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Maternal Dietary Intake and Human Milk Composition

MICRONUTRIENTS

Maternal intake of the below nutrients modify their levels in human milk[1-4]:

- **Vitamins A, B1, B2, B6, B12, C and D**
- **Choline**
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Pregnant women
134 mcg/L (**insufficient***)

Lactating women
65 mcg/L (**insufficient***)

Median UIC of women taking iodine-containing supplements[7^]

Pregnant Women
156 mcg/L (**adequate***)

Lactating Women
84 mcg/L (**insufficient***)

Abbreviation: UIC = urinary iodine concentration
*According to the WHO classification
^At an average daily iodine intake of at least 150 mcg/day

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January 2022, Volume 22, Number 1

EDITORIAL

OBSTETRICS

GYNAECOLOGY

REVIEW ARTICLES

PERSPECTIVE

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

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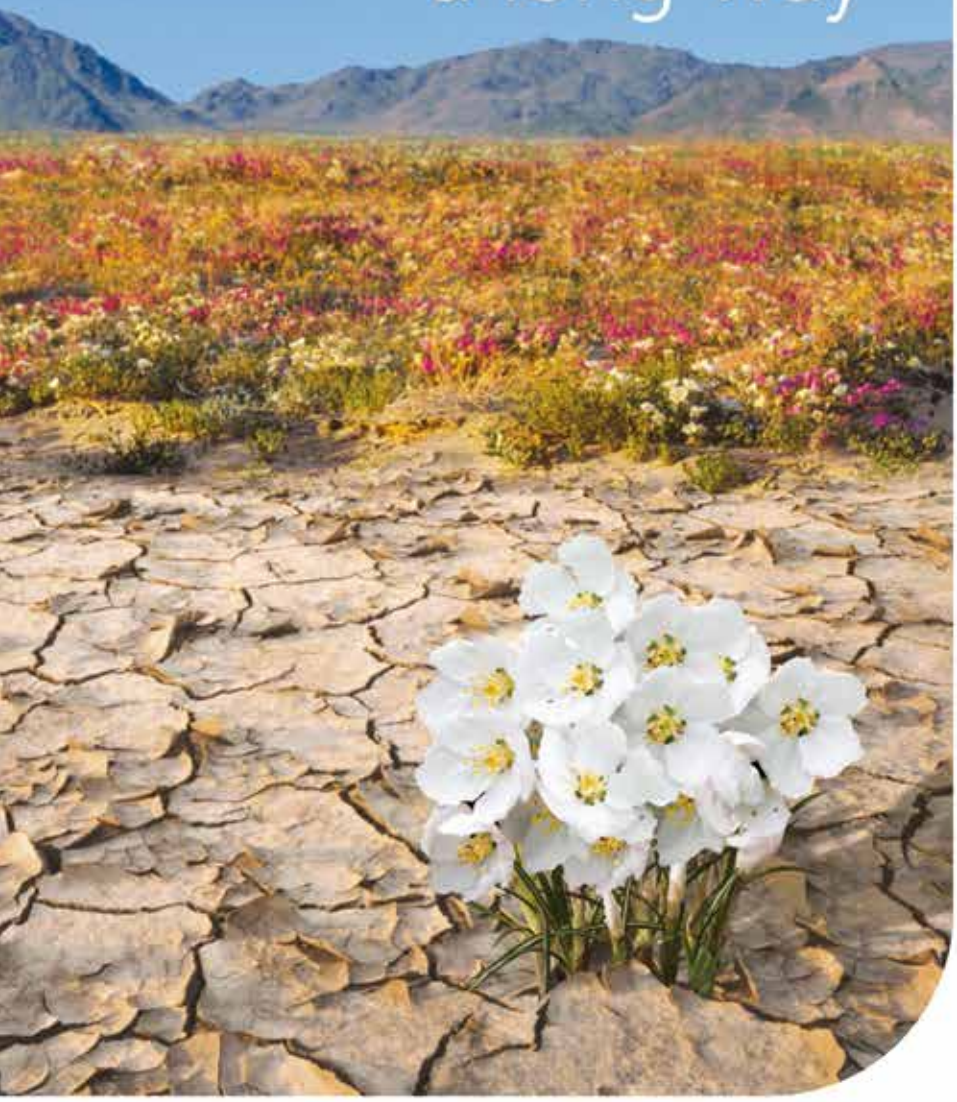

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Each tablet contains estradiol hemihydrate equivalent to 10 micrograms of estradiol.

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Reference:

1. Simon J et al. *Obstet Gynecol* 2008;112(5):1053-1060.

2. Vagifem 10µg Summary of Product Characteristics.

3. Rioux JE et al. *Menopause* 2000;7(3):156-161.

4. Dugal R et al. *Acta Obstet Gynecol Scand* 2000;79:293-297.

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Books edited by other authors of the article

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

Books edited by author

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

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Editorial

Obstetrics and gynaecology training in Hong Kong: where are we?

The last major update of the curriculum of Hong Kong College of Obstetricians and Gynaecologists (HKCOG) was in 2008. This curriculum has served us well; we have produced good specialists year after year; we should be proud of our training system. Why should we change it?

As discussed in an editorial of the *Hong Kong Journal of Gynaecology, Obstetrics and Midwifery* in 2020[1], the latest curriculum of the Royal College of Obstetricians and Gynaecologists (RCOG) adopts the concept of capabilities in practice under four professional identities to enable holistic development of the trainee. We used to believe that trainees should develop holistic qualities naturally during their medical career with accumulation of experience. Nonetheless, it is a good idea to emphasise these qualities early in the training to ensure all four professional identities are adequately achieved.

Over the past 13 years, obstetrics and gynaecology services have changed a lot. As interventional radiological techniques become more popular and the need for minimally invasive endoscopic surgery increases, fewer conventional laparotomies are performed. Indications for surgery has decreased, as better medical treatment options are available. The public expects better quality of service and communication with physicians. The advanced maternal age and the ageing population have led to a decrease in delivery rates but a significant increase in demand for assisted reproduction, urogynaecology, and gynaecological oncology services. Therefore, training needs to cover new techniques and knowledge of these trends and at the same time make up for the decreasing training experience in conventional procedures. For technical skills training, we should shift our emphasis from requiring trainees to fulfil a target number of cases to competence base training and skills assessment. Rotation in different specialised training centres, simulation training, and workplace-based assessment (WBA) can help to solve part of these problems.

The Hong Kong Academy of Medicine (HKAM) has promoted WBA for 2 years and has run several rounds of train-the-trainer workshop. WBA is a more realistic assessment of performance and can be used as a summative assessment to certify competence. It can also be used as a formative assessment for ongoing training. The HKCOG is one of the earliest colleges to adopt WBA as an integral part of specialty training, using objective structured assessment of technical skills for summative purposes. Its subspecialty training programmes use mini clinical evaluation exercise and case-based discussion as formative assessment tools. Trainees are required to complete a minimal number of mini clinical evaluation exercise and case-based discussion within a training period.

There are concerns about incorporating more WBA into our curriculum such as time and manpower constraints, appropriateness of the debriefing style for Hong Kong trainees and trainers, and reluctancy of trainers to explicitly record the deficiencies of trainees. However, the Hong Kong College of Anaethesiologists has successfully adopted formative WBA into its specialty training for years. The principles of debriefing have been well accepted in crew resources management courses and advance life support courses. Trainees understand that deficiencies exist during learning, and improvements should promptly be made when WBA is used as a formative assessment tool to help identify their deficiencies.

High-fidelity scenario-based simulation training is increasingly popular in courses attended by our trainees including the intensive peri-operative care course and the advance life support in obstetrics course. Unfortunately, the present curriculum does not include any specific simulation training modules. The requirement for technical resources and mandatory retraining at regular intervals make integration of high-fidelity simulation training into our curriculum difficult.

The use of electronic platform in medical training is another breakthrough. The e-portfolio of HKCOG was launched in July 2021. It helps trainees to log useful cases and acts as a one-stop centre for their application to the College. It facilitates trainers to follow the progress of trainees without lag time. It simplifies the logistic flow and connects different parties of the College (administrative support, trainers, and trainees) in one comprehensive platform. At present, only trainees recruited from July 2021

onwards use the e-portfolio. It still needs to be fine-tuned, and feedbacks and comments from users at all levels are welcomed.

During the Covid-19 pandemic, the use of online webinar becomes a new normal for didactic teaching and scientific seminars and conferences. The HKAM has received government funding for development of a learning management system to help implementation of e-learning in colleges. Apart from regular online continuing medical education multiple choice question exercises and ad hoc webinars, our College has not established any comprehensive e-learning programmes. Although our trainees are granted access to the extensive RCOG eLearning modules and materials, some contents may not be applicable to Hong Kong. The development of local learning management system can benefit both trainees and specialists. We should determine what we need and make good use of the technology. Should we be complacent, reminiscing previous achievements and feeling at ease in the next 5 years? Or should we take up the challenges, striving to define future directions and catching up with the others?

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Reference

1. Chan DLW. Editorial: Recent changes in the Royal College of Obstetricians and Gynaecologists core curriculum. Hong Kong J Gynaecol Obstet Midwifery 2020;20:60-1. Crossref

Hong Kong J Gynaecol Obstet Midwifery 2022;22(1):9-15 | https://doi.org/10.12809/hkjgom.22.1.02

Second-tier non-invasive prenatal screening for Down syndrome in a public obstetric unit: the first 12 months

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Objective: To review the uptake rate of non-invasive prenatal testing (NIPT) in the first 12 months of implementation in the obstetric unit of United Christian Hospital.
Methods: Between December 2019 and November 2020, women with a fetal Down syndrome (DS) risk ratio of ≥1:250 after first-trimester DS screening (using maternal serum markers and nuchal translucency thickness on ultrasonography) or second-trimester DS screening (using maternal serum markers) were offered free-of-charge second-tier NIPT or invasive testing. Results of NIPT and invasive testing and pregnancy outcome of these women were reviewed. Characteristics of those opting for NIPT versus invasive testing were compared. Univariate and logistic regression analyses were used to determine significant factors associated with opting for NIPT.
Results: During the study period, 2182 women underwent first-trimester DS screening (n=2086) or second-trimester DS screening (n=96). 117 women were screen positive, with a DS risk ratio of <1:250. The screen-positive rate was 5.36% overall and 5.23% for first trimester and 8.33% for second trimester. Of the 117 women, 26 had NIPT in private settings before or after being screened positive, 89 opted for NIPT (n=65) or invasive testing (n=24) in our hospital, and two did not have further testing owing to spontaneous miscarriage (n=1) or termination of pregnancy (n=1). Of 91 women with NIPT, 84 (92.3%) were at low risk for common aneuploidies, four were at high risk for T21 (n=2) or T18 (n=2), and three had abnormalities other than common aneuploidies. Six of the high-risk women underwent invasive testing and abnormalities were confirmed. Of the 24 women who opted for invasive testing, 14 had normal results and 10 had abnormal results. In logistic regression analysis, predictors for opting for invasive testing (rather than NIPT) were presence of abnormalities on ultrasonography (odds ratio (OR)=13.9, p=0.01), a nuchal translucency thickness of ≥3 mm (OR=7.62, p=0.01), and education level below tertiary level (OR=7.14, p=0.02).
Conclusion: In the first 12 months of implementation in United Christian Hospital, the uptake rate of NIPT as a second-tier test after positive DS screening was 77.8%, which is higher than that reported in previous studies when NIPT was a self-financed test.

Keywords: Down syndrome; Noninvasive prenatal testing

Introduction

Down syndrome (DS), or trisomy 21 (T21), is one of the few autosomal trisomies that allow continued fetal development and livebirth with prolonged survival, despite causing significant physical and neurodevelopmental delays and disabilities. In Hong Kong, prenatal screening and diagnosis of DS has evolved from direct invasive testing for all women with advanced maternal age to second-trimester DS screening (using maternal serum markers) and then to first-trimester DS screening (using both maternal serum markers and nuchal translucency thickness on ultrasonography). Since 2010, universal DS screening has been offered in all public obstetric units in Hong Kong[1].

Non-invasive prenatal testing (NIPT) for DS has a detection rate of 99.2% and a false-positive rate of 0.09%, which are better than the respective rates of 90% and 3.4% to 5.4% by first-trimester DS screening (using both maternal serum markers and nuchal translucency thickness on ultrasonography)[2-5]. NIPT reduces the need for invasive prenatal diagnostic tests, including chorionic villus sampling and amniocentesis, which carry a procedure risk of miscarriage of 0.1% to 0.2%6. However, NIPT is not a diagnostic test, as it occasionally gives non-reportable or false positive results[7]. A positive result requires confirmation by direct invasive testing[8,9]. Chromosomal aberrations other than the common aneuploidies may not be detected by NIPT that does not target these abnormalities[8,10].

In 2011, NIPT was first available in Hong Kong as a self-financed examination[11]. In the last quarter of

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2019, NIPT was implemented in all public obstetric units as a formal second-tier test for women with positive conventional DS screening, with an objective to reduce the need for invasive testing rather than to boaster the detection rate for DS. We review the uptake rate of NIPT in the first 12 months of implementation in the obstetric unit of United Christian Hospital.

Methods

This study was conducted at an obstetrics unit of United Christian Hospital, which manages 3500 deliveries per year. Between December 2019 and November 2020, women with <14 weeks gestation at booking were offered first-trimester DS screening, which includes ultrasonographic measurements of crown-rump length and nuchal translucency thickness, as well as assays of maternal serum markers of pregnancy-associated plasma protein A and free beta human chorionic gonadotrophin. Women with gestation between 14 and 19 weeks 6 days were offered second-trimester DS screening, which includes assays of maternal serum markers of serum alpha fetal protein, oestriol, inhibin A, and free beta human chorionic gonadotrophin. Those with a fetal DS risk ratio of ≥1:250 were considered screen positive and were offered second-tier NIPT, which is based on massive parallel sequencing techniques to detect common aneuploidies. Fetal sex is not routinely reported, but significant sex chromosomal aberrations, chromosomal duplications or deletions are reported selectively according to the discretion of the laboratory.

Within 1 week of results available, screen-positive women were invited by a designated midwife to attend a consultation regarding the risk ratio for DS, screen positivity for other aneuploidies such as trisomy 18 (T18) and trisomy 13 (T13), nuchal translucency thickness, and implications of having a baby with DS. The option of either NIPT or invasive testing (chorionic villus sampling or amniocentesis) was offered. The turn-around time for the former is <10 days and for the latter is <3 weeks. For invasive testing, quantitative fluorescent polymerase chain reaction (to exclude common aneuploidies) was used, followed by chromosomal microarray and/or karyotyping. The procedure-related miscarriage risk for chorionic villus sampling was 1% and for amniocentesis was 0.1% to 0.5%[6,11,12]. All screen-positive women were offered a detailed morphology scan at 20 weeks to exclude fetal structural abnormalities unless the NIPT or invasive testing already confirmed specific pathology.

Demographic data of all screen-positive women were retrieved from the Hospital Authority electronic database platforms, including the Antenatal Record System, the Specialty Clinical Information System, and the Clinical Management System, as well as from hardcopy records. In univariate analysis, characteristics of those opting for NIPT versus invasive testing were compared using the Chi-square test. Significant factors identified in univariate analysis were evaluated using the logistic regression analysis, with either NIPT or invasive testing as the dependent variable. A two tailed p value of <0.05 was considered statistically significant. SPSS (Windows Version 26, IBM Corp, Armonk, US) was used for statistical analysis.

Results

There were 2378 new antenatal bookings during the study period. Of 2268 eligible for DS screening, 86 opted out and were excluded and the remaining 2182 underwent first-trimester DS screening (n=2086, 92%) or second-trimester DS screening (n=96, 8%).

117 women were screen positive, with a DS risk ratio of <1:250. The screen-positive rate was 5.36% overall and 5.23% for first trimester and 8.33% for second trimester. Of the 117 women, 26 reported to have already had NIPT in private settings, 89 opted for NIPT (n=65) or invasive testing (n=24) in our hospital, and two opted out for further testing owing to spontaneous miscarriage (n=1) or termination of pregnancy after screen results showing nuchal translucency thickness of 5.1 mm and a DS risk ratio of 1:2 (n=1). Of 91 women with NIPT, 84 (92.3%) were at low risk for common aneuploidies, four were at high risk for T21 (n=2) or T18 (n=2), and three had abnormalities other than common aneuploidies (Figure). Among the seven women at high risk of abnormality, one woman at high risk for T18 underwent termination of pregnancy in a private hospital at 16 weeks after ultrasonography showed that the fetus had an omphalocoele and likely major congenital heart defects, and the remaining six women underwent invasive testing and were confirmed to have T21 (n=2), T18 (n=1), and other chromosomal aberrations (n=3). All six women underwent termination of pregnancy. One patient had a DS risk ratio of 1:15 but had a normal NIPT result in a private hospital. She insisted on undergoing amniocentesis at 16 weeks that showed a normal karyotype. Pregnancy outcomes of the 117 women are shown in Table 1.

