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Monday - 22 October

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Fetal anomalies and syndromes	Abnormally invasive placenta	Ovarian masses	Interactive Hubs

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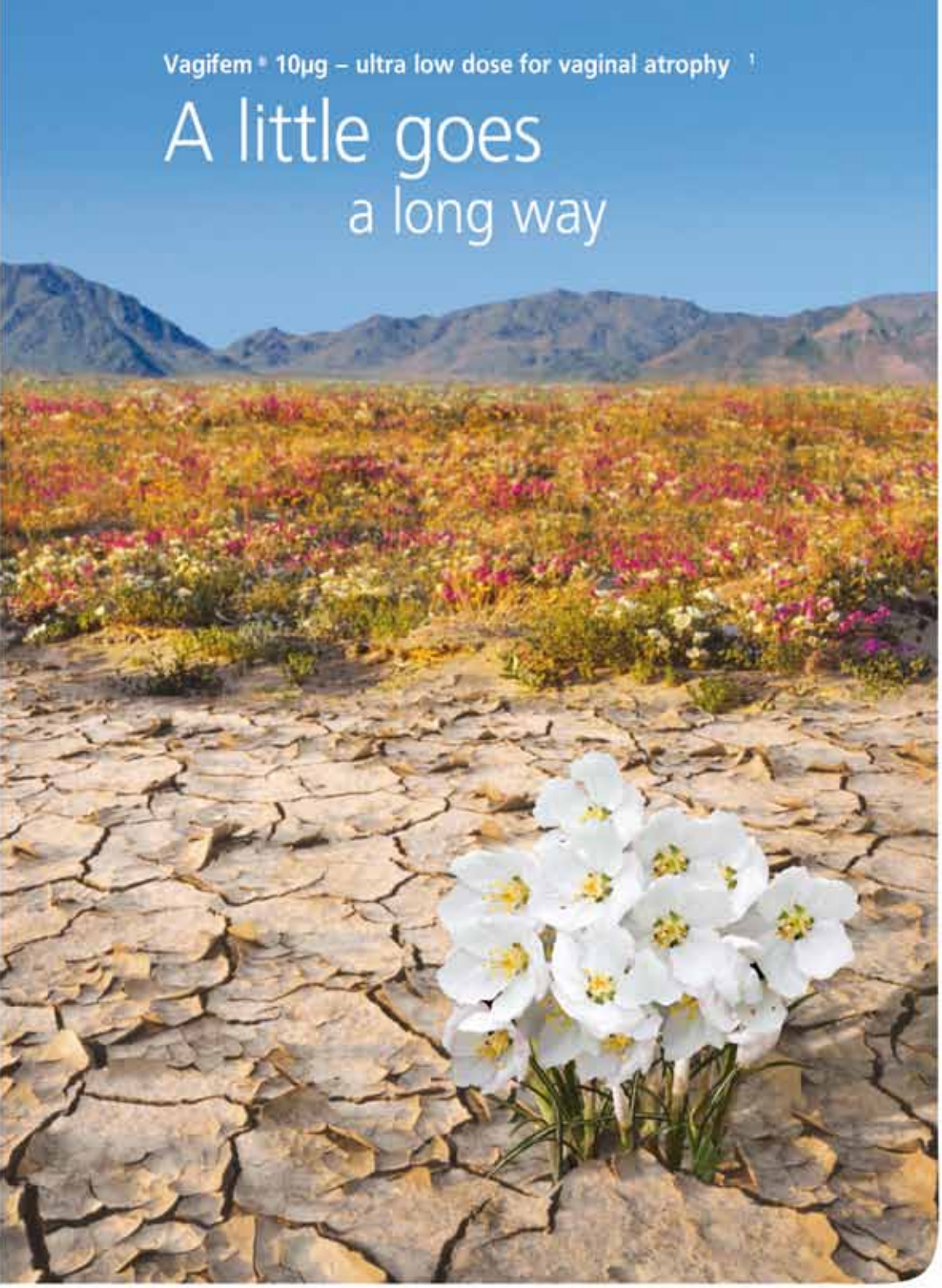

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Editorial
About Our College – the Challenges Ahead

Founded in 1988, the Hong Kong College of Obstetricians and Gynaecologists (HKCOG) celebrates its 30th anniversary this year. Our College was established to (1) encourage the study and advancement of the science and practice of Obstetrics and Gynaecology in Hong Kong; and (2) develop and maintain the good practice of Obstetrics and Gynaecology by ensuring the highest professional standards of competence and ethical integrity.

Over the years, with the efforts of our Past Presidents and Council Members, our College has developed a comprehensive and efficient infrastructure of committees and subcommittees. Human resources with continuous recruitment of trainees and good education and training are essential to continue the mission and success of our College.

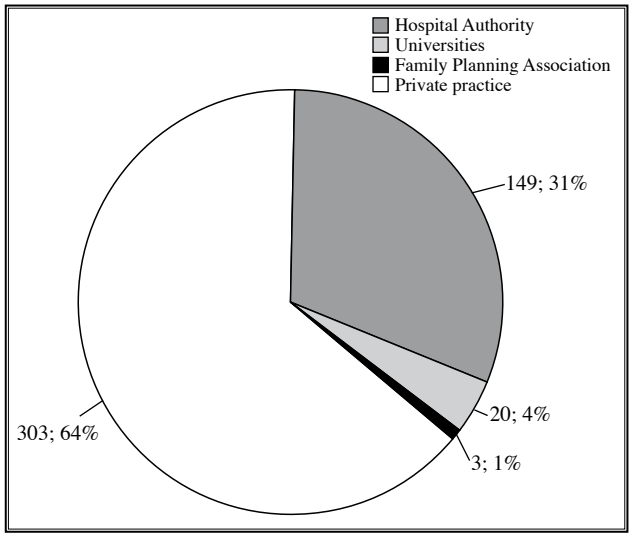

Figure 1. Distribution of practising specialists in various sectors in 2018.

Currently the HKCOG has 13 Honorary Fellows, 486 Fellows, and 55 Members. Of 475 practising obstetrics and gynaecology specialists, 35% work in the Hospital Authority or universities and are the major trainers of trainees (Figure 1). More than 50% of the specialists are female. This gender imbalance is more notable in the younger specialists, and the female-to-male ratio is even higher among trainees (Figure 2).

A survey published in the *Hong Kong Medical Journal* reported a low level of career interest in obstetrics and gynaecology among medical graduates and a decreasing popularity of the specialty as a career choice[1]. The three key influential factors were working style, clerkship experience, and career prospects. Despite this, in 2018, for the first time in recent years, all vacant resident posts in all eight training units have been filled (Table).

Our long-term goal of manpower planning over the next few years is to recruit more trainees from the Hospital Authority. A more flexible training and working schedule should be welcomed by female trainees so that they can better manage childcare and family responsibilities.

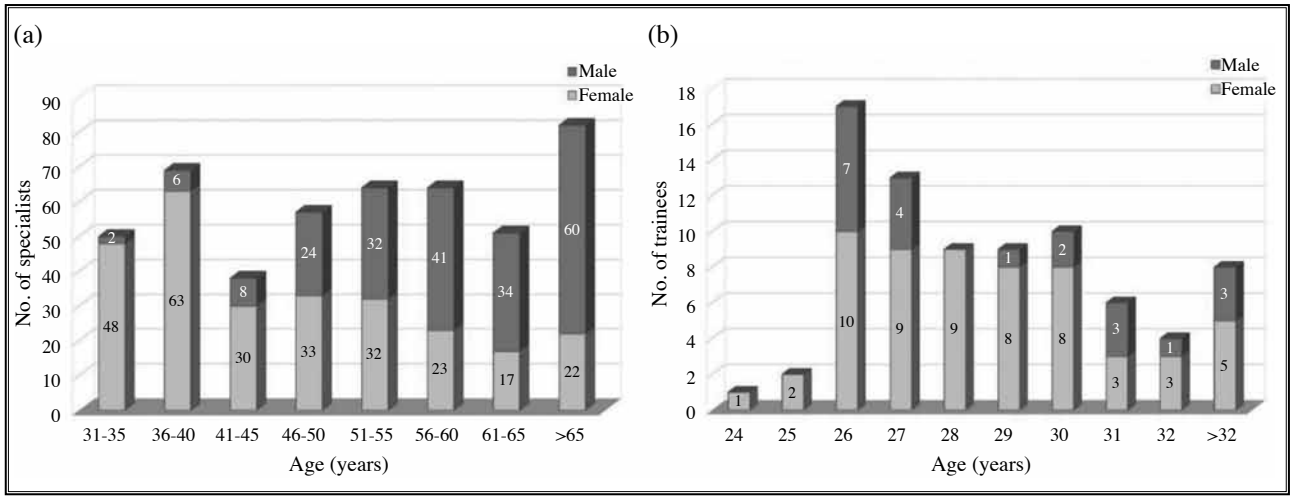

Figure 2. Age and sex distribution of practising (a) specialists and (b) trainees in 2018

Table. Recruitment of new trainees from 2013 to 2018

Year	2013	2014	2015	2016	2017	2018 (as of July)
No. of new trainees	9 (2 males)	10 (2 males)	11 (5 males)	22 (5 males)	19 (6 males)	22 (5 males)

Figure 3. (a) The lay examiner team (newly introduced) and (b) Part 3 Membership of the Royal College of Obstetricians and Gynaecologists examination faculty in Hong Kong on 13 November 2017

A new Part 3 Membership of the Royal College of Obstetricians and Gynaecologists (MRCOG) examination was introduced in November 2016, replacing the original Part 2 objective structured clinical examination. It assesses clinical knowledge, skills, attitudes, and competencies. After much preparatory work, the new Part 3 examination was first run in Hong Kong on 13 November 2017. Prior to this, a training course organised by the Royal College of Obstetricians and Gynaecologists (RCOG) for local clinical examiners and lay examiners (newly introduced) was conducted in October 2017 to prepare for the examination (Figure 3). A new memorandum of understanding was signed with the RCOG. The pass rate for local candidates was an impressive 100% (all eight trainees passed). Special thanks are due to our College Secretary, Ms Winnie Choi, for her coordination, great organisational skills, and hard work.

A revised subspecialist training programme and assessment methods were endorsed by the Hong Kong Academy of Medicine in 2016. In 2018, most subspecialists chose maternal and fetal medicine (n=55), followed by reproductive medicine (n=35), gynaecological oncology (n=18), and urogynaecology (n=11) [Figure 4].

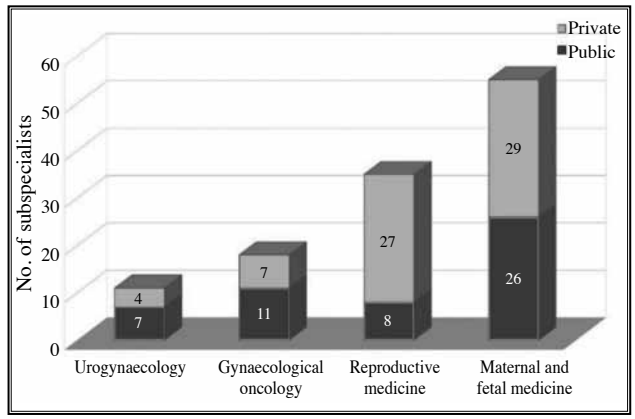

Figure 4. Distribution of subspecialists in public and private sectors in 2018

In 2015, the Medical Protection Society changed from occurrence-based to claim-based indemnity for obstetrics; this caused much uncertainty and anxiety. With the tremendous efforts of the Immediate Past President, Dr Ares Leung, the new Medical Professional Indemnity was launched by Aon in 2016 offering free coverage for an unlimited extended period following permanent retirement at age 55 years, provided that the insured has been with Medical Professional Indemnity for a minimum of 5 years immediately prior to retirement. In addition, since 2016, the Medical Protection Society has offered individuals the opportunity to make a single payment for extended reporting benefits when one retires. There are more medical insurance competitors and we have choices now. Whatever our choice is, risk management and credentialing are the

way forward. We should not be complacent because more work is required to ensure sustainability of the medical indemnity system.

The last RCOG Congress was held in Hong Kong in 1993. We made a bid for the RCOG World Congress 2021 to be held in Hong Kong once again. This involved a joint effort by the College, The Obstetrical and Gynaecological Society of Hong Kong, the two universities, and various working partners. Professor TY Leung, President-Elect of HKCOG 2019, has been appointed Chairman of the Organising Committee of this important project. On 9 June 2018, the RCOG informed us that our bid has been successful.

Wing-Cheong LEUNG
President, Hong Kong College of Obstetricians and Gynaecologists

Reference

1. Lam CY, Cheung CS, Hui AS. Factors influencing the career interest of medical graduates in obstetrics and gynaecology in Hong Kong: a cross-sectional questionnaire survey. *Hong Kong Med J* 2016; 22:138-43.

Effect of Smoking Cessation at Different Trimesters on Pregnancy Outcome

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Objective: To investigate the effect of smoking cessation at various trimesters on pregnancy outcome.
Methods: Pregnant smokers who were followed up at two public hospitals in Hong Kong between April 2011 and May 2015 were retrospectively reviewed. Based on their self-reported smoking status, women were categorised as having quit smoking in the (1) first trimester, (2) second trimester, or (3) third trimester, or (4) having continued to smoke throughout pregnancy. The four groups were compared in terms of maternal characteristics and pregnancy outcomes.
Results: During the study period, among 18,816 pregnant women, 314 (1.7%) still smoked. Of them, 275 were included: 147 (53.5%) continued to smoke throughout pregnancy and 74 (26.9%), 38 (13.8%), and 16 (5.8%) quit smoking in the first, second, and third trimester, respectively. The four groups were comparable in terms of maternal characteristics. Women who smoked fewer cigarettes were more likely to quit smoking at an earlier trimester ($p<0.001$). Women who smoked ≤5 cigarettes per day were more likely to quit smoking during pregnancy. Baby birthweight was 7% lower in women who continued to smoke throughout pregnancy than in women who quit smoking during the first trimester (2915 g vs. 3118 g, $p=0.048$).
Conclusion: Baby birthweight was lower in women who continued to smoke throughout pregnancy. Healthcare professionals should actively advise women about smoking cessation to improve pregnancy outcome, particularly those who smoke ≥6 cigarettes per day.

Hong Kong J Gynaecol Obstet Midwifery 2018; 18(2):68-72

Keywords: Cigarette smoking; Pregnancy outcome; Pregnancy trimesters; Smoking cessation

Introduction

According to the Hong Kong Census and Statistics Department in 2016, the percentage of female daily cigarette smokers aged 20 to 49 years was about 4.9%[1]. In a local cohort study of pregnant women between 1988 and 1990, the percentage of ever and current smokers was 1.57%; the baby birthweight of these ever and current smokers was 6.3% lower than that of non-smokers[2]. A Hong Kong study in 2004 reported that 60% of women who were ever-smokers stopped smoking during pregnancy[3]. Current local data on smoking cessation in pregnant women are lacking. This study aimed to investigate the effect of smoking cessation at various trimesters on pregnancy outcome.

Methods

This retrospective study was approved by the Kowloon Central/Kowloon East Clusters Research Ethics Committee of the Hospital Authority. Patient characteristics and pregnancy outcome from United Christian Hospital and Tseung Kwan O Hospital between April 2011 and May 2015 were retrieved from the Hospital Authority Obstetrics Clinical Information System, a part of the Clinical Data Analysis and Reporting System.

During universal Down syndrome screening, pregnant women were asked about their current smoking status and the number of cigarettes smoked per day, as maternal smoking affects levels of pregnancy-associated plasma protein-A, free beta human chorionic gonadotropin (in the first trimester), and inhibin-A (in the second trimester) and hence risk calculation[4,5]. Most women underwent first-trimester screening between 11 and 13+6 weeks. If they presented late, second-trimester screening was arranged between 16+0 and 19+6 weeks. During subsequent antenatal follow-up, the attending obstetrician enquired about current smoking status, time of cessation if any, and receipt of smoking cessation advice. On admission to the delivery suite, current smoking status was again recorded. Women who had a miscarriage or termination of pregnancy were excluded, as were those with missing smoking information. Women were considered lost to follow-up if they delivered at a private hospital with pregnancy outcome unknown.

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Email: kc451@ha.org.hk

Based on the self-reported smoking status, women were categorised as having quit smoking in the (1) first trimester (before 14 weeks of gestation), (2) second trimester (between 14 and 28 weeks of gestation), or (3) third trimester (after 28 weeks of gestation), or (4) having continued to smoke throughout pregnancy. The four groups were compared in terms of baseline characteristics and pregnancy outcomes including gestation at delivery, mode of delivery, birthweight, Apgar score, and baby admission location.

Statistical analysis was performed using SPSS (Version 20.0; IBM Corp, Armonk [NY], US). Continuous variables were compared using an analysis of variance, and dichotomous variables were analysed using the Chi squared test. A p value of <0.05 was considered statistically significant.

Results

During the study period, 18,816 pregnant women underwent Down syndrome screening. Among them, 314 (1.7%) still smoked. Of them, 275 were included: 147 (53.5%) continued to smoke throughout pregnancy and 74 (26.9%), 38 (13.8%), and 16 (5.8%) quit smoking during the first, second, and third trimester, respectively (Figure 1). 205 women received advice on smoking cessation during pregnancy. Of whom, 29 were offered referral to a smoking cessation clinic but 16 declined.

The four groups were comparable in terms of age, body mass index, marital status, education level, drinking status, history of recreational drug use, plan of pregnancy, parity, history of termination of pregnancy, history of preterm delivery, chronic hypertension, preeclampsia or pregnancy-induced hypertension, and pre-existing and gestational diabetes mellitus (Table). Women who smoked fewer cigarettes were more likely to quit smoking at an earlier trimester ($p<0.001$, Figure 2a). Women who smoked ≤5 cigarettes per day were more likely to quit smoking during pregnancy.

Baby birthweight was 7% lower in women who continued to smoke throughout pregnancy than in women who quit during the first trimester (2915±562 g vs. 3118±450 g, $p=0.048$, Figure 2b). Nonetheless, the four groups were comparable in terms of gestation at delivery, mode of delivery, Apgar score of <7 at 1 and 5 minutes, and neonatal admission location.

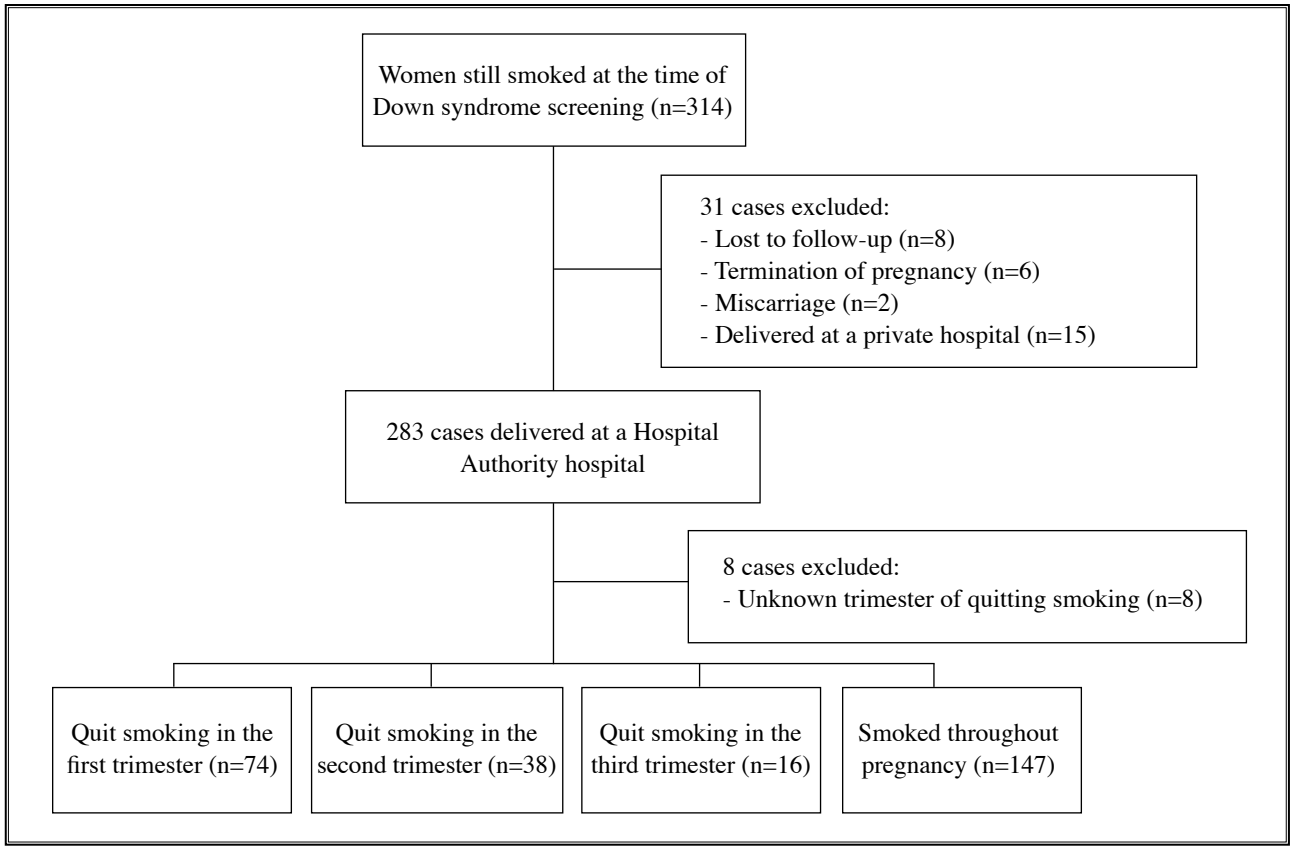

Figure 1. Flowchart of case selection

Table. Baseline maternal characteristics and pregnancy outcomes

	Quit smoking during			Continued to smoke throughout pregnancy (n=147)*	p Value
	First trimester (n=74)*	Second trimester (n=38)*	Third trimester (n=16)*		
Mean age, y	29.05±5.5	29.05±6.23	28.8±7.23	29.0±5.85	0.650
Body mass index, kg/m^2	21.8±4.7	22.0±4.4	22.2±6.3	21.9±4.9	0.992
No. of cigarettes per day	2.88±1.99	4.5±4.04	5.00±2.73	6.01±3.83	<0.001
Marital status					0.172
Single	28 (38)	12 (32)	7 (44)	40 (27)	
Married	45 (61)	26 (68)	9 (56)	94 (64)	
Divorced	1 (1)	0	0	10 (7)	
Education level					0.095
Tertiary	5 (6)	1 (3)	3 (19)	6 (11)	
Secondary	67 (91)	34 (89)	13 (81)	137 (93)	
Primary	2 (3)	3 (8)	0	3 (2)	
Drinking status					0.453
Drinker	1 (1)	2 (6)	0	5 (3)	
Non-drinker	67 (91)	33 (86)	16 (100)	137 (93)	
Ex-drinker	6 (8)	3 (8)	0	5 (3)	
Previous recreational drug use	11 (15)	6 (16)	2 (13)	35 (24)	0.313
Unplanned pregnancy	32 (43)	19 (50)	10 (63)	65 (44)	0.492
Nulliparity	41 (55)	20 (53)	10 (63)	66 (45)	0.321
History of termination of pregnancy	49 (66)	24 (63)	9 (56)	98 (67)	0.849
Chronic hypertension	0	0	0	2 (1)	0.760
Pre-eclampsia/pregnancy-induced hypertension	0	4 (11)	0	6 (4)	0.051
Pre-existing diabetes mellitus	1 (1)	1 (3)	0	1 (1)	0.836
Gestational diabetes mellitus	11 (15)	2 (5)	0	16 (11)	0.385
Gestation of delivery, w	38.57±2.06	38.61±1.93	39.25±1.29	38.3±2.12	0.260
Mode of delivery					0.651
Spontaneous vaginal delivery	48 (65)	25 (66)	9 (56)	107 (73)	
Instrumental delivery	8 (11)	3 (8)	3 (18)	11 (7)	
Caesarean section	18 (24)	10 (26)	4 (25)	29 (20)	
Baby birthweight, g	3118±450	3047±527	3007±413	2915±562	0.048
Apgar score					
<7 at 1 min	1 (1)	1 (3)	0	3 (2)	0.904
<7 at 5 min	0	1 (3)	0	1 (1)	0.462
Fetal admission location					0.246
Postnatal ward	43 (58)	13 (34)	8 (50)	71 (48)	
Special care baby unit	27 (36)	24 (63)	8 (50)	68 (46)	
Neonatal intensive care unit	3 (4)	1 (3)	0	7 (5)	

