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Nausea and Vomiting during Pregnancy

Nausea and vomiting in pregnancy (NVP) are common, especially during early pregnancy[1]. In a local report including 396 pregnant women (10-14 weeks), the prevalence of NVP was 90.9%[2].

Risk factors[3-5]

- ☐ First pregnancy
- ☐ Multiple pregnancy (e.g. twins, triplets)
- ☐ Family history of NVP
- ☐ History of migraine headaches
- ☐ History of motion sickness (e.g. car sick)
- ☐ Experiencing stress
- ☐ Severe nausea and vomiting in a previous pregnancy
- ☐ If mothers-to-be used to feel sick when taking contraceptives containing oestrogen
- ☐ Obesity (e.g. BMI ≥ 25)

Tips to help relieve NVP[1,3,6]

Medical treatment is not needed in most cases and some lifestyle changes may alleviate the symptoms:

- ✓ **Rest**
- ✓ **Food** – What and when to eat may be helpful, e.g.
  - Avoid fatty foods, coffee and spices like garlic
- ✓ **Drinks**
  - May try some sour drinks like lemonade and plum juice

Read ALL tips to help relieve NVP NOW:

Expert opinion

The American College of Obstetricians and Gynecologists (ACOG)[4]:

"The standard recommendation to take prenatal vitamins for 1 month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy"

References: *1. Health Direct. Morning sickness. https://www.healthdirect.gov.au/morning-sickness. Accessed on 04 Jan 2021. 2. Chan OK et al. Aust N Z J Obstet Gynaecol. 2010;50(6):512-518. 3. National Health Service (NHS). Vomiting and morning sickness. https://www.nhs.uk/pregnancy/related-conditions/common-symptoms/vomiting-and-morning-sickness/. Accessed on 04 Jan 2021. 4. American College of Obstetricians and Gynecologists (ACOG). ACOG practice bulletin. Number 189. 2018. 5. Centre for Health Protection. Body mass index chart. https://www.chp.gov.hk/en/resources/e_health_topics/pdfwrv_11012.html. Accessed on 05 Jan 2021. 6. Hong Kong Department of Health. Minor ailments in early pregnancy and their management. Available at: https://www.fhs.gov.hk/english/health_info/woman/15656.html. Accessed on 04 Jan 2021.*

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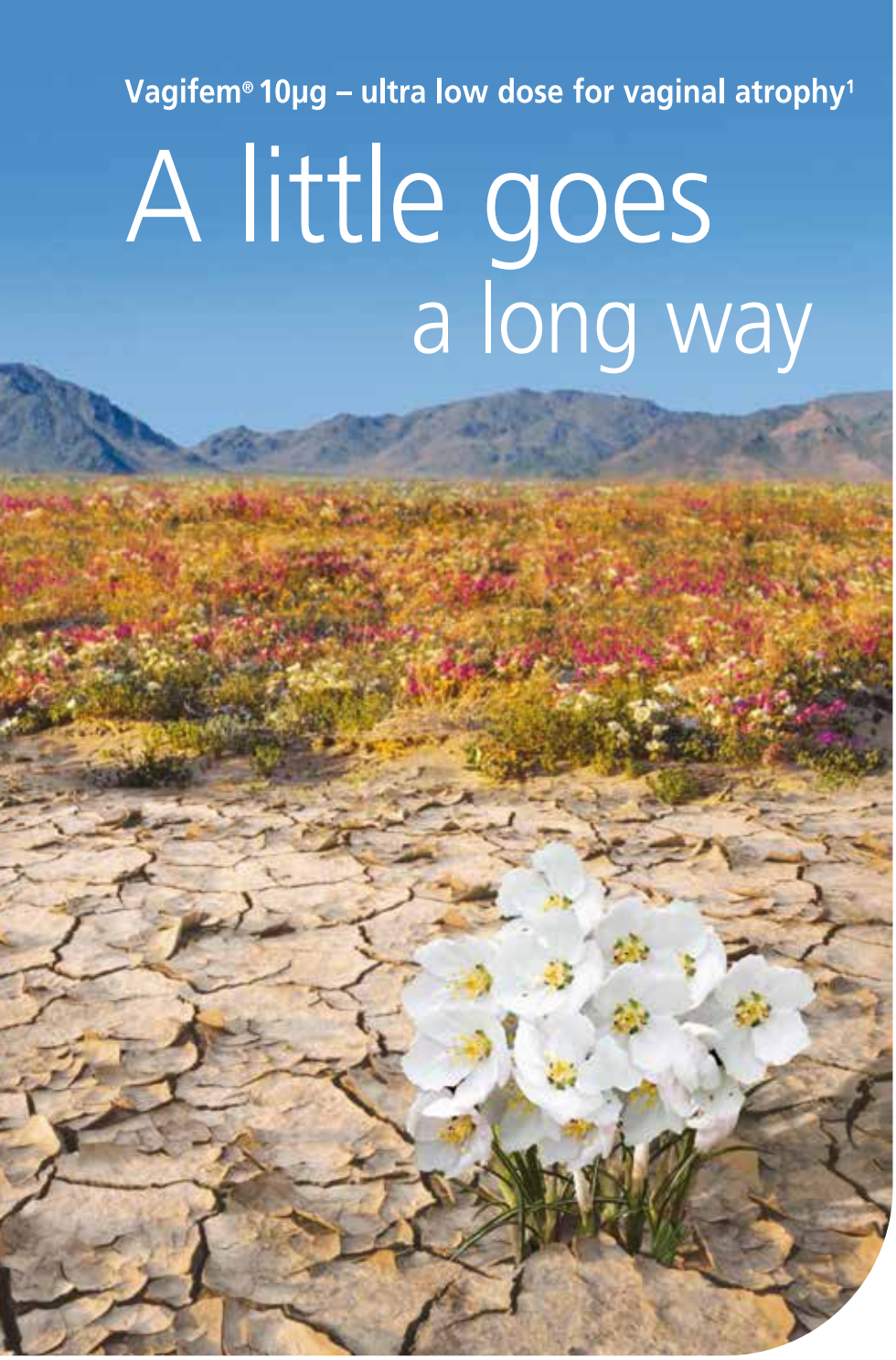

