HONG KONG JOURNAL

OF

GYNAECOLOGY, OBSTETRICS & MIDWIFERY

January 2020, Volume 20, Number 1

EDITORIAL

ORIGINAL ARTICLES (OBSTETRICS)

ORIGINAL ARTICLES (GYNAECOLOGY)

REVIEW ARTICLES

Wyeth® | Nutrition
SCIENCE CENTER

How much DHA should we eat?

Docosahexaenoic acid (DHA) is a long-chain polyunsaturated omega-3 fatty acid that is important for health[1]. Although human bodies can naturally make DHA from alpha-linolenic acid (ALA), it is very limited and it is critical to include foods rich in DHA in daily diet[1]. DHA is commonly found in fish and seafood[1,2], and the British Dietetic Association recommends that **everyone should consume 2 portions of fish every week** and oily fish (e.g. salmon) should be one of them (Table 1)[3].

Table 1 - Guideline on portion size[3]

Age	One portion size
18 months to 3 years	¼ - ¾ small fillet or 1 - 3 tablespoons
4 to 6 years	½ - 1 small fillet or 2 - 4 tablespoons
7 to 11 years	1 - 1 ½ small fillet or 3 - 5 tablespoons
12 years to adults	140 g (5 oz) fresh fish

"King mackerel, shark, swordfish and tilefish are rich in omega-3s, but contain higher levels of mercury and should be avoided" [4]

Different food sources of DHA and the Chinese dietary recommended intake (DRI)

DHA content in different food sources[5]

Food	DHA content (mg per 100 g of food)
Cooked salmon	1430
Cooked blue mussels	510
Cooked cod fish	150
Cooked egg	40
Cooked chicken feet	40
Cooked pork liver	30
Avocado	0
Whole milk	0

2013 Chinese DRI[6]

Life stages	DHA (mg/day)
0 - < 4 years	100
4 - 80 years	Not determined
Pregnant women	200
Lactating women	200

Remark: WHO advises adults should intake 250 mg of DHA and eicosapentaenoic acid (EPA) daily[7]

Emerging evidence implicates the potential influences of maternal DHA supplementation on early preterm birth (< 34 weeks of gestation)[8,9]. **European experts stated that higher DHA intake (600 - 800 mg) during pregnancy may provide greater protection against early preterm birth[10].**

Visit now to read more nutritional information!

https://hongkong.wyethnutritionsc.org

Wyeth Nutrition Science Center HK

References: *1. The Dietitians of Canada. Food sources of omega-3 fats. 2013. 2. Wen XX et al. Food Sci. 2010;31(21):446-450. 3. The British Dietetic Association (BDA). Omega-3. 2014. 4. The Academy of Nutrition and Dietetics. Safe sources of omega-3 fats for pregnant women. 2013. 5. USDA National Nutrient Database for Standard Reference Release 28. 6. Chinese Nutrition Society. Chinese DRIs Handbook. 2013. 7. FAO/WHO. FAO Food and Nutrition Paper 91. Fats and fatty acids in human nutrition – Report of an expert consultation. Geneva. November 2008. 8. Carlson SE et al. Am J Clin Nutr. 2013;97(4):808-815. 9. Pietrantoni E et al. Int J Mol Sci. 2014;15(5):8024-8036. 10. Koletzko B et al. Ann Nutr Metab. 2014;65(1):49-80.*

OLYMPUS®

BEYOND VISION

VISERA ELITE II

All-in-one design

3D Laparoscopy

IR observation

HKJGOM

EDITORIAL BOARD

Address for Submission of Manuscripts and Correspondence to Editors:

(Gynaecology and Obstetrics Section)
c/o Department of Obstetrics and Gynaecology
United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Hong Kong SAR, China
Tel: 3939 4851 Fax: 3949 5535 E-mail: towkw@ha.org.hk

(Midwifery Section)
Hong Kong Midwives Association
D1, 13/F, Hyde Centre, 223 Gloucester Road, Wanchai, Hong Kong
Tel: 2893 8800 Fax: 2572 5329 E-mail: midwives@netvigator.com

Address for Advertising & Subscription Enquiries:

The Obstetrical and Gynaecological Society of Hong Kong
Duke of Windsor Social Service Building, 4/F, 15 Hennessy Road, Hong Kong
Dr. KY Leung E-mail: leungky1@ha.org.hk
Dr. Danny TN Leung E-mail: dannytnleung@gmail.com
Dr. Dominic FH Li E-mail: dfhli@hkstar.com

HKJGOM

INSTRUCTIONS TO AUTHORS

The *Hong Kong Journal of Gynaecology, Obstetrics & Midwifery* publishes peer-reviewed articles on all aspects of gynaecology, obstetrics, midwifery and related fields, including original basic and clinical studies, review articles, case reports and abstracts or reports presented at scientific meetings or seminars.

Manuscripts submitted to this Journal must not be under simultaneous consideration by any other publication and should not have been published elsewhere in substantially similar form. A letter confirming the transfer of copyright to the Journal signed by all authors should accompany all submitted papers.

Manuscript Preparation

Manuscripts must be submitted in English or Chinese in an electronic format. This applies to all parts of the manuscript, i.e. references, legends, figures, illustrations etc. Liberal margins should be left at all edges. The manuscript should be submitted in the following order: Title Page, Abstract, Text, References, Tables, Legends, and Figures. Each page, beginning with the summary, should also include the senior author's surname in the upper left-hand corner. The author should not make any changes in the proofs except for the correction of editorial errors, if any, and/or correction of typesetter's errors. A commercial name should not be part of a manuscript title. If a trademark item is named, the name(s) and address(es) of the manufacturer(s) or supplier(s), in addition to the generic name, should be footnoted. Authors should make no claims of priority in their manuscripts.

Title Page

- Include full name(s), degree(s) and affiliations(s) of author(s): list under file
- Give a running title of 3 to 6 words
- At the bottom of the page, include information about grants, if applicable, and any conflicts of interest
- Add "Correspondence to: …", followed by full name, address, telephone and fax numbers, e-mail

Abstract

- The abstract should be after the title page and numbered page 1
- It should not exceed 250 words for major articles; case reports should have an abstract of no more than 100 words
- At the end of the abstract, provide a maximum of 6 key words suitable for indexing
- Abbreviations should be kept to a minimum and must be explained when they first appear; after first use, abbreviations alone may be used
- Standard abbreviations should be used for all measurements (SI units)

Text

- The text should follow the abstract and begin on a new page, as should references, tables and legends
- Abbreviations not defined in the abstract should be explained when they first appear in the text
- References should be cited in numerical order, as should tables and figures

References

- Number the references in the order they appear in the text
- Abbreviate titles of periodicals according to the style of *Index Medicus*. Follow the format (arrangement, punctuation) shown below:

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.

Abstract

4. Same as Periodicals and followed by (Abstract)

Tables

- Tables should supplement, but not duplicate, the text
- Tables should be numbered consecutively in their order of appearance in the text
- Each table must be given an Arabic numeral and a title, placed at the top of the page
- Abbreviations used in the table should be footnoted and explained in the order they appear in the table
- Any material which is not self-explanatory should be footnoted

Legends

- Be sure that legends and figures correspond
- Identify all abbreviations used in a figure at the end of each legend, if the abbreviation has not been used in the text
- Be sure abbreviations used for measurements are standard

Figures

- Submit written permission from publisher(s) for any figure which has been published elsewhere
- Do not send original art-work, X-rays, or CTGs
- Photographs in which a patient or other person is identifiable must have written permission from that person. The consent must state specifically what the person is consenting to and what restrictions, if any, the person has placed on the publication of the photograph; all restrictions must be strictly observed
- Colour illustrations will be charged to the author. Authors should inquire about cost from the publisher before submitting a colour illustration

Ethics

Published studies on humans should indicate the nature of consent and the approval of the institutional ethics committee. In reports of animal experiments, ethical approval must be enclosed.

Reprints

Reprints are available at authors' expense. Ordering information can be obtained from the Publisher.

96287003 TP 62 1.0 07/2018/P-E

IMAGE1 S™ – mORe than a camera

- High resolution camera system for universal use
- Optimal visibility conditions due to enhanced colour space, large depth of field and homogeneous illumination
- Greater richness of detail thanks to 4K resolution and enhanced image data processing
- Perfectly integrated peripheral units ensure the ideal image chain
- Maximum adaptability to all requirements through modular technologies (rigid and flexible endoscopy, 3D, ICG, PDD etc.)

STORZ
KARL STORZ — ENDOSKOPE
THE DIAMOND STANDARD

www.karlstorz.com

boostrix

Tetanus Toxoid, Reduced Diphtheria Toxoid & Acellular Pertussis Vaccine, Absorbed

THE ONLY Tdap vaccine with prospective pregnancy safety data on label.[1-2*]

Tdap = Tetanus toxoid, reduced diphtheria toxoid & acellular pertussis

The highest burden of pertussis is recognized in **young vulnerable infants** before completion of the primary vaccine series.[3-4]

Pertussis immunization during pregnancy is recommended by **WHO, CDC and ACOG**.[5-7]

Use of Boostrix may be considered during the third trimester of pregnancy.[1]

Safety Information:[1]

Boostrix is for deep intramuscular injection, preferably in the deltoid region. The vaccine should not be administered to subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines.

WHO = World Health Organization; CDC = Centers For Disease Control and Prevention; ACOG =American College of Obstetricians and Gynecologists * In Hong Kong Market, as of Nov 2018

Reference:

1. Boostrix Hong Kong Full Prescribing Information 2018. 2. Sanofi Tdap Hong Kong Full Prescribing Information 2017. 3. CDC. Pertussis - Clinical Complications 2015. Available at: https://www.cdc.gov/ pertussis/clinical/complications.html (accessed Nov 2016). 4. De Serres G, et al. Journal of Infectious Diseases 2000;182:174-179. 5. ACOG Committee Opinion. Update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination. Number 718, September 2017. [accessed June 2018]; Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Immunization-Infectious-Disease-and-Public-Health-Preparedness-Expert-Work-Group/MaternalImmunization 6. CDC. Pregnancy and Whooping Cough. Vaccinating pregnant patients. [accessed June 2018]; Available at: https://www.cdc.gov/pertussis/pregnant/hcp/pregnant-patients.html 7. WHO. Pertussis vaccines: WHO position paper. Weekly epidemiological record. 2015;90(35):433-458.

Abbreviated Prescribing Information

Name of the Medicinal Product: *Boostrix*. **Qualitative and Quantitative Composition:** 1 dose (0.5 ml) contains not less than 2 IU diphtheria toxoid, not less than 20 IU of tetanus toxoid, 8 mcg of pertussis toxoid, 8 mcg of filamentous haemagglutinin, 2.5 mcg of pertactin, adsorbed on aluminium hydroxide, hydrated and aluminium phosphate. **Indications:** *Boostrix* is indicated for booster vaccination against diphtheria, tetanus and pertussis of individuals from the age of four years onwards. **Posology and Administration:** A single 0.5 ml dose of the vaccine is recommended. The use of *Boostrix* may be considered during the third trimester of pregnancy. ***Method of administration:*** *Boostrix* is for deep intramuscular injection, preferably in the deltoid region. **Contraindications:** *Boostrix* should not be administered to subjects with known hypersensitivity to any component of the vaccine or to subjects having shown signs of hypersensitivity after previous administration of diphtheria, tetanus or pertussis vaccines. *Boostrix* is contraindicated if the subject has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis-containing vaccine. As with other vaccines, administration of *Boostrix* should be postponed in subjects suffering from acute severe febrile illness **Special Warnings and Precautions for Use:** If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give doses of pertussis-containing vaccines should be carefully considered: temperature of ≥ 40.0°C within 48 hours of vaccination, not due to another identifiable cause; collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination; persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination; convulsions with or without fever, occurring within 3 days of vaccination. *Boostrix* should under no circumstances be administered intravenously. As for any vaccination, the risk-benefit of immunising with *Boostrix* or deferring this vaccination should be weighed carefully in a child suffering from a new onset or progression of a severe neurological disorder. Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints. As with any vaccine, a protective immune response may not be elicited in all vaccinees. **Interactions:** If *Boostrix* is to be given at the same time as another injectable vaccine or immunoglobulin, the products should always be administered at different sites **Fertility, pregnancy and Lactation:** ***Pregnancy:*** The use of *Boostrix* may be considered during the third trimester of pregnancy. Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with *Boostrix* during pregnancy. The clinical relevance of this observation is unknown. ***Breastfeeding:*** The effect of administration of *Boostrix* during lactation has not been assessed. Nevertheless, as *Boostrix* contains toxoids or inactivated antigens, no risk to the breastfed infant should be expected. The benefits versus the risk of administering *Boostrix* to breastfeeding women should carefully be evaluated by the health-care providers. **Adverse Reactions:** ***Clinical Trial Data:*** Children from 4 to 9 years of age upper respiratory tract infection; anorexia; irritability; somnolence, headache and disturbances in attention; conjunctivitis; diarrhoea, vomiting, gastrointestinal disorders; rash; injection site reactions (including pain, redness and swelling), fatigue, fever ≥ 37.5 °C (including fever > 39 °C), other injection site reactions (such as induration) and pain. Adults, adolescents and children from the age of 10 years onwards: upper respiratory tract infection, pharyngitis; lymphadenopathy; headache, dizziness, syncope; cough; nausea, gastrointestinal disorders, diarrhoea, vomiting; hyperhidrosis, pruritus, rash; arthralgia, myalgia, joint stiffness, musculoskeletal stiffness; injection site reactions (including pain, redness and swelling), fatigue, malaise, fever ≥ 37.5°C, injection site reactions (such as injection site mass and injection site abscess sterile), fever > 39 °C, influenza like illness and pain. Data on 146 subjects suggests a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedules in adults (>40 years of age). Subjects fully primed with 4 doses of DTPw followed by a *Boostrix* dose around 10 years of age show an increase of local reactogenicity after an additional *Boostrix* dose administered 10 years later. ***Post Marketing Data:*** Angioedema, allergic reactions, including anaphylactic and anaphylactoid reactions, convulsions (with or without fever), urticaria, extensive swelling of the vaccinated limb, asthenia. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. Abbreviated Prescribing Information prepared in Oct 2018 based on version GDS09/IPI10.

Please read the full prescribing information prior to administration. For adverse events reporting, please call GlaxoSmithKline Limited at 90462498.

This material is for the reference and use by healthcare professionals only.

HKRX/BOO/0004/18b (11/2020) Date of preparation: 10/12/2018

GlaxoSmithKline Limited
23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong
Tel: (852) 3189 8989 Fax: (852) 2506 1378 GSKPro.com

Subscriptions

The *Hong Kong Journal of Gynaecology, Obstetrics & Midwifery* is distributed free to members of the Obstetrical & Gynaecological Society of Hong Kong and the Hong Kong Midwives Association as part of their membership. Subscription is HK$200/year for Hong Kong delivery and US$50/year for airmail delivery outside Hong Kong.

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):9-10 | https://doi.org/10.12809/hkjgom.20.1.00

Editorial
Gynaecological care for sexual minority women

Sexual minority women (SMW) are those whose sexual identity, orientation, or practices differ from the majority in the society. SMW can be lesbians, bisexuals, queers, those who have other non-heterosexual identities, or those who have same-gender partners. They may display a range of gender expressions, from very masculine to very feminine. Many SMW encounter barriers to healthcare because of their concerns about confidentiality, discrimination, labelling, or embarrassment on disclosure of their sexual orientation. Thus, they either do not seek medical care or hide their sexual orientation when they attend sexual health-related medical services. SMW have infrequent use of sexual and reproductive health services, including cervical cancer screening, sexually transmitted infection screening, and contraceptive use[1,2].

Sexual health is an important component of women's health care that most gynaecologists are less familiar with. I vividly remember a 42-year-old woman presenting with a 10-year history of painful sex, which developed after a fourth-degree perineal tear during her delivery at the age of 30 years. Despite seeing numerous gynaecologists, her pain persisted and resulted in infrequent and unsuccessful coitus, which she believed was the cause of her marital discord and putting her on the verge of divorce. Although studies have shown that women with obstetric anal sphincter injuries are associated with long-term sexual dysfunction and avoidance of intercourse[3,4], it was difficult to determine whether earlier provision of appropriate sexual counselling to this woman could have relieved her from sexual and marital difficulties. Nevertheless, there is no doubt that her sexual difficulties had never been optimally addressed by any healthcare providers whom she had encountered. Some gynaecologists may feel uncomfortable to care for women with sexual issues and may avoid treating such patients or refer them to sexual therapists, who are mostly non-gynaecologists.

Between 2017 and 2018, I participated in a Sex Therapy Professional Certification Course organised by the Hong Kong Association of Sexuality Educators, Researchers and Therapists, the only structured course on sexual therapy available locally. In Hong Kong, there is no formal registration or accreditation for any healthcare providers to be sex therapists. Nonetheless, I encourage practicing gynaecologists to acquire basic knowledge on sexual medicine, so that they can identify and provide basic help to women with sexual difficulties. During this Certification Course, health issues in relation to SMW were discussed. I encountered SMW and professionals who provided care and realised that basic women's health services are inaccessible for many SMW.

Gynaecologists should be prepared to care for individuals with gender dysphoria (female-to-male transgender) for gender reassignment hysterectomies, with or without salpingo-oophorectomies. The two hysterectomies that I have recently performed for this reason have broadened my clinical experience in caring for these individuals. Some aspects of care are exemplified as follows:

1. Healthcare providers should be familiar with the standards of care for the health of transgender individuals, especially on the assessment and preparation (includes counselling for informed consent) for gender reassignment surgery. Interested readers can refer to the Standard of Care Guidelines published by the World Professional Association for Transgender Health[5].

2. Clinics and hospital wards should create an appropriate and non-discriminatory environment by increasing the knowledge, understanding, and sensitivity of their staff towards transgender individuals.

3. Long-term testosterone therapy is associated with an increased risk of polycythaemia, but the evidence regarding its role on thromboembolic events is inconclusive[6]. There is also limited evidence that the use of exogenous testosterone is associated with an increased risk of venous thromboembolism or other complications during surgery[7]. Nevertheless, for peace of mind, I did give thromboprophylaxis to a patient with a haematocrit level of 0.52 before laparoscopic hysterectomy despite the lack of supporting evidence.

4. Some transgender (female-to-male) patients may have never had vaginal penetration, so insertion of a vaginal manipulator to facilitate laparoscopic hysterectomy, or vaginal retrieval of the uterus may be difficult, and may require an incision at the introitus (which I prefer not to call episiotomy) or may result in vaginal laceration. This has to

be discussed carefully preoperatively, as some patients may be quite sensitive on knowing the possible need for any of these 'minor' technical modifications.

5. The occurrence of postmenopausal symptoms is uncommon after bilateral salpingo-oophorectomy owing to peripheral conversion of exogenous testosterone to oestradiol. However, this possibility should still be discussed prior to surgery, as exceptions do occasionally happen[8].

As gynaecologists, we should prepare ourselves to care for women of different backgrounds including sexual orientation. Owing to enhanced community awareness and acceptance towards sexual minorities and more readily expression of sexual concerns, an increasing number of SMW and women with sexual difficulties are anticipated to seek medical care. Although care for these women is generally not emphasised during specialist and subspecialist training, it is time for us to start learning to understand the sexual needs and expectations of patients and to integrate sexual health as part of comprehensive women's healthcare.

Vincent YT CHEUNG, MBBS, FRCOG, FRCSC
Clinical Associate Professor, Department of Obstetrics and Gynaecology, The University of Hong Kong
President, The Obstetrical and Gynaecological Society of Hong Kong
Email: vytc@hku.hk

References

1. McCune KC, Imborek KL. Clinical care of lesbian and bisexual women for the obstetrician gynecologist. Clin Obstet Gynecol 2018;61:663-73. Crossref
2. Everett BG, Higgins JA, Haider S, Carpenter E. Do sexual minorities receive appropriate sexual and reproductive health care and counseling? J Womens Health (Larchmt) 2019;28:53-62. Crossref
3. Sayed Ahmed WA, Kishk EA, Farhan RI, Khamees RE. Female sexual function following different degrees of perineal tears. Int Urogynecol J 2017;28:917-21. Crossref
4. O'Shea MS, Lewicky-Gaupp C, Gossett DR. Long-term sexual function after obstetric anal sphincter injuries. Female Pelvic Med Reconstr Surg 2018;24:82-6. Crossref
5. World Professional Association for Transgender Health. Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People. 7th Version. 2012. Available at: https://www.wpath.org/media/cms/Documents/SOC%20v7/Standards%20of%20Care_V7%20Full%20Book_English.pdf. Accessed 1 December 2019.
6. Shatzel JJ, Connelly KJ, DeLoughery TG. Thrombotic issues in transgender medicine: a review. Am J Hematol 2017;92:204-8. Crossref
7. Boskey ER, Taghinia AH, Ganor O. Association of surgical risk with exogenous hormone use in transgender patients: a systematic review. JAMA Surg 2019;154:159-69. Crossref
8. Casimiro I, Cohen RN. Severe vasomotor symptoms post-oophorectomy despite testosterone therapy in a transgender man: a unique case study. J Endocr Soc 2019;3:734-6. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):11-5 | https://doi.org/10.12809/hkjgom.20.1.01

Outcome of placenta previa: inpatient versus outpatient management

Epiphania YC CHAN MBBS, MRCOG
Tsz-Kin LO MBBS, MRCOG, FHKAM (O&G), FHKCOG
Department of Obstetrics and Gynaecology, Princess Margaret Hospital, Hong Kong

Objective: To share our 10-year experience on outpatient care of patients with placenta previa with no antepartum haemorrhage (APH) prior to 34 weeks of pregnancy.
Methods: This was a retrospective observational study conducted at a regional obstetric unit in Hong Kong over a 10-year period. Patients with placenta previa with no vaginal bleeding before 34 weeks were included. Those with multiple pregnancy, preeclampsia, serious underlying medical disorders, morbidly adherent placenta, or vaginal delivery were excluded. Data analysed included maternal characteristics, delivery information, maternal morbidities (massive haemorrhage, intensive care unit admission, hysterectomy), and neonatal outcomes (delivery gestation, birth weight, Apgar scores, neonatal intensive care unit admission, perinatal mortality).
Results: A total of 419 women with minor (n=265) or major (n=154) placenta previa were evaluated. Of these cases, 149 (56%) cases of minor and 37 (24%) cases of major placenta previa (p<0.001) were managed as outpatients. For patients with major placenta previa, APH (62.2% vs 35%, p=0.004) and emergency Caesarean deliveries (70.3% vs 23.9%, p<0.001) were more common among outpatients than inpatients although APH >200 mL remained rare. Neonatal outcomes were similar between outpatients and inpatients except that patients with major placenta previa had more preterm deliveries in outpatients than inpatients (29.7% vs 10.3%, p=0.004). The maternal morbidity rate was higher in patients with major placenta previa than with minor placenta previa (31.8% vs 12.5%, p<0.001) but was similar between outpatients and inpatients.
Conclusion: Outpatient care of patients with placenta previa with no vaginal bleeding prior to 34 weeks of pregnancy was associated with more emergency deliveries, but there was no major adverse effect on maternal and neonatal outcomes.