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

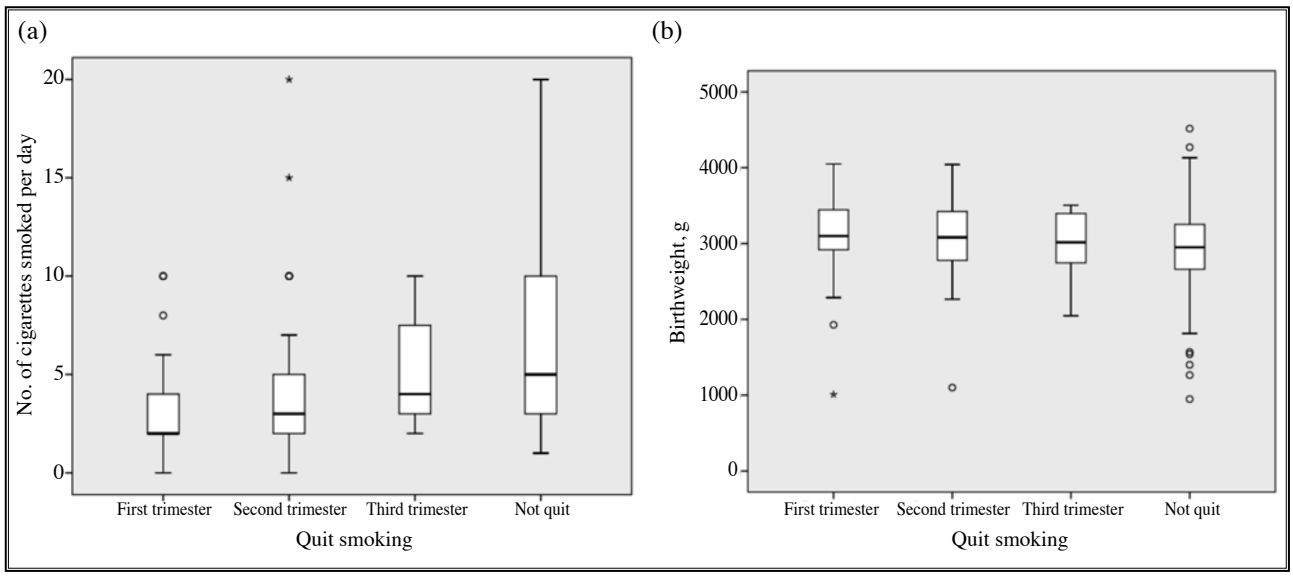

Figure 2. Box-and-whisker plot showing distribution of (a) the number of cigarettes smoked per day and (b) baby birthweight in the four groups

Discussion

In Hong Kong, 4.9% of the female population aged 20 to 49 years were smokers[1]. In our study, 1.7% of pregnant women still smoked at 11 weeks of gestation. This figure is comparable with the 1.57% reported in a local study in 1992[2]. The percentage of active smokers is likely to have increased, as the 1992 study also included ex-smokers. In our study, the overall smoking cessation rate during pregnancy was 46.5%, which was higher than the 35% reported in Australia[6] and 38.8% in the United States[7], but was lower than the 61.9% in Japan[8] and 65.6% in Taiwan[9]. Self-reported smoking status is usually underestimated when it is cross-checked with the urinary cotinine level, which is the gold standard[10]. Our subjects tended to be honest about their smoking status when they were told that this would affect the Down syndrome screening results. Nonetheless, self-reported cessation was not verified by urinary cotinine level.

In a local study in 1992, the baby birthweight of ever and current smokers was 6.3% lower than that of non-smokers[2]. In our study, baby birthweight was 7% lower in women who continued to smoke throughout pregnancy than in those who quit smoking during the first trimester. There appeared to be an exposure-response relationship in which earlier smoking cessation resulted in heavier baby birthweight. Baby birthweight may be comparable between women who quit smoking in the first trimester and non-smokers. This would have important implications for counselling. 87% of Hong Kong Chinese women agree that smoking is hazardous to the fetus[11]. Pregnant women should be counselled that smoking cessation at any gestational age can reduce adverse effects on birthweight.

Predictors of smoking cessation during pregnancy have been reported to be older maternal age, being married or living with partner, primiparity, higher socio-economic status (income, education, housing, employment), lower number of cigarettes smoked per day, and lower levels of depression, stress, and anxiety[12-16]. In our study, the number of cigarettes smoked per day was a predictor of smoking cessation. Women who smoked ≥6 cigarettes per day in early pregnancy were more likely to continue smoking throughout pregnancy. Extra efforts should be made to target these women such as active referral to a smoking cessation clinic, distribution of pamphlets, discussion of progress in terms of reduced number of cigarettes smoked or cessation of smoking and difficulties encountered in antenatal visits.

Cigarette smoking is a modifiable risk factor for pregnancy outcome, but only 23.1% of Hong Kong Chinese women strongly agree or agree that smoking will lead to pregnancy complications[11]. In our study 75% of women were advised by clinicians to quit smoking, compared with only 33% of antenatal clinicians in Pakistan who routinely enquire about smoking habit[17]. Brief advice from a physician can increase the chance of smoking cessation compared with no advice[18]. The NICE guideline recommends lifestyle advice, including smoking cessation, at the first contact of a pregnant woman with a

healthcare professional[19]. Psychosocial interventions to support women to quit smoking during pregnancy increase the smoking cessation rate and hence baby birthweight[20]. A maternity-specific smoking cessation service should be provided; in our study it is disappointing that only about 10% of women were offered referral to a smoking cessation clinic. Prioritisation of resources and patient care to heavy smokers is suggested; healthcare professionals should actively advise patients to quit smoking.

Conclusion

Baby birthweight was lower in women who continued to smoke throughout pregnancy. Healthcare professionals should actively advise women about smoking cessation to improve pregnancy outcome, particularly those who smoke ≥6 cigarettes per day.

Declaration

All authors have no conflicts of interest to disclose.

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Neonatal and Maternal Outcomes of Previable Preterm Prelabour Rupture of Membranes: a 10-Year Retrospective Cohort Study

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Introduction: To evaluate the neonatal survival rate and maternal and neonatal morbidities after conservative treatment for previable preterm prelabour rupture of membranes (PPROM) at our hospital over the past 10 years.
Methods: Maternal and neonatal records of women with PPROM before 24 weeks who delivered at Princess Margaret Hospital between 1 April 2007 and 31 March 2017 were retrospectively reviewed. Patients with PPROM before 20 weeks of gestation were compared with those with PPROM between 20 and 23+6 weeks of gestation. The primary outcome was neonatal survival rate until discharge. Secondary fetal/neonatal outcomes included the live birth rate, latency period, gestational age at delivery, and short- and long-term neonatal complications of survivors. Secondary maternal outcomes included chorioamnionitis, placental abruption, cord prolapse, caesarean section, postpartum haemorrhage, maternal intensive care unit admission, hysterectomy, and maternal death.
Results: Of 80 women (77 singleton and 3 twin pregnancies), 30 opted for pregnancy termination and 50 opted for conservative management. Of the latter, 18 and 32 had PPROM before 20 weeks and between 20 and 23+6 weeks of gestation, respectively. Maternal characteristics of the two groups were comparable. The mean gestational age at PPROM was 20.2 weeks and the mean latency period was 16 days. The overall neonatal survival rate until discharge was 32.1% (n=17); it was lower in women with PPROM before 20 weeks of gestation than after 20 weeks of gestation (10.5% vs. 44.1%, p=0.012). The surviving neonates had various neonatal complications including respiratory distress syndrome (100%), probable or confirmed neonatal sepsis (81.8%), bronchopulmonary dysplasia (59.1%), and intraventricular haemorrhage (31.8%). Maternal complications included caesarean section (71.4%) and chorioamnionitis (26%).
Conclusions: The prognosis of PPROM remains grave, with only one third of neonates surviving to discharge. The neonatal complication rate remains high for survivors.

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Keywords: Fetal membranes, premature rupture; Infant, newborn; Survival analysis

Introduction

Preterm prelabour rupture of membranes (PPROM) is an uncommon obstetric complication, occurring in <1% of pregnancies[1]. Neonatal survival is generally poor, with great variation from 4.8% to 56%[2-10]. Fetal and neonatal complications include spontaneous miscarriage, stillbirth, preterm delivery, neonatal sepsis, pulmonary hypoplasia, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, limb contractures, and other complications of prematurity. Chorioamnionitis is a major maternal morbidity, with a rate of 20% to 71%[2-4,7,8]. Other maternal and obstetric complications include placental abruptio, cord prolapse, postpartum haemorrhage, caesarean section, and hysterectomy[11].

Although advances in neonatal intensive care have increased neonatal survival, management of PPROM before 24 weeks of gestation remains challenging. There is no consensus on the optimal option between pregnancy termination and conservative management with close monitoring. Counselling of parents is often difficult, owing to the great variation of neonatal and maternal complication rates and lack of local data. This study aimed to evaluate the neonatal survival rate and maternal and neonatal morbidities after conservative management for previable PPROM at our hospital over the past 10 years.

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Methods

This retrospective cohort study was approved by the Kowloon West Cluster Research Ethics Committee. Using the Obstetrics Clinical Information System and Clinical Data Analysis and Reporting System, patients with a diagnosis of 'PPROM' or 'miscarriage' before 24 weeks of gestation between 1 April 2007 and 31 March 2017 at Princess Margaret Hospital were identified, and maternal and neonatal records reviewed. Patients with unknown timing of membrane rupture were excluded, as were those who delivered within 12 hours of membrane rupture (likely to be the process of inevitable miscarriage rather than PPROM). Patients with pregnancy termination were also excluded.

Gestation was calculated from the patient's estimated date of delivery and verified by a dating scan. In two patients with no dating scan, gestation was confirmed by ultrasonography on admission. Membrane rupture was established with either leaking on a sterile speculum examination (with pool of liquor, positive cough impulse or positive Actim PROM test) or oligohydramnios on ultrasonography on admission (with normal fetal size and anatomy), together with a reported leaking sensation. A high vaginal swab was collected for bacteriological examination. All patients were prescribed either ampicillin or clindamycin (for those allergic to penicillin) for 7 to 14 days. Patients were hospitalised and the presence of any infection investigated including a regular maternal temperature chart, white cell count, and C-reactive protein level. Ultrasonography was used to assess liquor volume weekly and fetal growth bi-weekly.

Patients were counselled about the possible neonatal and maternal mortalities and morbidities associated with previable PPROM; options of pregnancy termination and conservative management were discussed. Neonatal resuscitation was carried out in all fetuses delivered at or after 24 weeks of gestation and in selected cases at 23 weeks of gestation depending on the patient's wish. Antenatal steroid (two doses of betamethasome 12 mg every 24 hours) was given at delivery. In one exceptional case, antenatal steroid was given at 22 weeks of gestation because the parents strongly opted for neonatal resuscitation at 22 weeks despite counselling by neonatologists.

The primary outcome was neonatal survival rate until discharge. Secondary fetal/neonatal outcomes included the live birth rate, latency period, gestational age at delivery, and short- and long-term neonatal complications of survivors. Secondary maternal outcomes included chorioamnionitis, placental abruptio, cord prolapse, caesarean section, postpartum haemorrhage, maternal intensive care unit admission, hysterectomy, and maternal death.

Chorioamnionitis was defined as maternal fever (≥37.8°C) on two occasions at least 4 hours apart and two or more of the following: uterine tenderness, foul smelling vaginal discharge, maternal tachycardia of >100 beats per minute, maternal leukocytosis of >15,000/μl, and fetal tachycardia of >160 beats per minute[12]. Neonatal sepsis was defined as a positive culture from blood or cerebrospinal fluid. Neonatal sepsis was suspected in the presence of (1) one or more clinical signs of infection (neonatal fever or hypothermia, respiratory or circulatory compromise, altered level of consciousness), and (2) one or more abnormal blood test results (elevated or low white cell count of >30 or <5 x10^9/l, elevated C-reactive protein, low platelet count of <100,000/ml), despite administration of antibiotics for ≥5 days[13-15]. Miscarriage was defined as fetal demise before 24 weeks of gestation, whereas stillbirth was defined as fetal demise before birth at or beyond 24 weeks of gestation.

Patients with PPROM before 20 weeks of gestation were compared with those with PPROM between 20 and 23+6 weeks of gestation, using the Chi squared test for categorical variables and the Student's *t* test or Mann-Whitney *U* test for continuous variables. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 23; IBM, Armonk [NY], US).

Results

During the study period, there were 48 139 deliveries at our hospital in which 95 women with PPROM before 24 weeks of gestation were identified. Of these, 13 with spontaneous miscarriage within 12 hours of PPROM and two with uncertain timing of PPROM were excluded, and the remaining 80 women (77 singleton and 3 twin pregnancies) were included (Figure). Of these, 30 opted for pregnancy termination and 50 opted for conservative management. Of the latter, 18 and 32 had PPROM before 20 weeks and between 20 and 23+6 weeks of gestation, respectively. Maternal characteristics of the two groups were comparable (Table 1).

The overall live birth rate was 41.5% (22 of 53 cases); it was lower in women with PPROM before 20 weeks of gestation than in women with PPROM between 20 and 23+6 weeks of gestation (10.5% [n=2] vs. 58.8%

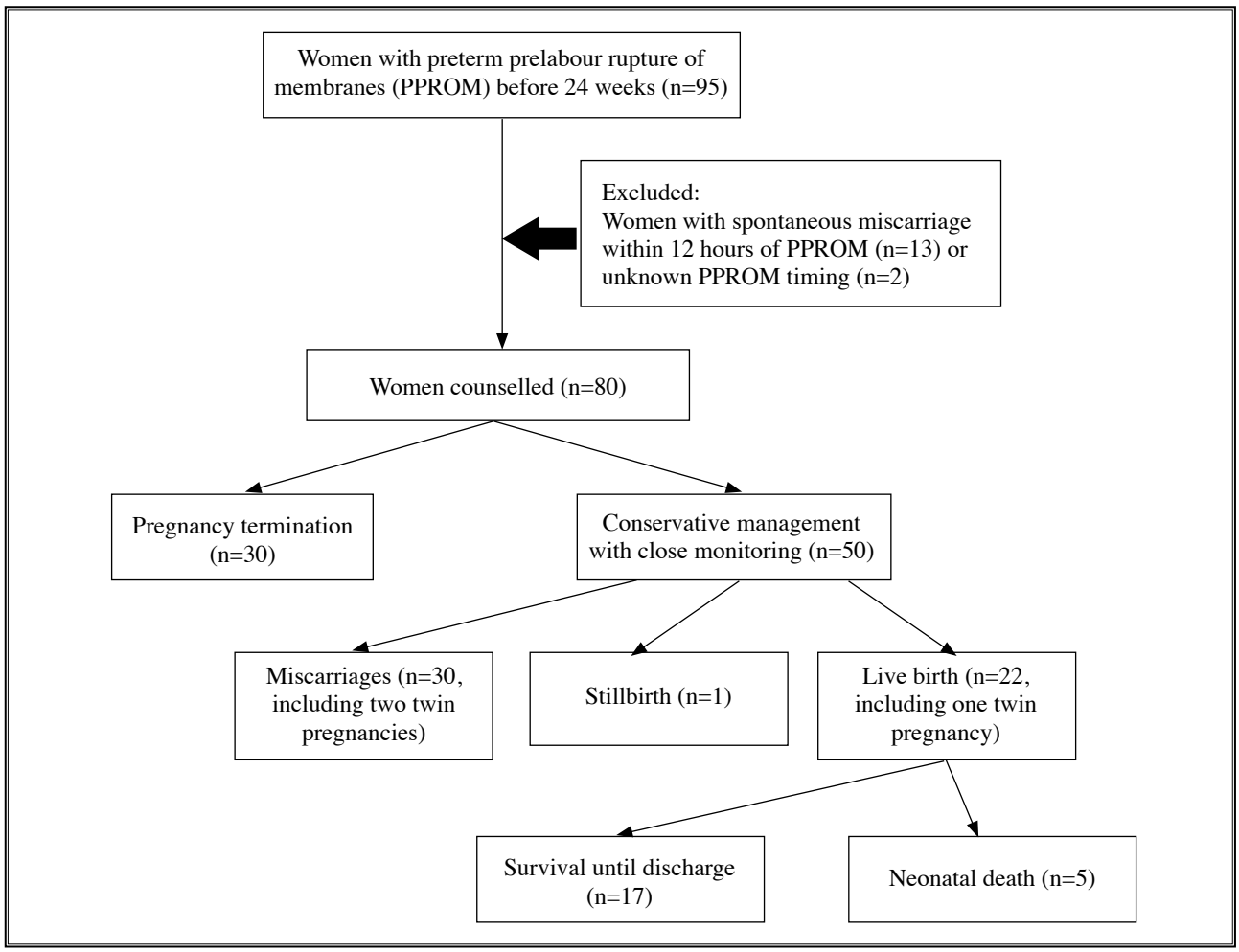

Figure. Flowchart of maternal and neonatal outcomes

[n=20], p=0.001, Table 1). Most miscarriages or stillbirths occurred in the first week of PPROM (n=26). Only two babies whose mothers had PPROM before 20 weeks of gestation were born alive. In one case, PPROM occurred at 18 weeks of gestation and delivery was at 25+6 weeks by caesarean section owing to chorioamnionitis. In another case, PPROM occurred at 12+5 weeks and delivery was at 29+2 weeks by caesarean section owing to fetal distress. All babies were delivered before 34 weeks; the median gestational age at delivery for babies born alive was 25.2 (range, 22+5 to 33+3) weeks. One woman with twin pregnancy by in-vitro fertilisation had PPROM at 21+3 weeks of gestation; she had spontaneous onset of labour at 22+5 weeks and opted for active neonatal resuscitation, but both babies died on day 1 and 4. The other two twin pregnancies had spontaneous miscarriage within one week of PPROM. All babies required neonatal intensive unit admission.

The overall neonatal survival rate until discharge was 32.1% (n=17); it was lower in women with PPROM before 20 weeks of gestation than after 20 weeks of gestation (10.5% [2/19] vs. 44.1% [15/34], p=0.012, Table 1). The neonatal survival rate was 34.8% (8/23) during the period from April 2007 to March 2012 and 30.0% (9/30) during the period from April 2012 to March 2017 (p=0.712). All five cases of neonatal death occurred within four days of birth. Among 23 cases that were delivered at least one week after PPROM, the overall neonatal survival rate until discharge was 56.5% (13 of 23).

Regarding neonatal complications, seven neonates had intraventricular haemorrhage (one grade 3 and six grade 1 or 2), 12 had retinopathy of prematurity (six of whom were of stage III and required laser therapy), and two had necrotising enterocolitis (none required surgery). Only four neonates survived without major neonatal morbidities (of neonatal sepsis, bronchopulmonary dysplasia, grade III or IV intraventricular haemorrhage, stage III or above retinopathy of prematurity, necrotising enterocolitis requiring surgery, and patent ductus arteriosus requiring surgery).

