71.4%**

finding of anencephaly who declined diagnostic test and opted for termination of pregnancy; the karyotype of placental tissue was normal. Patient 4 had findings of ventricular septal defect and echogenic bowel who declined diagnostic test and opted for continuation of pregnancy; neonatal karyotype was normal. 13 patients had normal ultrasound findings. Nine of them opted for diagnostic test through amniocentesis, which confirmed abnormal karyotype in three patients: mosaic 45,X/47,XXX in patients 5 and 6 and de novo isodicentric X chromosome in patient 7. Amniocentesis also identified two cases of confined placental mosaicism. Patient 8 had chorionic villus sampling, which yielded a mosaic karyotype of 45,X[14]/46,XX[16], but follow-up amniocentesis showed normal karyotype. Patient 12 showed normal karyotype after amniocentesis, but the karyotype of the placental tissue showed mos 45,X[3]/46,XY[27], whereas the neonatal karyotype was normal. Four patients with normal ultrasound findings declined diagnostic testing and opted for continuation of pregnancy. Patients 14 to 16 were true positive for mosaic 45,X[17]/47,XXX[33], mosaic 45,X[30]/46,XX[20], or 46,X,i(X)(q10).

10 patients had positive NIPT results for 47,XXY (Table 5). Five of them had amniocentesis, which confirmed the abnormal karyotype (patients 18 to 22). Another five declined diagnostic testing and opted for continuation of pregnancy; neonatal karyotype confirmed the positive NIPT result for 47,XXY in all (patients 23 to 27).

Six patients had positive NIPT results for 47,XXX (Table 6). Patient 28 had chorionic villus sampling, which confirmed the abnormal karyotype, and opted for termination of pregnancy. Patient 29 had amniocentesis,

Table 4. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for 45,X

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/neonatal outcome	Neonatal karyotype
1	45,X	10	Hydrops	Chorionic villus sampling: 45,X	-	-	Termination of pregnancy	-
2	45,X	10	Hydrops	Chorionic villus sampling: 45,X	-	-	Termination of pregnancy	-
3	45,X	14	Anencephaly	-	-	46,XX	Termination of pregnancy, anencephaly	-
4	45,X	20	Ventricular septal defect, echogenic bowel	-	-	-	Livebirth, ventricular septal defect, atrial septal defect	46,XX
5	45,X	11	Normal	Amniocentesis: mos 47,XXX[17]/45,X[13]	-	-	Livebirth	45,X[33]/ 47,XXX[17]
6	45,X	21	Normal	Amniocentesis: mos 45,X[6]/47,XXX[55]	-	-	Termination of pregnancy	-
7	45,X	11	Normal	Amniocentesis: 46,X,idic (X)(p22.3)dn.arr[GRCh37] Xp22.33(168551_1832879) x1,Xp22.33q28(1832912_ 155233098)x3	Maternal: 46,XX Paternal: 46,XY	-	Livebirth, small for gestational age	46,X,idic(X) (p22.3)
8	45,X	11	Normal	Chorionic villus sampling: mos 45,X[14]/46,XX[16] Amniocentesis: 46,XX	-	-	Livebirth	46,XX
9	45,X	14	Normal	Amniocentesis: 46,XX	-	-	Unknown decision/ outcome	-
10	45,X	22	Normal	Amniocentesis: 46,XN	-	46,XX	Livebirth	-
11	45,X	11	Normal	Amniocentesis: 46,XX	-	-	Follow-up until 34 weeks, unknown outcome	-
12	45,X	13	Normal	Amniocentesis: 46,XX	Maternal: 46,XX	mos 45,X[3]/46,X X[27]	Livebirth, small for gestational age, atrial septal defect	46,XX
13	45,X	10	Normal	Amniocentesis: 46,XX	Maternal: 46,XX	46,XX	Livebirth	-
14	45,X	15	Normal	-	-	45,X[26]/47,XXX [24]	Livebirth, patent ductus arteriosus, small for gestational age	45,X[17]/47,X XX[33]
15	45,X	10	Normal	-	-	45,X[21]/46,XX[9]	Livebirth	45,X[30]/46,X X[20]
16	45,X	20	Normal	-	-	mos 45,X[25]/46, X,i(X)(q10)[5]	Livebirth, developmental dysplasia of the hip	46,X,i(X)(q10)
17	45,X	14	Normal	-	Maternal: 46,XX	-	Livebirth	46,XX

which confirmed the abnormal karyotype, and opted for continuation of pregnancy and had a livebirth. Four patients declined diagnostic testing and opted for continuation of pregnancy; neonatal karyotype confirmed 47,XXX in three of them (patients 30-32).

Eight patients had positive NIPT results for 47,XYY (Table 7). Four of them had amniocentesis, which confirmed 47,XYY, and opted for continuation of pregnancy. Neonatal karyotype confirmed 47,XYY in patient 34. Another four patients declined diagnostic

Table 5. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for 47,XXY

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/neonatal outcome	Neonatal karyotype
18	47,XXY	12	Normal	Amniocentesis: 47,XXY	-	-	Unknown decision/outcome	-
19	47,XXY	11	Intrauterine growth restriction	Amniocentesis: 47,XXY	-	-	Livebirth, small for gestational age	-
20	47,XXY	11	Normal	Amniocentesis: 47,XXY	-	-	Livebirth	-
21	47,XXY	11	Normal	Amniocentesis: 47,XXY	-	-	Termination of pregnancy	-
22	47,XXY	13	Normal	Amniocentesis: 47,XXY	-	-	Termination of pregnancy	-
23	47,XXY	14	Curved penis	-	-	-	Livebirth, buried penis	47,XXY
24	47,XXY	20	Normal	-	-	-	Livebirth	47,XXY
25	47,XXY	12	Normal	-	-	47,XXY	Livebirth, small for gestational age	47,XXY
26	47,XXY	11	Normal	-	-	47,XXY	Livebirth, small for gestational age	47,XXY
27	47,XXY	11	Normal	-	-	-	Livebirth	47,XXY

Table 6. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for 47,XXX

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/neonatal outcome	Neonatal karyotype
28	47,XXX	13	Normal	Chorionic villus sampling: 47,XXX	-	-	Termination of pregnancy	-
29	47,XXX	14	Normal	Amniocentesis: 47,XXX	-	-	Livebirth	-
30	47,XXX	10	Normal	-	-	-	Livebirth, atrial septal defect	47,XXX
31	47,XXX	13	Normal	-	-	47,XXX	Livebirth, small for gestational age	47,XXX
32	47,XXX	10	Normal	-	-	47,XXX	Livebirth	47,XXX
33	47,XXX	13	Normal	-	-	-	Livebirth	46,XX

testing and opted for continuation of pregnancy. Neonatal karyotype confirmed 47,XYY in patient 38. Patient 40 had abnormal ultrasound finding of increased nuchal translucency. Subsequent ultrasound at 33 weeks of gestation revealed right-side pleural effusion with no signs of hydrops or anaemia. Maternal serologic tests for cytomegalovirus and toxoplasma gondii were negative. The baby was born vaginally at term with transient oxygen desaturation, which was self-resolved spontaneously. Chest radiography showed mildly blunted right costophrenic angle, which could be related to previous pleural effusion, and was resolved at day 14 after birth. Sepsis evaluation including skin surface swab, gastric lavage, and blood cultures were negative. The karyotype of placental tissue confirmed 47,XYY. Subsequent follow-up with clinical geneticists was arranged.

Eight patients had NIPT results that showed disproportional low level of Y chromosome (Table 8). Second trimester ultrasound scan suggested female genitalia in four cases. Three of them were dichorionic-diamniotic pregnancies with co-twin demise in early gestation. Two had amniocentesis, which showed 46,XX. Patient 45 had placental abruption and spontaneous preterm delivery at 25 weeks of gestation. The baby girl died at day 2 because of extreme prematurity. Karyotype of cord blood sample showed normal 46,XX, but that of the placental tissue showed 69,XXY[20]/46,XX[10]. Four cases showed

Table 7. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for 47,XYY

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/neonatal outcome	Neonatal karyotype
34	47,XYY	12	Normal	Amniocentesis: 47,XYY	-	47,XYY	Livebirth	47,XYY
35	47,XYY	11	Normal	Amniocentesis: 47,XYY	-	-	Livebirth	-
36	47,XYY	13	Normal	Amniocentesis: 47,XYY	-	-	Livebirth	-
37	47,XYY	14	Normal	Amniocentesis: 47,XYY	-	-	Follow-up until 36 weeks, unknown outcome	-
38	47,XYY	11	Normal	-	-	-	Livebirth	47,XYY
39	47,XYY	13	Normal	-	-	47,XYY	Livebirth	-
40	47,XYY	11	↑ Nuchal translucency, pleural effusion	-	-	47,XYY	Livebirth, pleural effusion	-
41	47,XYY	11	Normal	-	-	46,XY	Livebirth	46,XY

Table 8. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for disproportionate level of sex chromosomes

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/neonatal outcome	Neonatal karyotype
42	Low level Y	14	Dichorionic diamniotic twins: one missed abortion and another normal, female genitalia	Amniocentesis: 46,XX	-	-	Follow-up until 32 weeks, unknown outcome	-
43	Low level Y	12	Dichorionic diamniotic twins: one missed abortion and another normal, female genitalia	Amniocentesis: 46,XX	-	-	Livebirth, small for gestational age	-
44	Low level Y	12	Dichorionic diamniotic twins: one missed abortion and another normal, female genitalia	-	-	46,XX	Livebirth	-
45	Low level Y	21	Normal, female genitalia	-	-	mos 69,XXY [20]/46,XX[10]	Neonatal death at day 2, placental abruption	46,XX
46	Low level Y	16	Normal, male genitalia	Amniocentesis: 46,XY	-	46,XY	Livebirth	-
47	Low level Y	13	Normal, male genitalia	Amniocentesis: 47,XYY	-	-	Unknown decision/ outcome	-
48	Low level Y	12	Normal, male genitalia	Amniocentesis: 46,X,der(X)t(X;Y)(p22.3;p11.2).ish der(X)(SRY+,DXZ1+)	Maternal: 46,XX Paternal: 46,XY	-	Termination of pregnancy	-
49	Low level Y	11	Normal, male genitalia	-	-	46,XY	Livebirth	46,XY
50	Mild ↓ chromosome X DNA	14	Normal, female genitalia	-	-	46,XX	Livebirth	-

male genitalia. Three of them had amniocentesis, which revealed 46,XY in patient 46, 47,XYY in patient 47, and de novo 46,X,der(X)t(X;Y)(p22.3;p11.2) in patient 48. Patient 48 opted for termination of pregnancy; the abortus showed normal external male genitalia without other apparent abnormalities. The patient refused pathological examination of the fetus. Patient 50 had abnormal NIPT result of mild reduction of X chromosome DNA. A phenotypically normal female baby was delivered, and cytogenetic analysis of placental tissue showed normal 46,XX karyotype.

Three patients had NIPT results that showed copy number variants of X chromosome (Table 9). Amniocentesis confirmed de novo 46,X,idic(X)(p11.21) in patient 51, maternally inherited 46,X,del(X)(p21) in patient 52, and 45,X,inv(19)(p11q13.1)[15]/46,X,r(X)(p22.1q21),inv(19)[10]/46,X,inv(19),+mar[5] in patient 53. They opted for continuation of pregnancy. Neonatal karyotype confirmed amniocentesis findings.

Three patients had abnormal NIPT results that showed increased or decreased chromosome X DNA of possible maternal contribution (Table 10). Second trimester ultrasound scan showed male genitalia, and amniocentesis showed normal 46,XY karyotype. Cytogenetic analysis of maternal blood revealed abnormal 47,XXX karyotype in patients 54 and 55 and mosaic karyotype 45,X[12]/46,XX[18] in patient 56.

18 (85.7%) of 21 patients with prenatally confirmed sex chromosome abnormalities received genetic counselling by clinical geneticists. The remaining three patients were counselled by the maternal-fetal medicine specialist only. They included two cases with hydropic fetuses and 45,X and one case with fetal 47,XXY. Decision for pregnancy was available for 19 patients (Table 11). Seven of them opted for termination. The rates of termination of pregnancy were 75% for 45,X, 50% for 47,XXY, 50% for 47,XXX, 0% for 47,XYY, and 20% for structural sex chromosome abnormalities. The remaining 12 patients opted for continuation of pregnancy; all had livebirths, except for one who was lost to follow-up. For the 12 patients with normal karyotypes after diagnostic testing, all had livebirths, except for three who were lost to follow-up. 23 patients declined invasive diagnostic testing; patient 3 opted for termination of pregnancy based on abnormal ultrasound finding of anencephaly, and patient 45 had extreme preterm birth with early neonatal death.

Birth data were available for 40 infants. The median gestational age at delivery was 38 (range, 25-41) weeks; 92.5% of infants were born at term. 10 (25%) of the infants were small for gestational age. All except two infants with prenatal or postnatal confirmed sex chromosome abnormalities were delivered in private hospitals, had postnatal evaluation and follow-up by the paediatric team and/or clinical geneticists in our hospital.