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Date of preparation: December 2018.

Reference:

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

2. Vagifem 10µg Summary of Product Characteristics.

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

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

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- The abstract should be after the title page and numbered page 1
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Books edited by other authors of the article

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

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

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Editorial

Celebrating the 60th anniversary of the Obstetrical and Gynaecological Society of Hong Kong

I am honoured to be invited to write this editorial to commemorate the 60th anniversary of the Obstetrical and Gynaecological Society of Hong Kong (OGSHK). Since its establishment in 1961, OGSHK has provided a venue for continuous medical education and fraternity for its members. Under the hard work and dedication of our senior colleagues, OGSHK has developed rewarding relationships with the Hong Kong College of Obstetricians and Gynaecologists, the Asia and Oceania Federation of Obstetrics and Gynaecology, the International Federation of Gynecology and Obstetrics, and many other professional associations. I trust these relationships will continue, and our excellence and leading role in clinical service, training, and research in women's health will maintain.

I feel privileged to have served the Society for the past 10 years through the kind invitation by Dr KY Leung to join as a council member in 2011. The unforgettable memories of activities of the Society include the scientific meetings in 2014, 2016, and 2019, the FOCUS meetings co-organised with the Chinese University of Hong Kong in 2015 and 2018, the perinatal symposia co-organised with the Hong Kong Neonatal Society, and many scientific symposia on various topics.

One of the most memorable experiences is the organisation of the Asia and Oceania Congress of Obstetrics and Gynaecology in 2017, which attracted 1189 participants from 42 countries. In the Congress, I participated in organising the Young Gynaecologist Award (YGA) Fellowship Program, which involved 24 distinguished YGA Fellows from 18 countries[1]. These Fellows had the opportunity to immerse in various aspects of obstetrics and gynaecology training and care in Hong Kong by undertaking clinical observerships in five hospitals, learning the concept of Chinese medicine, and visiting training facilities and medical museums[1]. The friendships, collegiality, and memories acquired were long lasting.

OGSHK is also committed to providing health education to the public. Our colleagues have regularly provided health education through various channels including radio and television interviews, press conferences, magazine articles, and health talks.

The 60th anniversary is a significant milestone. This occasion gives us an opportunity to congratulate and thank all our senior colleagues who have established the Society and all those who have committed and contributed to the success of the Society. This milestone also marks the continual growth and maintenance of our excellence and leadership in promoting women's health in the coming decades.

The COVID-19 pandemic has caused difficulty to our specialty[2]. The impact on our workforce including frontline workers, colleagues, researchers as well as patients and their loved ones has been profound[2]. Most regular events and meetings were suspended, especially in the first half of 2020. We had to transform our on-site events, courses, and seminars into web-based activities. This transition gave our women's healthcare professionals some flexibility to continue their education and training. On behalf of OGSHK, I would like to thank our dedicated colleagues for their hard work and commitment during this pandemic. I am confident that with determination and perseverance, these difficulties and challenges can be overcome.

This special occasion allows us to not only proudly look back on what our Society has achieved, but also look forward to building the strategies to maintain its success. For the coming years, there are areas in which we may consider exploring further for possible improvement of women's health services such as academic collaboration with cities in the Greater Bay Area, expansion of public health education, and improvement of gynaecological care for women with sexual difficulties and sexual minority women[3].