Table 1. Maternal characteristics and neonatal outcome after conservative management for preterm prelabour rupture of membranes (PPROM)

Variable	Overall (n=50)*	PPROM at <20 weeks of gestation (n=18)*	PPROM at 20 to 23+6 weeks of gestation (n=32)*	p Value
Maternal characteristics				
Age, y	33.2	33.4	33.0	0.802
Smoking	4	5.56	3.13	0.674
Race				0.782
Chinese	82	83.3	81.2	
Others	18	16.7	18.7	
Parity				0.706
Primigravida	48	44.4	50	
Multigravida	52	55.6	50	
History of miscarriage	24	22.2	25	0.825
History of preterm birth	6	0	9.4	0.180
Pregnancy				0.921
Singleton	94	94.4	93.8	
Twins	6	5.6	6.2	
Cervical cerclage/Arabin ring before PPROM	6	11.1	3.1	0.254
Invasive procedures before PPROM	4	0	6.2	0.279
Oligohydramnios at PPROM	73.5	77.8	71.0	0.603
Oligohydramnios (persistent or new onset) during conservative management	88.9	71.4	95	0.088
Gestational age at PPROM, w	20.2±2.6	17.3±1.8	21.9±1.1	-
Latency period, d	16±23.4	14.1±28.3	17.2±20.6	0.686
Neonatal outcome	(n=53)	(n=19)	(n=34)	
Live birth rate	22 (41.5)	2 (10.5)	20 (58.8)	0.001
Gestational age at delivery, w	25.7±2.9	27.4±2.5	25.6±2.9	0.493
Birthweight, g	829±395	817.0±231	830.3±413	0.424
Apgar score at 1 min	4.2±2.6	3.5±3.5	4.3±2.5	0.603
Apgar score at 5 min	6.5±2.9	5.5±2.1	6.6±3.0	0.354
Need for cardiopulmonary resuscitation at birth	7/22 (31.8)	0 (0/2)	7/20 (35.0)	0.311
Survival until discharge	17 (32.1)	2 (10.5)	15 (44.1)	0.012
Morbidities of liveborn neonates until discharge	(n=22)	(n=2)	(n=20)	
Nursery stay for survivors, d	122.6±91.3	88.5±34.6	127.1±97.1	0.551
Probable neonatal sepsis	14 (63.6)	1 (50)	13 (65.0)	0.674
Confirmed neonatal sepsis	4 (18.2)	1 (50)	3 (15.0)	0.221
Respiratory distress syndrome	22 (100)	2 (100)	20 (100)	-
Neonatal jaundice	18 (81.8)	2 (100)	16 (80.0)	0.484
Persistent pulmonary hypertension	7 (31.8)	0 (0)	7 (35.0)	0.311
Bronchopulmonary dysplasia	13 (59.1)	1 (50)	12 (60.0)	0.784
Intraventricular haemorrhage	7 (31.8)	1 (50)	6 (30.0)	0.563
Retinopathy of prematurity	12 (54.5)	1 (50)	11 (55.0)	0.892
Disseminated intravascular coagulopathy	3 (13.6)	1 (50)	2 (10.0)	0.116
Anaemia of prematurity	14 (63.6)	1 (50)	13 (65.0)	0.674
Necrotising enterocolitis	2 (9.1)	0 (0)	2 (10.0)	0.639
Patent ductus arteriosus requiring surgery	1 (4.5)	0 (0)	1 (5.0)	0.746
Survival without major morbidities	4/17 (23.5)	1/2 (50)	3/15 (20.0)	0.347

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

The 17 survivors were followed up for 10 years. Eight underwent surgery for inguinal hernia, hydrocoele, or hypospadias. Seven had varying degrees of developmental delay. One failed to thrive. One had retinal detachment of the right eye. Nine had no developmental delay or major morbidities. Nonetheless, further observation of their future development is required.

Gestational age at PPROM or latency period had no significant impact on obstetric or maternal complication rates (Table 2). The overall incidence of chorioamnionitis was 26% (n=13). Of 21 women with a live birth, 15 (71.4%) required caesarean section, mostly because of chorioamnionitis or fetal distress. Five (23.8%) had a classic caesarean section because of extreme prematurity with the lower segment not yet formed. The incidence of caesarean section was higher when the latency period was ≥14 days compared with 1 to 13 days (84.6% vs. 37.5%, p=0.026). Two women required intensive care unit admission due to severe maternal sepsis after spontaneous miscarriage (n=1) and massive postpartum haemorrhage (4500 ml) during classic caesarean section for placental abruptio and chorioamnionitis (n=1). There was no case of maternal death or hysterectomy.

Higher neonatal survival rate until discharge was associated with higher gestational age at PPROM, higher gestational age at delivery, higher latency period, lower white cell count at PPROM, and lower C-reactive protein level before delivery (Table 3).

Discussion

Previable PPROM occurred in <2 per 1000 pregnancies at our hospital. Parents were always counselled about the poor neonatal outcome. In our study, the overall neonatal survival rate was 32.1%, which was higher than the 18%[3] and 23%[5] reported in two studies in 2006 and 2008, respectively, and was similar to the 34.3%[7] reported in a 2012 study of 31 cases with PPROM at a mean gestational age of 19 weeks. However, it was lower than the 47%[2] and 56%[6] reported in two studies in 2004 and 2009, in which the mean gestational age at PPROM was 22 weeks and 21.4 weeks, respectively. In our hospital, the perinatal and neonatal mortality rates were 3.6 and 0.8 per 1000 births, respectively, which were comparable with the mean of 4.5 and 1.5 per 1000 births reported by seven other public hospitals in Hong Kong. The neonatal survival rate until discharge was lower in women with PPROM before 20 weeks than after 20 weeks (10.5% vs. 44.1%, p=0.012). This finding was comparable with that of a study reporting a neonatal survival rate of 18% in women with PPROM at 14 to 19 weeks and 53% in women with PPROM at 20 to 24 weeks[7]. This information provides parents a realistic estimate of the neonatal outcome based on gestational age at PPROM.

Table 2. Maternal complications by gestational age at preterm prelabour rupture of membranes (PPROM) and by latency period

Maternal complication	Gestational age at PPROM				Latency period			
	Overall (n=50)*	<20 weeks (n=18)*	20 to 23+6 weeks (n=32)*	p Value	Overall (n=50)*	1-13 days (n=36)*	≥14 days (n=14)*	p Value
Chorioamnionitis	13 (26)	4 (22.2)	9 (28.1)	0.648	13 (26)	8 (22.2)	5 (35.7)	0.329
Cord prolapse	2 (4)	2 (11.1)	0 (0)	0.054	2 (4)	2 (5.6)	0 (0)	0.368
Placental abruptio	2 (4)	0 (0)	2 (6.3)	0.279	2 (4)	2 (5.6)	0 (0)	0.368
Caesarean section†	15/21 (71.4)	2/2 (100)	12/19 (63.2)	0.293	15/21 (71.4)	3/8 (37.5)	11/13 (84.6)	0.026
Classic caesarean section†	5/21 (23.8)	0/2 (0)	5/19 (26.3)	0.406	5/21 (23.8)	2/8 (25)	3/13 (23.1)	0.920
Postpartum haemorrhage	3 (6)	0 (0)	3 (9.4)	0.180	3 (6)	1 (2.8)	2 (14.3)	0.124
Retained products of gestation requiring surgery	4 (8)	2 (5.6)	3 (9.4)	0.633	4 (8)	3 (8.3)	1 (7.1)	0.889
Hysterectomy	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	-
Intensive care unit admission	2 (4)	1 (5.6)	1 (3.1)	0.674	2 (4)	2 (5.6)	0 (0)	0.368
Mortality	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)	0 (0)	-

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

† Only liveborn cases were considered (caesarean section was not required for miscarriage or stillborn)

Table 3. Factors associated with neonatal survival until discharge after conservative management for preterm prelabour rupture of membranes (PPROM)

Variable	Survivors (n=17)*	Non-survivors (n=36)*	p Value
Maternal age, y	34.1±5.3	32.6±4.5	0.334
Smoker	1 (5.9)	1 (2.8)	0.580
History of miscarriage	5 (29.4)	7 (19.4)	0.614
History of preterm delivery	1 (5.9)	2 (5.6)	0.681
Oligohydramnios at PPROM	12 (70.6)	26/34 (76.5)	0.650
Oligohydramnios (persistent or new onset) during conservative management	12/13 (92.3)†	14/16 (87.5)†	0.672
Latency period, d	33.88±31.9	6.83±8.4	<0.001
Gestational age at PPROM, w	21.4±2.7	19.7±2.4	0.029
Gestational age at delivery, w	26.2±3.1	20.6±2.7	<0.001
White cell count at PPROM, $x10^9$/l	10.8±3.6	14.1±4.5	0.005
White cell count before delivery, $x10^9$/l	14.1±4.5	16.9±6.0	0.127
C-reactive protein at PPROM, mg/dl	20.5±25.0	22.6±17.8	0.203
C-reactive protein before delivery, mg/dl	22.7±36.6	40.3±71.8	0.002
Presence of chorioamnionitis	6 (35.3)	8 (22.2)	0.314
Chorioamnionitis on placental section	14 (82.4)	30/35 (85.7)	0.753
Birth weight, g	896.4±428.7	600.4±67.0	0.066

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

† The remaining patients had spontaneous miscarriage or delivery within 1 week of PPROM

Severe oligohydramnios significantly affects neonatal survival, as the risk of pulmonary hypoplasia increases with decreasing liquor volume[1,16-18]. Such finding was not observed in our study or other studies[2,5]. Instead, the white cell count at PPROM and C-reactive protein level before delivery were predictors of neonatal survival. Nonetheless, a larger sample is needed to determine the threshold for action. Most miscarriages occurred within one week of membrane rupture. If the fetus could survive the first week after PPROM, >50% would survive until discharge. This information is useful for patients who remain well during close observation.

In our study, the incidence of neonatal complications was slightly higher than that reported in other studies[2,4,7]. This could be due to the lack of a unified definition for these complications. Our data were extracted from neonatal discharge records produced by the paediatricians in charge. Pulmonary hypoplasia and limb contracture were unique complications of mid-trimester PPROM and were seldom documented by paediatricians in neonatal records. Hence, the exact incidence of these two complications may have been under-reported. Most surviving neonates required a prolonged hospital stay, 3 months on average. Even after discharge from the neonatal unit, most still required long-term follow-up for various residual problems, particularly developmental delay that occurred in seven of 17 surviving neonates.

The maternal complication rate plays an important role in counselling. One in seven women with previable PPROM has significant maternal morbidity[11]. Over 70% of our patients required caesarean section for suspected chorioamnionitis or fetal distress, compared with 20% to 25% of the general population in our unit. One third of the total were classic caesarean section, as the lower segment was not yet formed owing to the extreme prematurity. Classic caesarean section has major implications for future pregnancies and may affect a women's decision on pregnancy termination or conservative management. Most studies did not report the rate of caesarean section; it is unknown if such a high caesarean section rate in our unit is common among women with previable PPROM or if it is due to obstetrician anxiety and preference for a quicker and 'safer' way of delivery. The rate of caesarean section increased significantly when the latency period was ≥14 days compared with 1 to 13 days. One reason could be that the risk of chorioamnionitis and other obstetric complications increases with increasing duration of PPROM, although this was not observed in our study. Another reason could be that a shorter latency period was

associated with miscarriage or stillbirth, hence eliminating the need for caesarean section. Although 26% of our patients had chorioamnionitis (comparable with that reported in other studies[2-4,7,8]), only one woman had severe sepsis and required intensive care unit admission. There was no case of maternal death or hysterectomy.

Limitations of our study included the small sample size and the retrospective nature. Our study cannot provide a long-term prognosis of PPROM, which is important in making decisions about pregnancy termination or conservative management. 37.5% of our patients opted for pregnancy termination. If they had opted for conservative management, the overall neonatal and maternal outcomes could have been changed. A multicentre randomised controlled trial of conservative management versus pregnancy termination is needed to determine the optimal option but this is ethically not feasible. It is uncertain whether the low neonatal survival rate was mainly due to extreme prematurity at delivery or PPROM that worsens the prognosis. Nonetheless, our findings provide local data to help parents and doctors in decision making.

Conclusion

The prognosis of PPROM remains grave, with only one third of neonates surviving to discharge. The neonatal complication rate remains high for survivors.

Declaration

All authors have no conflicts of interest to disclose.

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Optimal Gestational Weight Gain in Chinese Women with Twin Pregnancy

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Objectives: To propose an optimal gestational weight gain (GWG) guideline for Chinese women with twin pregnancy and to assess the neonatal and maternal outcomes based on the proposed guideline.
Methods: Records of women who delivered dichorionic diamniotic twins after 24 weeks of gestation at Tuen Mun Hospital between 2012 and 2016 were retrospectively reviewed. They were classified according to their pre-pregnancy body mass index (BMI) as underweight/normal weight or overweight/obese. An optimal GWG was proposed for each group by deriving the interquartile range of GWG in women who delivered twins with a birthweight of ≥2500 g at 37-42 weeks of gestation. Women were categorised as having GWG below, between, or above the proposed standard. Maternal characteristics and neonatal and maternal outcomes of the three GWG categories were compared.
Results: A total of 171 women were identified. Of them, 25 were underweight, 100 normal weight, 18 overweight, and 28 obese, according to the Asian BMI classification. Only 48 of 171 women delivered twins with a mean birthweight of ≥2500 g at 37-42 weeks of gestation. Respectively in underweight/normal weight and overweight/obese women with twin pregnancy, a GWG of 15.15 to 23.90 kg (0.41-0.65 kg per week) and 13.10 to 17.30 kg (0.35-0.47 kg per week) was proposed. In underweight/normal weight women, those with GWG below the standard had significantly increased odds of spontaneous preterm labour, one or both twins with a birthweight of <1500 g, one or both twins with a birthweight of <2500 g, delivery at ≤34 weeks, and any twin requiring neonatal intensive care unit admission.
Conclusion: In underweight/normal weight Chinese women with twin pregnancy, those with a GWG below 15.15 kg had increased risks of giving birth to low or very low birthweight babies, spontaneous preterm labour, and delivery at ≤34 weeks.

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Keywords: Asian Continental Ancestry Group; Pregnancy, twin; Weight gain

Introduction

Gestational weight gain (GWG) is associated with maternal and neonatal outcomes: a low GWG is associated with increased risk of having small-for-gestational-age babies and preterm delivery, whereas an excessive GWG is associated with increased risk of having large-for-gestational-age babies, macrosomia, and caesarean delivery[1]. Most such studies have been of singleton pregnancies; evidence for multiple pregnancies is lacking. The 2009 Institute of Medicine (IOM) guideline provisionally recommends specific ranges of GWG for women with twin pregnancy: those of normal weight should gain 17 to 25 kg, overweight 14 to 23 kg, and obese 11 to 19 kg. Information for underweight women with twins is insufficient. Nonetheless, the guideline was based on the interquartile range of GWG of American women who delivered twins weighing ≥2500 g at 37 to 42 weeks of gestation. Asian populations in general have less GWG[2]. According to a retrospective study of 8209 singleton pregnancies in Chinese, only 42.7% of pregnancies achieved the IOM recommended GWG and they were at increased risk of macrosomia[3]. The World Health Organization suggests a different body mass index (BMI) classification for Asians[4]. The IOM guideline may not be applicable to the Chinese population. This study aimed to propose an optimal GWG guideline for Chinese women with twin pregnancies, and to assess the maternal and neonatal outcomes based on the proposed guideline.

Materials and Methods

This retrospective cohort study was approved by the New Territories West Cluster Research Ethics Committee. Records of dichorionic diamniotic live twin deliveries after 24 weeks of gestation by Chinese women at Tuen Mun Hospital between 2012 and 2016 were retrospectively

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reviewed. The chorionicity and amnionicity were confirmed by histopathological examination of the placentae. Women with monochorionic twins were excluded, as they were at greater risk of poor perinatal outcomes owing to the risk of twin-twin transfusion syndrome and discordant fetal growth restriction[5]. Women with a twin pregnancy that resulted from fetal reduction or miscarriage were also excluded, as were women with intrauterine fetal demise of one or both twins, pregnancies with congenital anomalies, and women with chronic hypertension or pre-existing diabetes, as neonatal and maternal outcomes could be affected.

Maternal characteristics were collected including age, pre-pregnancy BMI, gravidity, parity, and smoking status. Primary neonatal outcomes were gestational age at delivery, birthweight of the larger and smaller twins, spontaneous preterm labour, one or both twins with birthweight of <1500 g or <2500 g, and neonatal intensive care unit (NICU) admission. Secondary maternal outcomes were preeclampsia and gestational diabetes.

Pre-pregnancy BMI was calculated at the first antenatal visit using the self-reported pre-pregnancy weight and height. Asian BMI classification was used to stratify the pre-pregnancy BMI: underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), or obese (≥25 kg/m^2)[4].

GWG was the weight at delivery minus the pre-pregnancy weight. GWG per week was calculated by dividing GWG with the gestational age at delivery in weeks. Our proposed GWG was derived from the interquartile range of GWG in our women who delivered twins with a birthweight of ≥2500 g at 37-42 weeks of gestation, as in the 2009 IOM guideline[1].

Women were categorised as having GWG below, between, or above the proposed standard. Maternal characteristics and neonatal and maternal outcomes of the three GWG categories were compared using the ANOVA for continuous variables and the Chi squared test or Fisher's exact test for categorical variables. Univariate analysis and logistic regression analysis of the neonatal and maternal outcomes were performed. A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (version 22; IBM Corp, Armonk [NY], US).

Results

A total of 171 women were identified. Of them, 25 were underweight, 100 normal weight, 18 overweight, and 28 obese, according to the Asian BMI classification (Table 1). Only 48 of 171 women delivered twins with a birthweight of ≥2500 g at 37-42 weeks of gestation (Table 1). Respectively in underweight/normal weight and overweight/obese women with twin pregnancy, a GWG of 15.15 to 23.90 kg (0.41-0.65 kg per week) and 13.10 to 17.30 kg (0.35-0.47 kg per week) was proposed. The two groups of women were further categorised as having GWG below, between, or above our proposed standard. Women of the three categories were comparable in terms of age, nulliparity, and smoking status (Table 2).

In univariate analysis, in underweight/normal weight women, birthweight of the larger and smaller twins increased with increasing GWG (p=0.001 and p=0.002, respectively). In women with GWG below the standard, 24.4% and 14.6% had one or both twins with a birthweight of <1500 g, respectively. In women with GWG above the standard, 0% had one or both twins with a birthweight of <1500 g. In overweight/obese women, those with GWG

Table 1. Calculation of proposed gestational weight gain (GWG) for Chinese women with twin pregnancy

Classification of Asian pre-pregnancy body mass index, kg/m^2	Gestation at delivery, w*	GWG, kg*	GWG per week, kg*	No. of women who delivered twins with a birthweight of ≥2500 g at 37-42 weeks of gestation	Proposed GWG per week, kg*	Proposed GWG at 37 weeks, kg*
Underweight (<18.5) [n=25]	34.8±2.2	19.2±6.0	0.55±0.16 (0.41-0.71)	2	0.41-0.65	15.15-23.90
Normal (18.5-22.9) [n=100]	35.4±2.6	17.0±5.4	0.48±0.16 (0.37-0.59)	35		
Overweight (23-24.9) [n=18]	34.7±2.6	15.2±4.3	0.44±0.12 (0.33-0.54)	5	0.35-0.47	13.10-17.30
Obese (≥25.0) [n=28]	35.1±2.5	10.4±6.0	0.29±0.17 (0.19-0.39)	6		

* Data are presented as mean±standard deviation, mean±standard deviation (interquartile range), or interquartile range

Table 2. Univariate analysis of maternal characteristics and neonatal and maternal outcomes by comparing women with gestational weight gain (GWG) below, between, or above the proposed standard

Variable	Underweight/normal weight women				Overweight/Obese women			
	GWG below the standard (n=41)	GWG between the standard (n=62)	GWG above the standard (n=22)	p Value	GWG below the standard (n=21)	GWG between the standard (n=14)	GWG above the standard (n=11)	p Value
Maternal age, y	33.2±5.1	33.3±4.0	31.3±5.5	0.2	32.8±4.5	35.4±3.0	32.2±2.4	0.07
Nullipara	30 (73.2)	50 (80.6)	18 (81.8)	0.6	12 (57.1)	8 (57.1)	6 (54.5)	0.99
Smoker	0 (0)	1 (1.6)	2 (9.1)	0.07	0 (0)	0 (0)	0 (0)	-
Pre-pregnancy BMI, kg/m^2	20.8±1.8	20.2±1.7	19.2±2.3	0.005	26.5±2.3	25.9±1.5	24.8±1.4	0.09
Birthweight, g								
Larger twin	2196±600	2539±409	2588±459	0.001	2182±475	2585±323	2393±476	0.034
Smaller twin	1946±573	2263±422	2321±419	0.002	1944±451	2308±272	2170±493	0.044
Gestation at delivery, w	34.3±3.5	35.9±1.7	35.6±2.0	0.007	34.4±3.0	36±1.5	34.7±2.4	0.18
Spontaneous preterm labour	18 (43.9)	13 (21)	7 (31.8)	0.046	4 (19)	3 (21.4)	6 (54.4)	0.08
Delivery at ≤34 weeks	12 (29.3)	7 (11.3)	2 (9.1)	0.033	8 (38.1)	1 (7.1)	4 (36.4)	0.12
Any twin <1500 g	10 (24.4)	3 (4.8)	0 (0)	0.01	6 (27.3)	1 (5.9)	1 (14.3)	0.21
Both twins <1500 g	6 (14.6)	1 (1.6)	0 (0)	0.009	2 (9.1)	0 (0)	1 (14.3)	0.35
Any twin <2500 g	35 (85.4)	42 (67.7)	15 (68.2)	0.11	18 (85.7)	12 (85.7)	8 (72.7)	0.61
Both twins <2500 g	24 (58.5)	25 (40.3)	10 (45.5)	0.19	14 (66.7)	3 (21.4)	5 (45.5)	0.031
Any twin neonatal intensive care unit admission	33 (76.7)	54 (90)	19 (86.4)	0.18	7 (33.3)	3 (21.4)	4 (36.4)	0.67
Preeclampsia	4 (9.8)	7 (11.3)	3 (13.6)	0.90	0 (0)	1 (7.1)	0 (0)	0.31
Gestational diabetes	18 (43.9)	29 (46.78)	5 (22.7)	0.14	10 (47.6)	4 (28.6)	4 (36.4)	0.52

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

above or below the standard had comparable neonatal and maternal outcomes (Table 2).