Table 9. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for copy number variants of sex chromosomes

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal/ paternal karyotype	Placental tissue for karyotype	Pregnancy/ neonatal outcome	Neonatal karyotype
51	↓DNA 53.5Mb Xp22.33-Xp11.21, ↑DNA 91.6Mb Xq11.2-Xq28	13	Normal, female genitalia	Amniocentesis: 46,X,idic(X)(p11.21).arr[GRCh37]Xp22.33p11.21(168551_56469081)x1,Xp11.21q28(56474956_155233098)x3	Maternal: 46,XX Paternal: 46,XY	-	Livebirth, small for gestational age	46,X,idic(X)(p11.21)
52	↓DNA 33.0Mb Xp22.33-Xp21.1	12	Normal, female genitalia	Amniocentesis: 46,X,del(X)(p21) mat.arr[GRCh37] Xp22.33p21.1(168551_35911065)x1	Maternal: 46,X,del(X)(p21.1)	-	Livebirth	46,X,del(X)(p21.1)
53	del (Xp22.33-p22.12, 16.94M)	13	Ventricular septal defect, intrauterine growth restriction, female genitalia	Amniocentesis: 45,X,inv(19)(p11q13.1)[15]/46,X,r(X)(p22.1q21),inv(19)[10]/46,X,inv(19),+mar[5].arr[GRCh37]Xp22.33p22.12(168551_20126011)x1,Xp22.12p11.1(20333106_58527155)x1~2,Xq13.1q21.31(67863904_87712575)x1~2,Xq21.31q28(87728897_155233098)x1	Maternal: mos 45,X,inv(19)(p11q13.1)[4]/46,XX,inv(19)[56] Paternal: 46,XY	-	Livebirth, small for gestational age	mos 46,X,+r(X)[27]/45,X[23]

Table 10. Ultrasound findings, decision, diagnostic results, and pregnancy/neonatal outcomes of patients with positive non-invasive prenatal testing (NIPT) results for suspected maternal sex chromosome imbalances

Patient	NIPT result	Gestational age at NIPT, weeks	Ultrasound findings	Prenatal diagnostic test result	Maternal karyotype	Placental tissue for karyotype	Pregnancy/ neonatal outcome	Neonatal karyotype
54	↑chromosome X, ? maternal contribution	12	Normal, male genitalia	Amniocentesis: 46,XY	47,XXX	-	Livebirth	-
55	↑chromosome X, ? maternal contribution	15	Normal, male genitalia	Amniocentesis: 46,XY	47,XXX	-	Livebirth	-
56	↓chromosome X, ? maternal contribution	13	Normal, male genitalia	Amniocentesis: 46,XY	mos 45,X[12]/46,XX[18]	-	Livebirth	-

Table 11. Pregnancy decision of patients with confirmed prenatal diagnostic results for sex chromosome abnormalities

Abnormal prenatal diagnostic result (mosaic or full-blown)	No. of patients with unknown decision	No. (%) of patients with continuation of pregnancy	No. (%) of patients with termination of pregnancy
45,X (n=4)	0	1 (25)	3 (75)
47,XXY (n=5)	1	2 (50)	2 (50)
47,XXX (n=2)	0	1 (50)	1 (50)
47,XYY (n=5)	1	4 (100)	0 (0)
Structural sex chromosome abnormalities (n=5)	0	4 (80)	1 (20)
Total (n=21)	**2**	**12 (63.2)**	**7 (36.8)**

Discussion

About half of our patients with positive NIPT result for sex chromosome abnormalities opted for follow-up invasive diagnostic testing. About 40% of patients affected by sex chromosome abnormalities opted for termination of pregnancy. The overall positive predictive value of NIPT in detecting fetal SCAs in clinical practice was 71.4%.

Prenatal genetic testing empowers women's reproductive autonomy[15]. Women can make informed decision for or against testing for SCA. Genetic counselling for women with positive NIPT results for SCA should provide up-to-date information about SCAs including general characteristics, possible treatments, detection rate, false-positive rate, and positive predictive value of NIPT, and options of prenatal or postnatal follow-up diagnostic testing. Their expectations toward prenatal testing should be explored, including termination of pregnancy and preparation for SCA if confirmed. Although the miscarriage risk of prenatal invasive diagnostic procedure is low (0.20% for chorionic villus sampling and 0.30% for amniocentesis)[16], if the definitive diagnosis is unlikely to affect continuation of pregnancy, diagnostic testing may be deferred until after delivery. Knowing the genetic diagnosis can help timely interventions (such as hormone replacement therapy and educational support) and optimise clinical outcomes[17-19]. Patient autonomy should be respected, and their decisions should be supported. In the literature, the uptake of prenatal diagnostic testing ranged from 34% to 100%[20,21]. In our study, it was about 50%. Acceptance of their children affected with SCAs might be their reason of avoiding prenatal diagnosis.

Multidisciplinary approach is suggested in management of women carrying fetuses with confirmed SCA, because different expertise is needed for advice on neonatal outcomes and provision of long-term care for newborns[10]. Participation of genetic professionals in the counselling can affect reproductive decision-making and facilitate continuation of pregnancy[22,23]. They can give a more accurate, updated, realistic, and positive picture of SCAs. In our study, 64.3% of women had genetic counselling with clinical geneticists. 40% of women opted for termination of pregnancy after diagnostic testing. The percentage is similar to other studies[20,24,25].

In a meta-analysis of 35 studies, the detection rate and false positive rate of NIPT were 95.8% and 0.14%, respectively, for monosomy X and 100% and 0.004%, respectively, for SCAs other than monosomy X[3]. In a systematic review of 13 case series[26], the overall average positive predictive value of NIPT was 48% for SCA, based on 76% of follow-up cytogenetic analysis. The positive predictive value of NIPT was 31% for 45,X, 73% for 47,XXY, 61% for 47,XXX, and 78% for 47,XYY. We achieved higher overall positive predictive value of NIPT for SCAs, particularly 100% for 47,XXY, 80% for 47,XXX, and 83.3% for 47,XYY, compared with 42.9% for monosomy X. NIPT analyses the circulating cell-free DNA from degraded placental cytotrophoblasts (not directly from fetus) and from the mother. The false-positive NIPT results for SCAs can be caused by placental/fetal mosaicism, a vanishing twin, maternal DNA contribution, and maternal neoplastic conditions[10]. NIPT is not always reflective of the fetal karyotype.

Mosaicism is the condition that the conceptus is made up of two or more populations of cells with different genetic constitution[27]. It is much more common with sex chromosomes than autosomal chromosomes[10]. In cases of positive NIPT result for monosomy X with abnormal cytogenetic analysis, the relative frequency was 67% for 45,X, 20% for mosaic 45,X/46,XX, 10% for mosaic 45,X/46,XY, and 3% for X chromosome rearrangement, whereas the relative frequency of mosaicism was 3% for 47,XXY, 7% for 47,XXX, and 12% for 47,XYY[26]. In the present study, in 10 patients with positive NIPT result for monosomy X and with abnormal follow-up cytogenetic analysis, the relative frequency was 20% for 45,X, 60% for mosaic 45,X, and 20% for X chromosome rearrangement. All other SCAs were full-blown. Mosaicism can only be confined to the placenta (confined placental mosaicism) and not extended into the fetal tissue. Confined placental mosaicism can affect about 1% to 2% of chorionic villus samples[28]. In a large study, confined placental mosaicism occurred in 122 (23.4%) of 522 SCAs[29]. In our study, three cases of false-positive results were secondary to confined placental mosaicism. Two with positive NIPT result for 45,X were confirmed normal 46,XX after birth but had mosaic 45,X cell line confined to placenta identified through karyotyping of chorionic villus sample in patient 8 and placental tissue in patient 12. Patient 45 was a confined placental mosaic triploidy with NIPT result showing fetal sex different from ultrasound finding, which resulted in poor perinatal outcomes. To prevent misdiagnosis of fetal genetic condition, any mosaic findings in chorionic villus samples must be confirmed by follow-up amniocentesis[30].

Amniocentesis is the optimal invasive diagnostic procedure to avoid the issue of confined placental mosaicism, because amniotic fluid cells are mainly fetal cells although low level mosaicism in fetal tissue cannot be entirely excluded, and site-specific variations in the proportion of abnormal cells can be present in different fetal tissues. The positive predictive value of NIPT is higher for 45,X with ultrasound abnormalities than 45,X with normal ultrasound finding (99% vs 51%)[29]. Therefore, ultrasound investigation may help the decision-making on the choice of confirmatory diagnostic procedure. Women with abnormal ultrasound findings (such as cystic hygroma or hydrops or increased nuchal translucency or fetal anomalies) can consider chorionic villus sampling for early diagnosis (as in patients 1 and 2). Women with normal ultrasound finding may wait and choose amniocentesis to avoid repeated invasive procedures[29].

Vanishing twin is a biological phenomenon that can cause false-positive NIPT results. The deceased twin is likely to be genetically abnormal (ie, aneuploid) while the viable twin has normal chromosomal constitution[31]. Depending on the individual contribution of each twin to the fetal fraction, the continuous release of DNA fragments from the placenta of demised co-twin into the maternal plasma can influence the NIPT results and mask the actual normal chromosomal condition of the remaining viable twin. The duration of persistence of DNA from a lost twin in maternal circulation is uncertain, but it may be detectable for up to 8 weeks after the co-twin demise[31]. Ultrasound examination in early first trimester can facilitate appropriate pre-test counselling if a failed twin pregnancy is identified before its absorption. In general, NIPT is not recommended for screening in vanishing twin pregnancy. Opposite sex of the vanished and viable twins can also manifest as discordance in fetal sex between NIPT and ultrasound observation of fetal genitalia and/or confirmatory karyotype[32,33]. In our cohort, the discordance of the male fetal sex predicted by NIPT and ultrasound examination findings of female external genitalia was observed in vanishing twin pregnancy in patients 42, 43, and 44. In view of the risk of XY disorder of sexual differentiation, two patients underwent amniocentesis and cytogenetic analysis confirmed normal female karyotype. Co-twin demise of a male fetus can be the reason for the discordant result. Other possible aetiologies are maternal transplantation or transfusion from male donors[34]. Thus, detailed maternal history should be taken. If there is a discrepancy between NIPT reported fetal sex and the ultrasound appearance of fetal external genitalia, options of amniocentesis or newborn genetic assessment should

be discussed for concordance between genotype and phenotype[35,36].

NIPT using massively parallel sequencing cannot distinguish between placental and maternal DNA; false positive results can arise from maternal X chromosome aneuploidy and mosaicism[37-39]. In patients 54 and 55, 47,XXX were incidentally discovered by karyotyping peripheral blood lymphocytes. Somatic age-related X chromosome loss of the women may also lead to high risk NIPT result for monosomy X[40]. This may account for the maternal mosaic 45,X/46,XX in patient 56. Thus, women should be well-informed about the possibility of this unanticipated discovery of maternal genomic information during counselling. Notably, the discovery of maternal SCAs does not exclude fetal SCA, further invasive diagnostic testing may be needed to exclude fetal SCA[10]. The use of single nucleotide polymorphism may potentially allow distinction between fetal (placental) and maternal aneuploidies by analysis of allele polymorphisms[41].

In our study, three women had positive NIPT result for X chromosome copy number variations. Follow-up fetal diagnostic tests confirmed unbalanced structural abnormalities of X chromosome namely deletion (patient 52), ring (patient 53), and isodicentric chromosome (patient 51). Studies have reported patients with an abnormal NIPT result for monosomy X who were eventually diagnosed with structural sex chromosome abnormalities[26,42]. Patient 48 had NIPT result showing disproportionate low level of Y signal. Follow-up diagnostic tests (karyotype and fluorescence in situ hybridisation) confirmed a de novo translocation between the Y chromosome and the X chromosome associated with the diagnosis of nonsyndromic 46,XX testicular disorders of sex development. This condition is characterised by male external genitalia ranging from normal to ambiguous, small testes, gynecomastia, azoospermia, and hypergonadotropic hypogonadism secondary to testicular failure[43].

Standardised management approach for pregnancies with positive NIPT result for SCAs involves collaboration of clinicians, geneticists, paediatricians, and prenatal diagnostic laboratory. Although not all patients opted for diagnostic testing, most had confirmation of positive NIPT results by karyotyping after birth, which provides good estimate of positive predictive value of SCA screening in clinical setting. Nonetheless, the sample is relatively small and is from a single centre. Larger multicentre studies are warranted to evaluate factors affecting the uptake of prenatal diagnostic testing and the clinical impact of the expanded use of NIPT for SCAs in Hong Kong.

Conclusion

Positive NIPT results for sex chromosome abnormalities can be caused by true fetal sex chromosome abnormalities, confined placental mosaicism/placental mosaicism, vanishing twins, and maternal X chromosome abnormalities. Multidisciplinary management can help prenatal counselling and genetic diagnosis. Follow-up confirmatory cytogenetic analysis prenatally and/or postnatally is useful to characterise the numeric or structural fetal sex chromosome abnormalities and their mosaic patterns, and can maximise the benefits of prenatal genetic screening in obtaining more genetic information to support pregnancy management and clinical care of affected unborn child.

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Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Central Institutional Review Board of Hospital Authority (reference: CIRB-2021-011-3).

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Mifepristone-misoprostol versus misoprostol alone for second trimester termination of pregnancy in a tertiary hospital in Hong Kong

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Objective: To compare the mifepristone-misoprostol regimen with the misoprostol-alone regimen in terms of safety and effectiveness in women who underwent second trimester medical termination of pregnancy (MTOP).
Methods: Medical records of all women with singleton pregnancy who underwent MTOP during the second trimester at Queen Elizabeth Hospital between 1 January 2018 and 31 December 2019 were reviewed. Patients were prescribed with misoprostol 400 μg every 3 hours up to a maximum of five doses per day orally or vaginally, or with mifepristone 200 mg followed by misoprostol after 36 to 48 hours. The primary outcome was the time from first misoprostol dose to fetal expulsion.
Results: Of 94 patients (mean age, 33.5 years) included, 48 received the mifepristone-misoprostol regimen and 46 received the misoprostol-alone regimen. The mean gestational age was 16 weeks 4 days. Compared with the misoprostol-alone group, the mifepristone-misoprostol group had shorter time to fetal expulsion (7.3 hours vs 11.3 hours, p=0.017), shorter time to placental expulsion (7.9 hours vs 12.2 hours, p=0.026), higher proportion of successful abortion within 10 hours (71.7% vs 43.8%, p=0.005) and 24 hours (95.7% vs 79.2%, p=0.016), and lower number (3 vs 5, p<0.001) and dosage (1200 μg vs 1600 μg, p<0.001) of misoprostol administered. Complication rate was similar between the two groups.
Conclusion: The mifepristone-misoprostol regimen is effective and safe for second trimester MTOP, with a shorter time to fetal expulsion.