I would like to express my sincere appreciation to all our members and all past and present council members who have made our Society prosper. I look forward to having your continued support and contribution, while we strive for further achievement and excellence in our Society.

Vincent YT CHEUNG, MBBS, FRCOG, FRCSC
President, The Obstetrical and Gynaecological Society of Hong Kong

Correspondence to: Dr Vincent YT CHEUNG
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Indications for induction of labour and mode of delivery in nulliparous term women with an unfavourable cervix

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Objectives: To determine the association between indications for induction of labour (IOL) and mode of delivery in nulliparous women with unfavourable cervix.
Methods: We identified nulliparous singleton term women with an unfavourable cervix who underwent IOL between 1 January 2013 and 31 December 2017 in an obstetrics unit. Clinical data of patients and their neonates were collected. The primary outcome was the mode of delivery (vaginal vs caesarean). Secondary outcomes were the instrumental delivery rate, indications for caesarean section, and maternal and neonatal complication stratified by indications of IOL.
Results: 1156 women were included for analysis. The IOL success (vaginal delivery) rate was 66.4%, the instrumental delivery rate was 19.2%, and the caesarean delivery rate was 33.6%. After controlling the confounding factors (maternal age, stature, weight gain during pregnancy, and Bishop score), indications for IOL independently associated with the mode of delivery were post-date pregnancy (adjusted odds ratio [OR_{adj}]=2.30, p<0.001), diabetes mellitus diseases (OR_{adj}=1.67, p=0.015), hypertensive disorders (OR_{adj}=1.72, p=0.015), and large-for-gestational-age fetus (OR_{adj}=2.32, p=0.001). Maternal age ≥35 years, body mass index ≥25 kg/m^2, more weight gain during pregnancy were associated with caesarean section, whereas taller stature and a more favourable Bishop score were associated with vaginal delivery.
Conclusion: Different indications for IOL affect the mode of delivery differently. Post-date pregnancy, diabetes mellitus diseases, hypertensive disorders, and large-for-gestational-age fetus are independent risk factors for caesarean delivery.

Keywords: Cervix uteri; Delivery, obstetric; Labor, induced

Introduction

Induction of labour (IOL) is commonly performed for various indications[1]. From 2004 to 2014, the incidence of IOL in all hospitals in Hong Kong had increased from 18.4% to 22.3%[2]. According to the Cochrane Review 2020, IOL after 37 weeks of gestation reduces the stillbirth rate, perinatal morbidity, and mortality[3].

Failed IOL results in caesarean section, which may result in maternal morbidity and adverse maternal experience in childbirth. The failure rate is higher in nulliparous women with an unfavourable cervix[4]. Predictors for IOL success (vaginal delivery) include multiparity, taller maternal statures, lower maternal body mass index (BMI), lower estimated fetal weight, and a favourable Bishop score[5-7]. There are limited studies on whether indications of IOL predict mode of delivery[8-11]. This study aims to determine the association between indications for IOL and mode of delivery in nulliparous women with unfavourable cervix.

Methods

This retrospective cohort study was approved by the Kowloon West Cluster Research Ethics Committee (reference: KW/EX-19-042(134-04)). Through the Clinical Data Analysis and Reporting System, we identified nulliparous women with a singleton pregnancy who underwent IOL at term for an unfavourable cervix (modified Bishops score of <7) and were prescribed with prostaglandin E2 (PGE2) vaginal tablet (3 mg) for pre-induction cervical priming between 1 January 2013 and 31 December 2017 in the obstetrics unit of Princess Margaret Hospital, Hong Kong. Individual patient records were reviewed, and demographic and clinical data of patients and their neonates were collected.

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Cases excluded were stillbirth before cervical priming, major fetal anomalies, allergy to PGE2, prelabour rupture of membranes (PROM) before cervical priming, and contraindications to vaginal delivery such as non-vertex presentation and placenta previa. Women who were prescribed with other doses or formulations of PGE2 under different IOL protocols (eg, 10 mg slow-release pessary or 1.5 mg vaginal tablet) were also excluded, as were non-Chinese patients and patients with PROM and stillbirth before IOL.

The primary outcome was the mode of delivery (vaginal vs caesarean). Secondary outcomes were the instrumental delivery rate, indications for caesarean section, and maternal and neonatal complication stratified by indications of IOL.

Reasons for caesarean section were categorised as fetal wellbeing related (fetal distress and non-reassuring cardiotocogram) and progress related (labour dystocia). The latter were further sub-categorised as (1) failed cervix dilatation despite serial PGE2 for cervical priming and oxytocin for IOL, (2) failure to enter active phase of labour despite 1 to <5 cm cervix dilatation, and (3) failure to progress despite active labour achieved, with ≥5 cm cervix dilatation.