In logistic regression analysis, in underweight/normal weight women, those with GWG below the standard had significantly increased odds of spontaneous preterm labour, one or both twins with a birthweight of <1500 g, one or both twins with a birthweight of <2500 g, delivery at ≤34 weeks, and any twin requiring NICU admission (Table 3). In women with GWG above the standard, none of the twins had a birthweight of <1500 g. Women with GWG above or below the standard were comparable in terms of spontaneous preterm labour, one or both twins with a birthweight of <2500 g, delivery at ≤34 weeks, preeclampsia, and gestational diabetes.

When classified according to the 2009 IOM guideline, 25 women were underweight, 118 normal weight, 26 overweight, and 2 obese. 52.5% of normal weight women, 73.1% of overweight women, and 100% of obese women had a GWG below the IOM recommendation (Table 4). The 2009 IOM guideline may not be applicable to Chinese women with twin pregnancy.

Discussion

The optimal GWG for Chinese, Korean, and Singaporean populations with a singleton pregnancy has been reported to be lower than that recommended by the IOM[3,6-9]. Asian populations that adhered to the IOM guideline have been reported to be at increased risk of macrosomia and caesarean delivery[3,8]. An ethnic-specific GWG standard for twin pregnancies is required.

In our study, respectively in underweight/normal weight and overweight/obese women with twin pregnancy, a GWG of 15.15 to 23.90 kg (0.41-0.65 kg per week) and

Table 3. Logistic regression of maternal and neonatal outcomes by comparing women with gestational weight gain (GWG) below or above the proposed standard

Variable	Adjusted odds ratio (95% confidence interval)			
	Underweight/normal weight women		Overweight/obese women	
	GWG below the standard	GWG above the standard	GWG below the standard	GWG above the standard
Preeclampsia	1.11 (0.29-4.18)	0.84 (0.18-3.86)	-	-
Gestational diabetes	1.18 (0.51-2.69)	2.37 (0.73-7.65)	0.38 (0.08-1.92)	0.87 (0.13-6.07)
Delivery at ≤34 weeks	3.31 (1.15-9.55)	0.72 (0.13-3.92)	7.34 (0.66-81.24)	14.09 (0.69-223.17)
Spontaneous preterm labour	3.56 (1.40-9.06)	1.35 (0.418-4.33)	0.92 (0.16-5.41)	10.1 (0.98-93.4)
Any twin <1500 g	8.78 (1.99-38.63)	-	-	-
Both twins <1500 g	9.34 (1.06-82.60)	-	-	-
Any twin <2500 g	3.62 (1.23-10.65)	0.56 (0.17-1.85)	0.48 (0.05-4.56)	0.17 (0.15-1.98)
Both twins <2500 g	2.76 (1.15-6.63)	0.67 (0.21-2.11)	5.82 (1.00-33.71)	2.33 (0.31-17.3)
Any twin neonatal intensive care unit admission	3.27 (1.05-10.15)	1.31 (0.29-5.93)	1.31 (0.22-7.71)	2.85 (0.33-24.82)

Table 4. Percentage of women with gestational weight gain (GWG) below the Institute of Medicine (IOM) recommendation

Classification of IOM pre-pregnancy body mass index, kg/m^2	IOM recommended GWG, kg	Mean±SD (interquartile range) GWG, kg	No. (%) of women with GWG below the IOM recommendation
Underweight (<18.5) [n=25]	-	19.2±6.0 (13.5-24.6)	-
Normal (18.5-24.9) [n=118]	17-25	16.7±5.3 (13.0-20.5)	62 (52.5)
Overweight (25.0-29.9) [n=26]	14-23	10.8±6.0 (6.6-14.2)	19 (73.1)
Obese (≥30.0) [n=2]	11-19	5.8±3.2 (3.5-8)	2 (100)

13.10 to 17.30 kg (0.35-0.47 kg per week) was proposed. This proposed standard was lower than the IOM GWG recommendation of 17-25 kg (0.46-0.68 kg per week) for normal weight women, 14-23 kg (0.38-0.62 kg per week) for overweight women, and 11-19 kg (0.3-0.51 kg per week) for obese women[1].

In our study, underweight/normal weight women with a GWG below the proposed standard had increased odds for spontaneous preterm labour, one or both twins with a birthweight of <1500 g and <2500 g, and preterm delivery at ≤34 weeks. In women with a GWG above the standard, neither of the twins had a birthweight of <1500 g. Birthweight of both the larger and smaller twins increased with increasing GWG. Studies that used the IOM standard for twin pregnancies have also reported similar neonatal outcomes[10,11]. Compared with women with GWG below the IOM standard, women with normal GWG had a reduced rate of preterm delivery before 34 weeks (odds ratio=4.97, 95% confidence interval=1.76-14.02)[12]. Women carrying twins who had normal BMI-specific GWG had an improved preterm birth rate, neonatal birthweight, and composite neonatal outcomes[13]. In a systematic review, GWG was positively associated with fetal size[14]. Nonetheless, the effect of GWG on hypertensive disorders and gestational diabetes in women with twin gestations was inconsistent, because maternal complications may also affect GWG[14]. According to the IOM guideline, GWG at the time of diagnosis of preeclampsia and gestational diabetes should be used instead of GWG at delivery[1].

In our study, GWG per week rather than total GWG was used to avoid the problem of prematurity, as >50% of twins were born before 37 weeks of gestation[15]. In addition, GWG is not linear throughout pregnancy. Women gain less weight in the first trimester than in the second and third

trimesters[16]. The proposed GWG should be interpreted with caution, especially during the first trimester, to avoid anxiety about inadequate weight gain. Trimester-specific GWG goals can provide better monitoring. To eliminate a potential error in self-reporting, body weight at first visit (if early enough) can be used although the time of the first visit may vary. In our study, the number of overweight/obese women was too small to determine the effect of GWG on neonatal and maternal outcomes. A territory-wide sample over a longer period is needed.

Conclusion

In underweight/normal weight Chinese women with twin pregnancy, those with a GWG below 15.15 kg had increased risks of giving birth to low or very low birthweight babies, spontaneous preterm labour, and delivery at ≤34 weeks.

Declaration

All authors have no conflicts of interest to disclose.

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Vaginal Progesterone to Prevent Preterm Delivery in Unselected Women with Twin Pregnancy: a Randomised, Placebo-controlled, Double-blind Trial

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Objective: To evaluate the efficacy of vaginal progesterone in preventing preterm birth before 34 weeks in unselected twin pregnancies.
Methods: Women with a twin pregnancy were randomised in a one-to-one ratio to receive either 100 mg daily vaginal progesterone or placebo from 24 to 34 weeks of gestation. Low vaginal swab, serum human chorionic gonadotrophin, progesterone, C-reactive protein, and 75 g oral glucose tolerance test were examined at recruitment and at 30 to 32 weeks of gestation. The primary outcome was the rate of preterm delivery before 34 weeks.
Results: Of 165 women recruited, 23 were excluded and 142 were included for analysis, of whom 71 received vaginal progesterone and 71 received placebo. Basic demographics of the two groups were similar. The treatment and placebo groups were comparable in terms of maternal, obstetric, and neonatal outcomes, including the preterm delivery rate before 34 weeks (31% vs. 20%, p=0.123) and gestational age at delivery (35.3±2.6 weeks vs. 35.7±2.1 weeks, p=0.614).
Conclusion: In unselected women with twin pregnancy, vaginal progesterone did not prevent preterm delivery.

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Keywords: Pregnancy, twin; Premature birth; Progesterone

Introduction

Preterm birth, defined as delivery before 37 gestational weeks, accounts for 75% of perinatal deaths and >50% of long-term neurological disabilities[1,2]. Preterm neonates are at increased risk of respiratory distress syndrome, chronic lung disease, retinopathy of prematurity, necrotising enterocolitis, intraventricular haemorrhage, cerebral palsy, motor and sensory impairment, learning difficulties, and chronic disease[3]. Complications from preterm birth are the leading cause of death for children under 5 years of age[4]. In the United States, the societal cost of preterm birth is estimated to be US$26 billion annually[5].

Twin pregnancy is associated with a higher risk of preterm labour compared with singleton pregnancy; the rate of preterm delivery has been reported as 59.1% and 7.8%, respectively[6]. In 2015, twin pregnancy accounted for 20.5% of preterm deliveries in the United States[6]. Strategies to prevent preterm birth in twin pregnancy include bed rest with and without hospitalisation[7], beta agonist therapy[8], cervical cerclage[9], cervical pessary[10], and progesterone[11-14]. Nonetheless, in unselected twin pregnancy, evidence to support the beneficial effect of these treatments is lacking. This study aimed to evaluate the efficacy of vaginal progesterone in preventing preterm birth before 34 weeks in unselected twin pregnancy.

Methods

This randomised, double-blind, placebo-controlled study was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (HKUCTR-2231). Written informed consent was obtained from each participant. Women aged >18 years with a twin pregnancy confirmed by ultrasonography at Queen Mary Hospital from May 2005 to December 2008 were invited to participate. Women were excluded if they were registered after 24 weeks, had contraindication to progesterone such as a history of vascular or thrombolic diseases, had allergy to progesterone

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or combined oral contraceptive pills, or planned to deliver outside our hospital.

Sample size calculation was based on our hospital's incidence of preterm delivery in twin pregnancies before 34 weeks (29.3%); 88 women in each group were required to show a three-fold risk reduction with a power of 80%, type I error of 5%, and 10% attrition rate.

Both women and clinicians were blinded to the group assigned; randomisation was done by the pharmacy in a one-to-one ratio. Women were instructed to self-administer daily a 100-mg natural progesterone pessary (Utrogestan, Besins Healthcare, UK) or placebo from 24 to 34 weeks. Low vaginal swab and tests for serum human chorionic gonadotrophin, progesterone, C-reactive protein, and 75 g oral glucose tolerance were performed at baseline and at 30 to 32 weeks of gestation. One-hour tocogram monitoring[15] was performed; a positive result was defined as ≥4 contractions in an hour before 30 weeks, and ≥6 contractions in an hour after 30 weeks. Women were given a contact number to report any adverse events. Women were followed up every 4 weeks before 30 weeks and thereafter 2 weeks until delivery. The timing and the mode of delivery were based on the obstetric condition and the preference of the woman.

The primary outcome was the rate of preterm delivery before 34 weeks. The Student's *t* test or Wilcoxon Rank Sum test was used to compare quantitative variables, whereas the Chi squared test or Fisher's exact test were used to compare qualitative variables. A p value of <0.05 was considered statistically significant.

Results

Of 165 women recruited, 23 were excluded and 142 were included for analysis, of whom 71 received vaginal progesterone and 71 received placebo (Figure). Basic demographics of the two groups were similar (Table 1). No women had a history of preterm delivery; 83.1% of pregnancies were conceived by assisted reproductive techniques; and >90% of women had a dichorionic diamniotic twin pregnancy.

The treatment and placebo groups were comparable in terms of maternal, obstetric, and neonatal outcomes, including the preterm delivery rate before 34 weeks (31% vs. 20%, p=0.123) and gestational age at delivery (35.3±2.6 weeks vs. 35.7±2.1 weeks, p=0.614), except that serum progesterone level at 30 weeks was higher in the treatment group (814.8±278.5 nmol/l vs. 751.6±218.9 nmol/l, p=0.032) [Table 2].

49 women required oral nifedipine for threatened preterm labour. Of them, 41 (83.7%) had excess uterine activity and required hospitalisation. Three patients required terbutaline for tocolysis.

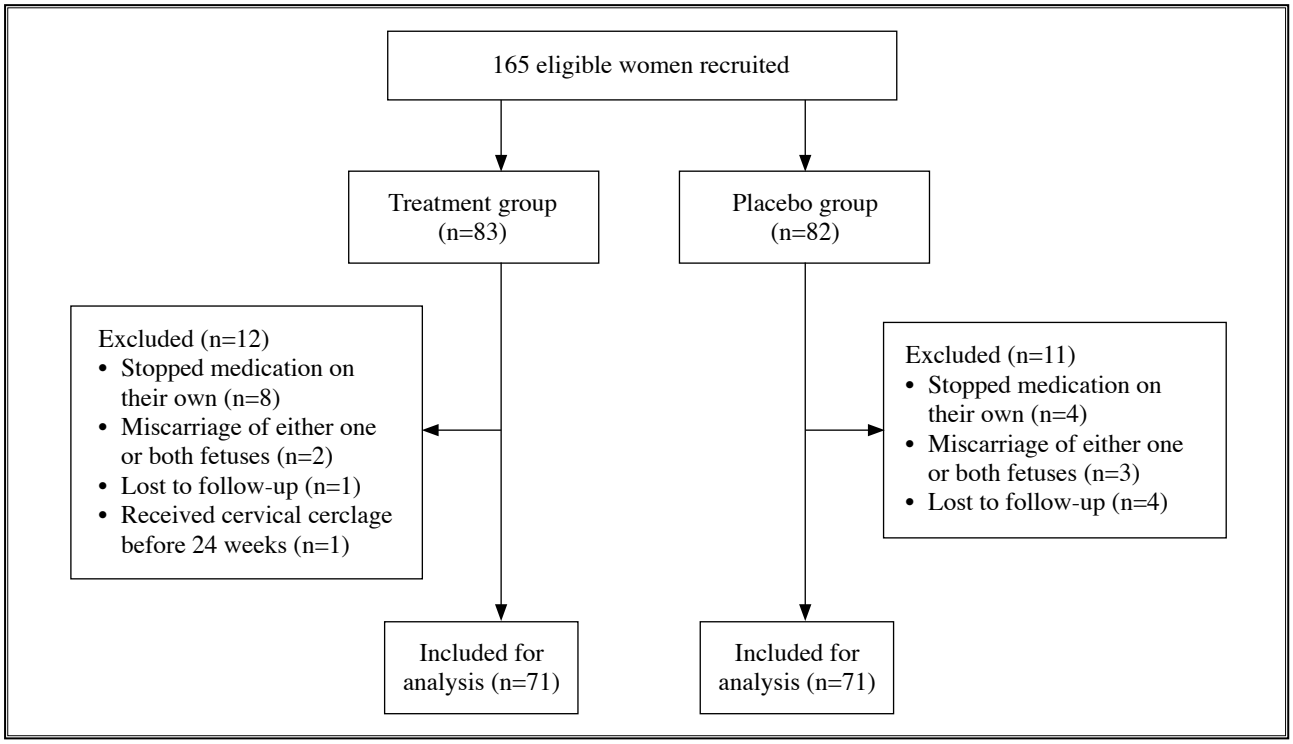

Figure. Flowchart of participant recruitment

Table 1. Basic demographics of unselected women with twin pregnancy

Variable	Placebo (n=71)*	Treatment (n=71)*	p Value
Age, y	34.1±3.02	34.6±3.39	0.393
Gravida	1.6±0.77	1.6±0.90	0.801
No. of termination of pregnancy	0.18±0.5	0.18±0.48	0.841
No. of miscarriage	0.20±0.40	0.21±0.56	0.598
Parity	0.17±0.41	0.13±0.34	0.609
History of preterm delivery	0	0	-
Educational level			0.300
Primary	5 (7)	2 (2.8)	
Secondary	43 (60.6)	39 (54.9)	
Tertiary	23 (32.4)	30 (42.3)	
Race			0.172
Chinese	67 (94.4)	70 (98.6)	
Asian, non-Chinese	4 (5.6)	1 (1.4)	
Occupation			0.402
Housewife	36 (50.7)	28 (39.4)	
Clerical	30 (42.3)	37 (52.1)	
Professional	5 (7)	6 (8.5)	
Medical history			0.220
Good past health	46 (64.8)	48 (67.6)	
Thyroid disease	9 (12.7)	5 (7.0)	
Polycystic ovaries	3 (4.2)	0 (0)	
History of tuberculosis	0 (0)	2 (2.8)	
Ovarian cyst	4 (5.6)	7 (9.9)	
Others	9 (12.7)	9 (12.7)	
Type of conception			0.370
Natural	10 (14.1)	14 (19.7)	
Ovulation induction	0 (0)	1 (1.4)	
Intrauterine insemination	2 (2.8)	6 (8.5)	
In vitro fertilisation	59 (83.1)	50 (70.4)	
Chorionicity			0.771
Dichorionic diamniotic	65 (91.6)	64 (90.1)	
Monchorionic diamniotic	6 (8.4)	7 (9.9)	
Antenatal complication	(n=69)	(n=71)	0.577
None	36 (52.2)	42 (59.2)	
Gestational diabetes	25 (36.2)	20 (28.2)	
Gestational hypertension	1 (1.5)	0 (0)	
Antepartum haemorrhage	2 (2.9)	2 (2.8)	
Pre-eclampsia	4 (5.7)	7 (9.9)	
Polyhydramnios	1 (1.5)	0 (0)	
Low vaginal swab at baseline	(n=70)	(n=71)	0.488
Commensal	53 (75.7)	51 (71.8)	
Streptococci B	6 (8.6)	9 (12.7)	
Gardnerella vaginalis	4 (5.7)	4 (5.6)	
Candida species	6 (8.6)	3 (4.2)	
Torulopsis glabrata	1 (1.4)	4 (5.6)	
Diphtheroid bacilli	1 (1.4)	0 (0)	
Human chorionic gonadotropin level at baseline, IU/L	67337±65588	71016±54400	0.469
Progesterone level at baseline, nmol/L	377.8±105.5	383.4±98.8	0.648
C-reactive protein level at baseline, mg/dL	0.52±0.57	0.47±0.25	0.863
Fasting glucose level at baseline, mmol/L	4.25±0.48	4.17±0.31	0.613
75 g oral glucose tolerance test 2-hour glucose level at baseline, mmol/L	6.44±1.58	6.46±1.62	0.913

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

Table 2. Maternal, obstetric and fetal outcomes

Variable	Placebo (n=71)*	Treatment (n=71)*	p Value
Delivery			
Before 28 weeks	1 (1.4)	2 (2.8)	0.560
Before 30 weeks	3 (4.2)	4 (5.6)	0.698
Before 32 weeks	6 (8.5)	11 (15.5)	0.196
Before 34 weeks	14 (20.0)	22 (31.0)	0.123
Gestation at delivery, w	35.69±2.06	35.30±2.62	0.614
Use of oral nifedipine	25 (35.2)	24 (33.8)	0.860
Uterine activity (No. of contractions in 10 minutes)			
At 24 weeks	0.06±0.25	1.1±4.33	0.062
At 26 weeks	0.54±1.33	1.15±2.60	0.159
At 28 weeks	1.23±2.92	1.16±2.12	0.512
At 30 weeks	1.13±2.62	1.24±1.87	0.206
At 31 weeks	0.83±2.00	1.67±2.76	0.079
At 32 weeks	1.97±3.79	1.87±2.88	0.861
At 33 weeks	2.00±4.30	1.91±3.21	0.438
At 34 weeks	2.02±3.46	2.47±4.66	0.962
Low vaginal swab at 30 weeks	(n=70)	(n=69)	0.296
Commensal	57 (81.4)	47 (68.1)	
Streptococci B	2 (2.9)	9 (13.0)	
Gardnerella vaginalis	3 (4.3)	6 (8.7)	
Candida species	4 (5.7)	2 (2.9)	
Proteus species	1 (1.4)	1 (1.5)	
Lactobacillus	1 (1.4)	1 (1.5)	
Torulopsis glabrate	2 (2.9)	3 (4.3)	
Human chorionic gonadotropin level at 30 weeks, IU/l	70876±63872	67401±38654	0.705
Progesterone level at 30 weeks, nmol/l	751.6±278.5	814.8±218.9	0.032
C-reactive protein level at 30 weeks, mg/dl	0.47±0.28	0.43±0.19	0.667
Fasting glucose level at 30 weeks, mmol/l	4.20±0.39	4.20±0.38	0.935
75 g oral glucose tolerance test 2-hour glucose level at 30 weeks, mmol/l	6.91±1.33	6.49±1.11	0.098
Placental histology			0.747
Normal	64 (90.1)	64 (90.1)	
Chorioamnionitis	3 (4.2)	2 (2.8)	
Placental or focal infarct	0 (0)	2 (2.8)	
Acute chorionitis and funistis	1 (1.4)	1 (1.4)	
Not applicable	3 (4.2)	2 (2.8)	
Mode of delivery of twin 1			0.187
Normal spontaneous delivery	5 (7.0)	5 (7.0)	
Vacuum extraction	3 (4.2)	0 (0)	
Low forceps	1 (1.3)	4 (5.6)	
Caesarean section	62 (87.3)	62 (87.3)	
Mode of delivery of twin 2			0.307
Normal spontaneous delivery	3 (4.2)	4 (5.6)	
Vacuum extraction	4 (5.6)	0 (0)	
Low forceps	1 (1.4)	2 (2.8)	
Assisted breech delivery	1 (1.4)	2 (2.8)	
Caesarean section	62 (87.3)	63 (88.7)	
Birth weight of twin 1, g	2367.8±466.4	2235.4±509.6	0.098
Birth weight of twin 2, g	2340.4±480.8	2239.1±518.1	0.264
Apgar score at 1 minute of twin 1	8.63±1.23	8.38±1.39	0.221
Apgar score at 1 minute of twin 2	8.62±1.29	8.41±1.25	0.204
Apgar score at 5 minutes of twin 1	9.77±0.51	9.65±0.74	0.495
Apgar score at 5 minutes of twin 2	9.82±0.54	9.66±0.66	0.055

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

Discussion

In unselected women with twin pregnancy, the use of 100 mg vaginal progesterone from 24 to 34 weeks did not reduce the risk of preterm delivery and had no significant impact on other obstetric or neonatal outcomes. Nonetheless, vaginal progesterone has been reported to be effective in reducing the rate of preterm delivery in women with a singleton pregnancy and asymptomatic short cervix at second trimester[16]. It was assumed that vaginal progesterone could have the same effect on twin pregnancy, which itself is a major risk factor for preterm delivery.