Keywords: Abortion, induced; Mifepristone; Misoprostol; Pregnancy trimester, second

Introduction

Termination of pregnancy can be performed medically or surgically. In the past, dilatation and evacuation was the primary way for abortion, even for second trimester abortion up to 14 weeks. Second trimester abortions constitute 10% to 15% of all induced abortions worldwide but account for two-thirds of major abortion-related complications[1]. Dilatation and evacuation for second trimester abortion requires specialised skills and instruments. It is at risk of surgical complications such as uterine perforation and cervical injury and precludes fetal post-mortem examination.

Over the past 20 years, with the increasing availability of prostaglandin and the introduction of mifepristone, medical termination of pregnancy (MTOP) has been increasingly used for second trimester abortion[2-4]. Prostaglandin is the principal agent, and its actions may be augmented by prior administration of mifepristone[5-10]. Pretreatment with mifepristone before misoprostol administration has been reported to increase the success rate, shorten the induction-to-abortion interval, and reduce the dosage of misoprostol required[11,12]. According to various international guidelines, mifepristone followed by a prostaglandin analogue for MTOP is considered appropriate, safe, and effective[13-15].

In Hong Kong, termination of pregnancy can be performed legally up to 23 weeks 6 days of gestation. In 2019, a total of 8272 abortions took place[16]. Because of improved ultrasound technology and prenatal diagnostic techniques, prenatal detection of fetal structural anomalies during the second trimester has improved substantially, and thus the demand for MTOP during the second trimester has increased. Because of the potential risk of serious complications, patients requesting second trimester abortion are often referred to the public sector. MTOP is now generally the standard of care in Hong Kong.

Mifepristone was registered in Hong Kong in April 2014. Only institutions (including public and private hospitals) listed in the Gazette as legal abortion providers

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can purchase mifepristone for abortion. However, mifepristone was not widely used in the public sector and was considered as second-line treatment. Since late 2017, Queen Elizabeth Hospital has started using mifepristone for second trimester abortion. This study aims to compare the mifepristone-misoprostol regimen with the misoprostol-alone regimen in terms of safety and effectiveness in women who underwent second trimester MTOP in a tertiary hospital in Hong Kong.

Methods

This study was approved by the Kowloon Central/ Kowloon East Research Ethics Committees (KC/KE-21-0193/ER-4). Medical records of all women with singleton pregnancy who underwent MTOP during the second trimester (13 weeks 0 days to 21 weeks 6 days of gestation) at Queen Elizabeth Hospital between 1 January 2018 and 31 December 2019 were reviewed through the Clinical Management System. Women were excluded if they had miscarriage, active bleeding or abdominal pain, premature rupture of membrane, multiple pregnancies, ectopic pregnancy, history of prior Caesarean section or uterine perforation, use of fetocide, hypersensitivity to mifepristone or misoprostol, bleeding tendency, inherited porphyria, chronic adrenal failure, chronic steroid use, renal or liver impairment, cardiovascular disease, epilepsy, severe asthma. Women who underwent MTOP at 22 weeks 0 days to 23 weeks 6 days were also excluded, as most of them received fetocide (fetal intracardiac potassium chloride).

Medical practitioners were required to certify the ground for termination of pregnancy. Depending on the clinician's decision and the patient's preference, patients were prescribed with misoprostol 400 μg every 3 hours up to a maximum of five doses per day orally or vaginally (as recommended by the World Health Organization), or with mifepristone 200 mg followed by misoprostol after 36 to 48 hours. Further courses of misoprostol were given until abortion. Oral paracetamol or intramuscular injection of pethidine was provided as pain relief when requested. Blood pressure, pulse, and body temperature were monitored every 4 hours until the abortion.

After the expulsion of the fetus and placenta, patients were assessed by the attending clinician. Intravenous oxytocin infusions were given as prophylaxis for haemorrhage. Abortuses and placentas were examined for completeness. Physical examinations and ultrasound scans of the pelvis were performed. Retained production of gestation (RPOG) was suspected if the endometrial thickness was >10 mm, and medical or surgical evacuation was performed. Patients were followed up until complete abortion. Psychological support and assessment was provided by clinical psychologists if necessary.

Data retrieved for analysis included demographics (age, weight, height, obstetric history, and gestational age), the time of fetal and placental expulsion, the number, dosage, and route of misoprostol administration, analgesic requirement, the length of hospital stay, and complications including RPOG, heavy bleeding, infection.

The primary outcome was the time from first misoprostol dose to fetal expulsion. Secondary outcomes included the time to placental expulsion, the proportion of successful abortion within 10 hours and 24 hours, the rate of complete abortion, the proportion of women requiring analgesics, the rate of complications, the length of hospital stay, and the readmission rate.

Statistical analyses were performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US). The mifepristone-misoprostol regimen and the misoprostol-alone regimen were compared using the Chi-squared test for categorical variables and the Mann-Whitney *U* test or independent t-test for continuous variables. Kaplan-Meier survival curve, with log-rank testing of the null hypothesis, was used to analyse the time to fetal expulsion between groups. Hazard ratio was calculated after adjusting for women's age, prior miscarriage or abortion, parity, gestational age, and route of misoprostol administration. A p value of <0.05 was considered statistically significant.

Results

Of 94 patients (mean age, 33.5±5.05 years) included, 48 received the mifepristone-misoprostol regimen and 46 received the misoprostol-alone regimen (Table). 46 patients were nulliparous and 48 were multiparous. The mean gestational age was 16 weeks 4 days (standard deviation, 2 weeks 3 days). The reason for abortion was fetal abnormalities in 80 patients and maternal anxiety in 14 patients. The mifepristone-misoprostol group and the misoprostol-alone group were comparable in terms of women's age, height, prior miscarriage or abortion, parity, gestational age, and route of misoprostol administration.

All women had successful fetal expulsion. One woman failed to have placental expulsion and required surgical evacuation. Compared with the misoprostol-alone group, the mifepristone-misoprostol group had shorter time to fetal expulsion (7.3 hours vs 11.3 hours, p=0.017, Table),

Table. Clinical characteristics and outcomes of patients who underwent medical termination of pregnancy

	Misoprostol-only (n=48)	Mifepristone-misoprostol (n=46)	p Value
Age, y	34.06±5.51	33.02±4.46	0.112
Weight, kg	57.42±10.21	58.29±8.41	0.327
Height, cm	158.54±4.70	159.90±6.38	0.235
Prior miscarriage or abortion			0.082
0	14 (29.2)	20 (43.5)	
≥1	34 (70.8)	26 (56.5)	
Parity			0.065
0	20 (41.7)	26 (56.5)	
≥1	28 (58.3)	20 (43.5)	
Gestational age, weeks	15.77±2.16	16.86±2.71	0.058
Route of misoprostol			0.164
Oral	19 (39.6)	12 (26.1)	
Vaginal	29 (60.4)	34 (73.9)	
Time to fetal expulsion, hours	11.3 (5.3-94.6)	7.3 (2.4-103.3)	0.017
Time to placental expulsion, hours	12.2 (5.8-95.6)	7.9 (2.6-103.5)	0.026
Successful abortion in 10 hours	21 (43.8)	33 (71.7)	0.005
Successful abortion in 24 hours	38 (79.2)	44 (95.7)	0.016
No. of doses of misoprostol	4 (2-20)	3 (1-15)	0.001
Total dosage of misoprostol, mg	1600 (800-6000)	1200 (400-6000)	0.001
Any analgesics use	39 (81.3)	39 (84.8)	0.649
Heavy bleeding	1 (2.1)	5 (10.9)	0.107
Infection	1 (2.1)	0 (0)	0.325
Complete abortion	4 (8.3)	6 (13.0)	0.459
Surgical evacuation for suspected retained production of gestation	35 (72.9)	32 (69.6)	0.72
Medical evacuation for suspected retained production of gestation	7 (14.6)	5 (10.9)	0.59
Histological proven retained production of gestation	28/42 (66.6)	28/37 (75.7)	0.802
Hospital stay, days	4 (2-17)	5 (4-8)	<0.001
Hospital stay since the first dose of misoprostol, days	3 (2-17)	3 (2-6)	0.109
Readmission	6 (12.5)	5 (10.9)	0.806

* Data are presented as mean ± standard deviation, median (range), or No. (%)

which was confirmed by the Kaplan-Meier survival curves and log-rank tests (p=0.001, Figure) and by Cox proportional models after adjusting for potential confounders (hazard ratio=2.63, 95% confidence interval=1.66-4.16, p<0.001). In addition, the mifepristone-misoprostol group had shorter time to placental expulsion (7.9 hours vs 12.2 hours, p=0.026), higher proportion of successful abortion within 10 hours (71.7% vs 43.8%, p=0.005) and 24 hours (95.7% vs 79.2%, p=0.016), and lower number (3 vs 5, p<0.001) and dosage (1200 μg vs 1600 μg, p<0.001) of misoprostol administered. Nonetheless, the mifepristone-misoprostol group had longer length of hospital stay (5 days vs 4 days, p<0.001), but the length of hospital stay from the time of the first dose of misoprostol was similar in both groups (3 days).

79 (84.0%) of women required further surgical or medical evacuation for suspected RPOG. Five of them did not receive treatment initially after diagnosis: one was later found to have complete abortion; one underwent surgical

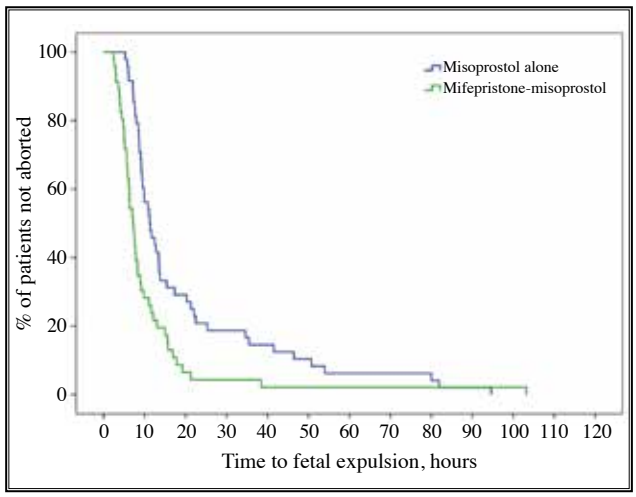

Figure. Kaplan-Meier curves for the time to fetal expulsion in the mifepristone-misoprostol group and the misoprostol-alone group

evacuation and one underwent medical evacuation; and the remaining two were lost to follow-up. 10 women were readmitted for management of RPOG and one was readmitted for post-abortal endometritis.

Severe complications included six cases of heavy bleeding and one case of infection requiring intravenous antibiotics. There was no uterine perforation, scar rupture, severe allergic reaction, or death.

Discussion

Pretreatment with mifepristone enables the use of lower dosage of misoprostol to achieve comparable efficacy, with a shorter induction-to-abortion interval for second trimester MTOP[17]. In the present study, the median time to fetal expulsion after the mifepristone-misoprostol regimen was 7.3 hours, which was similar to previous studies[9,18,19]. Mifepristone is a synthetic steroidal drug with anti-progesterone and anti-glucocorticoid actions. It binds with the progesterone receptors, which antagonises prostaglandin synthesis and metabolism, resulting in increased production and decreased deactivation of prostaglandins. It induces cervical softening and enhances the efficacy of the prostaglandins as an abortifacient[20,21]. It reduces the number and dosage of subsequent prostanglandin required for abortion.

Nonetheless, the use of mifepristone is not widely used in the public sector in Hong Kong. Possible reasons include its recent introduction (in 2014) and high cost (HK$440/tablet vs $1.6/200mcg for misoprostol). Although mifepristone is more expensive than misoprostol, it enables shorter abortion interval, which potentially improves patient satisfaction and reduces frustration and stress associated with the advancing of gestation or discomfort from repeated vagina suppositories.

The slightly more cases of heavy bleeding in the mifepristone-misoprostol group may be due to the small sample size and the rare occurrence of the complication[6]. There were one case of infection requiring intravenous antibiotics and one case of post-abortal endometritis; the infection rate was only 2.1%, which is consistent with a previous study[6]. Thus, antibiotic prophylaxis should not be offered routinely to women with MTOP[14].

Analgesic requirement was reported to be higher in women with prolonged induction to abortion interval and with an increased number of misoprostol doses[22]. However, in the present study, analgesic requirement was similar in women with or without mifepristone pretreatment. This may indicate that mifepristone pretreatment is unable to decrease the analgesic requirement, despite the reduction in the induction-to-abortion interval and misoprostol dosage. Thus, clinicians should provide adequate analgesics to women undergoing MTOP irrespective of abortion regimen.

The complete abortion rate was slightly higher in the mifepristone-misoprostol group than the misoprostol group (13.0% vs 8.3%, p=0.459), but the rate of RPOG of both groups remained high (89%), compared with 2.5% to 53% reported in previous studies[23,24]. The high rate of RPOG is likely to be contributed by over-reliance on ultrasound assessment immediately after abortion. This increases the early diagnosis rate of RPOG. Among those who received surgical or medical evacuation for RPOG, the histologically proven RPOG rate remained high (>60%-70%). Little evidence was available on the optimal timing and diagnostic criteria of post-MTOP ultrasound assessment in second trimester MTOP. Clinicians should make the diagnosis of RPOG based on both clinical findings and examination of abortus and placenta. Future research is needed to determine the role of ultrasound in post-MTOP assessment and to improve the complete abortion rate.