Keywords: Outpatients; Placenta previa; Pregnancy outcome

Introduction

Placenta previa is a serious obstetric complication associated with risks of major haemorrhage and maternal and fetal morbidities and mortalities[1]. The annual incidence of placenta previa among Asian women is around 12.2 per 1000 deliveries[2]. In 2001, the Royal College of Obstetricians and Gynaecologists published the first edition of a guideline on the management of placenta previa, recommending inpatient management for women with major placenta previa in the third trimester[3]. This was based on a small randomised controlled trial, in which the only significant difference was a reduction in hospital stay and cost for outpatient management[4]. The guideline was updated in 2011, recommending care customised to the individual needs of the patient[5]. Currently, there is no conclusive evidence on whether outpatient management can be applied to women with placenta previa. There are limited international data[7,11,12] and no local data to the best of our knowledge.

The aim of this study was to compare outpatient with inpatient management for patients with placenta previa with no vaginal bleeding prior to 34 weeks of pregnancy in terms of maternal and neonatal outcomes.

Methods

This study was approved by the Kowloon West Cluster Research Ethics Committee (Reference: KW/EX-15-063(85-16)(3)). We reviewed records of all women with placenta previa who had delivery by Caesarean section at Princess Margaret Hospital, Hong Kong, between January 2006 and December 2015. Women with no vaginal bleeding prior to 34 weeks of gestation were included. Patients with multiple pregnancy, preeclampsia, or serious underlying medical disorders such as chronic hypertension, insulin-dependent diabetes mellitus, chronic renal failure were excluded, as were those with minor placenta previa with vaginal delivery or those with morbidly adherent placenta.

Relevant information was extracted, including demographics (age, parity, history of Caesarean section,

Correspondence to: Dr Epiphania YC Chan
Email: epi_chan@yahoo.com

history of miscarriage/termination of pregnancy), delivery information (type of placenta previa, mode of delivery, reason of delivery, and last antepartum haemorrhage [APH] to delivery interval), maternal outcomes (massive haemorrhage, intensive care unit (ICU) admission, hysterectomy, and maternal death; maternal morbidity was defined as admission to intensive care unit, blood loss ≥1500 mL, or hysterectomy), and perinatal outcomes (gestation at delivery, birth weight, Apgar scores, admission to neonatal intensive care unit, and perinatal mortality).

The diagnosis of placenta previa was established by transabdominal ultrasound scan after 34 weeks of gestation. Transvaginal sonography was used when the diagnosis was uncertain. Major placenta previa is defined as when the placenta lies over the internal cervical os, whereas minor placenta previa is defined as when the placental leading edge is in the lower segment but not covering the cervical os[5]. Indications for ultrasound include follow-up scan for known low-lying placenta, or admission with antepartum haemorrhage. For patients with the placenta edge >2 cm from cervical os, an option of vaginal delivery was given. Patients with vaginal delivery were excluded from analysis.

In our unit, there was no protocol for the management of women with placenta previa. The decision of inpatient versus outpatient management, the timing of admission, and timing of delivery were determined on an individual patient basis. For outpatient management, the patient was electively admitted one day before her scheduled Caesarean section, or emergency Caesarean delivery was performed shortly after emergency admission for various reasons. For inpatient management, the patient may be electively admitted a few weeks before delivery for rest, or urgently admitted owing to vaginal bleeding, and stayed as inpatient until elective delivery. Premature delivery was indicated in cases of heavy vaginal bleeding, premature labour, fetal distress, or other obstetric complications.

Each episode of bleeding was defined as one occurring after >24 hours free from bleeding. The amount of antepartum haemorrhage was estimated visually by the attending medical officer.

Statistical analysis was conducted using PASW Statistics (version 18.0, SPSS Inc., Chicago [IL], US). For continuous data with a highly skewed distribution, Mann-Whitney *U* test was used to compare the difference among groups. Pearson Chi-square test or Fisher's exact test was used to investigate relationships between two categorical variables. Statistical significance was set at $p<0.05$.

Results

Of 47 595 deliveries from 2006 to 2015 at Princess Margaret Hospital, 9157 (19.2%) were by Caesarean section. Of these, 528 were due to placenta previa in the third trimester, giving its overall incidence of 1.11%. Of these 528 women, 426 (80%) had no bleeding before 34 weeks. Seven women were excluded because of multiple pregnancy, preeclampsia, or serious underlying medical disorder.

Of 419 women included in the analysis, 265 had minor placenta previa and 154 had major placenta previa. 149 (56%) cases of minor placenta previa and 37 (24%) cases of major cases ($p<0.001$) were managed as outpatients. The inpatient and outpatient groups were comparable in terms of maternal characteristics, except that outpatients in the major placenta previa group had a higher rate of previous miscarriage/termination of pregnancy (73% vs 53.8%, $p=0.04$, Table 1).

78.4% and 76.1% of inpatients with minor and major placenta previa, respectively, had elective Caesarean delivery, but only 63.8% and 29.7% of outpatients in the respective groups had elective Caesarean delivery (Table 1). The most common reason for emergency Caesarean section was APH (46%).

Of 419 women, 280 (66.8%) had no APH during the whole course of the pregnancy, accounting for 76.7% and 65% of inpatients and 67.8% and 37.8% of outpatients with minor and major placenta previa, respectively (Table 1). 76 (17.9%) patients had APH on the day of delivery and required emergency delivery, with more outpatients encountering this than inpatients. None required transfusion before operation, but two outpatients required fluid resuscitation before operation: one with minor placenta previa and the other with major placenta previa. 80 (19.1%) women had blood loss of >1500 mL. 28 (6.7%) women required admission to the intensive care unit. There was no maternal death. The overall maternal morbidity rate was 19.6% (n=82); it was higher in patients with major placenta previa than with minor placenta previa (31.8% vs 12.5%, $p<0.001$) but was similar between outpatients and inpatients.

Among women with major placenta previa, more outpatients than inpatients had preterm delivery at 34 weeks to 36+6 weeks gestation (30% vs 10%, $p=0.004$, Table 1). The two groups were comparable in terms of birth weight, Apgar score, and neonatal intensive care unit admission. There was only one neonatal death in an inpatient with minor placenta previa secondary to pulmonary lymphangiectasia after elective Caesarean section at 37 weeks gestation with blood loss of 1300 mL.

Table 1. Inpatients versus outpatients with placenta previa in terms of demographics, delivery data, antepartum haemorrhage (APH), maternal outcomes, and baby outcomes

Parameter	Minor placenta previa			Major placenta previa		
	Inpatient (n=116)*	Outpatient (n=149)*	p Value	Inpatient (n=117)*	Outpatient (n=37)*	p Value
Age, y	33 (30-37)	34 (31-36)	0.374	35 (31-38)	33 (30.5-36)	0.149
Body mass index, kg/m^2	21 (19.3-22.8)	20.7 (19.2-23.4)	0.916	21.4 (19.4-23.6)	21.5 (19.5-24.65)	0.426
Parity			0.666			0.154
Nulliparous	46 (39.7)	63 (42.3)		60 (51.3)	14 (37.8)	
Multiparous	70 (60.3)	86 (57.7)		57 (48.7)	23 (62.2)	
Previous Caesarean section	18 (15.5)	27 (18.1)	0.575	19 (16.2)	3 (8.1)	0.218
Previous miscarriage / termination of pregnancy	62 (53.4)	76 (51)	0.693	63 (53.8)	27 (73)	0.04
Elective Caesarean section	91 (78.4)	95 (63.8)	0.01	89 (76.1)	11 (29.7)	<0.001
Emergency Caesarean section	25 (21.6)	54 (36.2)		28 (23.9)	26 (70.3)	
Term labour	10 (8.6)	23 (15.4)		10 (8.5)	5 (13.5)	
Preterm labour	4 (3.4)	6 (4)		2 (1.7)	4 (10.8)	
Fetal distress	1 (0.9)	0 (0)		3 (2.6)	0 (0)	
Antepartum haemorrhage	8 (6.9)	24 (16.1)		9 (7.7)	17 (45.9)	
Others (intrauterine growth restriction of the fetus or chorioamnionitis)	2 (1.7)	1 (0.7)		4 (3.4)	0 (0)	
No APH	89 (76.7)	101 (67.8)	0.13	76 (65)	14 (37.8)	0.004
APH on the day of delivery:	10 (8.6)	34 (22.8)	0.0025	13 (11.1)	19 (51.3)	<0.0001
APH <100 mL	8 (6.9)	23(15.4)		10 (8.5)	16 (43.2)	
APH 100-200 mL	0 (0)	7 (4.7)		2 (1.7)	1 (2.7)	
APH >200 mL	2 (1.7)	4 (2.7)		1 (0.9)	2 (5.4)	
APH 1-7 days before delivery	10 (8.6)	7 (4.7)		13 (11.1)	4 (10.8)	
APH 8-14 days before delivery	3 (2.6)	1 (0.7)		5 (4.3)	0 (0)	
APH 15-21 days before delivery	2 (1.7)	4 (2.7)		5 (4.3)	0 (0)	
APH >21 days before delivery	2 (1.7)	2 (1.3)		5 (4.3)	0 (0)	
Blood loss >1500 mL	16 (13.8)	16 (10.7)	0.449	37 (31.6)	11 (29.7)	0.828
Intra-operative transfusion	22 (19)	25 (16.9)	0.662	41 (35)	18 (48.6)	0.138
Postoperative transfusion	13 (11.4)	14 (9.4)	0.595	16 (13.7)	10 (27)	0.059
Hysterectomy	1 (0.9)	2 (1.3)	1	6 (5.1)	1 (2.7)	1
Intensive care unit admission	5 (4.3)	5 (3.4)	0.752	14 (12)	4 (10.8)	1
Maternal death	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Maternal morbidity (intensive care unit admission / blood loss >1500 mL / hysterectomy)	17 (14.7)	16 (10.7)	0.338	38 (32.5)	11 (29.7)	0.754
Prematurity (<37 weeks)	9 (7.8)	11 (7.4)	0.908	12 (10.3)	11 (29.7)	0.004
Birth weight, g	3035 (2830-3310)	3100 (2845-3390)	0.497	3000 (2710-3310)	3010 (2630-3360)	0.764
1-minute Apgar score <4	0 (0)	0 (0)	-	0 (0)	1 (2.7)	0.24
1-minute Apgar score <7	3 (2.6)	12 (8.1)	0.056	18 (15.4)	4 (10.8)	0.488
5-minute Apgar score <7	1 (0.9)	0 (0)	0.438	0 (0)	2 (5.4)	0.057
Neonatal intensive care unit admission	4 (3.4)	3 (2)	0.703	2 (1.7)	3 (8.1)	0.09
Neonatal death	1 (0.9)	0 (0)	0.438	0 (0)	0 (0)	-

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

Discussion

The incidence of placenta previa in Princess Margaret Hospital between 2006 and 2015 was 1.11%, which is comparable to that reported in other Asian countries[2]. However, the Caesarean section rate and incidence of placenta previa increased over time. This is a global trend; together with increasing maternal age, the rate of placenta previa will continue to rise[6]. In view of the increasing incidence of placenta previa, outpatient management has been investigated.

Placenta previa occurs when the placenta partially or totally covers the lower uterine segment. According to the distance from the internal cervical os, placenta previa is conventionally classified into types I to IV: types I and II are considered minor with the leading edge of the placenta in the lower uterine segment but does not cover the cervical os, whereas types III and IV are considered major when the placenta lies over the internal os[5].

Traditionally, women with placenta previa are offered prolonged hospital stay to minimise the risk of severe haemorrhage causing maternal and fetal morbidity and mortality. However, the necessity for this inpatient management is questionable.

The 2011 Royal College of Obstetricians and Gynaecologists guideline stated that those with major previa who have previously bled should be admitted from approximately 34 weeks of gestation, whereas outpatient care can be considered for those with minor previa or those asymptomatic, but evidence is lacking[3]. The most updated 2018 guideline stated that antenatal care should be tailored to individual needs for patients with recurrent APH,

Table 2. Comparison of studies on outpatient management of placenta previa

Study	Population area	Sample size	Study type	Inclusion criteria	Results
Wing et al[4], 1996	Los Angeles	53	Randomised controlled	Women with placenta previa from 24 to 36 weeks gestation who required hospitalisation	The only significant difference was a reduction in hospital stay and cost for outpatient management
Love et al[7], 2004	Edinburgh	161	Retrospective observational	Women with placenta praevia delivering between 1994 and 2000	Women with a major placenta praevia were not significantly more likely to experience bleeding. Women with antepartum haemorrhage were significantly more likely to be delivered early, by emergency Caesarean section, of lower birthweight babies who required neonatal admission, compared with women with no antepartum haemorrhage
Lam et al[8], 2000	Hong Kong	252	Retrospective observational	Women with placenta praevia delivering between 1991 and 1997	Increased risk of premature delivery in women with antepartum haemorrhage and placenta praevia. Women without antepartum haemorrhage can be managed on an outpatient basis.
Mouer[11], 1994	Arizona	238	Retrospective cohort	Women with placenta previa who delivered after 28 weeks between 1981 and 1992	No significant difference in outcome of the two groups
Droste and Keil[12], 1994	Wisconsin	72	Retrospective cohort	Women with placenta previa managed expectantly with either hospitalisation or outpatient bed rest from 1985 to 1990	No significant differences in maternal and fetal morbidity between groups. Outpatient management achieved a hospital cost reduction of 48.5% for mothers ($p<0.001$) and 39.4% for mother-infant pairs ($p<0.05$).
Present study, 2019	Hong Kong	419	Retrospective observational	Women with placenta previa with no vaginal bleeding prior to 34 weeks of gestation, delivering between 2006 and 2015	Outpatient care of patients with placenta previa with no vaginal bleeding prior to 34 weeks of pregnancy is associated with more emergency delivery, but there is no major adverse effect on maternal and neonatal outcomes.

whereas those with no APH can be cared for as outpatients with similar outcomes at a lower cost[9].

The present study only included patients without APH prior to 34 weeks of gestation for consideration of outpatient management. We excluded patients with APH prior to 34 weeks who may require antenatal steroids or tocolytics and have a higher risk of preterm delivery and poor outcome[8]. Of 419 patients with no APH prior to 34 weeks gestation, 280 (67%) had no APH throughout the pregnancy. Among the 139 patients with APH, 76 (55%) required emergency delivery on the same day owing to APH or labour or fetal distress. Two-thirds of them were managed as outpatients. The incidence of emergency delivery was higher in outpatients than inpatients, especially for those with major placenta previa (70.3% vs 23.9%). This may explain the higher incidence of APH in outpatients and higher incidence of preterm deliveries in outpatients with major placenta previa, compared with inpatients (29.7% vs 10.3%). Nonetheless, all other baby outcomes were similar between inpatients and outpatients. The maternal morbidity rate for those with minor placenta previa was 10.7% for outpatients and 14.7% for inpatients (p=0.449). For major placenta previa, it was 29.7% for outpatients and 32.5% for inpatients (p=0.828). The maternal morbidity rate was was higher in patients with major placenta previa than with minor placenta previa (31.8% vs 12.5%, p<0.001) but was similar between outpatients and inpatients.

The present study has the largest sample size among currently available studies on outpatient management of placenta previa (Table 2). It provides updated local data useful for patient counselling. It showed that inpatient and outpatient management achieve similar outcomes for placenta previa with no APH prior to 34 weeks. Outpatients, especially those with major placenta previa, have a higher incidence of emergency delivery.

This study is limited by its retrospective nature. The findings in local settings may not be generalised to other settings. Hong Kong is a compact city with an efficient transport system. Women with APH can be transferred to tertiary hospitals swiftly. Large-scale randomised controlled trials are warranted to address the safety of hospitalisation for patients with placenta previa.

Conclusion

Outpatient management for placenta previa without APH prior to 34 gestational weeks has no significant adverse impact on pregnancy outcomes, except for a higher rate of emergency delivery. Maternal morbidity is more likely to be associated with major placenta previa that cannot be prevented by inpatient management.

Declaration

The authors have no conflict of interests to disclose.

References

1. Iyasu S, Saftlas AK, Rowley DL, Koonin LM, Lawson HW, Atrash HK. The epidemiology of placenta praevia in the United States, 1979 through 1987. Am J Obstet Gynecol 1993;168:1424-9. Crossref
2. Cresswell JA, Ronsmans C, Calvert C, Filippi V. Prevalence of placenta praevia by world region: a systemic review and meta-analysis. Trop Med Int Health 2013;18:712-24. Crossref
3. Royal College of Obstetricians and Gynaecologists guideline. Placenta praevia: diagnosis and management. January 2001.
4. Wing DA, Paul RM, Millar LK. Management of the symptomatic placenta previa: a randomized, controlled trial of inpatient versus outpatient expectant management. Am J Obstet Gynecol 1996;175:806-12. Crossref
5. Royal College of Obstetricians and Gynaecologists guideline. Placenta praevia, placenta praevia accreta and vasa praevia: diagnosis and management. January 2011.
6. Betrán AP, Ye J, Moller AB, Zhang J, Gülmezoglu AM, Torloni MR. The increasing trend in caesarean section rates: global, regional and national estimates: 1990-2014. PLoS One 2016;11:e0148343. Crossref
7. Love CD, Fernando KJ, Sargent L, Hughes RG. Major placenta previa should not preclude out-patient management. Eur J Obstet Gynecol Reprod Biol 2004;117:24-9. Crossref
8. Lam CM, Wong SF, Chow KM, Ho LC. Women with placenta praevia and antepartum haemorrhage have a worse outcome than those who do not bleed before delivery. J Obstet Gynaecol 2000;20:27-31. Crossref
9. Jauniaux E, Alfirevic Z, Bhide AG, et al. Placenta praevia and placenta accreta: diagnosis and management. green-top guideline No. 27a. BJOG 2019;126:e1-e48. Crossref
10. Neilson JP. Interventions for suspected placenta previa. Cochrane Database Syst Rev 2003;2:CD001998. Crossref
11. Mouer JR. Placenta previa: antepartum conservative management, inpatient versus outpatient. Am J Obstet Gynecol 1994;170:1683-6. Crossref
12. Droste S, Keil K. Expectant management of placenta previa: cost-benefit analysis of outpatient management. Am J Obstet Gynecol 1994;170:1254-7. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):16-21 | https://doi.org/10.12809/hkjgom.20.1.02

Effect of new diagnostic criteria on detection and pregnancy outcomes of gestational diabetes mellitus: a retrospective study

Suk-Ching YOUNG, MBBS, MRCOG, FHKAM (FM), FRACGP
Mei-Sin YIU, MBBS
Po-Lam SO, MBBS MRCOG FHKAM(OG), FHKCOG, Cert HKCOH (MFM)
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Hong Kong

Introduction: To determine the effect of changes in the diagnostic criteria on the number of gestational diabetes mellitus (GDM) detected and on pregnancy and neonatal outcomes.
Methods: We retrospectively reviewed results of the 75g oral glucose tolerance test and pregnancy and neonatal outcomes of Chinese women with singleton pregnancies delivered at Tuen Mun Hospital between January and December 2016. Those with GDM was treated with lifestyle modification with or without insulin. Women with GDM detected by the old and new criteria were compared in terms of the numbers of GDM detected, maternal characteristics, pregnancy outcomes, and neonatal outcomes.
Results: Of 733 pregnant women, 211 (28.8%) and 190 (25.9%) were identified as having GDM based on the old or new criteria, respectively (p=0.01). Women with GDM based on the old or new criteria were comparable in terms of maternal characteristics, pregnancy outcomes, and neonatal outcomes. Among the 190 women with GDM based on the new criteria, 33 (17.4%) had normal fasting blood glucose and 2-hour glucose results but abnormal 1-hour glucose result. Compared with women without GDM, women with GDM detected by 1-hour glucose test alone had lower birthweight neonates (3.04 kg vs 3.22 kg, p=0.01), more neonates small for gestational age (3.7% vs 15.2%, p=0.01), with hypoglycaemia (15.2% vs 3.9%, p<0.001), and admission to neonatal intensive care unit (12.1% vs 1.3%, p<0.001).
Conclusions: The new criteria detected 2.9% fewer women with GDM. 17.4% of women with GDM who were associated with poor neonatal outcomes were detected exclusively by 1-hour glucose test. The new criteria can help identify high-risk women for fetal monitoring.

Keywords: Blood glucose; Diabetes, gestational; Pregnancy outcome

Introduction

Gestational diabetes mellitus (GDM) has significant health impact on mothers and children. Clear diagnostic criteria can help identify high-risk mothers for appropriate treatment with better use of the limited healthcare resources.

In the old diagnostic criteria for GDM, the cut-off value for GDM was fasting blood glucose (FBG) of ≥7.0 mmol/L and/or 2-hour glucose (2HG) of ≥7.8 mmol/L[1]. In 2013, the World Health Organization (WHO) adopted the new diagnostic criteria for GDM proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010[2,3]. The new criteria were based on the Hyperglycemia and Adverse Pregnancy Outcomes study[4], which prospectively examined 23316 women using the 75-g oral glucose tolerance test (OGTT). In the new criteria, GDM was defined as FBG ≥5.1 mmol/L, 1-hour glucose (1HG) test ≥10 mmol/L, and/or 2HG test ≥8.5 mmol/L. The cut-off values were devised from the blood glucose levels at which the risks of neonatal large for gestational age, primary Caesarean section, neonatal hypoglycaemia, and neonatal cord c-peptide >90th centile increased by a factor of 1.75[4]. Using the new criteria, the global prevalence of hyperglycaemia in pregnancy is estimated at 17%, with variations from 10% in North America to 25% in Southeast Asia[5]. The International Federation of Gynecology and Obstetrics recommended the WHO criteria for diagnosis of diabetes mellitus in pregnancy and the WHO and the IADPSG criteria for diagnosis of GDM.

Universal OGTT is not practised in Hong Kong; only women with one or more risk factors for GDM receive 75-g OGTT at 24 to 28 weeks of gestation. These risk factors are age ≥35 years at the expected date of conception, a pre-pregnancy body mass index (BMI) of ≥25 kg/m^2, having a first-degree relative with diabetes, having a previous neonate weighing ≥4 kg at birth, and having a history of GDM, intrauterine fetal death or polycystic

Correspondence to: Dr Suk-Ching Young
Email: ysc932@ha.org.hk

ovary syndrome. OGTT is also recommended for women with signs suggestive of GDM such as fetal macrosomia or polyhydramnios.[6] In our department, pregnant women at high risk of developing diabetes mellitus in pregnancy are also offered OGTT at booking. These risk factors are BMI ≥30 kg/m^2, maternal age ≥40 years at the expected date of conception, and having co-morbidities of polycystic ovaries, coronary heart disease, chronic hypertension, or on long-term oral steroid.

Since 1 December 2014, our department has used the new diagnostic criteria for GDM. All women detected to have GDM are treated according to the Hong Kong College of Obstetricians and Gynaecologists guidelines on the management of GDM[6]. They are followed up and care for under the multidisciplinary team comprising obstetricians, endocrinologists, GDM specialty nurses, and dietitians. Lifestyle advice is given. The blood sugar profile at home is monitored and reviewed regularly. Ultrasonography is used to monitored fetal growth in the third trimester. Those with unsatisfactory glucose control are referred to endocrinologists for insulin treatment. Mode and time of delivery are advised depending on the glucose control and any antenatal and fetal complications. Women with well-controlled GDM can opt for a spontaneous onset of labour or induced labour by 40 weeks of gestation. Elective Caesarean section is offered to women with estimated fetal weight of ≥4 kg.

