ISSN 1608-9367 (Print)
ISSN 2225-904X (Online)

January 2018 • Volume 18 • Number 1　二零一八年一月 · 第十八期 · 第一號

香港婦產助產科雜誌

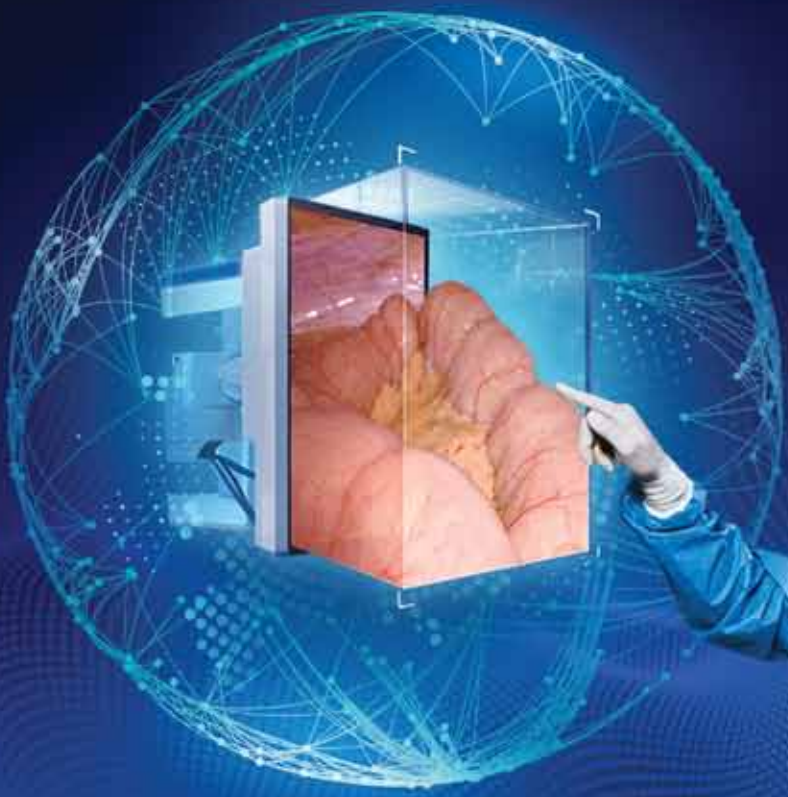
Hong Kong Journal of Gynaecology, Obstetrics and Midwifery

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS

HONG KONG JOURNAL OF GYNAECOLOGY, OBSTETRICS AND MIDWIFERY
JANUARY 2018
VOLUME 18 NUMBER 1
PAGES 1-56

OLYMPUS®

Your Vision, Our Future



BEYOND VISION

VISERA ELITE II

All-in-one design

3D Laparoscopy

IR observation

HONG KONG JOURNAL

OF

GYNAECOLOGY, OBSTETRICS & MIDWIFERY

January 2018, Volume 18, Number 1

EDITORIAL

ORIGINAL ARTICLES (OBSTETRICS)

ORIGINAL ARTICLE (GYNAECOLOGY)

CASE SERIES

REVIEWS

Duratocin®
CARBETOCIN

"Protecting mothers from postpartum haemorrhage[1]"

- Single injection for a long duration of action
- Administer either before or after delivery of the placenta[1]
- Significantly reduced blood loss versus oxytocin[2–3]
- Significantly reduced need for additional uterotonics versus oxytocin and syntometrine[2, 4–6]

References:
1. DURATOCIN Product Insert (Hong Kong) 2. El Behery MM *et al, J Matern Fetal Neonatal Med*. 2016;29(8):1257-60. 3. Borruto F *et al, Arch Gynecol Obstet*, 2009;280:707-12. 4. Razali N *et al, Eur J Obstet Gynecol Reprod Biol*. 2016;198:35-9. 5. Larciprete G *et al, J Prenat Med*. 2013; 7(1):12-8. 6. Mohamed Maged A *et al, Matern Fetal Neonatal Med*. 2016 Jun 8: 1-5. [Epub ahead of print].

Further product information is available upon request.

Ferring Pharmaceuticals Limited
Suites 2604-05, 26/F, AXA Tower, Landmark East,
100 How Ming Street, Kwun Tong, Kowloon, Hong Kong
Tel: +852 2622 8000 Fax: +852 2622 8001 Website: www.ferring.com

FERRING
PHARMACEUTICALS

OG020116/AUGHK

1. **Fast action** on symptoms[2]
   - Rapidly stops bleeding
   - Reduces pain and restores women's quality of life
2. **Significant and sustainable** reduction **of fibroids size**[3]
   - Maintained 6 months after treatment cessation
3. **Good safety** profile
4. **A first-in-class** Selective Progesterone Receptor Modulator (SPRM)
   - Direct and tissue specific effect on uterine fibroid cells[1]
5. **Convenient, oral, once-a-day treatment**
   - Repeated intermittent treatment has been studied up to 4 intermittent courses (12 months).[4]

- Esmya has been approved for intermittent treatment by the European Medicines Agendy and the Hong Kong Department of Health.

esmya® 5mg

Ulipristal acetate

Esmya 5 mg Tablets – Hong Kong Abbreviated Prescribing Information
Indications: Ulipristal acetate is indicated for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.
Dosage: The treatment consists of one tablet of 5 mg to be taken orally once daily for treatment courses of up to 3 months each. If required, repeated intermittent treatment has been studied up to 4 intermittent courses, starting at the earliest during second menstruation after completing initial courses.
Contraindications: Hypersensitivity to active substance or excipients. Genital bleeding of unknown aetiology or not caused by uterine fibroids. Uterine, cervical, ovarian or breast cancer. Pregnancy (to be excluded before starting). Lactation.
Precautions: Non hormonal contraception recommended. Not recommended for patients with severe renal or moderate to severe hepatic impairment. Not recommended for women with severe asthma insufficiently controlled by oral glucocorticoids. Changes in the histology of the endometrium may be observed with Esmya. Warn that reduction in menstrual blood loss or amenorrhoea likely within 10 days and advise to inform doctor if excessive bleeding persists.
Interactions: Progestogens, CYP3A4 inducers and inhibitors, P-gp substrates (e.g. digoxin, dabigatran, fexofenadine).
Side effects: Amenorrhea, endometrial thickening, headache, vertigo, abdominal pain, nausea, acne, hyperhidrosis, musculoskeletal pain, uterine haemorrhage, hot flushes, pelvic pain, ovarian cyst, breast tenderness/pain, oedema, fatigue, raised cholesterol.

References:
1. Yoshida S. Cell-type specific actions of progesterone receptor modulators in the regulation of uterine leiomyoma growth. Semin Reprod Med 2010. 28(3):260-73.
2. Donnez J. et al. and al. Ulipristal Acetate versus Placebo for Uterine Fibroids. N Engl J Med 2012;366:409-20.
3. Donnez J. et al. and al. Ulipristal Acetate versus Leurprolide Acetate for Uterine Fibroids. N Engl J Med 2012;366:421-32.
4. Donnez J. et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril 2016;105:165-173.

Full Prescription Information Available Upon Request.

友華股份有限公司
Orient EuroPharma Co., Ltd.
Room 605-6, Prosperity Centre,
25 Chong Yip Street, Kwun Tong, Kowloon, HK.
Tel: (852) 2578 7080 Fax: (852) 2578 1860

HRA Pharma

OEP/HKESY/0118/01

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.

HealthBaby
生寶臍帶血庫

Most Professional Accreditations
Most Recommended by O&G Doctors[1]
>70% Market Share[2]

HealthBaby's Cord Service Patented Technology

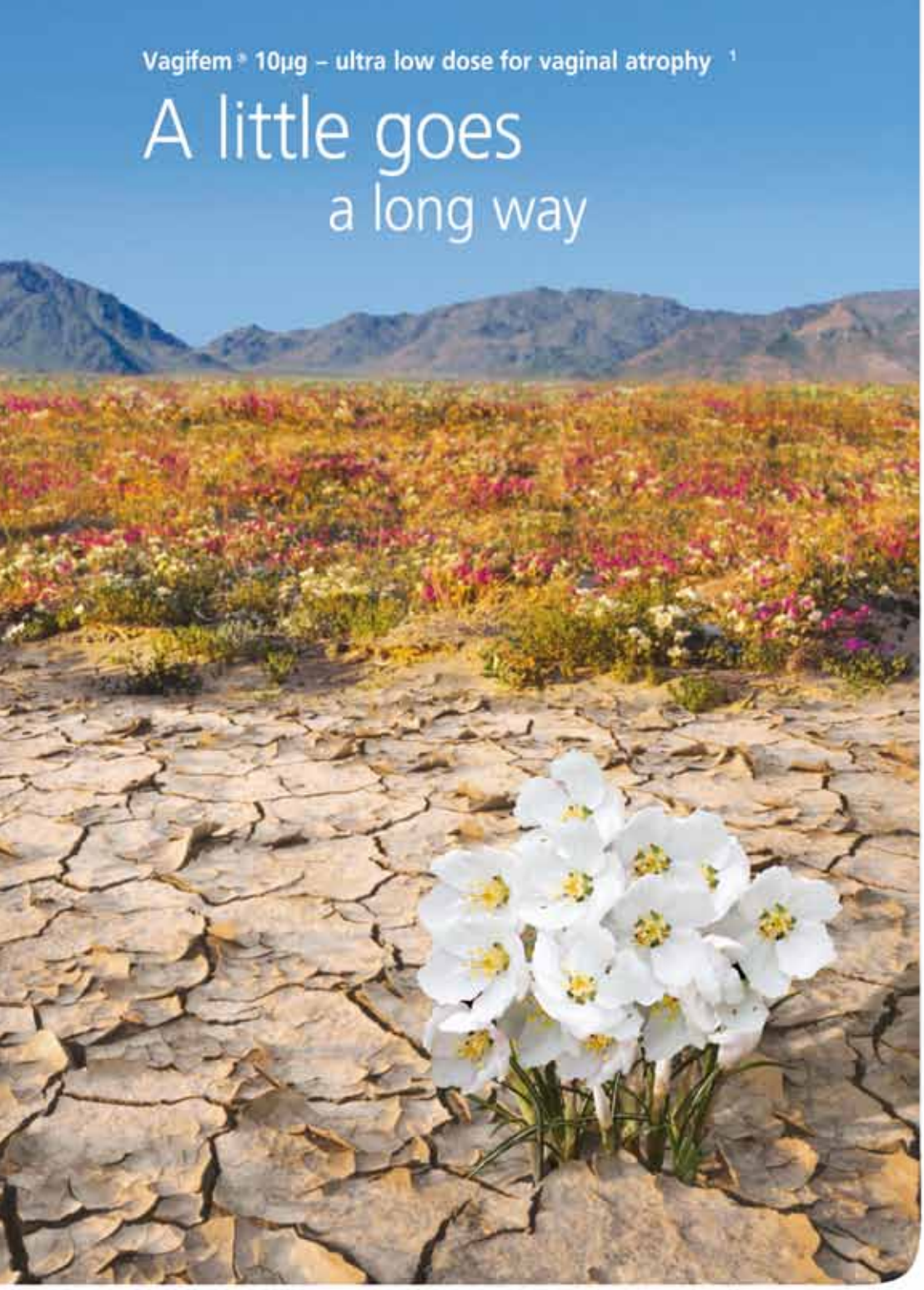
- H.K. FIRST cord storage service[3]
- Obtained H.K., U.S., Taiwan and China patent
- Exclusively extracts the whole cord tissue
- Unique processing, storage and culturing techniques
- Enhances the cells' quantity and viability after thawing

H.K. Patent | U.S. Patent | Taiwan Patent | China Patent

Source: 1. IMS 2010 Cord Blood Bank Market Research in Hong Kong (with Private O&G physicians) 2. Ipsos Healthcare 2009-2017 Cord Blood Bank Survey
3. Introduction to the Cord Tissue Market and Cord Tissue-Derived Mesenchymal Stem Cells (CT-MSCs)", BIOINFORMANT, Jun 2015

Vagifem® 10µg – ultra low dose for vaginal atrophy [1]

A little goes a long way



- Lowest effective dose* available[2,3]
- Significant long-term improvement in vaginal health[1]
- Precise dose,[3] locally administered,[3] locally effective[1]

novo nordisk®

Effective.[1] Convenient.[4] Clean.[5]

Vagifem®10
10µg 17ß-estradiol

Reference:

1. Simon J et al. *Obstet Gynecol* 2008;112(5):1053–1060. 2. Vagifem® 25µg Summary of Product Characteristics; October 2012. 3. Vagifem® 10µg Summary of Product Characteristics; January 2012. 4. Rioux JE et al. *Menopause* 2000;7(3):156–161. 5. Dugal R et al. *Acta Obstet Gynecol Scand* 2000;79(4):251–257.

* of local 17β-estradiol

Further information is available on request : DKSH Hong Kong Limited Tel : (852) 2895 9668 Fax : (852) 2895 9548

VAG-D-20170401

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.

Editorial

The Part 3 Membership of the Royal College of Obstetricians and Gynaecologists and Our Journal

The Part 3 Membership of the Royal College of Obstetricians and Gynaecologists (MRCOG) was first introduced in the United Kingdom in September 2016. Its first overseas Part 3 examination was conducted by our College on 13 November 2017. The Part 3 examination is a clinical assessment of knowledge, skills, attitude, and competency and consists of 14 tasks in a circuit, each task based on one of the 14 modules detailed in the MRCOG syllabus. Each module is assessed in the context of five domains: patient safety, communication with patients and their relatives, communication with colleagues, information gathering, and applied clinical knowledge. Each of the 14 tasks assesses three to four of the domains to reflect everyday clinical practice; for example, communicating with patients is associated with applied clinical knowledge, and communicating with colleagues involves aspects of patient safety. Trained clinical examiners score the candidate for each of the tasks, while trained lay examiners are involved in four of the 14 tasks and assess the domains of communication, patient safety, and information gathering from the patient's perspective. In the November examination, our eight local trainees did extremely well, with a pass rate of 100%.

As our next batch of trainees is preparing for this year's Part 2 and Part 3 examinations, it is an appropriate time to discuss what is really required of our candidates and ourselves in current clinical practice. Of the five domains, the Part 3 examination targets traditional training of our residents and focuses on applied clinical knowledge and patient safety. The other three domains, while discrete, are closely related. Information gathering from the patient, family members, and colleagues is closely associated with communication skills. When directly asked, most of us presume that our information gathering skills are excellent, but are they? In a survey, 75% of orthopaedic surgeons considered their communication with patients to be satisfactory, but only 21% of patients reported satisfactory communication with their doctors[1]. Communication skill workshops teach us to greet patients with open-ended questions such as "How can I help you?" This allows the patient to define the conversation. It takes most gynaecology patients 2 minutes to tell their story and explain why they are seeing you, and probably less for obstetric patients to tell you their pregnancy progress. You then realise that the hardest thing to do is to wait until the patient finishes speaking. It has been reported that the average physician interrupts the patient within 18 to 23 seconds[1]. Avoid this pitfall, listen for 2 minutes, and the patient will tell you 80% of what you need to know. The same probably goes with your residents. When they present their cases in a ward round, how much of the *blah blah blah* do you tolerate before you start jumping on them?

Communication skills are now formally taught in medical schools and residency programmes in many specialties all over the world[2,3]. Evidence from randomised controlled trials has proved that interactive continuing medical education is effective in improving clinical performance. This has stimulated the development of various models of integrated learning, such as the patient pathway tutorial, in which students have to perform a series of tasks that represent the temporal sequence of clinical and communication skills needed for management[4]. Indeed our midwifery colleagues use such models. In their introductory week, our student midwives are asked to pretend to be a pregnant woman or her husband, and to go through all the stages of pregnancy from booking an antenatal visit in our hospital to being discharged from the postnatal ward after delivery.

The ultimate objective of any doctor-patient communication is to improve the patient's health and medical care. The ultimate objective of our Journal is to improve patient health and care by sharing up-to-date research findings, professional knowledge, and state-of-the-art practices. The articles published in each issue are another form of communication that has to be learnt and practised by all our trainees. Our College has one of the most stringent and demanding requirements for research training. I am confident that most trainees will continue to practise their clinical skills after their Exit examination to become specialists, but I am not certain how many will continue to use the knowledge and skills they have acquired to design a research project, conduct a literature search, work out statistical analysis, and write up a scientific article in their post-exit years. It may be argued that the hard work put into acquiring research skills has already paid dividends during

journal reading and critical appraisal of the literature. Well, so be it, but the bliss and enchantment of seeing your ideas or hypotheses proven by science and published under your own name is something you will probably miss for a long time to come.

With an ageing population, pelvic organ prolapse becomes a more common problem encountered in urogynaecology and general gynaecology. Vaginal hysterectomy and laparoscopic-assisted vaginal hysterectomy are common treatment options. In this issue, Cheung et al[5] examine the prevalence of undetected genital tract malignancy and pre-malignancy in women undergoing hysterectomy for pelvic organ prolapse, and offer useful suggestions to reduce such unwanted surprises. Physical exercise is believed to be a key element of good health, but does this apply to pregnancy as well? Chan et al[6] examine the association of physical activity during pregnancy in Hong Kong Chinese women with the mode of delivery and delivery outcomes. Are our babies getting bigger and is maternal obesity the main culprit? Wong and To[7] examine the predictive risk factors for fetal macrosomia in a large local cohort and confirm the increased risks of maternal and neonatal morbidity. Are our residents overworked, and does working long hours into the night affect their performance? Chan et al[8] examine the association between the time of day of unscheduled Caesarean section and maternal and perinatal outcomes in a public training hospital and conclude that patients are in safe hands around the clock. Kong and To[9] report three cases of haemorrhagic stroke in pregnancy, a rare yet potentially fatal condition, and comprehensively review its pathology and current treatment options. In addition, Choi[10] presents a comprehensive update on developments in minimally invasive surgery in gynaecology. Wong[11] reviews the practicality of ovarian reserve testing before conception. I am confident you will gain something from these articles. Happy reading.

William WK TO
Editor-in-Chief, *Hong Kong Journal of Gynaecology, Obstetrics and Midwifery*

References

1. Tongue JR, Epps HR, Forese LL. Communication skills for patient centered care: research-based, easily learned techniques for medical interviews that benefit orthopaedic surgeons and their patients. *J Bone Joint Surg Am* 2005; 87:652-8.
2. Fong J, Longnecker N. Doctor-patient communication: a review. *Ochsner J* 2010; 10:38-43.
3. Ranjan P, Kumari A, Chakrawarty A. How can doctors improve their communication skills? *J Clin Diagnost Res* 2015; 9:JE01-4.
4. Kidd J, Patel V, Peile Ed, Carter Y. Clinical and communication skills: need to be learnt side by side. *BMJ* 2005; 330:374-5.
5. Cheung YS, Tung CW, Tong AW, Cheon WC. Prevalence of undetected genital tract pre-malignancy and malignancy in Hong Kong women having hysterectomy for uterine prolapse. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:30-5.
6. Chan JC, Put WM, Chan LW. Physical activity in pregnancy and its association with mode of delivery and delivery outcomes in Hong Kong Chinese women. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:12-7.
7. Wong PY, To WW. Risk factors and pregnancy outcomes of macrosomia: a retrospective cohort study. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:18-23.
8. Chan CW, Kong CW, To WW. Association between time of day of unscheduled Caesarean section and outcomes. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:24-9.
9. Kong CW, To WW. Haemorrhagic stroke in pregnancy. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:36-42.
10. Choi CK. Advances in minimally invasive gynaecological surgery. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:43-51.
11. Wong QH. Ovarian reserve tests in pre-conceptual healthy women. *Hong Kong J Gynaecol Obstet Midwifery* 2018; 18:52-6.

Wyeth® | Nutrition SCIENCE CENTER

https://hongkong.wyethnutritionsc.org

Connecting you to nutrition knowledge that matters

A nutrition resource platform which brings you the latest scientific trends and education resources for healthcare professionals

Practical Tools & Newsletters

Support your daily practice with **practical tools** on prenatal health and nutrition, ***e.g. DHA, Vitamin D Fact Sheets***

Guidelines & Recommendations

Stay updated with the latest **scientific literatures and guidelines** on periconceptional care, ***e.g. from ACOG, RCOG***

Symposium Highlights

Recap on **scientific meetings and symposia** for knowledge exchange

Expert Interviews

Learn from international & local experts discussing about **evidence-based nutrition topics**

Conference Videos

Watch **presentations from renowned experts** in the field of scientific research

LIKE & FOLLOW Us Now on Facebook!

Receive the latest scientific updates at first hand

Wyeth Nutrition Science Center HK

Physical Activity in Pregnancy and Its Association with Mode of Delivery and Delivery Outcomes in Hong Kong Chinese Women

Joyce Chung-Yin CHAN MBChB, MRCOG
Wing-Man PUT MBChB, MRCOG, FHKAM (Obstetrics and Gynaecology)
Lin-Wai CHAN MBChB, FRCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong

Objective: This study aimed to examine the effect of physical activity during pregnancy on the mode of delivery and delivery outcomes among Hong Kong Chinese women.
Methods: Self-administered questionnaires were distributed to pregnant women who presented to a regional hospital in Hong Kong in 2014. Women with a physical activity level of ≥7.5 compendium-based metabolic-equivalent mean weekly energy expenditure, which is equivalent to exercise at a moderate intensity for ≥30 min/day on most days of the week, were regarded as compliant with a recommendation of the American College of Obstetricians and Gynecologists (ACOG). Maternal characteristics, mode of delivery, and delivery outcomes were compared between women who were compliant and those who were non-compliant.
Results: The proportion of women compliant with the ACOG recommendation increased significantly as gestation advanced (from 23.6% in the first trimester to 30.3% in the second and 33.0% in the third, p=0.005). The mode of delivery differed significantly according to physical activity level in the third trimester (p=0.016), but not in the first (p=0.366) or second (p=0.575) trimester. Nonetheless, compliant and non-compliant women were comparable in terms of vaginal delivery, Caesarean section, and delivery outcomes.
Conclusion: Physical activity level in pregnancy is not associated with the rate of Caesarean section or adverse delivery outcomes.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):12-7

Keywords: Cesarean section; Delivery, obstetric; Exercise; Pregnancy

Introduction

In 2002, the American College of Obstetricians and Gynecologists (ACOG) recommended that women with low-to-moderate risk in pregnancy should exercise at a moderate intensity for ≥30 minutes/day on most days of the week[1]. In December 2015, the ACOG adjusted the recommendation to a more manageable target of ≥20 to 30 minutes/day[2]. Many studies have reported the benefits of physical activity during pregnancy, including improvement in general well-being[3-5], prevention of excessive weight gain[6], and reduction of obstetric risks such as gestational diabetes mellitus and pre-eclampsia[7,8]. In addition, being physically active has not been shown to have any adverse effect on pregnancy or delivery outcomes such as gestational age, preterm delivery, birthweight, or Apgar score[9,10]. Nonetheless, the effect of physical activity on the mode of delivery remains controversial, mainly because of the lack of large population-based studies and the presence of confounding factors. In a survey of 1342 women in North Carolina in 2004-2005, the self-reported frequency of exercise during pregnancy was not associated with a reduced risk of Caesarean delivery[11]. On the contrary, in a meta-analysis of 16 randomised controlled trials in 2014, structured physical exercise during pregnancy was associated with a reduced risk of Caesarean section[12].

A previous study reported attitudes towards and knowledge about physical activity, as well as patterns of physical activity during pregnancy in Hong Kong Chinese women[13]. The current study aimed to assess the association between the level of physical activity and the mode of delivery and delivery outcomes.

Methods

This study was approved by the ethics committee of the Kowloon Central Cluster of the Hospital Authority. From March to July 2014, self-administered semi-quantitative questionnaires in traditional Chinese were

Correspondence to: Dr Joyce Chung-Yin Chan
Email: ccy173@ha.org.hk

distributed to Chinese pregnant women when they attended the antenatal clinic of the United Christian Hospital, Hong Kong during their first trimester. Follow-up questionnaires were distributed in the second trimester at 24 to 28 weeks of gestation and in the third trimester at 32 to 40 weeks of gestation. The questionnaire was adopted from the Pregnancy Physical Activity Questionnaire, which has been validated by a Taiwan study[14]. The categorisation of approximate time spent per day or per week on household/caregiving activities, occupational activities, physical/exercise activities, transportational activities, and inactivity has been reported in another study[15].

The compendium-based metabolic equivalent (MET) value was used to estimate the intensity of different types of physical activity[16]. The duration of time spent on each activity was multiplied by its intensity to arrive at a measure of mean weekly energy expenditure (MET-h/week). Women with a physical activity level of ≥7.5 MET-h/week (equivalent to exercise at moderate intensity for ≥30 min/day on most days of the week) were regarded as compliant with the 2002 ACOG recommendation.

Women were excluded if they had any absolute contraindication to exercise or previous Caesarean section or if they did not plan to deliver in our hospital. All women were routinely offered dating scans to determine their expected date of confinement during their first trimester Down's syndrome screening test. Demographic data (age, body mass index, parity, education level, occupation, household income, history of miscarriage, previous low-birthweight baby) and obstetric and neonatal outcomes were retrieved from the hospital's computerised obstetric database and electronic antenatal record system.

The primary outcome was the mode of delivery in terms of normal vaginal delivery, instrumental delivery, and Caesarean section. The secondary outcome was delivery outcomes, including pregnancy duration, preterm birth, duration of the first and second stages of labour, Apgar score at 1 and 5 min, and birthweight.