In the present study, 71.7% of women with the mifepristone-misoprostol regimen achieved abortion within 10 hours. This makes outpatient day service feasible. Day service for MTOP should be aimed for, as women with MTOP are generally younger and more active. However, the length of hospital stay was longer in the mifepristone-misoprostol group than in the misoprostol-alone group

(5 days vs 4 days). As a safe practice during the initial phase of the introduction of mifepristone to our unit, mifepristone was not given in an outpatient setting. Further study on outpatient administration of mifepristone is warranted to determine its effect on the length of hospital stay.

Limitations to the present study are its retrospective nature and small sample size. Nevertheless, this study is the first study in Hong Kong comparing the use of misoprostol with or without mifepristone in second trimester MTOP. It can be a pilot study for future larger-scale studies and prospective studies. Patients at late second trimester (22 weeks to 23 weeks 6 days) were excluded owing to the possible confounding effect of fetocide on the time from induction to abortion[25]. Both vaginal and oral routes were used for misoprostol administration. Some studies reported the vaginal route more effective[26,27]; others reported inconclusive evidence[28,29]. A holistic approach to service delivery should be aimed at; patient satisfaction and acceptability should have been assessed in addition to objective outcome measures. Our findings are specific to a tertiary hospital in Hong Kong and may not be generalised to other settings.

Conclusion

The mifepristone-misoprostol regimen is associated with shorter induction-to-abortion interval and reduced misoprostol dosage, while maintaining similar complications rates, analgesics requirement, length of hospital stay, and readmissions. It is effective and safe for second trimester MTOP. Optimisation of the regimen should aim at improving the complete abortion rate and reducing the length of hospital stay.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central/Kowloon East Research Ethics Committees (KC/KE-21-0193/ER-4). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Risk factors for endometrial pathology in women with breast cancer and tamoxifen treatment

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Objectives: To identify risk factors for development of endometrial pathology in both premenopausal and postmenopausal women who received tamoxifen treatment for breast cancer.
Methods: Medical records of women who had breast cancer and tamoxifen treatment and received endometrial sampling at Queen Elizabeth Hospital between 1 January 2017 and 31 December 2020 were retrospectively reviewed. Histology of the endometrial tissue was classified as normal, endometrial polyp, endometrial hyperplasia (with or without atypia), and endometrial cancer. Women with normal endometrium were compared with women with endometrial cancer/hyperplasia or women with endometrial polyp. Risk factors of endometrial pathology were identified through univariate and multivariate analyses.
Results: 249 women (mean age, 50.8 years) were included. Of 249 endometrial samplings, 169 (67.9%) showed normal endometrium, 71 (28.5%) showed endometrial polyp, 5 (2.0%) showed endometrial hyperplasia, and 4 (1.6%) showed endometrial cancer. In univariate analysis, endometrial cancer/hyperplasia was associated with lower parity, longer duration of menopause, longer duration of breast cancer diagnosis, longer duration of tamoxifen treatment, completion of tamoxifen therapy, longer duration of tamoxifen cessation, endometrial thickness of ≥5 mm, and endometrial thickness of ≥9 mm, whereas endometrial polyp was associated with older age, postmenopausal status, abnormal endometrium on ultrasound, endometrial thickness of ≥5 mm, and endometrial thickness of ≥9 mm. In multivariate analysis, risk factors for endometrial cancer/hyperplasia were nulliparity (odds ratio [OR]=8.7, p=0.035), duration of breast cancer diagnosis >10 years (OR=11.6, p=0.019), and endometrial thickness ≥9 mm (OR=11.9, p=0.031), whereas the risk factor for endometrial polyp was endometrial thickness ≥9 mm (OR=5.3, p<0.001).
Conclusion: In women who had breast cancer and tamoxifen treatment, nulliparity, a history of breast cancer >10 years earlier, and endometrium thickness of ≥9 mm are independent risk factors for endometrial cancer/hyperplasia. Early hysteroscopic assessment should be arranged for these patients, especially when they presented with abnormal uterine bleeding.

Keywords: Breast neoplasms; Endometrial hyperplasia; Endometrial neoplasms; Tamoxifen

Introduction

Tamoxifen is the most-prescribed adjuvant treatment for oestrogen-receptor-positive breast cancer, as it reduces the risk of contralateral breast cancer and prevents tumour recurrence. Compared with the traditional 5-year regimen, the 10-year extended regimen has higher efficacy in improving both disease-free and overall survival[1,2]. However, breast cancer survivors are at risk of developing tamoxifen-induced endometrial malignancy. Being a selective oestrogen receptor modulator, tamoxifen has modest oestrogenic activity on the endometrium. Uterine pathologies including polyps, hyperplasia, and endometrial cancer are found in 30% to 40% of tamoxifen-treated women[3-7]. Changes develop in a dose- and time-dependent manner and last several years beyond drug cessation[7]. Therefore, tamoxifen-treated women remain at an increased risk of endometrial proliferation, even after completion of the treatment. The International Agency for Research on Cancer[8] labels tamoxifen as a carcinogen owing to the causal relationship between the drug and endometrial cancer, with the relative risk two to three times higher than that of an age-matched population[9,10].

According to the American College of Obstetricians and Gynaecologists[11], there are potential benefits in identifying postmenopausal women who have endometrial polyps before tamoxifen initiation[12,13]. However, for low-risk tamoxifen users, routine endometrial surveillance is not cost-effective and thus not recommended. Nevertheless, endometrial pathologies can arise, especially in those who received the 10-year extended regimen for high-risk breast cancer[14]. Therefore, it is important to identify other clinical predictors for endometrial pathologies so that an optimal surveillance plan can be formulated. Lower parity, increased

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endometrial thickness, and the presence of abnormal vaginal bleeding have been reported to be associated with the development of endometrial hyperplasia and cancer[4,6,15-17]. However, multivariate analysis was not performed in these studies, and only one study focused on premenopausal women treated with tamoxifen. This study aims to identify risk factors for development of endometrial pathology in both premenopausal and postmenopausal women who received tamoxifen treatment for breast cancer.

Materials and Methods

This study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-0218/ER-1). Medical records of women who had breast cancer and tamoxifen treatment and received endometrial sampling (including endometrial aspirate and uterine curetting) at Queen Elizabeth Hospital between 1 January 2017 and 31 December 2020 were retrospectively reviewed through the Clinical Data Analysis and Reporting System. Women were excluded if they had tamoxifen treatment for <3 months, unclear treatment duration, incomplete clinical data, inadequate sampling for histological diagnosis, or metastatic cancer to the uterus. Repeat sampling was performed in those with inadequate sampling, and the final endometrial sample was used for analysis.

As there was no pretreatment screening or regular gynaecological surveillance for endometrial pathology for these women, ultrasound scanning (preferably transvaginal) and endometrial sampling were offered only to those with symptoms (abnormal vaginal bleeding and/ or endometrium). Endometrial thickness was measured on the sagittal plane of the uterus, from the anterior basalis to the posterior basalis of the endometrial surfaces. An abnormal endometrium was defined as one with an endometrial thickness >4 mm in postmenopausal users, or ultrasound features suggestive of endometrial lesions such as polyps or tumours. Endometrial sampling was obtained through Pipelle aspiration or uterine curettage. Hysteroscopic evaluation was offered to women who could not tolerate bedside endometrial aspiration, had suspicious endometrial lesions on ultrasound scan, or had persistent vaginal bleeding. Women with normal endometrium and subsided symptoms were discharged and advised to seek early medical attention if symptoms recur.

Demographic data collected were age, parity, body weight and height, menopausal status (menopause is defined as amenorrhea for at least 12 months, combined with the postmenopausal range of serum oestradiol levels in women on tamoxifen[18]), medical history, and family history of cancer. Breast cancer data collected were cancer duration, treatment modality, tamoxifen treatment duration and status, and duration of tamoxifen cessation (if applicable). Clinical data collected were the presence of abnormal vaginal bleeding and endometrial thickness. Histology of the endometrial tissue was classified as normal, endometrial polyp, endometrial hyperplasia (with or without atypia), and endometrial cancer.

Statistical analysis was performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], US). Women with normal endometrium were compared with women with endometrial cancer/hyperplasia or women with endometrial polyp using the Mann-Whitney *U* test for continuous variables and the Chi-square test or Fisher exact test for categorical data. Multivariate analysis was performed to identify risk factors for endometrial cancer/ hyperplasia and endometrial polyp. A p value of <0.05 was considered statistically significant.

Results

Of 268 women recruited, 19 were excluded who had <3 months of tamoxifen treatment (n=9), incomplete clinical data (n=1), insufficient endometrial tissue for histological diagnosis (n=3), or metastatic cancer to the uterus (n=6). The remaining 249 were included for analysis (Table 1). None of the 249 women (mean age, 50.8 years) had received a pre-tamoxifen assessment for uterine pathology before drug initiation. 140 (56.2%) were menopausal, with 43.6% of them having chemotherapy-induced amenorrhea. The mean duration of breast cancer diagnosis was 4.7 years; 205 (81.4%) had stage I or II cancer. 67.9% and 75.1% received chemotherapy and radiotherapy, respectively. The mean duration of tamoxifen use was 41.0 months; 181 (72.7%) were on active tamoxifen treatment at the time of endometrial biopsy. The mean endometrial thickness was 8.3 mm. 77.5% had abnormal vaginal bleeding, and 38.6% had abnormal endometrium on ultrasound scan.

Indications for endometrial sampling included abnormal vaginal bleeding (n=151, 60.6%), abnormal endometrium on ultrasound scans (n=54, 21.7%), both (n=42, 16.9%), and other reasons (n=2, 0.8%). Two patients received an endometrial biopsy owing to non-specific fluorodeoxyglucose uptakes in the endometrium on positron emission tomography–computed tomography (n=1) or the presence of atypical glandular cells, not otherwise specified, on a routine cervical smear test (n=1).

Table 1. Clinical characteristics of 249 women who had breast cancer and received tamoxifen

Variable	Value*
Age at biopsy, y	50.8±8.4
No. of parity	1.1±1.0
Body mass index, kg/m^2	24.2±4.1
Menopause	140 (56.2)
Chemotherapy-induced amenorrhea	61 (43.6)
Age at menopause, y	49.1±4.1
Duration of menopause, y	6.2 ±6.3
Diabetes mellitus	19 (7.6)
Smoking	6 (2.4)
History of breast/ gynaecological cancers in 1st degree relatives	37 (14.9)
Stage of breast cancer	
I	111 (43.6)
II	94 (37.8)
III	37 (14.9)
IV	7 (2.8)
Duration of breast cancer diagnosis, y	4.7±3.8
Duration of tamoxifen treatment, months	41.0±27.0
Actively on tamoxifen treatment	181 (72.7)
Completed tamoxifen treatment	68 (27.3)
Duration since cessation, months	38.0±43.5
History of chemotherapy	169 (67.9)
History of radiotherapy	187 (75.1)
Endometrial thickness, mm	8.3±6.3
Abnormal vaginal bleeding	193 (77.5)
Abnormal endometrium on ultrasound	96 (38.6)

* Data are presented as mean ± standard deviation or No. (%) of participants

Of 249 endometrial samplings, 169 (67.9%) showed normal endometrium, 71 (28.5%) showed endometrial polyp, 5 (2.0%) showed endometrial hyperplasia, and 4 (1.6%) showed endometrial cancer. The four patients with endometrial cancer did not have any pre-existing endometrial pathology; all presented with postmenopausal bleeding and thickened endometrium (mean, 15 mm). Two of them had stage I endometrioid adenocarcinoma after 5 years of tamoxifen therapy. One had stage IIIC high-grade adenocarcinoma with mixed endometrioid, serous, and clear cell components. She received extended tamoxifen adjuvant therapy and developed postmenopausal bleeding at the 9th year of drug use. The remaining one had stage I malignant mixed mesodermal tumour of the uterus after 5 years of tamoxifen treatment. She underwent cancer surgery and adjuvant radiotherapy. However, she had pulmonary and pleural metastasis (uterine origin) 2 years later and died 2 more years later. All five women with endometrial hyperplasia had abnormal vaginal bleeding (postmenopausal bleeding or menorrhagia) and thickened endometrium (9-24 mm). Three had complex hyperplasia without atypia, one had simple hyperplasia without atypia, and one had hyperplasia with focal atypia. Histological examinations confirmed that all cases of hyperplasia without atypia were developed from endometrial polyps.

Compared with women with normal endometrium, women with endometrial cancer/hyperplasia were associated with lower parity (0.4 vs 1.1, p=0.026), longer duration of menopause (10.4 vs 5.5 years, p=0.016), longer duration of breast cancer diagnosis (9.9 vs 4.3 years, p=0.002), longer duration of tamoxifen treatment (58.0 vs 38.5 months, p=0.017), completion of tamoxifen therapy (66.7% vs 23.7%, p=0.010), longer duration of tamoxifen cessation (89.9 vs 31.8 months, p=0.021), endometrial thickness of ≥5 mm (100% vs 59.2%, p=0.013), and endometrial thickness of ≥9 mm (88.9% vs 27.2%, p<0.001) [Table 2]. Compared with women with normal endometrium, women with endometrial polyp were associated with older age (52.7 vs 49.9 years, p=0.027), postmenopausal status (67.6% vs 51.5%, p=0.022), abnormal endometrium on ultrasound (56.3% vs 31.4%, p<0.001), endometrial thickness of ≥5 mm (81.7% vs 59.2%, p=0.001), and endometrial thickness of ≥9 mm (64.8% vs 27.2%, p<0.001) [Table 2].