The effects of changes in cut-off values of FBG and 2HG on the detection rate of GDM and pregnancy outcomes have been reported[7,8]. However, studies of the additional 1HG test on the pregnancy outcomes are limited. This study aimed to determine the effect of changes in the diagnostic criteria on the number of GDM detected and on pregnancy and neonatal outcomes.

Methods

This study was approved by the New Territories West Cluster Clinical and Research Ethics Committee of Hospital Authority, Hong Kong (reference: NTWC/CREC/16047). We retrospectively reviewed OGTT results and pregnancy and neonatal outcomes of Chinese women with singleton pregnancies delivered at Tuen Mun Hospital between January and December 2016. The catchment area of the hospital has about 500,000 reproductive population according to the census in 2016[9]. Those with multiple pregnancies or non-Chinese ethnicity were excluded. For women with repeat OGTT when a new indication arose during pregnancy, their pregnancy outcomes were counted per woman to avoid repetition.

Women with GDM detected by the old and new criteria were compared in terms of the numbers of GDM detected, maternal characteristics, pregnancy outcomes, and neonatal outcomes. Maternal characteristics included age, smoking status, BMI and body weight at booking, education, parity, working status, conception by assisted reproductive technology. Pregnancy outcomes included pre-eclampsia, induction of labour, genital trauma, gestational age at delivery, and mode of delivery. Neonatal outcomes included prematurity, birthweight, stillbirth, Apgar score, hyperbilirubinemia requiring phototherapy, shoulder dystocia, neonatal hypoglycaemia (<1.7 mmol/L), and admission to neonatal intensive care unit.

Pre-eclampsia was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient together with the new onset of proteinuria or significant end organ dysfunction.[10] Genital trauma was defined as the third- or fourth-degree perineal tear, according to the Royal College of Obstetricians and Gynaecologists.[11] Gestational age was determined from the date of last menstrual period or by ultrasonography performed between 6 and 24 weeks of gestation. Prematurity was defined as delivery <37 weeks of gestation. Primary Caesarean section was defined as the first Caesarean section (excluding repeated Caesarean section for previous Caesarean section). Large for gestational age and small for gestational age were defined as birth weight above the 90th percentile and below the 10th percentile, respectively, according to the growth standards of newborns of ethnic Chinese origin in a prospective cross-sectional population study.[12] Stillbirth was defined as a baby delivered with no signs of life known to have died after 24 completed weeks of pregnancy, according to the MBRRACE-UK Perinatal Mortality Surveillance Report.[13] Clinical neonatal hypoglycaemia was considered present if there was a notation of neonatal hypoglycaemia in the medical record together with symptoms or treatment with a glucose infusion or a local laboratory report of a glucose level of ≤1.7 mmol/L in the first hour after birth.[14]

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US). Continuous data were presented as median and interquartile range in case of skewed distribution. Categorical data were presented as numbers and percentages. Comparisons between groups were made using Student's *t* test or Mann-Whitney *U* test for continuous variables and Chi-squared test or Fisher's exact test for dichotomous outcomes. All p values were two-tailed. Statistical significance was set at $p<0.05$.

Table 1. Maternal characteristics, pregnancy outcomes, and neonatal outcomes of women with gestational diabetes mellitus (GDM) detected by the old and the new criteria

Characteristics	Women with GDM detected by old criteria (fasting blood glucose ≥7.0 mmol/L and/or 2-hour glucose ≥7.8 mmol/L) [n=211]*	Women with GDM detected by new criteria (fasting blood glucose ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, and/or 2-hour glucose ≥8.5 mmol/L) [n=190]*	p Value
Maternal characteristics			
Age, y	34 (30-37)	33 (29-36)	0.21
Pre-pregnancy body mass index, kg/m^2	24.4 (21.7-26.6)	24.4 (21.4-26.8)	0.90
<25	124 (58. 8)	113 (59.5)	0.96
25-29.9	69 (32.7)	61 (32.1)	0.90
≥30	18 (8.5)	16 (8.4)	0.97
Body weight at booking, kg	59.5 (53.6-67.2)	59.4 (53.6-65.9)	0.68
Education			0.98
Tertiary or above	50 (23.7)	47 (24.7)	
Secondary	155 (73.5)	139 (73.2)	
Primary	5 (2.4)	3 (1.6)	
No education	1 (0.5)	1 (0.5)	
Nulliparous	108 (51.2)	99 (52.1)	0.60
Smoking during pregnancy	9 (4.3)	12 (6.3)	0.59
Working mother	115 (54.5)	111 (58.4)	0.44
Assisted reproductive technology treatment	13 (6.2)	10 (5.3)	0.53
Pregnancy outcomes			
Pre-eclampsia	5 (2.4)	7 (3.7)	0.44
Induction of labour	83 (39.3)	84 (44.2)	0.60
Genital trauma	1 (0.5)	1 (0.5)	0.94
Gestational age at delivery, weeks	38 (38-39)	38 (37-39)	0.34
Mode of delivery			
Vaginal	99 (46.9)	94 (49.5)	0.64
Instrumental	20 (9.5)	20 (10.5)	0.74
Primary Caesarean section	40 (19.0)	35 (18.4)	0.81
Neonatal outcomes			
Prematurity	20 (9.5)	25 (13.2)	0.25
Birthweight, g	3250 (2950-3520)	3260 (2910-3480)	0.68
Small for gestational age	11 (5.2)	11 (5.8)	0.68
Large for gestational age	52 (24.6)	46 (24.2)	0.90
Stillbirth	3 (1.4)	4 (2.0)	0.61
Apgar score <7 at 5 minutes	1 (0.5)	1 (0.5)	0.99
Hypoglycaemia	12 (5.7)	14 (7.4)	0.50
Shoulder dystocia	1 (0.5)	1 (0.5)	0.94
Phototherapy	38 (18.0)	36 (18.9)	0.97
Admission to neonatal intensive care unit	5 (2.4)	8 (4.2)	0.31

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

Table 2. Maternal characteristics, pregnancy outcomes, and neonatal outcomes of women with no gestational diabetes mellitus (GDM), women with GDM detected by 1-hour glucose (1HG) test only, and women with GDM detected by fasting blood glucose (FBG) test and/or 2-hour glucose (2HG) test, based on the new criteria

Characteristics	Women with no GDM (FBG <5.1 mmol/L, 1HG <10.0 mmol/L, and/or 2HG <8.5 mmol/L) [n=543]	Women with GDM detected by 1HG (≥10.0 mmol/L) only (with normal FBG and 2HG) [n=33]	p Value	Women with GDM detected by FBG (≥5.1 mmol/L) and/ or 2HG (≥8.5 mmol/L) [n=157]	p Value
Maternal characteristics					
Treatment for GDM					<0.001
Diet	0	33 (100)		150 (95.5)	
Insulin	0	0		7 (4.5)	
Age, y	33 (30-36)	34 (29-36)	0.99	33 (29-36)	0.26
Pre-pregnancy body mass index, kg/m^2	22.4 (20.3-25.7)	24.0 (20.2-27.2)	0.21	23.8 (21.4-26.6)	0.06
<25	371 (68.3)	19 (57.6)	0.18	97 (61.8)	0.06
25-29.9	136 (25.0)	9 (27.3)	0.73	51 (32.5)	0.04
≥30	36 (6.6)	5 (15.2)	0.66	11 (7.0)	0.91
Body weight at booking, kg	57.4 (50.7-65.1)	59.1 (52.9-64.7)	0.45	59.4 (53.5-66.1)	0.53
Education			0.78		0.89
Tertiary or above	133 (24.5)	10 (30.3)		39 (24.8)	
Secondary	394 (72.6)	22 (66.7)		115 (73.2)	
Primary	13 (2.4)	1 (3.0)		2 (1.3)	
No education	3 (0.6)	0		1 (0.6)	
Nulliparous	247 (45.5)	18 (54.5)	0.62	83 (52.8)	0.21
Smoking during pregnancy	111 (20.4)	7 (21.2)	0.20	27 (17.2)	0.95
Working mother	301 (55.4)	21 (63.6)	0.23	92 (58.6)	0.41
Assisted reproductive technology treatment	30 (5.5)	1 (3.0)	0.53	10 (6.4)	0.18
Pregnancy outcomes					
Pre-eclampsia	20 (3.7)	3 (9.1)	0.13	4 (2.5)	0.62
Induction of labour	154 (28.4)	13 (39.4)	0.40	72 (45.9)	<0.001
Genital trauma	8 (1.5)	0	0.488	1 (0.6)	0.40
Gestational age at delivery, week	39 (38-39)	38 (37-40)	0.10	38 (37-39)	<0.001
Mode of delivery					
Vaginal	311 (57.3)	15 (45.5)	0.19	24 (15.3)	0.11
Instrumental	19 (3.5)	3 (9.1)	0.10	17 (10.8)	<0.001
Primary Caesarean section	90 (16.6)	10 (30.0)	0.74	29 (18.5)	0.74
Neonatal outcomes					
Prematurity	54 (9.9)	3 (9.1)	0.22	20 (12.7)	<0.001
Birthweight, g	3220 (2940-3500)	3040 (2570-3320)	0.01	3280 (2960-3520)	0.12
Small for gestational age	20 (3.7)	5 (15.2)	0.01	6 (3.8)	0.21
Large for gestational age	107 (19.7)	4 (12.1)	0.28	43 (27.4)	0.05
Stillbirth	2 (0.4)	0	0.73	3 (1.9)	0.81
Apgar score <7 at 5 minutes	2 (0.4)	0	0.40	1 (0.6)	0.81
Hypoglycaemia	21 (3.9)	5 (15.2)	<0.001	11 (7.0)	0.13
Shoulder dystocia	2 (0.4)	0	0.73	1 (0.6)	0.66
Phototherapy	90 (16.6)	4 (12.1)	0.49	32 (20.4)	0.11
Admission to neonatal intensive care unit	7 (1.3)	4 (12.1)[†]	<0.001	4 (2.5)	0.28

[*] Data are presented as median (interquartile range) or No. (%) of cases

[†] Two had meconium aspiration syndrome (one discharged on day 10 and another on day 14). Two others had prematurity. One was born at 26 weeks with respiratory distress syndrome and chronic lung disease requiring oxygen until the age of 6 months. Another was born at 30 weeks with respiratory distress syndrome, premature gut, and neonatal jaundice requiring phototherapy and was discharged after 2 months

Results

Of 733 pregnant women, 211 (28.8%) and 190 (25.9%) were detected to have GDM based on the old or new criteria, respectively (p=0.01). Women with GDM based on the old or new criteria were comparable in terms of maternal characteristics, pregnancy outcomes, and neonatal outcomes (Table 1).

Based on the new criteria, women with and without GDM were comparable in terms of maternal characteristics, except that more women with GDM detected by FBG and/or 2HG tests were in the BMI category of 25-29.9 kg/m^2 (32.5% vs 25.0%, p=0.04, Table 2).

Among the 190 women with GDM based on the new criteria, 33 (17.4%) had normal FBG and 2HG results but abnormal 1HG result. Compared with women without GDM, women with GDM detected by 1HG test alone had comparable pregnancy outcomes (pre-eclampsia, induction of labour, genital trauma, and primary Caesarean section) but poorer neonatal outcomes: lower birthweight (3.04 kg vs 3.22 kg, p=0.01), more neonates small for gestational age (3.7% vs 15.2%, p=0.01), with hypoglycaemia (15.2% vs 3.9%, p<0.001), and admission to neonatal intensive care unit (12.1% vs 1.3%, p<0.001).

Compared with women without GDM, women with GDM detected by FBG and/or 2HG test were more likely to require induction of labour (45.9% vs 28.4%, p<0.001) and instrumental delivery (10.8% vs 3.5%, p<0.001) and have more neonates born prematurely at <37 weeks of gestation (12.7% vs 9.9%, p<0.001) and large for gestational age (27.4% vs 19.7%, p=0.05).

Discussion

Based on the new diagnostic criteria, the number of GDM cases detected in our cohort reduced 2.9%. Nonetheless, most studies reported an increase in the number of GDM cases[15-20], although some studies reported similar or decreased in number of GDM cases.[21,22] This reduction reflected that most GDM cases detected in the Chinese population was by the 2HG test. Therefore, a decrease in the number of GDM cases detected was due to the loosening of the 2HG test. Although women with 2HG in the range of 7.8-8.4 mmol/L were classified as non-GDM by the new criteria and were untreated, there was no change in pregnancy outcomes between the old and new criteria. This is reassuring to adopt the new criteria.

The additional 1HG test requires extra healthcare resource, but it can pick up cases with poor neonatal outcomes. Based on the new criteria, 17.4% of women with GDM were detected exclusively by 1HG test with normal FBG and 2HG results. Neonatal outcomes of these women were poorer, including lower birthweight, more hypoglycaemia, and more admission to neonatal intensive care unit. The additional 1HG test helps identify high-risk women for fetal surveillance. If the 1HG test was not implemented (old criteria), these women would have been classified as non-GDM. The poorer neonatal outcomes would have been the result of no treatment. Further randomised controlled trials on the treatment effects on women with GDM detected by the 1HG test alone are warranted.

This study has some limitations. There is no universal screening for GDM in Hong Kong; only women with one or more risk factors for GDM or signs suggestive of GDM are tested. Therefore, the number of pregnancies affected by GDM represented only women at higher risk of GDM (rather than the general obstetric population). In addition, the sample size may be too small to show any statistical significance. However, more samples will be included to increase the power of the study. Further randomised controlled trials are warranted to assess the effect of treatment for women with abnormal 1HG test result only on pregnancy outcomes.

Conclusion

The new criteria detected 2.9% fewer women with GDM. 17.4% of women with GDM who were associated with poor neonatal outcomes were detected exclusively by 1HG test. The new criteria can help identify high-risk women for fetal monitoring. More extensive or territory-wide studies on the effect and cost-effectiveness analysis of the new diagnostic criteria are warranted.

Acknowledgement

The authors wish to thank Mr Jaden CH Lam, statistical officer in the Quality and Safety Division of the New Territories West Cluster of Hospital Authority of Hong Kong.

Declaration

The authors have no conflict of interest to disclose.

References

1. World Health Organization. Definition and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. 1999.
2. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676-82. Crossref
3. World Health Organization. Diagnostic criteria and classification of hyperglycemia first detected in pregnancy. Available from http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf. Accessed 12 January 2019.
4. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002. Crossref
5. Guariguata L, Linnenkamp U, Beagley J, Whiting DR, Cho NH. Global estimates of the prevalence of hyperglycaemia in pregnancy. Diabetes Res Clin Pract 2014;103:176-85. Crossref
6. Guideline of Management of Gestational Diabetes Mellitus by The Hong Kong College of Obstetricians and Gynaecologists. Available from: www.hkcog.org.hk/hkcog/Download/Guidelines_on_GDM.pdf. Accessed 12 January 2019.
7. Jenum AK, Mørkrid K, Sletner L, et al. Impact of ethnicity on gestational diabetes identified with the WHO and the modified International Association of Diabetes and Pregnancy Study Groups criteria: a population-based cohort study. Eur J Endocrinol 2012;166:317-24. Crossref
8. Ekeroma AJ, Chandran GS, McCowan L, Ansell D, Eagleton C, Kenealy T. Impact of using the International Association of Diabetes and Pregnancy Study Groups criteria in South Auckland: prevalence, interventions and outcomes. Aust N Z J Obstet Gynaecol 2015;55:34-41. Crossref
9. 2016 Hong Kong Population census. Available from https://www.bycensus2016.gov.hk/en. Accessed 12 January 2019.
10. ACOG Practice Bulletin No. 202: Gestational Hypertension and Preeclampsia. Obstet Gynecol 2019;133:e1-e25. Crossref
11. Royal College of Obstetricians and Gynaecologists. RCOG Green-top Guideline No. 29: The Management of Third- and Fourth-degree Perineal Tears. London: RCOG; 2015.
12. Fok TF, So HK, Wong E, et al. Updated gestational age specific birth weight, crown-heel length, and head circumference of Chinese newborns. Arch Dis Child Fetal Neonatal Ed 2003;88:F229-36. Crossref
13. MBRRACE-UK Perinatal Mortality Surveillance Report. UK Perinatal Deaths for Births from January to December 2016. Available from: https://www.npeu.ox.ac.uk/mbrrace-uk/reports. Accessed 12 January 2019.
14. Alkalay AL, Sarnat HB, Flores-Sarnat L, Elashoff JD, Farber SJ, Simmons CF. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. Am J Perinatol 2006;23:115-9. Crossref
15. Koning SH, van Zanden JJ, Hoogenberg K, et al. New diagnostic criteria for gestational diabetes mellitus and their impact on the number of diagnoses and pregnancy outcomes. Diabetologia 2018;61:800-9. Crossref
16. Laafira A, White SW, Griffin CJ, Graham D. Impact of the new IADPSG gestational diabetes diagnostic criteria on pregnancy outcomes in Western Australia. Aust N Z J Obstet Gynaecol 2016;56:36-41. Crossref
17. Lapolla A, Dalfrà MG, Ragazzi E, De Cata AP, Fedele D. New International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendations for diagnosing gestational diabetes compared with former criteria: a retrospective study on pregnancy outcome. Diabet Med 2011;28:1074-7. Crossref
18. Erjavec K, Poljicanin T, Matijevic R. Impact of the implementation of new WHO diagnostic criteria for gestational diabetes mellitus on prevalence and perinatal outcomes: a population-based study. J Pregnancy 2016;2016:2670912. Crossref
19. Wong VW, Lin A, Russell H. Adopting the new World Health Organization diagnostic criteria for gestational diabetes: How the prevalence changes in a high-risk region in Australia. Diabetes Res Clin Pract 2017;129:148-53. Crossref
20. Claesson R, Ekelund M, Berntorp K. The potential impact of new diagnostic criteria on the frequency of gestational diabetes mellitus in Sweden. Acta Obstet Gynecol Scand 2013;92:1223-6. Crossref
21. Basri NI, Mahdy ZA, Ahmad S, et al. The World Health Organization (WHO) versus The International Association of Diabetes and Pregnancy Study Group (IADPSG) diagnostic criteria of gestational diabetes mellitus (GDM) and their associated maternal and neonatal outcomes. Horm Mol Biol Clin Investig 2018;34. Crossref
22. Yew TW, Khoo CM, Thai AC, Kale AS, Yong EL, Tai ES. The prevalence of gestational diabetes mellitus among Asian females is lower using the new 2013 World Health Organization diagnostic criteria. Endocr Pract 2014;20:1064-9. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):22-6 | https://doi.org/10.12809/hkjgom.20.1.03

Effect of depressive disorders and other psychiatric disorders on pregnancy and perinatal outcomes in a Hong Kong obstetrics unit

CC CHENG, MBChB (HK), MRCOG
KH SIONG, MBBS (HK), FRCOG, FHKCOG, FHKAM (O&G)
HC LEE, MBBS (HK), FRCOG, FHKCOG, FHKAM (O&G)
KC AU YEUNG, MBBS (HK), FRCOG, FHKCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Tuen Mun, Hong Kong

Objectives: To determine the prevalence of psychiatric disorders in Chinese pregnant women in Hong Kong, the effect of psychiatric disorders on pregnancy and perinatal outcomes, and the effect of antidepressants on pregnancy and perinatal outcomes.
Methods: We retrospectively reviewed medical records of women who delivered in Tuen Mun Hospital after 24 weeks of gestation between 1 January 2016 and 31 December 2017. Chinese pregnant women with psychiatric disorders were identified. Women with multiple pregnancy were excluded.
Results: Of 9049 Chinese pregnant women included, 216 (2.4%) reported psychiatric disorders, with depressive disorders being the most prevalent (1%). Compared to pregnant women with no psychiatric disorders, pregnant women with psychiatric disorders were more likely to have gestational diabetes (10.2% vs 5.7%, p=0.005) and/or pre-existing diabetes (4.2% vs 1.9%, p=0.018) and preterm births before 37 weeks (13.9% vs 7.5%, p=0.001). Similarly, women with depressive disorders were more likely to have gestational diabetes (11.4% vs 5.7%, p=0.022) and preterm birth before 37 weeks (13.6% vs 7.5%, p=0.031). In multiple logistic regression, pregnant women with psychiatric disorders or depressive disorders were associated with nearly two-fold increase in the risks of gestational diabetes mellitus and preterm birth before 37 weeks, after adjusting for cofounding factors.
Conclusion: Depression and psychiatric disorders were associated with preterm birth and gestational diabetes. Use of antidepressants had no adverse effect on maternal or fetal outcomes.

Keywords: Depression; Diabetes, gestational; Mental disorders; Premature birth

Introduction

Commonly encountered psychiatric disorders in pregnant women include depression, anxiety disorders, substance abuse, and schizophrenia-related disorders[1]. In meta-analyses, depression is estimated to complicate 12.8% and 12.0% of pregnancies in the second and third trimester, respectively, and increases the risks of preterm birth and low birthweight[2-5]. In a Caucasian-based meta-analysis, anxiety disorder increased the risks of preterm birth (odds ratio=1.54) and low birthweight (odds ratio=1.80)[6]. Nonetheless, there are limited data on the prevalence of psychiatric disorders in Asian pregnant women, particularly in Hong Kong populations. The available data mainly focus on the neonatal outcomes; data on pregnancy outcomes are scarce. Studies of antidepressant exposure during pregnancy have reported conflicting results about adverse delivery and perinatal outcomes[2,7]. Pregnant women are concerned about the possible harmful effects of psychiatric medications and thus compliance is low[8].

This study aims to determine the prevalence of psychiatric disorders in Chinese pregnant women in Hong Kong, the effect of psychiatric disorders on pregnancy and perinatal outcomes, and the effect of antidepressants on pregnancy and perinatal outcomes. The findings are useful for management and counselling of pregnant women with psychiatric disorders and to increase the awareness of healthcare workers on the possible risks in these women.

Methods

In the New Territories West Cluster, all pregnant women who report pre-existing mental illness, history of significant life event, postnatal depression, or other issues related to grief and loss leading to a higher risk of peripartum mental illness are assessed by the specialty nurses of the Comprehensive Child Development Service (CCDS) in the Maternal Child Health Centres or Tuen Mun

Correspondence to: Dr CC Cheng
Email: ccc755a@ha.org.hk

Hospital obstetrics unit. In addition to routine antenatal care, these women are also followed up by the CCDS nurses. Their psychiatric diagnoses, concurrent follow-up by the psychiatrist, use of psychiatric medications, and compliance with psychiatric management are documented. They are assessed by the CCDS team after delivery to ensure good postpartum recovery and childcare.

This study was approved by the New Territories West Cluster Research Ethics Committee (reference: NTWC/REC/19031). We retrospectively reviewed medical records of women who delivered in Tuen Mun Hospital after 24 weeks of gestation between 1 January 2016 and 31 December 2017 using the Obstetrics Specialty Clinical Information System. Chinese pregnant women with psychiatric disorders were identified. Women with multiple pregnancy were excluded to minimise confounding effects on pregnancy and perinatal outcomes.