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], US). Data were presented as percentage or median / interquartile range, as appropriate. Compliant and non-compliant women were compared using the Chi-square test (for categorical variables) or non-parametric Mann-Whitney *U* test or unpaired *t*-test (for continuous variables), as appropriate. A p value of <0.05 was considered statistically significant.

Results

Of 600 questionnaires distributed to eligible pregnant women, 534 (89%) in the first trimester, 261 (44%) in the second trimester, and 200 (33%) in the third trimester were adequately completed and returned. In the third trimester, the largest component of physical activity was household activities (42.5%), followed by occupational activities (21.4%), and physical and leisure activities (3.3%). The proportion of women who were

Table 1. Mode of delivery and the proportions of women who were compliant or non-compliant with American College of Obstetricians and Gynecologists (ACOG) recommendation for physical activity

Mode of delivery	No. (%) of women compliant with ACOG recommendation*		p Value
	Yes	No	
1st trimester (n=388)			0.366
Normal	63 (70.8)	227 (75.9)	
Instrumental	8 (9.0)	30 (10.0)	
Caesarean section	18 (20.2)	42 (14.0)	
2nd trimester (n=191)			0.575
Normal	37 (63.8)	95 (71.4)	
Instrumental	9 (15.5)	16 (12.0)	
Caesarean section	12 (20.7)	22 (16.5)	
3rd trimester (n=162)			0.016
Normal	35 (64.8)	81 (75.0)	
Instrumental	10 (18.5)	5 (4.6)	
Caesarean section	9 (16.7)	22 (20.4)	

* Percentages may not total 100 because of rounding

compliant with the ACOG-recommended physical activity level increased from 23.6% in the first trimester to 30.3% in the second trimester[13] and 33.0% in the third trimester, with a linear-by-linear association (p=0.005). Among 388 women in the first trimester, 191 women in the second trimester, and 162 women in the third trimester included for analysis, the mode of delivery differed significantly between women who were compliant or not in the third trimester (p=0.016) only, but not in the first (p=0.366) or second (p=0.575) trimester (Table 1).

Table 2. Characteristics of women who were compliant or non-compliant with American College of Obstetricians and Gynecologists (ACOG) recommendation for physical activity in the third trimester

Variable	Compliant with ACOG recommendation		
	Yes (n=54)*	No (n=108)*	p Value
Age (years)			0.923
≤20	1 (1.9)	2 (1.9)	
21-30	25 (46.3)	52 (48.1)	
31-40	27 (50.0)	50 (46.3)	
>40	1 (1.9)	4 (3.7)	
Parity			0.620
0	29 (53.7)	63 (58.3)	
1	19 (35.2)	34 (31.5)	
2	6 (11.1)	8 (7.4)	
3	0	3 (2.8)	
Occupation			0.825
Housewife	18 (33.3)	38 (35.2)	
Clerical work	13 (24.1)	28 (25.9)	
Manual work	0 (0)	2 (1.9)	
Professional	7 (13.0)	12 (11.1)	
Self-employed	2 (3.7)	6 (5.6)	
Others	13 (24.1)	18 (16.7)	
Did not specify	1 (1.9)	4 (3.7)	
History of miscarriage			0.778
0	35 (66.0)	74 (69.8)	
1	12 (22.6)	19 (17.9)	
≥2	6 (11.3)	13 (12.3)	
Education level			0.937
Primary	2 (3.7)	3 (2.8)	
Secondary	31 (57.4)	66 (61.1)	
Associate	7 (13.0)	9 (8.3)	
Tertiary or above	14 (25.9)	30 (27.8)	
Income (HK$) [n=155]			0.120
≤20 000	31 (57.4)	70 (64.8)	
20 001-50 000	19 (35.2)	27 (25)	
>50 000	3 (5.6)	5 (4.6)	
Did not specify	1 (1.9)	6 (5.6)	
Body mass index (kg/m^2)	20.5 / 3.9	21.1 / 4.6	0.367
Previous low-birthweight baby	2 (3.7)	5 (4.6)	0.678

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

Of 200 women who completed the questionnaire in the third trimester, 162 were included in the analysis and 38 were excluded (28 women with previous Caesarean section, four with placenta praevia, three with twin pregnancy, two with pre-existing hypertension, and one woman who did not deliver in our hospital). Of the 162 women, 54 (33.3%) were compliant with the ACOG recommendation and 108 (67.7%) were not. The two groups were comparable in terms of age, parity, occupation, history of miscarriage, education level, income, body mass index, and previous delivery of a low-birthweight baby (Table 2). The two groups were also comparable in terms of delivery outcomes, including pregnancy duration, preterm delivery, first-stage and second-stage duration, Apgar scores at 1 and 5 min, and birthweight (Table 3). Compliant and non-complaint women were comparable in term of vaginal delivery (83.3% and 79.6%, respectively, p=0.674). Nonetheless, compliant women had more instrumental deliveries than non-compliant women (18.5% vs. 4.6%, p=0.004), although the indications for instrumental delivery did not differ significantly (prolonged second stage: 70% [7/10] vs. 60% [3/5]; fetal distress: 30% [3/10] vs. 40% [2/5]).

Discussion

This is the first local study to investigate the relationship between physical activity during pregnancy and the mode of delivery and delivery outcomes. Compliance with the ACOG recommendation for physical activity during the third trimester increased the rate of instrumental delivery but did not affect the rate of Caesarean section or delivery outcomes. Physical activity in the first and second trimesters did not affect the mode of delivery.

The strength of our study is that it used the Pregnancy Physical Activity Questionnaire, which has been validated and widely used. It is a reliable tool to assess physical activity during pregnancy. The self-administered nature enables women to answer the questions at their convenience without interviewer bias. Women were asked to recall the data in the same trimester to maximise accuracy, and questionnaires were collected on the same day of distribution to maximise the response rate.

The finding of increased instrumental deliveries in women who were compliant with the ACOG recommendation in the third trimester is new. According to the ACOG, exercise is defined as physical activity consisting of planned, structured, and repetitive bodily movements to improve one or more components of physical fitness[1]. Household, occupational, and transportational activities are not considered as exercise, although they may influence the mode of delivery. The distribution pattern of physical activity in women during the third trimester is similar to that in the first and second trimesters[13]. In a United States survey, the proportion of women who were compliant with the ACOG recommendation was 12.9% to 45.0% when active transport (walking or cycling) was included, compared with 12.7% to 28.9% when only sport activities were included[17]. Although non-exercise activities may not be as effective as physical activities in improving physical fitness, they may still play an important role in maintaining cardiorespiratory fitness and musculoskeletal condition during pregnancy. Considering that a large proportion of women performed routine household and occupational activities during pregnancy, these activities

Table 3. Delivery outcomes of women who were compliant or non-compliant with American College of Obstetricians and Gynecologists (ACOG) recommendation for physical activity in the third trimester

Variable	Compliant with ACOG recommendation		
	Yes (n=54)*	No (n=108)*	p Value
Vaginal delivery	45 (83.3)	86 (79.6)	0.674
Pregnancy duration (days)	276 / 8	274 / 8	0.178
Preterm	2 (3.70)	1 (0.09)	0.216
1st stage of labour (min)	287.5 / 225	272.5 / 260	0.235
2nd stage of labour (min)	16.5 / 37	10 / 24	0.261
Apgar score at 1 min	9.72 / 0.69	9.71 / 0.61	0.649
Apgar score at 5 min	9.98 / 0.14	9.90 / 0.39	0.143
Apgar score of <7 at 5 min	0	0	-
Birthweight (g)	3305.2 ± 381.3	3232.2 ± 359.4	0.234

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

may have affected the mode of delivery. Exclusion of non-exercise activities may confound the mode of delivery and delivery outcomes.

In our study, the proportion of women compliant with the ACOG recommendation increased as gestation advanced (23.6% in the first trimester to 30.3% in the second and 33.0% in the third). This finding is in agreement with that of a cross-sectional survey in Taiwan, which reported an increase in the proportion of total energy expenditure in the physical/exercise category as pregnancy progressed, although this could reflect the behaviour of older and better educated participants in the third trimester[18]. In contrast, a cross-sectional study in Tianjin, China, reported the proportion of women meeting the ACOG recommendation being 11.6%, 11.3%, and 10.5% in each trimester[19]. In a cohort study in England, 48.8% and 48.9% of women spent ≥3 h/week on strenuous physical activity at 18 weeks and 32 weeks of pregnancy, respectively[20]. In our study, fatigue was the main reason for limited exercise during the first trimester[16]. Hong Kong pregnant women are usually told to be on bedrest in the presence of threatened abortion in the first trimester. Closer to term, pregnant women are encouraged to walk or even climb stairs, which is believed to promote engagement of the fetal head and normal delivery. All these factors can account for the lower and higher rates of compliance with exercise recommendations in the first and third trimesters, respectively.

In our study, most pregnant women were not compliant with the ACOG recommendation. In a United States survey, the proportion of women fulfilling the ACOG recommendation ranged from 12.7% to 28.9%[17]. In a study in China, only 9.1% to 10.7% of women participated in moderate physical activity during early pregnancy[21]. Higher education level, habitual exercise before pregnancy, and having a husband who exercised regularly increased the odds of fulfilling the ACOG recommendation[17]. More extensive local data are required to formulate strategies and interventions to promote exercise in pregnancy.

This study had several limitations. The response rate in the third trimester was only 33% (200 of 600) and the sample size was small. The low response rate was mainly because many women received antenatal care at other health centres, private hospitals, or in mainland China after the second trimester. Women who were lost to follow-up may have returned to our hospital only for check-ups until near term or on delivery. Some may have delivered in private hospitals. A reminder by telephone and mailing questionnaires to the women's home may have improved the response rate. Furthermore, there may have been reporting bias owing to the retrospective recall of data.

Conclusion

Physical activity during pregnancy is not associated with the rate of Caesarean section or adverse delivery outcomes. Our study supports the no-harm nature of exercise during pregnancy. Further studies on the benefits of specific types, duration, and intensity of exercise and their impact on delivery outcomes are warranted.

Declaration

All authors have disclosed no conflicts of interest.

References

1. ACOG Committee Obstetric Practice. ACOG Committee opinion. Number 267, January 2002: exercise during pregnancy and the postpartum period. *Obstet Gynecol* 2002; 99:171-3.
2. ACOG Committee Opinion No. 650: physical activity and exercise during pregnancy and the postpartum period. *Obstet Gynecol* 2015; 126:e135-42.
3. Sternfeld B. Physical activity and pregnancy outcome. Review and recommendations. *Sports Med* 1997; 23:33-47.
4. Clapp JF 3rd, Rokey R, Treadway JL, Carpenter MW, Artal RM, Warrnes C. Exercise in pregnancy. *Med Sci Sports Exerc* 1992; 24(6 Suppl):S294-300.
5. Melzer K, Schutz Y, Soehnchen N, et al. Effects of recommended levels of physical activity on pregnancy outcomes. *Am J Obstet Gynecol* 2010; 202:266.e1-6.
6. Tobias DK, Zhang C, van Dam RM, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. *Diabetes Care* 2011; 34:223-9.
7. Mottola MF. The role of exercise in the prevention and treatment of gestational diabetes mellitus. *Curr Sports Med Rep* 2007; 6:381-6.
8. Sorensen TK, Williams MA, Lee IM, Dashow EE, Thompson ML, Luthy DA. Recreational physical activity during pregnancy and risk of preeclampsia. *Hypertension* 2003; 41:1273-80.
9. Barakat R, Lucia A, Ruiz JR. Resistance exercise training during pregnancy and newborn's birth size: a randomised

controlled trial. *Int J Obes (Lond)* 2009; 33:1048-57.

10. Barakat R, Ruiz JR, Stirling JR, Zakynthinaki M, Lucia A. Type of delivery is not affected by light resistance and toning exercise training during pregnancy: a randomized controlled trial. *Am J Obstet Gynecol* 2009; 201:590.e1-6.
11. Bovbjerg ML, Siega-Riz AM. Exercise during pregnancy and cesarean delivery: North Carolina PRAMS, 2004-2005. *Birth* 2009; 36:200-7.
12. Domenjoz I, Kayser B, Boulvain M. Effect of physical activity during pregnancy on mode of delivery. *Am J Obstet Gynecol* 2014; 211:401.e1-11.
13. Put WM, Chuang SL, Chan LW. Physical activity in pregnancy: attitudes and practices of Hong Kong Chinese women. *Hong Kong J Gynaecol Obstet Midwifery* 2015; 15:138-47.
14. Lee CF, Chiang IC, Lin SS, Lin HM, Hsu CJ. Physical activity pattern and related factors among women during pregnancy [in Chinese]. *Formosan J Med* 2012; 16:103-11.
15. Chasan-Taber L, Schmidt MD, Roberts DE, Hosmer D, Markenson G, Freedson PS. Development and validation of a Pregnancy Physical Activity Questionnaire. *Med Sci Sports Exerc* 2004; 36:1750-60.
16. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci physical Exerc* 2000; 32(9 Suppl):S498-504.
17. Hesketh KR, Evenson KR. Prevalence of US pregnant women meeting 2015 ACOG physical activity guidelines. *Am J Prev Med* 2016; 51:e87-9.
18. Lee CF, Hwang FM, Lin HM, Chi LK, Chien LY. The physical activity patterns of pregnant Taiwanese women. *J Nurs Res* 2016; 24:291-9.
19. Zhang Y, Dong S, Zuo J, Hu X, Zhang H, Zhao Y. Physical activity level of urban pregnant women in Tianjin, China: a cross-sectional study. *PLoS One* 2014; 9:e109624.
20. Liu J, Blair SN, Teng Y, Ness AR, Lawlor DA, Riddoch C. Physical activity during pregnancy in a prospective cohort of British women: results from the Avon longitudinal study of parents and children. *Eur J Epidemiol* 2011; 26:237-47.
21. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol* 2017; 216:340-51.

Risk Factors and Pregnancy Outcomes of Macrosomia: a Retrospective Cohort Study

Pui-Ying WONG MBChB
William WK TO MBBS, MPH, MPhil, MD, Dip Med, FHKAM (Obstetrics and Gynaecology), Cert HKCOG (MFM)
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong

Objectives: To evaluate maternal risk factors associated with macrosomia (birthweight ≥4000 g), and perinatal outcomes in Hong Kong.
Methods: This was a retrospective cohort study conducted at a regional obstetric unit over a 5-year period. All singleton pregnancies with livebirths delivered at term (≥37 weeks of gestation) were analysed. Maternal epidemiological and anthropometric characteristics, presence of antenatal complications (gestational diabetes and medical disorders), and pregnancy outcomes (need for labour induction, mode of delivery, Apgar scores, occurrence of shoulder dystocia, and birth trauma) were compared between macrosomic and non-macrosomic pregnancies. Logistic regression analysis was conducted to identify risk factors associated with macrosomia.
Results: From 2012 to 2016, 19 614 singleton, term livebirths were identified. Of these, 567 (2.89%) babies had a birthweight of ≥4000 g. A logistic regression model confirmed that the most prominent risk factor for macrosomia was post-term pregnancy (adjusted odds ratio [OR]=4.80), followed by diabetic complications in pregnancy (adjusted OR=3.90), maternal obesity (adjusted OR=1.65), multiparity (adjusted OR=1.50), and previous miscarriages (adjusted OR=1.35). Women with macrosomic pregnancy were more likely to be delivered by Caesarean section (36.0% vs. 20.8%), have failed instrumental deliveries (11.10% vs. 4.18%), have wound complications (1.23% vs. 0.23%), and experience postpartum haemorrhage (16.60% vs. 6.48%). Macrosomic neonates were more likely to encounter shoulder dystocia (5.23% vs. 0.40%) and birth trauma (0.50% vs. 0.05%).
Conclusion: The incidence of macrosomic pregnancy in this local population (2.89%) was significantly lower than that reported in western populations. Our data confirm an increased likelihood of maternal and neonatal morbidities in these pregnancies.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):18-23

Keywords: Diabetes, gestational; Fetal macrosomia; Obesity; Risk factors

Introduction

Macrosomia is associated with excess risks of adverse pregnancy outcomes and is a challenge in obstetrics[1]. The definitions of macrosomia vary from a birthweight of ≥4000 g to ≥4500 g and ≥5000 g[2]. In many western countries, the rate of macrosomic births has increased since the 1990s[3,4]. Reports worldwide have in general documented an increase in mean birthweight, mean birthweight for gestational age, and the prevalence of large for gestational age in recent decades[5]. A study in Beijing reported an increase in overall birthweight over a 15-year period from 1996 to 2010[6]. Another study in China showed an increase in the prevalence of macrosomia from 6% in 1994 to 7.3% in 2014[7]. Macrosomia is associated with many adverse maternal and neonatal outcomes. For mothers, macrosomia has been associated with increased risks of Caesarean section, prolonged labour, postpartum haemorrhage, and third- and fourth-degree perineal lacerations. Macrosomic neonates are more prone to birth trauma, perinatal asphyxia, shoulder dystocia, and perinatal death[8]. In a Hong Kong study, increasing birthweight was strongly linked to the risk of shoulder dystocia[9]. In addition, children who are born macrosomic and exposed to an intrauterine environment of maternal obesity or diabetes are at increased risk of developing metabolic syndrome later in life[10].

We reviewed the incidence of macrosomia among singleton, term livebirths in a Hong Kong population and attempted to evaluate the risk factors of macrosomia. We also reviewed the pregnancy outcomes of macrosomia to determine whether the incidence of adverse perinatal outcomes was in line with that reported in the literature.

Correspondence to: Dr Pui-Ying Wong
Email: wpy377@ha.org.hk

Methods

This study was approved by the ethics committee of the Kowloon Central Cluster of the Hospital Authority. All singleton pregnancies with a livebirth delivered at term (≥37 weeks of gestation) over a 5-year period from 2012 to 2016 at the United Christian Hospital were analysed. Data were extracted from the electronic obstetrics clinical information system database and the antenatal record system. Additional clinical details were extracted from the labour ward registry, individual clinical notes of the women, and the paediatric clinical records of the neonates. Macrosomia was defined as a birthweight of ≥4000g. The gestation at delivery was defined as the number of completed weeks of gestation, according to either the number of weeks of amenorrhea or confirmation by ultrasonography. Special care baby unit admission was defined as admission of the neonate immediately and up to 28 days after birth. Maternal obesity was defined as a body mass index (BMI) of ≥25 kg/m^2 before pregnancy or in the first trimester of pregnancy. The diagnosis of gestational diabetes and diabetes in pregnancy was based on the 75-g oral glucose tolerance test, according to the World Health Organization 2013 criteria and in accordance with our departmental protocol. Birth trauma included cranial haemorrhage (subgaleal and subdural), clavicle and other long bone fractures, and brachial plexus injury.

Maternal epidemiological and anthropometric characteristics, presence of antenatal complications (gestational diabetes and medical disorders), and pregnancy outcomes (maternal need for labour induction, mode of delivery, Apgar scores, occurrence of shoulder dystocia, and birth trauma) were compared between macrosomic and non-macrosomic pregnancies. Continuous variables were compared with Student's *t* test, and categorical variables with the Chi-square test or Fisher's exact test, as appropriate. A logistic regression model was constructed using significant variables on univariate analysis to identify risk factors associated with macrosomia, with adjusted odds ratios (ORs) and 95% confidence intervals (CIs) reported. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US).

Table 1. Incidence of macrosomic pregnancy per year

Year	Frequency	Percentage
2012	144/4908	2.93
2013	107/3797	2.81
2014	114/4020	2.83
2015	107/3931	2.62
2016	95/3286	2.42

Results

Of the 19614 singleton term livebirths identified from 2012 to 2016, 567 (2.89%) were considered to be macrosomia (birthweight ≥4000 g). Over the 5 years, the annual incidence of macrosomia ranged from 2.42% to 2.93% (p=0.98, Table 1).

Univariate analysis showed that women with macrosomic pregnancies were significantly older than others (32.9 vs. 31.9 years, p<0.001), with a higher proportion having advanced maternal age (39.5% vs. 31.1%, OR=1.44, p<0.001), being multiparous (62.1% vs. 51.5%, OR=1.54, p<0.001), and having had previous miscarriages (56.4% vs. 45.0%, OR=1.58, p<0.001). In addition, a higher proportion of these women had previous Caesarean deliveries (21.5% vs. 17.9%, OR=1.25, p=0.03) probably related to the fact that more were multiparous. They also had a higher BMI in early pregnancy (24.4 vs. 23.3 kg/m^2, p<0.001) and a higher incidence of obesity with BMI of ≥25 kg/m^2 (38.6% vs. 26.0%, OR=1.78, p<0.001). Women with macrosomic pregnancies had a higher incidence of post-term delivery beyond 41 weeks (28.7% vs. 10.5%, OR=3.42, p<0.001), and a longer gestation at delivery (39.8 vs. 39.1 weeks, p<0.001). There was also a higher incidence of gestational diabetes or diabetes in pregnancy among macrosomic pregnancies (28.7% vs. 11.6%, OR=3.06, p<0.001), but the incidence of pre-eclampsia or other antenatal medical complications did not differ significantly between groups (Table 2).

A logistic regression model was constructed with macrosomia as the dependent variable and significant factors on univariate analysis as independent variables. The most prominent risk factor for macrosomia was post-term pregnancy (adjusted OR=4.80, 95% CI=3.93-5.87, p<0.001), followed by diabetic complications in pregnancy (adjusted OR=3.90, 95% Cl=2.92-4.40, p<0.001), maternal obesity (adjusted OR=1.65, 95% CI=1.38-1.97, p<0.001), multiparity (adjusted OR=1.50, 95% CI=1.23-1.83, p<0.001), and previous miscarriages (adjusted OR=1.35, 95% CI=1.12-1.60, p=0.001). Advanced maternal age and previous Caesarean section were excluded from the equation (Table 3).

Women with macrosomic pregnancy were more likely to have induced labour (30.5% vs. 15.4%, OR=2.4,

Table 2. Maternal characteristics in macrosomic and non-macrosomic pregnancies

Variable	Macrosomia (n=567)*	Non-macrosomia (n=19047)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	p Value
Maternal age (years)	32.9 ± 5.03	31.9 ± 5.13	1.01 (0.59-1.44)	-	<0.001
Advanced age (≥35 years)	224 (39.5)	5927 (31.1)	-	1.44 (1.21-1.71)	<0.001
Parity			-	1.54 (1.23-1.83)	<0.001
Nulliparous	215 (37.9)	9235 (48.5)			
Multiparous	352 (62.1)	9812 (51.5)			
Previous miscarriages	320 (56.4)	8571 (45.0)	-	1.58 (1.33-1.87)	<0.001
Previous Caesarean section	122 (21.5)	3417 (17.9)	-	1.25 (1.02-1.53)	0.03
Maternal height (cm)	158.3 ± 4.97	156.4 ± 5.41	1.87 (1.41-2.32)	-	<0.001
Early pregnancy weight (kg)	61.1 ± 7.95	56.9 ± 8.41	1.87 (1.42-2.32)	-	<0.001
Body mass index (kg/m^2)	24.4 ± 3.02	23.3 ± 3.22	1.14 (0.88-1.42)	-	<0.001
Maternal obesity (body mass index of ≥25 kg/m^2)	219 (38.6)	4963 (26.0)	-	1.78 (1.50-2.12)	<0.001
Gestation at delivery (weeks)	39.8 ± 1.06	39.1 ± 1.11	0.73 (0.64-0.82)	-	<0.001
Post-term pregnancy (≥41 weeks)	163 (28.7)	2009 (10.5)	-	3.42 (2.83-4.12)	<0.001
Gestational diabetes / diabetes in pregnancy	163 (28.7)	2213 (11.6)	-	3.06 (2.54-3.70)	<0.001
Pre-eclampsia	9 (1.58)	327 (1.71)	-	0.92 (0.47-1.80)	1.0
Other medical disorders†	20 (3.53)	479 (2.51)	-	1.41 (0.89-2.23)	0.13

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

† Including significant medical (cardiac, thyroid, neurological, autoimmune, renal) diseases in pregnancy requiring treatment

Table 3. Logistic regression analysis of risk factors for macrosomia

Variable	B	Standard error	Wald	Adjusted odds ratio (95% confidence interval)	p Value
Variables in the equation					
Post-term pregnancy	1.57	0.102	234	4.80 (3.93-5.87)	<0.001
Gestational diabetes	1.27	0.105	149	3.90 (2.92-4.40)	<0.001
Maternal obesity	0.50	0.089	31.6	1.65 (1.38-1.97)	<0.001
Multiparity	0.40	0.10	16.1	1.50 (1.23-1.83)	<0.001
Previous miscarriages	0.29	0.09	10.7	1.35 (1.12-1.60)	0.001
Variables not in the equation					
Advanced maternal age	0.07	0.094	0.61	1.08 (0.89-1.29)	0.43
Previous Caesarean section	-0.005	-0.12	0.002	0.99 (0.79-1.25)	0.96

p<0.001). They were more likely to be delivered by Caesarean section (36.0% vs. 20.8%, OR=2.12, p<0.001) rather than normal vaginal delivery (57.0% vs. 69.8%) or instrumental delivery (7.0% vs. 9.4%). Moreover, the risk of failed instrumental delivery was higher for macrosomic pregnancies (11.10% vs. 4.18%, OR=2.85, p=0.024) and the risk of shoulder dystocia was also higher (5.23% vs. 0.40%, OR=10.90, p<0.001). The average blood loss at delivery in macrosomic pregnancies was significantly higher (333 vs. 225 ml, p<0.001), and the incidence of postpartum haemorrhage was also higher (16.60% vs. 6.48%, OR=2.86, p<0.001). After delivery, those with macrosomic pregnancies were more likely to have abdominal or episiotomy wound complications, including significant wound infection and gaping wound requiring re-suturing (1.23% vs. 0.23%, OR=5.39, p=0.001) [Table 4].