Of the 24 women who opted for invasive testing, 14 underwent chorionic villus sampling and 10 underwent amniocentesis. Results were normal in 14 (58.3%) women. The remaining 10 women had T21 (n=2), T18 (n=4), T13 (n=1), other chromosomal aberrations (n=1), severe fetal

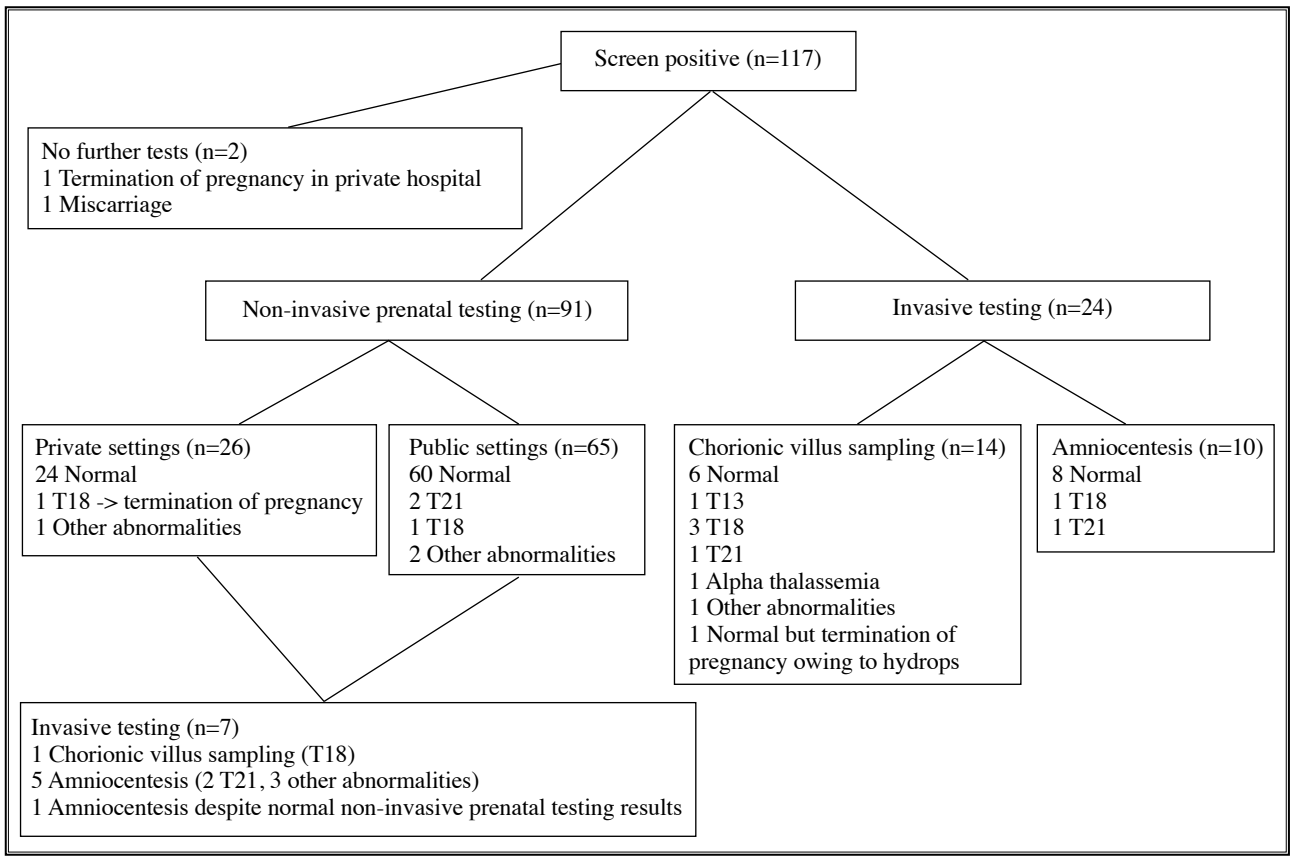

Figure. Flowchart of outcomes for 117 women with positive Down syndrome screening

Table 1. Pregnancy outcomes of 117 women

Pregnancy outcome	No. of women	Remarks
Term livebirths	96	-
Preterm livebirth	1	-
Spontaneous miscarriages	2	One had spontaneous miscarriage before any further testing One had normal non-invasive prenatal testing (NIPT) results
Termination of pregnancy	18	-
Chromosomal aberrations not detected	1	Ultrasonography showed fetal hydrops
No chromosomal microarray / karyotyping performed	2	One had Down syndrome risk and 1:2 cystic hygroma One had non-invasive prenatal testing (NIPT) showing high risk for T18
Chromosomal aberrations detected		
Trisomy 21	4	-
Trisomy 18	5	-
Trisomy 13	1	-
Alpha thalassemia major	1	-
Other chromosomal aberrations	4	46XY with 1.72 Mb copy loss in 2q13 (NIPT in private settings showed no abnormalities) 46,XX,der(18)ins(18;6)(q12;q15q22) [NIPT in private settings suspected 6q15-6q22.31 dup (31.39 Mbp); CMA of amniotic fluid sample showed 6q15q22.31x3] 46XX with 19.38Mb copy loss in 5p15.33-p14.3 (NIPT in public settings suspected copy number loss in chr5q15.3) 46 XY with interstitial deletion of 21.97 Mb in 21q11.2q22 (direct invasive testing with no NIPT performed)

Table 2. Characteristics of screen-positive women who opted for non-invasive prenatal testing or invasive testing

Characteristics	No further testing (n=2)	Non-invasive prenatal testing (n=91)	Invasive testing (n=24)	p Value
Ethnicity				0.87
Chinese	2	86 (94.5)	23 (95.8)	
Filipino	-	4 (4.4)	1 (4.2)	
Others	-	1 (0.1)	-	
Advanced maternal age ≥35 years	1	29 (31.9)	13 (54.2)	0.04
Education				0.001
Primary	-	-	5 (20.8)	
Secondary	-	42 (46.1)	12 (50)	
Tertiary	2	49 (53.9)	7 (29)	
Monthly family income, HK$				0.18
<20 000	-	16 (17.5)	5 (20.8)	
20 000-40 000	2	24 (26.3)	11 (45.8)	
40 000-60 000	-	34 (37.3)	5 (20.8)	
≥60 000	-	17 (18.6)	3 (12.5)	
Family history of abnormal babies or genetic disorders	-	-	-	-
Conception by assisted reproductive procedures	-	1 (1)	-	0.91
Parity				0.53
Nulliparous	1	29 (31.8)	8 (33.3)	
Multiparous	1	62 (68.2)	16 (66.7)	
Down syndrome screening				0.47
First trimester	2	84 (92.3)	23 (95.8)	
Second trimester	-	7 (7.7)	1 (4.2)	
Screen results				0.001
Positive for T21	2	85 (93.4)	16 (66.6)	
Positive for T18	-	2 (2.2)	4 (16.7)	
Positive for T21 and T18	-	4 (4.4)	4 (16.7)	
Down syndrome risk ratio		n=89	n=20	0.044
1:1-9	1	7 (7.9)	3 (15)	
1:10-100	-	28 (31.5)	11 (55)	
1:101-250	1	54 (60.6)	6 (30)	
Nuchal translucency thickness, mm		n=84	n=23	0.001
<3	1	73 (86.9)	11 (47.8)	
3-3.4	-	4 (4.8)	2 (8.7)	
≥3.5	1	7 (8.3)	10 (43.5)	
Presence of abnormalities on ultrasonography	1	7 (7.69)	6 (25)	0.028

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

hydrops (n=1) [together with a T21 risk ratio of 1:65 and a T18 risk ratio of 1:15 despite no chromosomal aberrations], or alpha thalassemia (n=1) [together with a nuchal translucency thickness of 3.9 mm, a DS risk ratio of 1:3, and known history of alpha thalassemia from previous pregnancies]. All 10 women underwent termination of pregnancy. One woman with a DS risk ratio of 1:65 but a normal NIPT had spontaneous miscarriage at 16 weeks.

In univariate analysis, compared with those who opted for NIPT, those who opted for invasive testing were more likely to have advanced maternal age (>35 years) [54.2% vs 31.9%, p=0.04], less likely to have tertiary education (29% vs 53.9%, p=0.001), more likely to be screen positive for T18 or both T21 and T18 (33.4% vs 6.6%, p=0.001), more likely to have a DS risk ratio of ≤1:100 (70% vs 39.4%, p=0.044), more likely to have a nuchal translucency thickness ≥3 mm (52.2% vs 13.1%, p=0.001), and more likely to have structural abnormalities detected on ultrasonography such as cystic hygroma, fetal hydrops, omphalocoele, congenital heart defects, single umbilical artery, suspected polydactyly, and fetal renal pelvic dilatation (25% vs 7.7%, p=0.028) [Table 2].

In logistic regression analysis, predictors for opting for invasive testing (rather than NIPT) were presence of abnormalities on ultrasonography (odds ratio (OR)=13.9, p=0.01), a nuchal translucency thickness of ≥3 mm (OR=7.62, p=0.01), and education level below tertiary level (OR=7.14, p=0.02) [Table 3].

Discussion

In the first 12 months of implementation of the free-of-charge second-tier NIPT in our obstetric unit, 77.8% of women with a positive conventional DS screening result opted for NIPT rather than invasive testing. The detection rate of DS and common aneuploidies by NIPT was 100%, with no false positives. There were no non-reportable cases from the Hospital Authority NIPT programme.

In a Hong Kong study in 2011-2012, the uptake rate of NIPT increased from 12.6% to 26.7% in the first 2 years as a self-financed test in public hospitals, whereas that of invasive testing decreased by 16.3% in the first year and by 25.6% in the second year[12]. In a study conducted from 2012-2013, the availability of NIPT after screen-positive for DS resulted in a 45% decrease in refusal to further testing and a decrease of invasive testing from 92.2% to 66.7%. Nevertheless, the overall uptake rate for NIPT was only 28.9% (362/1251)[13,14]. In 2014, when NIPT remained a self-financed item, 57.8% of women opted for NIPT as a second-tier test after screen positive, compared with 30.4% opting for NIPT as a primary screening test[14]. In 2015-2016, the uptake of NIPT in women with positive DS screening increased to 67%, whereas 31% opted for invasive testing and 2% had no further testing[11]. In 2015-2016, when NIPT was offered free-of-charge under a university research protocol, among 347 women with positive DS screening, 62.2% opted for NIPT and 37% opted for invasive testing with chromosomal microarray[15]. The NIPT uptake rate was not higher than that reported in previous studies despite similar costs and reporting time between options. In a study in the same period under similar settings, the NIPT uptake rate was 79% (207/262), with 31 women defaulted[16]. Financial arrangement affects the NIPT uptake rate in various settings in different counties[17-19]. In the present study, the NIPT uptake rate was 77.8%, but 28.6% of the NIPT were performed in private settings as a self-financed test although NIPT was offered free-of-charge in public hospitals. In 16 women, NIPT was performed in private settings as primary screening in parallel to the DS screening in our hospital. This highlights the preference of NIPT as the primary screening tool in some women. One study reported that 19.9% of women with positive DS screening already had a self-financed NIPT before taking DS screening test in public hospitals[15]. In the present study, 8.8% (8/91) of women did not wait for the consultation appointment and underwent further testing in private settings. Such behaviour underlines the high anxiety in decision making when informed of positive DS screening results[16,20]. In addition, private hospitals provide extended NIPT panels to identify sex chromosomes and atypical autosomal anomalies, in particular sex chromosome aberrations[8,21]. Currently, the NIPT in public settings do not report fetal sex, although major sex chromosomal aberrations are reported at the discretion of the laboratory. In a study of 260 women with NIPT, higher education level and higher NIPT knowledge score are associated with a preference for the extended NIPT report to the standard report[22]. In the present study, NIPT revealed one case of rare chromosomal aberration, which was confirmed by chromosomal microarray. The performance of the current NIPT in public settings is on par with international standards. Recent data have shown that the positive predictive values for detecting copy number variants, sex chromosomal aneuploidies, and selected microdeletions and duplications are around 60%, 40%, and 50%, respectively. These indicate a good scientific basis for expanded NIPT panels[23,24]. The option of revealing fetal sex could be added to enhance the current NIPT programme.

Although tertiary education and better NIPT knowledge are associated with NIPT uptake, only higher income is the independent predictor for NIPT uptake[25]. In addition, opting for NIPT are associated with nulliparity, first trimester status, advanced education, maternal employment, and conception by assisted reproductive techniques[11]. In North America during the early years of NIPT, NIPT was chosen by 43% of women who had a positive DS screening, 43% of women who had an ultrasonographic marker, and 36% of women who had an ultrasonographic abnormality[26]. NIPT is more likely to be chosen when

Table 3. Logistic regression analysis for predictors of opting for invasive testing over non-invasive prenatal testing

Variable	B	Standard error	Wald	P value	Odds ratio (95% confidence interval)
Presence of abnormalities on ultrasonography	2.63	1.07	6.07	0.01	13.9 (1.71-113.6)
Thick nuchal translucency ≥3 mm	2.03	0.784	6.70	0.01	7.62 (1.64-35.42)
Education level below tertiary level	-1.976	0.833	5.62	0.02	7.14 (1.41 -37.03)
Advanced maternal age ≥35 years	-0.156	0.608	0.07	0.79	1.17 (0.35 -3.84)
T18 risk positive (alone or combined with T21 positive)	0.004	0.001	0.17	0.68	1.01 (0.99-1.0)
T21 risk ratio >1:10	0.539	0.463	1.36	0.24	1.71 (0.69-4.24)

women perceive NIPT is widespread and routine, forward-thinking, and anxiety-relieving[27]. Our findings showed that NIPT was more likely to be chosen by women with more advanced education, which was consistent with previous local studies. Women with a higher knowledge score understand more about advantages and complicated issues of NIPT[14,22]. Nonetheless, the presence of ultrasonographic abnormalities or a thick nuchal translucency leads women to opt for invasive testing. This reflects the concerns of the women and the effects of counselling, as further invasive testing is indicated even if NIPT results are normal.

Fetal nuchal translucency of ≥3.5 mm is an indication for invasive testing by chromosomal microarray. However, in 522 fetuses with nuchal translucency thickness of 3.0 to 3.4 mm, up to 13.5% have a chromosomal aberration. Of them, 69% involve T21, T18, or T13, which are potentially detectable by NIPT. The residual risk for missing a (sub) microscopic chromosome aberration depends on the NIPT approach, ranging from 1:21 (for NIPT to detect only the common aneuploidies) to 1:464 (for genome-wide 10-Mb resolution NIPT). Thus, the nuchal translucency thickness cut-off for invasive testing should be 3.0 mm rather than 3.5 mm28. In public settings, diagnosis may be delayed because all abnormal NIPT results need to be confirmed by invasive testing. Thus, women should be allowed to opt for invasive testing earlier when nuchal translucency thickness is ≥3 mm.

There are some limitations to this study. The sample size is relatively small. Cumulative data from all public obstetric units should have included to better evaluate of the NIPT uptake in Hong Kong. Some women were not aware of the availability of free NIPT as a second-tier test at the time of booking and thus arranged NIPT in a private clinic. It is expected that the acceptance and uptake rates of NIPT will continue to rise. Further evaluation of NIPT uptake is warranted.

Conclusion

In the first 12 months of implementation in United Christian Hospital, the uptake rate of NIPT as a second-tier test after positive DS screening was 77.8%, which is higher than that reported in previous studies when NIPT was a self-financed test.

Contributors

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

Conflicts of interest

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

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Data availability

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

Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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Efficacy and safety of intravenous iron isomaltoside in postpartum anaemia

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Background: Postpartum anaemia adversely affects maternal mood, cognition, and maternal-infant interactions. Intravenous iron isomaltoside is effective and safe for non-pregnant patients with iron deficiency anaemia, but data on its use in Hong Kong women during peripartum period are limited. This study aims to determine the effectiveness and safety of iron isomaltoside (Monofer) in women with postpartum haemorrhage or anaemic symptoms.
Methods: Records of women who received iron isomaltoside (Monofer) when haemoglobin (Hb) level was <7g/dL (or ≥7g/dL when concomitant with anaemic symptoms) irrespective of mode of delivery between April 2018 and March 2021 were reviewed. Primary outcome measures included response to iron isomaltoside treatment (measured by pre- and post-treatment Hb levels), resolution of anaemic symptoms, and the number and types of adverse reactions related to treatment. Secondary outcome measures included associations between patient characteristics and Hb response.
Results: 126 women were included for analysis. Most were nulliparous, delivered vaginally, and had minor postpartum haemorrhage. Most had a baseline Hb level of <10.0 (mean, 7.36) g/dL, but only 53.2% of them had anaemic symptoms. No women experienced serious adverse events. Only four (3.2%) women had mild adverse events of rash (n=3) or pruritis (n=1). At the 6-week follow-up, the mean Hb level increased 4.39 g/dL to 11.8 g/dL (p<0.001), with only one woman reporting anaemic symptoms. 12 (9.5%) of 126 women had some form of haemoglobinopathy (usually thalassemia trait) and had lower Hb levels even before pregnancy. Compared with women with normal Hb pattern, women with haemoglobinopathy had lower post-treatment Hb responses (p=0.001). Hb response was positively associated with delivery blood loss (r=0.188) and negatively associated with baseline Hb level (r= -0.279).
Conclusion: Iron isomaltoside (Monofer) is effective and safe for postpartum anaemia. It enables rapid improvement in Hb level and anaemic symptoms, even for those with haemoglobinopathy.

Keywords: Anemia, iron deficiency; Iron isomaltoside 1000

Background

Iron deficiency anaemia is common among pregnant women worldwide, with a prevalence of 41.8% in various degrees[1]. Anaemia in pregnancy is a risk factor for postpartum anaemia[2], and therefore minimising anaemia before delivery is recommended[3]. However, peripartum blood loss may not be preventable[4], and postpartum anaemia remains common, with a prevalence of 22.3% to 22.7%, even in developed regions[5,6]. Postpartum anaemia adversely affects maternal mood, cognition, behaviour, maternal-infant interactions, and postpartum depression[7].

Parenteral/intravenous and oral iron supplementation can improve anaemic symptoms, maternal-infant bonding, and postpartum depression[8-11]. However, intravenous iron agents are associated with serious adverse drug events and should be used with caution[12]. Nonetheless, the newer agents have an estimated incidence of serious adverse drug events of <1 in 200 000[13,14].

Oral iron supplementation is limited by gastrointestinal adverse effects, with an incidence up to 32%[15]. The rate of absorption is low, as the iron transport system can become saturated[16]. In contrast, intravenous iron supplementation markedly reduces gastrointestinal symptoms and does not require long-term dosing[17], resulting in higher compliance to therapy. It reduces the need for transfusions and hence blood- and transfusion-related risks. Experiences with gynaecology patients in Hong Kong have been encouraging[18,19].

The third-generation intravenous iron formulations such as iron isomaltoside (Monofer) minimise labile iron release and hence toxicity[20] and have more complex shells to diminish adverse reactions[21]. This enables single-dose repletion and reduces the risk of adverse drug events[22]. Iron isomaltoside (Monofer) is appropriate for postpartum women after discharge from the maternity unit[23]. However,

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data on its use during antepartum and postpartum periods are limited.

Methods

This study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECREC-2021-062). A retrospective cross-sectional study was conducted in an obstetrics unit with around 2000 deliveries a year and an estimated prevalence of postpartum anaemia of 23%. Records of women who received iron isomaltoside (Monofer) between April 2018 and March 2021 were reviewed. Those who were lost to follow-up or those who received blood transfusion after having received iron isomaltoside were excluded.

Women complicated by postpartum haemorrhage (blood loss >500 mL) or anaemic symptoms irrespective of mode of delivery were assessed for complete blood count on day 2 post-delivery. Iron isomaltoside was offered when haemoglobin (Hb) level was <7g/dL (or ≥7g/dL when concomitant with anaemic symptoms). Blood transfusion was reserved for those with haemodynamic instability. Dosage was standardised as per hospital pharmacy guideline (500 mg for body weight <50 kg, 1000 mg for body weight ≥50 kg). Hb level was checked 4 weeks later to determine the need for further iron repletion.

Vital signs were charted before iron isomaltoside infusion and every 15 minutes during infusion and an hour afterwards. In addition to self-reporting by patients, nurses regularly enquired about adverse or hypersensitivity reactions. Any suspected reactions were managed in accordance with the international guidance[24]. Anaemic symptoms (shortness of breath, palpitation, fatigue, and weakness) were documented before and after infusion and at 6-week follow-up examination.

Primary outcome measures included response to iron isomaltoside treatment (measured by pre- and post-treatment Hb levels), resolution of anaemic symptoms, and the number and types of adverse reactions related to treatment. Secondary outcome measures included associations between patient characteristics and Hb response.