The anti-inflammatory effect of progesterone can maintain uterine quiescence[17]. In our study, women with vaginal progesterone had a higher serum progesterone level but similar uterine activity. One reason could be inadequate serum progesterone level to suppress uterine activity and subsequent preterm delivery. In four double-blind, randomised, controlled trials of various natural progesterone regimens to prevent preterm birth before 34 weeks, none reported a reduced preterm delivery rate in unselected women with twin pregnancy, regardless of the progesterone preparation, dosage, time of initiation, or duration of treatment[11-14]. In a systematic review of 13 trials involving 3768 women, neither vaginal progesterone nor 17-hydroxyprogesterone caproate had any beneficial effect in preventing preterm delivery or adverse perinatal outcomes[18]. Uterine overdistension may be the cause of preterm delivery in multiple pregnancy and therefore mere progesterone supplementation will not work.

There were limitations to our study. We originally aimed to recruit 176 subjects. The estimated three-fold risk reduction in preterm delivery by vaginal progesterone was based on a Brazilian study that reported vaginal progesterone could reduce 85% the risk of preterm delivery before 34 weeks in singleton pregnancy[15]. Twin pregnancy conceived with assisted reproductive technique has been reported to be at higher risk of preterm delivery before 34 weeks[19], with the risk reported as high as 36.1%[20]. In our study, over 80% of twin pregnancies were the result of an assisted reproductive technique, and the preterm delivery rate before 34 weeks was higher than that reported in other studies (25.4% vs. 12.4%-20.2%)[12-14]. Owing to the slower than expected recruitment rate, an unplanned interim analysis was performed after recruiting 165 women. Further recruitment was stopped because it was unlikely to obtain significant results. In addition, cervical length was not measured at 24 weeks as this was not our routine practice. Women with a shortened cervix at mid trimester have been reported to benefit from progesterone treatment[21]. A meta-analysis reported that a cervical length of ≤25 mm at 20-24 weeks is predictive of preterm birth before 28 weeks in asymptomatic twin pregnancy[22]. Another meta-analysis reported that in women with a shortened cervix and twin pregnancy, compared with placebo, vaginal progesterone significantly reduced the risk of preterm delivery before 33 weeks, neonatal mortality, birth weight of <1500 g, respiratory distress syndrome, and need for mechanical ventilation[21]. The underlying mechanism of progesterone in women with a shortened cervix remains poorly understood. In addition, we did not assess the compliance of women, which was important in a drug trial. Nonetheless, the observed higher progesterone level in the treatment group supported their compliance. Subjects' compliance has been reported to have no significant impact on preterm delivery rate[11-14]. Moreover, one third of our patients were given oral nifedipine for uterine activities based on tocogram monitoring. The frequent tocogram monitoring might have given a false positive alarm to both patients and obstetricians. As 80% of pregnancies were conceived by an assisted reproductive technique, the obstetricians might be more prone to prescribe oral nifedipine. The use of nifedipine might have reduced the overall preterm delivery rate in both groups. Finally, the study was carried out >10 years ago. Nonetheless, it was a double-blind, randomised controlled study of unselected twin pregnancy in the Chinese population. The mean gestational age at delivery (35-36 weeks) was comparable with other studies. We analysed the change in serum hormone level and vaginal microorganisms before and after vaginal progesterone. This has not been addressed in previous studies.

Conclusion

In unselected women with twin pregnancy, vaginal progesterone did not prevent preterm delivery.

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Declaration

All authors have no conflicts of interest to disclose.

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Dienogest Versus Medroxyprogesterone Acetate for Control of Menstrual Pain in Chinese Women with Endometriosis

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Objective: This study aimed to compare dienogest with medroxyprogesterone acetate for management of endometriosis in terms of menstrual pain, quality of life, adverse effects, tolerability, and overall satisfaction.
Methods: This was a cross-sectional, observational study of 60 Chinese women with endometriosis aged 18 to 55 years who were receiving active treatment for ≥6 months with either medroxyprogesterone acetate (150 mg intramuscularly every 3 months) [n=30] or dienogest (2 mg oral daily) [n=30, since 2013]. A questionnaire together with a written consent was posted in July 2017 to patients for completion. The questionnaire comprised 11 questions about pain (n=4), quality of life (n=3), adverse effects and tolerability (n=3), and overall satisfaction with treatment (n=1). Pain symptoms included menstrual pain, chronic pelvic pain, dyspareunia, and dyschezia. Quality of life assessment was based on questions derived from the SF-36 questionnaire and included daily living, work life, and social life. An 11-point rating scale was used.
Results: 25 patients from the dienogest group and 26 patients from the medroxyprogesterone acetate groups returned the questionnaire, with an overall response rate of 83%. Before treatment, the two groups were comparable in terms of baseline characteristics, pain symptoms, and quality of life. After treatment, the mean score for menstrual pain in the dienogest and medroxyprogesterone acetate groups reduced from 5.5 and 4.88 to 1.8 and 3.65, respectively, with the dienogest group achieving a greater absolute reduction (6.6 vs. 4.69, p=0.044). Satisfaction score was higher with dienogest than medroxyprogesterone acetate (8.2 vs. 6.81, p=0.024).
Conclusion: Dienogest is more effective than medroxyprogesterone acetate in treating symptomatic endometriosis and control of menstrual pain, with higher tolerability and satisfaction rate.

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Keywords: Dienogest; Dysmenorrhea; Endometriosis; Medroxyprogesterone acetate

Introduction

Endometriosis is a common gynaecological condition that affects 5% to 10% of women of reproductive age[1]. Symptoms include menstrual pain and chronic pelvic pain. Medications for endometriosis include gonadotrophin-releasing hormone agonists, combined oral contraceptives, and progestins. Nonetheless, gonadotrophin-releasing hormone agonists are associated with symptoms of oestrogen deprivation so long-term use is not recommended[2]. Empirical use of combined oral contraceptives for treatment of menstrual pain may increase the risk of deep-infiltrating endometriosis[3].

Progestin such as medroxyprogesterone acetate is more effective than placebo in pain relief[4,5]. A levonogestrel-releasing intrauterine system is as effective as leuprolide in controlling endometriosis-induced pain[6]. Progestin inhibits the hypothalamic-pituitary-ovarian axis and leads to anovulation, reduced serum level of oestrogen, and atrophy of eutopic endometrium and endometriotic lesions. Progestin also decreases peritoneal inflammatory markers and modulates the immune response involved in the pathogenesis of endometriosis[7], with consequent improvement of symptoms and reduced recurrence. Progestin can be administered orally, subcutaneously, or intramuscularly. Medroxyprogesterone acetate is a type of progestin. It has been reported to completely eliminate pelvic pain and menstrual pain in 35 women with endometriosis[8], and over 80% of patients achieved improvement in pain symptoms, pelvic nodularity, and tenderness[9]. It is similarly effective to leuprolide acetate[10]. However, owing to its non-specific binding to androgen and glucocorticoid receptors, adverse effects of a negative lipid profile, excessive weight gain, and acne have been increasingly reported[4,11].

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Prolonged use remains controversial owing to its effect on carbohydrate metabolism[12]. Alternative medication should be considered in such patients.

Dienogest is a fourth-generation progestin that has been used by our department since 2013. It binds to progesterone receptors more specifically, with a localised effect on endometriotic lesions by directly reducing proliferation and cytokine production in endometriotic stromal cells[13], while having little androgenic, oestrogenic, glucocorticoid, and mineralcorticoid activity. Thus, it exerts minimal impact on metabolic parameters[14]. In a study in Japan, dienogest resulted in ≥25% shrinkage of endometrioma in 77% and 85% of patients after 24 and 52 weeks of treatment, respectively[15]. It has also been shown to decrease the proportion of patients with severe endometriosis (stage III/IV) from 70% to 30%[16]. Treatment for 24 weeks markedly reduced endometriosis-related symptoms (dyspareunia, diffuse pelvic pain, menstrual pain, and premenstrual pain)[16]. Compared with placebo, dienogest significantly improved endometriosis-related pelvic pain while maintaining safety and tolerability[17]. Dienogest and a gonadotrophin-releasing hormone analogue showed a comparable efficacy and safety profile[18-20].

This study aimed to compare dienogest with medroxyprogesterone acetate for management of endometriosis in terms of menstrual pain, quality of life, adverse effects, tolerability, and overall satisfaction.

Methodology

This cross-sectional, observational study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee of the Hospital Authority. The sample size was calculated with the primary consideration to reduce menstrual pain score. We hypothesised that dienogest was superior to medroxyprogesterone acetate in reducing endometriosis-associated menstrual pain. After 6 months of treatment, the mean reduction in pain score was 82% for dienogest[17] and 53% for medroxyprogesterone acetate[21]. A difference of 30% between the study cohorts was considered clinically significant. To have a 90% chance of detecting such a difference at an overall significance level of 0.05, 20 patients per cohort were required. We aimed to recruit 30 patients per cohort to allow for dropouts.

A questionnaire together with a written consent was posted in July 2017 to 60 Chinese women with endometriosis aged 18 to 55 years for completion. They were receiving active treatment for ≥6 months with either medroxyprogesterone acetate (150 mg intramuscularly every 3 months) [n=30] or dienogest (2 mg oral daily) [n=30, since 2013]. They had good compliance and were followed up in the general gynaecology outpatient clinic of Queen Elizabeth Hospital. The diagnosis of endometriosis was based on either pathology (after surgery) or ultrasonography (with evidence of endometrioma >3 cm, nodules of the rectovaginal septum and bladder, combined with clinical symptoms of menstrual pain or pelvic pain).

Clinical records of patients were reviewed to ensure that different hormone treatment options were offered unless contraindicated. The questionnaire was in two sections (before and after treatment) and comprised 11 questions about pain (n=4), quality of life (n=3), side-effects and tolerability (n=3), and overall satisfaction with treatment (n=1) [Table 1]. Pain symptoms included menstrual pain, chronic pelvic pain, dyspareunia, and dyschezia. The latter three symptoms were derived from the pain symptoms enquiry in the Biberoglu and Beham score[22,23]. Quality of life assessment was based on questions derived from the SF-36 questionnaire[24] and included daily living, work life, and social life. An 11-point rating scale was used, according to the recommendation of the Method, Measurements and Pain Assessment in Clinical Trials[22].

The primary outcome was the mean menstrual pain scores before and after treatment. Secondary outcomes were other pain symptoms (chronic pelvic pain, dyspareunia, and dyschezia), quality of life score, side-effect profile, overall satisfaction, and tolerability of the two groups. Statistical analysis was based on the intention to treat principle. Baseline characteristics of the two groups were compared using the unpaired Student's *t* test or Fisher's exact test, as appropriate. The Mann-Whitney *U* test was used to compare the two groups before and after hormonal treatment. Non-parametric tests were used to avoid distributional assumption. All tests were two-sided. A p value of <0.05 was considered statistically significant.

Results

25 patients from the dienogest group and 26 patients from the medroxyprogesterone acetate groups returned the questionnaire, giving an overall response rate of 83%. Before treatment, the two groups were comparable in terms of baseline characteristics, pain symptoms, and quality of life (Table 2). Endometriosis staging was not routinely documented, as some patients had undergone surgery in the private sector. Nonetheless, endometriosis staging has not been shown to be consistently related to pain symptoms in terms of the revised American Fertility Society score[25].

Table 1. Questions about pain, quality of life, adverse effects, and tolerability, and overall satisfaction with hormonal treatment for endometriosis

Question
Before treatment
How bad was the pain with your periods?
Did you ever experience these symptoms? If yes, how severe was it?
Chronic pelvic pain (pain that is not related with period)
Pain during sexual intercourse
Pain during bowel opening
Did dysmenorrhea or chronic pelvic pain affect your daily activity? If yes, how bad was the impact?
Daily activity
Working (leading to absence from work or sick leave)
Social activities
After treatment
How bad was the pain with your periods?
Did you ever experience these symptoms? If yes, how severe was it?
Chronic pelvic pain (pain that is not related with period)
Pain during sexual intercourse
Pain during bowel opening
Did dysmenorrhea or chronic pelvic pain affect your daily activity? If yes, how bad was the impact?
Daily activity
Working (leading to absence from work or sick leave)
Social activities
Did the hormonal treatment affect your period? (irregular period, absence of period, or no change)
Did the hormonal treatment affect the flow of your period? (heavy flow, decreased flow, or no change)
Was there any side-effect from the hormonal treatment? If yes, what was it?
Did the side-effect mentioned affect your daily activities?
Overall, do you satisfy with the hormonal treatment?
Would you continue current hormonal treatment? (yes or no)
What is the reason for not to continue the hormonal treatment? (side-effects, unable to relieve symptoms, or not convenience to use)

After treatment, the mean score for menstrual pain in the dienogest and medroxyprogesterone acetate groups reduced from 5.5 and 4.88 to 1.8 and 3.65, respectively, with the dienogest group achieving a greater absolute reduction (6.6 vs. 4.69, p=0.044, Table 2). Nonetheless, the two groups were comparable in terms of absolute reduction in score for chronic pelvic pain, dyspareunia, or dyschezia. Regarding quality of life for daily living, work life, and social life, both groups achieved a significant improvement and were comparable in terms of absolute reduction in scores (Table 2).

No major adverse effects were reported in either group; minor adverse effects were reported in 14 (56%) and 13 (50%) patients in the dienogest and medroxyprogesterone acetate group, respectively. The most common adverse effect reported was weight gain (n=9). The impact of adverse effects on quality of life score was similar in both groups. Persistent per vaginal spotting was reported in 10 (40%) and 15 (58%) patients, respectively; more patients (though not significantly) in the medroxyprogesterone acetate group had an irregular cycle (p=0.057).

Respectively, 22 (88%) and 23 (88%) patients in the dienogest and medroxyprogesterone acetate group opted to continue treatment. Satisfaction score was higher with dienogest than medroxyprogesterone acetate (8.2 vs. 6.81, p=0.024, Table 2).

Table 1. Comparison of the dienogest and medroxyprogesterone acetate groups in terms of baseline characteristics, pain symptoms, quality of life, satisfaction, and adverse effects before and after treatment

Variable	Dienogest group (n=25)*	Medroxyprogesterone acetate group (n=26)*	p Value
Patient age, y	38±6.95	40±6.07	0.153
Previous delivery			
Primigravida	18 (72.0)	14 (53.8)	0.249
Multiparous	7 (28.0)	12 (46.1)	0.249
Treatment duration, m	25.16±13.2	41.26±43.8	0.085
Previous surgery for endometriosis	18 (72.0)	12 (46.1)	0.089
Endometriomas	21 (84.0)	15 (57.7)	0.064
Deep endometriosis	8 (32.0)	12 (46.2)	0.393
Previous use of other hormones	15 (60.0)	9 (34.6)	0.095
Pain symptom score			
Menstrual pain			
Before treatment	5.5 (4.03-7.01)	4.88 (3.47-6.3)	0.34
After treatment	1.8 (0.64-2.96)	3.65 (2.46-4.85)	0.008
Absolute reduction	6.6 (5.37-7.83)	4.69 (5.37-7.83)	0.044
Chronic pelvic pain			
Before treatment	5.04 (3.75-6.33)	5.00 (3.62-6.38)	0.970
After treatment	2.08 (0.9-3.26)	3.04 (1.85-4.22)	0.143
Absolute reduction	2.96 (1.5-4.42)	1.96 (0.41-3.52)	0.647
Dyspareunia			
Before treatment	2.72 (1.31-4.13)	2.5 (1.41-3.59)	0.833
After treatment	1.12 (0.19-2.05)	1.81 (0.91-2.71)	0.082
Absolute reduction	1.6 (0.35-2.85)	0.69 (-0.26-1.65)	0.828
Dyschezia			
Before treatment	2.64 (1.3-3.98)	2.85 (1.54-4.16)	0.829
After treatment	0.76 (0.02-1.5)	1.69 (0.7-2.69)	0.063
Absolute reduction	1.88 (0.66-3.1)	1.15 (0.43-1.87)	0.692
Quality of life score			
Impact on daily living			
Before treatment	7.32 (6.43-8.21)	7.23 (6.01-8.45)	0.600
After treatment	1.6 (0.52-2.68)	2.38 (1.28-3.49)	0.129
Absolute reduction	5.72 (4.5-6.93)	4.85 (3.31-6.38)	0.477
Impact on work			
Before treatment	7.2 (6.08-8.32)	7.19 (5.95-8.43)	0.803
After treatment	1.32 (0.35-2.29)	2.65 (1.47-3.84)	0.054
Absolute reduction	5.88 (4.65-7.1)	4.54 (2.87- 6.21)	0.324
Impact on social life			
Before treatment	6.6 (5.38-7.82)	7.42 (6.23-8.61)	0.211
After treatment	1.16 (0.18-2.14)	2.35 (1.24-3.45)	0.052
Absolute reduction	5.44 (4.26-6.61)	5.08 (3.42-6.72)	0.962
Adverse effects	14 (56)	13 (50)	0.668
Weight gain	4	5	
Headache	1	1	
Mood changes	4	1	
Insomnia	1	1	
Breast discomfort	1	0	
Tiredness	2	0	
Skin allergy	0	1	
Dizziness	0	2	
Non-specific	1	2	
Impact of adverse effects on quality of life score	2.16 (0.91-3.41)	2.58 (1.42-3.73)	0.33
Menstrual pain	5 (20)	6 (23)	0.79
Persistent per vaginal spotting	10 (40)	15(58)	0.21
Amenorrhoea	13 (52)	12 (46)	0.68
Irregular cycles	3 (12)	9 (35)	0.057
Overall satisfaction score	8.2 (7.43-8.97)	6.81 (5.83-7.78)	0.024

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

Discussion

Our study demonstrated that both dienogest and medroxyprogesterone acetate are an effective treatment for endometriosis-induced pain symptoms, with dienogest achieving a greater absolute reduction in menstrual pain than medroxyprogesterone acetate. This can be explained by dienogest's high specificity for the progesterone receptor and high oral availability. Dienogest has anti-androgenic activity but no mineralocorticoid or glucocorticoid activity. Dienogest creates a mild systemic hypoestrogenic and a potent local hyperprogestogenic environment that leads to atrophy of endometriotic lesions, in addition to a direct inhibitory effect on ovarian follicle development[15,16,26,27].

In our study, both dienogest and medroxyprogesterone acetate lessened the impact of endometriosis on daily living, social life, and work life. A study quantifying the impact of endometriosis symptoms on quality of life reported a mean of 13% loss in work time (absenteeism), 65% impairment in work (presenteeism), 64% loss in work productivity, and 60% impairment in daily activities[28].

In our study, both dienogest and medroxyprogesterone acetate were well tolerated with no severe adverse effects reported. Around half of the patients in each group experienced minor adverse effects such as weight gain, mood change, and headache. In a study that compared norethisterone with dienogest, 41% of patients with dienogest experienced an adverse effect after 6 months[29]. In another study, 86.9% of patients with subcutaneous medroxyprogesterone acetate experienced at least one side-effect during a treatment period of 6 months[30]. Dienogest is better tolerated than other progesterones, probably because dienogest conforms to the oestrogen threshold hypothesis that optimal endometriosis therapy enables suppression that is moderate enough to prevent hypoestrogenic adverse effects such as mood changes or bone mineral density loss[31]. It has been suggested that dienogest can be safely used for up to 5 years without adverse effects and can reduce the endometriosis recurrence rate to 4%, compared with 69% with placebo[32]. The VISADO study concluded that the efficacy of dienogest in relieving endometriosis-related symptoms in adolescents was comparable with that achieved in an adult population[33].

Irregular bleeding is a characteristic of progestin use[34]. In our study, both dienogest and medroxyprogesterone acetate groups reported comparable rates of persistent per vaginal spotting and irregular menstrual cycles. Nonetheless, longer-term treatment with dienogest has been reported to reduce bleeding intensity and frequency[35]. Although bleeding irregularities associated with progestin may adversely affect quality of life, the overall continuation rate was high in both groups, with the dienogest group reporting a significantly higher satisfaction score. Adequate counselling about the likely course of altered bleeding patterns is vital to promote treatment adherence and satisfaction.

Weight gain is a common adverse effect of progestin and often leads to discontinuation of treatment, particularly in young patients[36]. Dienogest has been reported to result in weight gain so small that it does not substantially differ to placebo[37].

In our study, 28% of patients in the dienogest group and only 7.7% of patients in the medroxyprogesterone group complained of mood changes. However, two studies that compared dienogest with norethisterone or gonadotrophin-releasing hormone analogue reported less mood changes or depression with dienogest[18,28]. One case report mentioned the use of dienogest to treat premenstrual mood changes in a patient with schizophrenia who was refractive to other hormonal treatment[38]. Whether dienogest is associated with more mood changes remains controversial. Further study is needed to confirm this suggestion, and the Hospital Anxiety and Depression Scale should be used to determine any clinically significant difference[39].

The resumption of ovulation is delayed following discontinuation of medroxyprogesterone acetate, potentially affecting pregnancy planning[40]. There is no such report for dienogest and hence it may be a more desirable choice. In our study, although 12% of patients in each group opted for discontinuation (mostly because of adverse effects and failure to respond to treatment), patients were more satisfied with dienogest than medroxyprogesterone acetate. Dienogest achieved significantly greater improvement in endometriosis-related menstrual pain. It achieved better control of other pain symptoms, improvement in quality of life, and adverse effect profile than medroxyprogesterone acetate, although not significantly. Dienogest has demonstrated its effectiveness in treating endometriosis in Chinese women[41]. Nonetheless, medroxyprogesterone acetate is a licensed contraceptive that can be delivered orally, subcutaneously, or intramuscularly to manage endometriosis[42]. These benefits may be useful for patients with poor compliance.