Table 4. Maternal and neonatal outcomes in macrosomic and non-macrosomic pregnancies

Variable	Macrosomia (n=567)*	Non-macrosomia (n=19047)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	p Value
Induction of labour	173 (30.5)	2942 (15.4)	-	2.40 (2.00-2.88)	<0.001
Mode of delivery			-	2.12 (1.78-2.53)†	<0.001
Normal vaginal	323 (57.0)	13285 (69.8)			
Instrumental	40 (7.0)	1785 (9.4)			
Caesarean section	204 (36.0)	3977 (20.8)			
Episiotomy	233/363 (64.25)	9423/15070 (62.50)	-	1.07 (0.86-1.33)	0.51
Failed instrumental delivery	5/45 (11.10)	78/1863 (4.18)	-	2.85 (1.09-7.44)	0.024
Wound complications (severe wound infection and gaping wound requiring re-suturing)	7 (1.23)	44 (0.23)	-	5.39 (2.42-12.00)	0.001
Blood loss at delivery (ml)	333 ± 287	225 ± 247	108 (88-129)	-	<0.001
Postpartum haemorrhage	94 (16.60)	1235 (6.48)	-	2.86 (2.28-3.60)	<0.001
Postnatal deep venous thrombosis	2 (0.35)	18 (0.09)	-	3.74 (0.86-16.20)	0.057
Birthweight (g)	4204 ± 195	3205 ± 332	998 (970-1025)	-	<0.001
Apgar score of ≤7 at 5 min	3 (0.50)	51 (0.26)	-	1.98 (0.61-6.36)	0.20
Shoulder dystocia	19 (5.23)	60 (0.40)	-	10.90 (6.50-18.50)	<0.001
Birth trauma	3 (0.50)	10 (0.05)	-	10.10 (2.78-36.90)	0.006
Cranial haemorrhage	1	2			
Brachial plexus palsy	2	1			
Fractures	0	6			
Special care baby unit admission	559 (98.6)	7304 (38.3)	-	112 (55-225)	<0.001
Neonatal death	0	1 (0.005)	-	11 (0.45-274)	1.0

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

† Caesarean section versus vaginal delivery

Macrosomic babies were of higher birthweight (4204 vs. 3205 g, p<0.001) and were more prone to have birth trauma (0.50% vs. 0.05%, OR=10.10, p=0.006). Their rate of special care baby unit admission was also higher (98.6% vs. 38.3%, OR=112, p<0.001). There was no significant difference in the rate of low Apgar scores or neonatal death between groups (Table 4).

Discussion

Our data confirm that post-term pregnancy, diabetic complications in pregnancy, and maternal obesity are the main risk factors associated with macrosomia. In our cohort, the overall incidence of macrosomia was 2.89%, which is lower than that in other studies in Chinese populations, of 7.3% to 8.7%[6,7]. The incidence of macrosomia in our cohort was also much lower than that reported in other populations. The incidence of macrosomia (birthweight >4 kg) was 7.1% in a large French cohort of 27 000 women and 9.5% in a Canadian cohort of 22 000 women[11]. Similarly, the incidence was 7.47% in a Turkish study, despite a gestational diabetes rate of only 4.8%[12].

There seem to be wide variations in the incidence of maternal obesity in different populations. Using the Asian BMI cut-off of 25 kg/m^2 in our cohort, the overall incidence of maternal obesity was 26.4%, whereas the incidence of women with pre-pregnant BMI of ≥24 kg/m^2 was only 13% to 16% in a Beijing survey[7]. Maternal obesity is more prevalent in western populations. The incidence of overweight (BMI 25-30 kg/m^2) and obesity (BMI >30 kg/m^2) was 18.6% and 9.1% in a French cohort and 23.5% and 16% in a Canadian cohort, respectively[11]. In a large cross-sectional survey of 268 000 deliveries from 2011 to 2014 in Wisconsin, United States, the incidence of maternal obesity (BMI >30 kg/m^2) was 27.8%[13]. In another North American study, the incidence of overweight and

obesity was 26.5% and 23.3%, respectively[14]. Although the incidence of obesity was quite high in this local cohort, maternal obesity seems to be a greater problem for concern for many western populations.

In our cohort, the most prominent risk factor for macrosomia was post-term pregnancy, with an adjusted OR of 4.80. Women with macrosomic pregnancy were more likely to have induced labour. This finding could be attributed to an increased induction rate for post-term pregnancy and for gestational diabetic complications. According to our hospital's protocol, post-term pregnancies with gestational age of ≥41 weeks are routinely offered induction of labour. Those who have gestational diabetes are offered induction of labour at ≥40 weeks if they are treated by diet control. If the diagnosis is diabetes in pregnancy or if the gestational diabetes requires insulin for control, induction of labour is offered even earlier, at ≥38 weeks, in line with the recommendations from the National Institute for Health and Care Excellence guidelines[15]. Many experts advocate induction of labour before 41 weeks when the estimated fetal weight is up to >2 standard deviations on ultrasonography. Our protocol does not specifically include suspected macrosomia as an indication for induction of labour. This practice remains controversial. In a retrospective series, an analysis of pregnancies in which neonates had a birthweight of 4 kg showed that induction of labour at 39 weeks' gestation was associated with a lower rate of Caesarean section when compared with deliveries at 40 to 42 weeks[16]. In a large multicentre trial in Europe in which women with a singleton fetus whose estimated weight exceeded the 95th centile were randomly assigned to either induction of labour between 37 and 39 weeks or expectant management, induction of labour was associated with a reduced risk of shoulder dystocia and morbidities and higher likelihood of spontaneous vaginal delivery[17]. In contrast, the 2016 updated Cochrane review[18] included four trials involving 1190 women and concluded that compared with expectant management, induction of labour for suspected macrosomia did not reduce the risk of Caesarean section or instrumental delivery. Although shoulder dystocia and any fractures were reduced in the induced labour group, perinatal morbidity was not significantly different between groups[18].

The issue of elective abdominal delivery for suspected macrosomia remains even more controversial. Elective Caesarean section has been proposed for suspected macrosomia of ≥5000 g in uncomplicated pregnancies and ≥4500 g if maternal risk factors such as diabetes or shoulder dystocia in previous pregnancies are identified[19]. Nonetheless, the estimation of fetal weight at such high ranges has been shown to be less accurate than when fetal weight is within the normal range[20], and specific formulae are needed to improve precision. In addition, any error could be due to the time lapse between ultrasonography and delivery[21]. A retrospective review reported that ultrasonography could detect only 33% of macrosomic fetuses, so a policy of elective Caesarean section for macrosomia would likely miss a large proportion of target pregnancies[22]. In addition, it was estimated that the number-needed-to-treat by Caesarean section would be 10.6 to avoid one shoulder dystocia, 52.6 to avoid one plexus injury, and 23.5 to avoid one sphincter laceration[1]. Thus, the role of elective Caesarean section may be appropriate only for extreme macrosomia.

Previous miscarriage is another risk factor for macrosomia and has been reported in other studies as higher gravida[2]. Women with macrosomic pregnancy are more likely to be multiparous and have had more pregnancies. They are more likely to be of advanced maternal age and obese; both factors are associated with an increased risk of miscarriage.

In general, women with macrosomic pregnancy experience a more difficult delivery and more adverse outcomes and have higher rates of failed instrumental delivery, birth trauma, and shoulder dystocia[23], as well as a higher rate of postpartum haemorrhage during delivery[24]. In a large Chinese cohort, neonates with a birthweight of >4.5 kg had higher rates of infant mortality, an Apgar score of ≤3 at 5 minutes, and respiratory and neurological disorders[23]. Nonetheless, our data showed no significant difference in Apgar scores between macrosomic and non-macrosomic neonates. This finding was probably related to the comparatively smaller size of our cohort, with only a very small proportion of neonates with a birthweight of ≥4.5 kg (n=43, 0.22%).

This study had several limitations. It was retrospective and the mode of delivery was often dictated by clinical suspicion of macrosomia. Ultrasonography for fetal weight estimation was performed selectively in indicated cases. In addition, we were unable to analyse total weight gain in pregnancy, as these data were heterogeneous owing to the incomplete recording of pre-pregnancy weight. The high rate of special care baby unit admission could be attributed to the routine admission of neonates with a birthweight of ≥4 kg, according to the paediatrician's protocol and may not reflect actual perinatal morbidity.

Conclusion

Our data confirm that macrosomic pregnancies are associated with higher maternal and neonatal morbidity as compared with non-macrosomic pregnancies. The main predictive factors associated with macrosomia were post-date pregnancies, gestational diabetes, maternal obesity, and multiparity. Further studies should focus on the role of induced labour at term for suspected macrosomia, more stringent control of gestational diabetes during pregnancy, and the reduction of maternal obesity in the general obstetric population.

Declaration

As an editor of this journal, William WK To was not involved in the peer review process of this article. Pui-Wing Wong has disclosed no conflicts of interest.

References

1. Bjørstad AR, Irgens-Hansen K, Daltveit AK, Irgens LM. Macrosomia: mode of delivery and pregnancy outcome. *Acta Obstet Gynecol Scand* 2010; 89:664-9.
2. Wang D, Hong Y, Zhu L, et al. Risk factors and outcomes of macrosomia in China: a multicentric survey based on birth data. *J Matern Fetal Neonatal Med* 2017; 30:623-7.
3. Stotland NE, Caughey AB, Breed EM, Escobar GJ. Risk factors and obstetric complications associated with macrosomia. *Int J Gynaecol Obstet* 2004; 87:200-6.
4. Alberman E. Are our babies becoming bigger? *J R Soc Med* 1991; 84:257-60.
5. Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* 2013; 381:476-83.
6. Li G, Kong L, Li Z, et al. Prevalence of macrosomia and its risk factors in China: a multicentre survey based on birth data involving 101,723 singleton term infants. *Paediatr Perinat Epidemiol* 2014; 28:345-50.
7. Shan X, Chen F, Wang W, et al. Secular trends of low birthweight and macrosomia and related maternal factors in Beijing, China: a longitudinal trend analysis. *BMC Pregnancy Childbirth* 2014; 14:105.
8. Ye J, Zhang L, Chen Y, Fang F, Luo Z, Zhang J. Searching for the definition of macrosomia through an outcome-based approach. *PLoS One* 2014; 9:e100192.
9. Cheng YK, Lao TT, Sahota DS, Leung VK, Leung TY. Use of birth weight threshold for macrosomia to identify fetuses at risk of shoulder dystocia among Chinese populations. *Int J Gynaecol Obstet* 2013; 120:249-53.
10. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 2005; 115:e290-6.
11. Fuchs F, Senat MV, Rey E, et al. Impact of maternal obesity on the incidence of pregnancy complications in France and Canada. *Sci Rep* 2017; 7:10859.
12. Donma MM. Macrosomia, top of the iceberg: the charm of underlying factors. *Pediatr Int* 2011; 53:78-84.
13. Gregor L, Remington PL, Lindberg S, Ehrenthal D. Prevalence of pre-pregnancy obesity 2011-2014. *WMJ* 2016; 115:228-32.
14. Lindberg S, Anderson C, Pillai P, Tandias A, Arndt B, Hanrahan L. Prevalence and predictors of unhealthy weight gain in pregnancy. *WMJ* 2016; 115:233-7.
15. National Collaborating Centre for Women's and Children's Health (UK). Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. London: National Institute for Health and Care Excellence (UK); 2015.
16. Cheng YW, Sparks TN, Laros RK Jr, Nicholson JM, Caughey AB. Impending macrosomia: will induction of labour modify the risk of caesarean delivery? *BJOG* 2012; 119:402-9.
17. Boulvain M, Senat MV, Perrotin F, et al. Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet* 2015; 385:2600-5.
18. Boulvain M, Irion O, Dowswell T. Thornton JG. Induction of labour at or near term for suspected fetal macrosomia. *Cochrane Database Syst Rev* 2016;5:CD000938.
19. Chauhan SP, West DJ, Scardo JA, Boyd JN, Joiner J, Hendrix NW. Antepartum detection of macrosomic fetus: clinical versus sonographic, including soft-tissue measurements. *Obstet Gynecol* 2000; 95:639-42.
20. Bamberg C, Hinkson L, Henrich W. Prenatal detection and consequences of fetal macrosomia. *Fetal Diagn Ther* 2013; 33:143-8.
21. Phillips AM, Galdamez AB, Ounpraseuth ST, Magann EF. Estimate of fetal weight by ultrasound within two weeks of delivery in the detection of fetal macrosomia. *Aust N Z J Obstet Gynaecol* 2014; 54:441-4.
22. Faschingbauer F, Dammer U, Raabe E, et al. Sonographic weight estimation in fetal macrosomia: influence of the time interval between estimation and delivery. *Arch Gynecol Obstet* 2015; 292:59-67.
23. Wang D, Zhu L, Zhang S, et al. Predictive macrosomia birthweight thresholds for adverse maternal and neonatal outcomes. *J Matern Fetal Neonatal Med* 2016; 29:3745-50.
24. Rossi AC, Mullin P, Prefumo F. Prevention, management, and outcomes of macrosomia: a systematic review of literature and meta-analysis. *Obstet Gynecol Surv* 2013; 68:702-9.

Association Between Time of Day of Unscheduled Caesarean Section and Outcomes

Constance Wing-Kei CHAN MBBS(HK), MRCOG
Choi-Wah KONG MBChB, MRCOG, FHKAM (Obstetrics and Gynaecology)
William WK TO MBBS, MPH, MPhil, MD, FRCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong

Objective: To evaluate the association between the time of day of unscheduled Caesarean section and maternal and perinatal outcomes.
Methods: This retrospective study was conducted at a regional hospital in Hong Kong. All unscheduled Caesarean sections performed between January 2014 and December 2016 were reviewed. Maternal outcomes included blood loss, postpartum haemorrhage, need for intra-operative blood transfusion, duration of operation, operative complications, postpartum fever, wound complications, and severe maternal morbidities. Perinatal outcomes included birthweight, Apgar scores, admission to the special care baby unit, birth trauma, stillbirths, and neonatal deaths. Data were stratified and compared according to three duty shifts: day shift (08:30-16:30), evening shift (16:31-00:30), and overnight shift (00:31-08:30).
Results: During the study period, 1631 unscheduled Caesarean sections were performed, accounting for 54.7% of all Caesarean sections. The highest proportion (40.4%) of unscheduled Caesarean sections were performed during the day shift. Blood loss was significantly more in the overnight shift than the day or evening shift (444 vs. 366 vs. 386 ml, p=0.005), although the rate of postpartum haemorrhage did not differ significantly. The rate of wound complications requiring re-suturing was higher in the overnight shift than the day or evening shift (3.2% vs. 0.3% vs. 0.16%, p<0.001). For perinatal outcomes, birthweight was lower in the day shift, probably related to the slightly earlier gestation at delivery (p<0.001). There were no significant differences among shifts in terms of Apgar score, special care baby unit admission, birth trauma, or perinatal mortality.
Conclusion: Unscheduled Caesarean sections performed during the overnight shift did not significantly increase maternal or perinatal complications. The current practice is safe for both mothers and neonates.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):24-9

Keywords: Cesarean section; Infant morbidity; Maternal mortality; Shift work schedule

Introduction

Ensuring high-quality care in the delivery suite is essential. Trainees in obstetrics and gynaecology need to be on call for ≥24 hours on a one-in-three to one-in-five rotation as per the College training requirement in Hong Kong[1]. There is controversy about whether performance of doctors is impaired as a result of shift work schedule. Errors in medical judgement tend to increase when physicians are deprived of sleep[2]. After a night on call in a surgical department, surgeons have been reported to show impaired speed and accuracy in simulated laparoscopic performance[3]. In addition, attention failure increases during night work hours[4].

Delivery room work shifts may affect delivery outcomes. The association between the time of day of delivery and maternal and neonatal outcomes has been inconsistent. Two observational studies have reported that infants born at night may be at increased risk of early neonatal death[5,6]. Population-based studies in Sweden and California have reported a significant increase in the risk of neonatal morbidities and mortalities in those born during the night shift[7,8]. Nonetheless, epidemiological studies have failed to demonstrate any significant differences in neonatal outcomes in terms of the time and day of birth[9-11].

This study aimed to examine the association between the time of day of unscheduled Caesarean section and maternal and perinatal outcomes in a regional obstetric unit over a 3-year period from January 2014 to December 2016. We hypothesised that maternal and neonatal complications would increase in unscheduled Caesarean deliveries performed during the overnight shift, compared with the day or evening shift.

Correspondence to: Dr Constance Wing-Kei Chan
Email: cwk391@ha.org.hk

Methods

This retrospective study was approved by the Hospital Authority Research Ethics Committee (Kowloon Central Cluster). The need for individual patient consent was waived. This study was conducted at the obstetric unit of the United Christian Hospital, which is a training centre for general specialist trainees and maternal-fetal medicine subspecialist trainees under the Hong Kong College of Obstetricians and Gynaecologists. Over 95% of unscheduled Caesarean sections were performed by first-call or second-call residents. During a call day, residents were on call from 08:30 to around 12:30 the next day, i.e. a continuous shift of 28 hours, before going off duty for a post-call half-day rest. Meanwhile, residents were on cover for labour ward emergencies from 08:30 to 08:30 the next day, and then usually had clinic duties the following day until 12:30. Occasionally, doctors were required to cover the labour ward until they went off duty at 12:30.

Cases were stratified to three groups according to the time of unscheduled Caesarean section: day shift (08:30-16:30), evening shift (16:31-00:30), and overnight shift (00:31-08:30). Most unscheduled Caesarean sections during the day shift were performed by residents who just started duty (duty hours, 0-8). Fewer than 5% of unscheduled Caesarean sections were performed by those during duty hours 24 to 28 after an overnight call. Caesarean sections during the evening shift and overnight shift were performed by those during duty hours 9 to 16 and 17 to 24, respectively.

Records of all pregnant women who underwent an unscheduled Caesarean section at the United Christian Hospital between January 2014 and December 2016 were retrospectively retrieved from the labour ward registry, electronic patient record, and antenatal record system. Demographic data included maternal age, parity, gestation at delivery, pregnancy complications, indication for Caesarean section, type of anaesthesia, type of Caesarean section, and degree of urgency. Surgical outcomes included blood loss, postpartum haemorrhage, need for intra-operative blood transfusion, duration of surgery, complications of surgery, postpartum fever, wound complications, peripartum hysterectomy, and maternal death. Neonatal outcomes included birthweight, Apgar score at 1 and 5 min, special care baby unit admission, birth trauma, stillbirths, and neonatal death.

SPSS (IBM Corp, Armonk [NY], US) was used for statistical analyses. Variables were compared across the day, evening, and overnight shifts using the Chi-square test for categorical variables and the analysis of variance for continuous variables. The post-hoc Bonferroni test was applied to delineate between-group differences. A p value of <0.05 was considered statistically significant.

Results

From January 2014 to December 2016, there were 12 861 deliveries (mean, approximately 4200 per year). Of these, 2982 (23.1%) were Caesarean deliveries, of which 1631 (54.7%) were unscheduled; of the latter, nearly all were lower-segment Caesarean section. Most of the unscheduled Caesarean deliveries occurred during the day shift (n=659, 40.4%), followed by the evening shift (n=500, 30.7%) and overnight shift (n=472, 28.9%) [Table 1].

The proportion of nulliparous women in the overnight shift was significantly higher, probably reflecting a longer labour. The mean gestational age at delivery significantly differed between the three groups, probably owing to a higher proportion of women with induction of labour for post-term pregnancy during the overnight shift. The most common indication for Caesarean section was no progress or labour dystocia. The rates of fetal distress ($p<0.001$) and no progress ($p=0.003$) were higher in the evening shift. The rate of previous Caesarean section ($p=0.037$) was higher in the day shift. The rates of failed instrumental delivery ($p=0.024$) and failed induction of labour ($p=0.004$) were higher in the overnight shift. The rate of general anaesthesia was higher in the evening shift ($p=0.012$). The rate of crash Caesarean sections ($p<0.001$) was higher in the day shift. The rate of second-stage Caesarean sections ($p=0.019$) was higher in the overnight shift.

Blood loss was higher in the overnight shift than the day or evening shift (444 vs. 366 vs. 386 ml, $p=0.005$, Table 2), although the absolute difference of 60-80 ml was not of clinical significance. The rates of primary postpartum haemorrhage, severe postpartum haemorrhage of >1 litre, and need for intra-operative blood transfusion were similar among the three shifts. The rate of wound complications requiring re-suturing was higher in the overnight shift than day or evening shifts (3.2% vs. 0.3% vs. 1.6%, $p<0.001$). Duration of operation and intra-operative complications such as uterine rupture or adjacent organ trauma were similar in the three shifts. There was one case of peripartum hysterectomy in each shift.

The mean birthweight was lower in the day shift than evening or overnight shift (2955 vs. 3096 vs. 3137 g,

Table 1. Baseline maternal characteristics

Variable	Day shift (n=659)*	Evening shift (n=500)*	Overnight shift (n=472)*	p Value
Maternal age (years)	33.5 ± 4.99	33 ± 5.12	33 ± 4.84	0.204
Parity				0.001
Nulliparous	412 (62.5)	354 (70.8)	340 (72.0)	
Multiparous	247 (37.5)	146 (29.2)	132 (28.0)	
Gestation at delivery (weeks)	37.9 ± 2.72	38.5 ± 2.61	38.7 ± 2.41	<0.001†
Multiple pregnancy	35 (5.3)	27 (5.4)	16 (3.4)	0.24
Diabetes mellitus				0.95
Gestational diabetes	116 (17.6)	81 (16.2)	82 (17.4)	
Pre-existing diabetes	6 (0.9)	4 (0.8)	3 (0.6)	
Pre-eclampsia	66 (10.0)	40 (8.0)	30 (6.4)	0.08
Main indications for Caesarean section				
Fetal distress	61 (9.3)	80 (16.0)	40 (8.5)	<0.001
No progress/ labour dystocia	131 (19.9)	142 (28.4)	113 (23.9)	0.003
Placenta praevia	25 (3.8)	11 (2.2)	9 (1.9)	0.11
Abruptio placenta	9 (1.4)	6 (1.2)	5 (1.1)	0.89
Breech	22 (3.3)	21 (4.2)	23 (4.9)	0.42
Previous Caesarean section	113 (17.1)	59 (11.8)	67 (14.2)	0.037
Failed instrumental delivery	8 (1.2)	4 (0.8)	16 (3.4)	0.024
Failed induction of labour	39 (5.9)	28 (5.6)	49 (10.4)	0.004
Type of anaesthesia				0.012
Spinal	507 (76.9)	349 (69.8)	341 (72.2)	
Epidural	42 (6.4)	46 (9.2)	52 (11.0)	
General	110 (16.7)	105 (21.0)	79 (16.7)	
Type of Caesarean section				0.53
Lower segment	656 (99.5)	495 (99.0)	468 (99.2)	
Classical	3 (0.5)	5 (1.0)	4 (0.8)	
Type of emergency				<0.001
Emergency	441 (66.9)	390 (78.0)	404 (85.6)	
Crash	218 (33.1)	110 (22.0)	68 (14.4)	
Second-stage Caesarean section	28 (4.2)	32 (6.4)	39 (8.3)	0.019

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

† By analysis of variance with post-hoc Bonferroni test: day vs. evening shift (mean difference [MD]= -0.54, 95% confidence interval [CI]= -0.91 to -0.17, p=0.001); day vs. overnight shift (MD= -0.77, 95% CI= -1.15 to -0.39, p<0.001); evening vs. overnight shift (MD= -0.23, 95% CI= -0.63 to 0.17, p=0.527)

p<0.001, Table 3), probably owing to the slightly earlier gestation at delivery. Other neonatal outcomes including Apgar scores and birth trauma were comparable among the three shifts. There were six stillbirths: two for placenta abruptio, one for severe pre-eclampsia, one for fetal distress, and one for maternal request. The sixth involved a peri-mortem Caesarean section in a patient with cardiac arrest following cerebrovascular haemorrhage complicating a severe hypertensive crisis. Of the four neonatal deaths, two were due to congenital abnormalities and two were due to complications of prematurity.

Unscheduled Caesarean sections performed during the overnight shift were associated with only minor increases in maternal morbidities (blood loss and wound complications) and not with any neonatal morbidities.