Elective IOL was not performed. Some women had more than one indication for IOL. Indications for IOL were categorised as (1) post-date pregnancy beyond 40 weeks, (2) diabetes mellitus (DM) including pre-existing DM and gestational DM (fasting plasma glucose of >5.1 mmol/l or 2-hour plasma glucose of >8.5 mmol/l[12]) on either diet or insulin control, (3) hypertensive disorder including pre-existing hypertension (≥140/90 mmHg pre-pregnancy or before 20 weeks of gestation), gestational hypertension (≥140/90 mmHg after 20 weeks), pre-eclampsia (gestational hypertension with proteinuria, maternal organ damage, or sign of uteroplacental dysfunction), gestational proteinuria (≥300 mg/day of urinary protein in the absence of hypertension after 20 weeks of gestation), eclampsia (seizure activity or unexplained coma during pregnancy or postpartum in women with pre-eclampsia), (4) small-for-gestational-age fetus (estimated fetal weight ≤10 percentile on ultrasonography), (5) large-for-gestational-age fetus (estimated fetal weight ≥90 percentile on ultrasonography), (6) polyhydramnios (single deepest pocket >8 cm or amniotic fluid index >95 percentile), (7) oligohydramnios (single deepest pocket <2 cm or amniotic fluid index <5 percentile), (8) reduced fetal movement (<10 discrete fetal movements in 2 hours by maternal counting), and (9) others including suboptimal cardiotocogram, antepartum haemorrhage, obstetrics cholestasis, and bad obstetrics history.

Dating ultrasonography was performed in most women in the first trimester or as part of first-trimester Down syndrome screening. For women with antenatal first visit beyond first trimester, ultrasonography was performed as soon as possible to confirm the gestation.

Patients with indication for IOL were admitted by obstetricians. The cervix was assessed digitally for Bishop score. Women with unfavourable cervix (Bishop score <7) were given 3 mg vaginal PGE2 tablet daily in posterior fornix until a favourable cervix (Bishop score ≥7) was achieved. Fetal heart was monitored immediately before and after each application of PGE2. The application of PGE2 was delayed during painful regular uterine contraction (>2 contractions in 10 minutes) until uterine contraction subsided. Once the cervix was ripened, patients were transferred to the delivery suite for artificial rupture

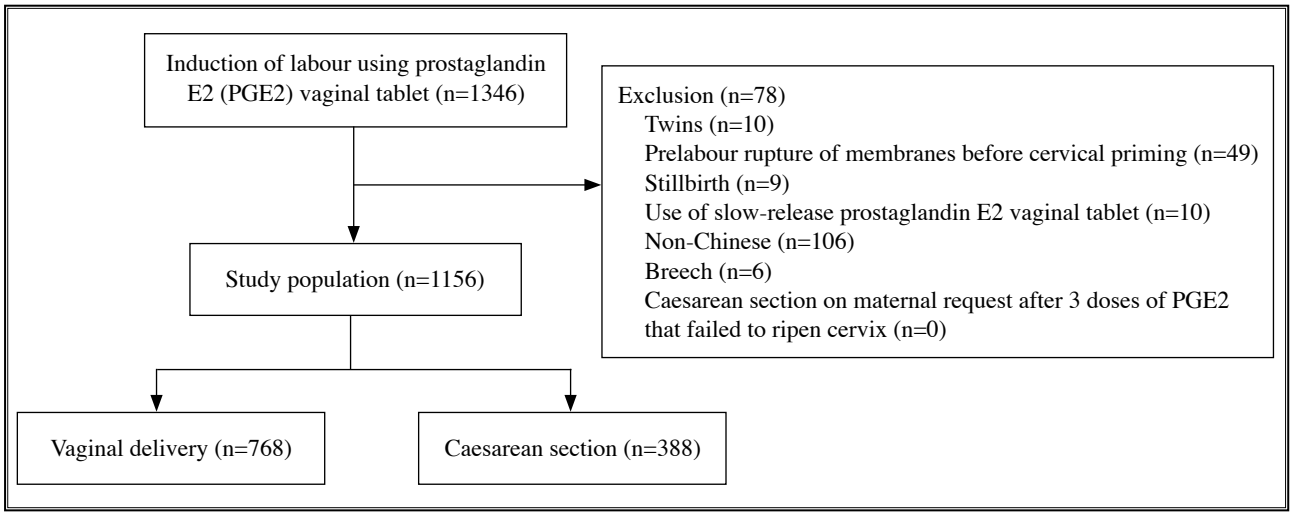

Figure. Recruitment flow diagram

of membranes and oxytocin infusion with continuous fetal heart monitoring. For patients with spontaneous PROM after application of PGE2 but without active labour, oxytocin infusion was initiated within 24 hours of PROM regardless of the Bishop score. Active labour is defined as cervical dilatation of ≥5 cm with regular uterine contraction[13]. If the cervix remained unfavourable after three consecutive applications of PGE2, the decision of further doses of PGE2 versus resting or elective caesarean section was made jointly with the patient. There was no upper limit on the number of PGE2 application.