There are several limitations in our study. The sample size was small. Dienogest was only introduced in 2013 and was not widely used initially. The pre- and post-test design

is commonly used to compare different medications[43], and has been used to compare dienogest with norethisterone[28]. Nonetheless, the design lacks randomisation and thus any association observed may be due to confounding factors rather than hormonal treatment. In addition, there may have been recall error, as patients were asked to complete both before and after treatment questionnaires at the same time. Objective measurement was lacking. Change in haemoglobin or endometrioma size was not measured, nor was the effect of treatment on bone mass density or lipid level. Medroxyprogesterone acetate is associated with a negative impact on lipid metabolism[44], but no such impact has been reported for dienogest[45,46]. Medroxyprogesterone acetate is associated with a small loss of bone mass density that can be recovered after discontinuation of treatment[47]. Dienogest is associated with minimal change in bone turnover markers and lumbar spine bone mass density after 24 weeks of use[36]. Larger-scale randomised controlled studies are warranted.

Conclusion

Dienogest is potentially more effective than medroxyprogesterone acetate in treating symptomatic endometriosis, especially in control of menstrual pain, with higher tolerability and satisfaction rate.

Declaration

The authors have no conflict of interests to declare.

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Expulsion of a Levonorgestrel-releasing Intrauterine System: a Retrospective Analysis

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Objective: To report the incidence of expulsion of a levonorgestrel-releasing intrauterine system (LNG-IUS) in Chinese patients and to determine the associated risk factors.
Methods: Medical records of patients who underwent insertion of a LNG-IUS between 1 November 2008 and 31 January 2017 at Tuen Mun Hospital were reviewed. The primary outcome was complete or partial expulsion of the device. Patients with or without expulsion were compared to determine the associated risk factors.
Results: A total of 185 patients (mean age, 44 years) with 263 episodes of LNG-IUS insertion were analysed. The mean follow-up was 38.49 (range, 3-113) months; 84.8% of patients were parous. The most common indication for insertion was menorrhagia (73.4%), followed by endometrial hyperplasia without atypia (24%), and endometrial hyperplasia with atypia (3%). The expulsion rate was 35% (n=92); 76 were complete and 16 were partial. 84.8% of expulsions occurred within the first year of insertion; the median time to expulsion was 4 (range, 1-53) months. Compared with patients without expulsion, those with expulsion were more likely to be parous (91.3% vs. 81.3%, p=0.031), have an abdominally palpable uterus (10.9% vs. 4.1%, p=0.033), a longer uterine cavity (8.51 vs. 8.04 cm, p=0.001), fibroids (44.6% vs. 29.8%, p=0.017), adenomyosis (23.9% vs. 11.1%, p=0.006), and the indication for insertion being menorrhagia (94.6% vs. 62%, p<0.001) or dysmenorrhoea (29.3% vs. 12.9%, p=0.001). In multivariable analysis, risk factors for expulsion were an abdominally palpable uterus (adjusted hazard ratio=2.01, p=0.04), menorrhagia (adjusted hazard ratio=6.59, p<0.001), and dysmenorrhoea (adjusted hazard ratio=1.96, p=0.005). 27 patients underwent reinsertion of a LNG-IUS after expulsion; 13 (48.1%) of whom experienced re-expulsion.
Conclusion: Patients with menorrhagia and dysmenorrhoea are at higher risk of expulsion of LNG-IUS. To reduce the risk of expulsion, the LNG-IUS should be inserted during the later part of the menstrual cycle after pregnancy has been excluded. For patients with an abdominally palpable uterus, the LNG-IUS may not be suitable as the first-line management for menorrhagia or dysmenorrhoea owing to the high risk of expulsion; detailed counselling and frequent follow-up should be provided.

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Keywords: Dysmenorrhea; Intrauterine device expulsion; Levonorgestrel; Menorrhagia

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an effective long-acting reversible contraceptive device that releases 20 micrograms of levonogestrel in utero every day[1]. It is recommended by the National Institute for Health and Care Excellence as the first-line management for menorrhagia[2]. The Royal College of Obstetricians and Gynaecologists and Hong Kong College of Obstetricians and Gynaecologists also recommend LNG-IUS as the first-line management for endometrial hyperplasia without atypia[3,4].

Expulsion of a LNG-IUS has been reported to occur in <1 in 20 women over a five-year period[1,2]. When expulsion occurs, women may fall pregnant, treatment for menorrhagia may fail with consequent anaemia, and endometrial hyperplasia may progress to endometrial carcinoma[5]. This study aimed to report the incidence of expulsion of a LNG-IUS in Chinese patients and to determine the associated risk factors.

Materials and Methods

This retrospective study was approved by the New Territories West Cluster Research Ethics Committee (Reference: 18028). Medical records of patients who underwent insertion of a LNG-IUS between 1 November 2008 and 31 January 2017 at Tuen Mun Hospital were

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reviewed. Some patients underwent repeat insertions; each episode was counted as a separate case. Patients were excluded if they were lost to follow-up within one year of insertion or if the LNG-IUS was removed within one year of insertion.

Patient characteristics including age at insertion, parity, size of uterus, length of uterine cavity, and indication for LNG-IUS insertion were collected, as were ultrasonographic findings of adenomyosis and fibroids. The primary outcome was complete or partial expulsion of the LNG-IUS. Complete expulsion was either reported by the patient or confirmed by ultrasonography or pelvic radiography after a report of a missed thread on speculum examination or incidental finding. Partial expulsion was defined as a part of the LNG-IUS visible during a speculum examination. Displacement of the LNG-IUS to the lower cavity or endocervical canal was not considered expulsion. Such patients underwent early removal and were excluded from analysis.

Patients with or without expulsion were compared using the Student's *t* test for continuous variables and the Chi squared test for nominal data. Cox regression analysis was performed; variables with a p value of <0.1 or with clinical significance were further analysed in the multivariable analysis. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 21.0; IBM Corp, Armonk [NY], US).

Results

A total of 245 patients with 323 episodes of LNG-IUS insertion were identified. 12 patients were lost to follow-up within one year of insertion and 48 patients discontinued within one year owing to acute pelvic inflammatory disease / tubo-ovarian abscess (n=3), hysterectomy as definitive treatment (n=4), newly diagnosed breast cancer (n=1), request for early removal secondary to spotting (n=4) or planning conception (n=1), removal of a displaced LNG-IUS (n=7), or endometrial assessment (n=28). The remaining 185 patients (mean age, 44 years) with 263 episodes of LNG-IUS insertion were analysed (Figure 1). The mean follow-up was 38.49 (range, 3-113) months; 84.8% of patients were parous. The most common indication for insertion was menorrhagia (73.4%), followed by endometrial hyperplasia without atypia (24%), and endometrial hyperplasia with atypia (3%).

The expulsion rate was 35% (n=92); 76 were complete and 16 were partial. 84.8% of expulsions occurred within the first year of insertion; the median time to expulsion was 4 (range, 1-53) months. Compared with patients without expulsion, those with expulsion were more likely to be parous (91.3% vs. 81.3%, p=0.031), have an abdominally palpable uterus (10.9% vs. 4.1%, p=0.033), a longer uterine cavity (8.51 vs. 8.04 cm, p=0.001), fibroids (44.6% vs. 29.8%, p=0.017), adenomyosis (23.9% vs. 11.1%, p=0.006), and the indication for insertion being menorrhagia (94.6% vs. 62%, p<0.001) and/or dysmenorrhoea (29.3% vs. 12.9%, p=0.001) [Table 1].

In multivariable analysis, risk factors for expulsion were an abdominally palpable uterus (adjusted hazard ratio=2.01, p=0.04), menorrhagia (adjusted hazard ratio=6.59, p<0.001), and dysmenorrhoea (adjusted hazard ratio=1.96, p=0.005) [Table 2]. The cumulative probability of the LNG-IUS remaining in situ over 5 years stratified with menorrhagia and dysmenorrhoea are shown in Table 3 and Figure 2.

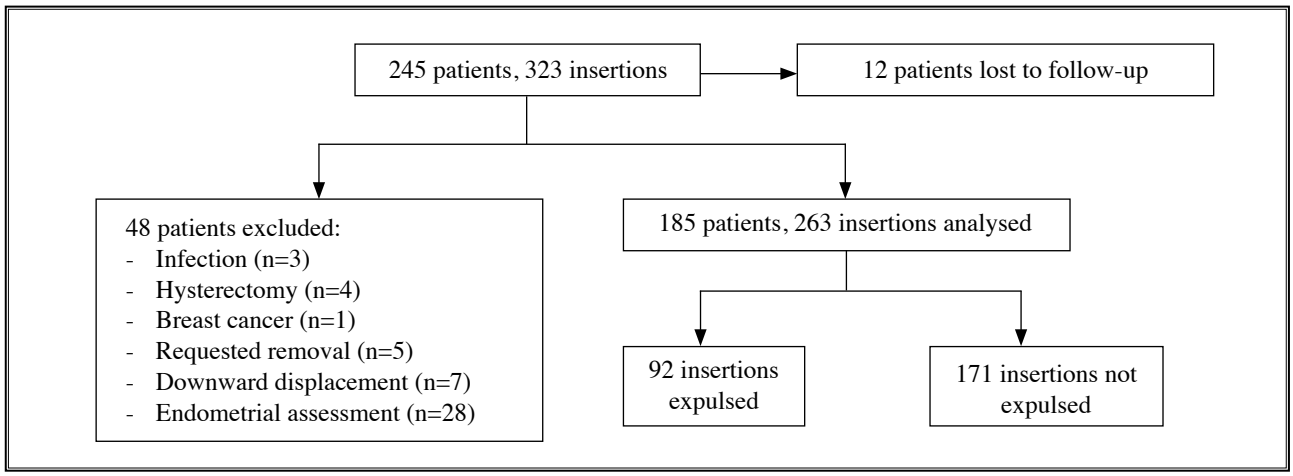

Figure 1. Flowchart of patients who underwent insertion of the levonorgestrel-releasing intrauterine system

Table 1. Patient characteristics

Characteristic	Expulsion		p Value
	No (n=171)*	Yes (n=92)*	
Age of insertion, y	43.63 ± 6.88	44.79 ± 5.57	0.16
Parity			0.031
0	32 (18.7)	8 (8.7)	
≥1	139 (81.3)	84 (91.3)	
Abdominally palpable uterus			0.033
No	164 (95.9)	82 (89.1)	
Yes	7 (4.1)	10 (10.9)	
Uterine cavity length, cm	8.04 ± 0.91	8.51 ± 1.11	0.001
Fibroids			0.017
No	120 (70.2)	51 (55.4)	
Yes	51 (29.8)	41 (44.6)	
Adenomyosis			0.006
No	152 (88.9)	70 (76.1)	
Yes	19 (11.1)	22 (23.9)	
Indication for insertion			
Menorrhagia			<0.001
No	65 (38)	5 (5.4)	
Yes	106 (62)	87 (94.6)	
Dysmenorrhoea			0.001
No	149 (87.1)	65 (70.7)	
Yes	22 (12.9)	27 (29.3)	
Endometrial hyperplasia without atypia			0.002
No	120 (70.2)	80 (87)	
Yes	51 (29.8)	12 (13)	
Endometrial hyperplasia with atypia			0.176
No	164 (95.9)	91 (98.9)	
Yes	7 (4.1)	1 (1.1)	
History of expulsion			0.13
No	157 (91.8)	79 (85.9)	
Yes	14 (8.2)	13 (14.1)	
Duration of usage, m	29.53 ± 18.59; 21 (12-88)	7.20 ± 10.04; 4 (1-53)	<0.001
Follow-up, m	38.74 ± 27.83; 24 (12-113)	38.01 ± 25.91; 33 (3-111)	0.84

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

Table 2. Risk factors for expulsion using the Cox regression model

Variable	Adjusted hazard ratio (95% confidence interval)	p Value
Parity ≥1	1.06 (0.50-2.24)	0.91
Abdominally palpable uterus	2.01 (1.02-3.95)	0.04
Menorrhagia	6.59 (2.57-16.90)	<0.001
Dysmenorrhoea	1.96 (1.23-3.12)	0.005
Endometrial hyperplasia without atypia	0.94 (0.50-1.77)	0.85

Table 3. Cumulative rate of expulsion

Parameter	Time after insertion			
	1 month	6 months	12 months	>12 months
Cumulative No. (%) of expulsions (n=92)	31 (33.7)	61 (66.3)	74 (81.5)	92 (100)
Cumulative rate of expulsion of cohort (n=263), %	11.8	23.2	28.1	35.0

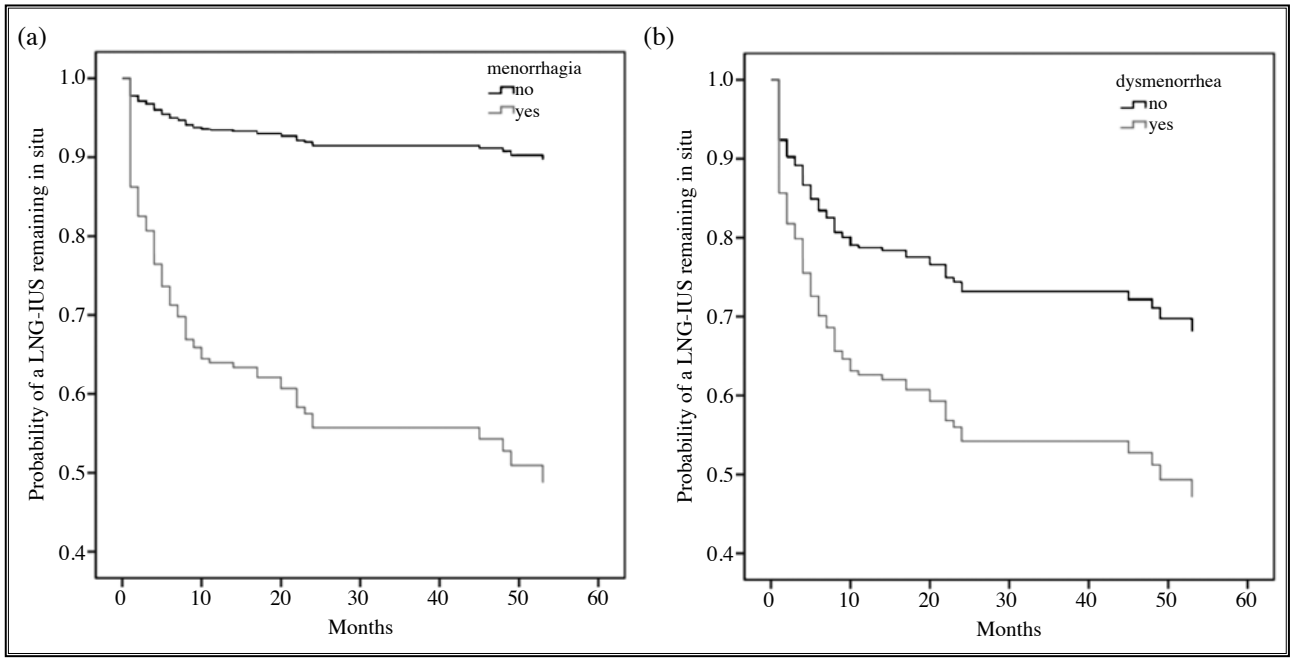

Figure 2. Cumulative probability of the levonorgestrel-releasing intrauterine system (LNG-IUS) remaining in situ stratified by (a) menorrhagia and (b) dysmenorrhoea

27 patients underwent reinsertion of a LNG-IUS after expulsion; 13 (48.1%) of whom experienced re-expulsion. The median interval to expulsion was 4 (range, 1-53) months for the first insertion and 2.5 (range, 1-33) months for the second insertion (p=0.86, paired sample t-test).

Discussion

The LNG-IUS is an effective long-acting device used in the management of menorrhagia and dysmenorrhoea[6]. LNG-IUS usage has been reported to increase haemoglobin level in patients with menorrhagia[7,8]. The prevalence of endometrial hyperplasia further expands the use of LNG-IUS[9]. If endometrial hyperplasia persists after 12 months of LNG-IUS use, hysterectomy should be discussed. Expulsion of LNG-IUS is a known complication and mostly occurs within the first year of insertion[10].

The mean age of our patients was 44.03 years, which was older than that reported in most studies. In our patients, LNG-IUS was used mainly for treatment of gynaecological problems (menorrhagia, dysmenorrhoea, and endometrial hyperplasia) rather than contraception.

According to the manufacturer and National Institute for Health and Care Excellence guideline, the risk of expulsion of a LNG-IUS is <5%[1,2]. This expulsion rate has been further reported to range from 5.7% in 5 years to 25.3% in 2 years[7,11-18]. In our study, the expulsion rate was much higher at 28.1% in the first year and 35% cumulatively. Nonetheless, most studies on the expulsion rate of the copper intrauterine device (IUD) and LNG-IUS have focused on patients whose primary indication was contraception. In contrast, none of our patients used the LNG-IUS solely for contraception; most had menorrhagia or dysmenorrhoea, and both are significant risk factors for expulsion[16,19-21]. The expulsion rate has been reported to be higher for LNG-IUS than IUD[16,17], probably because of increased menstrual flow in LNG-IUS patients; most patients reported expulsion during heavy menses. In

our patients, most of the LNG-IUS were inserted during admission for heavy menstrual flow; 31 (33.7%) expulsions occurred within 1 month of insertion. In a study that involved over 9000 women in Portland, the expulsion rate decreased if the IUD was inserted later in the menstrual cycle[22]. The LNG-IUS may be flushed out by heavy menses before levonorgestrel has had an adequate effect on the endometrium. In addition, the expulsion rate in other studies may have been underestimated, as most studies did not clearly define expulsion[7,11,12,14-18] or include partial expulsion[7,12,14-18]. One study relied only on patient reporting of expulsion that can be easily missed[15]. There were only a few studies of expulsion of a LNG-IUS in Chinese patients. A study in Taiwan of patients with adenomyosis reported the highest expulsion rate compared with studies among Caucasian populations[16]. Regional/ethnic differences in the expulsion rate have been reported in a multi-centre study[12]. Further study with a larger sample size is required to determine the expulsion rate in our local population with menorrhagia or dysmenorrhoea.

Adenomyosis and dysmenorrhoea increase the risk of expulsion[16,19,21]. Dysmenorrhoea is associated with increased prostaglandins in the uterus that increase the contractile force of the uterus and hence the chance of expulsion of a LNG-IUS[23]. Menorrhagia and dysmenorrhoea are common indications for LNG-IUS insertion. Despite the increased risk of expulsion, the use of LNG-IUS is still recommended, and can result in an increase in haemoglobin level by 1.17-1.8 g/dl[6-8]. LNG-IUS is also suitable for patients who opt for conservative treatment or while awaiting surgery. It is important to explain the risk of expulsion. Patients should be taught to self-check the thread regularly and attend follow-up to ensure appropriate management if the LNG-IUS is expulsed.

The manufacturer recommends the use of LNG-IUS on the uterus sounded to 6 to 10 cm[1]. Within this range, the uterine cavity length does not affect the risk of expulsion[19,24]. The risk of expulsion increases if the uterus is too large with a consequent higher chance of malposition of the LNG-IUS. Such patients should be counselled about the higher risk of expulsion and that the LNG-IUS may not be an appropriate first-line management for menorrhagia or dysmenorrhoea.

In case of expulsion, immediate reinsertion of a new LNG-IUS is advised after pregnancy has been excluded. About 34% of patients experience re-expulsion after the first IUD expulsion; the risk is much higher if the first expulsion occurred within 3 months of insertion[25]. In our study, 48.1% of patients had re-expulsion after reinsertion. Nonetheless, a history of expulsion was not a risk factor for expulsion. This may be due to the small number of patients who underwent reinsertion.

One limitation of this study was its retrospective nature. 28 patients with early removal of LNG-IUS for endometrial assessment were excluded; previous practice in our unit was to remove the copper IUD or LNG-IUS prior to endometrial assessment. Patients with a LNG-IUS in a stable condition were followed up in primary care centres; some of them may have already been transferred before expulsion occurred. Nonetheless, only 4.9% of patients were lost to follow-up and missing data were minimal. Our patients had a high continuation rate of LNG-IUS. Only 2.1% of patients requested early removal, compared with a discontinuation rate of 18% in the first year in one study[11]. With adequate counselling about adverse effects, a higher continuation rate of LNG-IUS for treatment of gynaecological conditions may be assured. The Cox regression model was used for multivariable analysis because expulsion could occur after premature removal.

Conclusion

Patients with menorrhagia and dysmenorrhoea are at higher risk of expulsion of LNG-IUS. To reduce the risk of expulsion, the LNG-IUS should be inserted during the later part of the menstrual cycle after pregnancy has been excluded. For patients with an abdominally palpable uterus, the LNG-IUS may not be suitable as the first-line management for menorrhagia or dysmenorrhoea owing to the high risk of expulsion; detailed counselling and frequent follow-up should be provided.

Declaration

The authors have no conflicts of interest to disclose.

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Should Mitochondrial Replacement Therapy be Legalised in Hong Kong?

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Mitochondrial replacement techniques (MRTs) of pronuclear transfer, maternal spindle transfer, polar body transfer, and mitochondrial gene editing can be used to prevent mitochondrial diseases. This study reviews the ethical principles for MRTs in terms of autonomy, beneficence, non-maleficence, and justification. MRTs appear to be compatible with existing norms and standards of reproductive medicine.

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Introduction

Human beings are eukaryotic organisms. All cells possess a double membrane-bound structure within the cell cytoplasm known as the mitochondria. This organelle serves as the energy warehouse that enables cells to function properly. Mitochondrial DNA (mtDNA) is located outside the cell nucleus and is passed on solely by maternal inheritance. mtDNA comprises 37 genes and accounts for only 0.1% of all human DNA materials[1]. mtDNA diseases occur when a sufficient proportion of mitochondria with deleterious DNA mutations affects cellular energy production to the extent that cell physiology is impaired. Such deleterious mutations can occur spontaneously during cell division and mtDNA replication or can be inherited from the maternal side. Homoplasmy is mutation in all mitochondrial genomes and affected women always pass this condition to their children. Heteroplasmy is mutation in some mitochondrial genomes and affected women pass a mix of normal and mutated mitochondria to their children. Manifestations of mitochondrial diseases depend on the type of DNA mutation and the proportion of deleterious mutated DNA.[2] Mitochondrial inheritance does not follow the simple Mendelian pattern. Instead, during production of primary oocytes, a variable number of mtDNA molecules are transferred to each oocyte followed by rapid replication of this mtDNA population. This sophisticated restriction-amplification mechanism results in a random shift of mutational mtDNA load between generations known as the mtDNA bottleneck effect[3,4]. In women with a heteroplasmic mutation, the phenotypical expression is likely to vary widely so the outcome is unpredictable. Deleterious mutation in mtDNA has been documented to cause various heritable diseases including Leigh syndrome, Leber hereditary optic neuropathy, and other conditions and syndromes that can lead to dementia, stroke, blindness, deafness, cardiac failure, and major organ failure[5,6].