Table 2. Maternal outcomes of unscheduled Caesarean section

Variable	Day shift (n=659)*	Evening shift (n=500)*	Overnight shift (n=472)*	p Value
Blood loss (ml)	366 ± 339	386 ± 364	444 ± 502	0.005†
Total postpartum haemorrhage	137 (20.8)	108 (21.6)	112 (23.7)	0.49
Severe postpartum haemorrhage	14 (2.1)	15 (3.0)	12 (2.5)	0.64
Peripartum hysterectomy	1 (0.2)	1 (0.2)	1 (0.2)	0.96
Intra-operative blood transfusion	9 (1.4)	7 (1.4)	10 (2.1)	0.58
Duration of operation (min)	44.3 ± 18.2	45.6 ± 18.4	45.6 ± 15.3	0.91
Lower segment tear	4 (0.6)	6 (1.2)	8 (1.7)	0.10
Adjacent organ trauma	1 (0.2)	0 (0.0)	0 (0.0)	0.48
Postpartum fever	34 (5.2)	20 (4.0)	26 (5.5)	0.51
Wound complications requiring re-suturing	2 (0.3)	8 (1.6)	15 (3.2)	<0.001
Maternal death	0 (0.0)	1 (0.2)	0 (0.0)	0.32

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

† By analysis of variance with post-hoc Bonferroni test: day vs. evening shift (mean difference [MD]= -19.8, 95% confidence interval [CI]= -76.7 to 37.1, p=1.0); day vs. overnight shift (MD= -77.6, 95% CI= -135.5 to -19.7, p=0.004); evening vs. overnight shift (MD= -57.8, 95% CI= -119.4 to 3.8, p=0.074)

Table 3. Neonatal outcomes of unscheduled Caesarean section

Variable	Day shift (n=694)*	Evening shift (n=527)*	Overnight shift (n=488)*	p Value
Birthweight (g)	2955 ± 729	3096 ± 684	3137 ± 615	<0.001†
Apgar score <4 at 1 min	6 (0.9)	7 (1.3)	3 (0.6)	0.48
Apgar score <7 at 5 min	16 (2.3)	15 (2.8)	10 (2.0)	0.70
Special care baby unit admission	466 (67.1)	361 (68.5)	327 (67.0)	0.85
Birth trauma				0.51
Lacerations	2 (0.3)	1 (0.2)	0 (0.0)	
Fractures	0 (0.0)	0 (0.0)	0 (0.0)	
Stillbirth	2 (0.3)	3 (0.6)	1 (0.2)	0.60
Neonatal death	2 (0.3)	1 (0.2)	1 (0.2)	0.93

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

† By analysis of variance with post-hoc Bonferroni test: day vs. evening shift (mean difference [MD]= -140.2, 95% confidence interval [CI]= -235.0 to -45.5, p<0.001); day vs. overnight shift (MD= -181.1, 95% CI= -278.0 to -84.2, p<0.001); evening vs. overnight shift (MD= -40.9, 95% CI= -143.9 to 62.2, p=1.000)

Discussion

In this study, unscheduled Caesarean sections performed during the overnight shift did not result in a significant increase in maternal or perinatal complications, compared with other shifts. Since the publication of the Doctor Work Reform Recommendation report by the steering committee on doctor work hours of the Hong Kong Hospital Authority[12], an upper limit of 28 continuous working hours has been used as a corporate audit standard for doctor work hours. Our resident call system and work hours have shown no negative effects on doctor performance. The current practice in a typical obstetric service and training unit is safe for both mothers and neonates.

The possible negative effects of fatigue and sleep deprivation on clinical performance have been reported[2]. In a study of the impact of partial sleep deprivation after an overnight call on the mood status and cognitive skills of anaesthesiologists, tension, anger, fatigue, confusion,

irritability, jitteriness, and sleepiness were significantly affected, and there was a decrease in vigour, energy, and confidence[13]. Even when anaesthesiology residents were required to do only shift duty, they spent less time on manual tasks and more on monitoring tasks during the night shift than during the day shift, and they experienced more negative moods at night[14]. Among junior physicians, post-on-call alert scores were significantly reduced compared with their pre-on-call scores if they slept fewer hours during the call compared with normal sleep hours[15]. When emergency medicine registrars were presented with simulated scenarios and tested with clinical questions of fellowship examination standard, their scores were significantly higher during their dayshift than nightshift[16]. When paediatric residents were challenged with a medical decision questionnaire after 24 hours on call, those with most sleep deprivation and nap time of <1 hour during the shift were significantly more likely to choose riskier medical options than those with more sleep[17]. In a meta-analysis of 16 studies on the impact of sleep deprivation and disturbed circadian rhythm on the performance of surgical residents, mixed results were obtained. Nonetheless, when results showed a negative impact, surgical residents with less training/experience appeared to be more affected than more senior residents[18]. When obstetrics and gynaecology residents were asked to complete a series of tasks to test fine-motor coordination before and after 24 hours on call, there was a significant decline in performance after an overnight call, and there were significant differences in performance when stratified by year of training and gender. Female residents appeared to tolerate better the lack of sleep than male residents, and third-year residents showed no changes in post-call compared with more junior colleagues[19].

The negative effects on performance can be due to fatigue, sleep deprivation, or disturbed circadian rhythm. Compelling evidence of the detrimental effects of sleep deprivation derives from comparisons between the effects of acute sleep deprivation and those of alcohol intoxication. Even 17 hours of continued wakefulness can decrease performance to a degree similar to that seen with a blood alcohol concentration of 0.05%[20,21] (The law against drunk driving in Hong Kong sets the maximum blood alcohol level at 55 mg per 100 ml or 0.055%). Although our findings did not show any major negative impact on maternal or neonatal morbidities in unscheduled Caesarean sections carried out during the overnight shift, there were still subtle differences such as slightly more blood loss and more wound complications requiring re-suturing. A large epidemiological study showed that the night shift is an independent risk factor for increases in severe maternal morbidities, such as third- and fourth-degree perineal tears, vaginal haematoma, re-laparotomy, and even hysterectomy[22]. It may be argued that the adrenaline response of the doctor during emergency operations will counteract the reduced alertness due to fatigue. However, 90% of our residents were female and could have tolerated sleep deprivation better than male residents. In addition, many of our residents were in their third year of training or above and their experience may have compensated for their slightly compromised performance[18,19]. Indeed, in sleep-deprived residents on a peg transfer task in two different laparoscopic skills simulators, level of expertise could override sleep hours and fatigue to be the only significant determinant of performance[23].

Neonatal outcomes can be affected by many other obstetric and neonatal management factors. It remains controversial whether the time of delivery is relevant. A large epidemiological study in California showed that the neonatal mortality per 1000 livebirths rose from 1.88 for daytime to 2.37 for early night and 2.31 for late night, and there was excess mortality in neonates with birthweight of <1500 g[8]. Similarly, in a population-based cohort study from Scotland, delivery of a baby outside the normal working week was associated with an increased risk of neonatal death at term ascribed to intrapartum anoxia[24]. Nonetheless, outcomes of vaginal and Caesarean births involve the performance of both the obstetric and neonatal teams and other supporting services. A Japanese retrospective series reported that Caesarean delivery during the night had an increased risk of neonatal but not maternal morbidity[25]. On the contrary, a large North American Caesarean registry failed to demonstrate any increase in maternal or neonatal complications after Caesarean sections performed during the night shift[9]. In addition, a retrospective cohort study from Israel showed that Caesarean section performed in the night shift was associated with a longer operative time and an increased risk of maternal but not neonatal morbidity[10]. The risks of out-of-hour neonatal death in the 1990s had become non-significant by 2000-2004, and had no significant association by 2005-2009[26]. Improvement in staffing patterns of neonatal units to provide consistent and standard care has mitigated the differences in perinatal outcome in relation to the time of delivery.

This study had limitations. Data were collected from a single regional hospital in Hong Kong and not from all tertiary care hospitals; this limited the sample size for assessing neonatal mortality. Although our on-call and duty-hour system and the level of experience of our

residents were largely similar to those of other teaching hospitals in Hong Kong, there could still be discrepancies and results might not be directly applicable.

Conclusion

Unscheduled Caesarean sections that were performed during the overnight shift were associated with only minor increases in maternal morbidities and were not associated with neonatal morbidities. It is reassuring that our current on-call system and practice are safe for both mothers and neonates.

Declaration

As an editor of this journal, William WK To was not involved in the peer review process of this article. All other authors have disclosed no conflicts of interest.

References

1. Structured Training in Obstetrics and Gynaecology (endorsed by the Council on 10th November 2016). Hong Kong College of Obstetricians and Gynaecologists. Available from: http://www.hkcog.org.hk/hkcog/Download/3-Basic_training.pdf.
2. Weinger MB, Ancoli-Israel S. Sleep deprivation and clinical performance. *JAMA* 2002; 287:955-7.
3. Grantcharov TP, Bardram L, Funch-Jensen P, Rosenberg J. Laparoscopic performance after one night on call in a surgical department: prospective study. *BMJ* 2001; 323:1222-3.
4. Lockley SW, Cronin JW, Evans EE, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J* Med 2004; 351:1829-37.
5. Luo ZC, Karlberg J. Timing of birth and infant and early neonatal mortality in Sweden 1973-95: longitudinal birth registry study. *BMJ* 2001; 323:1327-30.
6. Heller G, Misselwitz B, Schmidt S. Early neonatal mortality, asphyxia related deaths, and timing of low risk births in Hesse, Germany, 1990-8: observational study. *BMJ* 2000; 321:274-5.
7. Stephansson O, Dickman PW, Johansson AL, Kieler H, Cnattingius S. Time of birth and risk of intrapartum and early neonatal death. *Epidemiology* 2003; 14:218-22.
8. Gould JB, Qin C, Chavez G. Time of birth and the risk of neonatal death. *Obstet Gynecol* 2005; 106:352-8.
9. Bailit JL, Landon MB, Thom E, et al. The MFMU Cesarean Registry: impact of time of day on cesarean complications. *Am J Obstet Gynecol* 2006; 195:1132-7.
10. Peled Y, Melamed N, Chen R, Pardo J, Ben-Shitrit G, Yogev Y. The effect of time of day on outcome of unscheduled cesarean deliveries. *J Matern Fetal Neonatal Med* 2011; 24:1051-4.
11. Caughey AB, Urato AC, Lee KA, Thiet MP, Washington AE, Laros RK Jr. Time of delivery and neonatal morbidity and mortality. *Am J Obstet Gynecol* 2008; 199:496.e1-5.
12. Executive summary. Doctor Work Reform Recommendation Report. Hospital Authority 2007. Steering Committee on Doctor Work Hour.
13. Saadat H, Bissonnette B, Tumin D, et al. Time to talk about work-hour impact on anesthesiologists: The effects of sleep deprivation on Profile of Mood States and cognitive tasks. *Paediatr Anaesth* 2016; 26:66-71.
14. Cao CG, Weinger MB, Slagle J, et al. Differences in day and night shift clinical performance in anesthesiology. *Hum Factors* 2008; 50:276-90.
15. Wali SO, Qutah K, Abushanab L, Basamh R, Abushanab J, Krayem A. Effect of on-call-related sleep deprivation on physicians' mood and alertness. *Ann Thorac Med* 2013; 8:22-7.
16. Marcus L, Liew D, Knott J. The effect of nightshift on emergency registrars' clinical skills. *Emerg Med Australas* 2010; 22:211-5.
17. Aran A, Wasserteil N, Gross I, Mendlovic J, Pollak Y. Medical decisions of pediatric residents turn riskier after a 24-hour call with no sleep. *Med Decis Making* 2017; 37:127-33.
18. Sturm L, Dawson D, Vaughan R, et al. Effects of fatigue on surgeon performance and surgical outcomes: a systematic review. *ANZ J Surg* 2011; 81:502-9.
19. Ayalon RD, Friedman F Jr. The effect of sleep deprivation on fine motor coordination in obstetrics and gynecology residents. *Am J Obstet Gynecol* 2008; 199:576.e1-5.
20. Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. *Occup Environ Med* 2000; 57:649-55.
21. Clark SL. Sleep deprivation: implications for obstetric practice in the United States. *Am J Obstet Gynecol* 2009; 201:136.e1-4.
22. Lyndon A, Lee HC, Gay C, Gilbert WM, Gould JB, Lee KA. Effect of time of birth on maternal morbidity during childbirth hospitalization in California. *Am J Obstet Gynecol* 2015; 213:705.e1-11.
23. Olasky J, Chellali A, Sankaranarayanan G, et al. Effects of sleep hours and fatigue on performance in laparoscopic surgery simulators. *Surg Endosc* 2014; 28:2564-8.
24. Pasupathy D, Wood AM, Pell JP, Fleming M, Smith GC. Time of birth and risk of neonatal death at term: retrospective cohort study. *BMJ* 2010; 341:c3498.
25. Suzuki S. The effect of time of day on unscheduled cesarean delivery and perinatal outcome. *Int J Gynaecol Obstet* 2012; 116:117-8.
26. Gardosi J, Tonks A, Francis A. Risk of neonatal death due to intrapartum anoxia in out of hours deliveries in the West Midlands. Available from: http://www.bmj.com/rapid-response/2011/11/02/risk-neonatal-death-due-intrapartum-anoxia-out-hours-deliveries-west-midla

Prevalence of Undetected Genital Tract Pre-malignancy and Malignancy in Hong Kong Women Undergoing Hysterectomy for Uterine Prolapse

Yui-Shing CHEUNG MBChB, MRCOG
Chi-Wai TUNG MBChB, MRCOG, FHKAM (Obstetrics and Gynaecology)
Anny WM TONG RN, RM, MHSM
Willy Cecilia CHEON MBChB, FRCOG, FHKCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Jordan, Hong Kong

Objective: To determine the prevalence of undetected genital tract malignancy and pre-malignancy in women who underwent hysterectomy for pelvic organ prolapse (POP).
Methods: This was a retrospective study of 497 women who underwent vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy for POP from 2005 to 2014 at a local hospital. The prevalence of malignancy and pre-malignancy was compared between pre-menopausal and post-menopausal patients as well as between those with symptoms of malignancy and those without.
Results: Of the 497 women studied, 415 (83.5%) were menopausal and only 67 (13.5%) had symptoms suggestive of malignancy. Two (0.5%) uterine malignancies, one (0.2%) cervical cancer, and one (0.2%) borderline ovarian tumour were detected in four asymptomatic patients, two of whom were menopausal. Twelve patients had pre-malignant conditions, including five cases of cervical intraepithelial neoplasia, six cases of endometrial hyperplasia, and one case of vaginal intraepithelial neoplasia. Five of the patients were asymptomatic, and nine were menopausal. The overall risk of missed malignancy and pre-malignancy was 0.8% and 2.4%, respectively, in women who underwent hysterectomy for POP.
Conclusion: Routine histological examination of the hysterectomy specimens is recommended. Comprehensive preoperative examination is important especially in patients with symptoms suggestive of malignancy. Counselling of patients about the risks of missing malignancy is important in those who opt for uterus-preserving surgery.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):30-5

Keywords: Hysterectomy; Neoplasms; Pelvic organ prolapse; Prevalence; Uterine prolapse

Introduction

Pelvic organ prolapse (POP) usually affects parous women, particularly those of advanced age. In the United States, the prevalence of POP in women older than 50 years has been reported to be as high as 40%, and their lifetime risk of having a single operation for POP by 80 years of age was estimated to be 11.1%[1]. In Hong Kong, a territory-wide audit in 2009 reported an increasing prevalence of POP over the last decade[2]. POP not only causes vaginal bleeding and a dragging sensation but also is associated with acute retention of urine requiring catheterisation, constipation, and recurrent urinary tract infection in severe cases[3,4]. The treatment protocol usually starts with conservative treatment such as the use of a vaginal pessary, with >85% of gynaecologists prescribing a ring pessary[5]. However, vaginal pessary is associated with vaginal discharge, a foul odour, vaginal ulceration, and discomfort.

The most common surgical options for POP are vaginal hysterectomy and pelvic floor repair[5]. Both are minimally invasive with no abdominal wound and can treat POP in the anterior, middle, or posterior compartment. Increasingly more women opt to retain the uterus and cervix, as it may help maintain sexual satisfaction. Uterine-preserving surgery and vaginal hysterectomy achieve a similar functional outcome[6]. Nonetheless, preserving the uterus and cervix may be associated with the risk of missing malignancy of the genital tract[7]. This study aimed to evaluate the prevalence of undetected malignancy in hysterectomy specimens and determine the appropriateness of uterine-preserving surgery for women with POP. The risks of undetected malignancy and pre-malignancy were compared between symptomatic and asymptomatic patients as well as between pre-menopausal and post-menopausal patients.

Correspondence to: Dr Yui-Shing Cheung
Email: octoday@hotmail.com

Methods

This was a retrospective study of all women who underwent vaginal hysterectomy or laparoscopic-assisted vaginal hysterectomy for POP from 2005 to 2014 by the urogynaecology team at Queen Elizabeth Hospital in Hong Kong. Ethics approval was obtained from the Kowloon Central/Kowloon East Research Ethics Committee. Patient records were retrieved from the Clinical Management System. Demographic data such as age, parity, body mass index, menstrual history, and family history of gynaecological malignancy were obtained. Abdominal and pelvic examination and preoperative POP staging (using the POP quantification system from the International Continence Society) were reviewed. Ultrasonographic results for endometrial thickness, cervical smear results, and endometrial biopsy results were reviewed.

Symptomatic women were defined as those having symptoms suggestive of malignancy such as abnormal uterine bleeding, post-menopausal bleeding, and abdominal masses. Malignancy had been excluded prior to surgery. Women were referred to the gynae-oncology team and excluded if they were diagnosed with a pre-existing genital tract malignancy or pre-malignancy. All hysterectomy specimens were examined histopathologically, and the prevalence of undetected genital tract malignancy or pre-malignancy was determined.

Descriptive statistics such as frequency, mean, and standard deviation were used. Subjects were dichotomised to those with or without symptoms of genital tract malignancy, as well as those who were menopausal or not. Their demographic data, preoperative symptoms, and treatment outcomes were compared. Fisher's Exact test was used for categorical data. A two-tailed p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], US).

Results

Hysterectomy for POP was performed in 497 women over the 9-year study period (Figure). The mean patient age was 65.0 ± 11.2 years, mean body mass index was 25.15 ± 3.56 kg/m^2, and mean number of vaginal births was 3.38 ± 1.75. Of the women, 366 (73.6%) had stage I/II POP and the remaining 131 (26.4%) had stage III/V POP (Table 1). 415 (83.5%) women were menopausal and 430 (86.5%) women were asymptomatic. Among the 67 (13.5%) symptomatic women, 42 (62.7%) had post-menopausal bleeding and 25 (37.3%) had abnormal pre-menopausal uterine bleeding.

Of the 497 women, 439 (88.3%) underwent vaginal hysterectomy and 58 (11.7%) underwent laparoscopic-assisted vaginal hysterectomy. In addition, 47 (9.5%) women underwent concomitant bilateral salpingo-oophorectomy (BSO). All the specimens were examined histopathologically. Two (0.5%) uterine malignancies, one (0.2%) cervical cancer, and one (0.2%) borderline ovarian tumour were identified; these were in four asymptomatic women: two pre-menopausal and two menopausal.

Of the two pre-menopausal women with malignancy, one was 41 years old and referred in 2013 by a private doctor for uterine fibroid and genital prolapse. Cervical smear screening in 2012 was normal. Pathology showed adenocarcinoma and adeno-squamous carcinoma of the cervix. The other patient was 49 years old and also presented with uterine fibroid and genital prolapse.

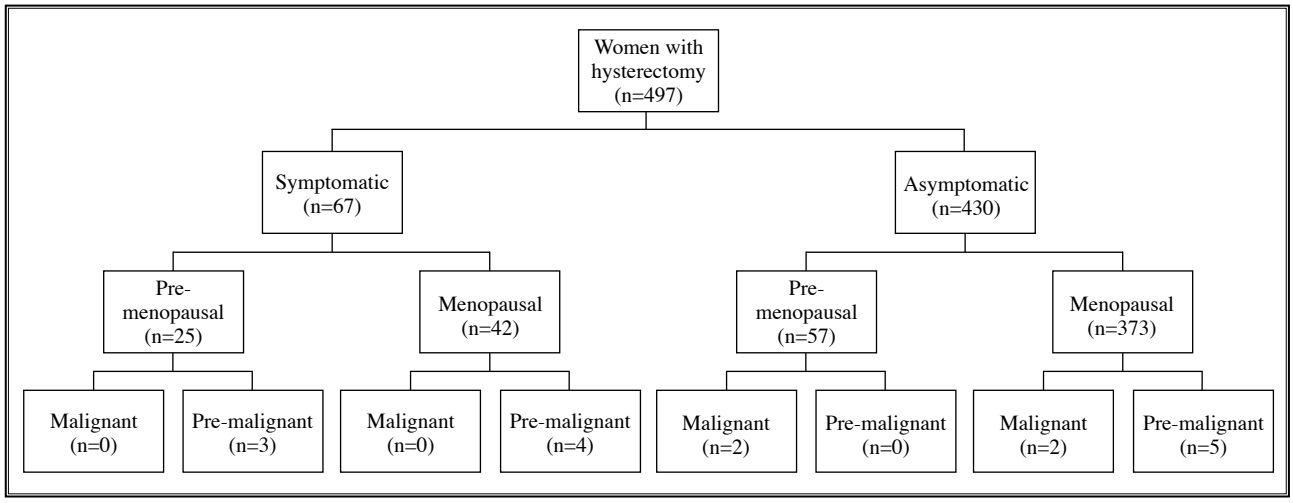


Figure. Flowchart showing outcomes of subjects

Table 1. Clinical characteristics of all subjects

Variable	Value*
Age (years)	64.98 ± 11.21
No. of vaginal births	3.38 ± 1.75
Body mass index (kg/m^2)	25.15 ± 3.56
Stage of pelvic organ prolapse	
Stage I/II	366 (73.6)
Stage III/V	131 (26.4)
Operative procedure	
Vaginal hysterectomy	439 (88.3)
Laparoscopic-assisted vaginal hysterectomy	58 (11.7)
Concomitant bilateral salpingo-oophorectomy	47 (9.5)

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

Preoperative ultrasonography showed an 8-cm ovarian cyst, and concomitant BSO was performed. The cyst was ruptured during surgery. Pathology of the right ovary showed borderline serous cystadenoma. The patient was followed up by the gynae-oncology team for a stage Ic borderline tumour of the ovary.

Of the two menopausal women with malignancy, one was 76 years old with an incidental finding of stage 1A endometrioid adenocarcinoma grade 1 of the uterine corpus. Subsequent laparoscopic BSO was performed for staging and showed no residual malignancy. The other patient was 71 years old with an incidental finding of smooth muscle cell tumour of uncertain malignant potential (STUMP). She presented with uterine prolapse with increasing urinary symptoms but no post-menopausal bleeding or abdominal mass. The uterine size was small and compatible with her menopausal status. Baseline computed tomography was normal. She was followed up yearly by the gynae-oncology team for surveillance of recurrence.

Twelve patients had pre-malignant conditions. In asymptomatic women, five (1.2%) pre-malignant conditions were detected including two cases of cervical intraepithelial neoplasia (CIN) in those aged >65 years with no prior cervical smear screening, two cases of endometrial hyperplasia, and one case of vaginal intraepithelial neoplasm. In symptomatic women, seven (10.4%) pre-malignant conditions were detected including three cases of CIN (two patients were aged >65 years; two patients had abnormal cervical smear and colposcopy but no malignant or pre-malignant conditions), and four cases of endometrial hyperplasia.

In asymptomatic women, the risks of malignancy and pre-malignancy were 0.9% and 1.2%, respectively. The risk of pre-malignancy in symptomatic women was significantly higher than that in asymptomatic women (p=0.037, Table 2).

Three (3.7%) cases of endometrial hyperplasia were detected in pre-menopausal women. Nine (2.2%) cases of pre-malignancy were detected in menopausal women, including three cases of endometrial hyperplasia, five cases of CIN, and one case of vaginal intraepithelial neoplasm (Table 2).

The overall risk of missed malignancy and pre-malignancy was 0.8% and 2.4%, respectively, in women who underwent hysterectomy for POP.

Discussion

In our study, the risk of missed pre-malignant and malignant gynaecological pathology was 3.2%, which is slightly higher than that reported in other studies[8-11]. The prevalence of unexpected pathology in menopausal women was 2.6%, which is comparable with a previous study[10].

Some argue that it is unnecessary to routinely perform microscopic assessment of macroscopically normal hysterectomy specimens after vaginal hysterectomy because the incidence of significant pathology is very low and does not alter subsequent patient management[8]. Nonetheless, given the risk of unanticipated abnormal pathology, we recommend routine histopathological examination of hysterectomy specimens.

In symptomatic women, seven (10.4%) had an undetected pre-malignant condition including four cases of endometrial hyperplasia and three cases of CIN. The prevalence of pre-malignancy was significantly higher in symptomatic women. This may reflect the long waiting time for elective surgery for genital prolapse, typically between 6 months and 1 year (the longest waiting time in this series was 18 months). Unexpected pathology can develop over such a long period. Furthermore, preoperative investigations may not be able to detect pre-malignancy. An endometrial biopsy may not be able to thoroughly sample the uterine cavity to detect pre-existing, pre-malignant endometrial pathology. Patients should be reviewed regularly for their presenting symptoms, and investigations repeated if necessary, before surgery.

Table 2. Prevalence of malignant and pre-malignant pathology in surgical specimens

Pathology	Symptomatic women (n=67)*	Asymptomatic women (n=430)*	p Value	Pre-menopausal women (n = 82)*	Menopausal women (n = 415)*	p Value
Total uterine malignancy + pre-malignancy	4 (6.0)	4 (0.9)	0.0139	3 (3.7)	5 (1.2)	0.1301
Uterine malignancy	0	2 (0.5)	1.00	0	2 (0.5)	1.00
Uterine pre-malignancy	4 (6.0)	2 (0.5)	0.0037	3 (3.7)	3 (0.7)	0.059
Complex hyperplasia with atypia	0	1 (0.2)	-	0	1 (0.2)	-
Complex hyperplasia without atypia	3 (4.5)	1 (0.2)	-	2 (2.4)	2 (0.5)	-
Focal hyperplasia without atypia	1 (1.5)	0	-	1 (1.2)	0	-
Total cervical malignancy + pre-malignancy	3 (4.5)	3 (0.7)	0.0347	1 (1.2)	5 (1.2)	1.00
Cervical malignancy	0	1 (0.2)	1.00	1 (1.2)	0	0.165
Cervical pre-malignancy	3 (4.5)	2 (0.5)	0.0192	0	5 (1.2)	1.00
Cervical intraepithelial neoplasia 2	3 (4.5)	1 (0.2)	-	0	4 (1.0)	-
Cervical intraepithelial neoplasia 3	0	1 (0.2)	-	0	1 (0.2)	-
Vaginal pre-malignancy	0	1 (0.2)	1.00	0	1 (0.2)	1.00
Vaginal intraepithelial neoplasm 2	0	1 (0.2)	-	0	1 (0.2)	-
Ovarian malignancy	0	1 (0.2)	1.00	1 (1.2)	0	0.165
All malignancy + pre-malignancy	7 (10.4)	9 (2.1)	0.0025	5 (6.1)	11 (2.7)	0.1593
All malignancy	0	4 (0.9)	1.00	2 (2.4)	2 (0.5)	0.1289
All pre-malignancy	7 (10.4)	5 (1.2)	0.0003	3 (3.7)	9 (2.2)	0.4278

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

Uterine Pathology

The prevalence of unexpected endometrial carcinoma and STUMP was 0.2% and 0.2%, respectively. Both uterine pathologies occurred in menopausal, asymptomatic women. The prevalence of endometrial carcinoma (0.2%) was in line with a local study[11] and was lower than that in other studies[9,10]. There was no uterine malignancy identified in symptomatic women. This may reflect an effective preoperative screening policy of detailed history taking, physical and pelvic examination, and review of previous endometrial investigation results. Those who were symptomatic of endometrial cancer had already been investigated and referred to the gynae-oncology team. In the case of STUMP, currently there is no effective screening method to detect this rare entity.