Statistical analysis was performed using SPSS (Windows version 27; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant. Hb levels and anaemic symptoms before and after treatment were compared using the paired-sample t-test. Continuous variables were analysed using linear regression, and discrete variables were analysed using analysis of variance.

Results

There were 6320 deliveries during the study period. 1454 women were estimated to have any degree of postpartum anaemia. Of 150 women who received iron isomaltoside, 11 were lost to follow-up, 13 received blood transfusion after having received iron isomaltoside (mostly owing to tachycardia or hemodynamic instability), and the remaining 126 were included for analysis. Most patients were of Chinese ethnicity, nulliparous, delivered vaginally, and had minor postpartum haemorrhage (Table 1). 15.9% of women received blood transfusion immediately postpartum owing to postpartum haemorrhage; their post-transfusion Hb levels were taken as the baseline Hb levels. In most women, the baseline Hb level were <10.0 (mean, 7.36) g/dL, but only 53.2% of them had anaemic symptoms such as dizziness, shortness of breath, and palpitations.

No women experienced serious adverse events. Only four (3.2%) women had mild adverse events of rash (n=3) or pruritis (n=1). One woman had generalised rash, which resolved with intravenous hydrocortisone. Two women had localised rashes, which subsided spontaneously or after the use of antihistamines. One woman had facial pruritis, which subsided spontaneously.

At the 6-week follow-up, the mean Hb level increased 4.39g/dL to 11.8 g/dL (p<0.001), with only one woman reporting anaemic symptoms (Table 2). 12 (9.5%) of 126 women had some form of haemoglobinopathy (usually thalassemia trait) and had lower Hb levels even before pregnancy. Compared with women with normal Hb pattern, women with haemoglobinopathy had lower post-treatment Hb responses (p=0.001). Hb response was positively associated with delivery blood loss (r=0.188) and negatively associated with baseline Hb level (r= -0.279).

Discussion

The safety profile of iron isomaltoside (Monofer) is good for non-pregnant individuals, with serious adverse drug event rates of 0.3%[25,26] to 0.9%[27], in line with other contemporary intravenous iron formulations[28]. However, mild reactions (particularly infusion site reactions) are not uncommon[29], with rates of 3.3%[30] to 14%[31]. Likewise, the safety profile of new intravenous iron formulations for pregnant women is also good[32], but mild reactions are also not uncommon. In pregnant women who received iron isomaltoside (Monofer), 4.7% developed mild hypersensitivity, which abated spontaneously, and none

Table 1. Characteristics of 126 women who received iron isomaltoside (Monofer)

Characteristic	Value*	p Value
Age, y	33.0±4.4	0.486
Parity	0.33±0.57	0.354
Mode of delivery		0.379
Normal spontaneous delivery	65 (51.1)	
Instrumental	36 (28.6)	
Caesarean section	25 (19.8)	
Ethnicity		0.194
Chinese	111 (8.1)	
Other Asian	13 (10.3)	
Caucasian	2 (1.6)	
Haemoglobinopathy†	12 (9.5)	0.001 (η=0.281/η^2=0.079)
Body mass index, kg/m^2	22.3±3.1	0.948
Delivery blood loss, mL	650±318	0.035 (r=0.188/R^2=0.027)
Transfusion	20 (15.9)	0.522
Baseline haemoglobin, g/dL	7.36±0.61	0.002 (r= -0.279/R^2=0.078)
Baseline mean corpuscular volume, unit	81.2±12.0	0.059
Anaemic symptoms	67 (53.2)	0.888

* Data are presented as mean±standard deviation or No. (%) of participants
† Alpha thal trait (n=4), beta thal trait (n=6), and others (n=2)

Table 2. Haemoglobin level and anaemic symptoms before and after iron isomaltoside infusion in 126 women

	Baseline	6-week follow-up	Change	p Value
No. (%) of women with anaemic symptoms	67 (53.2)	1 (0.8)	-66 (-52.4)	<0.001
Mean haemoglobin level, g/dL				
All women (n=126)	7.36	11.76	+4.39 (4.22-4.57)	<0.001
Women with normal haemoglobin pattern (n=114)	7.37	11.85	+4.48 (4.30-4.66)	<0.001
Women with haemoglobinopathy (n=12)	7.34	10.88	+3.53 (2.90-4.17)	<0.001

had severe reactions or anaphylaxis[33]. In Danish postpartum women, iron isomaltoside (Monofer) was well tolerated, with a mild adverse drug event rate of 13.3%, mostly related to infusion site[34]. Our findings are in line with those of the literature.

Intravenous iron supplementation is effective for iron deficiency anaemia, with Hb responses of 1.6 to 3.2 g/dL in non-pregnant patients[35]. Similarly, intravenous iron supplementation results in superior and faster Hb responses for women with postpartum anaemia[36-38]. Intravenous iron supplementation can reduce[39] or even prevent[40] blood transfusion in postpartum women. Iron isomaltoside (Monofer) enables faster Hb recovery and reduced fatigue, compared with oral iron supplementation, in women with postpartum haemorrhage[35].

In the present study, 12 (9.5%) women had some form of haemoglobinopathy, consistent with the prevalence of thalassemia in Hong Kong[41]. In women with haemoglobinopathy, although Hb improvement was smaller, their Hb level after treatment (10.88 g/dL) was similar to that in their first trimester (10.56 g/dL). This suggests almost complete correction of their iron deficiency

anaemia. Hb response was associated with delivery blood loss and pre-treatment Hb level but not with the pre-treatment mean corpuscular volume. The normal mean corpuscular volume is likely due to elevated haematocrit level secondary to acute blood loss in postpartum anaemia[42,43].

There are limitations to this study. It lacks a control group of oral iron supplementation, which is the standard treatment. The sample size is relatively small and is from a single centre. The study design is retrospective. Nonetheless, the use of iron isomaltoside (Monofer) and management of adverse reactions are based on standardised protocols. The selection bias is small, as only 7.3% of women were lost to follow-up.

Conclusion

Iron isomaltoside (Monofer) is effective and safe for postpartum anaemia. It enables rapid improvement in Hb level and anaemic symptoms, even for those with haemoglobinopathy.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

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

Ethics approval

The study was approved by the Hong Kong East Cluster Research Ethics Committee (reference: HKECREC-2021-062). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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Responsiveness of Urogenital Distress Inventory-6 and Incontinence Impact Questionnaire-7 after pelvic floor muscle training and surgical treatment

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Introduction: Urinary incontinence (UI) and pelvic organ prolapse (POP) significantly impair quality of life (QoL). Pelvic floor muscle training (PFMT) is the first-line intervention. This study aims to evaluate the responsiveness of the Chinese version of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) after PFMT and surgical treatment in women with UI and/or POP.
Methods: Between April 2017 and December 2018, women who were referred to our urogynaecology clinic to undergo PFMT and/or surgery for UI and/or POP were recruited. They were instructed to perform three sets of pelvic floor muscle contractions per day. Women were followed up after 3 to 6 months. Women with moderate or severe urodynamic stress incontinence after PFMT were offered tension-free vaginal tape procedure. Women were asked to complete the UDI-6 for urinary symptoms and IIQ-7 for QoL before and after treatment. The responsiveness of UDI-6 and IIQ-7 were evaluated by effect size and standardised response mean.
Results: In 452 women who received PFMT, the most common diagnosis was UI (n=318, 70.4%), followed by POP (n=47, 10.4%), and concomitant UI and POP (n=87, 19.2%). 44 women underwent tension-free vaginal tape procedure after PFMT failed. After PFMT, the UDI-6 score improved from 38.9 to 29.4 (p<0.001) and the IIQ-7 score improved from 27.1 to 19.8 (p<0.001). After tension-free vaginal tape procedure, the UDI-6 score improved from 60.3 to 22.1 (p<0.001) and the IIQ-7 score improved from 39.1 to 8.1 (p<0.001). Responsiveness to change in scores of UDI-6 and IIQ-7 was moderate and small, respectively.
Conclusion: The UDI-6 and IIQ-7 are modestly responsive to change after PFMT and tension-free vaginal tape procedure in women with UI and/or POP.

Keywords: Pelvic organ prolapse; Quality of Life; Urinary incontinence

Introduction

Urinary incontinence (UI) and pelvic organ prolapse (POP) are common health problems among women worldwide. The prevalence of UI is about 25% to 45% among women aged ≥40 years[1]. Up to 50% of cases presenting to gynaecological clinics involve POP[2]. Both UI and POP impair quality of life (QoL) and physical and psychosocial wellbeing[3,4]. Compared with patients with chronic diseases (eg, heart failure and interstitial lung disease), women with UI have poorer QoL[4]. Pelvic floor muscle training (PFMT) is an effective first-line intervention to improve UI and POP symptoms and daily activities[5,6].

The International Continence Society Committee recommends the use of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) to assess the severity of UI and the impact of UI on QoL, respectively, and to complement clinical assessment[7]. Both UDI-6 and IIQ-7 are UI-specific psychometric questionnaires[8,9].

Assessment of the responsiveness is an important step in validating a questionnaire. The responsiveness of the long form of the two questionnaires has been reported in Caucasian women with UI following conservative or surgical treatment[10]. The Chinese versions of UDI-6 and IIQ-7 have been validated for clinical use[11]. However, their responsiveness has not been assessed. Thus, this study aims to evaluate the responsiveness of the Chinese version of UDI-6 and IIQ-7 after PFMT and/or tension-free vaginal tape procedure in women with UI and/or POP.

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Methods

This study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (reference: CRE-2015.125). Between April 2017 and December 2018, women who were referred to our urogynaecology clinic at Prince of Wales Hospital to undergo PFMT and/or surgery for UI and/or POP were recruited. Those who were mentally incapable or who declined PFMT were excluded. The attending gynaecologists then assessed the staging of POP and UI and determined the individual treatment plan.

Women were then referred to a continence advisor for PFMT. They were asked to complete the Chinese version of UDI-6 and IIQ-7. A research assistant was available for those who were illiterate and/or unable to complete the questionnaires. They were instructed to perform three sets of pelvic floor muscle contractions per day. Each set consists of ten cycles of contraction and relaxation of the pelvic floor muscles that last for 10 seconds each[12]. The continence advisor conducted vaginal examination to confirm their skills and strength in PFMT.

Women with mixed UI or those self-reported to have symptoms frequently and negatively impacted QoL were referred for urodynamic study, which includes uroflowmetry study and filling and voiding cystometry, using the Maquet Radius multi-channel urodynamic machine (Maquet GMBH, Germany). The procedure and the diagnoses were based on the recommendations of the International Continence Society[13]. Vaginal pessary was inserted in those with concomitant UI and POP. Urodynamic stress incontinence is defined as involuntary leakage of urine with increased intra-abdominal pressure in the absence of a detrusor contraction. Detrusor overactivity refers to the occurrence of detrusor contraction(s), either spontaneous or provoked, during filling cystometry, with or without urgency and/or urgency incontinence or perception of contraction. Voiding dysfunction is defined as abnormally slow and/or incomplete micturition, based on urine flow rates and/or post-void residuals[14].

Women were followed up after 3 to 6 months by continence advisors for urinary symptoms and PFMT techniques. Compliance with PFMT was reviewed. Women with moderate or severe urodynamic stress incontinence after PFMT were offered tension-free vaginal tape procedure. They were followed up at 2 months and then 1 year and were asked to complete UDI-6 and IIQ-7 again to assess the treatment outcome.

UDI-6 assesses the level of distress associated with lower urinary tract dysfunction. It consists of six items (frequent urination, leakage related to feeling of urgency, leakage related to activity, small amounts of leakage during coughing or sneezing, difficulty emptying the bladder, and pain or discomfort in the lower abdominal or genital area) under three subscales (irritative, stress, and obstructive symptoms). Scores of each item range from 0 to 3; total scores range from 0 to 18; higher scores indicate higher severity of symptoms. IIQ-7 evaluates the impact of UI on different aspects of QoL. It consists of seven items (household chores, physical recreation, entertainment activities, travel >30 min away from home, social activities, emotional health [nervousness, depression], and feeling frustrated) under four subscales (physical activity, travel, social activities, and emotional health). Scores of each item range from 0 to 3; total scores range from 0 to 21; higher scores indicate poorer QoL. The total and subscale scores of both questionnaires were transformed to a range between 0 and 100 by subtracting the lowest possible raw score and then divided by the possible raw score range. Higher scores of UDI-6 and IIQ-7 indicate more severity of urinary symptoms and poorer QoL, respectively.

Statistical analysis was conducted using SPSS (version 23.0 for Windows, IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistical significant. Pre- and post-treatment scores were compared using the paired sample t-test. The responsiveness of UDI-6 and IIQ-7 were evaluated by effect size and standardised response mean. Effect size was calculated as the mean change in scores divided by the standard deviation of the baseline score, whereas standardised response mean was the mean change in scores divided by the standard deviation of the change in scores. Effect size of 0.2 to <0.5 is defined as small, 0.5 to <0.8 as medium, and >0.8 as large[15,16]. The rate of compliance to PFMT was calculated using the formula: (number of set of contraction performed / expected set of contractions) × 100%. A rate of >80% was considered high, 20%-80% moderate, and <20% low[17].

Results

In 452 women who received PFMT, the most common diagnosis was UI (n=318, 70.4%), followed by POP (n=47, 10.4%), and concomitant UI and POP (n=87, 19.2%) [Table 1]. Among the 134 women with POP or concomitant UI and POP, 72 (53.7%) had stage-I POP, 55 (41%) had stage-II POP, and seven (5.3%) had stage-III or -IV POP. 35 (26.1%) of them received vaginal pessary and were followed up for a mean of 4.1±3.3 months.

Table 1. Baseline characteristics of participants

Characteristic	Whole sample (n=452)	Urinary incontinence alone (n=318)	Pelvic organ prolapse alone (n=47)	Concomitant urinary incontinence and pelvic organ prolapse (n=87)
Age, y	58.6±12.4	56.2±12.2	71±12.8	64±11.1
Parity	2 (0-9)	2 (0-8)	3 (1-5)	3 (0-9)
body mass index, kg/m^2	25.5±3.3	24.6±3.3	29.3±2.8	26.3±3.8
Pelvic organ prolapse staging				
No prolapse	318 (70.4)	-	-	-
Stage I	72 (15.9)	-	20 (42.6)	52 (59.8)
Stage II	55 (12.2)	-	23 (48.9)	32 (36.8)
Stage III	6 (1.3)	-	3 (6.4)	3 (3.4)
Stage IV	1 (0.2)	-	1 (2.1)	0 (0)
Follow-up duration, months	4.1±3.3	4.3±3.5	3.9±3.1	3.6±2.3
Compliance to pelvic floor muscle training				
High	4 (0.9)	47 (14.7)	0 (0)	0 (0)
Moderate	389 (86.0)	267 (84.0)	39 (83.3)	83 (95.2)
Low	59 (13.1)	4 (1.3)	8 (16.7)	4 (4.8)

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

The rate of compliance to PFMT was moderate in 86% of patients. 44 women (mean age, 52.6±8.9 years) who remained to have moderate or severe urodynamic stress incontinence after PFMT underwent tension-free vaginal tape procedure.

Both urinary symptoms and QoL improved after PFMT compared with baseline. The UDI-6 score for urinary symptoms improved from 38.9 to 29.4 ($p<0.001$), whereas the IIQ-7 score for QoL improved from 27.1 to 19.8 ($p<0.001$) [Table 2]. At baseline, urinary symptoms and QoL were better in women with POP alone than in those with UI and in those with concomitant UI and POP, but the improvement was greater in the latter two groups. Responsiveness to change in scores of UDI-6 and IIQ-7 was moderate and small, respectively.

Of 380 women who underwent urodynamic study, 138 (36.3%), 41 (10.8%), 17 (4.5%), and 5 (1.3%) were diagnosed with urodynamic stress incontinence, detrusor overactivity, mixed urodynamic stress incontinence and detrusor overactivity, and voiding dysfunction, respectively, and the remaining 179 (47.1%) had no abnormal urodynamic findings (Table 3). For UDI-6 score, effect size for all diagnosis groups was small (0.22 to 0.38), except for the mixed group, which was negligible (0.1). For IIQ-7 score, effect size was even smaller and more negligible (0.06 to 0.23).

After PFMT, the UDI-6 and IIQ-7 scores improved significantly in women with stage-I or -II POP but not in those with stage-III or -VI POP (Table 4). The responsiveness of UDI-6 and IIQ-7 was small among all women with POP. 35 (26.1%) of them received vaginal pessary. The effect size of UDI-6 was large (0.81) in women with vaginal pessary but was small (0.36) in women without, whereas the effect size of IIQ-7 was small in women with or without vaginal pessary (0.38 and 0.33, respectively) [Table 4].

In 44 women who underwent tension-free vaginal tape procedure after PFMT failed, the UDI-6 score improved from 60.3 to 22.1 ($p<0.001$) and the IIQ-7 score improved from 39.1 to 8.1 ($p<0.001$) [Table 5]. All subscale scores of both questionnaires improved significantly. The effect size of subscales of both questionnaires was small (0.0 to 0.44), except for the stress subscale of UDI-6, which was medium (0.67), whereas the responsiveness of subscales of both questionnaires was small to moderate.