The vaginal delivery group and the caesarean section group were compared using Pearson Chi-squared test or Fisher's exact test (for categorical variables) and independent *t*-test (for continuous variables). Univariate binary logistic regression analysis was used to identify the indications for IOL related to the mode of delivery (vaginal vs caesarean) and potential risk factors. Factors with a p value of <0.1 were included in the multivariate regression. Statistical analysis was performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant.

Results

Of 1346 nulliparous women who received PGE2 vaginal inserts, 92.1% were of Chinese ethnicity. Among them, 1156 met the inclusion criteria (Figure). The IOL success (vaginal delivery) rate was 66.4%, the instrumental delivery rate was 19.2%, and the caesarean delivery rate was 33.6%. Compared with women in the caesarean delivery group, those in the vaginal delivery group were younger and taller and more likely to have lower pre-pregnant BMI and less weight gain during pregnancy, deliver at earlier gestational age, and have a Bishop score of ≥4 prior to cervical priming (Table 1).

The caesarean delivery group had more indications for IOL (p for trend=0.002, Table 2). The most common indication for IOL was post-date pregnancy, followed by DM diseases and hypertensive disorders. Caesarean section was associated with post-date pregnancy (p=0.027), DM diseases (p=0.006), hypertensive disorders (p=0.017), large-for-gestational-age fetus (p=0.001), and polyhydramnios (p=0.036), whereas vaginal delivery was associated with small-for-gestational-age fetus (p<0.001) and reduced fetal movement (p=0.002).

Table 1. Characteristics of nulliparous women who received prostaglandin E2 vaginal tablet

Maternal characteristic	Mode of delivery		p Value
	Vaginal delivery (n=768)*	Caesarean section (n=388)*	
Maternal age, y	30.3±5.2	32.0±5.0	<0.001
≥35	158 (20.6)	124 (32.0)	<0.001
Body height, cm	159.8±5.6	157.8±5.6	<0.001
<150	19 (2.5)	28 (7.2)	
150-159.9	350 (45.9)	219 (56.4)	
160-169.9	355 (46.5)	130 (33.5)	
≥170	39 (5.1)	11 (2.8)	
Pre-pregnant body mass index (BMI)			<0.001
Underweight	141 (18.4)	39 (10.1)	
Normal	504 (65.6)	249 (64.2)	
Pre-obesity (BMI, 25.0-29.9)	89 (11.6)	71 (18.3)	
Obesity class I (BMI, 30.0-34.9)	26 (3.4)	22 (5.7)	
Obesity class II (BMI, 35.0-39.9)	3 (0.4)	7 (1.8)	
Obesity class III (BMI, >40)	0	0	
Weight gain during pregnancy, kg	14.2±5.6	15.2±5.7	0.008
Gestational age at delivery, wks	39.7±1.4	40.0±1.4	0.003
Bishop score ≥4	668 (87.0)	276 (71.1)	<0.001
Group B streptococcus positive	139 (18.1)	86 (22.2)	0.099
Epidural analgesia	76 (9.9)	52 (13.4)	0.073
Presence of fibroid	48 (6.3)	30 (7.7)	0.343

* Data are presented as mean±SD or No. (%) of cases

In multivariate logistic regression analysis, after controlling the confounding factors (maternal age, stature, weight gain during pregnancy, and Bishop score), indications for IOL independently associated with the mode of delivery were post-date pregnancy (adjusted odds ratio [OR_{adj}]=2.30, p<0.001), diabetes mellitus diseases

Table 2. Mode of delivery stratified by indications for induction of labour (IOL)

Indication for IOL	Mode of delivery		p Value
	Vaginal delivery (n=768)*	Caesarean section (n=388)*	
No. of indications			0.006
1	674 (87.8)	313 (80.7)	
2	84 (10.9)	67 (17.3)	
≥3	10 (1.3)	8 (2.0)	
Post-date pregnancy	258 (33.6)	156 (40.2)	0.027
Diabetes mellitus diseases	132 (17.2)	93 (24.0)	0.006
Hypertensive disorders	133 (17.3)	90 (23.2)	0.017
Small-for-gestational-age fetus	147 (19.1)	30 (7.7)	<0.001
Large-for-gestational-age fetus	51 (6.6)	48 (12.4)	0.001
Polyhydramnios	21 (2.7)	20 (5.2)	0.036
Oligohydramnios	32 (4.2)	9 (2.3)	0.109
Reduced fetal movement	53 (6.9)	10 (2.6)	0.002
Others	45 (5.9)	17 (4.4)	0.292