In a study assessing the role of routine transvaginal ultrasonography prior to vaginal hysterectomy in 103 patients with uterine prolapse, six patients were identified to have endometrial abnormalities (four with endometrial hyperplasia and two with endometrial polyp)[12]. A thin and regular endometrial line has been shown to reliably exclude endometrial carcinoma in menopausal women[13]. Transvaginal ultrasonography is not sufficiently sensitive or cost-effective to screen for endometrial cancer[14]. We suggest evaluation of endometrial pathology with transvaginal ultrasonography and biopsy only in women who present with symptoms suggestive of malignancy.

Cervical Pathology

Patients with an abnormal cervical smear were referred to the gynae-oncology team to exclude pre-malignant or malignant lesions prior to hysterectomy. The sensitivity of a cervical smear to detect a high-grade lesion has been improved with the advent of human papillomavirus co-testing, especially in symptomatic women[15]. The sensitivity of a cervical smear to detect adenocarcinoma in situ has been reported to be 40% to 68%[16]. This may be due to the irregular distribution of the lesions within the glands (compared with the surface distribution of CIN lesions) and the smaller size of glandular abnormalities.

With the implementation of effective cervical cytology screening, the incidental finding of CIN lesions in hysterectomy specimens is 1% and of adenocarcinoma in situ is 0.2%. There were five cases of CIN in menopausal women and none in pre-menopausal women. Four of them were older than 65 years, and three of them had not

undergone any cervical smear screening. One of them had a cervical smear that showed a low-grade squamous intra-epithelial lesion with a colposcopy finding of condyloma 3 months prior to hysterectomy. The other patient with colposcopy 1 month prior to surgery for persistent atypical squamous cell of uncertain significance showed cervicitis only. In the routine cervical screening programme, screening stops after the age of 65 years in those with previously normal smears. Most of our patients were older than 65 years and thus may not have had a recent cervical smear test. Many elderly patients had undergone no previous cervical screening. This might partly explain the higher prevalence of CIN in menopausal patients. It is advised to perform a cervical smear before surgery, even in those aged >65 years, to reduce the chance of missing a pre-malignant condition of the cervix.

Ovarian Pathology

Of 47 (9.5%) women who underwent concomitant BSO, one (2.1%) was found to have malignancy. She was a 49-year-old pre-menopausal woman with prolapse symptoms and fibroid. An ovarian cyst was detected preoperatively by ultrasonography, with no evidence of malignancy. This highlights the importance of preoperative assessment including pelvic examination and ultrasonography. The true incidence of ovarian malignancy was difficult to estimate as not all women underwent concomitant BSO. For women with ovarian preservation after hysterectomy for benign pathology, the absolute risk of ovarian cancer is 0.1%-0.75%[17] and of ovarian cancer mortality is 0.3%[18]. To reduce the future risk of ovarian cancer, prophylactic bilateral salpingectomy at the time of hysterectomy should be discussed with patients. The benefits of ovarian preservation decrease with advancing age; concomitant BSO should be discussed with patients who are menopausal[19].

Vaginal Pathology

One asymptomatic menopausal woman had an incidental finding of vaginal intraepithelial neoplasm II. This raises concern about the risk of vaginal intraepithelial neoplasm or vaginal cancer in patients who undergo hysterectomy for benign pathologies. The incidence of pre-cancerous or invasive vaginal lesion was comparable between patients who underwent hysterectomy for benign pathology and those for malignant pathology[20,21]. Therefore, follow-up with a vault smear should be reserved for those with evidence of pre-cancerous disease or when hysterectomy is performed for a malignant condition[21].

Limitations

This study had limitations. It was a retrospective study of one urogynaecology team in Hong Kong over 9 years. A multicentre, long-term study with a larger sample size may be required to draw any conclusion about the prevalence of incidental malignant and pre-malignant lesions.

Conclusion

Routine histological examination of hysterectomy specimens is recommended to avoid missing any previously undetected malignancy or pre-malignancy. Symptomatic patients are at higher risk of developing pre-malignant lesions despite preoperative investigations to exclude malignancy. A comprehensive preoperative examination and close follow-up are recommended for symptomatic patients, even if initial findings are normal. A cervical smear test is recommended for all patients before surgery, especially for menopausal women who do not have recent cervical cytology screening. In Hong Kong, the mainstay surgical treatment for uterine prolapse is hysterectomy. The findings of this study can be used to counsel patients about their choice of uterine-preserving surgery for uterine prolapse. The life-time risk of uterine malignancy and the risk of missing an existing pathology should be stressed if women opt to conserve their uterus.

Declaration

All authors have disclosed no conflicts of interest.

References

1. Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. *Obstet Gynecol Clin North Am* 1998; 25:723-46.
2. Territory-wide obstetrics and gynaecology audit report 2004. *Hong Kong College of Obstetricians and Gynaecologists*; 2004.
3. Rortveit G, Brown JS, Thom DH, Van Den Eeden SK, Creasman JM, Subak LL. Symptomatic pelvic organ prolapse: prevalence and risk factors in a population-based, racially diverse cohort. *Obstet Gynecol* 2007; 109:1396-403.
4. Chan SS, Cheung RY, Yiu KW, Lee LL, Pang AW, Chung TK. Symptoms, quality of life, and factors affecting women's treatment decisions regarding pelvic organ prolapse. *Int Urogynecol J* 2012; 23:1027-33.

5. Oliphant SS, Jones KA, Wang L, Bunker CH, Lowder JL. Trends over time with commonly performed obstetric and gynecologic inpatient procedures. *Obstet Gynecol* 2010; 116:926-31.
6. Iliev VN, Andonova IT. Uterus preserving vaginal surgery versus vaginal hysterectomy for correction of female pelvic organ prolapse. *Pril (Makedon Akad Nauk Umet Odd Med Nauki)* 2014; 35:243-7.
7. Elkattah R, Brooks A, Huffaker RK. Gynecologic malignancies post-LeFort colpocleisis. *Case Rep Obstet Gynecol* 2014; 2014:846745.
8. Salmon HA, Smith JH, Balsitis M. Is microscopic assessment of macroscopically normal hysterectomy specimens necessary? *J Clin Pathol* 2002; 55:67-8.
9. Mahajan G, Kotru M, Batra M, Gupta A, Sharma S. Usefulness of histopathological examination in uterine prolapse specimens. *Aust N Z J Obstet Gynaecol* 2011; 51:403-5.
10. Frick AC, Walters MD, Larkin KS, Barber MD. Risk of unanticipated abnormal gynecological pathology at the time of hysterectomy for uterovaginal prolapse. *Am J Obstet Gynecol* 2010; 202:507.
11. Wan OY, Cheung RY, Chan SS, Chung TK. Risk of malignancy in women who underwent hysterectomy for uterine prolapse. *Aust N Z J Obstet Gynecol* 2013; 53:190-6.
12. Srikrishna S, Robinson D, Cardozo L, Yazbek J, Jurkovic D. Is transvaginal ultrasound a worthwhile investigation for women undergoing vaginal hysterectomy? *J Obstet Gynecol* 2008; 28:418-20.
13. Van den Bosch T, Van Schoubroeck D, Domali E, et al. A thin and regular endometrium on ultrasound is very unlikely in patients with endometrial malignancy. *Ultrasound Obstet Gynecol* 2007; 29:674-9.
14. Havrilesky LJ, Maxwell GL, Myers ER. Cost-effectiveness analysis of annual screening strategies for endometrial cancer. *Am J Obstet Gynecol* 2009; 200:640.
15. Guideline for cervical cancer screening and prevention. *Hong Kong College of Obstetricians and Gynaecologists Guideline*; 2016.
16. Schoolland M, Segal A, Allpress S, Miranda A, Frost FA, Sterrett GF. Adenocarcinoma in situ of the cervix. *Cancer* 2002; 96:330-7.
17. Parker WH. Bilateral oophorectomy versus ovarian conservation: effects on long-term women's health. *J Minim Invasive Gynecol* 2010; 17:161-6.
18. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009; 113:1027-37.
19. Committee on Gynecologic Practice. Committee opinion no. 620: Salpingectomy for ovarian cancer prevention. *Obstet Gynecol* 2015; 125:279-81.
20. Mouithys P, Papadopoulos C, Allier G, et al. Is it necessary to make screening pap smears after hysterectomy? [in French]. *Gynecol Obstet Fertil* 2003; 31:620-3.
21. Frega A, French D, Piazze J, Cerekja A, Vetrano G, Moscarini M. Prediction of persistent vaginal intraepithelial neoplasia in previously hysterectomized women by high-risk HPV DNA detection. *Cancer Lett* 2007; 249:235-41.

Haemorrhagic Stroke in Pregnancy

Choi-Wah KONG MBChB, MRCOG, FHKAM (Obstetrics and Gynaecology)
William WK TO MBBS, MPH, MPhil, MD, Dip Med, FRCOG, FHKAM (Obstetrics and Gynaecology), Cert HKCOG(MFM)
Department of Obstetrics and Gynaecology, United Christian Hospital, Kwun Tong, Hong Kong

Stroke in pregnancy is rare, with a reported incidence of 8.9 to 67.1 per 100 000 deliveries. With significant improvements in antenatal and intrapartum care, stroke has become the leading non-obstetric cause of maternal mortality in high-income countries such as Canada, United States, United Kingdom, and Japan. Strokes are classified as ischaemic (arterial or venous) or haemorrhagic (subarachnoid or intracerebral). Asians have more haemorrhagic strokes than ischaemic strokes in pregnancy than Caucasians. We report three patients who had haemorrhagic stroke in pregnancy with various causes, symptoms, treatments, and outcomes, and then review the literature on haemorrhagic stroke in pregnancy.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):36-42

Keywords: Intracranial hemorrhages; Pregnancy; Stroke; Subarachnoid hemorrhage

Case Series

Patient 1

In September 2017, a 25-year-old, parity 0, woman with good past health and uneventful antenatal care was diagnosed with gestational diabetes at 25 weeks. While awaiting an appointment with a dietitian, she was admitted to the United Christian Hospital at 25+3 weeks of gestation for sudden onset of severe headache and vomiting. She was noted by her husband to be drowsy with reduced responsiveness. She had no history of illicit drug use or head injury.

Her Glasgow Coma Scale (GCS) score was 14/15 (E4V5M5). Her blood pressure was 106/67 mm Hg, and urinalysis was positive for albumin. Her bilateral lower limb power had decreased to grade 4/5, but reflexes were normal. The cardiotocogram was reactive. Blood tests showed a haemoglobin level of 10.1 g/dl, but the platelet count, clotting profile, liver and renal function tests were normal. Ultrasonography showed normal fetal parameters and liquor volume and normal umbilical artery Doppler indices. Urgent computed tomography (CT) of the brain showed diffuse subarachnoid haemorrhage (SAH) with mild hydrocephalus (Figure 1a). The patient was transferred to the Queen Elizabeth Hospital (QEH) for neurosurgical treatment. CT angiography showed a 7x4 mm fusiform aneurysm arising from the right posterior cerebral artery, suggestive of a dissecting aneurysm (Figure 1b). The patient underwent endovascular occlusion of the intracranial vessel by coiling (Figure 1c). A course of dexamethasone was given to enhance fetal lung maturity in case of maternal deterioration and consequent need for urgent delivery.

Two days later, the patient complained of headache. CT of the brain revealed an infarct over the territory of the posterior cerebral artery. She developed weakness of the left side 7 days after coiling. Repeat CT showed a new right parietal infarct. Emergency classical Caesarean section was performed at 26+4 weeks owing to maternal deterioration with a progressive and enlarging maternal brain infarct. A baby with birthweight of 860 g was born with Apgar scores of 5 at 1 min and 8 at 5 mins. Cord arterial pH was 7.33. The patient subsequently recovered gradually and was discharged 25 days after coiling. She could walk unaided with normal limb power and had no neurological deficits on follow-up.

Patient 2

In April 2011, a 33-year-old, parity 2, woman presented to the United Christian Hospital with spontaneous onset of labour at 39 weeks of gestation. Her first pregnancy had been complicated by transient postpartum convulsion at the time of episiotomy repair following vaginal delivery; it was suspected to be an episode of eclampsia. Results of subsequent examinations by CT of the brain and electroencephalography were normal, and she was lost to follow-up. Eight years later, her second pregnancy was uneventful, with a normal vaginal delivery without pre-eclampsia or eclampsia.

Three years later, she had her third pregnancy, and the antenatal course was uneventful. On admission, her

Correspondence to: Dr Choi-Wah Kong
Email: melizakong@gmail.com

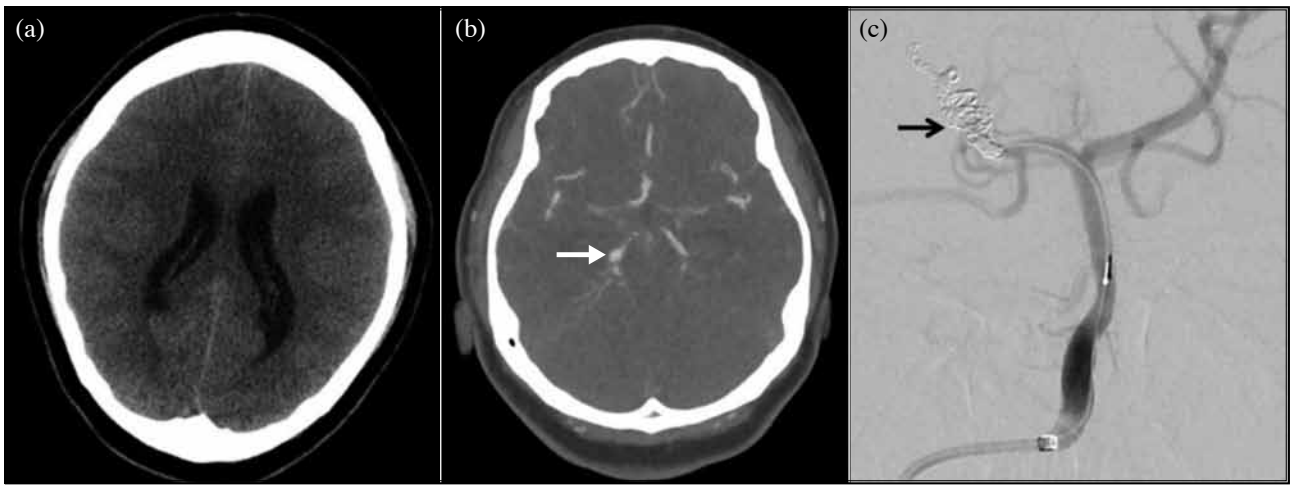


Figure 1. Patient 1: (a) A computed tomography scan showing diffuse subarachnoid haemorrhage with bilateral sulcal spaces effaced. (b) A computed tomography angiogram showing a cerebral aneurysm (arrow) arising from the right posterior cerebral artery. (c) A digital subtraction angiogram showing endovascular coiling (arrow) of an intracranial vessel

blood pressure was 160/80 mm Hg and urinalysis revealed proteinuria. Neurological examination was normal. Her haemoglobin level was 9.3 g/dl, but the platelet count, clotting profile, liver and renal function tests were normal. Three hours after admission, she was noted be drowsy. Neurological examination showed increased tone on the left side of her body. Magnesium sulphate was given in view of possible eclampsia. Twenty minutes later, she had a tonic-clonic convulsion and transient fetal bradycardia. Emergency Caesarean section was performed and the baby was born in good condition. The patient was transferred to the intensive care unit (ICU) and had two more episodes of seizure despite the magnesium sulphate treatment. Phenytoin was given. Urgent CT of the brain showed a left intracranial haemorrhage and intraventricular haemorrhage with blood in the fourth ventricle with mass effect (Figure 2).

Two hours after delivery, the patient was transferred to QEH and immediately underwent left craniotomy. Large blood clots were evacuated from the left basal ganglia, but bleeding tendency continued. Platelet and fresh frozen plasma transfusion was commenced. The operative blood loss was 2000 ml. One hour later, her intracranial pressure increased again. CT revealed a large haematoma (5 cm) over the left cerebral hemisphere and the left basal ganglia, with midline shift to the right side. Four hours later, decompression was performed. The brain was found herniating out after the scalp was opened. Frontal lobectomy was performed anterior to the Sylvian vein and the blood clots were evacuated. The operative blood loss was 3000 ml.

On day 6, CT showed cerebral oedema and further

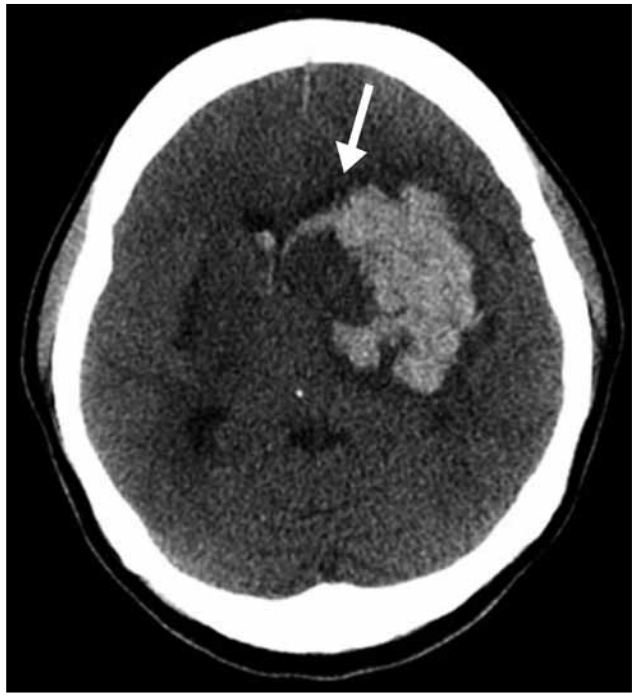


Figure 2. Patient 2: a computed tomography scan showing left intracranial and intraventricular haemorrhage (arrow)

intracerebral haemorrhage. She underwent decompression and evacuation of the necrotic brain tissue and haematoma and partial left temporal lobectomy. On day 16, the patient was transferred to the general ward. Cranioplasty was performed 2 months after delivery, but was subsequently removed 5 weeks later owing to infection. Six months later, the patient developed hydrocephalus, and a ventriculo-peritoneal shunt was inserted. The patient stayed at QEH for 1 year and was transferred to the Kowloon Hospital for rehabilitation, with a GCS score of 11/15 (E4V2M5). She had right hemiparesis and receptive and expressive

dysphasia. She underwent physiotherapy and training for 3 years and was finally discharged home with a GCS score of 13/15 (E4V3M6). She could walk a few steps with the aid of a walking frame and could speak a few single words. Cranioplasty was performed 6 years after delivery.

Patient 3

In October 2015, a 35-year-old, parity 2, woman with two uneventful normal vaginal deliveries was scheduled for morphology scanning in our antenatal clinic at 19+4 weeks of gestation. Incidentally, she presented to the United Christian Hospital in a wheelchair with severe dizziness for 1 week and headache and neck pain that were not improved by paracetamol. She also had nausea and vomiting. Morphology scan was normal. Her blood pressure was normal and urinalysis was negative for albumin. Neurological examination was normal. Her haemoglobin level was 12.3 g/dl, and the platelet count, clotting profile, liver and renal function tests were normal. Urgent CT of the brain revealed haemorrhage in the right basal ganglia (Figure 3a), and the patient was transferred to QEH for further management.

A ruptured arteriovenous malformation (AVM) was suspected, but the patient declined magnetic resonance angiography. Her headache subsequently improved and there was no immediate need for neurosurgical intervention. She was counselled by joint neurosurgery and obstetrics teams and the risk of acute rupture of AVM was explained. Nonetheless, the patient refused any neuroimaging and surgical intervention during pregnancy. The agreed plan was to undergo emergency Caesarean section followed by neurosurgical operation if there was re-rupture of the AVM. Otherwise, delivery was planned at 34 weeks of gestation by elective Caesarean section to avoid the risk of rupture during labour. Neuroimaging and surgical intervention would then be performed after delivery.

The patient's dizziness gradually improved. She had one course of steroid injections to enhance fetal lung maturity. Lower-segment Caesarean section was performed at 34 weeks and the baby was born in good condition. Two days after delivery, CT of the brain showed a 2-cm AVM at the right medial frontal lobe. Digital subtraction angiography (DSA) and magnetic resonance angiography showed a right frontal lobe AVM and a 2-mm-wide aneurysm at the junction of the left anterior cerebral artery and anterior communicating artery (Figure 3b). The neurovascular team at QEH suggested embolisation of the AVM followed by surgery or radiosurgery. The patient sought a second opinion from the neurosurgical team at Queen Mary Hospital and was offered radiosurgery instead of embolisation. She underwent radiosurgery at Queen Mary Hospital 11 months after Caesarean section. Seven weeks later, CT and magnetic resonance imaging (MRI) of the brain showed no cerebral oedema. 11 months later, the patient presented to Queen Mary Hospital with left lower limb weakness and unbalanced gait. CT of the brain revealed right parietal oedema. Dexamethasone was given and her limb power improved. She was discharged in good condition, pending repeat MRI later.

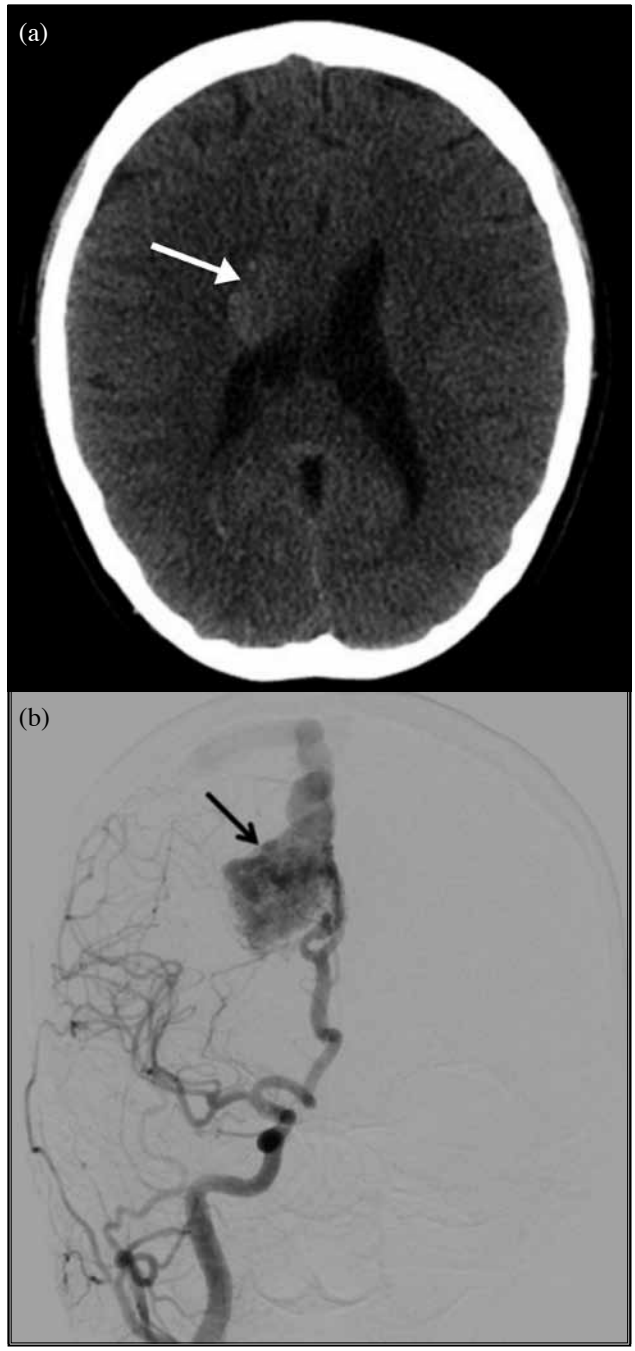


Figure 3. Patient 3: a computed tomography scan showing haemorrhage in the right basal ganglia (arrow). (b) A digital subtraction angiogram showing a right frontal lobe arteriovenous malformation (arrow)

Discussion

Haemorrhagic strokes account for 29% to 46% of all strokes in pregnancy among Caucasians and 43% to 74% among Taiwanese and Japanese[1-5]. Japanese have a 2.8-fold increased risk of aneurysm rupture. Non-white people including Asians have a 3.09-fold increased risk in rupture of AVM than white people[1]. In a Hong Kong study of 49 368 deliveries from 1952 to 1994, five patients were diagnosed with a haemorrhagic stroke, accounting for an incidence of 10 per 100 000 deliveries[6]. In pregnant women, haemorrhagic stroke is associated with higher maternal mortality and morbidity than ischaemic stroke; the average maternal mortality has been reported to be 13.8% and 3.9%, respectively[5].