In multivariate analysis, risk factors for endometrial cancer/hyperplasia were nulliparity (odds ratio [OR]=8.7, p=0.035), duration of breast cancer diagnosis >10 years (OR=11.6, p=0.019), and endometrial thickness ≥9 mm (OR=11.9, p=0.031), whereas the risk factor for endometrial polyp was endometrial thickness ≥9 mm (OR=5.3, p<0.001) [Table 3].

Discussion

In the present study, nulliparity was associated with 8.7-fold higher risk of developing endometrial pathology in tamoxifen users. It is believed that the elevated progesterone level during pregnancy protects against endometrial cancer through inhibition of the oestrogen-driven endometrial cell proliferation. The postpartum involution of the uterus also helps in shedding the premalignant lesions[19]. As tamoxifen activates the oestrogenic receptors and stimulates endometrial proliferation, nulliparous users are more susceptible to developing pathologies such as cancer and hyperplasia.

Table 2. Women with normal endometrium versus women with endometrial cancer/hyperplasia versus women with endometrial polyp

Variable	Normal endometrium (n=169)*	Endometrial cancer/ hyperplasia (n=9)*	P value	Endometrial polyp (n=71)*	P value
Age at biopsy, y	49.9±8.1	52.9±10.6	0.511	52.7±8.6	**0.027**
No. of parity	1.1±0.9	0.4±0.9	**0.026**	1.2±1.3	0.721
Body mass index, kg/m^2	24.1±4.0	23.8±7.0	0.198	24.4±3.8	0.687
Menopause	87 (51.5)	5 (55.6)	1.000	48 (67.6)	**0.022**
Chemotherapy-induced amenorrhea	34 (39.1)	2 (40)	1.000	25 (52.1)	0.145
Age at menopause, y	49.1±4.2	50±3.7	0.539	49.0±4.1	0.761
Duration of menopause, y	5.5±5.5	10.4±4.7	**0.016**	7.2±7.5	0.115
Diabetes mellitus	12 (7.1)	1 (11.1)	0.503	6 (8.5)	0.925
Smoking	3 (1.8)	0 (0)	1.000	3 (4.2)	0.365
History of breast/ gynaecological cancers in 1st degree relatives	21 (12.4)	3 (33.3)	0.105	13 (18.3)	0.233
Duration of breast cancer diagnosis, y	4.3±3.4	9.9±5.2	**0.002**	5.2±3.9	0.073
Duration of tamoxifen treatment, months	38.5±25.9	58.0±23.9	**0.017**	44.7±28.9	0.109
Actively on tamoxifen treatment	129 (76.3)	3 (33.3)	**0.010**	49 (69.0)	0.237
Completed tamoxifen treatment	40 (23.7)	6 (66.7)	**0.010**	22 (31.0)	0.237
Duration since tamoxifen cessation, months	31.8±38.9	89.9±45.8	**0.021**	35.4±43.4	0.926
History of chemotherapy	110 (65.1)	7 (77.8)	0.720	52 (73.2)	0.219
History of radiotherapy	123 (72.8)	8 (88.9)	0.448	56 (78.9)	0.322
Endometrial thickness ≥ 5mm	100 (59.2)	9 (100)	**0.013**	58 (81.7)	**0.001**
Endometrial thickness ≥ 9mm	46 (27.2)	8 (88.9)	**<0.001**	46 (64.8)	**<0.001**
Abnormal vaginal bleeding	134 (79.3)	9 (100)	0.208	50 (70.4)	0.138
Abnormal endometrium on ultrasound	53 (31.4)	3 (33.3)	1.000	40 (56.3)	**<0.001**

* Data are presented as mean ± standard deviation or No. (%) of participants

Table 3. Risk factors for endometrial cancer/hyperplasia and endometrial polyp in women with breast cancer treated with tamoxifen

	Odds ratio (95% confidence interval)	P value
Endometrial cancer/ hyperplasia		
Nulliparous	8.687 (1.162-64.950)	**0.035**
Duration of menopause	1.242 (0.748-2.062)	0.403
Duration of breast cancer diagnosis ≥10 years	11.594 (1.502-89.473)	**0.019**
Duration of tamoxifen	0.999 (0.963-1.036)	0.953
Completed tamoxifen treatment	2.483 (0.317-19.419)	0.386
Duration since tamoxifen cessation, months	0.991 (0.760-1.294)	0.950
Endometrial thickness ≥9 mm	11.935 (1.257-113.293)	**0.031**
Endometrial polyp		
Age >50 years	1.815 (0.901-3.658)	0.905
Menopaused	1.413 (0.704-2.839)	0.331
Abnormal endometrium on ultrasound	1.017 (0.530-1.949)	0.960
Endometrial thickness ≥9 mm	5.313 (2.605-10.839)	**< 0.001**

In the present study, tamoxifen users who had a history of breast cancer >10 years earlier had an 11.6-fold increased risk of endometrial pathology. Breast cancer survivors are at a higher risk of developing uterine malignancy, compared with the general population[4,20-22], because breast cancer and endometrial cancer share similar risk-factor profiles such as obesity and older age[4]. Endometrial neoplastic changes are more likely to occur in those with a longer history of breast cancer.

Tamoxifen induces cystic changes and subepithelial stromal hypertrophy[23-25]. After a year of tamoxifen treatment, ≥80% of women have an endometrial thickness ≥5 mm[26,27]. In the present study, an endometrial thickness of ≥9 mm was a risk factor of both endometrial cancer/hyperplasia and endometrial polyp in tamoxifen-treated women. This finding is consistent with that in previous studies[4,28,29]. Early hysteroscopic assessment should be arranged for these women.

According to the Early Breast Cancer Trialists Collaborative Group[30], the incidence of endometrial cancer quadrupled after 5 years of tamoxifen treatment. However, in the present study, a longer duration of tamoxifen treatment was not associated with endometrial cancer/hyperplasia in the multivariate analysis. Further study is warranted to clarify the association between tamoxifen duration and pathological endometrial lesions.

Although the endometrial thickness reduces significantly after discontinuation of tamoxifen treatment[31], we cannot conclude that this change represents a reversal of abnormal endometrial stimulation. Women with breast cancer should be aware of escalating endometrial proliferation over time even after discontinuation of tamoxifen, because the effect of tamoxifen can last several years beyond drug cessation[7,9].

Tamoxifen-related polyps have a higher rate of cancerous change at 3.0% to 10.7%[3,5-7,25,32]. However, only about 50.0% of patients with endometrial polyps are symptomatic before malignant transformation[7,33]. The present study showed that older age and menopausal status were associated with the development of endometrial polyp, but the association was not significant in the multivariate analysis. Larger scale studies are needed to identify the independent risk factors of polyp formation to aid early detection and treatment.

International guidelines are of the consensus that regular surveillance for low-risk tamoxifen users is not recommended[11,34], as their overall cancer prevalence is low, and universal screening substantially increases healthcare costs. However, endometrial cancer in women treated with tamoxifen tends to be less favourable subtypes with poorer prognosis[6,7,9,35,36]. In the present study, 50% of patients had more aggressive tumour cell types (high-grade adenocarcinoma and malignant mixed mesodermal tumour). The presence of postmenopausal bleeding was the primary trigger for these women to seek gynaecological opinion[10]. Therefore, it is important to identify the risk factors for endometrial pathology in tamoxifen users so that early endometrial screening can be provided to improve the overall cancer prognosis. Large-scale multicentre randomised trials can be conducted to assess the cost-effectiveness of selected screening.

There are several limitations to the present study. Patient selection may be biased, as patients presented to our clinic were symptomatic with abnormal vaginal bleeding or abnormal endometrium, and the decisions on performing endometrial sampling vary among medical practitioners. In addition, the sample size is small and of a single centre. However, the prevalence of endometrial cancer over the 4-year study period (1.6%) is similar to the 1.9 per 1000 women per year reported by the Early Breast Cancer Trialists' Collaborative Group[37]. Large-scale multicentre randomised controlled trials are needed to address the potential small number variations effect.

Conclusion

In women who had breast cancer and tamoxifen treatment, nulliparity, a history of breast cancer >10 years earlier, and endometrium thickness of ≥9 mm are independent risk factors for endometrial cancer/hyperplasia. Early hysteroscopic assessment should be arranged for these patients, especially when they presented with abnormal uterine bleeding.

Contributor

The author designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The author has disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee (reference: KC/KE-21-0218/ER-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Sentinel lymph node mapping in endometrial cancer: an updated review

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Sentinel lymph node mapping (SLNM) is widely used in staging of both low- and high-risk early-stage endometrial cancer. It has a high detection rate, high sensitivity, high negative predictive value, and low false negative rate in detection of lymph node metastasis. Cervical injection of indocyanine green for SLNM is the preferred method. SLNM reduces the number of lymph node removal and reduces complications from lymphadenectomy without compromising oncological safety. This review discusses the latest evidence of SLNM in endometrial cancer staging in terms of technique, accuracy, limitations, impact on lymphadenectomy complications, and cancer survival.

Keywords: Endometrial neoplasms; Lymph node excision; Neoplasm staging; Sentinel lymph node

Introduction

Endometrial cancer is the commonest gynaecological malignancy in the developed world, with the incidence increasing rapidly. It is the 4th commonest female cancer in the USA, with a 1% increase in incidence every year[1]. In Hong Kong, a similar trend is observed. According to the Hong Kong Cancer Registry, the incidence increased from 15/100 000 in 2015 to 17/100 000 in 2019[2]. Lymphadenectomy has been an integral part in the management of endometrial cancer since the use of surgical staging[3] and the incorporation of positive lymph nodes as stage IIIC in the International Federation of Gynecology and Obstetrics staging[4]. Chemotherapy and/or radiotherapy improves the 5-year overall survival (OS) of stage IIIC endometrial cancer from 69.8% to 78.7%[5,6]. Thus, accurate assessment of lymph node involvement is crucial for the optimal management of endometrial cancer, especially in high-risk endometrial cancer, which has a 10% chance of lymph node metastasis[7]. However, complete pelvic and para-aortic lymphadenectomy lacks a therapeutic effect and is associated with morbidities such as lymphedema. Sentinel lymph node mapping (SLNM) may decrease morbidity without compromising survival. It is widely used in the management of early-stage low-risk (well-differentiated or moderately differentiated, grade 1-2, <50% myometrial invasion, <2 cm tumour) endometrial cancer[8]. It also achieves similar oncological safety and accuracy in early-stage high-risk (grade 3 endometrioid histology, non-endometrioid histology, deep myometrial invasion, cervical invasion, and presence of lymphovascular space invasion) endometrial cancer. 82% of US gynae-oncology surgeons[9] and 50% of gynae-oncology surgeons among 69 countries self-report to use SLNM when managing endometrial cancer[10].

Controversies on lymphadenectomy

The standard treatment of endometrial cancer is total hysterectomy + bilateral salpingoophorectomy +/- pelvic lymphadenectomy +/- para-aortic lymphadenectomy. However, the role and extent of complete pelvic and para-aortic lymphadenectomy remain controversial. Some studies reported therapeutic benefits from lymphadenectomy[11-13]. Others reported that lymphadenectomy provided no additional therapeutic benefit for early-stage endometrial cancer, with similar progression-free survival (PFS) and OS between those with or without lymphadenectomy[14,15], but the proportion of low-risk patients was larger and the adjuvant therapy was not standardised in the two studies. The risk of lymph node involvement is only 1% to 2%[7,16] for early-stage low-risk endometrial cancer. In a retrospective study of 268 low-risk endometrial cancer patients, 2.4% had lymph node metastasis. Although the risk of lymph node metastasis is 11.4% for high-risk endometrial cancer patients, 88.6% of patients will still receive unnecessary lymphadenectomy and thus had morbidities such as

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lymphedema[7]. Given the lack of therapeutic benefit, low risk of lymph node metastasis, and morbidity, the role of complete lymphadenectomy is questionable in low-risk endometrial cancer. Some centres advocate complete pelvic +/- para-aortic lymphadenectomy for all patients[13], whereas others advocate lymphadectomy for high-risk endometrial cancers only[12,17]. The strategy of Mayo Clinic is to omit complete lymphadenectomy in low-risk endometrial cancers[8]. However, upstaging of disease on final histology is not uncommon, only 47% of presumed stage 1A, grade 1 disease remain so on final histology[18]. Neither preoperative clinical risk factors nor imaging is accurate in predicting metastasis to lymph nodes. Magnetic resonance imaging, positron emission tomography computed tomography, and positron emission tomography magnetic resonance imaging have a low sensitivity of 60% to 70%[19].

Sentinel lymph node mapping

Sentinel lymph node refers to the first lymph node that receives lymphatic drainage from the primary malignant tumour. SLNM is based on the presumption that lymphatic drainage occurs stepwise from the most proximal lymph node to the tumour site to more distal lymph nodes. Theoretically, SLN is the first to metastasise in a regional lymphatic drainage area. With a negative SLN, the whole lymphatic drainage area is considered negative for metastasis. SLNM involves selective removal of lymph nodes at highest risk of metastasis as identified by tracers injected near the primary malignant tumour. The detection rate, bilateral detection rate, sensitivity, negative predictive value (NPV), and false negative rate of SLNM are key parameters for its performance. Detection rate is the percentage of patients with at least one SLN being detected. Bilateral detection rate refers to the percentage of patients with SLN being detected at bilateral pelvis. Sensitivity is defined as the proportion of positive SLN to the total number of patients with lymph node metastasis. NPV is defined as the percentage of patients with negative SLN to the total number of patients with negative non-SLN. False negative rate is defined as the percentage of patients with negative SLN but positive non-SLN. SLNM is the standard of practice in breast cancer, vulval cancer, and melanoma. SLNM was first reported in 1996 in 15 endometrial cancer patients[20]. The SENTICO-ENDO study in 2011 showed a promising result, with a sensitivity of 84% and NPV of 97%[21].