Data collected included maternal characteristics, antepartum complications (hypertensive disorders, gestational diabetes, pre-eclampsia, antepartum haemorrhage, preterm labour, and intrauterine fetal demise), peripartum outcomes (need for induction of labour, mode of delivery, postpartum haemorrhage), and fetal and perinatal outcomes (gestational age at birth, stillbirth, neonatal death, birth weight, Apgar scores, admission to neonatal unit).

Pregnant women with or without psychiatric disorders were compared using independent *t* test for continuous variables and Pearson Chi-squared test or Fisher's exact test for categorical variables. Multiple logistic regression analysis was used to determine the risks of psychiatric disorders for adverse pregnancy and perinatal outcomes, with adjustment of cofounding factors. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US).

Results

Of 9049 Chinese pregnant women included, 216 (2.4%) reported psychiatric disorders, with depressive disorders being the most prevalent (1%) [Table 1].

Table 1. 216 pregnant women reporting psychiatric disorders during 2016-2017

Psychiatric disorder	No. (%) of pregnant women (n=9049)
Depressive disorders	88 (1.0)
Adjustment disorders	66 (0.7)
Substance abuse	35 (0.4)
Anxiety	27 (0.3)
Personality disorders	20 (0.2)
Schizophrenia	20 (0.2)
Bipolar affective disorders	6 (0.07)
Other psychiatric diseases (eating disorder and conduct disorder)	4 (0.04)
Mixed diagnoses	41 (0.5)

Compared with pregnant women with no psychiatric disorders, pregnant women with psychiatric disorders were more likely to be aged <20 years (4.2% vs 1.5%) or ≥35 years (29.6% vs 25%) [p=0.002], multiparous (60.6% vs 52.4%, p=0.016), have gestational diabetes (10.2% vs 5.7%, p=0.005) and/or pre-existing diabetes (4.2% vs 1.9%, p=0.018), and have preterm birth before 37 weeks (13.9% vs 7.5%, p=0.001) [Table 2]. Similarly, women with depressive disorders were more likely to be multiparous (65.9% vs 52.4%, p=0.011), have gestational diabetes (11.4% vs 5.7%, p=0.022), and have preterm birth before 37 weeks (13.6% vs 7.5%, p=0.031) [Table 2].

Among 88 pregnant women with depressive disorders, those on or not on antidepressants were comparable in terms of maternal characteristics and maternal and perinatal outcomes (Table 3).

In multiple logistic regression, pregnant women with psychiatric disorders or depressive disorders were associated with nearly two-fold increase in risks of gestational diabetes mellitus and preterm birth before 37 weeks, after adjusting for cofounding factors (Table 4).

Discussion

The prevalence of psychiatric disorders in pregnant women who delivered in Tuen Mun Hospital was 2.4%, which was lower than 15% to 29% reported in a US national survey[9]. This could be due to underreporting of mental health problems in our pregnant women despite detailed history taking during the antenatal care.

Pregnant women with depression or other psychiatric disorders were more likely to have gestational diabetes. Depression was the most prevalent psychiatric disorder. A prospective cohort study in the United States also observed a bidirectional association between depression and gestational diabetes mellitus[10]. This can be attributed to the positive association between depression and metabolic perturbations (such as increased oxidative stress, chronic

Table 2. Comparison of pregnant women with or without psychiatric disorder in terms of maternal characteristics and pregnancy and fetal outcomes

Characteristic	Pregnant women with no psychiatric disorder (n=8833)	Pregnant women with psychiatric disorder (n=216)	p Value	Pregnant women with depressive disorder (n=88)	p Value
Age, y			0.002		0.633
<20	136 (1.5)	9 (4.2)		2 (2.3)	
20-35	6490 (73.5)	143 (6.2)		61 (69.3)	
≥35	2207 (25)	64 (29.6)		25 (28.4)	
Parity			0.016		0.011
Primiparous	4207 (47.6)	85 (39.4)		30 (34.1)	
Multiparous	4626 (52.4)	131 (60.6)		58 (65.9)	
Body mass index, kg/m^2	24.13±4.26	24.11±4.97	0.995	23.28±4.55	0.556
Diabetes	669 (7.6)	31 (14.4)	<0.001	12 (13.6)	0.033
Gestational diabetes mellitus	500 (5.7)	22 (10.2)	0.005	10 (11.4)	0.022
Pre-existing diabetes mellitus	169 (1.9)	9 (4.2)	0.018	2 (2.3)	0.807
Pre-eclampsia	60 (0.7)	3 (1.4)	0.215	2 (2.3)	0.073
Hypertension	167 (1.9)	6 (2.8)	0.347	3 (3.4)	0.300
Antepartum haemorrhage	607 (6.9)	13 (6)	0.624	3 (3.4)	0.200
Intrauterine fetal demise	25 (0.3)	0 (0)	0.434	0 (0.0)	0.617
Induction of labour	2676 (30.3)	63 (29.2)	0.721	25 (28.4)	0.702
Mode of delivery			0.287		0.150
Vaginal delivery	5877 (66.5)	138 (63.9)		52 (59.1)	
Instrumental delivery	551 (6.2)	10 (4.6)		4 (4.5)	
Caesarean section	2405 (27.2)	68 (31.5)		32 (36.4)	
Postpartum haemorrhage	451 (5.1)	9 (4.2)	0.535	3 (3.4)	0.471
Intrauterine growth restriction / small for gestational age	574 (5.6)	15 (6.9)	0.793	8 (9.1)	0.327
Preterm birth before 37 weeks	665 (7.5)	30 (13.9)	0.001	12 (13.6)	0.031
Preterm birth before 34 weeks	196 (2.2)	7 (3.2)	0.316	2 (2.3)	0.973
Apgar score <7 at 1 min	290 (3.3)	7 (3.2)	0.972	4 (4.5)	0.509
Apgar score <7 at 5 min	53 (0.6)	1 (0.5)	0.796	0 (0.0)	0.466
Neonatal intensive care unit admission	192 (2.2)	6 (2.8)	0.549	3 (3.4)	0.430
Neonatal death	10 (0.1)	0 (0)	0.621	0 (0.0)	0.752

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

inflammation, and insulin resistance), which subsequently contribute to the development of hyperglycaemia[11]. Healthcare workers should be more vigilant for gestational diabetes mellitus in women with depression or other psychiatric disorders.

Depression in pregnancy is associated with preterm births[3,12-14]. The underlying mechanism is not well understood, but it is hypothesised that stress leads to activation of inflammatory pathways involving maternal cortisol that results in premature delivery[15,16]. Hence, pregnant women with psychiatric disorders should be advised on the increased risk of preterm birth and on signs and symptoms of preterm labour for timely management.

In our study, use of antidepressants was not associated with adverse change in pregnancy and perinatal outcomes. Hence, pregnant women with psychiatric

Table 3. Comparison of pregnant women with depressive disorder on or not on antidepressants in terms of maternal characteristics and pregnancy and fetal outcomes

Characteristic	On antidepressants (n=36)	Not on antidepressants (n=52)	p Value
Age, y			0.374
<20	0	2 (3.8)	
20-35	24 (66.7)	37 (71.2)	
≥35	12 (33.3)	13 (25.0)	
Parity			0.901
Primiparous	12 (33.3)	18 (34.6)	
Multiparous	24 (66.7)	34 (65.4)	
Body mass index (kg/m^2)	23.8±4.01	22.89±5.50	0.819
Diabetes mellitus	7 (19.4)	5 (9.6)	0.186
Gestational diabetes mellitus	6 (16.7)	4 (7.7)	0.192
Pre-existing diabetes mellitus	1 (2.8)	1 (1.9)	0.791
Pre-eclampsia	1 (2.8)	1 (1.9)	0.791
Hypertension	2 (5.6)	1 (1.9)	0.356
Antepartum haemorrhage	1 (2.8)	2 (3.8)	0.786
Intrauterine fetal demise	0	0	-
Induction of labour	11 (30.6)	14 (26.9)	0.710
Mode of delivery			0.830
Vaginal delivery	20 (55.6)	32 (61.5)	
Instrumental delivery	2 (5.6)	2 (3.8)	
Caesarean section	14 (38.9)	18 (34.6)	
Postpartum haemorrhage	2 (5.6)	1 (1.9)	0.356
Intrauterine growth restriction / small for gestational age	2 (5.6)	6 (11.5)	0.337
Preterm birth before 37 weeks	5 (13.9)	7 (13.5)	0.954
Preterm birth before 34 weeks	1 (2.8)	1 (1.9)	0.791
Apgar score <7 at 1 min	1 (2.8)	3 (5.8)	0.508
Apgar score <7 at 5 min	0	0	-
Neonatal intensive care unit admission	2 (5.6)	1 (1.9)	0.356
Neonatal death	0	0	-

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

Table 4. Multiple logistic regression for risk factors

Variable	Adjusted odds ratio (95% confidence interval)	
	Pregnant women with psychiatric disorders*	Pregnant women with depressive disorder*
Gestational diabetes mellitus	1.84 (1.17-2.91), p=0.008	2.01 (1.07-4.12), p=0.031
Preterm birth before 37 weeks	1.91 (1.29-2.84), p=0.001	1.88 (1.02-3.48), p=0.045

* Comparison with 8833 pregnant women with no psychiatric disorder

disorders should be reassured that antidepressants do not have detrimental effects on pregnancy. They should be advised to continue the medication if indicated according to psychiatrist.

One limitation of this study was its retrospective nature. Some socioeconomic factors such as smoking status and family income could not be retrieved from the system. Recognition of psychiatric disorders relied on self-reporting and therefore the true number of affected patients might be under-reported[17]. Nonetheless, under-reporting exists even in prospective studies if stigmatisation of psychiatric disorders remains unchanged. The sample size was too small to determine the effect of psychiatric medication on pregnancy outcomes.

Conclusion

Depression and psychiatric disorders were associated with preterm birth and gestational diabetes. Use of antidepressants had no adverse effect on maternal or fetal outcomes.

Declaration

The authors have no conflict of interest to disclose.

References

1. Andersson L, Sundstrom-Poromaa I, Bixo M, Wulff M, Bondestam K, åStröm M. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. Am J Obstet Gynecol 2003;189:148-54. Crossref
2. Ross LE, Grigoriadis S, Mamisashvili L, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA Psychiatry 2013;70:436-43. Crossref
3. Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Clin Psychiatry 2013;74:e321-41. Crossref
4. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal depression compared with women without depression: a systematic review and meta-analysis. JAMA Psychiatry 2016;73:826-37. Crossref
5. Eastwood J, Ogbo FA, Hendry A, Noble J, Page A; Early Years Research Group (EYRG). The impact of antenatal depression on perinatal outcomes in Australian women. PLoS One 2017;12:e0169907. Crossref
6. Grigoriadis S, Graves L, Peer M, et al. Maternal anxiety during pregnancy and the association with adverse perinatal outcomes: systematic review and meta-analysis. J Clin Psychiatry 2018;79.pii:17r12011. Crossref
7. Einarson A, Choi J, Einarson TR, Koren G. Adverse effects of antidepressant use in pregnancy: an evaluation of fetal growth and preterm birth. Depress Anxiety 2010;27:35-8. Crossref
8. Brameld KJ, Jablensky A, Griffith J, Dean J, Morgan VA. Psychotropic medication and substance use during pregnancy by women with severe mental illness. Front. Psychiatry 2017;8:28. Crossref
9. Vesga-López O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. Arch Gen Psychiatry 2008;65:805-15. Crossref
10. Hinkle SN, Buck Louis GM, Rawal S, Zhu Y, Albert PS, Zhang C. A longitudinal study of depression and gestational diabetes in pregnancy and the postpartum period. Diabetologia 2016;59:2594-602. Crossref
11. Rustad JK, Musselman DL, Nemeroff CB. The relationship of depression and diabetes: pathophysiological and treatment implications. Psychoneuroendocrinology 2011;36:1276-86. Crossref
12. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 2006;63:898-906. Crossref
13. Szegda K, Markenson G, Bertone-Johnson ER, Chasan-Taber L. Depression during pregnancy: a risk factor for adverse neonatal outcomes? A critical review of the literature. J Matern Fetal Neonatal Med 2014;27:960-7. Crossref
14. Venkatesh KK, Riley L, Castro VM, Perlis RH, Kaimal AJ. Association of antenatal depression symptoms and antidepressant treatment with preterm birth. Obstet Gynecol 2016;127:926-33. Crossref
15. Osborne LM. Monk C. Perinatal depression: the fourth inflammatory morbidity of pregnancy? Theory and literature review. Psychoneuroendocrinology 2013;38:1929-52. Crossref
16. Wadhwa PD, Culhane JF, Rauh V, Barve SS. Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. Matern Child Health J 2001;5:119-25. Crossref
17. Kelly R, Zatzick D, Anders T. The detection and treatment of psychiatric disorders and substance use among pregnant women cared for in obstetrics. Am J Psychiatry 2001;158:213-9. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):27-31 | https://doi.org/10.12809/hkjgom.20.1.06

Risk factors for Caesarean delivery after induction of labour among nulliparous women at term

Selina Tsz-Ching LEE, MBChB
Winnie Wai-Yan YEUNG, MBBS
Kwok-Yin LEUNG, MBBS, FRCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong

Objectives: To determine risk factors for Caesarean section after induction of labour (IOL) at term among nulliparous women, and to develop and validate a predictive model.
Methods: We retrospectively reviewed records of all nulliparous women with term, singleton, cephalic pregnancies and induction of labour from 1 January to 31 December 2017 in Queen Elizabeth Hospital. The cervix was examined on admission using the Modified Bishop Score for cervical dilatation, effacement, position, consistency, fetal station. Women with unfavourable cervix received cervical priming. Those with favourable cervix proceeded to induction of labour by combining artificial rupture of membrane and oxytocin infusion. Risk factors for Caesarean delivery were identified using univariable analysis and multivariable logistic regression. A nomogram was constructed using the independent risk factors. A receiver-operating characteristics curve and the area under the curve were generated to assess the discriminative power of the predictive model. An external validation was performed.
Results: A total of 1557 women who were nulliparous and had term, singleton, cephalic pregnancies and induction of labour were included for analysis. 1426 (91.6%) of them were of Chinese ethnicity. Of the 1557 women, 473 (30.4%) underwent Caesarean delivery and the remaining 1084 women delivered vaginally. In the multivariable logistic regression, independent risk factors for Caesarean delivery were maternal age (odds ratio [OR]=1.04, p=0.005), baseline height (OR=0.954, p=0.001), final body mass index (OR=1.11, p=0.001), and need for cervical priming (OR=1.32, p=0.033). The discriminative power of the predictive model was assessed by the area under the curve, which was 0.661 for the study cohort and 0.613 for the external validation set of 142 women.
Conclusion: Among Hong Kong nulliparous women with induction of labour at term, independent risk factors for Caesarean delivery were older maternal age, lower baseline height, higher final body mass index, and more need for cervical priming. The predictive model based on these risk factors can calculate the probability of Caesarean section for counselling these women.

Keywords: Cesarean section; Labor, induced; Nomograms

Introduction

Induction of labour aims at stimulating uterine contractions to accomplish delivery prior to the onset of spontaneous labour. Induction of labour is advocated to reduce fetal or neonatal morbidity and mortality, to minimise maternal morbidity, or to benefit both[1]. There is a trend of rising induction rates. The induction rate was >25% in the United States in 2017[2] and was 31.4% in 2016 and 33.4% in 2017 in public hospitals in Hong Kong. Nulliparous women have an increased risk of Caesarean delivery after induction of labour[3,4]. Caesarean section is associated with short-term and long-term complications such as postpartum haemorrhage, morbid adherence of placenta, and uterine rupture in future pregnancies[5-7]. Risk factors for Caesarean delivery after induction of labour include nulliparity, more advanced maternal age, greater body mass index, hypertension, and diabetes[8-12]. These risk factors have an overall predictive value around 70%[8,9]. This study aimed to determine risk factors for Caesarean section after induction of labour at term among nulliparous women in Hong Kong, and to develop and validate a predictive model to help counsel women at risk of Caesarean section.

Materials and Methods

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (Ref: KC/KE-19-0123/ER-3). We retrospectively reviewed records of all nulliparous women with term (≥37 weeks of gestation), singleton, cephalic pregnancies and induction of labour from 1 January to 31 December 2017 in Queen Elizabeth Hospital, using the Clinical Data Analysis and Reporting System. In addition, external validation was performed using a validation set of patients recruited using the same inclusion criteria from 1 January to 31 January 2018. Multiparous women or women with previous Caesarean were excluded.

Correspondence to: Dr Selina Tsz-Ching Lee
Email: ltc947@ha.org.hk

Data retrieved included maternal age, baseline weight (pre-pregnancy weight or weight at first antenatal visit), baseline height, final body mass index (BMI) before delivery, group B Streptococcus screening result, gestational age on induction, need for cervical priming, and outcome of induction.

The cervix was examined on admission using the Modified Bishop Score for cervical dilatation, effacement, position, consistency, fetal station[13]. The cervix was considered unfavourable if the Modified Bishop Score was <6. Women with unfavourable cervix received cervical priming by vaginal prostaglandin E2, either 3 mg tablet or 10 mg sustained release system (Propess) or both, in single or multiple doses. The choice of medication was based on patient and physician preference and the Modified Bishop Score. In patients with Modified Bishop Score ≤3, Propess was preferred because of its sustained release nature. Women with favourable cervix proceeded to induction of labour by combining artificial rupture of membrane and oxytocin infusion.

Statistical analyses were performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US) and STATA (version 14.2; StataCorp, College Station [TX], US). Risk factors for Caesarean delivery were identified using univariable analysis by Chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables. All p values were two-sided. Variables with a p value of <0.2 were included in the multivariable logistic regression model to identify independent risk factors. A nomogram was constructed using the independent risk factors[14]. A receiver-operating characteristics curve and the area under the curve were generated to assess the discriminative power of the predictive model.

Results

Of 5695 deliveries in 2017 in Queen Elizabeth Hospital, 2105 (37.0%) had spontaneous onset of labour, 2573 (45.2%) had induction of labour, 740 (13.0%) had Caesarean section without labour, and 277 (4.9%) had augmentation of labour. Among the 2573 women with induction of labour, we excluded those with multiparity (n=908, 35.3%), preterm gestation (n=429, 16.7%), and/or multiple pregnancies (n=5, 0.194%). A total of 1557 (60.5%) women who were nulliparous and had term, singleton, cephalic pregnancies and induction of labour were included for analysis (Table 1). 1426 (91.6%) of them were of Chinese ethnicity.

Table 1. Indications for induction of labour

Indications	No. (%) of cases (n=1557)*
Hypertension/proteinuria/pre-eclampsia	84 (5.39)
Gestational diabetes/diabetes	129 (8.29)
Maternal disease	13 (0.83)
Past term	272 (17.47)
Antepartum haemorrhage/ persistent show	220 (14.13)
Leaking	462 (29.67)
Abnormal fetal heart	188 (12.07)
Small fetal growth	112 (7.19)
Large fetal growth	77 (4.95)
Meconium stained liquor	15 (0.96)
Polyhydramnios	14 (0.90)
Oligohydramnios	42 (2.70)
Reduce fetal movement	31 (1.99)
Prolonged latent phase	21 (1.35)
Maternal fever	6 (0.39)
Maternal anxiety	6 (0.39)
Others	6 (0.39)

* Total exceed 1557 because some had >1 indication

Among the 1557 women included, 473 (30.4%) underwent Caesarean delivery for failed induction (n=340, 71.9%), non-reassuring fetal heart status (n=74, 15.6%), arrest of first stage of labour (n=40, 8.5%), and cord prolapse, prolonged second stage, and failed instrumental delivery (n=19, 4.0%). The remaining 1084 women delivered vaginally: 807 (74.4%) spontaneous vaginal delivery, 240 (22.1%) by vacuum extraction, and 37 (3.4%) by forceps delivery.

The Caesarean group and vaginal delivery group were compared in terms of maternal antepartum characteristics. In the univariable analysis, variables with a p value of <0.2 were included in the multivariable logistic regression model, namely maternal age, baseline weight, baseline height, final BMI, gestational age on induction, and need for cervical priming (Table 2). In the multivariable logistic regression, independent risk factors for Caesarean delivery were maternal age (odds ratio [OR]=1.04, p=0.005), baseline height (OR=0.954, p=0.001), final BMI (OR=1.11, p=0.001), and need for cervical priming (OR=1.32, p=0.033) [Table 3]. A nomogram was constructed using the independent risk factors (Figure 1). The discriminative power of the predictive model was assessed by the area under the curve, which was 0.661 (95% confidence interval=0.629-0.692, Figure 2a).

Table 2. Univariate analysis of risk factors for Caesarean delivery after induction of labour at term in nulliparous women

Characteristics	Caesarean delivery (n=473)*	Vaginal delivery (n=1084)*	p Value
Maternal age, y	31.3±4.4	30.7±4.3	0.078
Baseline weight, kg	56.0±9.8	53.9±8.9	<0.0005
Baseline height, cm	157.4±5.7	159.2±5.7	<0.0005
Final body mass index, kg/m^2	28.2±3.9	26.96±3.4	<0.0005
Positive group B streptococcus status	111 (23.5)	275 (25.4)	0.444
Gestational age on induction, weeks	38.9 (38-40)	39.0 (38-40)	0.037
Need for cervical priming	172 (36.4)	313 (28.9)	0.004

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

Table 3. Multivariate analysis of risk factors for Caesarean delivery after induction of labour at term in nulliparous women

Characteristics	Odds ratio (95% confidence interval)	p Value
Maternal age	1.04 (1.01-1.07)	0.005
Baseline weight	1.00 (0.976-1.03)	0.915
Baseline height	0.954 (0.927-0.982)	0.001
Final body mass index	1.11 (1.04-1.18)	0.001
Gestational age on induction	1.09 (0.984-1.21)	0.098
Need for cervical priming	1.32 (1.02-1.71)	0.033

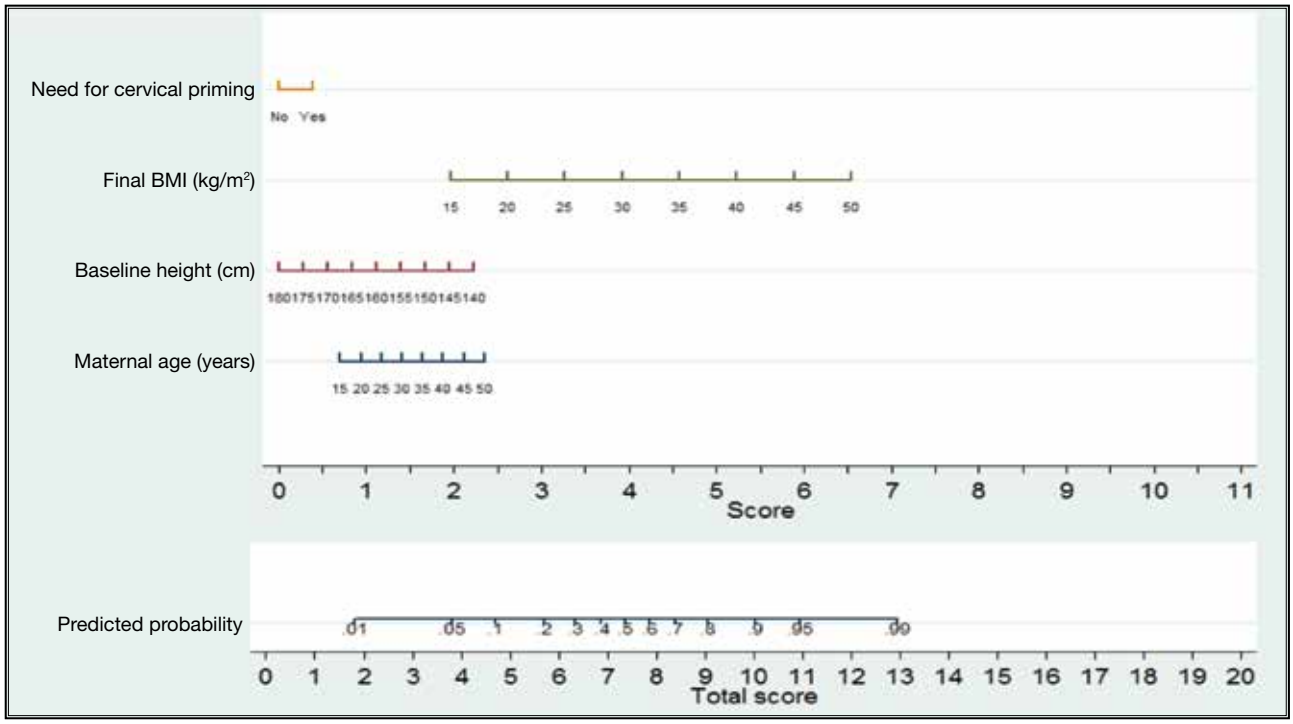

Figure 1. A nomogram predicting the probability of Caesarean delivery for nulliparous women with induction of labour at term based on the independent risk factors (maternal age, baseline height, final body mass index (BMI), and need for cervical priming).