Table 2. Change in scores of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) after pelvic floor muscle training (PFMT)

Scale	Pre-PFMT*	Post-PFMT*	Mean change in score*	Effect size	Standardised response mean	p Value
UDI-6						
Whole sample (n=452)						
Total score	38.9±19.8	29.4±18.2	-9.4±17.2	0.47	0.55	<0.001
Irritative	48.5±26.7	39.0±25.1	-9.4±24.9	0.35	0.38	<0.001
Stress	45.1±25.7	35.0±25.0	-10.1±23.6	0.39	0.43	<0.001
Obstructive	23.0±23.5	14.3±20.0	-8.6±22.0	0.37	0.39	<0.001
Urinary incontinence alone (n=318)						
Total score	41.2±19.4	31.2±18.0	-10.0±17.8	0.52	0.56	<0.001
Irritative	51.5±26.9	41.8±25.3	-9.6±26.1	0.36	0.37	<0.001
Stress	48.8±25.3	38.0±24.9	-10.8±24.0	0.43	0.45	<0.001
Obstructive	23.4±24.3	13.9±18.8	-9.4±21.6	0.39	0.44	<0.001
Pelvic organ prolapse alone (n=47)						
Total score	21.5±13.3	15.2±13.2	-6.3±8.6	0.47	0.73	<0.001
Irritative	38.3±22	29.4±17.5	-8.9±15.5	0.45	0.57	<0.001
Stress	16.3±18.9	9.9±15.4	-6.4±12.8	0.34	0.50	0.001
Obstructive	9.9±15.0	6.4±16.5	-3.5±13.4	0.23	0.26	0.077
Concomitant urinary incontinence and pelvic organ prolapse (n=87)						
Total score	35.8±18.8	27.8±18.1	-8.1±16.7	0.43	0.49	<0.001
Irritative	43.6±24.1	33.7±24.3	-9.9±22.8	0.41	0.43	<0.001
Stress	38.7±24.0	31.7±22.6	-7.0±22.4	0.29	0.31	0.003
Obstructive	25.2±22.6	17.9±22.6	-7.3±25.1	0.32	0.29	0.006
IIQ-7						
Whole sample (n=452)						
Total score	27.1±23.5	19.8±23.5	-7.4±20.0	0.31	0.37	<0.001
Physical activity	26.9±26.0	20.2±23.9	-6.7±25.2	0.26	0.27	<0.001
Travel	23.6±26.5	17.0±24.2	-6.6±24.5	0.25	0.27	<0.001
Social activities	26.5±29.3	21.4±28.4	-5.2±29.8	0.17	0.17	<0.001
Emotional health	31.1±30.0	21.1±26.2	-10.0±27.4	0.33	0.36	<0.001
Urinary incontinence alone (n=318)						
Total score	29.3±24.2	21.8±22.9	-7.7±19.9	0.31	0.39	<0.001
Physical activity	29.2±26.5	22.4±23.9	-6.9±24.6	0.26	0.28	<0.001
Travel	25.7±27.4	19.0±25.8	-6.7±24.3	0.24	0.28	<0.001
Social activities	28.4±29.7	23.6±29.7	-4.8±29.8	0.16	0.16	<0.001
Emotional health	33.6±30.7	22.8±26.6	-11.0±27.8	0.35	0.40	<0.001
Pelvic organ prolapse alone (n=47)						
Total score	7.9±13.7	4.4±8.9	-3.5±11.6	0.26	0.30	<0.001
Physical activity	7.1±15.4	4.3±4.1	-2.8±16.0	0.18	0.18	0.004
Travel	6.4±16.5	2.8±8.7	-3.5±13.4	0.22	0.26	<0.001
Social activities	7.1±16.9	3.5±12.5	-3.5±15.9	0.21	0.22	0.002
Emotional health	10.6±20.1	6.4±12.3	-4.3±20.1	0.21	0.21	0.037
Concomitant urinary incontinence and pelvic organ prolapse (n=87)						
Total score	25.1±21.8	17.3±19.2	-7.8±21.6	0.36	0.36	0.001
Physical activity	24.1±23.8	17.4±23.2	-6.7±27.5	0.28	0.24	0.022
Travel	22.8±25.2	14.5±19.5	-8.2±26.3	0.33	0.31	0.003
Social activities	25.8±29.1	19.0±24.8	-6.8±32.4	0.23	0.21	0.046
Emotional health	28.3±27.8	19.2±26.6	-9.1±26.4	0.33	0.34	0.001

* Data are presented as mean±standard deviation

Table 3. Change in scores of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) after pelvic floor muscle training (PFMT) in women assessed by urodynamic study (n=380)

Urodynamic diagnosis	Pre-PFMT*	Post-PFMT*	Mean change in score*	Effect size	Standardised response mean	p Value
UDI-6						
Urodynamic stress incontinence (n=138)	39.9±19.0	31.2±19.2	-8.7±16.8	0.22	0.52	<0.001
Detrusor overactivity (n=41)	42.4±21.9	29.2±19.5	-13.2±21.5	0.38	0.61	<0.001
Mixed urodynamic stress incontinence and detrusor overactivity (n=17)	32.2±17.6	28.5±19.3	-3.7±16.8	0.10	0.22	0.020
Voiding dysfunction (n=5)	34.4±12.7	23.3±20.2	-11.1±10.4	0.31	1.1	0.038
No urodynamic abnormality (n=179)	39.8±20.7	30.0±18.4	-9.84±18.0	0.24	0.55	<0.001
IIQ-7						
Urodynamic stress incontinence (n=138)	27.2±23.8	20.3±22.4	-6.9±21.1	0.15	0.33	<0.001
Detrusor overactivity (n=41)	29.6±21.5	18.8±24.8	-10.8±21.6	0.23	0.50	0.001
Mixed urodynamic stress incontinence and detrusor overactivity (n=17)	26.9±21.2	24.4±20.5	-2.5±18.1	0.06	0.14	0.013
Voiding dysfunction (n=5)	36.6±35.7	23.8±28.2	-12.8±15.9	0.20	0.81	0.036
No urodynamic abnormality (n=179)	29.2±23.7	22.2±23.1	-7.0±20.4	0.12	0.34	<0.001

* Data are presented as mean±standard deviation

Table 4. Change in scores of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) after pelvic floor muscle training (PFMT) in women with pelvic organ prolapse (POP) with or without vaginal pessary (n=134)

POP stage	Pre-PFMT*	Post-PFMT*	Mean change in score*	Effect size	Standardised response mean	p Value
UDI-6						
POP stage I (n=72)	26.2±16.4	18.6±14.5	-7.6±11.2	0.49	0.68	<0.001
POP stage II (n=55)	35.2±18.2	28.1±18.7	-7.1±18.0	0.38	0.39	0.005
POP stage III & IV (n=7)	41.5±16.9	38.5±21	-3.0±13.7	0.16	0.22	0.447
With vaginal pessary (n=35)	32.9±19.8	18.6±15.1	-10.0±15.5	0.81	0.65	0.001
Without vaginal pessary (n=99)	30.4±17.9	23.8±18.4	-6.6±14.1	0.36	0.39	<0.001
IIQ-7						
POP stage I (n=72)	13.0±18.4	8.4±14.9	-4.6±15.0	0.28	0.31	<0.001
POP stage II (n=55)	24.3±20.4	15.7±18.0	-8.7±22.1	0.45	0.39	0.01
POP stage III & IV (n=7)	31.8±26.8	25.6±21.9	-6.2±23.7	0.26	0.26	0.362
With vaginal pessary (n=35)	22.1±20.5	14.7±18.6	-7.4±18.1	0.38	0.41	0.026
Without vaginal pessary (n=99)	18.7±21.5	12.3±17.4	-6.4±20.2	0.33	0.32	0.002

* Data are presented as mean±standard deviation

Table 5. Change in scores of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) in women with tension-free vaginal tape procedure (n=44)

Scale	Pre-surgery	Post-surgery	Mean change in score	Effect size	Standardised response mean	p Value
UDI-6 total score	60.3±19.5	22.1±23.6	-38.2±29.6	0.44	1.29	<0.001
Irritative	68.6±37.2	28.8±31.6	-39.8±45.1	0.25	0.88	<0.001
Stress	96.9±25.8	22.1±29.0	-74.8±38.6	0.67	1.94	<0.001
Obstructive	16.3±21.1	15.9±24.6	-0.4±31.0	0.00	0.01	<0.001
IIQ-7 total score	39.1±24.6	8.1±13.2	-31.0±21.8	0.39	1.42	<0.001
Physical activity	43.9±27.2	7.6±12.7	-36.3±29.7	0.43	1.22	<0.001
Travel	31.4±29.4	4.9±12.2	-26.5±25.8	0.26	1.03	<0.001
Social activities	35.6±34.8	7.6±15.9	-28.0±31.3	0.22	0.89	<0.001
Emotional health	41.7±31.6	12.1±21.1	-29.6±30.5	0.24	0.97	<0.001

* Data are presented as mean±standard deviation

Discussion

UDI-6 and IIQ-7 are relatively simple and easy to use and thus facilitate clinical application and research, compared with other health-related QoL assessment tools for UI, Pelvic Floor Distress Inventory, and Pelvic Floor Impact Questionnaire[18-20]. The Chinese version of IIQ-7 is more sensitive than Short Form-36 Health Survey[21] for assessment of Cantonese-speaking patients with lower urinary tract symptoms. The Chinese versions of UDI-6 and IIQ-7 have been validated among Hong Kong women with UI (one-third with concomitant POP)[11]. UI and POP share similar pathophysiology and commonly occur concomitantly. Approximately 50% of women with POP have symptomatic stress UI[22]. The Hospital Authority advocates the use of the Chinese version of UDI-6 and IIQ-7 to assess the QoL in older adults with UI[23] and the effectiveness of intensive behavioural therapy in improving UI in women[24].

Responsiveness is an important psychometric property; a tool with poor responsiveness may result in type II error (ie, assuming no difference when a difference in fact exists) and estimation of the treatment effect[25]. The change in QoL scores is lower after conservative management than after surgical treatment[26]. Overall, after PFMT, the responsiveness of UDI-6 was moderate and that of IIQ-7 was small, whereas the effect size of both questionnaires was small. Nonetheless, PFMT was effective in improving urinary symptoms and QoL in women with UI and/or POP. The effect size of UDI-6 was large (0.81) in women after vaginal pessary, which may be attributed to the relief of voiding and irritative symptoms caused by POP. Results of the present study are consistent with those of other studies[27,28]. After tension-free vaginal tape procedure, the effect size of UDI-6 and IIQ-7 and their subscales was small, except for the stress subscale of UDI-6, which was moderate (0.67), and the obstructive subscale of UDI-6, which was minimal (0.00). The procedure improved or cured the stress symptoms and did not cause complication of voiding difficulty.

Characteristics of our patients are similar to those in other studies involving nurse-led continence service[6,11,29,30]. Thus, results of the present study may be generalised to other Chinese patients with UI and/or POP. Although the mean follow-up of 4.1 months is short, the effect of PFMT can still be observed. The follow-up protocol is consistent with the National Institute for Health and Care Excellence guidelines on the management of UI and POP[31]. The sample size was large, and urodynamic study was performed for women with mixed UI or more severe symptoms. Women who were referred to a tertiary unit are motivated to seek treatment. This could lead to selection bias, as women with milder symptoms in the community may not seek medical care. All UDI-6 and IIQ-7 and their subscales scores improved significantly after conservative and surgical treatment, except for the obstructive subscale score of UDI-6 in women with POP alone after PFMT (p=0.077), the total UDI-6 score in women with stage-III or -IV POP after PFMT (p=0.447), and the total IIQ-7 score in women with stage-III or -IV POP after PFMT (p=0.362). This may be due to the small sample size in these subgroups and lower responsiveness to conservative management (compared with surgical treatment). The

minimally important difference of UDI-6 and IIQ-7 should be addressed in future research evaluating different treatment options. A 3-day bladder diary is more objective may provide more information to the change in symptoms after PFMT.

Conclusion

The UDI-6 and IIQ-7 are modestly responsive to change after PFMT and/or tension-free vaginal tape procedure in women with UI and/or POP.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

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Data availability

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

Ethics approval

The study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (reference: CRE-2015.125). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures

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Pregnancy and live birth after high-intensity focused ultrasound ablation for fibroids and adenomyosis: two case reports

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We report two cases of high-intensity focused ultrasound ablation for fibroids and adenomyosis in women having difficulty conceiving. After the ablation, one woman got pregnant spontaneously and the other after in vitro fertilisation. Both women delivered by Caesarean section uneventfully.

Keywords: Adenomyosis; High-intensity focused ultrasound ablation; Leiomyoma

Introduction

Patients with large fibroids or adenomyosis are associated with heavy bleeding, severe anaemia, severe pain, and fertility problems. High-intensity focused ultrasound (HIFU) ablation is effective in treating uterine fibroids[1] and adenomyosis[2]. It was introduced to Hong Kong in 2019 from mainland China[3]. It focuses the ultrasound energy into the tumour to induce thermal, cavitational, and mechanical effects, with a temperature of 60°C to 90°C. It is accurate and can be used to treat fibroids and adenomyosis without harmful effects on the surrounding myometrium or fertility. We report two cases of HIFU ablation for fibroids and adenomyosis in women having difficulty conceiving. After HIFU ablation, the two woman became pregnant: one spontaneously and the other by in vitro fertilisation. Both women delivered by Caesarean section uneventfully.

Case presentation

Patient 1

In March 2020, a 33-year-old woman presented with severe dysmenorrhea and heavy menstrual flow secondary to a uterine lesion (5.3 × 9.1× 7.3 cm^3). Magnetic resonance imaging showed mixed T1 hyperintense or isointense foci consistent with adenomyosis. In July 2020, she underwent ultrasound-guided HIFU ablation of 90% to 95% of the lesion. The patient then received 3 monthly injection of gonadotrophin-releasing hormone agonist as adjuvant treatment. At the 3-month follow-up, ultrasonography showed the lesion had reduced to 4.5 × 3 cm. At 5 months after HIFU ablation, the patient experienced decreased menstrual flow and conceived spontaneously. After an uneventful antenatal period, she gave birth by Caesarean section at 37 weeks to a healthy baby weighing 2800 g. At 6 weeks after delivery, ultrasonography showed a normal uterus with no features of adenomyosis.

Patient 2

In June 2020, a 34-year-old woman presented with menorrhagia with anaemia and failure to conceive for over a year. Ultrasonography and magnetic resonance imaging confirmed an anterior intramural fibroid (5.6 × 5.2 × 7.2 cm). In July 2020, she underwent ultrasound-guided HIFU ablation. Microbubble contrast-enhanced ultrasonography confirmed ablation of over 95% of the fibroid. Four months later, her menstrual flow reduced considerably, and the fibroid reduced to 5.17 × 3.67 × 4.55 cm, approximately 60% (Figure 2). At 6 months after HIFU ablation, she underwent in-vitro fertilisation and successfully conceived. Throughout the pregnancy, the size of the fibroid remained approximately 4 cm. The patient had an uneventful antenatal period and gave birth to a 2680-g baby by Caesarean section at 38 weeks. During the procedure, the endometrial cavity was found to have no injury or adhesion secondary to the previous HIFU ablation.

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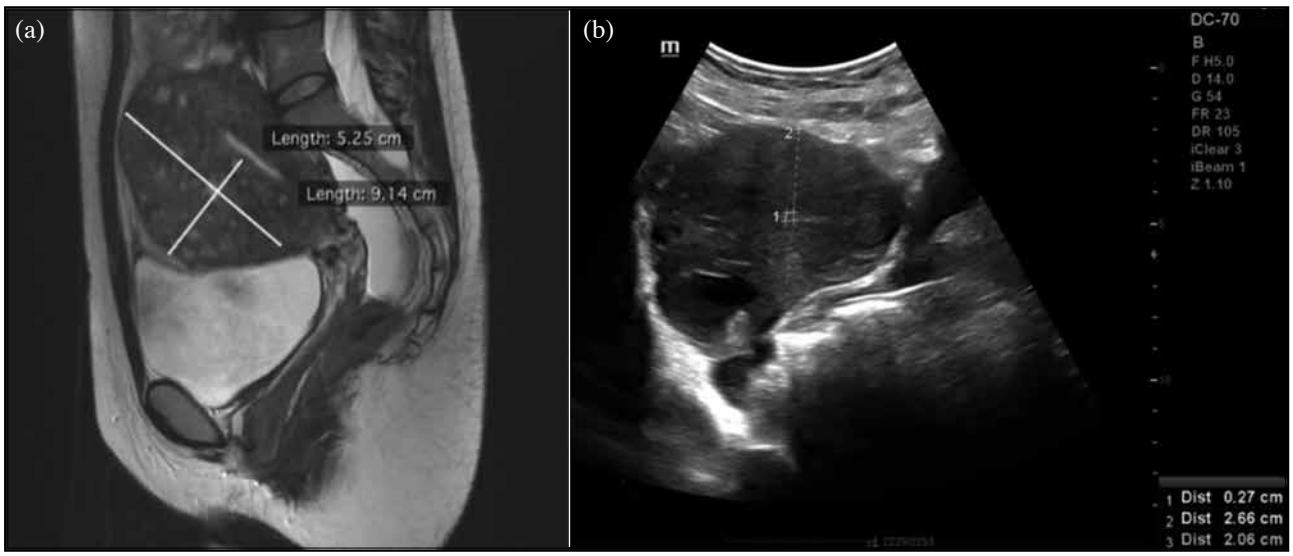

Figure 1. (a) Magnetic resonance imaging showing an extensive adenomyosis at the anterior wall of the uterus, with the wall thickness being 5.25 cm. (b) Ultrasonography at 8 weeks after delivery showing the uterus without features of adenomyosis, with the anterior wall thickness reduced to 2.66 cm.

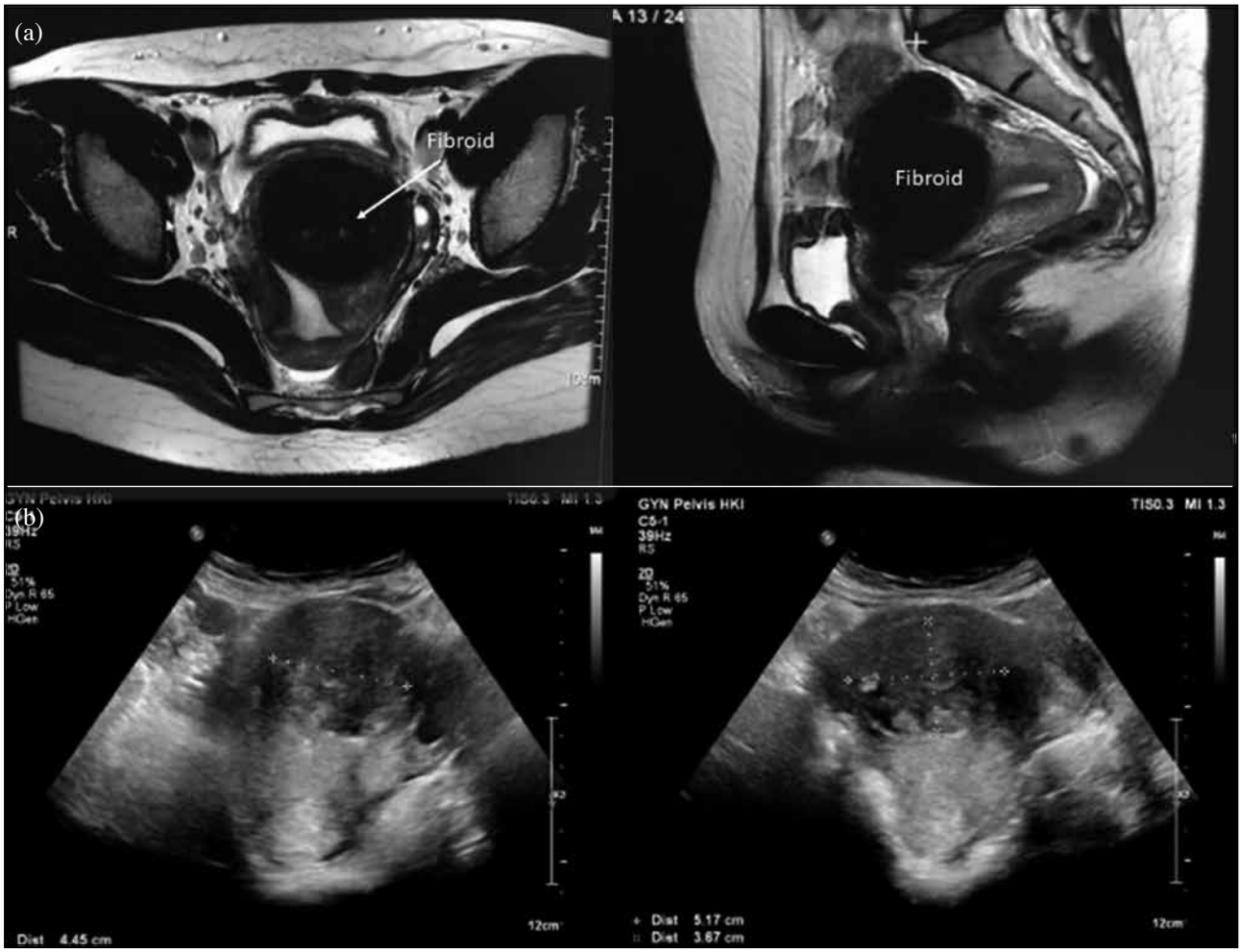

Figure 2. (a) The axial and sagittal views of T2-weighted magnetic resonance images showing a uterine fibroid. (b) Ultrasonography showing the uterus at 3 to 4 months after high-intensity focused ultrasound ablation.