What tracer to inject?

Technetium-99m (Tc-99m), blue dye (isosulfan blue, methylene blue), indocyanine green (ICG), and combinations of tracers have been used to locate the SLN. ICG is the most recommended tracer, owing to its high detection rate, consistency, and ease of administration.

Radiolabelled Tc-99m can drain through lymph nodes and emit gamma rays that can be detected by preoperative nuclear imaging and intraoperative gamma counters. Tc-99m is usually injected 1 day before surgery for preoperative lymphoscintigraphy, which can be fused with single-photon emission computed tomography for greater precision[22]. A collaboration with a nuclear medicine unit is required. Injection of tracer is painful to the patient. The required injection dose is calculated based on the estimated time interval to the surgery; this limits flexibility should the surgery be advanced or deferred and requires meticulous preoperative planning. Thus, the use of intraoperative gamma counters only is proposed[22]. However, radio-injury to surgeons and patients and the lack of equipment remain potential problems[17,23]. The detection rate of Tc-99m is lower than that of ICG (53.3% vs 73.8%)[24]. Tc-99m is often used with the colorimetric method to increase the detection rate. The gamma counters can identify areas of hot signals, and coloured dye can guide the dissection. ICG is superior to combined blue dye and Tc-99m, with higher SLN detection rate (100% vs 96%) and bilateral mapping rate (98.5% vs 76.3%)[25]. The COMBITEC study concluded that there is no benefit to add Tc-99m to ICG, owing to increased procedure time and no difference in the SLN detection rate[26].

Colorimetric lymphatic mapping involves visual detection of lymphatic channels with coloured dye in white light[17]. Isosulfan blue is costly and associated with a risk of potentially life-threatening allergic reactions[27]. Approximately 1% to 2% of patients experience allergic reactions with isosulfan blue. Methylene blue is less expensive and associated with much less allergic reactions[27]. However, SLNM with methylene blue is an off-label use. It carries a risk of paradoxical methemoglobinemia and serotonin syndrome in patients taking serotonergic psychiatric medications[17]. Breast cancer studies showed a similar SLN detection rate for isosulfan blue and methylene blue[27]. Injection of methylene blue and ICG to each side of the cervix in the same patient showed a higher SLN detection rate with ICG than with methylene blue (90.9% vs 64.4%)[28]. The use of ICG increases the SLN detection rate per hemi-pelvis by 26.5%[28].

ICG emits fluorescent signal in near-infrared light range (830 nM wavelength). An equipment for near-infrared light range imaging is required to identify the SLN (Figure). The risk of adverse event is extremely low (0.07%

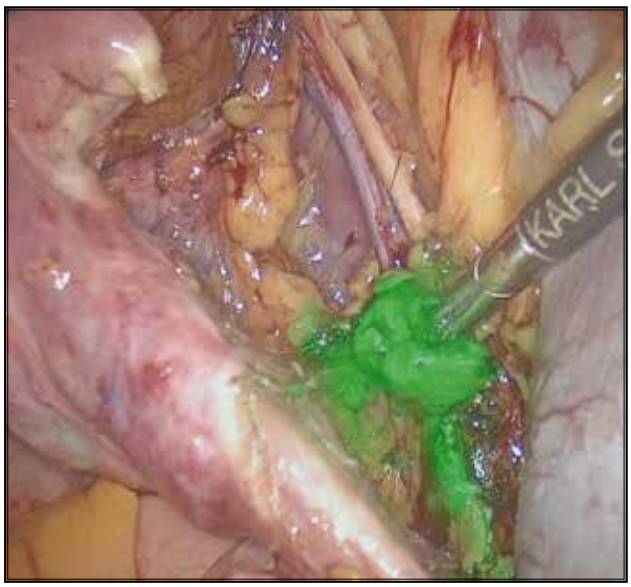

Figure. Laparoscopic sentinel lymph node identification in endometrial cancer with cervical injection of indocyanine green.

to 0.5%)[29], but it should be avoided in patients with iodine allergy and hepatic failure because it is metabolised by the liver[17]. ICG has an excellent toxicity profile and higher overall and bilateral detection rates, compared with blue dye alone or a combination of Tc-99m and blue dye[22,30]. The bilateral mapping rate of SLN was significantly higher with ICG than with methylene blue (78% vs 61%) for endometrial cancer and cervical cancer[31]. The complete lymphadenectomy rate secondary to failed mapping was 9% in the ICG group and 28% in the methylene blue group. ICG yielded a higher overall detection rate (95% vs 81%) and higher bilateral detection rate (85% vs 54%) than methylene blue did[32]. The increase in SLN detection rate reduced the need for complete lymphadenectomy in the ICG group (39% vs 61%, p<0.001)[32].

Where to inject?

Uterine corpus injection can be peri-tumoral, subserosal, or myometrial via direct injection, ultrasound guidance or hysteroscopy[33]. Deep and superficial injection of ICG at 3 and 9 o'clock or 3, 6, 9, and 12 o'clock of the cervix is the most common method[34]. The mixture involves 25 mg of ICG powder with 10 to 20 mL of sterile water and 4 to 8 mL of the diluted ICG solution[33,34]. Cervical injection is easy to master, with high reproducibility and detection rate, as cervical deformation secondary to pathology is much less common, compared with that in the uterine corpus[34]. The main lymphatic drainage to the uterus is from the parametria. Therefore, a combined superficial (1-3 mm) and deep (1-2 cm) cervical injection is adequate[34]. A uterine fundal serosa injection is less favoured because it does not reflect the parametrial lymphatic drainage[34], most early endometrial cancer does not invade to the serosal layer, and the injection is commonly affected by anatomical uterine distortion secondary to fibroid. When initial SLNM fails, reinjection with an additional 1 mL of diluted ICG to the superficial cervix of the no SLN detection side can increase the detection rate[35].

A meta-analysis reported that all studies with ≥100 patients had overall detection rates of >80%, regardless of the injection site[36]. A systematic review reported an overall detection rate of 62% to 100% after cervical injection, which is higher than the 73% to 95% after uterine corpus injection[36]. A retrospective study of 221 hysteroscopic injections reported a high overall detection rate of 94.1% and bilateral mapping rate of 62.5%[24]. However, hysteroscopic injection is more technically demanding than cervical injection, with less reproducible results. A combination of cervical and uterine fundus injection can increase the detection rate, with an overall detection rate being 92.8% for any SLN, 89.2% for pelvic SLN, 61.3% for bilateral SLN, and 4% for isolated para-aortic SLN[37].

Although cervical injection has higher overall detection rate of SLN, it has lower para-aortic SLN detection rate than uterine corpus injection. Metastasis to the para-aortic nodes through gonadal vessels and infundibulopelvic ligaments may be missed when cervical injection is used. A systematic review reported that cervical injection has a higher bilateral SLN detection rate (56% vs 33%) but a lower paraaortic SLN detection rate (7% vs 27%, p=0.001), compared with uterine corpus injection[30]. A meta-analysis reported that para-aortic mapping was most frequent after uterine corpus injection (39%), follow by deep cervical injection (17%) and superficial cervical injection (2%)[36]. Compared with cervical injection, hysteroscopic injection detects 10% more para-aortic lymph node metastasis and is superior in detecting isolated para-aortic SLN (5.8% vs 0%)[38]. Bilateral cornu follow by cervical injection increases the upper para-aortic SLN detection rate from 5.7% to 38.2% and the lower para-aortic SLN detection rate from 18.7% to 67.1%, compared with cervical injection only[39]. The number of metastatic para-aortic SLN detected increases from 2.4% to 7.9% (p=0.070). Cervical injection missed five of eight para-aortic lymph node metastases, but none was missed after cornu plus cervical injection.

ICG should be injected after the induction of anaesthesia. Dissection of the retroperitoneum is

commenced once the injection is completed. It takes a median of 10 minutes to complete SLNM for each pelvis side[28]. Most SLNs are identified in the external iliac (38% to 50.2%), followed by obturator (25% to 39.8%), inframesenteric para-aortic (14%), common iliac (4.8% to 8%), internal iliac (10%), presacral (3%), infrarenal para-aortic (1% to 5.2%), and other sites (1%)[40,41].

Sentinel lymph node algorithm

The Memorial Sloan Kettering Cancer Center advocates the implementation of the SLN algorithm when performing SLNM in endometrial cancer[42]. The National Comprehensive Cancer Network recommends adoption of the SLN algorithm to ensure a low false negative rate[43]. The algorithm involves peritoneal and serosal evaluation and washings, retroperitoneal evaluation including removal of all SLNs and any suspicious nodes, and a side-specific pelvic, common iliac, and interiliac lymph node dissection if there is no mapping in a hemipelvis. A para-aortic lymphadenectomy is left to the attending surgeon's discretion[42]. This approach results in approximately 40% of patients requiring unilateral and 10% requiring bilateral complete lymphadenectomy[40]. The implementation of the algorithm with side-specific lymphadenectomy for mapping failure decreases the false negative rate of SLNM from 14.9% to 1.9% and increases the sensitivity from 85.1% to 98.1%, and NPV from 98.1% to 99.8%[42]. The use of the SLN algorithm in endometrial cancer patients after SLNM revealed a high sensitivity of 95%, NPV of 99%, and low false negative rate of 5%[36].

Frozen section of the SLN is generally not performed, owing to its cost, low sensitivity in diagnosing low volume metastasis, and potential alteration to ultrastaging of the SLN[17]. Intra-operative frozen section has a low sensitivity of 50% to 83% in identifying lymph node metastasis[44,45]. The aim of SLN removal is to guide adjuvant therapy, rather than to determine whether complete lymphadenectomy should be performed. If a SLN showed metastasis, adjuvant chemotherapy should be administered to improve survival[6].

Performance of SLNM

SLNM in endometrial cancer has a high detection rate, high sensitivity, high NPV, and low false negative rate. The FIRES trial with 340 patients receiving SLNM through cervical injection of ICG reported a detection rate of 86%, bilateral detection rate of 52%, sensitivity of 97.2%, NPV of 99.6%, and a false negative rate of 3%[40]. Early-stage low-risk cases comprised 71% of cases, and the positive lymph node rate was 12%[40]. A meta-analysis involving 4915 patients reported an overall detection rate of SLN of 81% (range, 75.4%-90.4%), bilateral pelvic node detection rate of 50% (range, 33%-74.6%), and paraaortic lymph node detection rate of 17% (range, 6.7%-26.8%)[30]. The sensitivity was 96%[30]. When early-stage low-risk endometrial cancer (with low risk of lymph node metastasis) comprises most cases, SLNM is accurate for lymph node assessment and is widely accepted as a routine procedure for staging.

In early-stage high-risk endometrial cancer, the evidence is not as strong, as the number of such cases is relatively small. In the SENTI-ENDO study in 2011 using blue dye with Tc-99m, all three false negative cases among 133 cases occurred in patients with type 2 histology. A retrospective multicentre study in 2015 that included the SENTI-ENDO cohort reported an exceedingly high false negative rate of 20% for high-risk endometrial cancer[46], raising the concern of the effectiveness of SLNM in high-risk endometrial cancer[21]. The higher risk of lymph node metastasis in high-risk cases also increases the concern of missing a metastatic case, leading to understaging and inappropriate adjuvant treatment, thereby compromising patient survival. Nonetheless, early-stage high-risk endometrial cancer was comparable with low-risk endometrial cancer in terms of sensitivity, NPV, and false negative rate of SLNM. In a prospective study that evaluated 101 patients with high-risk endometrial cancer (grade 3, serous, clear cell, carcinosarcoma) who underwent pelvic and para-aortic lymphadenectomy, the detection rate of SLN per patient was 89%, the bilateral detection rate was 58%, and the sensitivity was 95%[40]. Only one patient had bilateral negative SLN and positive non-SLNs on final pathology (false negative). In a retrospective review of 128 patients with high-risk endometrial cancer (endometrioid grade 3, serous, clear cell, carcinosarcoma, undifferentiated), the overall detection rate was 89.8% for SLN and 63.2% for bilateral SLN, the overall sensitivity was 95.8%, the NPV was 98.2%, and the false negative rate was 4.2%[47]. In the SHREC trial, a prospective study with 257 stage I-II endometrial cancer cases with adherence to the SLN algorithm, the sensitivity and NPV for lymph node involvement was 100%, with a bilateral mapping rate of 95%[48]. The SENTOR study included only early-stage high-grade endometrial cancer; all patients underwent SLNM followed by complete lymphadenectomy, with adherence to the SLN algorithm[49]. Node positive disease was found in 17% of patients; the SLN detection rate per patient was 97.4%, the bilateral detection rate was 77.6%, the sensitivity was 96%, the NPV was 99%, and the false negative rate was 4%. Only one (0.6%) patient was misclassified by the SLN

algorithm. A meta-analysis including 16 studies targeting high-grade endometrial cancer with cervical injection of ICG reported a detection rate of 91% per patient, a bilateral detection rate of 64%, with a sensitivity of 92%, NPV of 97%, and false negative rate of 8%[50]. These studies showed that in high-risk early-stage endometrial cancer, SLNM is also feasible with a high detection rate, sensitivity, NPV, and low false negative rate.