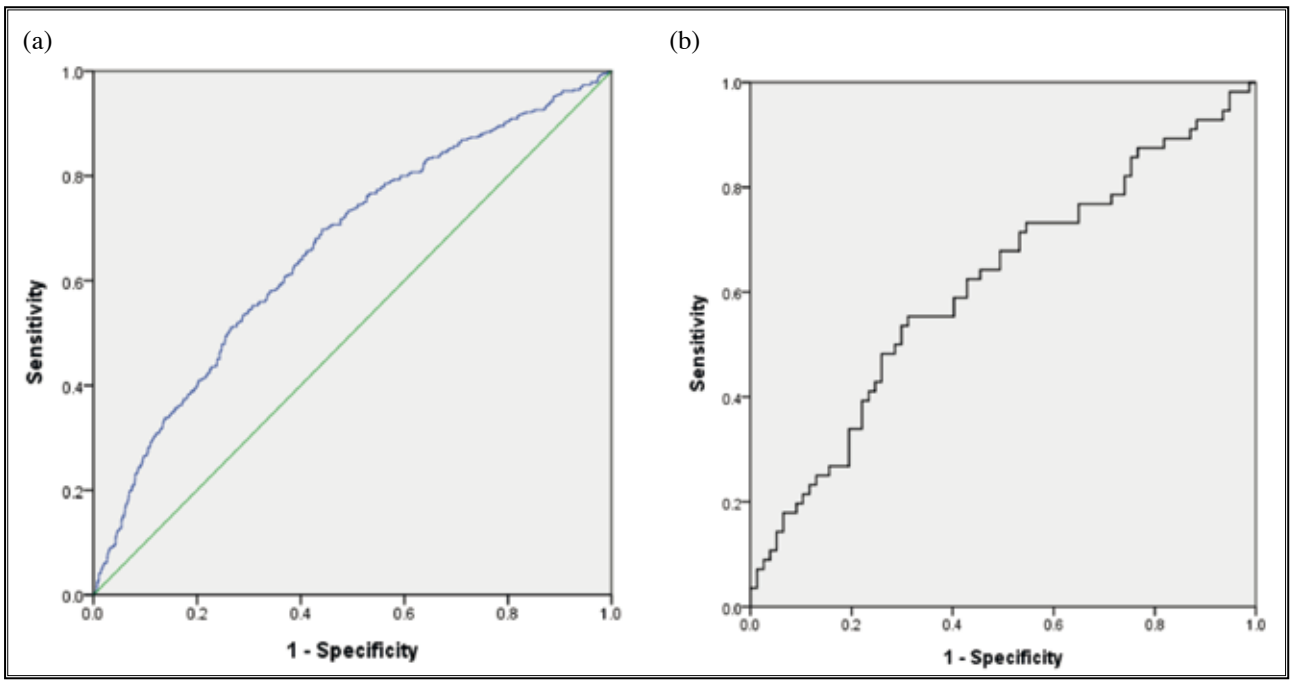

Figure 2. The area under the receiver operating characteristic curve was (a) 0.661 (95% CI=0.629-0.692) for 1557 nulliparous women with induction of labour at term and (b) 0.613 (95% CI=0.515-0.711) for the external validation set of 142 women.. Perpetrator of abuse

An external validation was performed using a validation set of 142 women recruited using the same inclusion criteria from 1 January to 31 January 2018. Of the 142 women with induction of labour, 60 (42.3%) underwent Caesarean delivery for failed induction (n=37, 61.7%), non-reassuring fetal heart status (n=16, 26.7%), arrest of first stage of labour (n=3, 5%), and cephalopelvic disproportion or prolonged second stage (n=4, 6.7%). The remaining 82 women delivered vaginally: 65 (79.3%) spontaneous vaginal delivery, 14 (17.1%) by vacuum extraction, and 3 (3.7%) by forceps delivery. The nomogram was applied to the external validation set, and the area under the curve was 0.613 (95% confidence interval=0.515-0.711, Figure 2b).

Discussion

Among Hong Kong nulliparous women with induction of labour at term, independent risk factors for Caesarean delivery were older maternal age, lower baseline height, higher final BMI, and more need for cervical priming. The risk factors identified in our study were consistent with those reported in studies on Western populations[9-12]. We aimed to develop and validate a predictive model to help counsel local nulliparous women with induction of labour at term at risk of Caesarean section whose antepartum characteristics (especially height, weight, and body mass index) may differ from Western populations. Previous studies have also included other risk factors such as ultrasound cervical length and birth weight in the prognostic model[10-12]. We included only four readily available antepartum risk factors to the predictive model; it is more user-friendly for obstetricians in patient counselling. In addition, the predictive model was externally validated to ensure the discriminative power and reproducibility[15].

Nonetheless, the predictive model and nomogram were limited to nulliparous women with induction of labour at term and cannot be generalisable to multiparous women, preterm deliveries, or those with previous Caesarean deliveries. We included only nulliparous women because they accounted for most of Caesarean deliveries after induction of labour. Although the model was externally validated, the validation set was from the same institute and the sample size was small. External validation with a larger sample from multiple centres can increase the generalisability. The discriminative power of the predictive model was only 0.661; other antepartum or intrapartum factors (such as indications for induction of labour, Modified Bishop Score, and presence of diabetes/hypertension) should have been evaluated to generate a more powerful predictive model[8,16-20].

The predictive model should be used in conjunction with the overall clinical information. It should not be used

alone for decision making on the mode of delivery. There is no threshold above which a direct Caesarean section is indicated instead of induction of labour. For example, in a 17-year-old nulliparous woman with a height of 155.4 cm, final BMI of 23.98 kg/m^2, and favourable cervix, her risk score is 0+0.8+1.4+3.2=5.4, and the predicted probability of Caesarean delivery is 18%. The patient can expect a higher chance of achieving vaginal delivery, hence proceeding to induction of labour if clinically indicated. In another example, in a 25-year-old nulliparous woman with a height of 149 cm, final BMI of 38.74 kg/m^2, and unfavourable cervix, her risk score is 0.4+1.6+5+1.2=8.2, and the predicted probability of Caesarean delivery is 68%. The patient can be counselled for short trial of induction of labour or direct Caesarean section based on clinical indications.

Conclusion

Among Hong Kong nulliparous women with induction of labour at term, independent risk factors for Caesarean delivery were older maternal age, lower baseline height, higher final BMI, and more need for cervical priming. The predictive model based on these risk factors can calculate the probability of Caesarean section for counselling these women.

Declaration

The authors have no conflict of interest to disclose.

References

1. ACOG Committee on Practice Bulletins -- Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009;114:386-97. Crossref
2. Osterman MJK, Martin JA. Recent declines in induction of labor by gestational age. Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/nchs/data/databriefs/db155.pdf. Accessed 29 July 2019.
3. Seyb ST, Berka RJ, Socol ML, Dooley SL. Risk of cesarean delivery with elective induction of labor at term in nulliparous women. Obstet Gynecol 1999;94:600-7. Crossref
4. Rouse DJ, Weiner SJ, Bloom SL, et al. Failed labour induction: toward an objective diagnosis. Obstet Gynecol 2011;117:267-72. Crossref
5. Field A, Haloob R. Complications of caesarean section. Obstet Gynaecol 2016;18:265-72. Crossref
6. Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol 1997;177:210-4. Crossref
7. Kwee A, Bots ML, Visser GH, Bruinse HW. Obstetric management and outcome of pregnancy in women with a history of caesarean section in the Netherlands. Eur J Obstet Gynecol Reprod Biol 2007;132:171-6. Crossref
8. Tolcher MC, Holbert MR, Weaver AL, et al. Predicting cesarean delivery after induction of labour among nulliparous women at term. Obstet Gynecol 2015;126:1059-68. Crossref
9. Levine LD, Downes KL, Parry S, Elovitz MA, Sammel MD, Srinivas SK. A validated calculator to estimate risk of cesarean after an induction of labor with an unfavorable cervix. Am J Obstet Gynecol 2018;254:e1-254.e7. Crossref
10. Vrouenraets FP, Roumen FJ, Dehing CJ, van den Akker ES, Aarts MJ, Scheve EJ. Bishop score and risk of cesarean delivery after induction of labour in nulliparous women. Obstet Gynecol 2005;105:690-7. Crossref
11. Peregrine E, O'Brien P, Omar R, Jauniaux E. Clinical and ultrasound parameters to predict the risk of cesarean delivery after induction of labor. Obstet Gynecol 2006;107:227-33. Crossref
12. Rane SM, Guirgis RR, Higgins B, Nicolaides KH. Models for the prediction of successful induction of labor based on pre-induction sonographic measurement of cervical length. J Matern Fetal Neonatal Med 2005;17:315-22. Crossref
13. Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266-8.
14. Grobman WA, Lai Y, Landon MB, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. Obstet Gynecol 2007;109:806-12. Crossref
15. Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: a clinical example. J Clin Epidemiol 2003;56:826-32. Crossref
16. Ware V, Raynor BD. Transvaginal ultrasonographic cervical measurement as a predictor of successful labor induction. Am J Obstet Gynecol 2000;182:1030-2. Crossref
17. Chandra S, Crane JM, Hutchens D, Young DC. Transvaginal ultrasound and digital examination in predicting successful labor induction. Obstet Gynecol 2001;98:2-6. Crossref
18. Ennen CS, Bofill JA, Magann EF, Bass JD, Chauhan SP, Morrison JC. Risk factors for cesarean delivery in preterm, term and post-term patients undergoing induction of labor with an unfavorable cervix. Gynecol Obstet Invest 2009;67:113-7. Crossref
19. Crane JM. Factors predicting labor induction success: a critical analysis. Clin Obstet Gynecol 2006;49:573-84. Crossref
20. Lange AP, Secher NJ, Westergaard JG, Skovgard I. Prelabor evaluation of inducibility. Obstet Gynecol 1982;60:137-47.

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):32-8 | https://doi.org/10.12809/hkjgom.20.1.04

Incidence and risk factors for pelvic lymph node metastasis in early-stage endometrial cancer: a retrospective study

Tony SC LING, MBBS, MRCOG
Hoi-Fong HUI, MBBS, MRCOG, FHKAM(O&G)
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, Hong Kong

Objective: We aimed to determine the incidence and risk factors of pelvic lymph node metastasis in patients with presumably early-stage endometrial cancer in a hospital in Hong Kong.
Methods: We retrospectively reviewed medical records of patients with endometrial cancer confined to the uterus who underwent total hysterectomy with bilateral salpingo-oophorectomy, with or without pelvic lymphadenectomy at Tuen Mun Hospital between 1 January 2011 and 31 December 2015. Patients with gross uterine serosa involvement, extrauterine disease, synchronised ovarian cancers, or sarcomatous tumour (adenosarcoma and endometrial stromal sarcoma) were excluded. Pelvic lymph node metastasis is defined as the presence of metastasis in the excised lymph nodes or within 12 months if pelvic lymphadenectomy was not performed.
Results: Of 268 patients (mean age, 54.8 years), 249 (92.8%) had endometrioid or mucinous adenocarcinoma, 14 (5.3%) had serous or clear cell carcinoma, and 5 (1.9%) had carcinosarcoma. Overall, 33 (12.5%) patients had high-grade pathology. 179 (66.8%) patients underwent pelvic lymphadenectomy with a mean of 25.2 (range, 7-85) pelvic lymph nodes removed; 16 of them had pelvic lymph node metastasis. Among the remaining 89 patients with no pelvic lymphadenectomy, 14 had selective lymph node sampling and 2 of them had pelvic lymph node metastasis. The incidence of pelvic lymph node metastasis in our cohort was 6.7% (n=18). In univariate logistic regression, large tumour size, deep myometrial invasion, cervical stromal invasion, and lymphovascular space invasion were significant risk factors of pelvic lymph node metastasis. In multivariate logistic regression, only large tumour size (adjusted OR=9.18, 95% CI=1.12-75.48, p=0.039) and cervical stromal invasion (adjusted OR=5.14, 95% CI=1.72-15.3, p=0.003) were significant independent risk factors.
Conclusion: Large tumour with maximal tumour diameter >2 cm and cervical stromal invasion are independent risk factor for pelvic lymph node metastasis in patients with early-stage endometrial cancer. Pelvic lymphadenectomy may not be necessary in patients with small tumour and absence of cervical involvement, especially when there is no evidence of high-grade pathology or deep myometrial invasion.

Keywords: Endometrial neoplasms; Lymph node excision

Introduction

Endometrial cancer is the most common gynaecological malignancy in high-income regions including Hong Kong.[1,2] The cumulative risk of endometrial cancer up to the age of 75 years was estimated to be 1.6% in high-income regions (1.75% in Hong Kong) and 0.7% in low-income regions.[2,3] The increased risk is attributed to the increased rate of obesity in high-income regions[4]. Total hysterectomy with bilateral salpingo-oophorectomy remains the gold standard treatment for most patients with early-stage endometrial cancer confined to the uterus.

The International Federation of Gynecology and Obstetrics (FIGO) has recommended surgical staging since 1988[5]. The pelvic lymph nodes are the most common site of extrauterine spread of endometrial cancer and metastasis is often clinically occult[6]. Pelvic lymph node metastasis is associated with worse outcome in terms of both disease-free and overall survival[7]. Pelvic lymphadenectomy was therefore proposed as a staging procedure (by providing prognostic information and stratifying patients for adjuvant therapy) and a potentially therapeutic procedure (by removing metastasis). However, it is associated with significant morbidity such as lymphoedema and lymphocysts in 11% to 38% of cases[8-10]. Prospective randomised studies and meta-analysis failed to demonstrate survival benefit of pelvic lymphadenectomy[11-13], as did a recent population-based registry study in Germany[14]. Hence, there is an international trend to reserve pelvic lymphadenectomy for patients with high risk of pelvic lymph node metastasis[5,15].

Correspondence to: Dr Tony SC LING
Email: lsc721@ha.org.hk

Risk factors for pelvic lymph node metastasis include large tumour size (maximal tumour diameter >2 cm), high-grade histology (FIGO grade 3 endometrioid adenocarcinoma and non-endometrioid carcinoma), deep myometrial invasion, cervical stromal invasion, and lymphovascular space invasion[16-20]. There is no international or local consensus on treatment[21,22], although validated protocols have been proposed by institutions such as the Mayo Clinic.

This study aimed to determine the incidence and risk factors of pelvic lymph node metastasis in patients with early-stage endometrial cancer in a hospital in Hong Kong so as to develop a protocol for stratifying patients to undergo lymphadenectomy.

Materials and Methods

The study was approved by the New Territories West Cluster Research Ethics Committee (reference number: NTWC/REC/18095). We retrospectively reviewed medical records of patients with endometrial cancer confined to the uterus who underwent total hysterectomy with bilateral salpingo-oophorectomy, with or without pelvic lymphadenectomy, by either laparotomy or laparoscopy, without neoadjuvant treatment in the Department of Obstetrics and Gynaecology, Tuen Mun Hospital between 1 January 2011 and 31 December 2015. Patients with gross uterine serosa involvement, extrauterine disease, synchronised ovarian cancers, or sarcomatous tumour (adenosarcoma and endometrial stromal sarcoma) were excluded.

All operations were performed by two consultant gynaecologists or under their supervision. Preoperative computed tomography or magnetic resonance imaging (MRI) were not routinely performed. Pelvic lymphadenectomy was routinely performed unless in very low risk cases (tumour was grossly limited to endometrium and <2 cm in maximal diameter, and preoperative biopsy did not yield high-grade pathology (ie, FIGO grade 3 endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, and carcinosarcoma) or when the operation was limited by patient factors such as old age, obesity, previous pelvic irradiation, and medical comorbidities. Pelvic lymphadenectomy involved dissection and removal of all lymph node–bearing tissues along the iliac vessels (from the deep circumflex vein to common iliac bifurcation) and in the obturator fossa (anterior to the obturator nerve), between the genitofemoral nerve and iliopsoas muscle laterally and obliterated umbilical artery medially. If pelvic lymphadenectomy was not performed, pelvic lymph node regions were routinely explored and any suspicious lymph nodes were sampled, as were any suspicious para-aortic lymph nodes. Postoperatively, patients were referred to the department of clinical oncology for assessment; adjuvant treatment was given if indicated. Patients were followed up for any recurrence or metastasis every 3 to 4 months in the first 3 years, every 6 months in the fourth and fifth year, and annually from the sixth to the tenth year.

Data collected included age at surgery, menopausal state, parity, body mass index, comorbidities (hypertension, diabetes mellitus, hyperlipidaemia, polycystic ovarian syndrome), hereditary nonpolyposis colorectal cancer gene mutation carrier status, history of other malignancies or pelvic irradiation, and histopathological variables of the endometrial tumour (maximal tumour dimension, tumour type and grade, depth of myometrial invasion, any cervical stromal invasion, and any lymphovascular space invasion).

FIGO grade 1 and 2 endometrioid adenocarcinoma and mucinous adenocarcinoma are considered low-grade pathology[23,24], whereas FIGO grade 3 endometrioid adenocarcinoma, serous carcinoma, clear cell carcinoma, and carcinosarcoma were considered high-grade pathology. Pelvic lymph node metastasis is defined as the presence of metastasis in the excised lymph nodes or within 12 months if pelvic lymphadenectomy was not performed.

Statistical analyses were performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US). Patients with or without pelvic lymph node metastasis were compared using two-tailed *t*-test for continuous variables and Fisher's exact test or Pearson Chi-squared test for categorical variables. A p value of <0.05 was considered statistically significant. Univariate and multivariate binary logistic regression models were used to identify risk factors for pelvic lymph node metastasis.

Results

Of 268 patients with a mean age of 54.8±9.7 years, 249 (92.8%) had endometrioid or mucinous adenocarcinoma, 14 (5.3%) had serous or clear cell carcinoma, and 5 (1.9%) had carcinosarcoma (Table 1). Overall, 33 (12.5%) patients had high-grade pathology.

179 (66.8%) patients underwent pelvic lymphadenectomy with a mean of 25.2±10.9 (range, 7-85) pelvic lymph nodes removed; 16 of them had pelvic lymph node metastasis. Among the remaining 89 patients with no pelvic lymphadenectomy, 14 had selective lymph node sampling and 2 of them had pelvic lymph node metastasis.

Table 1. Patients with or without pelvic lymph node metastasis in terms of clinical characteristics and pathological variables

Parameter	Overall (n=268)*	Pelvic lymph node metastasis		p Value
		No (n=250)*	Yes (n=18)*	
Age, y	54.8±9.7	54.9±9.7	53.1±9.9	0.553
Parity	1.87±1.50	1.85±1.43	2.11±2.32	0.474
Body mass index, kg/m^2	26.6±5.3	26.6±5.2	26.4±5.6	0.900
Menopaused	143 (53.4)	134 (53.6)	9 (50)	0.810
Diabetes mellitus	60 (22.4)	56 (22.4)	4 (22.2)	1.000
Hypertension	110 (41.0)	106 (42.4)	4 (22.2)	0.135
Hyperlipidaemia	8 (17.9)	45 (18.0)	3 (16.7)	1.000
Polycystic ovary syndrome	6 (2.2)	6 (2.4)	0	1.000
Hereditary nonpolyposis colorectal cancer gene mutation carrier	3 (1.1)	3 (1.2)	0	1.000
Previous pelvic irradiation	4 (1.5)	3 (1.2)	1 (5.6)	0.244
Previous malignancy, overall	26 (9.7)	24 (9.6)	2 (11.1)	0.689
Previous breast cancer on tamoxifen	12 (4.5)	12 (4.8)	0	1.000
Previous malignancy, colon	4 (1.5)	3 (1.2)	1 (5.6)	0.244
Tumour types and grades (according to International Federation of Gynecology and Obstetrics)				0.140
Endometrioid or mucinous grade 1	154 (58.6)	148 (60.4)	6 (33.3)	
Endometrioid grade 2	76 (28.9)	67 (27.3)	9 (50.0)	
Endometrioid grade 3	14 (5.3)	13 (5.3)	1 (5.6)	
Serous or clear cell carcinoma or carcinosarcoma	19 (7.2)	17 (6.9)	2 (11.1)	
Maximal tumour diameter >2 cm	142 (53.0)	125 (50)	17 (94.4)	<0.001
Myometrial invasion ≥50%	69 (25.7)	59 (23.6)	10 (55.6)	0.009
Cervical stromal invasion	31 (11.6)	22 (8.8)	9 (50.0)	<0.001
Lymphovascular space invasion	40 (15.0)	34 (13.7)	6 (33.3)	0.037
Microscopic uterine serosal involvement	4 (1.5)	3 (1.2)	1 (5.6)	0.244
Microscopic adnexal involvement	5 (1.9)	4 (1.6)	1 (5.6)	0.296
Para-aortic lymph node involvement	1 (0.04)	0 (0.0)	1 (5.6)	0.067
Pelvic lymphadenectomy done	179 (66.8)	163 (65.2)	16 (88.9)	0.04
No. of pelvic lymph nodes removed	25.2±10.9	25.5±11.1	22.3±9.1	0.264

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

The incidence of pelvic lymph node metastasis in our cohort was 6.7% (n=18). None of the patient without pelvic lymphadenectomy had pelvic lymph node recurrence both in the immediate 12 months and in the entire review period.

Compared with patients without pelvic lymph node metastasis, patients with pelvic lymph node metastasis were more likely to have large tumour size (maximal tumour diameter >2 cm) [94.4% vs 50%, p<0.001], deep myometrial invasion (≥50% myometrial thickness) [55.6% vs 23.6%, p=0.009], cervical stromal invasion (50.0% vs 8.8%, p<0.001), and lymphovascular space invasion (33.3% vs 13.7%, p=0.037) [Table 1]. More (but not significantly) patients with pelvic lymph node metastasis had high-grade pathology (16.7% vs 12.2%, p=0.481).