Mitochondrial Replacement Techniques

Pronuclear Transfer

During in-vitro fertilisation, two zygotes are produced, one using the intended parents' gametes and the other using an oocyte donated from a healthy woman and the intended spouse's sperm. Within the first 24 hours of fertilisation, the male and female pronuclei are manually removed from the zygotes before fusion to form an embryo. The pronucleus produced from the donor oocyte's nuclear material is disposed of, and the intended parents' pronuclei are enucleated from the original zygote and transferred to this enucleated donor zygote. The intended parents' nuclear material continues to develop in a zygote that comprises healthy mitochondrial DNA. The zygote is then transferred back to the woman as an embryo[4,6,7] (Figure 1).

Maternal Spindle Transfer

Using standard IVF techniques, oocytes are obtained from the woman with mitochondrial mutations and from a healthy donor. During metaphase II of cellular division, the chromosomes are aligned to one side of the oocyte in a spindle shape group, and the chromosomes of both oocytes are removed. The donor's chromosomes and the woman's enucleated oocyte are disposed of, and the woman's chromosomes are transferred to the donor's enucleated oocyte. The reconstructed oocyte carries healthy mitochondria of the donor and the chromosomes

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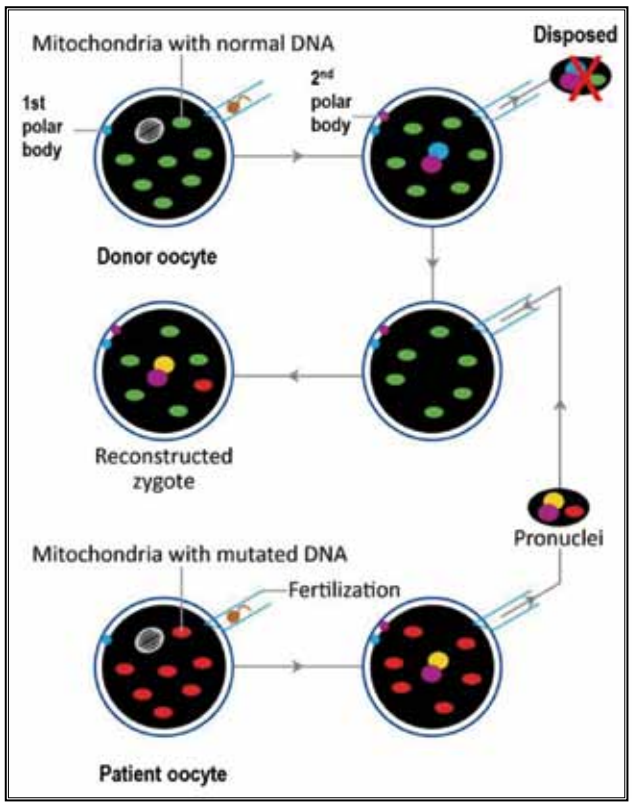

Figure 1. Pronuclear transfer

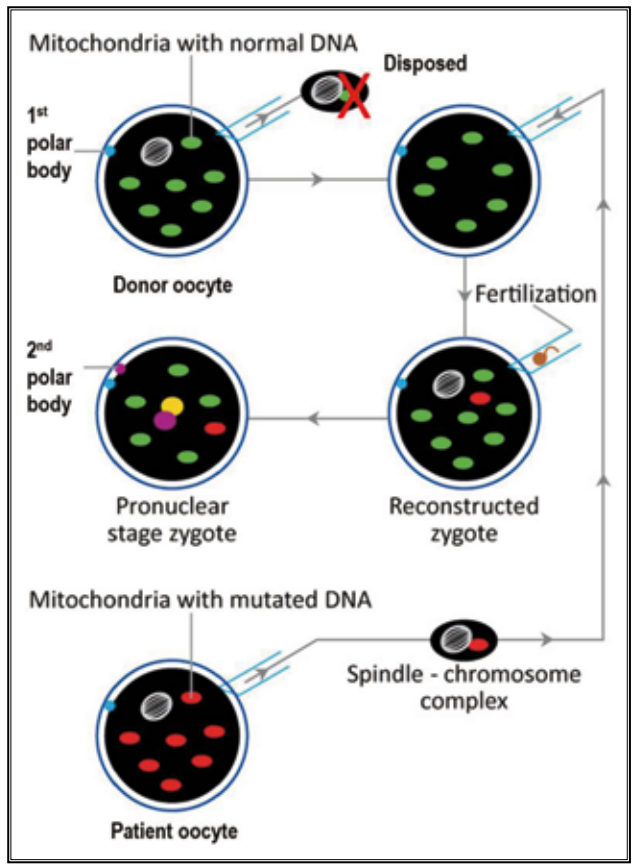

Figure 2. Maternal spindle transfer

of the woman. This oocyte is fertilised with the spouse's sperm using standard IVF techniques and then transferred to the woman for conception[5,6,8,9] (Figure 2).

Polar Body Transfer

During oocyte maturation, the first polar body is formed as DNA duplication occurs, so that the oocyte contains four sets of chromosomes. Of these, two remain within the oocyte, and the other two are packaged into the polar body and subsequently extruded and not present in the embryo. Similarly, when the second polar body is formed during fertilisation, one set of the remaining chromosomes is packaged into the second polar body, and the remaining set joins the sperm DNA of the male to become the nuclear DNA of the embryo. Polar bodies have very few mitochondria and may avoid mitochondrial carry-over. Polar body transfer is the transfer of the first polar body to an unfertilised enucleated donor egg (which is stringently preventive) or transfer of the second polar body to a half-enucleated zygote (not stringently preventive)[5,7,10] (Figure 3).

Mitochondrial Gene Editing

CRISPR/Cas9 is a natural system that enables bacteria with an adaptive response against viruses[11,12]. TALENs are engineered nucleases that comprise a transcription activator-like effector DNA-binding domain from Xanthomonas fused to a FokI nuclease domain. Mito-TALENs are TALENs that are directed specifically at the mitochondrial DNA. These mitochondrial gene editing techniques are undergoing animal phase studies[5,7,9] (Figure 4).

Comparison of the different techniques

Mitochondrial replacement of DNA has specific relevance to law and regulation as well as to ethical considerations. Pronuclear transfer involves zygotes, and destruction of an early embryo to reconstitute another selected embryo is controversial as the law considers all human embryos to have the same legal or moral status as human being and forbids experimenting with and selection of embryos. Maternal spindle transfer involves oocytes, with the donor oocyte being discarded. Similarly, transfer of the first polar body involves the oocyte, whereas transfer of the second polar body after fertilisation involves destruction of one embryo for every healthy embryo produced. From an ethical point of view, procedures that involve oocytes alone are more acceptable[8,9,12]. Gene editing techniques do not involve any donor and hence evade the legal and ethical problem of the genetic linkage of three persons[7,9].

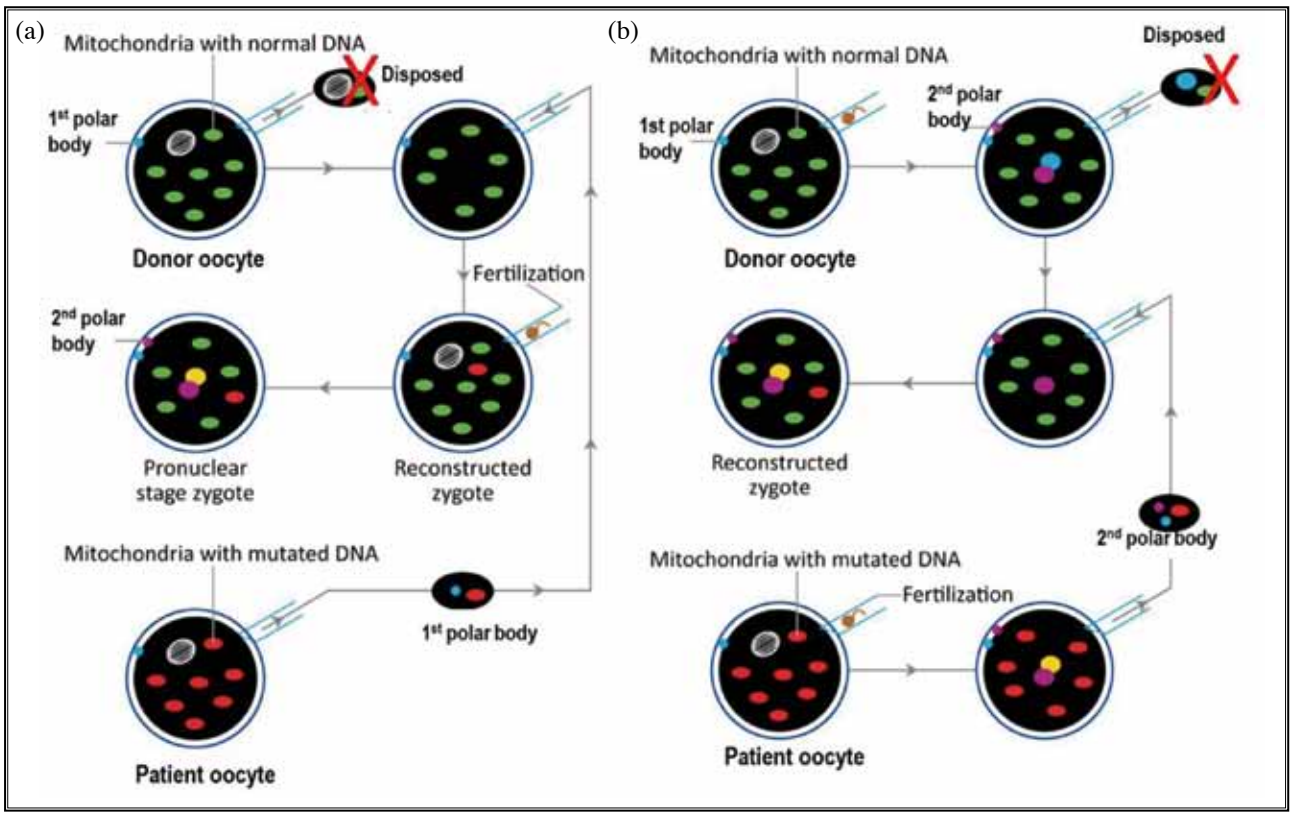

Figure 3. (a) First and (b) second polar body transfer

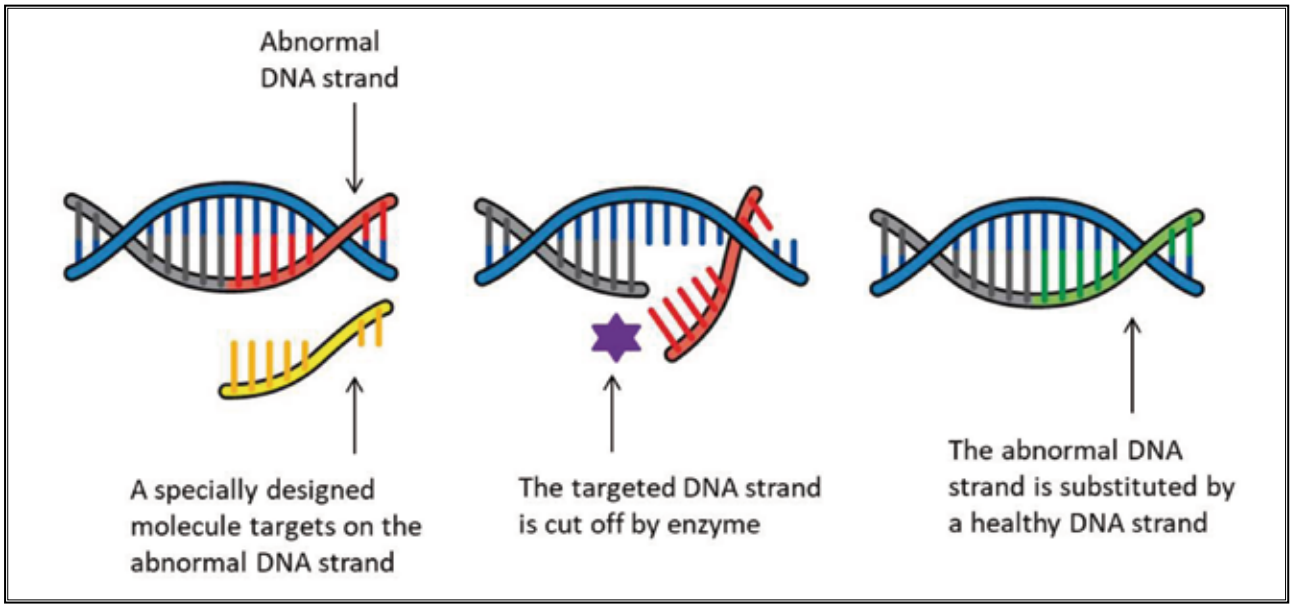

Figure 4. Mitochrondrial gene editing

Ethical Principles

Autonomy

Prior to the availability of mitochondrial replacement techniques (MRTs), the possible option for a woman with mitochondrial disorders was prenatal genetic diagnosis after normal conception with termination of the pregnancy if the fetus was affected, or preimplantation genetic diagnosis that involves selection of embryos with

the lowest proportion of abnormal mtDNA for implantation so as to reduce (rather than eliminate) the risk of having a baby severely affected by mitochondrial disease[7]. These options are relevant only to heteroplasmic women. The only choice for homoplastic women was oocyte or embryo donation from a healthy woman, with consequent children having no genetic linkage to the mother.

The 'slippery slope' argument is the main argument against the principle of autonomy. There is a fear of playing God by changing mtDNA or any DNA and eventually producing 'designer' babies. By tampering with the germline genetic constitution that will be inherited by future generations, altering genetics intentionally to enhance humans and to produce mutants deprive future generations of their right to receive an un-manipulated gene pool[13]. This is an example of a weak 'slippery slope' argument[14]. It is unreasonable to argue that MRTs inevitably lead to the pursuit of germline modifications to enhance healthy embryos and lead to human mutants. Such projection is speculative and can be safely put aside if internal and external monitoring systems are established under legislation to ensure technology is used appropriately and with proper restrictions[15]. Thus, women should have the autonomy to choose MRTs if they are fully counselled about the implications of all the options available.

Beneficence

Although vitamin supplements, drugs, and physical exercise have been used to treat mitochondrial diseases in isolated cases and clinical trials, evidence for their effectiveness is lacking[16]. Preventing a child from being born with a severely handicapping and non-curable mitochondrial disorder appeals to both affected families and the general public. The conventional management of pregnancy termination is unacceptable to many families and religions. Pregnancy termination seems to be the greater evil compared with manipulating oocytes or sacrificing donor embryos. In addition, MRTs enable healthy mtDNA to be passed on and terminate the family history of mitochondrial disease.

Non-maleficence

Safety Issues

Germline modification involves ooplasmic transfer (injection of donor ooplasm with normal mitochondria into an oocyte with mutant mtDNA) and has been developed as a fertility technique for women with repeat embryonic development failure. Its first applications resulted in a relatively high number of children with chromosomal abnormalities (two of 16 pregnancies); there were concerns about mitochondrial heteroplasmy (two of 15 born children carried mtDNA from the donor and recipient) and the possible epigenetic effects of ooplasmic transfer[17]. Results of animal experiments and the first human case indicate that MRTs are free of such problems.

Evolutionary biologists have raised concerns about the safety of MRTs based on the extent to which nuclear and mitochondrial DNA co-evolve within natural populations, i.e. the nuclear-mitochondrial mismatch hypothesis. Animal models have provided evidence of incompatibility between nuclear and mitochondrial genomes from divergent populations of the same species. Nonetheless, a study of a naturally occurring nuclear-mitochondrial mismatch across 26 populations revealed that mitochondrial and nuclear genomes from divergent human populations could co-exist in healthy humans, indicating that mismatched nuclear DNA-mtDNA combinations are not deleterious, and are unlikely to challenge the safety of MRT[18].

The UK Human Fertilization and Embryology Act (HFEA) expert panel has reviewed the safety and effectiveness of MRTs and concluded that there is no evidence to show that such techniques are unsafe or one method is superior to the other[11]. The Nuffield Council on Bioethics also concluded that if the treatments were acceptably safe and effective, it would be ethical for families to use[13]. A public consultation exercise conducted by HFEA concluded that "there is general support for permitting mitochondria replacement in the UK, so long as it is sufficiently safe to be offered in a treatment setting and done so within a regulatory framework".

In pregnancies conceived after MRTs, polar body biopsy, preimplantation genetic diagnosis, ultrasonography, and prenatal diagnosis can be used to determine whether the embryo is developing normally and whether any affected mitochondria have been transferred. Follow-up studies of children conceived by MRTs are also necessary to determine long-term safety issues.

Donor Status and Parenthood

Theoretically, any embryo created by pronuclear transfer or maternal spindle transfer contains DNA of three people, the so-called three-parent in-vitro fertilisation. Genetically, the woman and her spouse contribute 99.9% of the genetic materials and the oocyte donor contributes

only the 0.1% mitochondrial DNA, unlike conventional oocyte donation that contributes 50% of the DNA. The Nuffield ethics review suggested that mitochondria donors should have the same status as women who donate eggs or embryos for conventional in-vitro fertilisation[11]. Mitochondria donors should receive compensation and be safeguarded, as they undergo the same invasive procedures of ovarian stimulation and oocyte retrieval as those who undergo conventional in-vitro fertilisation. While the panel saw no reason why they should be identifiable to the adults born as a result of their donation, a person conceived by MRTs can have a legitimate interest in knowing who contributed to his or her genetic make-up. Following public consultation, the HFEA expert panel advised that mitochondrial donors should be awarded similar status to tissue donors. Under common law, the legal mother is the woman who carried and gave birth to the child and the father is the man who provided the sperm. The expectation of the oocyte donor in MRTs to claim parenthood is much lower than the conventional oocyte donor or surrogate mother[19].

Impact on the Child

Having three genetic 'parents' may cause a person to suffer[13]. Nonetheless, there is no reason for any particular parenting arrangement to be followed[19]. Concerns that children with genetic ties to three persons will experience psychosocial problems are likely unfounded. Evidence from families created by gamete donation can provide valuable insight into the psychosocial development of children who share genetic ties with an individual who may not play any role in their daily living.

Justification

The UK Department of Health estimated that around one in every 6500 children born in the country has a mtDNA disease; it has been estimated that about 10 to 150 children per year would have benefited from mitochondrial therapy[14,20]. Similar figures are not available in Hong Kong. When considering the bioethical tenet of beneficence, there is a consensus that MRTs are worth pursuing if the quality of life of those affected can be improved, even if the number is small[16]. Nonetheless, MRTs are expensive. Whether the government should fund such services remains controversial. In Hong Kong public hospitals, in-vitro fertilisation is partially self-financed; government subsidy of MRTs may motivate academic institutions to invest in the development of the technology.

Legislation

Although the US National Academy of Sciences Panel considered MRTs to be ethically acceptable, the Congress blocked the technology through a federal spending bill by prohibiting the Food and Drug Administration from considering applications to carry out MRTs[6,21]. In the UK, the HFEA prohibits implantation in a woman of eggs or embryos with altered DNA. However, the HFEA makes provision, subject to parliamentary consent, to permit this for a single specific purpose of "preventing the transmission of serious mitochondrial disease". In 2015, both houses of parliament approved regulations put forward by the Department of Health, and the UK became the first country in which MRTs are explicitly legal and yet under stringent control of the authorities. Centres must apply for and be granted a license from the HFEA for each proposed procedure. Nonetheless, a petition brought forward by the European Union parliament aimed to stop the legalisation of MRTs in the UK on the basis of the risks of eugenics and the harm to human dignity. Nonetheless, the arguments were weak and did not address the issues at stake in a convincing manner[22,23].

In Hong Kong, the Human Reproductive Technology Council was established with reference to the HFEA. To legalise such practices, clear indications for carrying out each proposed procedure should be documented and strictly confined to patients with mitochondrial diseases that have a significant health impact. As the assisted reproductive procedures are highly sophisticated, confining the licensee to one or two institutions with academic background enables more stringent monitoring. Donor information should be kept confidentially in a central registry, with a similar legal handling of semen donors.

Conclusion

MRTs can be used to prevent mitochondrial diseases. The ethical principles for MRTs appear to be compatible with existing norms and standards of reproductive medicine. Legislation of MRTs in Hong Kong can be based on the existing Human Reproductive Technology Ordinance with stringent surveillance by the Human Reproductive Technology Council.

Declaration

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Treatment of Primary Epithelial Ovarian Cancer

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Maximal cytoreduction and platinum-based chemotherapy remain the mainstay treatments for epithelial ovarian cancer. New modalities include targeted therapy, intraperitoneal chemotherapy, and hyperthermic intraperitoneal chemotherapy. With different characteristics in different patients and the complexity of diseases, treatment should be individualised and reviewed by a multidisciplinary team.

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Introduction

Ovarian cancer is the seventh most common cancer among women globally[1]. In 2015 in Hong Kong, ovarian cancer was the sixth most common cancer among women and the seventh most common cause of cancer death among women[2]. There were 578 new cases of ovarian cancer (median patient age, 52 years), accounting for 3.9% of all cancer cases. The lifetime risk before age 75 years was 1 in 107.

Most epithelial ovarian cancers are diagnosed at a late stage[3]. Despite cytoreductive surgery and platinum-based chemotherapy, more than half of patients with advanced disease have recurrence and a poor prognosis[4,5]. We review the management of primary epithelial ovarian cancers.