Obesity, surgeon experience, and lymphovascular space invasion decrease the detection rate of SLNM[36,51-53]. A retrospective study with 472 cases reported that cases with successful and unsuccessful mapping had a median body mass index of 29.8 kg/m^2 and 34.7 kg/m^2, respectively[53]. A meta-analysis reported that all studies with ≥100 patients had an overall detection rates of >80%, indicating the importance of surgical experience in achieving a high detection rate[36]. After the first 30 cases, the rate of successful mapping significantly increased from 77% to 94%[52]. A Korean study reported that at least 27 cases were required to achieve proficiency in SLNM[54]. The learning curve for successful bilateral mapping plateaus at around 40 cases[55]. Before competence in SLNM is achieved, an add-on completion pelvic lymphadenectomy is recommended to avoid missing any lymph node metastasis and to establish the performance and accuracy[17].

Benefit of SLNM

SLNM offers an appropriate balance between morbidity of a complete lymphadenectomy and the risk of missing lymph node metastasis. SLNM is a relatively safe procedure with no adverse events[35]. Lymphadenectomy is associated with complications such as lymphedema (37%), lymphocele (17%), lymph-ascites, and peripheral nerve injury and vessel injury[56]. The risk of lymphedema correlates with the number of lymph nodes removed, with the risk increasing from <8% with <5 lymph nodes removed to 30% to 40% with >15 lymph nodes removed[57]. The chance of infected lymphocyst also increases with the increasing number of pelvic lymph nodes removed[58]. SLNM reduces the number of lymph nodes removed, thus reducing the risk of complications. In a study comparing SLNM (n=642, 57%) with complete pelvic and para-aortic lymphadenectomy (n=493, 43%) based on clinical high-risk factors (grade 3 cancer and/or primary tumour diameter >2 cm) in two centres, the median number of lymph nodes removed was six in the SLNM group and 34 in the complete lymphadenectomy group, whereas the median number of para-aortic lymph nodes removed was 5 and 16, respectively[59]. SLN removal alone resulted in a lower incidence of leg lymphedema than complete pelvic and paraaortic lymphadenectomy (1.3% vs 18.1%, p=0.0003)[60]. In a retrospective review of 348 patients, lymphocele was found in 3.4% (n=6/178) of SLNM-only patients, compared with 14.1% (n=24/170) in the SLNM with complete lymphadenectomy group (p=0.009)[61]. Complete lymphadenectomy was the only risk factor for lymphocele in a multivariate analysis (odds ratio=3.68, p=0.009)[61]. The operative time (244 min vs 140 min), blood loss (240 mL vs 94 mL), length of hospital stay, and postoperative complication were lower in the SLN removal group than in the complete lymphadenectomy group[16,62]. A before and after study reported that adoption of SLNM decreased the mean number of pelvic lymph nodes removed (15 vs 4, p<0.0001), the mean operative time (181 min vs 137 min, p<0.0001), the estimated blood loss (80 mL vs 56 mL, p=0.004), and the rate of postoperative complications (13% vs 5.2%, p=0.04)[63]. The mean additional operative time for removal of SLN was 33 min; 91 min were saved compared with a complete pelvic and paraaortic lymphadenectomy[60]. A retrospective review of 154 endometrial cancer patients with 109 SLNM procedures reported that the adoption of SLNM spared 26 pelvic and para-aortic lymphadenectomy[64]. SLNM minimised surgical risk without compromising oncological safety, thereby improving the quality of life of patients.

SLNM increases the identification of lymph node metastatic disease, with a lower number of lymph nodes removed when compared with complete lymphadenectomy[65,66]. SLNM allows more accurate assessment of the lymph nodes status in endometrial cancer. An increase detection of lymph node involvement with SLNM is associated with an increase in detection of stage IIIC disease. In the FIRES trial, 17% of the positive SLN were found in regions outside the routine lymphadenectomy area (eg pre-sacral area) and would have been missed if SLNM was not performed[40]. Similarly, in the SENTOR trial, 26% of node positive cases were outside routine lymphadenectomy boundaries or required immunohistochemistry (IHC) for diagnosis[49]. More stage IIIC1 disease were identified in the SLNM group than the complete lymphadenectomy group (16.7% vs 7.3%)[66]. Comparing 661 endometrial cancer cases with pelvic +/- para-aortic lymphadenectomy with 119 endometrial cancer cases with SLNM + pelvic +/- para-aortic lymphadenectomy, the SLNM group had more lymph node metastasis detected (30.3% vs. 14.7%, p<0.001), more stage IIIC (30.2% vs 14.5%, p<0.001), and received more chemotherapy + radiation (28.6% vs 16.3%, p<0.003)[65]. The SLN was the only metastasis in 50% of SLNM cases with positive nodes, and the SLN false negative rate was

1/36 (2.8%)[65]. In a retrospective study on high-risk early-stage endometrial cancer, the SLNM group had more pelvic node metastases detected than the non-SLNM group (pelvic +/- para-aortic lymphadenectomy) [26.7% vs 14.3%, p=0.02] and received more adjuvant chemotherapy (48% vs 33.5%, p=0.03)[67]. In meta-analysis including 1249 (35.3%) patients with SLNM and 2287 (64.7%) patients with complete lymphadenectomy, positive pelvic nodes were detected in 184/1249 (14.7%) patients with SLNM and 228/2287 (9.9%) patients with complete lymphadenectomy (odds ratio=2.03, p=0.002). No difference in detection of positive nodes located in the paraaortic region was observed (odds ratio=93)[68]. SLN biopsy upstaged 10% of patients with low risk and 15% of those with intermediate risk endometrial cancer[21]. Patients staged with SLNM were more likely to receive adjuvant treatment[30,65], because of the higher detection rate of metastatic disease. These data indicate that SLNM is more accurate in identifying lymph node metastasis and provides better guidance to adjuvant therapy. The higher detection rate is partly due to ultrastaging. SLNM can identify lymph nodes at particular high risk of metastasis, allowing pathologist to concentrate on these smaller number of more relevant lymph nodes with ultrastaging.

Ultrastaging and low volume metastasis

Ultrastaging is a pathological technique to increase the accuracy of lymph node assessment. In the SENTOR study, 26% of node-positive cancer were identified outside traditional pelvic lymph node boundaries or required IHC for diagnosis[49]. Initial pathological examination only detects half of the lymph node metastasis, whereas ultrastaging detects the other half in the form of low volume metastasis[24,40]. There is no standardised protocol for ultrastaging and various protocols have been reported[69]. More comprehensive and exhaustive protocols do not appear to be superior in comparative studies[69,70]. In essence, it involves performing more serial sections of the negative SLN and the use of IHC for cytokeratin rather than only haematoxylin and eosin (H&E) staining. In the FIRES trial, SLN were cut at 3-mm intervals, in a bread loaf fashion, or bivalved if <1.5 cm. Two paraffin embedded slides were created from each section, 50 um apart. One slide was stained for H&E and the other for IHC if no metastatic disease was found on the H&E slide[40]. Ultrastaging picks up low volume metastasis, which is not detected by routine histology, thereby increasing detection of lymph node metastasis. Similar to axillary SLN of breast cancers, macrometastasis is defined as foci of metastasis of >2 mm. Low volume metastasis includes micrometastasis, which is defined as metastasis of 0.2-2 mm, and isolated tumour cells (ITC), which is defined as foci of metastasis <0.2 mm or cells stained positive for cytokeratins[40]. IHC and serial sectioning were shown to detect metastases undiagnosed by conventional histology in 8% patients with detected SLN, representing 47% of metastases[21]. In a retrospective study with 26 lymph node metastases identified, 46.2% were macrometastases, 23.1% were micrometastases, and 30.7% were ITCs[24]. In the FIRES trial, 54% of positive lymph nodes are micrometastasis or ITC[40]. Among the low volume metastasis cases, 47% were micrometastases and 53% were ITCs. In high-risk early-stage endometrial cancers, 40% of positive SLN were detected only after IHC[67]. The risk of ITC increases with depth of myometrial invasion: 25% for deeply invasive grade 1/2 and 18% for deeply invasive grade 3 tumours[71]. The clinical implications of micrometastasis and ITC are yet to be determined. Excellent prognosis of ITC patients after receiving adjuvant therapy was demonstrated: the PFS at 3 years was 95.5%, similar to node negative patients (87.6%) and micrometastasis patients (85.5%), and better than patients with macrometastasis (58.5%)[72]. The survival rate was comparable between those with node negative disease and those with micrometastasis treated with adjuvant chemotherapy, but the survival rate was worse for those with micrometastasis without adjuvant therapy[73]. This supports the need of adjuvant therapy for micrometastasis. However, the benefit of adjuvant therapy for ITC is not proven. ITC is not considered as stage IIIC disease but should be noted on staging. The National Comprehensive Cancer Network recommends to designate ITC as stage pN0 (i+)[43]. In a world-wide survey of gynae-oncologists in 2019, 52% recommended adjuvant therapy if micrometastases were detected, but only 13.8% recommended adjuvant therapy for ITC[10]. Further studies are required to clarify the impact of low volume metastasis on prognosis and whether adjuvant therapy should be given.

Oncological safety of SLNM

The decrease in radicality of surgery with SLNM does not compromise oncological safety in terms of OS and PFS[66,74,75]. The long-term results of the SENTI-ENDO study with a median follow-up of 50 months and 14.4% rate of recurrence, the 50 months recurrence-free survival (RFS) was 84.7%, with no difference between patients with and without detected SLN (p=0.09)[76]. In 802 patients with preoperative stage 1 endometrial cancer, positive pelvic lymph nodes were found in 16.7% of patients who underwent surgical staging by SLNM +/- complete lymphadenectomy and in 7.3% of patients who underwent complete lymphadenectomy (p=0.002)[66]. Three-year

disease-free survival was 90.4% in the SLNM group and 89.6% in the complete lymphadenectomy group.

No difference in survival was found in patients with uterine serous carcinoma undergoing SLNM alone versus complete lymphadenectomy. In a retrospective study involving 245 cases with 60.1% of stage I or II cases, the 2-year OS was 96.6% in the SLNM and 89.6% in the complete lymphadenectomy group (p=0.8), whereas the 2-year OS in those with stage III disease was 73.6% in the SLNM group and 77.3% in the complete lymphadenectomy group (p=0.8)[77].

In a multi-institutional retrospective study evaluating long-term outcomes (≥3 years) of endometrial cancer patients who underwent (1) complete lymphadenectomy, (2) SLNM followed by lymphadenectomy, or (3) SLNM alone, the three groups were comparable in terms of DFS and OS[78]. The treatment strategies did not affect survival outcomes after stratification into low-, intermediate-, and high- risk patients.

In addition, the recurrence rate was comparable after SLNM or complete lymphadenectomy. In a retrospective study with 279 patients (103 with no lymphadenectomy, 118 with SLN removal, 59 with pelvic +/- para-aortic lymphadenectomy), the risk of recurrence was comparable after complete lymphadenectomy or SLN removal[59]. In a meta-analysis including 1249 (35.3%) patients with SLNM and 2287 (64.7%) patients with lymphadenectomy, the overall recurrence rate was 4.3% and 7.3%, and the nodal recurrence rate was 1.2% and 1.7%, respectively[68].

Some studies reported an improvement in survival with SLNM. In a retrospective study with 472 consecutive patients with endometrial cancer who underwent either SLNM and complete lymphadenectomy (n=275) or complete lymphadenectomy (n=197) from sequential, non-overlapping historical time points, there was no significant difference in overall RFS between the two groups at 48 months[79]. Patients with SLNM and complete lymphadenectomy had a reduced recurrence rate in the pelvic sidewall (30% vs 71.4%) and thus improved RFS (hazard ratio=0.32)[79]. Similarly, in a study with 193 patients with complete lymphadenectomy and 250 patients with SLNM and completion lymphadenectomy after a median follow-up period of 6.9 years, the addition of SLNM was associated with improved 6-year OS (90% vs 81%, p=0.009), improved 6-year PFS (85% vs 75%, p=0.01), and improved 6-year RFS (95% vs 90%, p=0.04)[80]. This improvement in survival may be due to the more accurate lymph node assessment by SLNM and ultrastaging, thus allowing more accurate provision of adjuvant therapy.

The comparison on oncological safety is hindered and complicated by the fact that only a small number of studies compared SLNM only with complete lymphadenectomy, while most studies compared SLNM and completion lymphadenectomy with complete lymphadenectomy only, particularly for high-risk early-stage endometrial cancer. Moreover, para-aortic lymphadenectomy is not performed in many of the studies. The survival comparison is also affected by the imbalance of adjuvant therapy given and the lack of prospective study and long-term follow-up. Nonetheless, studies are supportive of SLNM, with a similar survival rate but lower morbidity. Both the International Federation of Gynecology and Obstetrics and the National Comprehensive Cancer Network supported the use of SLNM with adherence to the SLN algorithm in early-stage endometrial cancer[33] and in high-risk early-stage endometrial cancer[81], although 66% of gynae-oncological surgeons among 69 countries self-reported to perform a backup lymphadenectomy in high-risk patients[10].

Non-SLN metastasis

There are concerns over non-SLN metastasis that are not removed when the SLN algorithm is adopted. In a study with 268 endometrial cancer treated with SLNM and lymphadenectomy, 16% of patients were found to have SLN metastasis, and non-SLN metastases were found in 34.8% of patients with positive SLN[82]. In cases of low volume metastasis, the risk of having another positive lymph node was only 5%[82]. A prospective study with 200 cases reported a 40% rate of non-SLN metastasis[83]. Lymph nodes should be inspected carefully intra-operatively, and strict adherence to the SLN algorithm with removal of macroscopically suspicious lymph nodes should be performed. Theoretically, non-macroscopic metastasis can be controlled with adjuvant therapy[6]. A retrospective study comparing SLNM only with SLNM plus backup lymphadenectomy reported that backup lymphadenectomy removed 11% non-SLN metastasis but had no impact on survival[84]. However, further studies are required to clarify the optimal strategy to tackle non-SLN metastasis. The role of repeat surgery to remove the remaining lymph nodes that are not macroscopically involved is doubtful, because adjuvant chemotherapy can treat the non-SLN metastasis and repeat surgery carries surgical risk and delays chemotherapy administration.