Discussion

In Hong Kong, HIFU ablation for fibroids and adenomyosis was established in a private clinic in 2019[4] after a training journey in China[3]. As of August 2021, 300 patients have been treated as day-procedure outpatients in Hong Kong. Of them, one third had adenomyosis and the remaining had uterine fibroids, together with a small number with coexisting adenomyosis.

Uterine fibroids and adenomyosis are associated with fertility problems. HIFU ablation may improve the endometrial environment for pregnancy and hence the pregnancy rate. Nonetheless, large randomised case series are needed to support this. When HIFU was first introduced, clinical reports concentrated on treating symptomatic women without the need of pregnancy. HIFU ablation was contraindicated for women expecting a baby because of the weakness of the myometrium after ablation and inadvertent ovarian failure secondary to indirect sonication at the neighbouring ovaries. However, no case report of changes in endocrine parameters or inadvertent ovarian failure after HIFU ablation has been reported. The anti-Mullerian hormone level (a marker for ovarian reserve) is similar before and after HIFU ablation in 12 women[5].

Successful vaginal delivery after magnetic resonance-guided focused ultrasound treatment of fibroids has been reported[6]. In 2012, Chinese authors reported no obstetric or labour problems after ultrasound-guided HIFU ablation in a series of patients[7,8]. Surgical myomectomy is associated with risks of infection, bleeding, adhesion formation, and early recurrence of fibroids. HIFU ablation is non-invasive and does not impair fertility. The elective caesarean section rate is 50% to 80% among women with HIFU ablation, although vaginal delivery is safe for them[7]. This may be due to the women's desire for safe and uncomplicated delivery, as in our two patients.

A waiting period of 8 months to 1 year before pregnancy was initially recommended after HIFU ablation because of the fear of uterine rupture. However, increasing evidence suggests that a shorter waiting period of 3 to 6 months is an acceptable safe practice[9]. Our two patients were conceived <6 months after HIFU ablation, with no miscarriage, premature labour, or labour complications. However, larger studies are needed to determine the safety of HIFU ablation before pregnancy.

Although HIFU ablation has shown favourable pregnancy outcomes in China[10,11], it is not commonly performed in western countries and is labelled as an experimental procedure by insurance companies. Hopefully, the two case reports can raise the awareness of physicians on HIFU ablation for fibroids and adenomyosis.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

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

Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Difficulties in diagnosing polycystic ovarian syndrome in adolescents: a narrative review

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We review the diagnostic criteria of polycystic ovarian syndrome (PCOS) in adolescents. It is important to recognise PCOS early for timely management. Clinicians should be aware of the difficulties in diagnosing PCOS in adolescents. A multi-disciplinary approach for diagnosis and treatment is suggested. For high-risk cases, re-evaluation may avoid under-diagnosing or over-diagnosing PCOS.

Keywords: Adolescent; Polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting reproductive women[1], with an estimated prevalence of 6% to 10%[2] to 18%[3]. It has complex genetic and environmental aetiologies[4]. Diagnosing PCOS is difficult because it has a broad spectrum of presentation, which is further complicated in adolescents, as the symptoms may mimic normal pubertal events[5]. PCOS is associated with subfertility, increased risk of endometrial pathology and metabolic diseases, emotional disturbances, and hirsute features resulting from excessive androgen.[1] Early diagnosis is crucial to optimise care and health outcomes.

Adolescents are individuals aged 10 to 19 years who undergo a transitional phase from childhood to adulthood with rapid physical and psychological development[6]. Functional variations in the hypothalamic-pituitary-ovarian axis result in overlapping features of PCOS with physiological changes of puberty[5]. Thus, the diagnostic criteria of PCOS for adults may result in mis- or over-diagnosis in adolescents.

Diagnostic criteria for PCOS in adolescents

To diagnose PCOS, clinicians commonly use the National Institute of Health Criteria[7], the Rotterdam Criteria[8], and the Androgen-Excess and PCOS Society Criteria[9] (Table). The three major clinical features are ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology. However, these criteria are not appropriate for adolescents[10]. In 2018, the international evidence-based guideline for assessment and management of PCOS suggest including only hyperandrogenism and irregular cycles for diagnosing PCOS in adolescents.[12] Ultrasonographic features are not indicative owing to PCOS features overlapping with normal reproductive physiology during adolescence period[12].

Ovarian dysfunction reflected by irregular menstrual cycles is the key diagnostic feature of PCOS. In the Rotterdam criteria, there is no specific definition of oligo-/anovulation in terms of pubertal status. This poses a challenge to defining adolescents as having irregular menstrual cycles because maturation of the hypothalamic-pituitary-ovarian axis may take years to complete[13], with anovulatory cycles lasting up to 5 years after menarche. Therefore, the latest guideline defines irregular menstrual cycles with respect to menarche and age[12]. Irregular menstrual cycles are normal within the first year of menarche. Within 1 to 3 years of menarche, irregular menstrual cycles are defined as cycles <21 days or >45 days or >90 days for any one cycle, whereas from >3 years of menarche to perimenopausal, irregular menstrual cycles are defined as cycles <21 days or >45 days or >90 days for any one cycle or <8 cycles per year. Primary amenorrhea is defined as amenorrhea by the age of 15 years or after >3 years of thelarche. Clinicians should undertake further assessment for possible PCOS in adolescents with irregular menstrual cycles.

Hyperandrogenism refers to both clinical and biochemical hyperandrogenism. It includes acne, alopecia, and hirsutism in adults, as well as severe acne

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Table. Diagnostic criteria for polycystic ovarian syndrome (PCOS) according to the National Institute of Health Criteria, the Rotterdam Criteria, and the Androgen-Excess and PCOS Society Criteria

Feature	National Institute of Health criteria	Rotterdam criteria	Androgen-Excess and PCOS Society criteria
Hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Ovulation	Chronic anovulation	Oligo/anovulation	Oligo/anovulation
Ovarian morphology	Not specified	Polycystic ovarian morphology	Polycystic ovarian morphology
Exclusion of other pathologies needed?	Yes	Yes	Yes
Number of criteria needed	Both hyperandrogenism and ovulation as well as exclusion of other endocrinopathies	Two of the three features as well as exclusion of other endocrinopathies	Hyperandrogenism and either ovulation or ovarian morphology as well as exclusion of other endocrinopathies

and hirsutism in adolescents[12]. Alopecia refers to the loss of terminal hair, usually on the scalp[14]. Alopecia is a poor marker for hyperandrogenaemia[15] and is rarely seen in adolescents[16] and should not be used for assessment in adolescents. Acne is common in adolescents even without hyperandrogenism. Its severity is categorised based on the number of facial lesions and lesion types[11]. However, medications for treatment of acne may render assessment difficult[18]. Hirsutism refers to the male-like pattern of terminal hair distribution. Over 70% of women with hirsutism show elevated androgens, whereas <5% of women with hirsutism do not demonstrate other PCOS features[17]. Hirsutism is the most recognisable sign of hyperandrogenism. It can be assessed visually using the modified Ferriman-Gallwey score with photographic atlas[19]; the cut off scores were ≥4 to 6. However, hirsutism has ethnic variation. Visual assessment is subjective and thus inter- and intra-observer variability are high[20]. Self-treatment for excessive terminal hair may further complicate visual assessment[21].

Identifying biochemical hyperandrogenism in adolescents remain challenging, as testosterone levels rise since puberty[23]. Calculated free testosterone or free androgen index has higher sensitivity than direct free testosterone assays[12]. It is uncertain whether mild hyperandrogenaemia represents a physiological peri-menarcheal situation and whether genuine adolescent hyperandrogenaemia persists into adulthood[23].

Polycystic ovaries are defined based on the ovarian volume and the number of follicles. According to the Rotterdam criteria, polycystic ovaries are defined as having one or both ovaries with ≥12 follicles measuring 2 to 9 mm in diameter or with >10 cm^3 of ovarian volume[24]. However, polycystic ovarian morphology is highly prevalent (30% to 40%) in adolescent girls[25], owing to the physiological changes during puberty (Figure). Using these ultrasonographic criteria may result in over-diagnosis in adolescents. Transvaginal ultrasonography is not appropriate for sexually inactive adolescents. Transabdominal ultrasonography is technically difficult for inexperienced operators and may not detect up to 30% of polycystic ovaries that are otherwise identified on transvaginal ultrasonographic study[24]. Ovaries maybe obscured in patients with an inadequately distended urinary bladder, and an over-distended urinary bladder may compress the ovaries and result in inadequate application of the ellipsoid model in calculation of ovarian volume[24]. Therefore, ultrasonography is not recommended for diagnosing PCOS in patients <8 years after menarche. Magnetic resonance imaging of the pelvis is an alternative because it enables assessment of the number of follicles and ovarian volume. However, it is expensive and is not warranted solely for the assessment for possible polycystic ovarian morphology.

The diagnosis of PCOS requires exclusion of other pathologies. In adolescents, the most frequent differential diagnosis of PCOS is congenital adrenal hyperplasia, which has similar phenotypic features[26], followed by thyroid disease, hyperprolactinaemia, and adrenocortical diseases[27]. Exclusion of other pathologies should be based on combined clinical, radiological, and biochemical assessments.

Difficulties in diagnosing PCOS in adolescents

After excluding ultrasonography as a diagnostic tool for polycystic ovarian morphology in adolescents,

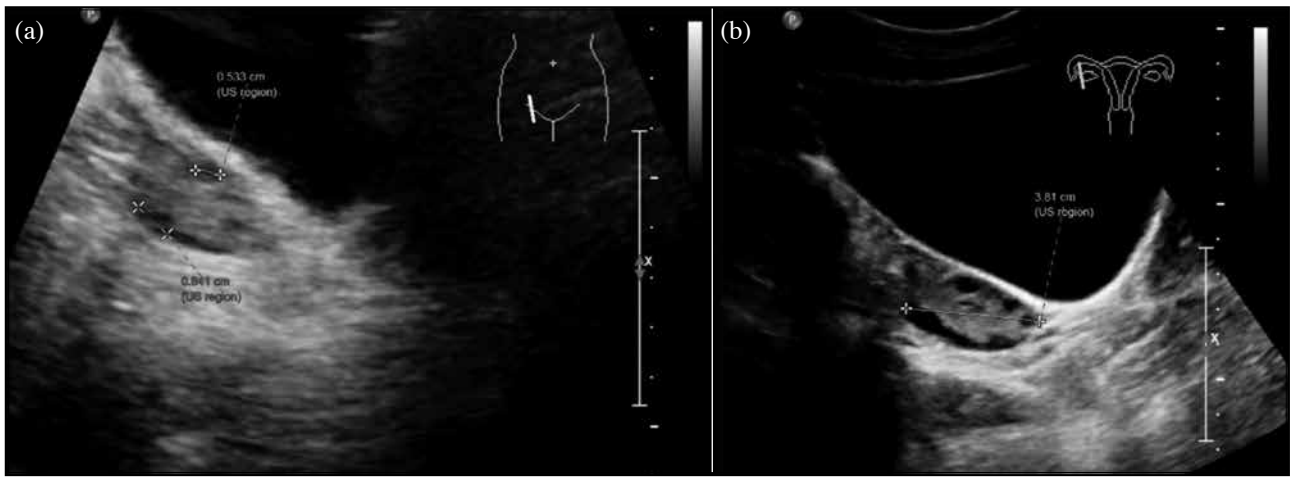

Figure. A 14-year-old girl presented with irregular long cycles with prolonged bleeding. Her menarche was at 12 years old. (a) Transabdominal ultrasonography showing no polycystic ovarian morphology. She continued to have irregular long cycles and secondary amenorrhea. (b) Follow-up transabdominal ultrasonography at 17 years old showing polycystic ovaries. This case illustrates the need of regular follow-up for at-risk teenagers.

the diagnosis of PCOS necessitates presentation of both hyper-androgenism and irregular menstrual cycles. Ultrasonographic assessment is not necessary even for adults if the other two criteria are fulfilled. For adolescents who have features of PCOS but do not fulfil the diagnosis should be considered at risk and be followed up until full reproductive maturity[12]. At-risk adolescents include those with PCOS features before use of combined oral contraceptive pills, those with significant weight gain, and those with persisting clinical features.

Patients may first present to non-gynaecologists for reasons other than irregular menstrual cycles such as acne, hirsutism, and obesity. The presentation may further be complicated by psychosocial morbidity and low self-esteem from discrimination or strained peer relationships[28], and by self-treatment such as using over-the-counter medication for acne, shaving or waxing hair, and dieting. For young adolescents who present with irregular menstrual cycle, clinicians may wrongly attribute it to normal pubertal development and therefore under-diagnosing ovarian dysfunction.

Over-diagnosis or incorrect diagnosis of PCOS may lead to unjustified investigations, interventions, and anxiety. A prompt diagnosis of PCOS enables therapeutic interventions[29], but over-diagnosis or incorrect diagnosis affects the patient's quality of life and creates unnecessary anxiety. Clinicians are reluctant to make a diagnosis of PCOS in young adolescents. Hence, identifying at-risk adolescents with possible PCOS and follow-up for re-evaluation can avoid under- or over-diagnosis and their implications[12].

Conclusion

It is important to recognise PCOS early for timely management. Clinicians should be aware of the difficulties in diagnosing PCOS in adolescents. A multi-disciplinary approach for diagnosis and treatment is suggested. For high-risk cases, re-evaluation may avoid under-diagnosing or over-diagnosing of PCOS.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

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

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Vaginal mesh surgery: a review of current practice

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We review the risks and benefits of vaginal mesh surgery for pelvic organ prolapse and compare the existing guidelines and recommendations from different regions and academic bodies. We then provide recommendations on the use of vaginal mesh surgery for pelvic organ prolapse.

Keywords: Pelvic organ prolapse; Surgical mesh

Introduction

Pelvic organ prolapse (POP) is a common but distressing problem in older women, affecting 40% to 60% of women[1,2]. The risk of recurrence after surgery is 16% to 33%[3]. Owing to the high rate of recurrence after native tissue repair surgery, a mesh graft material has been used in abdominal sacrocolpopexy since 1960s[4], and via the transvaginal route since 1990s. In 2002, the transvaginal mesh device was approved by the US Food and Drug Administration (FDA). However, vaginal mesh surgery is associated with serious adverse events and complications[5,6]. In 2008 and 2011, the FDA released two public health notifications[7]. This study aims to review the risks and benefits of vaginal mesh surgery for POP, compare the existing guidelines and recommendations from different regions and academic bodies, and provide recommendations on its use.

Polypropylene mesh

Polypropylene has been used for >60 years as suture material for repair of hernias in various anatomic locations. In urogynaecology, type I polypropylene mesh is first used as the mid-urethral sling for treatment of urinary stress incontinence. The mesh has been widely used as an adjuvant material for repair of POP for >20 years. However, polypropylene mid-urethral sling induces a minimal inflammatory reaction without significant change in collagen solubility. The polypropylene sling causes more intense and longer-lasting inflammatory reaction and greater visceral penetration than an autologous fascial sling[8,9]. In animals, normal-weight polypropylene has a negative impact on the metabolism of both collagen and elastin, resulting in catabolic reactions, whereas lighter more-porous and less-stiff meshes have less negative impact[10]. However, polypropylene mid-urethral sling surgery for urinary stress incontinence is not associated with an increased cancer risk later in life[11]. Exposed and unexposed women are comparable in terms of pelvic organ cancers including ovarian cancer (hazard ratio [HR]=0.8, 95% confidence interval [CI]=0.5-1.2), endometrial cancer (HR=1.1, 95% CI=0.8-1.4), cervical cancer (HR=0.4, 95% CI=0.2-1.0), and bladder and urethral cancer (HR=0.7, 95% CI=0.4-1.2)[11]. Nonetheless, in 2019, the International Consultation on Incontinence Research Society Meeting was held to discuss alternative materials and tissue-engineering techniques that may improve interactions and host response in vagina[12].

Benefits and risks of vaginal mesh surgery for POP

Benefits

Vaginal mesh surgery is developed owing to the high failure rate of traditional native tissue repair. It has lower risk of recurrence. In a study in 2011, the benefit of synthetic mesh for the anterior compartment was confirmed, but the study was limited by the non-blinded assessment and industry affiliation[13].

In the multi-centre PROSPECT of women who underwent primary transvaginal anterior or posterior compartment prolapse surgery, the native tissue group and the mesh group were comparable in terms of the patient-reported Pelvic Organ Prolapse Symptom Score and condition-specific quality of life score[14]. However, the follow-up was up to 2 years, and longer-term outcomes were not available.

In the Cochrane review of 37 randomised controlled studies involving 4023 women who underwent transvaginal mesh repair or native tissue repair for anterior

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or multi-compartment POP[15], the awareness of prolapse at 1 to 3 years was significantly lower in women with transvaginal mesh repair (risk ratio [RR]=0.66, 95% CI=0.54-0.81). This indicates that only 10% to 15% of women with transvaginal mesh repair are aware of prolapse, compared with 19% of women with native tissue repair. Nonetheless, the two groups were comparable in terms of the extent of repair and the awareness of prolapse. In addition, women with transvaginal mesh repair were less likely to have a stage-2 or greater prolapse (RR=0.40, 95% CI=0.30-0.53) upon examination. This shows that 11% to 20% of women with transvaginal mesh repair have a stage-2 or greater prolapse, compared with 38% of women with native tissue repair. Furthermore, the rate of repeat surgery for prolapse after 1 to 3 years was lower in those with transvaginal mesh repair (RR=0.53, 95% CI=0.31-0.88). This suggests that 1% to 3% of women with transvaginal mesh repair need repeat surgery, compared with 3% of women with native tissue repair. When the PROSPECT data were added, transvaginal mesh repair remains superior in terms of awareness of prolapse (RR=0.83, 95% CI=0.71-0.96) and recurrence (RR=0.42, 96% CI=0.32-0.56). However, there is heterogeneity in the included trials; some trials include women with uterine or vault prolapse; few trials differentiate primary from secondary repairs. There are variations in inclusion criteria regarding concomitant procedures and continence surgery.