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

Table 3. Logistic regression analyses for predictors for caesarean section

Variable	Univariable		Multivariable	
	Odds ratio (95% confidence interval)	p Value	Adjusted odds ratio (95% confidence interval)	p Value
Maternal age ≥35 y	1.81 (1.38-2.39)	<0.001	1.54 (1.13-2.11)	0.007
Body height	0.94 (0.92-0.96)	<0.001	0.93 (0.91-0.95)	<0.001
Pre-pregnant body mass index (reference: normal)				
Underweight	0.56 (0.38-0.82)	0.003	0.74 (0.49-1.13)	0.166
Pre-obesity and obesity classes I-III	1.72 (1.26-2.33)	<0.001	1.66 (1.17-2.35)	0.005
Weight gain during pregnancy	1.03 (1.01-1.05)	0.008	1.04 (1.02-1.07)	0.001
Bishop score	0.65 (0.57-0.73)	<0.001	0.65 (0.57-0.75)	<0.001
Group B streptococcus positive	1.29 (0.95-1.74)	0.100	-	-
Epidural analgesia	1.41 (0.97-2.05)	0.074	1.21 (0.80-1.83)	0.375
Presence of fibroid	1.26 (0.78-2.02)	0.344	-	-
Indication for induction of labour				
Post-date pregnancy	1.33 (1.03-1.71)	0.027	2.30 (1.49-3.54)	<0.001
Diabetes mellitus diseases	1.52 (1.13-2.05)	0.006	1.67 (1.10-2.52)	0.015
Hypertensive disorders	1.44 (1.07-1.95)	0.017	1.72 (1.11-2.66)	0.015
Small-for-gestational-age fetus	0.35 (0.23-0.54)	<0.001	0.66 (0.39-1.14)	0.137
Large-for-gestational-age fetus	1.98 (1.31-3.00)	0.001	2.32 (1.39-3.87)	0.001
Polyhydramnios	1.93 (1.03-3.61)	0.039	1.45 (0.70-3.01)	0.318
Oligohydramnios	0.55 (0.26-1.16)	0.114	-	-
Reduced fetal movement	0.36 (0.18-0.71)	0.003	0.62 (0.29-1.31)	0.210

(OR_{adj}=1.67, p=0.015), hypertensive disorders (OR_{adj}=1.72, p=0.015), and large-for-gestational-age fetus (OR_{adj}=2.32, p=0.001) [Table 3].

Labour dystocia was the main reason for caesarean section. Fetal wellbeing was the main reason for caesarean section for small-for-gestational-age fetus (53.3%). There were six cases of second-stage caesarean section; three of which were due to DM diseases (Table 4).

There was no case of maternal death or hysterectomy. Four mothers who were induced for DM disease (n=3) and hypertensive disorder (n=1) required admission to the intensive care unit. The duration of IOL was >48 hours in at least half of cases of polyhydramnios and large-for-gestational-age fetus, and the postpartum haemorrhage was ≥1 L in over 5% for these two indications for IOL (Table 5). One baby induced for post-date pregnancy died from antepartum haemorrhage owing to undiagnosed vasa previa after application of PGE2. Meconium-stained amniotic fluid was observed in 24.6% of cases of post-date pregnancy.