Para-aortic lymph node disease

The SLN algorithm leaves the decision of whether to perform para-aortic lymphadenectomy to the surgeons' discretion. The risk of para-aortic metastasis is as high as 51% in the presence of pelvic lymph node metastasis[85]. In cases where pelvic SLN is positive but para-aortic lymphadenectomy has not been performed, adjuvant chemotherapy for positive pelvic SLN can theoretically treat the microscopic para-aortic metastasis, assuming macroscopic para-aortic metastasis has been removed according to the SLN algorithm. However, the SLN algorithm can miss the rare occurrence of isolated para-aortic metastasis, in which the para-aortic lymph nodes are positive when the pelvic lymph nodes are negative for metastasis[34]. In the MSKCC data when SLNM is a routine procedure for both low-risk and high-risk early-stage endometrial cancer, only one among 498 patients had an isolated positive right paraaortic lymph node with a negative ipsilateral SLN and pelvic lymphadenectomy[42]. In the FIRES trial with 66% of low-risk stage 1A endometrial cancer, isolated para-aortic metastases were reported in 0.5% of cases[40]. Even in high-risk endometrial cancer with higher risk of lymph node metastasis, the SHREC trial reported isolated para-aortic metastases in only 1% of patients[48]. A literature review reported a 1.5% incidence of isolated para-aortic lymph node metastasis in endometrial cancer[86]. Failure to identify para-aortic metastasis in a negative pelvic lymph node patient may lead to the failure to administer appropriate adjuvant therapy. SLNM can increase the detection rate of pelvic lymph node metastasis by ultrastaging and can decrease the prevalence of isolated para-aortic metastases[87]. In a study with 236 high-risk cases, 3.5% in the non-SLN group had isolated para-aortic node metastases versus none in the SLNM group[67]. However, the sensitivity, NPV, and false negative rate of SLNM for para-aortic disease were not described. Preoperative imaging and para-aortic lymphadenectomy based on clinical risk factors should be performed to mitigate the problem of isolated para-aortic metastasis. Para-aortic lymphadenectomy should be performed in cases of macroscopically enlarged lymph nodes, high-risk histology, deep myometrial invasion, and suspicious nodes on imaging[17].

Conclusion

SLNM with adherence to the SLN algorithm provides an effective option for lymph node assessment in endometrial cancer, balancing the morbidity of complete lymphadenectomy with the risk of missing lymph node involvement. SLNM is considered a routine practice in low-risk early-stage endometrial cancer, allowing accurate staging while decreasing morbidity. Recent evidence suggests similar staging performance in high-risk early-stage endometrial cancer, making SLNM an reasonable alternative in high-risk endometrial cancer. Further prospective studies with long-term follow-up comparing SLNM only with complete lymphadenectomy in high-risk endometrial cancer are required. The role of para-aortic lymphadenectomy and optimal therapy for low volume metastasis also warrant further investigations.

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Designated antenatal clinic for pregnant women with COVID in the fifth wave of pandemic

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We report our experience in setting up a designated antenatal clinic in the Kowloon East Cluster during the fifth wave of COVID pandemic for infected pregnant women.

Keywords: COVID-19; Pregnancy; Prenatal care

Background

In Hong Kong, the fifth wave of the COVID pandemic started in January 2022. In the first 2 weeks of February, there were 12 344 positive cases (94 imported and 12 250 local cases)[1]. A high proportion of cases involved pregnant women, as the vaccination rate among pregnant women was lower than that in the adult population, owing to unfounded concerns about the safety of vaccination during pregnancy. According to the survey conducted in our unit from 16 August 2021 to 15 October 2021, 87.6% of 816 pregnant women who attended our antenatal clinic did not have any COVID vaccination, and only 1.7% of them would consider having vaccination during pregnancy[2]. Between 6 January and 21 March 2022, the fifth wave resulted in 1 049 959 confirmed cases and 5906 COVID-19–associated deaths[3]. The proportion of pregnant women in confirmed cases is not known, as pregnancy status is not a parameter in the Department of Health statistics.

Need for a designated antenatal clinic

In early February, increasingly more pregnant women with confirmed COVID were unable to attend antenatal visits as scheduled. Our initial tactic was to postpone the date of antenatal visits until they recovered and until they passed the quarantine period of 14 days from the onset of symptoms if they were unvaccinated, or 7 days from the onset of symptoms if they completed two doses of vaccination. However, most of them had not completed vaccination, and the postponement of antenatal visits for 14 days was clinically risky, if not unfeasible, particularly for women in late third trimester. Even routine checking of blood pressure and urine albumin for signs of pre-eclampsia or checking the symphysis fundal height for signs of fetal intrauterine growth restriction could not be provided for these women with COVID infection. In addition, many infected women were concerned about fetal wellbeing. Some women complained of decreased fetal movement, which we could not disregard without proper assessment. Some obstetric units provide tele-consultation for such women. Nonetheless, assessment of blood pressure, urine albumin, symphysis fundal height, and fetal heart rate cannot be provided through tele-consultation.

Some infected women attended the accident and emergency (A&E) department for decreased fetal movement or other concerns about fetal well-being. However, the A&E department was already overwhelmed by infected patients, particularly elderly patients with severe symptoms. Many were put in camp beds in temporary tents or in the underground corridors between two main clinical buildings. Two of our obstetric and gynaecological wards were converted to COVID-enhanced surveillance wards, and thus admitting these women presenting at the A&E department was practically impossible. To reduce unnecessary admissions, we advised our A&E colleagues to call the on-call obstetric residents to assess these women directly in the A&E department. However, equipment such as cardiotocography and ultrasonography machines with obstetric biometry could not be transported to the A&E department owing to a lack of space. Occasionally, the on-call obstetric team was engaged in emergency operations

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and hence a long wait for these women. After the first week of disarray, a proposal was made to set up a designated antenatal clinic for infected pregnant women within the Kowloon East Cluster to ensure maternal and fetal safety and to relieve the pressure of A&E department.

Place for the designated antenatal clinic

A suitable place for the designated antenatal clinic should provide a 'quarantined' route to enter into our hospital and antenatal clinic without risks of cross-infection to other non-infected patients and staff.

On 16 February 2022, the Hospital Authority designated seven general out-patient clinics (in Shau Kei Wan, Kennedy Town, San Po Kong, Kowloon Bay, Kwai Chung, Sha Tin, and Tin Shui Wai) for confirmed COVID-19 patients, as the number of confirmed cases overwhelmed the capacity of isolation facilities of public hospitals and the community treatment and isolation facilities. On 15 March 2022, the number of designated clinics gradually increased to 23 at the peak of the fifth wave. Dr Pang Fai CHAN, Chief of Service of the Department of Family Medicine and Primary Healthcare in the Kowloon East Cluster was aware of our difficulty in finding a suitable place. After further discussion, the designated antenatal clinic was set up at the Kowloon Bay Health Centre General Out-patient Clinic on 23 February 2022.

Appointment and triage in the designated antenatal clinic

There was one consultation session every Wednesday morning. Further sessions would be added if the number of infected pregnant women increased exponentially. Fortunately, the number of infected cases started to fall from its peak in late March.

Pregnant women booked in Kowloon East Cluster and infected with COVID were diverted to two designated midwives who contacted the women by phone to gather further clinical details, including date of onset of COVID symptoms, the date of diagnosis of COVID-19, vaccination status, specific COVID symptoms, pregnancy symptoms such as vaginal bleeding, decreased fetal movement, results of most recent antenatal assessment, and the scheduled date of next follow-up. Patients with severe COVID symptoms such as high fever and shortness of breath were advised to attend A&E department. A consultant of maternal fetal medicine in charge of the designated antenatal clinic reviewed the clinical details and the ARS for any antenatal risk factors, pre-existing medical problems such as hypertension, or any on-going obstetric problems that need close surveillance. If a patient had pregnancy symptoms or specific concerns, the consultant would contact the patient by phone to determine whether admission was needed. For those with mild and non-urgent symptoms, appointment was arranged within the next few days. For those without symptoms or concerns, appointment would depend on gestation and findings of the most recent antenatal assessment. For those due for an antenatal check, appointment would be arranged accordingly. Antenatal appointments may be arranged in the usual antenatal clinic after the patient was taken off isolation. For example, a low-risk woman with 37-week gestation who had her last antenatal visit at 35 weeks would be arranged an appointment at the designated antenatal clinic as soon as possible, whereas a woman at 22-week gestation with her last antenatal visit at 20-week gestation would be followed up in the usual antenatal clinic after she recovered from COVID and passed the quarantine period. Based on the triage by the consultant, the midwives would inform the women the date and place for the antenatal follow-up as appropriate. Doctors in the Kowloon Bay designated clinic can also refer pregnant women to our designated antenatal clinic for obstetric assessment. Referrals from private sector was allowed, as pregnant women were unable to seek consultations from private sector once confirmed with COVID infection.

Staff and equipment in the designated antenatal clinic

The designated antenatal clinic has access to the Clinical Management System (CMS) and Antenatal Record System (ARS) of the Kowloon East Cluster. Patient registration and future appointment booking can be done through the CMS. Laboratory tests can be ordered as usual, and results can be traced directly from the CMS. Consultation notes can be entered into the ARS via the CMS.

Ultrasonography and cardiotocography machines, and single-use speculums were transferred to the designated antenatal clinic (Figure). Blood tests for complete blood picture, liver and renal functions and high vaginal swabs can be ordered. Group B streptococcus culture bottles were not available, as a refrigerator for storage is needed and the expiry date for the bottles is short. The bottles were brought to the designated clinic every week by the attending doctor for Group B streptococcus screening at the appropriate gestation to prepare for delivery. Simple medications such as paracetamol and cough mixtures can be prescribed through the CMS.

Figure. The designated antenatal consultation room is equipped with cardiotocography and ultrasonography machines and has access to the Clinical Management System

The nursing staff checked the blood pressure, urine albumin, and sugar levels of pregnant women. The consultant then performed routine antenatal care, ultrasound scanning (for fetal viability, preliminary fetal morphology, and fetal growth), and cardiotocography (if necessary). To minimise the number of staff exposed to infected patients, the consultation room is manned by one consultant without any supporting nursing staff, as the consultant can provide comprehensive antenatal care and can handle all clinical scenarios independently without any backup. This minimises the need for referring patients back to the hospital.

Experience in the designated antenatal clinic

The designated antenatal clinic has operated smoothly since the fifth wave of the COVID pandemic. The only difference from the usual antenatal clinic is the need to wear a full set of personal protective equipment and performing all clinical assessments without any nursing support. Fortunately, the number of patients attending the designated clinic has not been overwhelming.

The designated antenatal clinic has been welcomed by those who attended it. They were satisfied that routine antenatal care was catered for, concerns were addressed, and fetal wellbeing was reassured. We encountered women who previously had antenatal care in private sector but were turned down once confirmed COVID positive. In their desperation to seek medical care, they attended the general designated clinic and were referred to our designated antenatal clinic. We also encountered patients in early pregnancy (as early as 6-week gestation) complaining of threatened miscarriage who normally would have attended a private gynaecologist or regular early pregnancy assessment clinic. As these options were not feasible once they were confirmed COVID positive, they attended the general designated clinic and were referred to our designated antenatal clinic. With ultrasound scanning, a viable intrauterine pregnancy can be confirmed at the first consultation. This avoids the need to refer patients to the A&E department during the fifth wave. In addition, the settings of the designated clinic enable assessment of near-term patients in details and scheduling admissions for elective induction of labour or elective caesarean sections immediately after completion of 14-day isolation period.

Conclusion

Setting up the designated antenatal clinic during the peak of the fifth wave of COVID pandemic has been beneficial to all stakeholders, particularly women infected with COVID who are desperate to seek medical care amidst uncertainties. Consultation at the designated antenatal clinic is similar to that in usual obstetric clinics. With education on safety of COVID vaccination during pregnancy and increased uptake of vaccination by pregnant women, the number of infected pregnant women is expected to be lower. Nevertheless, with the possibility of emergence of new strains, we suggest that the obstetrics and gynaecology department of each cluster to consider setting up a designated antenatal clinic in case of occurrence of the sixth wave or an outbreak of other infectious diseases in future.

Contributors

CW Kong designed the manuscript. CW Kong, KY Chan, and WY Shiu drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors contributed to the manuscript, approved

the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, CW Kong and WWK To were not involved in the peer review process of this article. All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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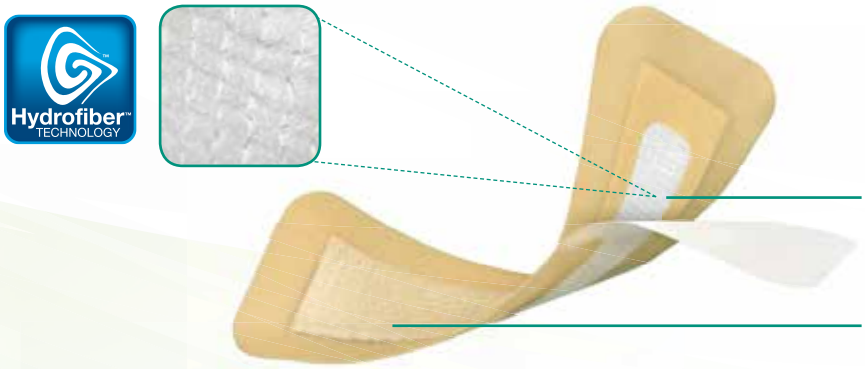

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† As demonstrated *in vitro*.

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