Subarachnoid Haemorrhage

The most common cause of SAH in pregnancy is rupture of cerebral aneurysms. Other causes include rupture of AVM, eclampsia, coagulopathy, and vasculopathy such as connective tissue disorders[7]. The incidence of SAH is higher in pregnant patients than non-pregnant patients[7,8]. The postulated causes include an increased plasma volume during pregnancy, pregnancy-induced hypertension, and pregnancy-related hormonal changes that lead to remodelling of arterial and venous intima and media of vessel walls[7,9]. Aneurysmal rupture may occur in any trimester of pregnancy[2], with the highest incidence in the third trimester[10-12]. The risk of aneurysmal rupture increases because of gross haemodynamic fluctuations during the intrapartum period, particularly in association with the Valsalva manoeuvre during delivery. However, one study reported that 90% of the aneurysmal ruptures occur in the antepartum period, and only 2% in the intrapartum period and 8% in the puerperium[13]. Hypertension is associated with 10% to 20% of SAH in pregnancy and is the most important risk factor. Pre-eclampsia or eclampsia is present in 14% to 40% of intracranial haemorrhages in pregnancy. Other risk factors include use of anticoagulants and cigarette smoking[7-10].

The most common symptom of SAH is severe and sudden onset of headache. It is commonly described as 'an explosion within the head' and 'the worst headache of my life'. The headache is usually sub-occipital or frontal, and associated with nausea and vomiting. There may be blurring of vision and other focal neurological deficits[7]. The most common sign of SAH is neck stiffness, which is present in 90% of patients, but it may not develop until hours after SAH. Intraocular bleeding, which is seen as unilateral or bilateral subhayloid haemorrhage on ophthalmoscopy, is present in 25% of patients. Seizures are found in 15% of patients[14]. It is sometimes difficult to distinguish SAH from severe pre-eclampsia or eclampsia, as both result in headache, blurring of vision, seizures, and neurological deficits. Blood pressure may be transiently elevated following aneurysmal rupture due to raised intracranial pressure or increased catecholamine release. In addition, proteinuria can be detected in up to 30% of patients[7].

A prompt diagnosis and treatment are important to achieve good maternal outcomes[15]. CT is the first choice for diagnosing intracranial haemorrhage, as it is quick to perform and available 24 hours a day in most clinical settings. Nonetheless, MRI has lower radiation risks to the fetus[7] and should be the first choice for diagnosis if the pregnancy is <10 weeks of gestation, which is the time for fetal organogenesis and most susceptible to radiation. Precautions to limit radiation exposure to the fetus by abdominal shielding should be adopted. Diagnosis of intracranial haemorrhage can be made by CT, MRI, intra-arterial DSA (a fluoroscopy technique to visualise blood vessels), or CT-angiography (a contrast angiogram visualised by CT) to determine the cause of bleeding such as ruptured aneurysms and AVM[7,10]. Magnetic resonance angiography may be used to detect cerebral aneurysms but its specificity is lower than DSA[7].

The risk of re-bleeding is 4% over the first 24 hours following aneurysmal rupture and increases to 10% to 20% in the first month. Re-bleeding occurs in 33% to 50% of untreated ruptured aneurysms within 4 to 6 weeks[7]. Up to 33% of SAH patients have cerebral vasospasm that leads to delayed cerebral ischaemia[16]. The maternal mortality due to rupture of cerebral aneurysm ranges from 13% to 35%[17]. It is the third leading cause of maternal death from non-obstetric causes, accounting for 5% to 12% of total mortality during pregnancy in United States[10].

As there is a risk of re-bleeding after ruptured aneurysm, a conservative approach is associated with a maternal mortality of 63% and a fetal mortality of 27%; early surgery can lower these mortalities to 11% and 5%, respectively[9]. Therefore, early surgery is recommended for aneurysmal rupture during pregnancy. Traditional surgery for aneurysmal rupture involves craniotomy and clipping of the aneurysm. In 1990, a detachable platinum coil was introduced to exclude aneurysm from the parent vessel by exciting thrombosis within the sac[18]. It was initially used in aneurysms in the posterior part of the Circle of Willis or in the cavernous segment where surgical clipping was technically difficult. Subsequently, endovascular coiling was widely performed for aneurysms in both anterior and

posterior parts of the circulation. Since the publication of the International Subarachnoid Aneurysm Trial (ISAT) in Europe in 2002, endovascular coiling has become the first-line treatment for cerebral aneurysm[19]. Patients treated by coiling have been reported to have significantly better survival and less disabilities at 1-year follow-up than those treated by surgical clipping[19]. The risk of death or severe disability after coiling is 22.6% lower than that after surgical clipping at 1-year follow-up[19].

Nonetheless, not all patients are suitable for endovascular coiling. Patients with middle cerebral artery aneurysms where terminal branches frequently arise from the sac itself are not appropriate candidates[20]. Presence of cerebral vasospasm may obstruct endovascular access. Aneurysms with an excessive dome-to-neck ratio are not suitable for coiling as the coil may prolapse back into the parent lumen. Endovascular coiling is more likely to succeed in aneurysms with a dome-to-neck ratio of >1.6 and with a neck size of <4 mm, and is more likely to fail in aneurysms with a dome-to-neck ratio of <1.2[20].

Endovascular coiling has been a successful treatment for ruptured aneurysm in pregnancy[21,22]. Nonetheless, studies to compare endovascular coiling with surgical clipping for cerebral aneurysms in pregnant patients are limited. There are concerns about whether the ISAT trial results can be extrapolated to pregnant patients[23,24]. Endovascular coiling in pregnancy has the disadvantages of prolonged fetal radiation exposure under DSA and full systemic heparinisation throughout the procedure. Heparinisation carries risks of haemorrhage if pre-term labour or delivery is needed in case of fetal distress or maternal deterioration. It is difficult to have concurrent fetal monitoring in the DSA suite and to arrange immediate Caesarean section in case of fetal distress during the procedure[7,10,17,23]. The ISAT trial showed that endovascular coiling is inferior to surgical clipping in terms of subtotal occlusion rate or residual aneurysmal neck; two patients had re-bleeding after endovascular coiling but none after surgical clipping[19]. Incomplete obliteration of the aneurysm by coiling may result in regrowth of the remnant aneurysm and risk of re-bleeding[24].

Surgical clipping has additional advantages, as craniotomy enables direct vision for aneurysm exclusion and concurrent treatment of other associated neurosurgical conditions such as obstructive hydrocephalus and intracerebral haematoma. In addition, intra-procedural rupture, which occasionally occurs during coiling[7], can be avoided or salvaged.

The choice of treatment should be individualised according to the gestational age, patient condition, and expertise and experience of the neurosurgeon. Surgical clipping is preferred for gestational age of <10 weeks to avoid prolonged fetal radiation exposure. Endovascular coiling requires an experienced radiologist who may not be available in some units. Multidisciplinary assessment involving obstetricians, neurosurgeons, radiologists, anaesthetists, paediatricians, and intensivists should be conducted to provide best management.

Delivery by emergency Caesarean section should be considered if the maternal status is life-threatening and the pregnancy exceeds the gestation for viability (≥24 weeks gestation)[10]. In patient 1, emergency Caesarean section was performed because of maternal deterioration with a repeated and enlarging cerebral infarct. When the maternal condition is stable and the gestational age exceeds 34 weeks, delivery can be considered, as the risk from prematurity is small and the concern about radiation risks of subsequent imaging and endovascular procedures is less after delivery. In addition, surgical clipping can be performed simultaneously with Caesarean section in the same operation theatre after the baby is delivered. When the gestation is <34 weeks, treatment of the aneurysm should be proceeded while the pregnancy is allowed to continue[7]. There is no contraindication for vaginal delivery after aneurysm occlusion. Adequate pain relief by epidural analgesia and use of instrumental delivery to shorten the second stage is advised[7]. Caesarean section is preferable if labour occurs shortly after treatment of the aneurysm or if there is incomplete occlusion of the aneurysm[10].

Intracerebral Haemorrhage

The most common cause of intracerebral haemorrhage in pregnancy is ruptured AVM. Other causes include trauma and brain tumour. In patient 2, although ruptured AVM was not identified intraoperatively, it was postulated that her intracerebral haemorrhage was likely due to a ruptured AVM. She had an episode of an eclamptic fit during her first delivery that may have been due to a mild rupture of her AVM. During her third pregnancy, her AVM could have severely ruptured and no longer be identified intraoperatively, with the presence of massive bleeding.

The prevalence of AVM has been reported to be 0.01% to 0.5% in the general population, and most patients have symptoms at 20 to 40 years of age[25]. The risk of haemorrhagic cerebral AVM during pregnancy has been reported to be 3.5%, similar to the 3.1% in non-pregnant populations[26]. Rupture of AVM may occur in any trimester,

Table. Spetzler-Martin grading system for cerebral arteriovenous malformation

Features	Score
Size of nidus (cm)	
<3 (small)	1
3-6 (medium)	2
>6 (large)	3
Location	
Non-eloquent brain (frontal and temporal lobe or cerebellar hemispheres)	0
Eloquent brain (sensorimotor, language, visual cortex, hypothalamus, thalamus, brainstem, cerebellar nuclei, or regions immediately adjacent to these structures)	1
Venous drainage	
Superficial only	0
Deep	1

with the highest incidence in the second trimester[1,2,27]. More than 50% of patients with AVM present as intracranial haemorrhage. Intracerebral haemorrhage occurs more commonly than SAH and intraventricular haemorrhage. 20% of patients present with generalised or focal seizure.

After diagnosing intracerebral haemorrhage by CT or MRI, the gold standard for diagnosing AVM is by DSA, which can delineate its size, location, feeding artery, flow rate, arteriovenous fistula, coexisting aneurysm, venous drainage, and ectasia of drainage veins[25].

Rupture of AVM is associated with high maternal mortality of 35% to 83%[28], and is responsible for 5% to 12% of maternal deaths during pregnancy and 17% of fetal mortality[29].

Urgent operations (emergent nidus resection, ventricular drainage, and haematoma removal) are necessary for pregnant patients with ruptured AVM and worsening neurological symptoms or signs of impending cerebral herniation[25,27]. If bleeding of the AVM is stopped and the patient is stable, conservative management can be adopted[29]. The risk of re-bleeding from ruptured AVM during pregnancy is 26%[9]. The operative outcomes for cerebral AVM depend on its grade according to the Spetzler-Martin system (Table) that takes account of the size, location, and drainage of the AVM. Higher grades indicate poorer prognosis. Grade 1 or 2 AVMs are usually treated by surgical excision; grade 3 lesions should be treated by embolisation followed by surgical excision; and grade 4 or 5 lesions should be treated conservatively because of high surgical risk[27]. Recent advances in radiosurgery enable treatment for small deeply seated AVMs that carry high operative risks[27]. Stereotactic radiosurgery focuses a narrow X-ray beam on the AVM such that a high dose is concentrated on the AVM and a much lower dose to the rest of the brain. It induces thickening in the walls of the AVM and then closes the AVM. It has successfully closed AVMs in around 80% of patients over a period of 2 to 3 years. Nonetheless, it is suitable only for small AVMs, and 3% to 5% of patients may develop long-term side-effects such as limb weakness or numbness. Patients have a 4% chance of bleeding from the AVM yearly until the AVM is completely closed[30]. There is no randomised controlled trial to compare different treatment options (surgery, radiosurgery, embolisation, and a combination of these). In the largest systematic review that compared outcomes of different treatments for AVM, results were inconclusive because of differences in patient conditions and AVM characteristics (size and location) among different studies[31]. Therefore, the treatment choice for AVM depends on the experience and expertise of the neurosurgeons and interventional radiologists. The timing of delivery for ruptured cerebral AVMs should be similar to that for ruptured aneurysms. There is no contraindication to vaginal delivery for a completely excised AVM[25]. There is no consensus as to whether vaginal delivery increases the risk of rupture for an intact AVM, but Caesarean section is recommended for patients with ruptured AVM[32].

Conclusion

Haemorrhagic stroke is rare in pregnancy. Its symptoms are sometimes similar to severe pre-eclampsia or eclampsia. A high index of suspicion, early diagnosis, and prompt management are crucial to improve maternal and neonatal outcomes. A multidisciplinary approach involving different specialties and expertise to provide the most optimal management is essential.

Declaration

As an editor of this journal, William WK To was not involved in the peer review process of this article. Choi-Wah Kong has disclosed no conflicts of interest.

References

1. Yoshida K, Takahashi JC, Takenobu Y, Suzuki N, Ogawa A, Miyamoto S. Strokes associated with pregnancy and puerperium: a nationwide study by the Japan Stroke Society. *Stroke* 2017; 48:276-82.
2. Jaigobin C, Silver FL. Stroke and pregnancy. *Stroke* 2000; 31:2948-51.
3. James AH, Bushnell CD, Jamison MG, Myers ER. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Gynecol* 2005; 106:509-16.
4. Ban L, Sprigg N, Abdul Sultan A, et al. Incidence of first stroke in pregnant and nonpregnant women of childbearing age: a population-based cohort study from England. *J Am Heart Assoc* 2017; 6:e004601.
5. Liang CC, Chang SD, Lai SL, Hsieh CC, Chueh HY, Lee TH. Stroke complicating pregnancy and the puerperium. *Eur J Neurol* 2006; 13:1256-60.
6. To WK, Cheung RT. Neurological disorders in pregnancy. *Hong Kong Med J* 1997; 3:400-8.
7. Selo-Ojeme DO, Marshman LA, Ikomi A, et al. Aneurysmal subarachnoid haemorrhage in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2004; 116:131-43.
8. Grear KE, Bushnell CD. Stroke and pregnancy: clinical presentation, evaluation, treatment, and epidemiology. *Clin Obstet Gynecol* 2013; 56:350-9.
9. Feske SK, Singhal AB. Cerebrovascular disorders complicating pregnancy. *Continuum (Minneap Minn)* 2014; 20:80-99.
10. Robba C, Bacigaluppi S, Bragazzi NL, et al. Aneurysmal subarachnoid hemorrhage in pregnancy: case series, review, and pooled data analysis. *World Neurosurg* 2016; 88:383-98.
11. Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. *Neurosurgery* 1990; 27:855-66.
12. Stehbens WE. Aetiology of cerebral aneurysms. *Lancet* 1981; 2:524-5.
13. Stoodley MA, Macdonald RL, Weir BK. Pregnancy and intracranial aneurysms. *Neurosurg Clin N Am* 1998; 9:549-56.
14. Giannotta SL, Daniels J, Golde SH, Zelman V, Bayat A. Ruptured intracranial aneurysms during pregnancy. A report of four cases. *J Reprod Med* 1986; 31:139-47.
15. Liang ZW, Lin L, Gao WL, Feng LM. A clinical characteristic analysis of pregnancy-associated intracranial haemorrhage in China. *Sci Rep* 2015; 5:9509.
16. Dorsch NW. A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage. Part III: mechanisms of action of calcium antagonists. *J Clin Neurosci* 1994; 1:151-60.
17. Kataoka H, Miyoshi T, Neki R, Yoshimatsu J, Ishibashi-Ueda H, Iihara K. Subarachnoid hemorrhage from intracranial aneurysms during pregnancy and the puerperium. *Neurol Med Chir (Tokyo)* 2013; 53:549-54.
18. Guglielmi G, Viñuela F, Dion J, Duckwiler G. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: preliminary clinical experience. *J Neurosurg* 1991; 75:8-14.
19. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002; 360:1267-74.
20. Brinjikji W, Cloft HJ, Kallmes DF. Difficult aneurysms for endovascular treatment: overwide or undertall? *AJNR Am J Neuroradiol* 2009; 30:1513-7.
21. Piotin M, de Souza Filho CB, Kothimbakam R, Moret J. Endovascular treatment of acutely ruptured intracranial aneurysms in pregnancy. *Am J Obstet Gynecol* 2001; 185:1261-2.
22. Pumar JM, Pardo MI, Carreira JM, Castillo J, Blanco M, Garcia-Allut A. Endovascular treatment of an acutely ruptured intracranial aneurysm in pregnancy: report of eight cases. *Emerg Radiol* 2010; 17:205-7.
23. Marshman LA, Aspoas AR, Rai MS, Chawda SJ. The implications of ISAT and ISUIA for the management of cerebral aneurysms during pregnancy. *Neurosurg Rev* 2007; 30:177-80.
24. Tarnaris A, Haliasos N, Watkins LD. Endovascular treatment of ruptured intracranial aneurysms during pregnancy: is this the best way forward? Case report and review of the literature. *Clin Neurol Neurosurg* 2012; 114:703-6.
25. Lv X, Liu P, Li Y. The clinical characteristics and treatment of cerebral AVM in pregnancy. *Neuroradiol J* 2015; 28:234-7.
26. Horton JC, Chambers WA, Lyons SL, Adams RD, Kjellberg RN. Pregnancy and the risk of hemorrhage from cerebral arteriovenous malformations. *Neurosurgery* 1990; 27:867-72.
27. Lv X, Liu P, Li Y. Pre-existing, incidental and hemorrhagic AVMs in pregnancy and postpartum: gestational age, morbidity and mortality, management and risk to the fetus. *Interv Neuroradiol* 2016;22:206-11.
28. Liu XJ, Wang S, Zhao YL, et al. Risk of cerebral arteriovenous malformation rupture during pregnancy and puerperium. *Neurology* 2014; 82:1798-803.
29. Wei HY, Lien YS, Tee YT, et al. Intracerebral hemorrhage with cerebral arteriovenous malformation rupture during pregnancy. *Taiwan J Obstet Gynecol* 2008; 47:460-2.
30. The Toronto Brain Vascular Malformation Study Group. Radiation treatment of brain arteriovenous malformations. Available from: http://brainavm.uhnres.utoronto.ca/malformations/rad_treat_avm_index.htm.
31. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA* 2011; 306:2011-9.
32. Carvalho CS, Resende F, Centeno MJ, Ribeiro I, Moreira J. Anesthetic approach of pregnant woman with cerebral arteriovenous malformation and subarachnoid hemorrhage during pregnancy: case report. *Braz J Anesthesiol* 2013; 63:223-6.

Advances in Minimally Invasive Gynaecological Surgery

Carmen Ka-Man CHOI MBBS, MPH, MRCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

Laparoendoscopic single-site surgery, robotic-assisted laparoscopic surgery, and natural orifice transluminal endoscopic surgery are major innovations in minimally invasive surgery. These techniques have the potential to improve patient outcomes such as quicker recovery, less postoperative pain, and better cosmetic results. Moreover, complicated laparoscopic procedures can be facilitated with the robotic surgical system. Current available data suggest that these techniques are feasible, safe, and effective, with similar perioperative outcomes to conventional laparoscopic techniques. Nonetheless, robotic-assisted surgery is more costly and may preclude its use in financially constrained areas. There is no good-quality evidence to support the use of these new techniques over conventional laparoscopy, and the purported benefits of better patient outcome are yet to be confirmed. Further prospective trials and randomised controlled trials with long-term data are required to determine their effectiveness and safety.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):43-51

Keywords: Minimally invasive surgical procedures; Natural orifice endoscopic surgery; Robotic surgical procedures

Introduction

Since Professor Kurt Semm, a German gynaecologist and a pioneer in operative laparoscopy, performed the first laparoscopic appendectomy in 1981[1], laparoscopic surgery has developed rapidly. Laparoscopic surgery is minimally invasive and superior to laparotomy in terms of less intraoperative blood loss, less postoperative pain, less postoperative fever, fewer wound complications, shorter hospital stay, and a faster return to normal activities[2-5]. Minimally invasive surgery is now considered to be the standard of care for the treatment of many benign and malignant gynaecological conditions.

The early-phase development of minimally invasive surgery was hampered by a lack of advanced instruments and good-quality imaging system to facilitate complex surgical procedures. With advances in technologies (three-dimensional image system, ergonomic instruments, instruments to cater special operative needs, and advanced energy sources to allow quick and secure haemostasis), many complex procedures can now be accomplished. This study reviews the major advances in minimally invasive surgery, namely laparoendoscopic single-site surgery (LESS), robotic-assisted laparoscopic surgery, and natural orifice transluminal endoscopic surgery (NOTES).

Laparoendoscopic Single-site Surgery

Conventional laparoscopic surgery typically requires one camera port at the umbilicus and two to three assistant ports at the lower abdomen. LESS was originated in a consortium at The Cleveland Clinic in 2010[6]. It is also known as single-port access surgery, single-incision laparoscopic surgery, and embryonic NOTES. The concept of single-incision laparoscopic surgery can be dated back to the 1960s. The first report of single-incision laparoscopic female sterilisation (by cauterisation and excision of a 5-mm segment of the fallopian tubes) was published in 1969[7]. In the 1970s, single-incision laparoscopy was limited to simple sterilisation procedures only. By reducing the number of incisions to one, LESS can potentially reduce postoperative pain and enable better cosmetic results, shorter hospital stay, faster recovery, and fewer port-related complications (e.g. hernia, vascular injury, nerve injury)[8].

In LESS, there are two common approaches to access the abdominal cavity and maintain the pneumoperitoneum during the procedure. The first approach is to make an initial single umbilical incision of 2-3 cm and then move off the underlying fascia of the umbilical skin and soft tissue flap. Multiple small incisions are then made in the fascia to insert two or three 5- to 10-mm trocars[9]. The second approach is to make a single 2- to 3-cm incision at the umbilicus from the skin down to the fascia to enter the abdominal cavity directly. Specialised access ports

Correspondence to: Dr Carmen Ka-Man Choi
Email: choikm@ha.org.hk

with different channels on top are then introduced for insertion of laparoscopic instruments. These access ports are commercially available but costly. A Korean group described a more economic approach by using a glove-port system, in which an Alexis wound retractor (Applied Medical, Rancho Santa Margarita [CA], USA) is inserted transumbilically with the outer rim covered with a surgical glove[10]. Holes are cut in the glove fingers through which trocars of different sizes can be placed and secured to the glove fingers with sutures, allowing insertion of a camera and other laparoscopic instruments[10].

There are several technical challenges to LESS. Instrument crowding can be a problem; in such a confined space, instruments are close together and range of movement is limited. Instrument collision inside the abdominal cavity or hand collision outside the ports is common. In addition, triangulation is not feasible. Triangulation enables approaching the surgical targets with two instruments in two directions to facilitate traction-countertraction and dissection. To overcome these technical challenges, a larger outer cap is used to increase the instrument distance outside the abdomen, and curved or articulating instruments are developed to restore the loss of triangulation. Nonetheless, LESS remains technically demanding and requires a long learning curve[11].

A number of gynaecological procedures can use the LESS approach, including adnexal surgery, hysterectomy, myomectomy, sacrocolpopexy, and lymphadenectomy, but the most common ones are LESS hysterectomy and adnexal surgery. In a meta-analysis of six randomised controlled trials that involved 624 women who underwent single-port versus multiport laparoscopic hysterectomy for benign indications, the single-port approach resulted in a longer operative time by 13 minutes, and there was no significant difference in intra- or post-operative complication rates, pain score, estimated blood loss, or length of hospital stay between the two groups[12]. The conversion rate was higher (but not significantly) in the single-port group (3.6% vs. 1.2%). The reason for conversion was dense adhesions or inadequate visualisation. Most conversions in the single-port group required only placement of an additional laparoscopic port. For cosmetic outcome, the results were inconsistent: two studies reported better cosmetic satisfaction for the single-port approach[13,14], but others failed to confirm this[15].

In another meta-analysis of six randomised controlled trials comparing single-port laparoscopy with conventional laparoscopy for benign adnexal diseases, single-port surgery was associated with a longer operative time, but there was no significant difference in postoperative pain, blood loss, mean length of hospital stay, or cosmetic results[16]. No case required conversion to laparotomy.

There were two randomised controlled trials comparing single-port with conventional laparoscopic myomectomy[17,18]. One study randomised 100 patients to either the single-port or the conventional laparoscopy groups and reported that the two groups were comparable in terms of the mean suturing time to close the uterine defect and surgical outcomes including operative time, blood loss, haemoglobin change, postoperative pain scores, operative complications, and length of hospital stay[17]. The other study randomised 66 patients to either single-port or conventional laparoscopic myomectomy and reported that the single-port group achieved a more favourable cosmetic outcome and better patient satisfaction; other surgical outcomes such as operation time, estimated blood loss, and complications were similar in both groups[18].

Studies of LESS in the treatment of gynaecological malignancies are limited. No randomised controlled trial could be identified. In one case series of 13 patients, LESS was feasible in the treatment of gynaecological cancer in selected patients[19].

In a retrospective case series of 110 patients who underwent single-port laparoscopic full staging (including pelvic and para-aortic lymphadenectomy) for endometrial cancer, the single-port approach was considered safe and feasible and comparable with other minimally invasive modalities in terms of operative time, complication rates, and length of hospital stay[20]. The conversion rate was 6.3% (7/110), six cases of which required laparotomy due to complications arising from the procedure. The mean number of pelvic lymph nodes harvested was 30, whereas that of para-aortic lymph nodes was 15.