In univariate logistic regression, high-grade pathology had increased odds of pelvic lymph node

metastasis but not significantly (odds ratio [OR]=1.43, 95% confidence interval [CI]=0.39-5.24, p=0.586). Large tumour size, deep myometrial invasion, cervical stromal invasion, and lymphovascular space invasion were significant risk factors of pelvic lymph node metastasis (Table 2). In multivariate logistic regression, only large tumour size (adjusted OR=9.18, 95% CI=1.12-75.48, p=0.039) and cervical stromal invasion (adjusted OR=5.14, 95% CI=1.72-15.3, p=0.003) were significant independent risk factors.

Discussions

In 1987, the Gynecologic Oncology Group established the role of surgical staging and popularised lymphadenectomy in the treatment of endometrial cancer. In that seminal large-scale prospective study, the incidence of pelvic lymph node metastasis was 9% for all women with presumably early-stage endometrial cancer, 18% for those with high-grade pathology, 25% for those with deep one-third myometrial invasion, and 34% for those with high-grade pathology with deep one-third myometrial

Table 2. Incidence of pelvic lymph node metastasis by different pathological variables and predictors of lymph node metastasis

Variables	No. (%) of patients with pelvic lymph node metastasis	Univariate logistic regression		Multivariate logistic regression	
		Odds ratio (95% confidence interval)	p Value	Adjusted odds ratio (95% confidence interval)	p Value
Tumour types and grades (according to International Federation of Gynecology and Obstetrics)					
Grade 1 & 2	15 (6.5)	Reference			
Grade 3, serous or clear cell carcinoma, or carcinosarcoma	3 (9.1)	1.43 (0.39-5.24)	0.586	-	-
Maximal tumour diameter					
≤2 cm	1 (0.8)	Reference			
>2 cm	17 (12)	17 (2.23-129.69)	0.006	9.18 (1.12-75.48)	0.039
Depth of myometrial invasion					
<50%	8 (4)	Reference			
≥50%	10 (14.5)	4.05 (1.53-10.72)	0.005	1.52 (0.51-4.55)	0.457
Cervical stromal invasion					
Negative	9 (3.8)	Reference			
Positive	9 (29)	10.36 (3.73-28.81)	<0.001	5.14 (1.72-15.3)	0.003
Lymphovascular space invasion					
Negative	12 (5.3)	Reference			
Positive	6 (15)	3.15 (1.11-8.95)	0.031	1.31 (0.42-4.12)	0.646

Table 3. Comparison of the current study and a population-based study by Vargas et al.22 in terms of incidence of pelvic lymph node metastasis by tumour grade and depth of myometrial invasion

Depth of myometrial invasion	No. (%) of patients			
	Low-grade pathology		High-grade pathology	
	Current study	Vargas et al.	Current study	Vargas et al.
<50%	6/176 (4.6)	250/11771 (2.12)	0/16 (0.0)	147/2591 (5.6)
≥50%	7/54 (13.0)	411/3576 (11.5)	3/17 (17.6)	229/1391 (16.5)

invasion[6]. In our study, however, the incidence of pelvic lymph metastasis was 6.7% for the entire cohort, 9.1% for those with high-grade pathology, 14.5% for those with deep myometrial invasion, and 17.6% for those with high-grade pathology and deep myometrial invasion. The true incidence of pelvic lymph node metastasis could be underestimated because of the retrospective design of our study. Patients with undiagnosed occult pelvic lymph node metastasis may have undergone adjuvant radiotherapy and did not present as clinical disease. Nonetheless, in a population-based study of the United States Surveillance, Epidemiology, and End Results registry involving 19 329 women with surgically staged endometrial cancer diagnosed between 1988 and 2010[22], the incidences of pelvic lymph node metastasis were consistent with those in our cohort (Table 3).

In our study, tumour size >2 cm was independent risk factor for pelvic lymph node metastasis. Only one patient with tumour size ≤2 cm had pelvic lymph node metastasis. In a cohort of 91 patients with early-stage endometrial cancer, tumour size was independently associated with lymph node metastasis[25]. In a retrospective study involving 328 patients with low-grade endometrial cancer confined to the uterus who underwent surgery with or without pelvic lymphadenectomy and followed up for a median of 88 months, no patient with tumour diameter ≤2 cm and myometrial invasion <50% had positive lymph nodes or died of disease, and thus pelvic lymphadenectomy was deemed unnecessary[16].

Although the validity of the Mayo criteria was confirmed[18,21], assessment of the depth of myometrial invasion by intraoperative frozen section is not available in many institutions. In our unit, intraoperative gross evaluation was used instead. In a meta-analysis of 35 studies, intraoperative frozen section is superior to intraoperative gross evaluation in both sensitivity (85% vs 71%, p=0.0008) and specificity (97% vs 91%, p=0.0021) in determining deep myometrial invasion[26]. Thus, traditionally we performed pelvic lymphadenectomy if intraoperative gross evaluation suggested any degree of myometrial invasion or when tumour size >2 cm. With the introduction of Enhancing Radiological Investigation Services through Collaboration with the Private Sector project (Radi Collaboration) of the Hospital Authority, we have routinely referred patients with endometrial cancer for preoperative MRI of pelvis in the private sector since 2016. A meta-analysis of nine studies showed that MRI had a pooled sensitivity and specificity of both 86% in detecting deep myometrial invasion[27], which is comparable to intraoperative frozen section. There is no study comparing intraoperative frozen section with MRI yet.

In the Gynecologic Oncology Group study, high-grade pathology is a risk factor for pelvic lymph node metastasis[6]. However, in our study such correlation was not significant. This may be because our cohort had fewer patients with high-grade pathology (12.5%), compared with 20.6% in the registry study by Vargas et al.[22] and 25% in the Gynecologic Oncology Group study[6]. Our study is insufficient to disprove the correlation between high-grade pathology and pelvic lymph node metastasis because of its retrospective nature and absence of pathological re-review of specimens, and large-scale prospective study or population-based registry study is needed to confirm this observation.

Lymphovascular space invasion and cervical involvement have been reported to be independent risk factors for pelvic lymph node metastasis[17,19]. In our study, only cervical stromal invasion was an independent risk factor for pelvic lymph node metastasis. This is of importance as lymphovascular space invasion can only be assessed postoperatively. For patients with suspected cervical stromal invasion, the current paradigm is to perform total extrafascial 'simple' hysterectomy (rather than radical hysterectomy) because of a lack of survival benefits[28,29]. Pelvic lymphadenectomy remains an important staging procedure for patients with suspected cervical stromal invasion, and adjuvant radiotherapy should be considered especially when pelvic lymphadenectomy is not performed.

The main limitation of this study is its retrospective design, which cannot confirm correlations. A low rate of high-grade pathology is insufficient to disprove its correlation with pelvic lymph node metastasis. Para-aortic lymph node metastasis, late lymph node recurrence, and long-term survival data were not analysed, as were preoperative CA-125 level and MRI tumour volume index, which have been identified as independent risk factors for pelvic lymph node metastasis[30,31].

The incidence of endometrial cancer in Hong Kong has increased to 1050 new cases in 2016 from 570 new cases in 2006[2], but local data on pelvic lymph node metastasis are scarce. Pelvic lymphadenectomy is currently not indicated for small endometrial tumour, unless there is evidence suggestive of cervical involvement, deep myometrial invasion, or high-grade pathology.

Conclusion

Large tumour with maximal tumour diameter >2 cm and cervical stromal invasion are independent risk factor for pelvic lymph node metastasis in patients with early-stage endometrial cancer. Pelvic lymphadenectomy may not be necessary in patients with small tumour and absence of cervical involvement, especially when there is no evidence of high-grade pathology or deep myometrial invasion.

Acknowledgements

Dr Yin-Fong KWOK and Dr Man-Chi CHAN of the Department of Obstetrics and Gynaecology, Tuen Mun Hospital contributed to the design of the study. Dr Edmond Pui-Hang CHOI of the School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong contributed to the statistical analysis.

Declaration

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors have no conflict of interest to disclose.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Crossref
2. Hong Kong Cancer Registry, Hospital Authority. Overview of Hong Kong Cancer Statistics of 2016. Available at: http://www3.ha.org.hk/cancereg/pdf/overview/Summary%20of%20CanStat%202016.pdf Updated: October 2018. Assessed 24 May 2019.
3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108. Crossref
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78. Crossref
5. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. Int J Gynaecol Obstet 2018;143(Suppl 2):37-50. Crossref
6. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60(8 Suppl):2035. Crossref
7. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55-65. Crossref
8. Nunns D, Williamson K, Swaney L, Davy M. The morbidity of surgery and adjuvant radiotherapy in the management of endometrial carcinoma. Int J Gynecol Cancer 2000;10:233-8. Crossref
9. Todo Y, Yamamoto R, Minobe S, et al. Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy. Gynecol Oncol 2010;119:60. Crossref
10. Yost KJ, Cheville AL, Al-Hilli MM, et al. Lymphedema after surgery for endometrial cancer: prevalence, risk factors, and quality of life. Obstet Gynecol 2014;124:307-15. Crossref
11. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100:1707. Crossref
12. ASTEC study group; Kitchener H, Swart AM, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373:125. Crossref
13. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev 2017;10:CD007585. Crossref
14. Pölcher M, Rottmann M, Brugger S, et al. Lymph node dissection in endometrial cancer and clinical outcome: a population-based study in 5546 patients. Gynecol Oncol 2019. Crossref
15. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: Diagnosis, treatment and follow-up. Ann Oncol 2016;27:16-41. Crossref
16. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000;182:1506. Crossref
17. Akbayir O, Corbacioglu A, Goksedef BP, et al. The novel criteria for predicting pelvic lymph node metastasis in endometrioid adenocarcinoma of endometrium. Gynecol Oncol 2012;125:400-3. Crossref
18. Milam MR, Java J, Walker JL, Metzinger DS, Parker LP, Coleman RL. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012;119:286-92. Crossref
19. Solmaz U, Mat E, Dereli M, et al. Lymphovascular space invasion and cervical stromal invasion are independent risk factors for nodal metastasis in endometrioid endometrial cancer. Aust N Z J Obstet Gynaecol 2015;55:81-6. Crossref
20. Al Hilli MM, Podratz KC, Dowdy SC, et al. Preoperative biopsy and intraoperative tumor diameter predict lymph node dissemination in endometrial cancer. Gynecol Oncol 2013;128:294-9. Crossref

21. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109:11. Crossref
22. Vargas R, Rauh-Hain JA, Clemmer J, et al. Tumor size, depth of invasion, and histologic grade as prognostic factors of lymph node involvement in endometrial cancer: a SEER analysis. Gynecol Oncol 2014;133:216-20. Crossref
23. Melhem MF, Tobon H. Mucinous adenocarcinoma of the endometrium: a clinico-pathological review of 18 cases. Int J Gynecol Pathol 1987;6:347-55. Crossref
24. Soslow RA, Tornos C, Park KJ, et al. Endometrial carcinoma diagnosis: use of FIGO grading and genomic subcategories in clinical practice: Recommendations of the International Society of Gynecological Pathologists. Int J Gynecol Pathol 2019;38(Suppl 1):S64-S74. Crossref
25. Schink JC, Lurain JR, Wallemark CB, Chmiel JS. Tumor size in endometrial cancer: a prognostic factor for lymph node metastasis. Obstet Gynecol 1987;70:216-9. Crossref
26. Alcazar JL, Dominguez-Piriz J, Juez L, Caparros M, Jurado M. Intraoperative gross examination and intraoperative frozen section in patients with endometrial cancer for detecting deep myometrial invasion: a systematic review and meta-analysis. Int J Gynecol Cancer 2016;26:407-15. Crossref
27. Andreano A, Rechichi G, Rebora P, Sironi S, Valsecchi MG, Galimberti S. MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis. Eur Radiol 2014;24:1327-38. Crossref
28. Phelippeau J, Koskas M. Impact of radical hysterectomy on survival in patients with Stage 2 Type1 endometrial carcinoma: a matched cohort study. Ann Surg Oncol 2016;23:4361-7. Crossref
29. Takano M, Ochi H, Takei Y, et al. Surgery for endometrial cancers with suspected cervical involvement: Is radical hysterectomy needed (a GOTIC study)? Br J Cancer 2013;109:1760-5. Crossref
30. Todo Y, Okamoto K, Hayashi M, et al. A validation study of a scoring system to estimate the risk of lymph node metastasis for patients with endometrial carcinoma for tailoring the indication of lymphadenectomy. Gynecol Oncol 2007;104:623-8. Crossref
31. Kang S, Kang WD, Chung HH, et al. Preoperative identification of a low-risk group for lymph node metastasis in endometrial cancer: a Korean gynecologic oncology group study. J Clin Oncol 2012;30:1329-34. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):39-42 | https://doi.org/10.12809/hkjgom.20.1.05

Cosmetic outcome of single-port versus multiple-port laparoscopic surgery in gynaecology

Menelik Man-Hin LEE, MBBS, MRCOG, FHKCOG, FHKAM (O&G)
Ivy Yin-Yan WONG, MBBS, MRCOG, FHKCOG, FHKAM (O&G)
Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong

Objective: To compare single-port laparoscopic surgery (SPLS) with multiple-port laparoscopic surgery (MPLS) in terms of cosmetic outcome, operating time, and length of hospital stay.
Methods: We retrospectively retrieved all SPLS cases performed in the gynaecology department at Queen Elizabeth Hospital during 2017 to 2018. Same number of matched MPLS cases performed within the same period was retrieved randomly for comparison. Patient satisfaction regarding surgical scar was assessed using the modified Patient Scar Assessment Questionnaire. Only the satisfaction rating was used. Score for each item ranges from 1 (least satisfied) to 4 (very satisfied).
Results: 12 patients who underwent SPLS were compared with 12 randomly selected matched patients who underwent MPLS. Both SPLS and MPLS groups scored highly for the Patient Scar Assessment Questionnaire. SPLS group generally scored slightly higher than MPLS group and significantly higher in items: the colour of the wound associated with surrounding tissue, the height of the scar, overall appearance, and overall symptoms from the scar. 91.7% of SPLS patients and 58.3% of MPLS patients preferred the respective techniques if given a choice.
Conclusion: Both SPLS and MPLS achieved exceptional cosmesis outcomes, but SPLS was superior to MPLS in some items. More patients may prefer SPLS if they are aware of the technology.

Keywords: Cosmetics; Gynecology; Laparoscopy

Introduction

Single-port laparoscopic surgery (SPLS) is gaining popularity worldwide. In gynaecology, SPLS has been performed for ectopic pregnancy, ovarian cystectomies, hysterectomies, and other laparoscopic gynaecological surgieries[1,2]. Compared with multiple-port laparoscopic surgery (MPLS), SPLS is reported to be associated with reduced time for specimen retrieval, fewer ruptured retrieval bags, lower pain score, and less frequency in analgesia use[2,3], with comparable length of hospital stay and improvement in quality of life[4,5]. SPLS results in better cosmetic appearance and scar satisfaction, compared with MPLS[6]. We aimed to compare SPLS with MPLS in terms of cosmetic outcome, operating time, and length of hospital stay.

Methods

This study was approved by the Kowloon Central / Kowloon East Research Ethics Committee (Reference: KC/KE-19-0291/ER-1). We retrospectively retrieved all SPLS cases performed in the gynaecology department at Queen Elizabeth Hospital during 2017 to 2018 by gynaecologists with advanced level laparoscopic accreditation under the Hong Kong College of Obstetrics and Gynaecologists. Same number of matched MPLS cases performed within the same period was retrieved randomly for comparison.

SPLS was performed via a 2-3 cm umbilical port using a transumbilical tripod system (Olympus TriPort15) with non-articulated instruments. The rectus layer was closed using continuous 1-0 vicryl, and the fascia layer was approximated by continuous 1-0 vicryl with subcuticular vicryl to skin. MPLS was performed via a routine 1-cm umbilical port of entry with two to three 0.5-cm accessor ports at left iliac fossa, left lateral (umbilical level), right iliac fossa, or suprapubic site of entry. The umbilical wound was closed using interrupted 1-0 vicryl, whereas accessary ports were closed using sterile strips.

Patient satisfaction regarding surgical scar was assessed using the modified Patient Scar Assessment Questionnaire[7] at 8-week follow-up or via phone interview at 8 to 12 weeks. The questionnaire is validated and has two components: attribute and satisfaction. Only the satisfaction rating was used and translated to Chinese for those preferred the Chinese version. Score for each item ranges from 1 (least satisfied) to 4 (very satisfied). There was one additional question: do you prefer SPLS or MPLS if given a choice.

Correspondence to: Dr Menelik Lee
Email: menelik.lee@gmail.com

Data retrieved included operating time and length of hospital stay. When comparing operating time, those with multiple surgeries (hysteroscopy dilatation and curettage or extensive adhesiolysis) at the same settings or those with hysterectomy or myomectomy were excluded, as their operating time was longer than those with laparoscopic surgeries for ovarian cysts. When comparing ovarian cyst size, the mean size was calculated as per largest diameter for unilocular cysts and as combined diameters for multiloculated unilateral or bilateral cysts.

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US). The SPLS and MPLS groups were compared using analysis of variance. A value of $p<0.05$ was considered statistically significant.

Results

12 patients underwent SPLS for unilateral oophorectomy (for ovarian fibroma) [n=1], bilateral salpingoophrectomy (n=2), bilateral salpingoophrectomy and hysteroscopy dilatation and curettage (for irregular menstruation) [n=1], unilateral ovarian cystectomy (n=7), and unilateral ovarian cystectomy and hysteroscopy dilatation and curettage (n=1). In addition, 12 matched patients were randomly selected who underwent MPLS for myomectomy (n=1), bilateral salpingoophrectomy (n=3), unilateral ovarian cystectomy (n=8), and unilateral ovarian cystectomy and hysteroscopy dilatation and curettage (n=1) [Table 1].

The SPLS and MPLS groups were comparable in terms of patient age (34.8 vs 37.3 years, p=0.717), time of interview for questionnaire (8.25 vs 9.08 weeks, p=0.147), ovarian cyst size (after excluding 2 cases of fibroid removal) [3.5 vs 5.83 cm, p=0.347], and operating time (after excluding 3 cases of combined procedures and 1 case of myomectomy) [74.9 vs 70.6 mins, p=0.661]. No patients had body mass index exceeding 30.

Both SPLS and MPLS groups scored highly for the Patient Scar Assessment Questionnaire. SPLS group generally scored slightly higher than MPLS group and significantly higher in items: Q1 (the colour of the wound associated with surrounding tissue), Q5 (height of the scar), Q9 (overall appearance), and Q15 (overall symptoms from the scar) [Table 2]. 91.7% of SPLS patients and 58.3% of MPLS patients preferred the respective techniques if given a choice.

Discussion

SPLS has been demonstrated to be safe in multiple surgical and gynaecological surgeries[8]. Nonetheless, it remains a relatively new technique in Hong Kong. SPLS has been reported to offer better cosmesis and patient satisfaction than MPLS in cholecystectomy[9-14]. Cosmetic outcome is particularly important for women. Nonetheless, there are few studies on cosmetic outcomes of SPLS in gynaecology.

Our study suggested that both SPLS and MPLS achieved exceptional cosmesis outcomes as measured by the Patient Scar Assessment Questionnaire, but SPLS was superior to MPLS in terms of the colour of the wound associated with surrounding tissue, the height of the scar, overall appearance, and overall symptoms from the scar. The overall score between the SPLS and MPLS groups was comparable. This may be due to the comparable cosmesis outcome. It may also be due to the lack of public awareness of SPLS and hence no higher expectation on MPLS by patients. This was reflected by the fact that more patients preferred SPLS if given a choice.

Table 1. Types of surgery performed using single-port versus multiple-port laparoscopic surgery

Type of surgery	No. of patients	
	Single-port laparoscopic surgery (n=12)	Multiple-port laparoscopic surgery (n=12)
Myomectomy	0	1
Unilateral oophorectomy	1	0
Bilateral salpingoophrectomy	2	3
Bilateral salpinoophrectomy and hysteroscopy dilatation and curettage	1	0
Unilateral ovarian cystectomy	7	8
Unilateral ovarian cystectomy and hysteroscopy dilatation and curettage	1	1

Table 2. Cosmetic outcomes, operating time, and length of hospital stay of single-port versus multiple-port laparoscopic surgery

Parameter	Single-port laparoscopic surgery (n=12)	Multiple-port laparoscopic surgery (n=12)	p Value
Mean patient age, y	34.8	37.3	0.717
Mean time of interview for questionnaire, follow-up weeks	8.25	9.08	0.143
Mean Patient Scar Assessment Questionnaire score	54.58	50.33	0.114
Q1	3.67	3.25	0.045
Q2	3.58	3.25	0.180
Q3	3.83	3.5	0.09
Q4	3.75	3.5	0.216
Q5	3.58	3.08	0.03
Q6	3.5	3.25	0.216
Q7	3.42	3.0	0.092
Q8	3.58	3.25	0.105
Q9	3.67	3.25	0.045
Q10	3.42	3.5	0.688
Q11	3.67	3.58	0.680
Q12	3.67	3.42	0.229
Q13	3.83	3.58	0.187
Q14	3.67	3.67	1.000
Q15	3.75	3.25	0.016
Mean ovarian cyst size, cm	3.5	5.83	0.347
Mean operating time (excluding combined procedures or myomectomy), mins	74.89	70.6	0.661
Mean length of hospital stay, d	2.33	2.33	1.000
Do you prefer single-port or multiple-port laparoscopic surgery if given a choice	11/12 (91.7%)	7/12 (58.3%)	

Nonetheless, SPLS is technically more difficult than MPLS. Proximity of instruments and difficult ergonomics may hinder the freedom of movement and affect operating time. However, operating time does not vary a great deal in experienced hands[4]. In our study, operating time was longer in SPLS for smaller ovarian cysts but not significantly. The operating time can be reduced with simulation training, increased experience, use of articulate instruments, and proper case selection.

There are limitations to this study. The sample size was too small to have sufficient statistical power. The study was retrospective, and randomised controlled trials are needed to confirm the findings. Only the satisfaction rating of the Patient Scar Assessment Questionnaire was used; the attribute rating was removed. The Chinese version of the questionnaire was not validated, and meanings of certain questions may be lost in translation. Objective evaluation of cosmetic outcomes by an independent observer could have reduced bias. Reasons for the preference for SPLS and complications of SPLS and MPLS should have been investigated. Our study could not demonstrate SPLS to be superior to MPLS.

Conclusion

Both SPLS and MPLS achieved exceptional cosmesis outcomes, but SPLS was superior to MPLS in some items. More patients may prefer SPLS if they are aware of the technology. SPLS also has benefits of reduced pain and reduced analgesia used.

Declaration

The authors have no conflict of interest to disclose.