Early-stage Epithelial Ovarian Cancers

Ovarian cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system. Pre-operative imaging such as chest radiography, computed tomographic and magnetic resonance imaging of the abdomen and pelvis, and positron emission tomography computed tomography are commonly used to assess the extent of disease and the feasibility of complete debulking of the tumour.

In apparently early-stage disease, the standard treatment is staging laparotomy, which can serve diagnostic and treatment purposes. After a midline skin incision, the procedure comprises peritoneal washing for cytology, exploration of the whole abdomen and pelvis, total abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal biopsies, and biopsy of any suspicious lesions. Fertility-sparing surgery (unilateral salpingo-oophorectomy, full staging, and endometrial sampling) can only be considered if the disease is at clinical stage 1 and the histology is relatively indolent such as low-grade serous carcinoma, low-grade endometrioid carcinoma, or mucinous carcinoma.

Minimally invasive surgery may be considered in selected patients[6]. In a meta-analysis of five comparative studies[7], compared with laparotomy, laparoscopy resulted in less blood loss (mean difference [MD], -175.7 ml; 95% confidence interval [CI], -219 to -132.3 ml), longer operative time (MD, 16.8 min; 95% CI, 8.8-24.8 min), shorter length of hospitalisation (MD, -3.3 days; 95% CI, -3.9 to -2.7 days), and earlier commencement of adjuvant chemotherapy (MD, -4.9 days; 95% CI, -6.7 to -3.2 days). Laparotomy and laparoscopy were comparable in terms of the rates of spillage (7.2% vs. 9.5%; 95% CI, 0.35-1.73), upstaging (17.1% vs. 16.6%; 95% CI, 0.38-1.27), and recurrence (5.3% vs. 8.3%; 95% CI, 0.21-1.21). The incidence of port-site metastasis ranges from 0.89% to 17%[8,9]. Independent risk factors for abdominal wall metastasis are FIGO stage 4 (compared with stage 3) and the presence of ascites of >500 ml. Minimally invasive surgery is an acceptable option for small-volume disease.

After surgery, platinum-based chemotherapy is given to high-risk patients, including those with stage 1C disease or beyond and those with more aggressive tumours such as high-grade endometrioid carcinoma, high-grade serous carcinoma, small cell carcinoma, and carcinosarcoma.

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Late-stage Epithelial Ovarian Cancers

The treatment options depend on the chance of optimal or complete debulking, patient fitness, and surgical morbidity[10]. There are two main options: (1) primary debulking surgery (PDS) followed by adjuvant chemotherapy, and (2) neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) with or without further adjuvant chemotherapy.

The definition of optimal cytoreduction has changed from ≤2 cm to ≤1 cm (R1); complete debulking refers to no gross macroscopic disease (R0)[10]. Different models have been proposed to predict the possibility of achieving optimal cytoreduction and to identify patients whose disease is unlikely to be optimally debulked. Computed tomography has been used to predict the presence of residual disease[11-13]. Nonetheless, most models have not been systematically validated and the accuracy is around 34% to 77%. The Fagotti model of laparoscopic assessment has been validated and is most commonly used; it comprises seven parameters: the presence of omental cake, peritoneal, and diaphragmatic carcinomatosis, mesenteral retraction, bowel and stomach infiltration, and liver metastasis (Table 1)[14]. The presence of each parameter is allocated two points. A total score of ≥8 indicates zero probability of optimal debulking at laparotomy, with an overall accuracy rate of 77.3% to 100%[15].

Primary debulking surgery

For patients with advanced disease, the aim of upfront surgery is to achieve maximal cytoreduction. There is robust evidence on the survival benefit after complete or optimal debulking. In patients with stage 3 to 4 ovarian cancer who underwent PDS and subsequent platinum-based chemotherapy, each 10% increase in the maximal cytoreduction led to a 5.5% increase in median survival time[16]. For each 10% increase in the proportion of patients who achieved R0 or R1, the median survival time increased 2.3 and 1.8 months, respectively[17]. In a Cochrane review of the effectiveness and safety of optimal PDS for advanced ovarian cancer[18], complete cytoreduction was associated with prolonged overall survival and progression-free survival; such survival benefit was observed in patients with optimal cytoreduction with residual disease of <1 cm, compared with those with suboptimal (>1 cm) debulking.

To achieve R0, extensive pelvic and upper abdominal procedures (diaphragmatic surgery, liver resection, splenectomy, pancreatomy, porta hepatis dissection, and bowel resection) may be necessary. The rate of these procedures has increased in the United States[19], as has the optimal debulking rate[20]. The rates of complications (haemorrhage, vascular injury, nerve injury, and prolonged hospitalisation) are lower in high-volume hospitals than in low- and medium-volume hospitals (10.2% vs. 21.2% vs. 21.7%, p=0.01)[19]. In a retrospective review of 620 patients, 138 (22.3%) developed grade ≥3 complications and 55 (8.9%) died within 90 days of surgery[21].

Systematic Lymph Node Dissection

In a randomised trial that compared the survival outcomes of 427 patients with stage 3B to 4 disease[22], compared with debulking of enlarged lymph nodes only, systematic lymph node dissection improved the 5-year progression-free survival (31.2% vs. 21.6%; 95% CI, 1.5%-21.6%) but not the 5-year overall survival (48.5% vs. 47%; 95% CI, -8.4% to 10.6%) in patients with optimally debulked ovarian cancer. The intra-operative complication rates were similar in both arms, but the rates of post-operative lymphocysts and lymphoedema were higher in those with systematic lymph node dissection.

In the Lymphadenectomy In Ovarian Neoplasm study that randomised 647 patients with stage 2B to IV disease (who had no clinical lymph node involvement with apparently R0 at PDS) to undergo systematic lymph node dissection or not, the preliminary results presented at the American Society of Clinical Oncology meeting in 2017

Table 1. Fagotti laparoscopic scoring system[14]

Parameter	Score	Remark
Peritoneal carcinomatosis (massive unresectable/ military pattern)	2	Score 0 if carcinomatosis involving limited area that are surgically removable by peritonectomy
Diaphragmatic disease	2	-
Mesenteric disease	2	Score 0 if small nodules that are potentially treated by argon beam coagulator
Omental disease	2	Score 0 if isolated localisation
Bowel infiltration	2	-
Stomach infiltration	2	-
Liver metastasis	2	Any surface lesion

revealed that the two groups were comparable in terms of median overall survival and progression-free survival. It appears legitimate to omit systemic lymph node dissection and debulk only enlarged lymph nodes to achieve R0.

Adjuvant chemotherapy

Platinum-based chemotherapy is the standard adjuvant treatment for advanced epithelial ovarian cancers. The most commonly used regimen is 3-weekly carboplatin and paclitaxel. The role of dose-dense chemotherapy has been evaluated.

In the Japanese Gynecologic Oncology Group (GOG) 3016 study[23], in patients with stage 2 to 4 epithelial ovarian cancers, compared with the conventional 3-weekly regimen, the use of dose-dense paclitaxel (80 mg/m^2) once a week (on day 1, 8, and 15) combined with carboplatin (area under curve, 6) on day 1 of a 21-day cycle improved the progression-free survival (28.2 vs. 17.5 months, p=0.0037) and overall survival (100.5 vs. 62.2 months, p=0.039), although the rate of anaemia was higher in the dose-dense group (69% vs. 44%, p<0.0001).

However, such survival benefit could not be demonstrated by the Multicentre Italian Trials in Ovarian cancer (MITO) 7 study[24], which used a lower dosage in the dose-dense regimen and included stage 1C patients. The MITO-7 study showed a lower incidence of grade 3-4 neutropenia, neutropenic fever, grade 3-4 thrombocytopenia, and grade ≥2 neuropathy in the dose-dense arm than the conventional arm.

The GOG-262 trial compared progression-free survival of patients who received either dose-dense or conventional carboplatin and paclitaxel with or without bevacizumab[25]. For those who did not receive bevacizumab, progression-free survival was longer in the dose-dense arm than the conventional arm (14.2 vs. 10.3 months, p=0.03). For those received bevacizumab, no difference in progression-free survival was seen.

In the International Collaborative Ovarian Neoplasm (ICON) 8 study that randomised patients with stage 1C to 4 epithelial ovarian / peritoneal / fallopian tube carcinoma in a 1:1:1 ratio into 3-weekly carboplatin and paclitaxel, 3-weekly carboplatin and weekly paclitaxel, or weekly carboplatin and paclitaxel, the preliminary results reported in the European Society for Medical Oncology 2017 Congress showed that there was no difference in progression-free survival[26]. The ICON 8b study included only stage 3 to 4 patients and they were randomised to a conventional regimen with bevacizumab, dose-dense regimen, or dose-dense with bevacizumab.

Targeted Therapy

Bevacizumab is an intravenously administered target therapy; it is a recombinant humanised monoclonal IgG1 antibody that neutralises vascular endothelial growth factor A. It acts via two mechanisms. First, it inhibits neovascularisation and regresses existing microvessels and hence suppresses tumour growth. Second, it improves the structure and function of the tumour vessels that in turn improves the delivery of chemotherapeutic agents to the tumour.

In the GOG 218 trial that randomised patients with suboptimally debulked stage 3 or 4 ovarian cancer to receive standard adjuvant intravenous paclitaxel / carboplatin, chemotherapy with five cycles of concurrent bevacizumab (15 mg/kg), or chemotherapy with concurrent bevacizumab and subsequent bevacizumab maintenance for 16 more cycles[27], the median progression-free survival was 10.3, 11.2, and 14.1 months, respectively, and the overall survival of the three groups was similar.

The ICON 7 study randomised patients with high-risk early-stage disease or FIGO stage 2B to 4 disease that was optimally or suboptimally debulked to either standard adjuvant paclitaxel / carboplatin, or concurrent bevacizumab (7.5 mg/kg) with chemotherapy with maintenance bevacizumab up to 12 more cycles or until disease progression[28,29]. Progression-free survival at 42 months for suboptimally debulked stage 3 or 4 patients was 14.5 and 18.1 months, respectively (p=0.04), and the median overall survival was 28.8 and 36.6 months, respectively (p=0.002). Bevacizumab was well tolerated with adverse effects of hypertension, proteinuria, delayed wound healing, fistula and bowel perforation, and a small risk of thromboembolic events.

Other than bevacizumab, olaparib, a poly (ADP-ribose) polymerase inhibitor, has also been investigated in the SOLO-1 study[30]. Patients with stage 3 (with one attempt at optimal debulking) or stage 4 (either following PDS or IDS) disease who had a *BRCA* mutation and responded to first-line platinum-based chemotherapy were randomised to receive olaparib tablet maintenance or placebo. Preliminary results showed that olaparib improved progression-free survival. The GINECO/ENGOTov25 PAOLA-1 Trial evaluates a combination of olaparib and bevacizumab as maintenance therapy in women with newly diagnosed advanced ovarian cancer irrespective of their *BRCA* status[30]. Results are expected to be published in 2019.

Intraperitoneal chemotherapy

The peritoneal cavity is a common site of metastasis in epithelial ovarian cancers. Intraperitoneal (IP) chemotherapy exerts its cytotoxic effect both locally and systemically. Locally, the drug can directly penetrate the tumour mass on the peritoneal surface by free-surface diffusion[31], but the depth of penetration is a few millimetres only[32]. Systemically, the drug enters the circulation through uptake by the peritoneum and passage through the portal circulation, and reaches the tumour through capillary flow[31]. This enables delivery of a higher dose of the chemotherapeutic agent to the tumour while minimising systemic toxicity[33-39]. Because of the limited depth of direct penetration of chemotherapeutic agents, IP chemotherapy is more likely to benefit those with microscopic disease or low-volume residual disease of <0.5-1 cm[32].

Compared with IV chemotherapy alone, IP chemotherapy (with cisplatin) increased overall survival by 10 to 16 months in patients with advanced ovarian cancer (Table 2)[40-42]. The National Cancer Institute states that women with stage 3 ovarian cancer who have undergone optimal cytoreduction should be considered for IP chemotherapy. Carboplatin is less toxic than cisplatin and is the standard drug for IV chemotherapy for ovarian cancer. IP chemotherapy with carboplatin combined with a dose-dense IV paclitaxel regimen has been investigated in the Japanese iPOCC study, with results expected to be available in 2019[43].

Despite the promising results of IP chemotherapy, it is not widely adopted, mainly because of its high toxicity. Patients who received IP chemotherapy experienced greater haematological, gastrointestinal, and metabolic toxicities than those who received IV chemotherapy (Table 2)[41,42]. In the GOG 172 study, only 42% of patients in the IP arm could complete six cycles of IP chemotherapy, with catheter-related complications being the primary reason for discontinuation[42]. A Cochrane review also demonstrated that compared with IV chemotherapy, IP chemotherapy was associated with more severe adverse events such as gastrointestinal toxicities (e.g. bowel obstruction), pain, fever, and infection[44]. Another barrier to IP chemotherapy is the increased costs related to more complicated logistics[45].

Neoadjuvant Chemotherapy

For patients with a poor condition or whose disease is so extensive that optimal debulking is not feasible, NACT may be an alternative. A biopsy or at least a cytological sample with adequate cell numbers for immunostaining is mandatory before NACT. After 3 to 4 cycles, IDS is performed if there is a good response and further chemotherapy may be required.

The European Organisation for Research and Treatment of Cancer 55971 trial compared the outcomes of platinum-based NACT followed by IDS and additional chemotherapy with conventional treatment of PDS followed by platinum-based chemotherapy in 632 patients

Table 2. Intraperitoneal (IP) versus intravenous (IV) chemotherapy in overall survival and progression-free survival

Study	Eligible patients	Interventions	IP vs. IV chemotherapy		Toxicity
			Overall survival, m	Progression-free survival, m	
GOG 104[40]	Stage 3; residual ≤2 cm; n=546	Control arm: IV cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2); experiment arm: IP cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2)	49 vs. 41, p=0.02	-	Toxicity more frequent in IV group (moderate to severe tinnitus, clinical hearing loss, neuromuscular toxic effects)
GOG 114[41]	Stage 3; residual ≤1 cm; n=462	Control arm: IV paclitaxel (135 mg/m^2, 24 h) + IV cisplatin (75 mg/m^2); experiment arm: IV carboplatin (area under curve, 6) every 28 days for 2 courses), then IV paclitaxel (135 mg/m^2, 24 h) + IP cisplatin (100 mg/m^2)	63 vs. 52, p=0.05	28 vs. 22, p=0.01	Neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities were greater in the IP arm
GOG 172[42]	Stage 3; residual ≤1 cm; n=415	Control arm: IV paclitaxel (135 mg/m^2, 24 h) + IV cisplatin (75 mg/m^2); experiment arm: IV paclitaxel (135 mg/m^2, 24 h) + IP cisplatin (100 mg/m^2) + IP paclitaxel (60 mg/m^2) on day 8	65.6 vs. 49.7, p=0.03	23.8 vs. 18.3, p=0.05	Grade 3 or 4 pain, fatigue, hematologic, gastrointestinal, metabolic and neurologic toxic effects were more common in IP group

with stage 3C or 4 ovarian cancer[46]. Patients in the NACT arm had similar survival rates but a lower incidence of surgical morbidity (severe haemorrhage, infection, and venous thromboembolism) than patients in the PDS arm. The CHORUS trial also demonstrated a non-inferiority of NACT and IDS in comparison to PDS and adjuvant chemotherapy in terms of median overall survival (22.6 vs. 24.1 months, p>0.05)[47]. The NACT groups had fewer major postoperative adverse events (14% vs. 24%, p=0.0007) and deaths (<1% vs. 6%, p=0.001). Similarly, the SCORPION trial showed that NACT was associated with less perioperative major morbidity (52.7% vs. 5.7%, p=0.0001) and better quality of life, compared with conventional treatment[48].

Nevertheless, results should be interpreted with caution. Patient characteristics were heterogeneous between different study groups, as were the skill and experience of the surgeons. The optimal treatment option for advanced epithelial ovarian cancer remains controversial[49]. PDS can reduce the tumour load in a short time before chemotherapy and may reduce the risk of developing chemo-resistance, whereas NACT may shrink the tumour and reduce peri-operative morbidity and help evaluate the response to the chemotherapy and identify any non-responders early so as to modify the drug regimen.

The ANTHALYA trial showed that bevacizumab, together with carboplatin and paclitaxel, could achieve a 58.6% complete resection rate at IDS, compared with the pre-defined complete resection rate of 45% and the complete resection rate of 51.4% in the chemotherapy alone arm[50]. Bevacizumab resulted in more grade ≥3 toxicities but the pre-specified safety threshold was not reached. Preliminary results showed that the response rate and progression-free survival could be improved for those with stage 3C or 4 ovarian, tubal, or peritoneal carcinoma not eligible for PDS[51]. Further investigation is required to establish safety and efficacy of bevacizumab in neoadjuvant chemotherapy.

Interval debulking surgery

The aim of IDS is to debulk all tumours to R0 as in PDS. The optimal timing of IDS should be based on the health of the patient, recovery from any chemotherapy-related toxicity, especially myelosuppression, and the likelihood of achieving optimal debulking. A decrease in cancer antigen 125 level and the disappearance of clinical ascites were predictors of complete cytoreduction[52-54]. Nonetheless, no prospective trials have examined the role of systematic lymph node dissection in IDS. A case-control study showed that there was no difference in 2-year survival (69% vs. 88%, p=0.0777), recurrence (70.0% vs. 62.4%, p>0.05), or death (30% vs. 23.7%, p>0.05) between systematic lymph node dissection and debulking of enlarged nodes only at the time of IDS with R1 residual disease[55].

Hyperthermic intraperitoneal chemotherapy

Distinctly different to postoperative IP chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) involves a single administration of heated chemotherapeutic agents into the peritoneal cavity at the time of cytoreductive surgery, followed by conventional IV chemotherapy. Compared with normothermic IP chemotherapy, HIPEC has following advantages. First, the use of heat can increase the cytotoxic effects of chemotherapeutic drugs by directly inducing thermal cellular damage, increasing DNA-crosslinking and increasing drug penetration into tumour cells[56-58]. Second, hyperthermia has been shown to increase the sensitivity of tumour cells to cisplatin in both platinum-sensitive and resistant cell lines[59]. Third, by giving chemotherapy intra-operatively, drugs can disperse to all areas of the peritoneal cavity without being hindered by adhesions. Surgeons can also control the dwell time and optimise the drug exposure in the peritoneal cavity. Cytoreductive surgery and HIPEC have been well-established for the treatment of peritoneal carcinomatosis in gastrointestinal malignancies, peritoneal mesothelioma, and pseudomyxoma peritonei. Nonetheless, its role in ovarian cancer has only recently been examined.

In a meta-analysis that included nine comparative studies and 28 cohort studies, cytoreduction and HIPEC followed by chemotherapy achieved a significantly better overall survival than cytoreduction and chemotherapy alone, and the benefit continued for up to 8 years in primary disease, and up to 3 years in recurrence disease[60]. The mortality and morbidity rates were similar in both groups. A multicentre phase III trial showed that the addition of HIPEC with cisplatin to IDS resulted in longer recurrence-free survival (10.7 vs 14.2 months) and overall survival (33.9 vs 45.7 months) than surgery alone, and the addition of HIPEC did not result in higher rates of adverse events[61]. Many centres in the world increasingly adopt HIPEC following NACT.

Conclusion

Maximal cytoreduction and platinum-based chemotherapy remain the mainstay treatments for epithelial ovarian cancer. New modalities include targeted therapy, IP chemotherapy, and HIPEC. With different characteristics in different patients and the complexity of diseases, treatment should be individualised and reviewed by a multidisciplinary team.

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Reference

*The efficacy report for silicone pro (Dermscan Asia Co., Ltd. #DA16A024-1) (2016)

Prescribing information:

WHEN SHOULD HIRUSCAR® SILICONE PRO BE STARTED?

It is recommended to start early in the treatment of scars, for example fresh scars (up to 3 months old) and as soon as the wound has healed and closed.

HOW TO USE HIRUSCAR® SILICONE PRO?

1. After cleaning the affected area and gently patting dry, apply a pea size amount at the tip of the scar and gently spread thinly over the whole affected area in one direction. No need to rub. It is recommended to use a pea size of 6 mm. in diameter for 8-cm scar.
2. Allow to dry for about 1-2 minutes. Once dry, cover the affected area with makeup or sunscreen if needed.
3. Apply Hiruscar® Silicone Pro gel twice daily (morning and evening).
4. To protect against scar formation, it should be used once the wound has closed.

HOW LONG SHOULD HIRUSCAR® SILICONE PRO BE USED?

Use Hiruscar® Silicone Pro gel for 2 months and may continue to use for as long as you continue to see improvements in your scars. For more prominent scar, it may take over 3-6 months or more to experience the full benefit of Silicone gel product.

A 10g tube of Hiruscar® Silicone Pro gel will last for about 1.5 - 2 months on an 8-cm scar and 4g tube will last for about 0.5 - 1 month.

WARNINGS: Hiruscar® Silicone Pro gel is formulated for external use only. Do not apply on open wounds and avoid contact with eyes and mucous membrane. If any side effect occurs with product use, stop using the product immediately and consult your pharmacist or physician. Keep out of reach of children and store in a cool dry place. Please do not apply over antibiotic skin preparations.

INGREDIENTS: Cyclomethicone, DimethiconeNinyl Dimethicone Crosspolymer, Cyclopentasiloxane, Isononyl Isononanoate, Cetyl PEG/PPG-10/1 Dimethicone, Dimethicone, Water, Ascorbyl Tetraisopalmitate, Tocopheryl Acetate, Glycosaminoglycans

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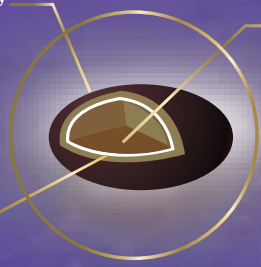

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* Pineda, O., et al. (1994). Effectiveness of iron amino acid chelate on the treatment of iron deficiency anemia in adolescents. Journal of Applied Nutrition, 46(1), 2-13.

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