In two studies of women with severe POP, transvaginal mesh repair achieved better 5-year outcomes for both anterior compartment and multi-compartment prolapse, compared with native tissue repair[16,17]. However, the sample size of these trials is small. Further research and systematic review are needed to reach a conclusion.

Risks

The main risks of transvaginal mesh repair are mesh exposure and erosion and hence the subsequent repeated surgery. The reported complication rates vary and may be due to heterogeneity in surgical techniques, definition of exposure, and small sample size. In the PROSPECT[14], in women who received only synthetic mesh as part of anterior or posterior prolapse repair, with no other concomitant mesh procedure or mesh inserted, the mesh complication rate in the first 2 years was 14%. 76% of the complications were asymptomatic mesh exposure and required only conservative or partial removal, except for one case that required complete mesh removal owing to severe infection.

In a New York state database, in 3798 women with vaginal mesh surgery and 5070 women with vaginal mesh plus sling surgery, the rates of mesh erosion were 1.95% and 2.72%, respectively, and the rate of repeat surgery for mesh erosion were 1.23% and 2.16%, respectively[18].

In the Cochrane review of 19 randomised controlled trials[15], 134 (12%) of 1097 women with transvaginal mesh repair had mesh exposure. In subgroup analysis of women with anterior transvaginal mesh repair, the mesh exposure rate was 10%. Women with transvaginal mesh repair were more likely to have repeat surgery (for prolapse, stress urinary incontinence, or mesh exposure) at 1 to 3 years, compared with those with native tissue repair (RR=2.4, 95% CI=1.51-3.81). However, the rate of repeat surgery for prolapse was lower in those with transvaginal mesh repair (RR=0.53, 95% CI=0.31-0.88). The two groups were comparable in terms of the rate of repeat surgery for stress urinary incontinence (RR=1.07, 95% CI=0.62-1.83). Surgery for mesh exposure was required in 8% of women. The operative time was longer in mesh surgery, but the two groups were similar in terms of the need for blood transfusion and the length of hospital stay. The operative risks for mesh repair were higher, particularly the risk of bladder injury (RR=3.92, 95% CI=1.62-9.50). However, there was no significant difference in serious adverse events or complications during or after surgery. Women with transvaginal mesh repair were more likely to develop de novo stress urinary incontinence (RR=1.39, 95% CI=1.06-1.82)[15]. In a study in Scotland, the risk of subsequent incontinence surgery is also higher in women with anterior mesh repair for POP[19]. However, in UK, those with mesh, graft, or standard repair were comparable in terms of 2-year urinary outcomes and quality of life related to urinary, bowel, vaginal, and sexual symptoms[14]. Long-term data are limited. More robust studies with larger sample size and longer follow-up are needed to determine the benefits and risks of transvaginal mesh repair.

Complications

Vaginal mesh–related complications can result in severe symptoms and necessitate specialised surgical management (from simple transecting the mesh to complete removal of the mesh). The complication rates reported vary and are mostly under-reported.

In a retrospective study in France, the rate of reoperation for mesh-related complications in 1123 patients with POP surgery over 8 years was 2.8%, of which 4.2% after transvaginal mesh operation and 1.3% after sacrocolpopexy[20]. The most common indication for reoperation was vaginal exposure of mesh (48%), followed by symptomatic mesh contraction (20.3%) with pain,

voiding dysfunction, and overactive bladder symptoms. 83% of reoperations were performed transvaginally and 9% laparoscopically. For treatment outcomes, 78% were cured, 13% were improved, and 7.4% were failed. Of all complications, residual pain or dyspareunia was reported in 11.8% of patients.

In a review of mesh-related complaints at a tertiary referral centre in the United States, of 92 women with mesh revision, 56.5% involved a midurethral sling, 26.1% a transvaginal mesh, 2.2% both, and 13% a sacrocolpopexy mesh[6]. The median interval from mesh implantation to presentation was 2.4 to 3.2 years. In 69.4% of women, the mesh for prolapse repair was revised owing to pain or dyspareunia. Around 85% of women reported improvement of symptoms after surgical intervention.

Thus, pain syndrome can be a serious complication after mesh repair. Other severe complication reported was fistulas, which have a poor prognosis even after surgery. All these complications are rare but difficult to treat. Surgeons must be aware of the specific risks associated with surgery for pelvic floor disorders. Intensive training of new techniques is encouraged. Complications should be recognised promptly to enable subsequent management.

Trends and regulations worldwide

The debate on when, where, and how to use mesh for POP remains controversial, especially regarding the safety of the synthetic mesh. In 2008, the FDA issued a safety concern after receiving >1000 reports of mesh-associated complications. In 2011, another safety concern was issued. In 2016, the FDA reclassified surgical mesh for transvaginal repair of POP as class III (high risk). Multiple class-action lawsuits have been brought against mesh manufacturers, particularly against those of transvaginal mesh. The use of mesh has dramatically reduced since 2008; multiple manufacturers suspended the sale of vaginal mesh devices[21]. In 2019, the FDA issued a public notice to order all manufacturers to stop selling and distributing surgical mesh intended for transvaginal repair of POP. Therefore, fewer vaginal mesh procedure and more native tissue repairs and minimally invasive sacrocolpopexies are performed for prolapse[22,23].

In 2014 in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency concluded that the benefits of vaginal mesh outweigh the risks and hence there is no justification to take regulatory action to ban mesh devices from UK hospitals. However, in 2017 a Scottish Independent Review concluded that transvaginal mesh procedures must not be offered routinely, as it has no extra benefit compared with native tissue repair. However, the review did not consider studies on the long-term safety and effectiveness of mesh surgery. There is a lack of long-term follow-up data such as quality of life and activities of daily living.

In the PROSPECT in 2017, conventional anterior colporrhaphy, anterior mesh repair with synthetic implants, and anterior mesh repair with biological implants are comparable in terms of prolapse-related quality of life and adverse events[14]. However, 12% of complications were mesh-related. Thus, in July 2018, a high vigilance restriction was imposed on the use of mesh to treat stress urinary incontinence and POP. This included restriction of the use of synthetic tape and mesh to procedures for stress urinary incontinence and vaginally inserted mesh for POP, as well as high vigilance scrutiny on procedures involving abdominally inserted mesh such as sacrocolopopexy. In March 2019, the high vigilance restriction was extended. In 2019, the National Institute for Health and Care Excellence guideline states that transvaginal mesh in the anterior compartment is only allowed in research, whereas the use of mesh in the posterior compartment is prohibited[24].

In the position statement by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the transvaginal polypropylene mesh is not recommended as the first-line treatment for any vaginal prolapse in September 2017[25]. Sales of mesh are halted. Transvaginal mesh products with the sole use for treatment of POP via transvaginal implantation are removed from the Australian Register of Therapeutic Goods.

The International Federation of Gynecology and Obstetrics concludes that use of transvaginal mesh for the treatment of POP should be considered only in complex cases, in which the benefits of mesh placement justify the known risks[26]. Such complex cases include recurrent POP, especially in the presence of poor-quality collagen, increased intra-abdominal pressure, and large anterior compartment prolapse, and cases with contraindication to abdominal surgery. Transvaginal mesh procedure should be performed by a surgeon with expertise in mesh placement techniques who is capable of recognising, diagnosing, and treating potential mesh-related complications. Surgical management of mesh erosion and contraction may be particularly challenging owing to the proximity of the bladder and bowel. Thus, referral to an expert is recommended to avoid further complications such fistula formation.

In Asia, no restrictions have been imposed on the use of mesh. It remains a treatment option. In 2019 in the Pan Asia meeting of the International Urogynecological Association, urogynaecologists shared their practice of performing mesh repair for POP. Most performed mesh repair only for advanced stage of prolapse or recurrent cases, mainly for older patients and for the anterior compartment only, and operations were performed by trained urogynaecologists or urologists or subspecialty trainees with supervision.

Local experience and recommendations

In 2004, the tension-free vaginal mesh was proposed for repairing POP[27]. In 2006, commercial mesh kits became available in Hong Kong, and synthetic mesh surgery was more readily available. In a Hong Kong study of 47 women who underwent transvaginal mesh surgery for stage III or IV POP, the mean operating time was 94 minutes, the mean estimated blood loss was 163 mL, and the mean hospital stay was 4 days[28]. Four (8.5%) patients had visceral injuries, which were identified and repaired intra-operatively, and all recovered uneventfully. POP quantification improved significantly. Nine (19%) patients had recurrent stage-II prolapse but only one was symptomatic. Six (13%) patients had postoperative mesh exposure, three of whom underwent mesh excision. Five (11%) patients had de-novo urodynamic stress incontinence, which was mostly mild and managed conservatively. 91% of patients were satisfied with the outcomes.

Regarding intermediate-to-long-term outcomes, in 183 sexually inactive women aged >65 years who underwent transvaginal mesh surgery with concomitant vaginal hysterectomy or uterine-preserving operation for advanced stage of POP (ie stage III/IV) with or without urodynamic stress incontinence, after a mean follow-up duration of 50 months in 156 of those women, the subjective recurrence rate was 5.1% and the objective recurrence rate was 10.9%[29]. The re-operative rate for prolapse was 1.3%. The mesh erosion rate was 9.6%. De novo stress urinary incontinence occurred in 12 (7.7%) women. Only one (1.9%) woman underwent tension-free transvaginal tape procedure (transobturator route) for stress urinary incontinence, and the others received pelvic floor training to improve symptoms. The overall satisfaction rate was 98.1%.

Regarding complications, in 134 cases of vaginal mesh surgery with a mean follow-up duration of 40 months, the rate of mesh-related complications was 13.4% and the mesh exposure rate was 11.9%[30]. The main indication for re-operation was vaginal spotting; no re-operations were related to pelvic pain or dyspareunia. All 13 surgical excisions (in eight patients) of exposed mesh were performed vaginally under local anaesthesia on the same day, except for one patient who opted for general anaesthesia. The median time between primary operation to first surgical excision of exposed mesh was 14 months (interquartile range=8.8-37.3 months); the longest time was 66 months. The mean operating time for surgical excision of the exposed mesh was 20±6 (range, 10-30) minutes, with estimated blood loss of 2 to 10 mL. 95% of patients were well at their latest follow-up. Transvaginal mesh with posterior insertion was associated with increased risk of mesh-related complications (OR=4.3, 95% CI=1.6-11.5, p=0.002). Mesh exposure was associated with total vaginal mesh surgery (OR=5.0, 95% CI=1.8-13.6, p=0.002), coital activity (OR=2.8, 95% CI=1.1-6.9, p=0.03), and obesity (OR=4.7, 95% CI=1.5-14.4, p=0.007). As total vaginal mesh and posterior vaginal mesh are no longer available in Hong Kong, this risk is eliminated.

In 154 Chinese women with stage-III or stage-IV POP who underwent mesh repair or native tissue repair and were followed up to 2 to 5 years, those with mesh repair was associated with a five-fold reduction in the risk of subjective recurrence and a six-fold reduction in the risk of objective recurrence[31]. In women with concomitant levator ani muscle avulsion, mesh repair was associated with a four-fold reduction in both objective and subjective recurrence of POP.

Findings of studies in Hong Kong are consistent with those in the Cochrane review. The rates of recurrence and repeat surgery were lower in women with mesh repair than with native tissue repair. In our unit, sexually inactive women aged ≥65 years with advanced stage of prolapse and levator ani muscle avulsion were offered vaginal mesh repair for anterior compartment. The rate of mesh exposure was just 10%. In our patients with mesh exposure, the symptoms were much milder; most patients were asymptomatic or with mild vaginal spotting. The treatment was thus conservative or minor. The overall satisfaction rate was high. Strict patient selection of mainly sexually inactive women for mesh repair resulted in fewer dyspareunia or coital problems. Operations were performed by urogynaecologists or gynaecologists experienced in prolapse surgery. In Hong Kong, no major litigation has been lodged against mesh manufactures.

Conclusion

The benefits of vaginal mesh surgery for POP outweigh its risks in patients at risk of recurrence, with advanced stage of prolapse, sexually inactive, and with levator ani muscle injury. Vaginal mesh surgery may be performed in selected patients by trained surgeons who can promptly recognise and manage any complications. The recurrence rate is low, and the overall satisfaction rate is high. The mesh-related complication rate is low; most complications are mild and can be resolved by conservative or simple surgical interventions.

Contributors

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

Conflicts of interest

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Data availability

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

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Association between vacuum extraction and subgaleal haemorrhage: can intrapartum ultrasound reduce the risks?

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Vacuum extraction is a common procedure in the labour ward. Subgaleal haemorrhage is a rare neonatal complication that can be life threatening. We examine the risk factors associated with subgaleal haemorrhage after vacuum extraction, including fetal head malposition and inappropriate cup placement, and the role of intrapartum ultrasound in reducing perinatal complications. Although there is an increasing trend for using intrapartum ultrasound for more precise diagnosis of fetal head position, there is no evidence that this practice reduces failed vacuum delivery rates or perinatal morbidity.

Keywords: Hemorrhage; Ultrasonography; Vacuum extraction, obstetrical

Vacuum extraction and subgaleal haemorrhage

Vacuum extraction (VE) is widely performed to expediate delivery in the second stage of labour for various maternal and fetal indications. Compared with forceps delivery, VE is more commonly used because of its ease of application and low incidence of maternal trauma. Forceps delivery is more likely to achieve vaginal birth with decreased fetal trauma but has a greater risk of perineal trauma and higher pain relief requirement[1]. In Hong Kong, one study reported that the decreasing instrumental delivery rates were associated with an increase in second-stage caesarean section and a higher failed instrumental delivery rate[2].

The failure rate of VE is 4% to 6%[3-5]. VE is the most common factor associated with neonatal subaponeurotic or subgaleal haemorrhage (SGH)[6-8]. SGH is a life-threatening condition caused by bleeding into the space between the galea aponeurosis and pericranium of the scalp (Figure 1). The loose areolar tissue that lies in this potential space can accommodate a large volume of blood; newborns with SGH can lose more than half of total blood volume and result in hypovolaemic shock, coagulopathy, anaemia, hyperbilirubinaemia, and death[6,9]. The incidence of SGH is estimated to be 0.4 per 1000 spontaneous vaginal deliveries and 5.9 per 1000 VE deliveries[10], whereas 60% to 89% of SGH occur as a result of VE[7]. Perinatal mortality secondary to SGH can be as high as 25%, but prompt recognition greatly decreases mortality[8]. A study demonstrated that a mean time to diagnosis of 1 hour was achievable with a formal surveillance for all babies born following VE, and that the mortality rate can be as low as 2.8% with prompt recognition and active management[11].

Mild SGH with no clinical sequelae is often not detected, which results in an over-estimation of the overall morbidity and mortality from SGH based on moderate or severe cases. In a retrospective review of SGH cases in 10 years, 19% were mild, 48% were moderate, and 33% were severe[12]. Hypovolemic shock occurred in 48% of cases, encephalopathy in 62%, coagulopathy in 24%, and neonatal death in 14%. Nonetheless, long-term outcomes were good in surviving infants.

According to the Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines, risk factors for SGH include VE or attempted VE, particularly with inappropriate placement of vacuum cup, prolonged vacuum application over >20 minutes, ≥3 tractions during contractions, detachment of vacuum cup, VE at <36 weeks gestation (relatively contra-indicated at <36 weeks and contraindicated at <34 weeks), nulliparity, and fetal coagulation defects such as congenital haemophilia[8]. However, most babies delivered by VE with these risk factors do not have SGH. When VE fails, sequential instrumental (usually forceps) delivery or second-stage caesarean section is associated with increased risks

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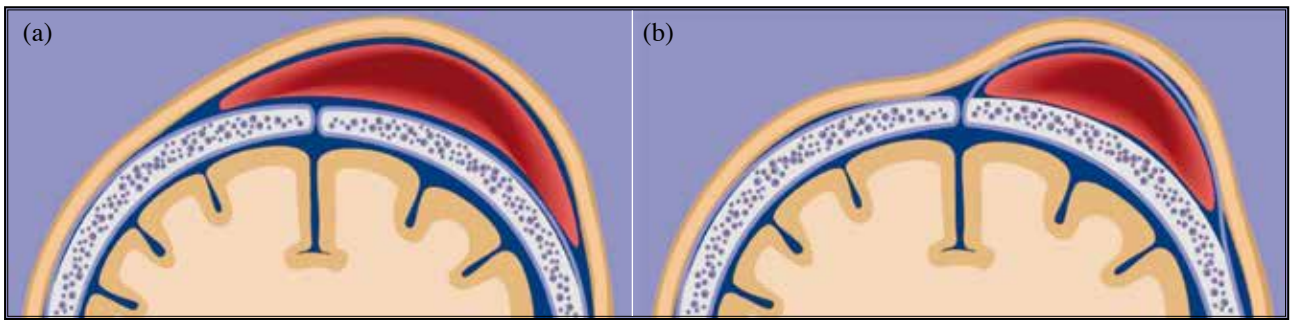

Figure 1. (a) Subgaleal haematoma crossing the suture line, (b) cephalohaematoma does not cross the suture line (reproduced from ALSO course materials 2020 with permission from ALSO (HK) Advisory Board)

of maternal and fetal complications including postpartum haemorrhage, neonatal intracranial haemorrhage, cranial facture, other birth trauma, and neonatal asphyxia[4,13-15].

Comparing babies with or without SGH after attempted VE, six independent risk factors have been identified: second-stage duration (for each 30-minute increase: adjusted odds ratio (aOR)=1.13, p=0.006), presence of meconium-stained amniotic fluid (aOR=2.61, p=0.001), presence of caput succedaneum (aOR=1.79, p=0.01), duration of VE (for each 3-minute increase: aOR=2.04, p<0.001), number of dislodgments (aOR=2.38, p<0.001), and fetal head station (aOR=3.57, p=0.006). VE duration of ≥15 minutes has 96.7% sensitivity and 75.0% specificity in predicting SGH, with the area under the receiver operating characteristic curve being 0.849[9]. Various factors that contribute to a difficult VE are associated with increased risks of SGH.