Table 4. Operative delivery stratified by indications for induction of labour*

Indication for induction of labour	Mode of delivery			Reason for caesarean section					
	Vaginal delivery	Operative delivery		Progress related			Progress related total	Fetal wellbeing related	Others
		Instrumental delivery	Caesarean section	Failed cervical dilation	1 to <5cm dilatation	≥5cm dilatation			
Post-date pregnancy (n=414)	258 (62.3)	79 (19.1)	156 (37.7)	75 (48.1)	40 (25.6)	11 (7.1)	126 (80.8)	27 (17.3)	3 (1.9)
Diabetes mellitus diseases (n=225)	132 (58.7)	44 (19.6)	93 (41.3)	49 (52.7)	17 (18.3)	9 (9.7)	75 (80.6)	16 (17.2)	2 (2.2)
Hypertensive disorders (n=223)	133 (59.6)	39 (17.5)	90 (40.4)	50 (55.6)	9 (10)	6 (6.7)	65 (72.2)	16 (17.8)	9 (10)
Small-for-gestational-age fetus (n=177)	147 (83.1)	24 (13.6)	30 (16.9)	12 (40)	1 (3.3)	1 (3.3)	14 (46.7)	16 (53.3)	0
Large-for-gestational-age fetus (n=99)	51 (51.5)	21 (21.2)	48 (48.5)	26 (54.2)	6 (12.5)	7 (14.6)	39 (81.2)	7 (14.6)	2 (4.2)
Polyhydramnios (n=41)	21 (51.2)	6 (14.6)	20 (48.8)	12 (60)	2 (10)	1 (5)	15 (75)	3 (15)	2 (10)
Oligohydramnios (n=41)	32 (78.0)	8 (19.5)	9 (22.0)	7 (77.8)	0	0	7 (77.8)	2 (22.2)	0
Reduced fetal movement (n=63)	53 (84.1)	15 (23.8)	10 (15.9)	6 (60)	1 (10)	0	7 (70)	2 (20)	1 (10)
Others (n=62)	45 (72.6)	13 (21.0)	17 (27.4)	8 (47.1)	4 (23.5)	1 (5.9)	13 (76.5)	4 (23.5)	0

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

Table 5. Maternal and neonatal outcomes stratified by indications for induction of labour (IOL)*

Indication for IOL	Postpartum haemorrhage ≥1 L	Duration of IOL >48 hours	5-min Apgar <7	Meconium-stained amniotic fluid
Post-date pregnancy (n=414)	5 (1.2)	103 (24.9)	1 (0.2)	102 (24.6)
Diabetes mellitus diseases (n=225)	8 (3.6)	95 (42.2)	1 (0.4)	20 (8.9)
Hypertensive disorders (n=223)	6 (2.7)	86 (38.6)	1 (0.4)	22 (9.9)
Small-for-gestational-age fetus (n=177)	1 (0.6)	42 (23.7)	2 (1.1)	8 (4.5)
Large-for-gestational-age fetus (n=99)	5 (5.1)	49 (49.5)	0	7 (7.1)
Polyhydramnios (n=41)	3 (7.3)	23 (56.1)	0	2 (4.9)
Oligohydramnios (n=41)	0	18 (43.9)	0	4 (9.8)
Reduced fetal movement (n=63)	0	15 (23.8)	0	8 (12.7)
Others (n=62)	4 (6.5)	17 (27.4)	0	5 (8.1)

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

Discussion

Post-date pregnancy, hypertensive disorder, DM diseases, and large-for-gestational-age fetus were independent predictors of caesarean section, after adjusting for maternal age, stature, weight gain in pregnancy, and Bishop score. In the present study, patients may have multiple indications for IOL, and the independent effect of each indication on the mode of delivery was analysed. In contrast, previous studies arbitrarily assigned a single dominant indication for each case, and heterogenous indications for IOL were grouped into four categories: maternal, fetal, PROM, and hypertensive disorder[8,9]. Macrosomia and intrauterine growth restriction are contrasting indications but become indistinguishable under the fetal indication. Retrospectively deciding which indication is predominant in a particular case may introduce selection bias. Decision for IOL in some cases may be due to multiple indications, all similarly weighed, without one being predominant. In the present study, large-for-gestational-age fetus was associated with caesarean section, but small-for-gestational-age fetus was not.

Prolonged pregnancy ≥40 weeks is an independent risk factor for caesarean delivery (OR=2.028, p=0.016)[9]. Fetal compromise is associated with post-date pregnancy, and the caesarean section rate increases in those induced for post-date pregnancy[9]. In the present study, labour dystocia was the main reason (80.8%) for caesarean section in post-date pregnancy, whereas only 17.3% were for fetal distress. Although the proportion of cases of meconium-stained amniotic fluid in post-date pregnancy was relatively high, this was compatible with more advanced maturity in post-date babies, not necessarily reflecting impaired fetal wellbeing.

In the present study, hypertensive disorders were associated with a higher rate for caesarean section in nulliparous women; this may be due to a relatively larger sample size of 223. This association was demonstrated in multiparous women only but not in nulliparous women[8]. Although pre-eclampsia is the result of placental trigger, the present study failed to demonstrate any association between hypertensive disorders and caesarean for fetal wellbeing.

The caesarean section rate increases in women with gestational DM[14,15]. In the present study, a relatively higher proportion of women with DM had labour dystocia despite achieving active labour. This finding is consistent with that in a study that significantly more nulliparous women with gestational DM had caesarean section for cephalopelvic disproportion[14].

In the present study, several maternal factors were identified to predict the mode of delivery, consistent with those reported in previous studies[5-7,16-22]. The IOL success (vaginal delivery) rate was 66.4%, similar to the 63.7% reported in an epidemiological study[23].