In a study that compared a prospective group of 37 patients with endometrial cancer who underwent LESS hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with a historical group of 74 patients who underwent the same procedure using a 4-port conventional laparoscopic approach, the LESS group had significantly lower postoperative pain scores and analgesic requirements[21]. There were no significant differences in the operating time, estimated blood loss, need for transfusion, postoperative hospital stay, or intra- or post-operative complications between the two groups. No patients required conversion, and the number of pelvic or para-

aortic lymph nodes retrieved in both groups was similar. Respectively in the LESS and conventional laparoscopy groups, the mean number of pelvic nodes harvested was 24.6 and 23.3, and that of para-aortic nodes was 4.9 and 6.9.

One retrospective case series compared the perioperative outcomes of LESS radical hysterectomy with the mini-laparoscopic approach in 46 patients with stage 1A2-1B1/IIA1 cancer according to the International Federation of Gynecology and Obstetrics[22]. For the mini-laparoscopic group, one 5-mm umbilical camera port with three additional 3-mm secondary ports were used. The LESS group was associated with longer operative time but shorter hospital stay; the two groups were comparable in term of the number of lymph nodes removed, perioperative outcome, and oncological outcome. After a median follow-up of 27 months, only one patient in the mini-laparoscopic group died of pelvic recurrence.

The current evidence suggests that LESS is a feasible approach for treatment of benign and malignant gynaecological diseases; it is safe and as effective as conventional laparoscopic surgery. LESS is associated with a longer operative time, but the proposed advantages of less postoperative pain and higher cosmetic satisfaction have not been consistently demonstrated. Therefore, the benefit of LESS over conventional laparoscopic surgery has yet to be confirmed. Incisional herniation is a potential drawback of LESS and has been poorly examined. In one retrospective study of 211 women who underwent LESS, umbilical herniation occurred in 2.4% of patients after a median follow-up of 16 months[23]. When women with additional risk factors for herniation were excluded (e.g. obesity, connective tissue diseases), the rate of umbilical herniation was 0.5%, which is comparable to that after the conventional laparoscopic route. For the treatment of malignant diseases, oncological outcomes seem to be comparable between LESS and conventional laparoscopy. Nonetheless, data are limited and follow-up periods are short. More long-term data are required to establish the oncological safety of LESS.

Robotic-assisted Laparoscopic Surgery

The da Vinci Surgical System (Intuitive Surgical, Sunnyvale [CA], US) was the first robotic surgical system approved by the US Food and Drug Administration for general laparoscopic surgery in 2000 and for gynaecological procedures in 2005. It has been extensively used for performing hysterectomy and other complex laparoscopic procedures (myomectomy, sacrocolpopexy), and staging for gynaecological cancers. The laparoscopic trocars are docked to robotic arms to which surgical instruments are attached. The surgeon sits at the console to perform the surgery by remotely controlling the movement and function of different robotic arms using hand and foot controls.

The major advantages of robotic surgery over conventional laparoscopic surgery include improved visualisation through three-dimensional stereoscopic vision, wider range of motions and improved dexterity with robotic-wristed instruments, improved surgical precision by eliminating hand tremor, and better ergonomics to improve surgeon comfort during the procedure. These features potentially enable easier and more precise complex laparoscopic procedures and may lead to shortening of the learning curve. Nonetheless, its drawback is the loss of tactile feedback during surgery, reduced flexibility, longer operative time, and increased cost.

Although there has been a florid growth in the number of robotic procedures since its introduction in the 2000s, clinical trials that compare the performance of robotic-assisted surgery with conventional laparoscopic surgery in gynaecology are limited and involve only a small number of patients.

In a meta-analysis of four randomised trials that encompassed 326 women undergoing total hysterectomy in the robotic-assisted group (n=162) or conventional group (n=164), the two groups were comparable in terms of rates of major or minor complications, length of hospital stay, operating time, rate of conversion to laparotomy, and estimated blood loss[24]. Only two of the four trials reported quality of life[25,26], but results were inconsistent owing to heterogeneity of metrics used, and thus pooling of results was not possible.

Laparoscopic sacrocolpopexy is a procedure that requires advanced laparoscopic skills and demanding suturing and knot-tying techniques, with a steep learning curve and long operating time. The robotic system can facilitate such procedures. Only two randomised trials (each with a sample size of 78) have compared robotic-assisted with conventional laparoscopic sacrocolpopexy[27,28]. One study included patients with post-hysterectomy vaginal prolapse and reported that the robotic route was associated with a significantly longer operative time (suturing time and sacrocolpopexy time), with a mean difference of 67 minutes[27]. Patients in the robotic group had more pain at rest and during activity from weeks 3 to 5 and required

analgesics for a longer duration[27]. The cost incurred by the robotic route was also significantly higher, with a mean difference of US$1936. Both robotic and laparoscopic groups were equally effective in improving vaginal support and functional outcomes.

Another study included patients with pelvic organ prolapse grade II or greater, with 58% of patients undergoing concomitant hysterectomy[28]. When the initial costs of robot purchase and maintenance were excluded, the robotic route and laparoscopic route did not differ significantly in terms of initial day of surgery costs or hospital costs over 6 weeks. Nonetheless, the robotic system was associated with longer operative time; the rate of adverse events was similar between the two groups.

There is no randomised controlled trial to compare robotic with laparoscopic myomectomy. In a systematic review of robotic-assisted versus laparoscopic and/or open myomectomy, there were no significant differences in operative time, estimated blood loss, need for transfusion, length of hospital stay, complication rate, or postoperative fertility outcomes between the two groups[29].

Robotic-assisted surgery has been widely used in treatment of gynaecological malignancies. In a systematic review that comprised 24 comparative non-randomised studies comparing robotic-assisted laparoscopic hysterectomy with laparoscopic hysterectomy for endometrial cancer, the robotic route was associated with a shorter length of stay, less estimated blood loss, fewer conversions to laparotomy, and less postoperative pain, as well as fewer intra-operative complications, urinary tract injuries, and cystotomy incidence[30]. The postoperative complications and the numbers of pelvic lymph nodes and para-aortic lymph nodes retrieved were similar between the two groups[30]. Three of the studies reported oncological outcomes up to 36 months; there was no significant difference in the overall survival, disease-free survival, or recurrence rate between the two groups[31-33].

One randomised controlled trial compared robotic-assisted (n=50) with conventional (n=49) laparoscopy surgery for endometrial cancer, the robotic group achieved a shorter operation time, shorter total time spent in the operating room, and lower rate of conversion to laparotomy[34]. The two groups were comparable in terms of the number of lymph nodes retrieved, blood loss, length of hospital stay, and intra- and post-operative complications.

In a systematic review that included 11 studies that compared robotic-assisted with laparoscopic radical hysterectomy for early-stage cervical cancer, robotic-assisted surgery was associated with shorter length of hospital stay and less need for transfusion[35]. The two groups were similar in terms of operation time, estimated blood loss, intra- and post-operative complication rates, number of lymph nodes removed, rate of positive margin, and overall and disease-free survival.

The evidence for robotic-assisted radical trachelectomy and staging surgery for ovarian tumour is even more limited. Overall, the robotic approach is deemed safe and feasible, with results comparable to those of the laparoscopic approach[36-38].

For the treatment of benign gynaecological conditions, the available evidence suggests that robotic surgery is safe and effective with similar perioperative outcomes in terms of complication rates, conversion rates, blood loss, and length of hospital stay. Operative time is significantly longer in robotic-assisted laparoscopic sacrocolpopexy. For the treatment of gynaecological malignancies, the evidence is very limited. Patients with endometrial cancer may benefit from robotic-assisted surgery with advantages of shorter operative time and lower conversion rates. Robotic-assisted radical hysterectomy is better than the conventional laparoscopic route in terms of shorter hospital stay and less need for blood transfusion, with similar oncological survival data.

Robotic-assisted Laparoendoscopic Single-site Surgery

Robotic-assisted LESS can potentially have the benefits of less postoperative pain, better cosmetic results, and fewer port-related complications. The robotic surgical platform may help overcome the technical challenges associated with conventional LESS. Robotic-assisted LESS is feasible in many gynaecological procedures such as adnexal surgery, hysterectomy, sacrocolpopexy, myomectomy, radical hysterectomy, lymph node removal, and ovarian staging surgery. There is no randomised or prospective trial that compares robotic-assisted LESS with conventional LESS or multiport robotic-assisted surgery. Most studies are small retrospective cohort studies or case series to demonstrate the feasibility and safety.

Four retrospective cohort studies have compared robotic-assisted LESS with robotic-assisted multiport surgery for (mostly) early endometrial cancer (Table 1)[39-42]. Robotic-assisted LESS is associated with less operating blood loss and is less costly than multiport robotic surgery.

Six retrospective studies have compared robotic-assisted LESS with LESS (Table 2)[43-48]. The robotic route is associated with longer operative time and is more costly although surgical outcomes were similar.

Natural Orifice Transluminal Endoscopic Surgery

In the 1940s, culdoscopy was performed by gynaecologists to view the pelvic organs using an endoscope through the recto-uterine pouch for diagnostic pelvic examinations and sterilisation procedures[49]. Subsequent development of NOTES was impeded by the lack of appropriate technology to facilitate more complex procedures. The first human NOTES is believed to be the transgastric appendectomy performed in India in 2006[50]. It was presented but has not been published. The

Table 1. Comparative studies of robotic-assisted laparoendoscopic single-site surgery (RA-LESS) versus robotic-assisted multiport surgery (RA-MP)[39-42]

Study	Study type	Surgery	No. of patients	Results
Moukarzel et al[39], 2017	Retrospective cohort	Hysterectomy and sentinel lymph node mapping	RA-LESS=14; RA-MP=13	RA-LESS is associated with lower costs; no difference in operative time, console time, blood loss, or complication rates
Corrado et al[40], 2016	Retrospective case-control	Hysterectomy	RA-LESS=23; RA-MP=46	RA-LESS is associated with less blood loss, fewer hospital stay; RA-MP is associated with higher costs; no difference in operative time or complication rate
Bogliolo et al[41], 2016	Retrospective cohort	Hysterectomy	RA-LESS=45; RA-MP=59	RA-LESS is associated with less blood loss and shorter hospital stay; RA-MP is associated with shorter docking time and higher costs; no difference in console time, surgical complication rate, conversion rate, or postoperative pain
Khafagy et al[42], 2015	Retrospective cohort	Pelvic lymph node	RA-LESS=10; RA-MP=41	RA-LESS is feasible for pelvic lymph node dissection

Table 2. Comparative studies of robotic-assisted laparoendoscopic single-site surgery (RA-LESS) versus laparoendoscopic single-site surgery (LESS)[43-48]

Study	Study type	Surgery	No. of patients	Results
Gungor et al[43], 2017	Retrospective cohort	Hysterectomy	RA-LESS=20; LESS=25	No difference in conversion rate, operative time, blood loss, operative and post-operative complications, length of hospital stay
Hachem et al[44], 2016	Retrospective case-control	Adnexal surgery, hysterectomy, pelvic lymph node dissection	RA-LESS =33; LESS=59	8 cases in RA-LESS were aborted or converted to laparotomy (due to adhesions or technical difficulty); RA-LESS is associated with longer operative time and higher costs; no difference in blood loss, length of stay, or complication rates
Paek et al[45], 2016	Retrospective cohort	Adnexal surgery	RA-LESS =20; LESS=228	RA-LESS has longer operative time and lower complication rate (0% vs. 1.3%)
Lopez et al[46], 2016	Retrospective cohort	Hysterectomy	RA-LESS =50; LESS=50	No difference in conversion rate, complication rate, estimated blood loss; RA-LESS has shorter length of stay (by 8.12 hours) but longer operative time (by 24.9 minutes)
Paek et al[47], 2016	Retrospective cohort	Hysterectomy	RA-LESS =25; LESS=442	No difference in conversion; RA-LESS has longer operative time but less blood loss and lower major complication rate (0% vs. 1.4%)
Akdemir et al[48], 2015	Retrospective cohort	Hysterectomy	RA-LESS =24; LESS=34	RA-LESS has longer operative time; intraoperative outcomes and postoperative pain scores are similar

first published NOTES was a transvaginal endoscopy cholecystectomy performed in Brazil in 2007[51]. Vaginal hysterectomy is a traditional natural orifice surgery. It is superior to laparoscopic or abdominal hysterectomy with faster recovery[2]. Nonetheless, it can be difficult in nulliparous patients with a non-descent uterus or patients with a large uterus or with pelvic adhesions. Concomitant salpingo-oophorectomy can be challenging because of a limited operative field and difficulty in inspecting the entire abdominal and pelvic cavity. Other potential advantages of transvaginal NOTES include better cosmetic results, less incisional herniation, less postoperative pain, less postoperative wound infection, and a shorter hospital stay[52].

Approaches of NOTES include transgastric, transvaginal, transcolonic, and transvesical. The transvaginal route has the advantage of fewer complications arising from wound closure or leakage, compared with other routes. For transvaginal NOTES, prophylactic antibiotics and disinfection of the vagina are required. It typically starts with a 2- to 3-cm posterior colpotomy. The pouch of Douglas is opened and a vaginal NOTES port is inserted vaginally. The commercially available ports and the more economic glove-port system for LESS can be used as a NOTES port. A standard laparoscope (rigid or flexible, 0° or 30°) and conventional laparoscopic instruments can be inserted through the NOTES port. The NOTES port is removed at the end of procedure and the specimen is retrieved via the colpotomy wound. The wound is then closed with absorbable sutures. NOTES is technically challenging and can have the same problems of instrument crowding, hand collision, and loss of triangulation as encountered in LESS.

In pure NOTES, natural body orifices (mouth, urethra, anus, vagina) are used to access the peritoneal cavity without the need for an abdominal incision. In hybrid NOTES, natural body orifices are used in addition to transabdominal laparoscopic port. In vaginal-assisted NOTES hysterectomy, the first part of the operation is a vaginal procedure to dissect the caudal part of the uterus under direct vision. After that, the procedure is completed with transvaginal NOTES. In total vaginal NOTES hysterectomy, the whole procedure is performed by means of transvaginal NOTES with laparoscopic instruments.

Since the first published case of the NOTES in 2004, NOTES in gynaecology has remained limited. NOTES has been reported to be feasible and safe for adnexal surgery, hysterectomy, myomectomy, and sacrocolpopexy. Most reports are small case series with <20 patients; no randomised controlled trial for gynaecological NOTES has been published. In a case series of 137 patients who underwent NOTES hysterectomy, the success rate was 94.9% (130/137) and seven patients required conversion to conventional laparoscopy (two due to intraoperative complications of unintended cystotomy and bleeding, and five due to failure as a result of a narrow vagina, location of pathology obstructing the route of entry, or adhesions)[53]. Postoperative febrile morbidity and urinary tract infection occurred in five patients, but all resolved with conservative treatment.

In one retrospective matched case-control study that compared NOTES hysterectomy (n=147) with laparoscopic-assisted vaginal hysterectomy (LAVH) [n=365], NOTES was associated with less operative time, less blood loss, less need for blood transfusion, and shorter postoperative stay[54]. There was no conversion to laparotomy in either group. The overall complication rate was comparable between groups, but if the uterine weight was >500 mg, LAVH was associated with more complications (4.3% vs. 0%). NOTES resulted in higher hospital charges[54].

In another retrospective matched case-control study that compared NOTE hysterectomy (n=16) with single-port LAVH (n=32), NOTES was associated with shorter operative time (70.6 vs. 93.2 min) and shorter hospital stay (3.5 vs. 4 days)[55]. There was no conversion to laparotomy in either group and no significant difference in perioperative outcomes (estimated blood loss, amount of analgesic drugs used, postoperative visual analogue scale pain score, and febrile complications).

In a retrospective matched case-control study that compared NOTES salpingo-oophorectomy (n=33) with conventional laparoscopic approach (n=203), NOTES was associated with shorter operative time and shorter hospital stay, but higher hospital charges[56]. There was no conversion in either group.

In a similar case-controlled study that compared NOTES-assisted ovarian cystectomy (n=34) with laparoscopic ovarian cystectomy (n=243), NOTES had shorter operative time and shorter hospital stay but higher hospital charges[57].

In an on-going randomised controlled trial comparing transabdominal laparoscopic hysterectomy with NOTES in patients with a non-prolapsed uterus and benign gynaecological diseases, the primary outcome was the success rate and secondary outcomes included perioperative

outcomes, postoperative pain, sexual function, costs, and health-related quality of life[58].

It is proposed that the robotic platform may help overcome the difficulties associated with NOTES. In the first robotic-assisted NOTES for hysterectomy, all four patients with benign disease were successfully treated, with no intra- or post-operative complications[59]. Nonetheless, patients were highly selected due to the lack of appropriate instruments. Further development of surgical instruments are required to facilitate its implementation. For the treatment of benign disease, NOTES is associated with shorter operative time and shorter hospital stay but higher costs; the postoperative pain score does not seem to decrease.

Conclusion

The robotic system may help solve some technical challenges associated with LESS or NOTES. Nonetheless, the evidence to support the use of these minimally invasive techniques over conventional laparoscopic surgery remains limited. The available evidence suggests that LESS, robotic-assisted laparoscopic surgery, and NOTES are safe and effective for different gynaecological diseases. More prospective randomised controlled trials with long-term follow-up are needed to determine whether they enable better patient outcomes in terms of less pain, better cosmetic results, and faster recovery.

Declaration

The author has disclosed no conflicts of interest.

References

1. Litynski GS. Kurt Semm and the fight against skepticism: endoscopic hemostasis, laparoscopic appendectomy, and Semm's impact on the "laparoscopic revolution". *JSLS* 1998; 2:309-13.
2. Bhave Chittawar P, Franik S, Pouwer AW, Farquhar C. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. *Cochrane Database Syst Rev* 2014; 10:CD004638.
3. Aarts JW, Nieboer TE, Johnson N, et al. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database Syst Rev* 2015; 8:CD003677.
4. Galaal K, Bryant A, Fisher AD, Al-Khaduri M, Kew F, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. *Cochrane Database Syst Rev* 2012; 9:CD006655.
5. Wang YZ, Deng L, Xu HC, Zhang Y, Liang ZQ. Laparoscopy versus laparotomy for the management of early stage cervical cancer. *BMC Cancer* 2015; 15:928.
6. Gill IS, Advincula AP, Aron M, et al. Consensus statement of the consortium for laparoendoscopic single-site surgery. *Surg Endosc* 2010; 24:762-8.
7. Wheeless CR. A rapid, inexpensive, and effective method of surgical sterilisation by laparoscopy. *J Reprod Med* 1969; 3:65-9.
8. Uppal S, Frumovitz M, Escobar P, Ramirez PT. Laparoendoscopic single-site surgery in gynecology: review of literature and available technology. *J Minim Invasive Gynecol* 2011; 18:12-23.
9. Tacchino R, Greco F, Matera D. Single-incision laparoscopic cholecystectomy: surgery without a visible scar. *Surg Endosc* 2009; 23:896-9.
10. Lee YY, Kim TJ, Kim CJ, et al. Single-port access laparoscopic-assisted vaginal hysterectomy: a novel method with a wound retractor and a glove. *J Minim Invasive Gynecol* 2009; 16:450-3.
11. Cox DR, Zeng W, Frisella MM, Brunt LM. Analysis of standard multiport versus single-site access for laparoscopic skills training. *Surg Endosc* 2011; 25:1238-44.
12. Xie W, Cao D, Yang J, Yu M, Shen K, Zhao L. Single-port vs multiport laparoscopic hysterectomy: a meta-analysis of randomized controlled trials. *J Minim Invasive Gynecol* 2016; 23:1049-56.
13. Li M, Han Y, Feng YC. Single-port laparoscopic hysterectomy versus conventional laparoscopic hysterectomy: a prospective randomized trial. *J Int Med Res* 2012; 40:701-8.
14. Song T, Cho J, Kim TJ, et al. Cosmetic outcomes of laparoendoscopic single-site hysterectomy compared with multi-port surgery: randomized controlled trial. *J Minim Invasive Gynecol* 2013; 20:460-7.
15. Kim TJ, Shin SJ, Kim TH, et al. Multi-institution, prospective, randomized trial to compare the success rates of single-port versus multiport laparoscopic hysterectomy for the treatment of uterine myoma or adenomyosis. *J Minim Invasive Gynecol* 2015; 22:785-91.
16. Schmitt A, Crochet P, Knight S, Tourette C, Loundou A, Agostini A. Single-port laparoscopy vs conventional laparoscopy in benign adnexal disease: a systematic review and meta-analysis. *J Minim Invasive Gynecol* 2017; 24:1083-95.
17. Song T, Kim TJ, Lee SH, Kim TH, Kim WY. Laparoendoscopic single-site myomectomy compared with conventional laparoscopic myomectomy: a multicentre, randomized, controlled trial. *Fertil Steril* 2015; 104:1325-31.
18. Lee D, Kim SK, Kim K, Lee JR, Suh CS, Kim SH. Advantages of single-port laparoscopic myomectomy compared with conventional laparoscopic myomectomy: a randomised controlled study. *J Minim Invasive Gynecol* 2018; 25:124-32.

19. Fader AN, Escobar PF. Laparoendoscopic single-site surgery (LESS) in gynecologic oncology: technique and initial report. *Gynecol Oncol* 2009; 114:157-61.
20. Barnes H, Harrison R, Huffman L, Medlin E, Spencer R, Al-Niaimi A. The adoption of single-port laparoscopy for full staging of endometrial cancer: surgical and oncology outcomes and evaluation of the learning curve. *J Minim Invasive Gynecol* 2017; 24:1029-36.
21. Park JY, Kim DY, Suh DS, Kim JH, Nam JH. Laparoendoscopic single-site versus conventional laparoscopic surgical staging for early-stage endometrial cancer. *Int J Gynecol Cancer* 2014; 24:358-63.
22. Fagotti A, Ghezzi F, Boruta DM, et al. Minilaparoscopic radical hysterectomy (mLPS-RH) vs laparoendoscopic single-site radical hysterectomy (LESS-RH) in early stage cervical cancer: a multicenter retrospective study. *J Minim Invasive Gynecol* 2014; 21:1005-9.
23. Gunderson CC, Knight J, Ybanez-Morano J, et al. The risk of umbilical hernia and other complications with laparoscopic single-site surgery. *J Minim Invasive Gynecol* 2012; 19:40-5.
24. Albright BB, Witte T, Tofte AN, et al. Robotic versus laparoscopic hysterectomy for benign disease: a systematic review and meta-analysis of randomized trials. *J Minim Invasive Gynecol* 2016; 23:18-27.
25. Paraiso MF, Ridgeway B, Park AJ, et al. A randomized trial comparing conventional and robotically assisted total laparoscopic hysterectomy. *Am J Obstet Gynecol* 2013; 208:368.e1-7.
26. Sarlos D, Kots L, Stevanovic N, von Felten S, Schär G. Robotic compared with conventional laparoscopic hysterectomy: a randomized controlled trial. *Obstet Gynecol* 2012; 120:604-11.
27. Paraiso MF, Jelovsek JE, Frick A, Chen CC, Barber MD. Laparoscopic compared with robotic sacrocolpopexy for vaginal prolapse: a randomized controlled trial. *Obstet Gynecol* 2011; 118:1105-13.
28. Anger JT, Mueller ER, Tarnay C et al. Robotic compared with laparoscopic sacrocolpopexy: a randomized controlled trial. *Obstet Gynecol* 2014; 123:5-12.
29. Iavazzo C, Mamais I, Gkegkes ID. Robotic assisted vs laparoscopic and/or open myomectomy: systematic review and meta-analysis of the clinical evidence. *Arch Gynecol Obstet* 2016; 294:5-17.
30. Park DA, Lee DH, Kim SW, Lee SH. Comparative safety and effectiveness of robot-assisted laparoscopic hysterectomy versus conventional laparoscopy and laparotomy for endometrial cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 2016; 42:1303-14.
31. Chiou HY, Chiu LH, Chen CH, Yen YK, Chang CW, Liu WM. Comparing robotic surgery with laparoscopy and laparotomy for endometrial cancer management: a cohort study. *Int J Surg* 2015; 13:17-22.
32. Coronado PJ, Herraiz MA, Magrina JF, Fasero M, Vidart JA. Comparison of perioperative outcomes and cost of robotic-assisted laparoscopy, laparoscopy and laparotomy for endometrial cancer. *Eur J Obstet Gynecol Reprod Biol* 2012; 165:289-94.
33. Cardenas-Goicoechea J, Shepherd A, Momeni M, et al. Survival analysis of robotic versus traditional laparoscopic surgical staging for endometrial cancer. *Am J Obstet Gynecol* 2014; 210:160.e1-160.e11.
34. Maenpaa MM, Nieminen K, Tomas El, Laurila M, Luukkaala TH, Mäenpää JU. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. *Am J Obstet Gynecol* 2016; 215:588.e1-588.e7.
35. Park DA, Yun JE, Kim SW, Lee SH. Surgical and clinical safety and effectiveness of robot-assisted laparoscopic hysterectomy compared to conventional laparoscopy and laparotomy for cervical cancer: a systematic review and meta-analysis. *Eur J Surg Oncol* 2017; 43:994-1002.
36. Api M, Boza A, Ceyhan M. Robotic versus laparoscopic radical trachelectomy for early-stage cervical cancer: case report and review of literature. *J Minim Invasive Gynecol* 2016; 23:677-83.
37. Nezhat FR, Finger TN, Vetere P, et al. Comparison of perioperative outcomes and complication rates between conventional versus robotic-assisted laparoscopy in the evaluation and management of early, advanced, and recurrent stage ovarian, fallopian tube, and primary peritoneal cancer. *Int J Gynecol Cancer* 2014; 24:600-7.
38. Gallotta V, Cicero C, Conte C, et al. Robotic versus laparoscopic staging for early ovarian cancer: a case-matched control study. *J Minim Invasive Gynecol* 2017; 24:293-8.
39. Moukarzel LA, Sinno AK, Fader AN, Tanner EJ. Comparing single-site and multiport robotic hysterectomy with sentinel lymph node mapping for endometrial cancer: surgical outcomes and cost analysis. *J Minim Invasive Gynecol* 2017; 24:977-83.
40. Corrado G, Cutillo G, Mancini E, et al. Robotic single site versus robotic multiport hysterectomy in early endometrial cancer: a case control study. *J Gynecol Oncol* 2016; 27:e39.
41. Bogliolo S, Ferrero S, Cassani C, et al. Single-site versus multiport robotic hysterectomy in benign gynecologic diseases: a retrospective evaluation of surgical outcomes and cost analysis. *J Minim Invasive Gynecol* 2016; 23:603-9.
42. Khafagy AM, Kashi PK, Iskander GB, Tabbarah RZ, Rose GS. Comparing the robotic single-port approach to multi-port, for pelvic lymph node dissection in the treatment of endometrial pathology. *J Minim Invasive Gynecol* 2015; 22:S11.
43. Gungor M, Kahraman K, Dursun P, Ozbasli E, Genim C. Single-port hysterectomy: robotic versus laparoscopic. *J Robot Surg* 2017 [Epub ahead of print].
44. El Hachem L, Andikyan V, Mathews S, et al. Robotic single-site and conventional laparoscopic surgery in gynecology: clinical outcomes and cost analysis of a matched case-control study. *J Minim Invasive Gynecol* 2016; 23:760-8.
45. Paek J, Lee JD, Kong TW, Chang SJ, Ryu HS. Robotic-single-site versus laparo-endoscopic single-site surgery for adnexal tumours: a propensity score-matching analysis. *Int J Med Robot* 2016; 12:694-700.
46. Lopez S, Mulla ZD, Hernandez L, Garza DM, Payne TN, Farnam RW. A comparison of outcomes between robotic-assisted, single-site laparoscopy versus laparoendoscopic