Malposition of fetal head

Occipital-posterior positioning of the fetal head is associated with the need for rotational delivery and failed VE. Malposition of fetal head complicates 2% to 13% of births at delivery, leading to increased obstetric interventions and adverse fetal and maternal outcomes[16]. In a cohort of 17 533 women in Hong Kong in 2000, the overall incidence of malposition was 14%, and the operative delivery rate of this group was 82.5%, which was higher than the 20.7% in the occipital-anterior position (control) group[17]. After excluding cases of operative delivery for non-mechanical indications such as fetal distress, the malposition group had higher odds of all assisted deliveries (aOR=9.8) and caesarean sections (aOR=30.2). In addition, the malposition group had longer duration of second stage, higher birth weight, higher incidence of low Apgar scores (0.52% vs 0.29%), and more birth trauma (2.15% vs 0.95%). Compared with infants born after a successful VE, those with failed VE had higher risks of SGH (OR=7.3), convulsions (OR=1.9), and low Apgar score (OR=2.6)[18]. Of 12 063 women with singleton pregnancies, 9.2% underwent VE, of whom 77.9 % were in the occipital-anterior position group and 22.1% were in the occipital-posterior position group[19]. The latter had a higher rate of single detachment of vacuum cup (11.3% vs 6.7 %, p=0.02) and higher risks for SGH (aOR=4.36, p=0.03) and low 5-min Apgar score (aOR=4.63, p=0.02). Independent factors associated with vaginal delivery failure include ethnicity, arrest or maternal exhaustion as an indication, occipital-posterior position, and a low (vs outlet) pelvic application[20]. Malposition of fetal head is a consistent risk factor for failed VE, and occipital-posterior position is an independent risk factor for SGH.

Vacuum cup placement

Suboptimal placement of the vacuum cup as a risk factor for SGH was controversial. In a study measuring both midline and anterior-posterior line deviations from the ideal cup placement, the mean deviation from the mid anterior-posterior line was 3.72±1.46 cm, and the mean midline-lateral deviation was 1.92±1.33 cm[21]. Cup placement deviations were similar between residents and consultants as well as between successful and failed procedures, despite a high failure rate of 8.6%. The authors asked for scientific proof that accurate placement of the vacuum cup would improve outcome; if this was clinically important, the deviation from ideal placement location ought to become a universal quality measure[21].

Of 338 (3.4%) of 10 066 babies delivered by VE, 71 (21.0%) had SGH[11]. The exceedingly high incidence of SGH was based on the clinical detection of a tender fluctuant scalp swelling across the skull suture lines rather than on radiological imaging. Risk factors for SGH were maternal nulliparity (aOR=4.0), failed VE (aOR=16.4), Apgar score of <8 at 5 minutes (aOR=5.0), marks of vacuum cup over the sagittal suture (aOR=4.4), and marks

of leading edge of vacuum cup at <3 cm away from the anterior fontanel of infant head (aOR=6.0). Conventional teaching, including acute life support in obstetrics training, dictates that the vacuum cup should be placed over the flexing median position[22,23], with the leading edge of the cup at least 3 cm away from the anterior fontanelle (Figure 2). Therefore, placement of the vacuum cup at a distance too near the anterior fontanelles is a risk factor for SGH and may lead to deflection of the fetal head during delivery and hence difficulty in delivery[22,23]. When downward traction is applied with the cup placed in such a position, the traction force has slanting or shearing effects on the scalp, as the direction of traction is not perpendicular to the scalp, resulting in lacerations or tears of the transosseous emissary veins and hence SGH[11]. Paradoxically, when the vacuum cup is placed to one side of the sagittal suture, particularly at a distance of ≥3.0 cm away from the anterior fontanelle, the resultant deflection of the head decreases the risk of SGH[11]. This is contradictory to conventional teaching, as by the nature of the deflection that is apparently protective against SGH produces asynclitism that makes delivery more difficult[24]. These findings imply that even when the vacuum cup is optimally placed on the flexion point in the midline, SGH may still occur when the direction of traction is not perpendicular to the scalp. However, suboptimal placement with lateral deviation to one side of the sagittal suture may spare the central emissary veins as long as delivery of the fetal head is achieved. Therefore, although cup placement on the flexion point should be the most desirable mechanically to effect delivery, such optimal cup placement does not guarantee prevention of SGH.

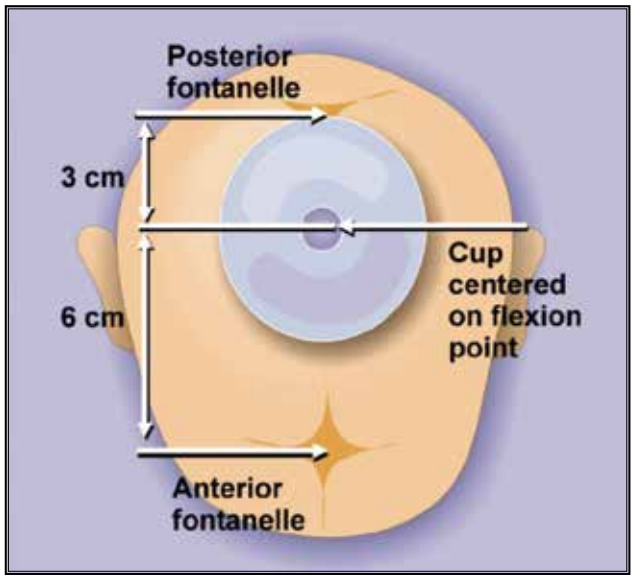

Figure 2. Proper vacuum cup position at the flexion point (reproduced from ALSO course materials 2020 with permission from ALSO (HK) Advisory Board)

Intrapartum ultrasound

Intrapartum ultrasound has been advocated in the recent two decades, challenging the conventional practice in the labour ward of assessing the progress of labour and position of the fetal head based solely on clinical vaginal examination. Intrapartum ultrasound provides a more objective assessment of fetal head position than digital vaginal examination. Correct identification of fetal head position is particularly useful before instrumental delivery, although fetal head position in the first stage of labour should not be used to predict successful vaginal delivery[25]. Early studies showed that transabdominal ultrasound is more accurate than clinical examination,

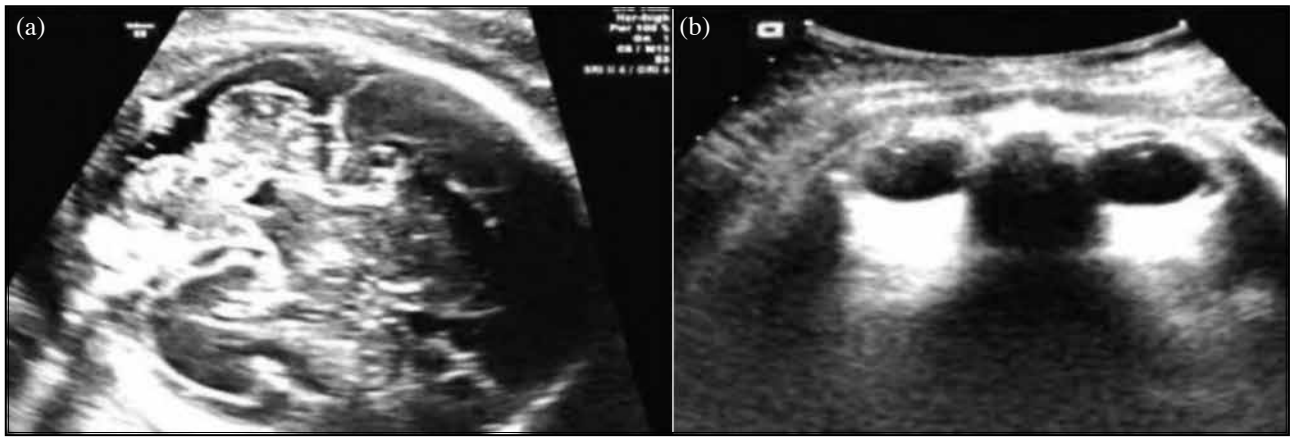

Figure 3. Intrapartum transabdominal ultrasound showing the fetal head position: (a) occiput and cerebellum shown anteriorly in occipital anterior position, and (b) anterior pointing orbits in occipital posterior position (reproduced from ALSO course materials 2020 with permission from ALSO (HK) Advisory Board)

while transperineal ultrasound was later introduced to measure the head perineal distance to demonstrate the fetal head station and to visualise the descent of the fetal head during the second stage of labour[25-28] (Figure 3).

In a prospective study among Hong Kong women with prolonged second stage of labour, transabdominal ultrasound assessment of the fetal head position improves the accuracy of vacuum cup placement during VE[29]. The mean distance between the centre of the chignon and the flexion point was shorter in those with both digital examination and ultrasound assessment than in those with digital examination alone (2.1±1.3 cm vs 2.8±1.0 cm, p=0.039). However, the study was underpowered to determine pregnancy outcomes.

In 478 nulliparous term women, instrument placement was suboptimal in 28.8% of deliveries[30]. Factors associated with suboptimal instrument placement included fetal malposition (OR=2.44), mid-cavity station (OR=1.68), and forceps as the primary instrument (OR=2.01). Compared with optimal instrument placement, suboptimal placement was associated with prolonged hospital stay (aOR=2.28), neonatal trauma (aOR=4.25), and more frequent use of sequential instruments (aOR=3.99) and caesarean section (aOR=3.81) for failed instrumental delivery. The mean decision-to-delivery interval was 4 minutes longer in the suboptimal placement group. Suboptimal instrument placement was associated with increased maternal and neonatal morbidity and procedural complications.

To reduce the incidence of suboptimal placement and subsequent morbidity, 514 nulliparous women at term with singleton cephalic pregnancies were randomised to receive clinical assessment with or without ultrasound assessment[13]. The incidence of incorrect diagnosis was lower in those with both clinical and ultrasound assessments (1.6% vs 20.2%, OR=0.06, p<0.001). However, the two groups were comparable in terms of the decision-to-delivery interval and the rates of maternal and neonatal complications, failed instrumental delivery, and caesarean section. Ultrasound assessment prior to instrumental delivery reduced the incidence of incorrect diagnosis of the fetal head position without delaying delivery but did not reduce morbidity.

In a study to evaluate the effect of ultrasound determination of fetal head position on the mode of delivery, women with a singleton term pregnancy in vertex presentation, cervical dilation of ≥8 cm, and epidural anaesthesia were randomly assigned to receive digital vaginal and ultrasound examinations (n=944) or digital vaginal examination alone (n =959). Those with both examinations had higher overall rate of operative delivery (33.7% vs 27.1%, p=0.002), rate of caesarean delivery (7.8% vs 4.9%, p=0.01), and rate of instrumental vaginal delivery (25.8% vs 22.2%, p=0.07)[31]. Neonatal outcomes were similar between the two groups. Addition of ultrasound examination did not improve management of labour and increased the rate of operative delivery without decreasing maternal and neonatal morbidity.

In the RISPOSTA (Randomised Italian Sonography for occiput position trial ante vacuum) trial to assess whether sonographic assessment of fetal head position before VE can reduce the risk of failure and perinatal complications in singleton, term cephalic presenting fetuses, 653 women per group was initially planned based on the hypothesis that the risk of failed VE would be 5% when vaginal examination alone was used and decrease to 2% when ultrasound assessment was used[32]. The study was terminated for futility after an interim analysis of 222 women. The two groups were comparable with respect to the incidence of emergency caesarean section owing to failed VE and other maternal outcomes. Women assessed by both vaginal and ultrasound examinations had a higher incidence of non-occipital anterior position of the fetal head and a lower incidence of incorrect diagnosis of the fetal head position. Recruitment was slow, as many women were excluded because ultrasound examination was a routine before instrumental delivery. Although ultrasound examination enables more accurate knowledge of fetal head position, the authors projected that the study was unlikely to demonstrate any clinical benefits or improved delivery outcomes.

In a similar trial, women at term, with full cervical dilatation, singleton fetus in cephalic presentation, and an established indication for instrumental vaginal delivery were randomised to undergo no ultrasound assessment (n=109) or both transabdominal ultrasound (to determine the fetal head position) and transperineal ultrasound (to evaluate the angle of progression) before instrumental vaginal delivery (n=113)[33]. The two groups were comparable in terms of composite measures of maternal morbidity (23.9% vs 22.9%, OR=1.055) and neonatal morbidity (9.7% vs 6.4%, OR=1.57). The trial was stopped for futility before reaching the required sample size.

In a meta-analysis of 1463 women, compared with standard care, ultrasound assessment prior to instrumental vaginal delivery did not affect the caesarean

section rate (p=0.805), the composite adverse maternal outcome (p=0.428), perineal lacerations (p=0.800), postpartum haemorrhage (p=0.303), shoulder dystocia (p=0.862), prolonged stay in hospital (p=0.059), and composite adverse neonatal outcome (p=0.400)[34]. There was no increased risk of abnormal Apgar score (p=0.882), umbilical artery pH of <7.2 (p=0.713), base excess of >-12 (p=0.742), admission to neonatal intensive care unit (p=0.879), or birth trauma (p=0.968). The risk of incorrect diagnosis of fetal head position was lower when ultrasonography was performed before instrumental delivery, with a relative risk of 0.16 (p<0.001). Although ultrasound examination was associated with a lower rate of incorrect diagnosis of fetal head position and station, it failed to translate to improvement of maternal or neonatal outcomes[34].

Controversy of inclusion of intrapartum ultrasound in guidelines

One explanation for the failure of intrapartum ultrasound to improve delivery outcomes is the complexity of instrumental delivery. In addition to fetal head position and cup placement, other factors such as engagement, station of the presenting part, fetal size, and maternal pelvic dimensions should be taken into account[34]. The enhanced diagnosis of fetal head malposition by intrapartum ultrasound may not have enhanced the ability of the accoucheur to deal with the malposition. The inherent difficulty for the accoucheur to place the cup on the optimal flexion point in the presence of malposition is well recognised, and the use of occipital-posterior cups has not been shown to improve success rates. In addition, even when cup placement can be improved, this benefit has not been sufficient to reduce the failure rate of such procedures. Although the misdiagnosis rate for fetal head position without ultrasound assessment is >20%, the failure rate for instrumental delivery is consistently around 5%, and the success rate for VE in misdiagnosed cases is still around 70% to 80%. Although maternal and neonatal complication rates from these cases are higher, major complications including severe SGH remain low. Indeed, severe neonatal complications in those without intrapartum ultrasound are low. Given that accuracy of the fetal head position has little impact on the management decision in most scenarios apart from improvement in cup placement, it is not surprising that the morbidity rates are similar in those with or without intrapartum ultrasound.

According to the updated guidelines of the Royal College of Obstetricians and Gynaecologists in 2020[5], ultrasound assessment of the fetal head position prior to assisted vaginal birth is recommended where uncertainty exists following clinical examination. Although ultrasound assessment is more reliable than clinical examination, there is insufficient evidence to recommend the routine use of abdominal or perineal ultrasound to assess the station, flexion, and descent of the fetal head in the second stage of labour[5]. In practice, most misdiagnoses of fetal head position are made by accoucheurs who are certain they are correct. The more experienced the accoucheurs, the more likely they are confident with their perception and the less likely they resort to ultrasonography for verification. No significant alterations in clinical management are expected in such situations.

The International Society of Ultrasound in Obstetrics and Gynaecology published the first international guideline to endorse the use of intrapartum ultrasound before operative vaginal delivery[35], stating that the sonographic demonstration of fetal head position before considering or performing vaginal delivery is strongly recommended. The recommendation is based on Aristotelian logic, with the syllogism: if ultrasonography before placement of vacuum cup or forceps (A) enables a more precise determination of fetal position (B), and if the exact knowledge of position (B) makes safer the traction manoeuvre (C) owing to more accurate placement of the instrument (A), then ultrasonography may improve the safety and effectiveness of the operative vaginal delivery (A=B, B=C, so A=C)[36]. However, clinical data do not support this argument. The assumption that B=C is too optimistic, as the inherent difficulties with malpositions render this assumption only partially valid. Nevertheless, theoretically, knowing the precise fetal position is better than not knowing, and more routine use of intrapartum ultrasound as part of standard labour ward protocols is the trend. One may foresee the use of intrapartum ultrasound to trace the paths of electronic fetal heart monitoring in labour, where despite the lack of irrefutable evidence that it may improve perinatal outcome, would insidiously become part and partial of our everyday labour ward practice. It is anticipated that with the more and more routine use of intrapartum ultrasound, further attempts in conducting randomised trials on its use would be even more difficult and futile. The potential harm of the increasing rate of second stage caesarean section associated with the routine use of intrapartum ultrasound is a concern. It is unknown whether the overall incidence of clinically significant SGH secondary to VE decreases with the increase in the rate of second stage caesarean section.

Contributors

All authors designed and drafted the manuscript, and

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

Conflicts of interest

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

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Data availability

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

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Maternal special care unit in the delivery suite: experience from Prince of Wales Hospital

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This article summarises the history of the establishment of the first maternal special care (MSC) unit in Hong Kong. The authors highlight the use of obstetric early warning system, the levels of care for critically ill mothers, the equipment used in MSC, and the midwifery training in maternal critical care. The authors also present the statistics of MSC admissions at Prince of Wales Hospital from 2018 to 2020.

Keywords: Critical care; Maternal mortality; Midwifery

Background

The maternal mortality ratio in Hong Kong is <5 per 100 000 registered live births, which is among the lowest in the world[1]. However, the number of maternal mortalities may be under-reported,[2,3] as Hong Kong does not have confidential enquiries into maternal deaths or obstetric surveillance programme for severe and near-miss maternal morbidities[4,5]. In addition, the median age for first childbirth among Hong Kong women is consistently rising. In the latest census report, the number of live births born by younger women has reduced by half, whereas that by women of advanced maternal age has doubled[6]. The ageing maternity population is associated with higher rates of co-existing medical diseases and obstetrics complications[7-9]. According to the World Health Organization, the top three causes for maternal deaths are obstetric haemorrhage, sepsis, and hypertensive disorders, accounting for 50% of all maternal mortalities[10]. Other common causes are venous thromboembolism and amniotic fluid embolism. The disease pattern of maternal death in Hong Kong is similar, based on data of intensive care unit (ICU) admissions for obstetric patients[11-13] and maternal mortalities[2,3,14,15]. Maternal critical care comes into play, as management of these deathly obstetric conditions often involves intensive care.

Introduction of maternal critical care

In the confidential enquiries into maternal deaths report in 1985 to 1987 in the UK, delay and difficulty in recognising critical illness in mothers has been identified as a recurring problem leading to maternal mortality[16,17]. This prompted the establishment of proper facilities for mothers in need[18,19]. Since then, centralised high dependency care with appropriately trained staff and monitoring equipment and techniques has been promoted across UK. In 2011, the Maternal Critical Care Working Group in the UK published the first document specifically for maternal critical care provision[20].

In the United States, with the rising maternal morbidity and mortality secondary to increasing medically complex obstetric population, critical care in obstetrics is considered the key strategy to address the issue[21]. In 2009, the American College of Obstetricians and Gynecologists published the first clinical management guideline for critical care in pregnancy. The latest version was updated in 2019[22]. Although the service models of maternal critical care vary widely among different healthcare systems with no globally agreed standard, it is now recognised as an important tool to reduce maternal morbidity and mortality[21,23-25].

Establishment of maternal special care unit

In 2013/14, a proposal of setting up a high dependency unit in the delivery suite was submitted to the Hospital Authority New Territories East Cluster annual planning exercise by the Prince of Wales Hospital, which has the highest birth rates among all birth units. A service gap was identified as the number of high-risk pregnancies was increasing, and the service need was reviewed at the Service Management Meeting. In 2015/16, a proposal further expanded to include all birth units was submitted to the Clinical Coordinating Committee. It was agreed that

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the service gap was big for all birth units as there were significant manpower shortage, lack of staff training, lack of modernised monitoring equipment, and lack of resources allocated. The proposal obtained full support, with funding to improve obstetric care by setting up maternal special care beds with modern equipment and trained staff.