References

1. Kim MK, Kim JJ, Choi JS, Eom JM, Lee JH. Prospective comparison of single port versus conventional laparoscopic surgery for ectopic pregnancy. J Obstet Gynaecol Res 2015;41:590-5. Crossref
2. Huang BS, Wang PH, Tsai HW, Hsu TF, Yen MS, Chen YJ. Single-port compared with conventional laparoscopic cystectomy for ovarian dermoid cysts. Taiwan J Obstet Gynecol 2014;53:523-9. Crossref
3. So KA, Lee JK, Song JY, et al. Tissue injuries after single-port and multiport laparoscopic gynecologic surgeries: a prospective multicenter study. Exp Ther Med 2016;12:2230-6. Crossref
4. Wang SY, Yin L, Guan XM, Xiao BB, Zhang Y, Delgado A. Single port transumbilical laparoscopic surgery versus conventional laparoscopic surgery for benign adnexal masses: a retrospective study of feasibility and safety. Chin Med J (Engl) 2016;129:1305-10. Crossref
5. Eom JM, Kim KH, Yuk JS, Roh SI, Lee JH. Quality of life after single-port laparoscopic surgery versus conventional laparoscopic surgery for benign gynecologic disease. Surg Endosc 2015;29:1850-5. Crossref
6. Borle FR, Mehra B, Ranjan Singh A. Comparison of cosmetic outcome between single-incision laparoscopic cholecystectomy and conventional laparoscopic cholecystectomy in rural Indian population: a randomized clinical trial. Indian J Surg 2015;77(Supp 3):877-80. Crossref
7. Durani P, McGrouther DA, Ferguson MW. The Patient Scar Assessment Questionnaire: a reliable and valid patient-reported outcomes measure for linear scars. Plast Reconstr Surg 2009;123:1481-9. Crossref
8. Far SS, Miraj S. Single-incision laparoscopy surgery: a systematic review. Electron Physician 2016;8:3088-95. Crossref
9. Eom JM, Ko JH, Choi JS, Hong JH, Lee JH. A comparative cross-sectional study on cosmetic outcomes after single port or conventional laparoscopic surgery. Eur J Obstet Gynecol Reprod Biol 2013;167:104-9. Crossref
10. Marks J, Tacchino R, Roberts K, et al. Prospective randomized controlled trial of traditional laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy: report of preliminary data. Am J Surg 2011;201:369-72. Crossref
11. Bucher P, Pugin F, Buchs NC, Ostermann S, Morel P. Randomized clinical trial of laparoendoscopic single-site versus conventional laparoscopic cholecystectomy. Br J Surg 2011;98:1695-702. Crossref
12. Gangl O, Hofer W, Tomaselli F, Sautner T, Fugger R. Single incision laparoscopic cholecystectomy (SILC) versus laparoscopic cholecystectomy (LC): a matched pair analysis. Langenbecks Arch Surg 2011;396:819-24. Crossref
13. Garg P, Thakur JD, Raina NC, Mittal G, Garg M, Gupta V. Comparison of cosmetic outcome between single-incision laparoscopic cholecystectomy and conventional laparoscopic cholecystectomy: an objective study. J Laparoendosc Adv Surg Tech A 2012;22:127-30. Crossref
14. Phillips MS, Marks JM, Roberts K, et al. Intermediate results of a prospective randomized controlled trial of traditional four-port laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy. Surg Endosc 2012;26:1296-303. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):43-7 | https://doi.org/10.12809/hkjgom.20.1.07

Clinical features, diagnosis, and management of abdominal wall endometriosis: a review

Deborah YL WANG, MBChB
Department of Obstetrics and Gynaecology, United Christian Hospital, Hong Kong
Mona WC LAM, MBChB, MPH(CUHK), FRCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, Tseung Kwan O Hospital, Hong Kong

Abdominal wall endometriosis is characterised by presence of ectopic endometrial tissue in the subcutaneous and muscle layer of the abdomen. It is usually related to previous surgical scars (commonly of Caesarean section). This article aims to review the pathogenesis, clinical features, diagnosis, and treatment of abdominal wall endometriosis.

Keywords: Abdominal wall; Cesarean section; Endometriosis; Pelvis

Introduction

Endometriosis is characterised by uterine endometrial mucosal tissue found outside the uterus[1]. It usually involves pelvic organs, but 9% to 15% of cases involve extraperitoneal regions[2], including the bowels, the ureter, and the lungs. Abdominal wall endometriosis (AWE) is defined as the presence of ectopic endometrium between the skin and parietal peritoneum[3]. AWE is very rare and usually related to Caesarean section and pelvic surgeries. With the increasing trends of Caesarean section rates, the frequency of abdominal wall endometriosis is expected to rise, and it is useful for gynaecologists to be familiar with this condition.

Epidemiology

AWE is likely to be underreported owing to its rarity. The true prevalence is unknown and is estimated as 0.03% to 1%[4]. The mean patient age at presentation is 31.4 (range, 29.1-33.8) years[5]. AWE can be of primary or secondary origin. Primary AWE is not caused by surgery and accounts for around 20% of all cases; the location of ectopic tissue is often at the umbilical or groin area. Secondary AWE is associated with prior surgery and accounts for >70% of all cases, with >50% of cases relating to Caesarean section[5].

Pathogenesis

The exact pathogenesis of AWE remains unknown. The most accepted theory to explain the formation of AWE is the direct implantation theory[5,6]. It states that endometrial cells seed during pelvic surgery and are transported to ectopic sites. The endometrial cells then proliferate to form endometrioma. Another theory is lymphatic or haematogenous spread of endometrial cells, which may lead to deposition at scar region. This can explain the occurrence of AWE in patient without prior surgical history[6]. In addition, there is the theory of metaplasia of abdominal wall cells into endometrial tissue under the influence of hormones[7].

Risk factors

Prior history of abdominal or pelvic surgery is the greatest risk factor for the development of AWE. Horton et al[5] reviewed 445 cases of AWE and reported that 57% of the cases had a prior Caesarean section and 11% had prior hysterectomy; the mean interval from index surgery to presentation was 3.6 (range, 2.5-4.8) years. Khan et al[8] reported that body mass index was higher in the 34 patients with AWE than controls. It is hypothesised that suboptimal closure of the uterine incision or abdominal layers owing to obesity contributes to the development of AWE. Pelvic endometriosis is also a risk factor for the development of AWE. Horton et al[5] reported that 13% of AWE has concurrent pelvic endometriosis and such incidence is similar to that of the general population (8% to 15%).

Pathology

Depending on the location at abdominal wall layers, AWE can be superficial (affecting subcutaneous tissue only and above the fascia), intermediate (infiltrating rectus muscles fascia), and deep (affecting rectus muscles)[9]. Endometriotic tissue can appear as a bluish, dark red, or black cyst or nodule with brown material, distinguishing itself from surrounding yellow subcutaneous fat. It has a hard consistency and irregular surface when found in muscles[10]. Microscopy shows the presence of endometrial glands, stroma, or haemosiderin pigment.

Correspondence to: Dr Mona WC LAM
Email: lamwc2@ha.org.hk

Diagnosis

Typical presentations of AWE comprise a triad of prior history of Caesarean section, cyclical pain localised at the site of the lesion associated with menstruation, and presence of a mass lesion near a surgical scar[11]. However, only 60% of patients demonstrate this triad of presentations[12]. Abdominal mass (96%) and pain in the mass (87%) are the most common symptoms, whereas cyclic pain occurs in only 57%[5]. Patients may also complain of increase in size, bleeding, and skin discoloration of the mass in relation to menstruation[2].

On physical examination, there is an immobile abdominal mass that can be tender upon palpation, and the overlying skin may show discolouration[13]. The mass is usually located cephalad and lateral to the Pfannenstiel scar in Caesarean section–related cases, because the facial incision is often extended more lateral and cephalad than the skin incision[3].

Careful history taking and physical examination is essential for diagnosing AWE. It is estimated that 20% to 50% of scar endometriosis are correctly diagnosed preoperatively[2,14]. Diagnosis is difficult when the mass is not palpable or presentation is atypical such as a mass without cyclical pain. The differential diagnoses include non-tumoural lesions (hernia, granuloma, haematoma, abscess, fat necrosis), benign neoplasms (lipoma, neuroma, desmoid tumour), malignant neoplasms (carcinomas, melanoma, sarcoma, metastasis) and secondary tumours (Sister Mary Joseph node).

Imaging modalities aid the diagnosis and facilitate surgical planning, especially for large AWE in which mesh placement for large fascial defects or complex abdominal closure may be required.

Ultrasonography

Ultrasonography is used to confirm the presence of lesion, to assess its size, content, location, and margin, and to differentiate cystic from solid masses. AWE usually appears as solid heterogeneous hypoechoic masses with ill-defined and irregular margins[15,16] (Figure 1a). Echogenic spots (haemorrhage) or thick echogenic strands (fibrosis) can also be seen, depending on menstrual phase of patient[17]. A hyperechoic ring at the periphery of lesion represents inflammatory changes of adipose tissue[18]. Vascular pattern of lesion varies with the size of AWE. Lesions >15 mm are found to have intralesional vascularisation that can be demonstrated by Doppler velocimetry[19] (Figure 1b). However, these findings are non-specific for AWE.

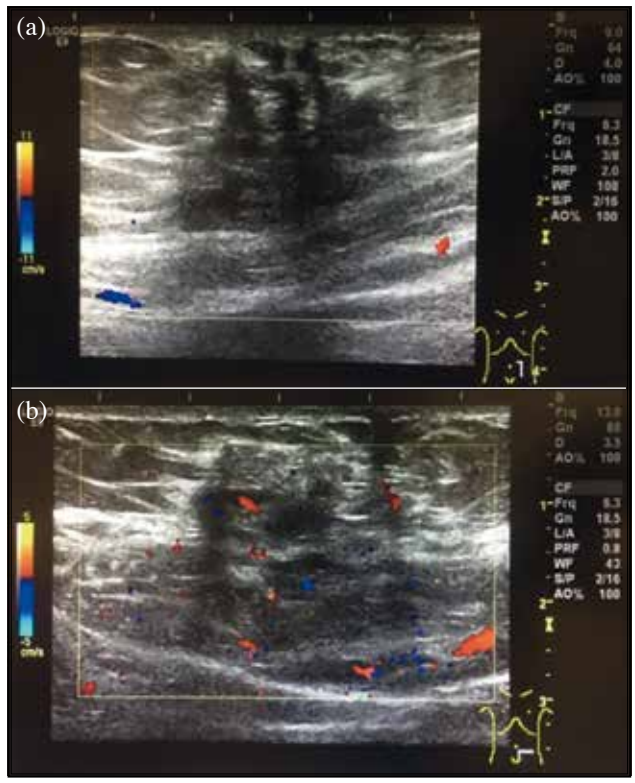

Figure 1. (a) A heterogeneous hypoechoic mass with ill-defined and irregular margins; and (b) intralesional vascularisation on Doppler ultrasonograph.

Nonetheless, ultrasonography is low cost, non-invasive, and radiation-free. Three-dimensional ultrasonography is more useful to demonstrate the depth of infiltration of the mass and the relation to surrounding tissues[20,21].

Magnetic resonance imaging

Magnetic resonance imaging is the modality of choice to assess soft-tissue mass. AWE appears as hyperinetense heterogeneous mass on T1-weighted (with or without fat suppression) and T2-weighted images (Figure 2). For chronic scar endometriosis, lesions have speculated margins and low-signal intensity on T2-weighted images owing to its fibrotic component[22,23]. The chronicity of the haematoma is demonstrated by the presence of haemorrhage inside the lesion[23]. Advantages of magnetic resonance imaging include clearer delineation of subcutaneous tissues and muscles, more accurate assessment of the location and depth of infiltration of AWE, no ionising radiation, and the ability to detect small lesion[22].

Computed tomography

AWE appears as a solid soft-tissue mass with mild to moderate contrast enhancement[17,23], depending on the phase of menstrual cycle, degree of fibrosis, bleeding, and inflammatory response (Figure 3). Feeding vessels may also be seen within or near the lesion[16,23].

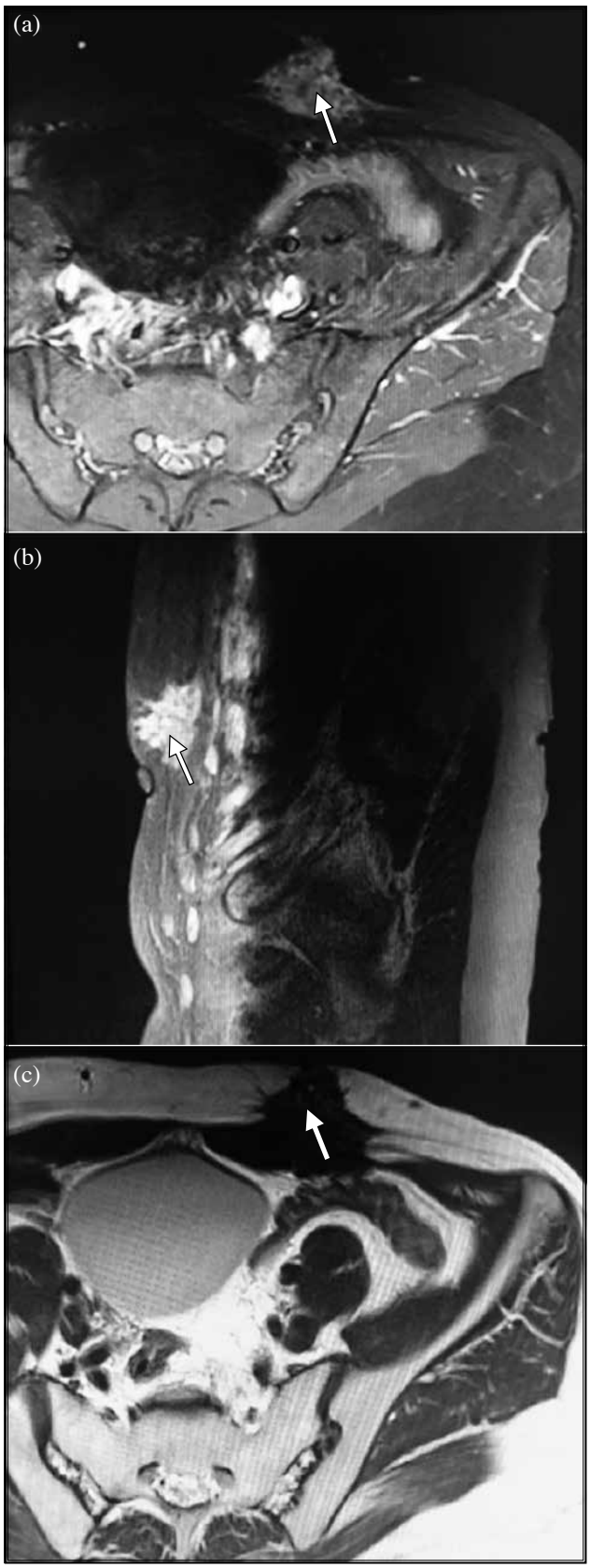

Figure 2 (a) Axial T1-weighted image showing heterogeneous hyperintense lesion (arrow); (b) sagittal T1-weighted image showing enhancement of the lesion with contrast (arrow); and (c) T2-weighted image showing speculated margins and low-signal intensity (arrow).

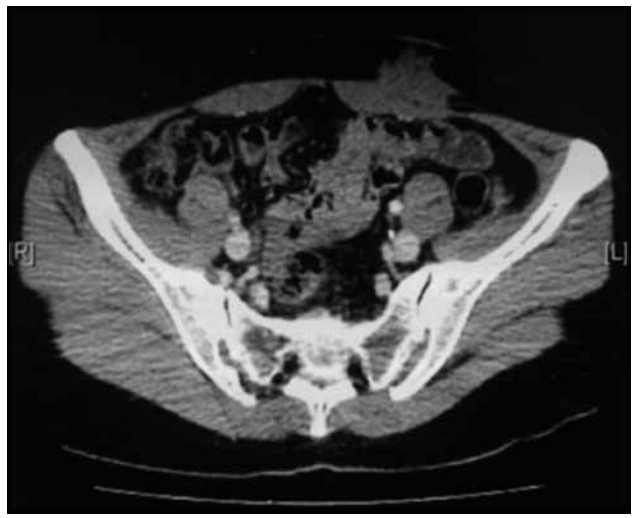

Figure 3. Axial contrast-enhanced computed tomography showing speculated irregular soft-tissue mass in abdominal wall.

Fine needle aspiration

Ultrasound-guided fine needle aspiration is used to confirm the diagnosis of AWE and to exclude malignancy. Incisional hernia must be ruled out before aspiration. However, its use for the diagnosis of AWE is controversial because of the risk of spreading endometriosis at the puncture site. It is advisable to include the biopsy tract in the field of resection intra-operatively[24]. In old AWE lesions with large fibrotic content, fine needle aspiration may not yield enough tissue for sampling and lead to inconclusive results. Histologic biopsy may be required in such cases.

Risk of malignancy

Malignant change in abdominal wall endometriosis is rare and estimated to be 0.3% to 1%[17]. Risk factors include advanced age, postmenopausal, and lesion diameter >9 cm[25]. Malignancy should be suspected in cases with multiple recurrences, lack of response to treatment, and sudden rapid growth[26]. Clear cell carcinoma is the most common histological subtype[27]. Wide excision with clear margins is a preventive option.

Management

Wide local excision with negative margins is the treatment of choice for AWE, as it provides both definitive diagnosis and treatment, with a success rate of 95%. Complete excision of the lesion and adjacent fascia (with a clear margin of at least 1 cm on all sides of the lesion) is important in reducing the chance of recurrence[10]. Inadequate resection results in around 9% of recurrence[2]. Large lesions and involvement of rectus muscles are associated with a higher recurrence rate[28]. So far, no study

has assessed the relationship between the size of surgical margin and the recurrence rate.

Small lesions located at subcutaneous layer can be removed easily, whereas large infiltrating lesions extending to aponeurosis, muscles, or even peritoneum are technically difficult to be excised. A large fascial defect may require placement of a mesh or constructing an aponeurotic muscle flap to cover the defect, and the procedure is usually performed by general surgeons[29]. For large and deep lesions, preoperative assessment with magnetic resonance imaging or computed tomography and planning with the general surgeon is essential. Surgery should be performed at the end of menstrual cycle, as the lesion is minimal[12,30]. For lesions with ill-defined borders, frozen section can be obtained intra-operatively to ensure adequate negative margin and minimise resecting unaffected tissues.

High-intensity focused ultrasound ablation is non-invasive and has favourable outcome, although pathological diagnosis of the lesion is not feasible. Ultrasound wave is used to induce coagulative necrosis in targeted endometrial tissues. In 51 women followed up for 4 years, high-intensity focused ultrasound ablation resulted in reduction of pain at the mass to visual analogue score 1 and significant reduction of lesion volume to 25% at 1 month, although one case had first-degree skin burn and the overall relapse rate was 3.9%[31].

Percutaneous cryotherapy administers tissue ablative freezing temperature to induce tissue necrosis by inserting a cryoprobe into the lesion. Maillot et al[32] compared outcome of surgical excision versus cryotherapy and reported similar pain relief and lesion size reduction. Cryotherapy preserves abdominal wall integrity and function and has better cosmetic outcome, compared with surgery. However, it is not suitable for large and deep AWE. More prospective studies with larger sample size are required to establish the effectiveness and safety of high-intensity focused ultrasound ablation and percutaneous cryotherapy.

Medical treatment is not effective for AWE. Oral contraceptives, progesterone, and Danazol result in improvement on symptoms only but not resolution of the lesion[3,5,33]. Risk of recurrence is high with discontinuation of medication[34]. Use of gonadotrophin agonist promptly improves symptoms but does not change lesion size[35]. Medical treatment is mainly for symptomatic control and shrinkage of the lesion size before operation. Combination of surgical re-excision and postoperative adjuvant medical therapy is suggested in patients with recurrent AWE[36].

Follow-up

Patients should be followed up to monitor recurrence. Recurrence rate after surgical treatment is 4% to 11% and usually occurs in a year after surgery[37].

Prevention

Preventive measures to reduce occurrence of AWE include meticulous haemostasis during uterine surgery, irrigating intra-abdominal cavities vigorously with high jet solution before abdominal closure, prompt removal of surgical sponges from operative field, gentle handling of uterine tissue, and using separate needles for suturing uterine and abdominal wall[38-40]. However, no trials have been conducted to evaluate the effectiveness of these measures in prevention of AWE.

Conclusion

AWE is rare. Careful history taking and physical examination are crucial to make the diagnosis. Imaging modalities enable assessment of the lesion extent and preoperative planning. Surgical excision with negative margin offers curative treatment. High-intensity focused ultrasound ablation and cryotherapy are non-invasive new alternatives.

Declaration

The authors have no conflict of interest to disclose.