single site for benign hysterectomy. *J Minim Invasive Gynecol* 2016; 23:84-8.
47. Paek J, Lee JD, Kong TW, Chang SJ, Ryu HS. Robotic single-site versus laparoendoscopic single-site hysterectomy: a propensity score matching study. *Surg Endosc* 2016; 30:1043-50.
48. Akdemir A, Yildirim N, Zeybek B, Karaman S, Sendag F. Single incision trans-umbilical total hysterectomy: robotic or laparoscopic? *Gynecol Obstet Invest* 2015; 80:93-8.
49. Halim I, Tavakkolizadeh A. NOTES: the next surgical revolution? *Int J Surg* 2008; 6:273-6.
50. Rao GV, Reddy DN. Transgastric appendectomy in humans. Presented at: World Congress of Gastroenterology. Montreal. Canada; September 2006.
51. Zorron R, Filgueiras M, Maggioni LC, Pombo L, Lopes Carvalho G, Lacerda Oliveira A. NOTES. Transvaginal cholecystectomy: report of the first case. *Surg Innov* 2007; 14:279-83.
52. Clark MP, Qayed ES, Kooby DA, Maithel SK, Willingham FF. Natural orifice translumenal endoscopic surgery in humans: a review. *Minim Invasive Surg* 2012; 2012:189296.
53. Lee CL, Wu KY, Su H, Wu PJ, Han CM, Yen CF. Hysterectomy by transvaginal natural orifice transluminal endoscopic surgery (NOTES): a series of 137 patients. *J Minim Invasive Gynecol* 2014; 21:818-24.
54. Wang CJ, Huang HY, Huang CY, SU H. Hysterectomy via transvaginal natural orifice transluminal endoscopic surgery for nonprolapsed uteri. Surg Endosc 2015; 29:100-7.
55. Yang YS, Kim SY, Hur MH, Oh KY. Natural orifice transluminal endoscopic surgery-assisted versus single-port laparoscopic-assisted vaginal hysterectomy: a case-matched study. *J Minim Invasive Gynecol* 2014; 21:624-31.
56. Li YC, Ku FC, Kuo HH, Tseng HJ, Wang CJ. Transvaginal endoscopic surgery-assisted versus conventional laparoscopic adnexectomy (TVEA vs. CLA): a propensity-matched study and literature review. *Taiwan J Obstet Gynecol* 2017; 56:336-41.
57. Wang CJ, Wu PY, Kuo HH, Yu HT, Huang CY, Tseng HT. Natural orifice transluminal endoscopic surgery-assisted versus laparoscopic ovarian cystectomy (NOAC vs. LOC): a case-matched study. *Surg Endosc* 2016; 30:1227-34.
58. Baekelandt J, De Mulder PA, Le Roy I, et al. HALON-hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol). *BMJ Open* 2016; 6:e011546.
59. Lee CL, Wu KY, Su H, Han CM, Huang CY, Yen CF. Robot-assisted natural orifice transluminal endoscopic surgery for hysterectomy. *Taiwan J Obstet Gynecol* 2015; 54:761-5.

Ovarian Reserve Tests in Pre-conceptual Healthy Women

Queenie Ho-Yan WONG MBBS, MRCOG, FHKCOG, FHKAM (Obstetrics and Gynaecology)
Department of Obstetrics and Gynaecology, Princess Margaret Hospital, Laichikok, Hong Kong

Women's fertility declines with age. The worldwide trend of delaying childbirth has led to more women facing fertility problems at the time they wish to conceive. There are various ultrasound and biochemical markers available for ovarian reserve testing. The common markers are antral follicle count, follicle-stimulating hormone, and anti-Mullerian hormone. Tests for these markers have their own strengths and limitations. Clinical application of ovarian reserve tests in predicting fertility in pre-conceptual healthy women remains controversial. Clinicians should be cautious when applying and interpreting these ovarian reserve tests for fertility prediction in pre-conceptual women.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(1):52-6

Keywords: Anti-Mullerian hormone; Fertility; Follicle stimulating hormone; Ovarian follicle; Ovarian reserve

Introduction

Worldwide, women are delaying childbirth until a more advanced age because of the availability of effective contraception and desire for higher educational achievement and professional status[1,2]. In Hong Kong, the median age of women at first childbirth has increased from 25.1 years in 1981 to 31.4 years in 2015[3]. More women face reduced fertility at the time they plan to conceive, as their fertility declines with age[4]. The rate of fertility decline differs in different women, as does the process of menopause. Understanding the fertility potential in pre-conceptual women may affect their family-planning decision so as to avoid under- or over-treatment of their infertility. This article aims to review the evidence of age and ovarian reserve testing for fertility prediction in healthy pre-conceptual women.

Age and Fecundability

Increasing age is associated with decreasing fecundability. Fecundability peaks between the late 20s to early 30s, with a steady decline thereafter[5,6]. This age-related decline in fecundability is more pronounced in nulliparous women[7,8].

In a prospective fecundability study involving 782 European couples who practised natural family planning, the pregnancy rate decreased and the time to pregnancy lengthened as the woman's age increased[9]. In a prospective cohort study of fecundability in 2962 couples trying to conceive without a history of infertility, increasing female age was associated with an approximately linear decline in fecundability, with the peak at the age of 21 to 24 years; the association was stronger among nulligravid women[10].

Ovarian Reserve Markers

Ovarian reserve indicates the number of oocytes that remains in the ovaries[11], and is widely applied to predict fertility. Nonetheless, there is controversy about whether it reflects oocyte quality and helps to predict pregnancy in both natural conception and in-vitro fertilisation (IVF). Ovarian reserve markers can be classified as imaging (ultrasound) markers and biochemical markers. Ultrasound markers include antral follicle count (AFC) and ovarian volume. Biochemical markers can be subdivided into those studied in provocative tests (such as clomiphene citrate challenge test) and basal markers that include follicle-stimulating hormone (FSH), oestradiol, inhibin B, and anti-Mullerian hormone (AMH). Among them, AFC, FSH, and AMH are more commonly tested.

Antral Follicle Count

AFC is measured by transvaginal ultrasonography on day 2 to 4 of the menstrual cycle and indicates the number of follicles between 2 and 10 mm in the longitudinal and transverse planes in both ovaries. It is a reflection of the primordial follicle count. It is easy to perform and has good inter-cycle variability and inter- and intra-observer reliability if performed by experienced clinicians[12]. Nonetheless, it is limited by intra-cycle variation and needs to be measured during the early follicular phase in women with a regular cycle. Accuracy depends on the resolution of the ultrasound machine, experience of the operator, and

Correspondence to: Dr Queenie Ho-Yan Wong
Email: queeniehoyan@gmail.com

body build of the woman[13]. Both intra-cycle and inter-cycle variability increase in obese women[14].

The role of AFC as an ovarian reserve marker has been mainly studied in women undergoing IVF. AFC predicts ovarian response to gonadotrophin stimulation[15] but not pregnancy[13,16]. A low AFC count is associated with a poor response to controlled ovarian stimulation. When the AFC count is 3 to 4, the sensitivity is low (9%-73%) but the specificity is high (73%-97%) in predicting poor ovarian response[13].

Evidence for the association of AFC with natural conception is limited. The AFC is lower in infertile women than in fertile women aged 25 to 40 years[17]. Nonetheless, the absolute difference between infertile and fertile women aged 31 to 35 years is only 4. AFC was not shown to predict the time to pregnancy in 102 pregnancy planners after controlling for the women's age (hazard ratio=1.03, 95% confidence interval=1.00-1.07, p=0.08)[18].

Follicule-stimulating Hormone

FSH is produced by the anterior pituitary, which regulates the recruitment and growth of ovarian follicles from the antral stage to graafian follicles. Oestradiol is produced by the growing follicle, whereas inhibin B is produced by granulosa cells on small and large antral follicles. Both oestradiol and inhibin B inhibit pituitary secretion of FSH. FSH increases when the follicular pool is depleted owing to decreased negative feedback by inhibin B and oestradiol[19]. FSH is an indirect measure of the antral follicle pool and depends on an intact hypothalamic-pituitary ovarian axis. Its use therefore needs to be coupled with serum oestradiol measurement to avoid false negative results. In addition, FSH has significant intra-cycle and inter-cycle variability[20,21]. It should be measured in the early follicular phase, on days 2 to 5 of the menstrual cycle.

Although a high FSH level indicates decreased oocyte number, it cannot be translated into decreased fecundibility. There is no study to compare FSH levels between infertile and fertile women. In a retrospective cohort study of women with an elevated FSH level of >12 IU/L, younger women had a more favourable natural fertility prognosis than their older counterparts in terms of clinical pregnancy rate[22]. This finding suggests that FSH can reflect the quantity of ovarian reserve but not necessarily the quality of the oocytes.

Anti-Mullerian Hormone

AMH is a glycoprotein produced by granulosa cells of secondary, prenatal, and small antral follicles[23]. As it is produced by follicles that are not gonadotrophin sensitive, the AMH level has minimal fluctuation throughout the menstrual cycle[24] and little inter-cycle variation[25]. High AMH is associated with high AFC and a high number of resting primodial follicles. Its level declines with age[26]; it peaks at 25 to 30 years followed by a decline until it becomes undetectable prior to menopause[27,28].

There are different AMH assays available: AMH Gen II ELISA (Beckman Coulter Diagnostics, CA, US), Ultra-Sensitive AMH/MIS ELISA kit (Ansh Labs, TX, US), the automated Access AMH assay (Beckman-Coulter Diagnostics, CA, US), and the Elecsys AMH Immunoassay (Roche Diagnostics International, IN, US). There is a lack of correlation between different assays, making interpretation of AMH results and comparison of results from various studies difficult. AMH values measured by the Ansh Labs assay are significantly higher, and by the Roche assay are significantly lower ($p<0.05$), compared with the Gen II and Beckman Coulter automated assays[29]. In addition, the pre-assayed storage conditions of the serum affect AMH assay results[29-31]. There is no universally accepted diagnostic AMH level for decreased ovarian reserve. Levels can be affected by a number of factors (Table)[19], and the clinician should be aware of these when interpreting AMH levels.

The role of AMH in predicting natural fecundability

Table. Factors affecting serum Anti-Mullerian hormone (AMH) levels[19]

Factors
Factors increasing serum AMH level
Caucasian (higher than Chinese and Black)
Parity
Polycystic ovarian syndrome
Granulosa cell tumour
Factors decreasing serum AMH level
Smoking
Systemic illness
Breast cancer gene-1 carrier
Fragile X mental retardation 1 premutation
Ovarian suppression (oral contraceptive pills, gonadotrophin releasing-hormone agonist)
Pregnancy
Endometriosis
History of ovarian surgery
History of chemotherapy

is inconclusive; more data suggest that it does not predict short-term natural fertility. In a cross-sectional study of ovarian reserve markers in 277 women with unexplained infertility and 226 reproductive healthy controls, the two groups were comparable in terms of AFC and AMH levels[32]. AFC, AMH, and FSH do not affect the time to pregnancy in women without a history of infertility[18]. In women with a history of one or two miscarriages, AMH is not associated with fecundability in natural conception[33].

In IVF, AMH has been shown to predict ovarian response. An AMH level of 0.1-1.66 ng/ml has a sensitivity of 44%-97% and specificity of 41%-100% in predicting poor response, whereas an AMH level of 3.36-5.0 ng/ml has a sensitivity of 53%-90.5% and specificity of 60%-94.9% in predicting ovarian hyperstimulation[19].

There is some evidence that AMH can help predict the age of menopause. Its prediction is more accurate in women of late reproductive age, and the precision range in younger age women (21-46 years) is broad[34,35].

Ovarian Reserve Testing in Pre-conceptual Women

Although ovarian reserve markers are indicators of oocyte quantity, there is controversy about whether ovarian reserve tests reflect oocyte quality. Should these tests be performed in general reproductive-age women without any history or risk factor of infertility in the era of delaying childbirth? It is important to educate women on the issue; women are often unaware of the age-related decline in fertility and may overestimate the success of IVF[36-38].

Opponents of ovarian reserve screening argue that there is no solid evidence that a decreased ovarian reserve has any implication for immediate fertility potential. Low ovarian reserve can create unnecessary anxiety for women[39] and potentially lead to adverse consequences such as premature termination of education or a career or seeking parenthood outside of a stable relationship. Conversely, a result of satisfactory ovarian reserve can give false reassurance to a woman who may then delay her pregnancy planning. In addition, age affects the fertility potential on top of ovarian reserve.

Proponents of ovarian reserve screening argue that a proportion of women with low ovarian reserve will require IVF. Current evidence only shows that fecundability is not affected in the short term (6 to 12 months)[18,40-42]. A low AMH level and AFC are associated with decreased ovarian response to gonadotrophin stimulation and thus adversely affect IVF outcome. Women with low AMH levels for their age have an earlier menopause[43-45]. This information is useful for both women and clinicians. Early initiation of fertility treatment can be planned if natural conception does not occur. Personalised risk assessment may facilitate a more informed decision; 80% of women will advance their fertility planning if they know they have a low ovarian reserve[46,47]. Anticipation of oocyte exhaustion does not influence a woman's future relationship and life-choices[48], although preventive oocyte banking can provide psychological reassurance.

Conclusion

There are limited studies on the use of ovarian reserve markers to predict fecundability in generally healthy pre-conceptual women. Limitations of ovarian reserve makers should be explained to women before performing these tests. Clinicians should be prepared to provide an evidence-based explanation of the results and their clinical application. Age remains the most reliable predictor of fecundibility in healthy pre-conceptual women.

Declaration

The author has disclosed no conflicts of interest.

References

1. Schmidt L, Sobotka T, Bentzen JG, Nyboe Andersen A; ESHRE Reproduction and Society Task Force. Demographic and medical consequences of the postponement of parenthood. *Hum Reprod Update* 2012; 18:29-43.
2. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2012. *Natl Vital Stat Rep* 2013; 62:1-68.
3. Marriage, fertility and family conditions. Available from: https://www.censtatd.gov.hk/hkstat/sub/gender/marr_fert_and_family_con/index.jsp
4. te Velde ER, Eijkemans R, Habbema HD. Variation in couple fecundity and time to pregnancy, an essential concept in human reproduction. *Lancet* 2000; 355:1928-9.
5. Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986; 233:1389-94.
6. O'Connor KA, Holman DJ, Wood JW. Declining fecundity

and ovarian ageing in natural fertility populations. *Maturitas* 1998; 30:127-36.
7. Rothman KJ, Wise LA, Sorensen HT, Riis AH, Mikkelsen EM, Hatch EE. Volitional determinants and age-related decline in fecundability: a general population prospective cohort study in Denmark. *Fertil Steril* 2013; 99:1958-64.
8. Steiner AZ, Jukic AM. Impact of female age and nulligravidity on fecundity in an older reproductive age cohort. *Fertil Steril* 2016; 105:1584-8.e1.
9. Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Obstet Gynecol* 2004; 103:51-6.
10. Wesselink AK, Rothman KJ, Hatch EE, Mikkelsen EM, Sørensen HT, Wise LA. Age and fecundability in a North American preconception cohort study. *Am J Obstet Gynecol* 2017; 217:667.e1-667.e8.
11. Ledger W, Cheong Y. Reproductive ageing. Scientific impact paper No. 24. London: Royal College of Obstetricians and Gynaecologists; 2011.
12. Scheffer GJ, Broekmans FJ, Bancsi LF, Habbema JD, Looman CW, Te Velde ER. Quantitative transvaginal two- and three-dimensional sonography of the ovaries: reproducibility of antral follicle counts. *Ultrasound Obstet Gynecol* 2002; 20:270-5.
13. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006; 12:685-718.
14. Broer SL, Mol BW, Hendriks D, Broekmans FJ. The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril* 2009; 91:705-14.
15. Ng EH, Tang OS, Ho PC. The significance of the number of antral follicles prior to stimulation in predicting ovarian responses in an IVF programme. *Hum Reprod* 2000; 15:1937-42.
16. Hendriks DJ, Mol BW, Bancsi LF, Te Velde ER, Broekmans FJ. Antral follicle count in the prediction of poor ovarian response and pregnancy after in vitro fertilization: a meta-analysis and comparison with basal follicle-stimulating hormone level. *Fertil Steril* 2005; 83:291-301.
17. Rosen MP, Johnstone E, Addauan-Andersen C, Cedars MI. A lower antral follicle count is associated with infertility. *Fertil Steril* 2011; 95:1950-4.e1.
18. Depmann M, Broer SL, Eijkemans MJ, et al. Anti-Müllerian hormone does not predict time to pregnancy: results of a prospective cohort study. *Gynecol Endocrinol* 2017; 33:644-8.
19. Tal R, Seifer DB. Ovarian reserve testing: a user's guide. *Am J Obstet Gynecol* 2017; 217:129-40.
20. Scott RT Jr, Hofmann GE, Oehninger S, Muasher SJ. Intercycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in vitro fertilization. *Fertil Steril* 1990; 54:297-302.
21. Kwee J, Schats R, McDonnell J, Lambalk CB, Schoemaker J. Intercycle variability of ovarian reserve tests: results of a prospective randomized study. *Hum Reprod* 2004; 19:590-5.
22. Check JH, Peymer M, Lurie D. Effect of age on pregnancy outcome without assisted reproductive technology in women with elevated early follicular phase serum follicle-stimulating hormone levels. *Gynecol Obstet Invest* 1998; 45:217-20.
23. Weenen C, Laven JS, Von Bergh AR, et al. Anti-Müllerian hormone expression pattern in human ovary: potential implications for initial and cyclic follicle recruitment. *Mol Hum Reprod* 2004; 10:77-83.
24. Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy CH, Englert Y. Stable serum levels of anti-Mullerian hormone during the menstrual cycle: a prospective study in normo-ovulatory women. *Hum Reprod* 2007; 22:1837-40.
25. Fanchin R, Taieb J, Lozano DH, Ducot B, Frydman R, Bouyer J. High reproducibility of serum anti-Mullerian hormone measurements suggests a multi-staged follicular secretion and strengthens its role in the assessment of ovarian follicular status. *Hum Reprod* 2005; 20:923-7.
26. van Rooij IA, Broekmans FJ, Scheffer GJ, et al. Serum antimullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: a longitudinal study. *Fertil Steril* 2005; 83:979-87.
27. van Disseldorp J, Faddy MJ, Themmen AP, et al. Relationship of serum antimullerian hormone concentration to age at menopause. *J Clin Endocrinol Metab* 2008; 93:2129-34.
28. Kelsey TW, Wright P, Nelson SM, Anderson RA, Wallace WH. A validated model of serum anti-mullerian hormone from conception to menopause. *PLoS One* 2011; 6:e22024.
29. Li HW, Wong BP, Ip WK, Yeung WS, Ho PC, Ng EH. Comparative evaluation of three new commercial immunoassays for anti-Mullerian hormone measurement. *Hum Reprod* 2016; 31:2796-802.
30. Dewailly D, Andersen CY, Balen A, et al. The physiology and clinical utility of anti-Mullerian hormone in women. *Hum Reprod Update* 2014; 20:370-85.
31. Rustamov O, Smith A, Roberts SA, et al. Anti-Mullerian hormone: poor assay reproducibility in a large cohort of subjects suggests sample instability. *Hum Reprod* 2012; 27:3085-91.
32. Greenwood EA, Cedars MI, Santoro N, et al. Antimullerian hormone levels and antral follicle counts are not reduced compared with community controls in patients with rigorously defined unexplained infertility. *Fertil Steril* 2017; 108:1070-7.
33. Zarek SM, Mitchell EM, Sjaarda LA, et al. Is anti-mullerian hormone associated with fecundability? Findings from the EAGeR Trial. *J Clin Endocrinol Metab* 2015; 100:4215-21.
34. Depmann M, Eijkemans MJ, Broer SL, et al. Does anti-Mullerian hormone predict menopause in the general population? Results of a prospective ongoing cohort study. *Hum Reprod* 2016; 31:1579-87.
35. Finkelstein JS, Burnett-Bowie S, Santoro N, et al. Utility of anti-mullerian hormone for predicting the time to final menstrual period: the Study of Women's Health Across the Nation (SWAN). Endocrine Society Meeting; 2016.
36. Bavan B, Porzig E, Baker VL. An assessment of female university students' attitudes toward screening technologies for ovarian reserve. *Fertil Steril* 2011; 96:1195-9.
37. Peterson BD, Pirritano M, Tucker L, Lampic C. Fertility awareness and parenting attitudes among American male and

female undergraduate university students. *Hum Reprod* 2012; 27:1375-82.
38. MacDougall K, Beyene Y, Nachtigall RD. Age shock: misperceptions of the impact of age on fertility before and after IVF in women who conceived after age 40. *Hum Reprod* 2013; 28:350-6.
39. Loh JS, Maheshwari A. Anti-Mullerian hormone—is it a crystal ball for predicting ovarian ageing? *Hum Reprod* 2011; 26:2925-32.
40. Steiner AZ, Herring AH, Kesner JS, et al. Antimullerian hormone as a predictor of natural fecundability in women aged 30-42 years. *Obstet Gynecol* 2011; 117:798-804.
41. Hagen CP, Vestergaard S, Juul A, et al. Low concentration of circulating antimüllerian hormone is not predictive of reduced fecundability in young healthy women: a prospective cohort study. *Fertil Steril* 2012; 98:1602-8.e2.
42. Streuli I, de Mouzon J, Paccolat C, et al. AMH concentration is not related to effective time to pregnancy in women who conceive naturally. *Reprod Biomed Online* 2014; 28:216-24.
43. van Rooij IA, Tonkelaar ID, Broekmans FJ, et al. Anti-mullerian hormone is a promising predictor for the occurrence of the menopausal transition. *Menopause* 2004; 11:601-6.
44. Broer SL, Eijkemans MJ, Scheffer GJ, et al. Anti-mullerian hormone predicts menopause: a long-term follow-up study in normoovulatory women. *J Clin Endocrinol Metab* 2011; 96:2532-9.
45. Tehrani FR, Solaymani-Dodaran M, Tohidi M, Gohari MR, Azizi F. Modeling age at menopause using serum concentration of anti-mullerian hormone. *J Clin Endocrinol Metab* 2013; 98:729-35.
46. Bavan B, Porzig E, Baker VL. An assessment of female university students' attitudes toward screening technologies for ovarian reserve. *Fertil Steril* 2011; 96:1195-9.
47. Aguinaldo ET, Morgan DC, Julliard K. What would you do if you knew? *Obstet Gynecol* 2014; 123(Suppl 1):187S.
48. Stoop D, Maes E, Polyzos NP, Verheyen G, Tournaye H, Nekkebroeck J. Does oocyte banking for anticipated gamete exhaustion influence future relational and reproductive choices? A follow-up of bankers and non-bankers. *Hum Reprod* 2015; 30:338-44.

NESTLÉ® MOM

Vitamins and Minerals with DHA

An All-In-One maternal supplement to help moms-to-be meet their nutritional needs from pre-pregnancy to lactation

- Multi Vitamins and Minerals
- DHA*
- Folic Acid
- Iron with Patented Technology

UNIQUE **Trio-Pro**

3-Layer Nutrient Lock Technology

NEWLY LAUNCHED

MADE IN ITALY

NESTLÉ® MOM All-In-One capsule has a unique Trio-Pro 3-layer nutrient lock technology to protect nutrients from being broken down in the stomach before they can be absorbed in the intestines with maximum efficacy.

One NESTLÉ® MOM capsule a day helps to bring a healthy foundation to the mother's immune system.^

*Each capsule contains 200mg DHA, helping adult pregnant/ lactating moms to meet the daily recommended intake by World Health Organization (WHO) / Food and Agriculture Organization (FAO)
^Along with balanced diet and regular exercise

Nestlé Start Healthy Stay Healthy™

1st 1000 Days Allergy Prevention Program

Information for medical profession only