The Prince of Wales Hospital was one of the pilot hospitals to kick off this project. Two additional nurses were allocated, and funding was provided to procure equipment and to train doctors and midwives. In May 2018, the first maternal special care (MSC) bed was set up within the delivery suite. It serves as an intermediary unit between the ICU and the general ward to help to reduce the number of admissions to ICU and shorten the duration of ICU stay. Patient safety is enhanced by intensive monitoring of high-risk cases, prompt recognition of deteriorated cases, early consultation to ICU, and emergency care before transferring to ICU. Placing MSC within the delivery suite enables optimal management of specific obstetric conditions and reduction of mother-baby separation. MSC is managed by a multidisciplinary team of maternal medicine specialists, obstetricians, obstetric anaesthetists, and midwives with critical care training. Owing to high utilisation rate in the first year, more funding was given to expand MSC to two beds.

Obstetric early warning system

The early warning system to detect early symptoms or/and signs of maternal deterioration is highly accurate in predicting death among critically ill obstetric patients[26]. As obstetric patients have altered physiological parameters secondary to pregnancy, several different early warning systems have been modified for this special group of patients[27]. The aim is to raise clinical awareness of potential serious events and to trigger urgent patient evaluation and hence timely diagnosis and prompt intervention so as to reduce maternal morbidity and mortality.

We referenced several different early warning systems[27-29] and generated our own system that is applicable to all obstetric patients in our unit. A colour-coded (yellow or red) observation chart is used to guide the escalation of care (Table 1). It is important to note that the respiratory rate is an early indicator of patient deterioration[30]. Despite its clinical importance, the respiratory rate is the least accurately measured vital sign. Its assessment is often neglected or inaccurately performed owing to a lack of training or knowledge or a lack of time under heavy workload[31]. Therefore, highlighting assessment of the respiratory rate is important in nursing education, particularly critical care training. However, the early warning system has limitations. It cannot replace proper attainment of the vital signs, prompt reaction to escalation, effective communication, accurate clinical judgment, and prompt management[32]. In addition, the early warning system only provides a snapshot of a patient's current vital signs; any insidious changes over time may be missed if the situation awareness is low[33]. Although obstetric patients are mostly young and fit with a good compensatory capacity, failure to identify these subtle changes may result in a point of no return when the patient decompensates and enters a catastrophic stage.

Three levels of care for critically ill mothers

In August 2018, the Royal College and Obstetricians and Gynaecologists, the Royal College of Midwives, The Royal College of Anaesthetists and the Faculty of Intensive Care Medicine jointly published a guideline titled Care of the Critically Ill Woman in Childbirth: Enhanced Maternal Care. Collaboration among maternity units, critical care units, and other specialities' is important to provide appropriate levels of care in a timely manner[34]. The levels of competency and the role required by midwives are clearly defined, which include management of the central venous access and the arterial line.

Table 1. Obstetric early warning system in Prince of Wales Hospital

Parameter	Yellow (if any one parameter occurs, then inform case nurse or house officer)	Red (if any one parameter occurs, then inform nurse in charge and medical officer)
Level of consciousness	-	Response only to voice/pain/unresponsive
Blood pressure, mmHg	Systolic ≥140 or diastolic≥90	Systolic ≤90 or ≥160 or diastolic ≤50 or ≥100
Heart rate, beats per minute	≤50 or ≥110	≤40 or ≥120
Temperature, °C	≥37.5	≤35 or ≥38
Respiratory rate, breaths per minute	9-11 or 21-24	≤8 or ≥25
Oxygen saturation, %	-	≤94

MSC provides level 1 care to patients at risk of deterioration who require enhanced monitoring or need additional clinical interventions, clinical input or advice, and/or as a stepping down of care from a higher level (Table 2). Level 2 care is provided to patients with greater illness severity, at higher risk of deterioration, and requiring closer or invasive monitoring. It also includes single organ support, preoperative optimisation, extended postoperative care, and/or stepping down from higher levels of care. Patients at level 2 care may decompensate rapidly, and therefore caretakers should be alert and proactively monitor for any deterioration. Additional input from the critical care team should be promptly sought to facilitate early transferal to the ICU. Level 3 care is intensive care provided in the ICU for patients requiring ≥2 organs support or advanced respiratory support such as mechanical ventilation. The staff-to-patient ratio is one critical care nurse per patient, and active management is led by intensivists.

Experience of Prince of Wales Hospital from 2018 to 2020

From May 2018 to December 2020, 815 obstetric patients (mean age, 35 years) received MSC (a mean of 25 cases per month), accounting for 5.66% of the total deliveries (Table 3). The mean length of stay in MSC was 23.8 hours. Of them, 503 (61.7%) required level 1 care and 312 (38.3%) required level 2 care. 55 women were admitted to ICU or cardiac care unit, accounting for 0.38% of the total deliveries. 430 (52.8%) women were of advanced maternal age (≥35 years). 760 (93.3%) women were booked cases in our unit. For non-booked cases, most had antenatal care in other hospitals or from mainland China. 162 (19.9%) women with gestation of <32 weeks on admission. The mean gestational age at delivery was 35 weeks. The earliest gestation on admission to MSC was 16 weeks and 3 days owing to maternal sepsis.

Table 2. Conditions equivalent to level-1 and level-2 care

Conditions equivalent to level-1 care
1-2 L oxygen supplement via nasal cannula or face mask to maintain oxygen saturation
Severe pre-eclampsia on magnesium sulphate prophylaxis with or without oral anti-hypertensive
Magnesium sulphate infusion for neuroprotection in preterm labour <32 weeks gestation
Postpartum haemorrhage at risk of further bleeding, requiring additional monitoring or additional medical treatment (transamine or haemabate)
Cardiac diseases requiring cardiac monitoring
Diabetes mellitus requiring insulin infusion
Sepsis requiring close monitoring (early consultation to intensive care unit [ICU] if patient is not responding to initial treatment or showing signs of deterioration despite treatment)
Morbidly obese women who received general anaesthesia
Other medical conditions requiring close monitoring as requested by obstetrician/anaesthetist
Stepping down from higher level of care for monitoring eg ICU
Conditions equivalent to level-2 care
Invasive monitoring by arterial line or central venous catheter line
>2L oxygen supplement via nasal cannula or face mask to maintain oxygen saturation
Use of AirVO2 to maintain oxygen saturation (early consultation to ICU if escalating respiratory support)
Pulmonary oedema/ fluid overload requiring intravenous furosemide
Severe hypertension or pre-eclampsia requiring intravenous anti-hypertensive
Eclampsia requiring magnesium sulphate infusion to control seizure (not prophylaxis)
Cardiac conditions requiring use of intravenous anti-arrhythmic drug eg ATP, verapamil
Monitoring for acute renal or hepatic failure eg HELLP syndrome or acute fatty liver
Major postpartum haemorrhage requiring additional surgical management eg compression sutures/Bakri balloon/uterine artery embolisation/hysterectomy
Severe sepsis or septic shock (interim while consulting ICU)
Other medical conditions requiring close monitoring as requested by obstetrician/anaesthetist
Stepping down from higher level of care for monitoring eg ICU

Table 3. Maternal special care unit admissions in Prince of Wales Hospital, 2018-2020

	May to December 2018*	2019*	2020*
Total deliveries	3954	5871	4583
Intensive care unit admission	15 (0.38)	22 (0.37)	18 (0.39)
Maternal special care unit admission	177 (4.5)	362 (6.2)	276 (6)
No. per month	22.1	30.2	23
Level 1 care	97 (55)	235 (65)	171 (62)
Level 2 care	80 (45)	127 (35)	105 (38)
Duration of stay, hours	25.8 (1.4-144.5)	24.1 (0.4-120)	21.7 (0.1-117.9)
Stay for ≥72 hours	2 (1.1)	6 (1.7)	4 (1.4)
Maternal age, y	35 (18-48)	34 (19-48)	35 (21-46)
Advanced maternal age (≥35 y)	96 (54)	184 (51)	150 (54)
Non-booked cases	13 (7.3)	27 (7.5)	15 (5.4)
Gestation on admission, weeks	16+6 to 41+3	16+3 to 41+5	19+2 to 41+3

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

Table 4. Patient distribution in terms of levels of care and conditions

Condition	Level 1 care*	Level 2 care*
Pre-eclampsia/eclampsia	220 (59.6)	149 (40.4)
Massive haemorrhage	62 (35.6)	112 (64.4)
Preterm labour <32 weeks	108 (94.7)	6 (5.3)
Sepsis	21 (61.8)	13 (38.2)
Endocrine conditions	43 (100)	0
Cardiac diseases	21 (63.6)	12 (36.4)
Respiratory diseases	9 (29)	22 (71)
Acute fatty liver / HELLP syndrome	0	20 (100)
Others	17 (38.6)	27 (61.4)

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

The most common indication for MSC was pre-eclampsia/eclampsia (n=369, 45%), followed by massive haemorrhage (n=174, 21%), preterm labour before 32 weeks requiring magnesium sulphate for neuroprotection (n=114, 14%), endocrine conditions (most frequently diabetes mellitus requiring dextrose-potassium-insulin infusion) (n=43, 5%), cardiac diseases requiring continuous cardiac monitoring (eg, hypertrophic obstructive cardiomyopathy, severe supraventricular tachycardia, Wenckebach heart block, Barlow's disease, cardiomegaly, Wolff-Parkinson-White syndrome, transposition of the great arteries, non-specific chest pain) (n=33, 4%), severe sepsis (n=31, 4%), respiratory diseases (n=31, 4%), acute fatty liver or HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome (n=20, 2%), and others (such as malignancies, acute pancreatitis) (n=44, 5%). Some women had more than one indication; the most common co-existing indication was severe pre-eclampsia complicated by massive postpartum haemorrhage secondary to uterine atony. All women with endocrine conditions required level 1 care only. About 40% of women with hypertensive disorders, sepsis, or cardiac diseases required level 2 care. Women with massive haemorrhage, respiratory diseases, or other less common conditions required more intensive monitoring and interventions such as arterial line and central venous line monitoring (Table 4).

Of 55 (0.38%) ICU admissions, 44 (80%) were during the postpartum period and 11 (20%) were during antenatal period. The most common mode of delivery was Caesarean section (n=39, 88.6%), followed by vacuum extraction (n=2), normal vaginal birth (n=2), and assisted breech delivery (n=1). The most common indication for ICU admission was sepsis or septic shock (n=13, 23.6%), followed by severe pre-eclampsia/eclampsia (n=11, 20%), massive haemorrhage (n=10, 18.2%), respiratory disease (n=8, 14.5%), others (n=8, 14.5%), and cardiac disease (n=5). The mean duration of ICU stay was 38.6 (range, 4.7-410.8) hours; four (7.3%) women stayed in ICU for >3 days. The mean blood loss secondary to massive postpartum haemorrhage was 5.3 L. Postpartum haemorrhage was mainly caused by placenta accreta spectrum (n=2) or uterine atony (n=8) and was controlled by compression sutures (n=8), insertion of a Bakri Balloon (n=6), or hysterectomy (n=3). One patient had cardiac arrest secondary to severe haemorrhage and was revived after cardiopulmonary resuscitation for 4 minutes. The total estimated blood loss was 8 L.

Of 11 women admitted to ICU for severe preeclampsia, two had concomitant eclampsia and three had concomitant HELLP syndrome. Other complications included acute pulmonary oedema and deranged renal function. Of 13 women admitted to ICU for sepsis or septic shock, one developed septic shock after medical termination of pregnancy and the remaining 12 were for non-obstetric reasons such as pyelonephritis and urosepsis. Five of the 12 patients had cardiovascular problems (pulmonary hypertension, moderate to severe mitral regurgitation, moderate to severe mitral stenosis, moderate ventricular septal defect, and infective endocarditis). The most common respiratory problem was asthmatic attacks. Other problems include acute pancreatitis, stomach cancer, and brain cavernoma.

There was one maternal death among the 14 408 deliveries. The woman had multiple obstetric complications including massive postpartum haemorrhage, severe pre-eclampsia, and severe sepsis. She was initially stabilised in ICU and transferred back to MSC unit for close monitoring after postpartum day 1. She deteriorated on day 3 and was transferred back to ICU. She developed asystole arrest that did not respond to cardiopulmonary resuscitation. Autopsy confirmed the cause of death was severe sepsis.

Equipment in maternal special care unit

The high-flow nasal cannula system is used for respiratory support. It enhances comfort with humidification and efficiency with ventilation by washout of nasopharyngeal dead space and provision of a small positive airway pressure effect[35]. In patients with hypoxaemic respiratory failure, it improves oxygenation and decreases the need for intubation[36,37]. It is commonly used in the emergency department and ICU.

Blood gas analyser (RAPIDPoint 500e blood gas analyser, Siemens Healthineers) is used for measurements of pH, partial pressure of carbon dioxide, partial pressure of oxygen, electrolytes (ionised sodium, potassium, calcium), and lactate levels in the blood[38]. It has a short turnaround time and is particularly useful for severe sepsis[39].

Thromboelastography (TEG®6s, Haemonetics, Braintree, MA, USA) is used as the point-of-care coagulation test to identify any coagulopathy at an early stage of postpartum haemorrhage[40]. In obstetric patients, fibrinogen plays a major role in postpartum haemorrhage and is an early predictor of coagulopathy[41,42]. It enables real-time assessment of fibrinogen and platelet functions, which may guide early intervention[43]. Current guidelines recommend maintaining a fibrinogen concentration of at least 1.5 g/L[44]. Starting from December 2020, fibrinogen concentrates are stocked in the labour ward for urgent use. Fibrinogen concentrates are superior to cryoprecipitate in terms of administration speed, as they are stored in the labour ward and transportation time is minimal. Conventional blood products such as fresh frozen plasma or cryoprecipitate take about 20 minutes to defrost in addition to time for compatibility testing and transportation[45]. In cases of massive obstetric haemorrhage or suspected amniotic fluid embolism, the combination of real-time assessment of clotting abnormalities and administration of fibrinogen concentrates is the optimum approach[46,47].

Midwifery training in maternal critical care

Patients admitted to MSC unit are cared for by midwives specialised in maternal critical care. In 2018, an overseas visit was organised for midwife leaders to learn setting up an MSC unit. They visited the Liverpool Women's Hospital, Queen Charlotte's Hospital, and St Thomas' Hospital. These hospitals have a maternal high dependency unit within the delivery suite. In 2019, the second overseas training was co-organised by The Hong Kong College of Midwives and Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong. The aim was to strengthen the knowledge in caring critically ill obstetric women. The team also visited the Texas Children's Hospital Pavilion for Women in Houston, USA, and attended the Fundamental of Critical Care in Obstetrics course organised by the Society of Critical Care Medicine.

Local trainings are available to enhance the competence of midwives in critical care. The Institute of Advanced Nursing Studies provides different levels of intensive care nursing programme: (1) Enhancement Program on High Dependency Obstetric Care (4-full-days lectures and 4 weeks clinical attachment to the adult ICU), (2) Elementary Course in Adult Intensive Care Nursing (3 days of lectures and 2 weeks clinical attachment to the adult ICU), (3) Fundamental Course in Intensive Care Nursing (3-day theory course), and (4) High Dependency Obstetrics Care (1-day seminar). Professional Training Course in Critical Care in Obstetrics is a course within the Advanced Midwifery Practice Series of Master in Obstetric and Midwifery Care organised by the Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong. This 22-hour course is designed to enhance the advanced clinical and decision-making skills in caring for women with complicated obstetric related problems.

Table 5. In-house training at Prince of Wales Hospital

In-house training	Topic	Frequency
Case review	Risk watch in obstetrics (~5 cases/month)	Monthly
Audit	Postpartum haemorrhage	Yearly
Drills	Massive transfusion protocol for obstetrics: transfer of critically ill patients, desaturation, postpartum haemorrhage, pre-eclampsia and eclampsia, maternal cardiac arrest, sepsis in pregnancy and childbirth	Half-yearly to yearly
Workshops	High dependency monitoring for obstetrics: Safe Obstetric Practice in High risk and Emergency, crew resource management	Yearly

The BASIC for Nurses course is an entry course organised by the Department of Anaesthesia and Intensive Care Faculty of Medicine, The Chinese University of Hong Kong. It is a 2-day introductory course for novice ICU and high dependency unit nurses. The Certificate Course on Essential Critical Care Nursing is organised by the Hong Kong Tuberculosis, Chest and Heart Disease Association. It is a 4-half-day course to strengthen, update, and enhance the knowledge on critical care nursing. In addition, in-house training is essential for continuous learning. Meetings, drills, workshops, and special equipment demonstrations are regularly arranged (Table 5). All aim to strengthen frontline midwives' skills and techniques to manage critically ill women and emergencies.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

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

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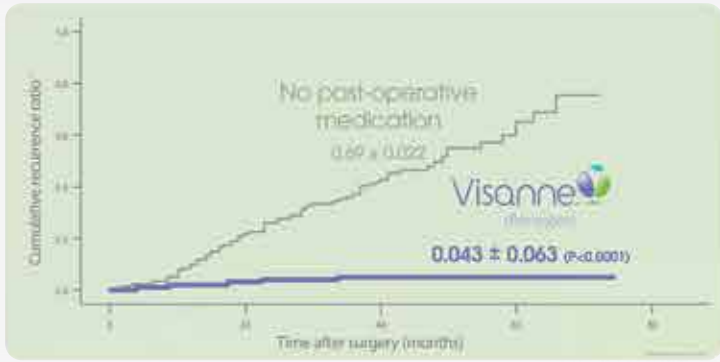

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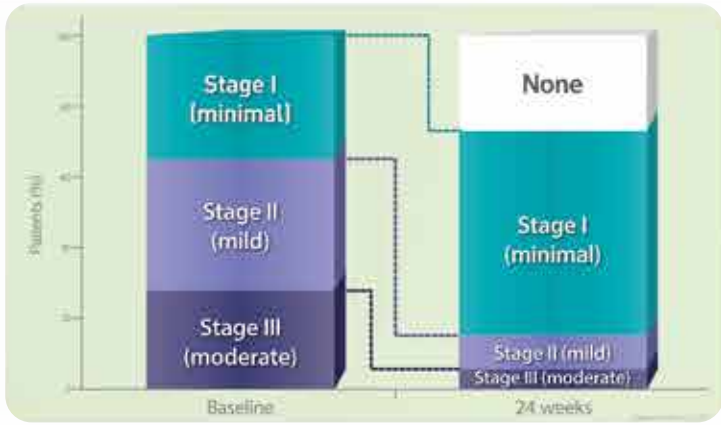
15 patients required reoperation*

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



The LONG TERM treatment for Endometriosis[1]

There's a way out of the pain

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

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

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

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