References

1. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril 2012;98:511-9. Crossref
2. Bektaş H, Bilsel Y, Sari YS, et al. Abdominal wall endometrioma; a 10-year experience and brief review of the literature. J Surg Res 2010;164:e77-81. Crossref
3. Rindos NB, Mansuria S. Diagnosis and management of abdominal wall endometriosis: a systematic review and clinical recommendations. Obstet Gynecol Surv 2017;72:116-22. Crossref
4. Firilas A, Soi A, Max M. Abdominal incision endometriomas. Am Surg 1994;60:259-61.
5. Horton JD, Dezee KJ, Ahnfeldt EP, Wagner M. Abdominal wall endometriosis: a surgeon's perspective and review of 445 cases. Am J Surg 2008;196:207-12. Crossref
6. Celik M, Bülbüloglu E, Büyükbese MA, Cetinkaya A. Abdominal wall endometrioma: localizing in rectus

abdominis sheath. Turk J Med Sci 2004;34:341-3.
7. Steck WD, Helwig EB. Cutaneous endometriosis. Clin Obstet Gynecol 1966;9:373-83. Crossref
8. Khan Z, Zanfagnin V, El-Nashar SA, Famuyide AO, Daftary GS, Hopkins MR. Risk factors, clinical presentation, and outcomes for abdominal wall endometriosis. J Minim Invasive Gynecol 2017;24:478-84. Crossref
9. Grigore M, Socolov D, Pavaleanu I, Scripcariu I, Grigore AM, Micu R. Abdominal wall endometriosis: an update in clinical, imagistic features, and management options. Med Ultrason 2017;19:430-7. Crossref
10. Sumathy S, Mangalakanthi J, Purushothaman K, Sharma D, Remadevi C, Sreedhar S. Symptomatology and surgical perspective of scar endometriosis: a case series of 16 women. J Obstet Gynaecol India 2017;67:218-23. Crossref
11. Esquivel-Estrada V, Briones-Garduño JC, Mondragón-Ballesteros R. Endometriosis implant in cesarean section surgical scar [in Spanish]. Cir Cir 2004;72:113-5.
12. Leite GK, Carvalho LF, Korkes H, Guazzelli TF, Kenj G, Viana Ade T. Scar endometrioma following obstetric surgical incisions: retrospective study on 33 cases and review of the literature. Sao Paulo Med J 2009;127:270-7. Crossref
13. Anand M, Deshmukh SD. Massive abdominal wall endometriosis masquerading as desmoid tumour. J Cutan Aesthet Surg 2011;4:141-3. Crossref
14. Blanco RG, Parithivel VS, Shah AK, Gumbs MA, Schein M, Gerst PH. Abdominal wall endometriomas. Am J Surg 2003;185:596-8. Crossref
15. Francica G, Giardiello C, Angelone G, Cristiano S, Finelli R, Tramontano G. Abdominal wall endometriomas near cesarean delivery scars: sonographic and color doppler findings in a series of 12 patients. J Ultrasound Med 2003;22:1041-7. Crossref
16. Hensen JH, Van Breda Vriesman AC, Puylaert JB. Abdominal wall endometriosis: clinical presentation and imaging features with emphasis on sonography. AJR Am J Roentgenol 2006;186:616-20. Crossref
17. Wolf Y, Haddad R, Werbin N, Skornick Y, Kaplan O. Endometriosis in abdominal scars: a diagnostic pitfall. Am Surg 1996;62:1042-4.
18. Savelli L, Manuzzi L, Di Donato N, et al. Endometriosis of the abdominal wall: ultrasonographic and Doppler characteristics. Ultrasound Obstet Gynecol 2012;39:336-40. Crossref
19. Francica G, Scarano F, Scotti L, Angelone G, Giardiello C. Endometriomas in the region of a scar from Cesarean section: sonographic appearance and clinical presentation vary with the size of the lesion. J Clin Ultrasound 2009;37:215-20. Crossref
20. Grigore M, Iliev G, Gafitanu, Cojocaru C. The fetal abdominal wall defects using 2D and 3D ultrasound. Pictorial essay. Med Ultrason 2012;14:341-7.
21. Grigore M, Iliev G. Diagnosis of sacrococcygeal teratoma using two and three-dimensional ultrasonography: two cases reported and a literature review. Med Ultrason 2014;16:274-7. Crossref
22. Balleyguier C, Chapron C, Chopin N, Hélénon O, Menu Y. Abdominal wall and surgical scar endometriosis: results of magnetic resonance imaging. Gynecol Obstet Invest 2003;55:220-4. Crossref
23. Gidwaney R, Badler RL, Yam BL, et al. Endometriosis of abdominal and pelvic wall scars: multimodality imaging findings, pathologic correlation, and radiologic mimics. Radiographics 2012;32:2031-43. Crossref
24. Solak A, Genç B, Yalaz S, Sahin N, Sezer TÖ, Solak I. Abdominal wall endometrioma: ultrasonographic features and correlation with clinical findings. Balkan Med J 2013;30:155-60. Crossref
25. Kobayashi H, Sumimoto K, Moniwa N, et al. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. Int J Gynecol Cancer 2007;17:37-43. Crossref
26. Carr D, Pootrakul L, Harmon J, Trotter S. Cutaneous malignancies of the perineum. Clin Obstet Gynecol 2015;58:158-71. Crossref
27. Sergent F, Baron M, Le Cornec JB, Scotté M, Mace P, Marpeau L. Malignant transformation of abdominal wall endometriosis: a new case report [in French]. J Gynecol Obstet Biol Reprod (Paris) 2006;35:186-90. Crossref
28. Pados G, Tympanidis J, Zafrakas M, Athanatos D, Bontis JN. Ultrasound and MR-imaging in preoperative evaluation of two rare cases of scar endometriosis. Cases J 2008;1:97. Crossref
29. Vaz-de-Macedo C, Gomes-da-Costa A, Mendes S, et al. Abdominal wall endometriosis excision with mesh closure: report of two cases. Surg Technol Int 2016;28:196-201.
30. Kyamidis K, Lora V, Kanitakis J. Spontaneous cutaneous umbilical endometriosis: report of a new case with immunohistochemical study and literature review. Dermatol Online J 2011;17:5.
31. Xiao-Ying Z, Hua D, Jin-Juan W, et al. Clinical analysis of high-intensity focused ultrasound ablation for abdominal wall endometriosis: a 4-year experience at a specialty gynecological institution. Int J Hyperthermia 2019;36:87-94. Crossref
32. Maillot J, Brun JL, Dubuisson V, Bazot M, Grenier N, Cornelis FH. Mid-term outcomes after percutaneous cryoablation of symptomatic abdominal wall endometriosis: comparison with surgery alone in a single institution. Eur Radiol 2017;27:4298-306. Crossref
33. Chatterjee SK. Scar endometriosis: a clinicopathologic study of 17 cases. Obstet Gynecol 1980;56:81-4.
34. Sengul I, Sengul D, Kahyaoglu S, Kahyaoglu I. Incisional endometriosis: a report of 3 cases. Can J Surg 2009;52:444-5.
35. Rivlin ME, Das SK, Patel RB, Meeks GR. Leuprolide acetate in the management of cesarean scar endometriosis. Obstet Gynecol 1995;85:838-9. Crossref
36. Ding Y, Zhu J. A retrospective review of abdominal wall endometriosis in Shanghai, China. Int J Gynaecol Obstet 2013;121:41-4. Crossref
37. Steck WD, Helwig EB. Cutaneous endometriosis. JAMA 1965;191:161-70. Crossref
38. Bozkurt M, Çil AS, Bozkurt DK. Intramuscular abdominal wall endometriosis treated by ultrasound-guided ethanol injection. Clin Med Res 2014;12:160-5. Crossref
39. Muto MG, O'Neill MJ, Oliva E. Case records of the Massachusetts General Hospital. Case 18-2005. A 45-year-old woman with a painful mass in the abdomen. N Engl J Med 2005;352:2535-42. Crossref
40. Ozel L, Sagiroglu J, Unal A, et al. Abdominal wall endometriosis in the cesarean section surgical scar: a potential diagnostic pitfall. J Obstet Gynaecol Res 2012;38:526-30. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2020;20(1):48-52 | https://doi.org/10.12809/hkjgom.20.1.08

Expanded carrier screening for recessive genetic disorders: a review

Olivia Yiu-Man CHAN,[1] MD
Tze-Kin LAU,[2] MD
[1] Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Hong Kong
[2] Fetal Medicine Centre, Paramount Medical Centre, Hong Kong

The American College of Obstetricians and Gynecologists recommends carrier screening for couples planning for pregnancy or in early pregnancy. Expanded carrier screening is cost-effective to identify the carrier status of multiple debilitating recessive disorders. Knowledge of the reproductive risk enables carrier couples to decide the best reproductive options for their family. Nonetheless, proper pre-test and post-test genetic counselling is necessary to explain the limitation of testing methodologies and potential phenotypic variabilities.

Keywords: Genetic carrier screening; Genetic counseling; Genetic diseases, X-linked

Introduction

Recessive genetic disorders include autosomal and X-linked recessive disorders. If a couple are both carriers of pathogenic variants in the same gene responsible for an autosomal recessive disorder, their offspring has 25% risk of inheriting both defective gene copies and becomes affected by the disorder. The risk is independent of the fetal sex. If a woman is a carrier of an X-linked recessive disorder, her male offspring has 50% risk of inheriting the defective chromosome and becomes affected by the disorder, and her female offspring has 50% risk of being a carrier of the disorder.

Carriers of autosomal recessive disorders are usually asymptomatic and do not have family history of an affected individual. Without prior genetic screening, couples are found to be carriers only after an affected child is born and diagnosed with a severe autosomal recessive disorder. The risk of inheritance depends on the probability of a couple having the same defective gene. Those with autosomal recessive disorder are commonly identified as the first affected person in the family. Family history is less informative owing to the decreasing family size; a negative family history is not reassuring for not being a carrier of recessive disorders.

To identify couples at risk of having children with severe recessive disorders, carrier screening should be offered before pregnancy or at early stage of pregnancy. Couples who are both carriers of autosomal recessive disorders or women who are carriers of X-linked recessive disorders should receive genetic counselling for their reproductive options. Pre-pregnant couples at risk of having children with severe recessive disorders can be offered in-vitro fertilisation and pre-implantation genetic diagnosis. Pregnant women can be offered prenatal diagnostic testing using chorionic villi sample or amniotic fluid sample to guide pregnancy management and improve early neonatal care.

Recommendations by professional bodies

American College of Obstetricians and Gynecologists (ACOG) recommends carrier screening for women considering pregnancy or already pregnant regardless of screening strategy or ethnicity[1]. ACOG and the American College of Medical Genetics and Genomics (ACMG) used to recommend carrier screening based on racial or ethnic background for a limited number of diseases such as cystic fibrosis and haemoglobinopathies for Asian[2,3]. Since 2008, ACMG has recommended carrier screening for spinal muscular atrophy for all ethnic groups as the disease is present in all populations[4]. Since 2017, ACOG has recommended carrier screening for spinal muscular atrophy for all couples[5]. However, ethnicity-based screening is limited by the difficulty in assigning ethnic groups, changes in social structures, inter-ethnic marriage, and unknown ancestry. Individual genetic disorders are rare and thus ethnicity-based screening is not cost-effective, as only a small number of genetic disorders are screened for different ethnic groups.

Correspondence to: Dr Olivia Yiu-Man Chan
Email: chanyiuman@cuhk.edu.hk

Instead of single gene testing for individual genetic disorders, next generation sequencing enables expanded carrier screening for hundreds of genetic disorders using a single sample and results in a quick turnaround time and markedly reduction in cost. In a retrospective review of expanded carrier screening for 108 disorders in a multiethnic population, at least one mutation was found in 24% of subjects, and 127 couples were identified to be carrier couples[6]. Expanded carrier screening identified 77% and 66% of carriers who would have been missed based on the ethnic-based approach by the ACOG guidelines and the ACMG recommendations, respectively.[6] Since 2017, ACOG has recommended expanded carrier screening for pre-pregnancy and prenatal carrier screening[1].

ACOG recommends genetic counselling for consanguineous couples on the increased risk of recessive disorders being expressed in their offspring and the limitations and benefits of ethnicity-based screening[1]. In Hong Kong, the overall prevalence of parental consanguinity was 0.6%, of which most were ethnic Pakistani[7]. Offspring of consanguineous parents has significantly higher risk of recessive disorders (odds ratio [OR]=8.7), structural abnormalities (OR=4.55), and developmental delay (OR=6.72)[7]. It is important to identify consanguineous couples for preconception or prenatal genetic counselling on the increased risk of recessive disorders. Thorough review of family history of consanguineous couples is required to identify any suspicious recessive disorder for specific diagnosis and carrier screening. Expanded carrier screening should be offered to consanguineous couples who are considering pregnancy even without a positive family history. However, expanded carrier screening cannot include all recessive disorders and is not 100% sensitive. Detailed pre-test and post-test counselling for the limitation of expanded carrier screening is necessary.

When should expanded carrier screening be offered?

ACOG recommends carrier screening before pregnancy to allow adequate time for detailed counselling for reproductive options such as preimplantation genetic testing or prenatal diagnostic testing[5]. One option is to screen women first followed by men if women are found to be a carrier. This sequential testing minimises the test cost. In addition, ACOG recommends provision of information about carrier screening to every pregnant woman[5]. If the couple are both carriers of a severe autosomal recessive disorders, prenatal diagnostic testing should be arranged if time allowed. Owing to the time constraint, concurrent carrier screening of the couple can shorten the turnaround time despite an increased test cost. The limited time for prenatal diagnostic testing and decision making may increase the anxiety of the couple and the risk of termination of pregnancy in second trimester.

The acceptance of carrier screening is higher for couple who received genetic counselling before pregnancy. The uptake of carrier screening was 68.7% and 35.1% for couple who were counselled preconceptionally and during pregnancy, respectively[8]. Factors such as indication for genetic counselling, maternal and paternal family history of genetic diseases, maternal and paternal age, ethnicity, multigestational pregnancies, and previous miscarriages were not significantly associated with the acceptance rate of expanded carrier screening[8]. Although the underlying cause of the difference in uptake was not identified, it was postulated that limited pregnancy options after prenatal diagnostic testing affected the willingness of couple to undergo expanded carrier screening[8].

Expanded carrier screening

ACOG recommends screening for disorders having a carrier frequency of 1 in ≥100, a well-defined phenotype, and a detrimental effect on quality of life; requiring surgical or medical intervention; or having an early onset in life[5]. ACOG does not recommend screening of disorders with an adult onset[5]. ACMG recommends screening for disorders that most at-risk couples would consider having a prenatal diagnosis to facilitate decision-making[9]. ACMG recommends clinicians to provide options to patients to include disorders with mild phenotype, variable expressivity, or incomplete penetrance. ACMG recommends provision of consent for screening for adult-onset disorders.

Commercial carrier screening panels include a variety of disorders. Some panels only include disorders that are recommended by the ACOG and ACMG with elevated carrier frequency across ethnicities and well-defined severe phenotypes that impact quality of life. Other panels include expanded number of disorders that may not fulfill the ACOG and ACMG recommendations and have variable phenotype, reduced penetrance, or adult onset. Pre-test and post-test counselling for disorders with variable phenotype, reduced penetrance, or adult onset is complicated and time consuming. Clinician may review the disorder lists by different providers and decide the most appropriate panel for their patients.

Pre-test counselling

Disease panel

According to the joint statement by ACMG, ACOG, National Society of Genetic Counselors, Perinatal Quality Foundation, and the Society of Maternal Fetal Medicine, it is not practical or necessary to fully explain the clinical and test characteristics of all disorders in the panel individually[3]. The committee recommends clinicians to broadly describe the types of disorders being screened for, the common features, and the limitation of the screening in the pretest education and consenting[3]. For example, couple should be simply advised that the panel includes screening for disorders with shortened life expectancy such as spinal muscular atrophy, cystic fibrosis, Krabbe disease; disorders that carry risk for intellectual disability such as Fragile X syndrome, Smith-Lemli-Opiz syndrome; disorders that carry risk for significant morbidity (blindness or deafness) such as Bardet-Biedl syndrome, Pendred syndrome; and disorders that may improve with early intervention of the fetus or infant such as congenital adrenal hyperplasia and galactosemia.

Benefits of testing

Expanded carrier screening enables identification of the carrier status and understanding of the risk of inheriting recessive disorder to the offspring so as to provide pregnancy options including pre-implantation genetic testing or prenatal diagnostic testing for carrier couples. As effective treatment is not available in many of disorders, knowing the reproductive risks enables couple to make decision.

In Hong Kong, universal antenatal screening for thalassaemia carrier relies on the detection of low mean corpuscular volume, which is included in the routine antenatal blood testing[10]. For women with low mean corpuscular volume, haemoglobin pattern is investigated for beta thalassaemia (increased in A2 level) or alpha thalassaemia carriers (presence of H inclusion bodies). Further genotyping is required if prenatal diagnostic testing is needed or for cases with uncertain results. In expanded carrier screening, sequencing is performed for *HBB* gene and *HBA* gene responsible for beta thalassaemia and alpha thalassaemia, respectively. Expanded carrier screening enables direct genotyping of thalassaemia carriers to shorten the time and minimise resources required for the diagnosis.

For some genetic disorders, knowledge of at-risk couple enables earlier diagnosis and intervention for the affected child and might improve outcome. For example, prenatal treatment with dexamethasone for fetus of congenital adrenal hyperplasia carrier couple can be provided to reduce virilisation of female fetus in utero owing to the increased exposure to androgens. Early dexamethasone initiation before 7-week gestation with maintenance dose during the whole gestation resulted in normal feminine genitalia in 80% to 85% of girls with congenital adrenal hyperplasia[11]. Non-invasive prenatal testing for fetal sex enables early fetal sex determination to guide cessation of dexamethasone treatment for male fetus. In addition, affected infants can benefit from early initiation of glucocorticoid and mineralocorticoid treatment before a potentially life-threatening salt-wasting crisis.

Identification of carrier status in one family member may trigger carrier screening of other members planning for pregnancy. This improves understanding of reproductive risks in the family and promotes autonomy in reproductive choices.

Limitation of testing

To avoid difficult interpretation and counselling of uncertain results, most laboratories only report well-established pathogenic variants. Although this approach is well accepted by clinicians, it may miss potentially clinically significant variants that is unknown to be pathogenic at present owing to limited genetic knowledge[12]. A negative screening report is issued for individuals with variants that may be reclassified as pathogenic in future. Thus, clinician must explain to patients in details that expanded carrier screening only reports well-established variants and that interpretation of pathogenicity of the variants is based on the best available evidence at the time of testing. A negative screening report could not totally exclude their carrier status. There is still residual risk of their offspring being affected with disorders included in the panel because the couple may be carriers of a pathogenic variant that is classified as of uncertain clinical significance at the time of testing, or because of new mutation.

Spinal muscular atrophy is a common genetic disease across all ethnic groups; detection of carriers relies on targeted copy number analysis to determine the copy number of exon 7 of the *SMN1* gene. Individuals are classified as carrier if only one copy of *SMN1* is detected. However, about 4% of carriers lack *SMN1* in one of the chromosomes but have two gene copies in the other[13]. These '2/0 carriers' cannot be detected by the copy number analysis[14]. In addition, copy number analysis cannot

exclude carriers secondary to single point mutation in the *SMN1* genes. Thus, the detection rate of carriers for spinal muscular atrophy is 93% only. Clinicians should counsel the couple about the chance of residual risk of being a carrier owing to the limitation of the methodology. For couple with a family history of spinal muscular atrophy, genotyping of the proband is important to guide familial carrier screening. If the proband is found to have mutation in the *SMN1* gene instead of deletion, targeted mutation testing should be arranged for the family members instead of the expanded carrier screening panel.

The phenotype of some genetic disorders varies depending on the genotype. Some disorders are associated with incomplete penetrance and intra-familial variability so that not all individuals with the same variant of the gene manifest, and for those who manifest may have various severity of symptoms. Thus, clinicians should explain that a positive screening result may not precisely predict the phenotype of an affected individuals.

Post-test counselling

Negative result

Couple should be counselled about the possibility of residual risk of being carrier of the disorders screened. Also, the screening can only lower the risk of the couple being a carrier of the disorders included in the panel. Owing to the limitation of testing, newborn screening for inborn error of metabolism is still recommended after a negative carrier screening.

Positive result (carrier)

Genetic counselling should be offered to carriers of recessive disorders. Depending on the manifestation, partner testing may be offered for autosomal recessive disorders to screen for partner carrier status.

GJB2-related non-syndromic hearing loss has variable phenotypes and poses challenges in counselling regarding prognosis and pregnancy options. Variants in *GJB2* gene is a common cause of hereditary non-syndromic hearing loss. However, the phenotype of variants in the *GJB2* gene is highly variable. For example, *GJB2* c.109G>A is a common variant for the Chinese population. The total heterozygous and homozygous carrier frequencies of *GJB2* c.109G>A were 10.29% and 0.22%, respectively[15]. Therefore, this variant is commonly identified in expanded carrier screening. However, c.109G>A variant is associated with milder degree of hearing loss compared with c.35delG and c.235delC variants[16-21]. Thus, for carrier couple of variants in *GJB2* gene, genetic counselling about the possible phenotype should be provided before consideration of pregnancy options such as prenatal diagnostic testing or preimplantation genetic diagnosis.

Female carriers of X-linked recessive disorders or couple carriers of the same gene should be counselled about the inheritance risk and the option of prenatal diagnosis or preimplantation genetic testing.

Positive result (adult-onset disorders or disorders with variable phenotype)

Those found to be affected with adult-onset disorders or disorders with variable phenotype should be referred to clinical geneticists and physicians for thorough assessment and counselling.

Conclusion

Expanded carrier screening is cost-effective to identify carriers of severe debilitating recessive disorders. Clinicians should provide detailed pre-test and post-test counselling regarding the limitation of testing methodology, the possibility of residual reproductive risk, and the phenotypic variability.

Declaration

The authors have no conflicts of interest to disclose.

References

1. Committee on Genetics. Committee opinion No. 690: carrier screening in the age of genomic medicine. Obstet Gynecol 2017;129:e35-e40. Crossref
2. ACOG Committee on Obstetrics. ACOG Practice Bulletin No.78: hemoglobinopathies in pregnancy. Obstet Gynecol 2007;109:229-37. Crossref
3. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. Obstet Gynecol 2015;125:653-62. Crossref
4. Prior TW; Professional Practice and Guidelines Committee.

Carrier screening for spinal muscular atrophy. Genet Med 2008;10:840-2. Crossref
5. Committee on Genetics. Committee Opinion No. 691: carrier screening for genetic conditions. Obstet Gynecol 2017;129:e41-e55. Crossref
6. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med 2013;15:178-86. Crossref
7. Siong KH, Au Yeung SKC, Leung TY. Parental consanguinity in Hong Kong. Hong Kong Med J 2019;25:192-200. Crossref
8. Larsen D, Ma J, Strassberg M, Ramakrishnan R, Van den Veyver IB. The uptake of pan-ethnic expanded carrier screening is higher when offered during preconception or early prenatal genetic counseling. Prenat Diagn 2019;39:319-23. Crossref
9. Grody WW, Thompson BH, Gregg AR, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med 2013;15:482-3. Crossref
10. Leung TN, Lau TK, Chung TKH. Thalassaemia screening in pregnancy. Curr Opin Obstet Gynecol 2005;17:129-34. Crossref
11. Bachelot A, Grouthier V, Courtillot C, Dulon J, Touraine P. Management of endocrine disease: congenital adrenal hyperplasia due to 21-hydroxylase deficiency: update on the management of adult patients and prenatal treatment. Eur J Endocrinol 2017;176:R167-R181. Crossref
12. Antonarakis SE. Carrier screening for recessive disorders. Nat Rev Genet 2019;20:549-61. Crossref
13. McAndrew PE, Parsons DW, Simard LR, et al. Identification of proximal spinal muscular atrophy carriers and patients by analysis of SMNT and SMNC gene copy number. Am J Hum Genet 1997;60:1411-22. Crossref
14. Alias L, Bernal S, Calucho M, et al. Utility of two SMN1 variants to improve spinal muscular atrophy carrier diagnosis and genetic counselling. Eur J Hum Genet 2018;26:1554-7. Crossref
15. Choy KW, Cao Y, Lam ST, Lo FM, Morton CC, Leung TY. Target-enriched massively parallel sequencing for genetic diagnosis of hereditary hearing loss in patients with normal array CGH result. Hong Kong Med J 2018;24(Suppl 3):11-4.
16. Abe S, Usami S, Shinkawa H, Kelley PM, Kimberling WJ. Prevalent connexin 26 gene (GJB2) mutations in Japanese. J Med Genet 2000;37:41-3. Crossref
17. Wilcox SA, Saunders K, Osborn AH, et al. High frequency hearing loss correlated with mutations in the GJB2 gene. Hum Genet 2000;106:399-405. Crossref
18. Kenna MA, Wu BL, Cotanche DA, Korf BR, Rehm HL. Connexin 26 studies in patients with sensorineural hearing loss. Arch Otolaryngol Head Neck Surg 2001;127:1037-42. Crossref
19. Lin D, Goldstein JA, Mhatre AN, Lustig LR, Pfister M, Lalwani AK. Assessment of denaturing high-performance liquid chromatography (DHPLC) in screening for mutations in connexin 26 (GJB2). Hum Mutat 2001;18:42-51. Crossref
20. Marlin S, Garabedian EN, Roger G, et al. Connexin 26 gene mutations in congenitally deaf children: pitfalls for genetic counseling. Arch Otolaryngol Head Neck Surg 2001;127:927-33. Crossref
21. Snoeckx RL, Huygen PL, Feldmann D, et al. GJB2 mutations and degree of hearing loss: a multicenter study. Am J Hum Genet 2005;77:945-57. Crossref