In the present study, nulliparous women induced for small-for-gestational-age fetus had a high vaginal delivery rate of 83.1% and a low instrumental delivery rate of 13.6%. Similarly, women induced for reduced fetal movement and oligohydramnios had a high vaginal delivery rate of 84.1% and 78%, respectively, whereas caesarean section was performed in nearly 50% of the women induced for large-for-gestational-age fetus and polyhydramnios. These findings may guide clinicians on counselling patients for option of elective caesarean section when the chance of successful vaginal delivery is low.

Limitations of our study were its retrospective nature and the inter-rater variability in assessment of the Bishop score as well as the unavailability of more comprehensive outcome measures for babies such as arterial cord blood gas values, rates of admission to neonatal intensive care unit, and long-term baby outcome. Nonetheless, our study is the largest study that addresses the associations between indications for IOL and the mode of delivery in nulliparous Chinese women with unfavourable cervix. We used a unified IOL protocol. The original indications for IOL were retained to avoid the bias in retrospective re-interpretation and grouping. In addition, confounding factors were controlled. Studies with better case selection and stratification of gestation for IOL for each indication are warranted, especially for indications with lower success rate such as large-for-gestational-age fetus[24]. Indication-specific induction strategy may be the way forward.

Conclusion

Different indications for IOL affect the mode of delivery differently. Post-date pregnancy, DM diseases, hypertensive disorders, and large-for-gestational-age fetuses are independent risk factors for caesarean delivery.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Cholangiocarcinoma in pregnancy: a case report

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A 35-year-old pregnant woman presented at 19 weeks of gestation with epigastric pain and mildly elevated alanine transaminase level. She subsequently developed acute cholangitis, with deteriorated liver function. Imaging revealed features of cholangiocarcinoma. Termination of pregnancy was performed at 22 weeks of gestation to facilitate maternal treatment. She underwent hepatectomy, followed by multiple courses of chemotherapy and immunotherapy. However, she died from hepatorenal failure with hepatic encephalopathy 1 year later. Cholangiocarcinoma in pregnancy is rare. Although it is a differential diagnosis of deranged liver function in pregnancy, a precise diagnosis can be challenging as the presenting signs and symptoms are not obvious.

Case presentation

In June 2019, a 35-year-old, gravida 2, para 1 woman with a history of cesarean section for breech presentation 8 years earlier presented at 19 weeks of gestation with epigastric pain, and mildly elevated alanine transaminase (ALT) level. The antenatal blood test results were all normal, including negative hepatitis B surface antigen. The first trimester Down syndrome screening showed low risk for Down syndrome. Blood tests showed mildly deranged liver function, with elevated ALT level up to 78 IU/L while the alkaline phosphatase level (90 IU/L) and the total bilirubin level (10 μmol/L) were normal. She did not have any drug or herbal medication exposure. Her pain gradually subsided and her ALT level decreased to 52 IU/L 2 days later. She was discharged with liver function monitoring in outpatient clinic.

One week later, her ALT level elevated to 124 IU/L and her alkaline phosphatase level elevated to 335 IU/L, but the total bilirubin level was normal at 14 μmol/L. At 21 weeks of gestation, she was asymptomatic with no fever or epigastric pain. Morphology scanning showed normal fetal morphology. Blood test results for hepatitis C antibodies and hepatitis B surface antigen were negative.

She was admitted to our hospital for further examination. While awaiting ultrasonography of the liver and assessment by the medical team, she developed right upper quadrant pain, with on and off fever up to 38.8°C. At 2 days after admission, blood tests showed elevated bilirubin level up to 53 μmol/L, ALT level up to 162 IU/L, aspartate transaminase level up to 92 IU/L, and gamma-glutamyl transferase level up to 186 IU/L. The clinical picture was compatible with acute cholangitis complicating pregnancy. Intravenous antibiotics was started. Ultrasonography of the liver revealed a dilated intrahepatic duct with a 3-cm ductal stone and sludge at confluence as well as a prominent common duct. Magnetic resonance cholangiopancreatogram showed evidence of a high-grade hilar stricture causing severe bilobed intrahepatic ductal dilatation, with features of cholangiocarcinoma (CCA). A 2.5-cm ductal stone with small fluid level was noted within the grossly dilated segment 8 and 4 intrahepatic duct (Figure). These were compatible with the clinical findings of superimposed acute cholangitis. Contrast computed tomography showed a tumour at the hilar region suggestive of CCA (Figure). A multidisciplinary team involving hepatobiliary surgeons, oncologists, radiologists, obstetricians, and midwives was arranged for the patient and her family. The need for percutaneous drainage to treat the biliary obstruction and the plan for definitive surgical treatment for CCA were explained. The option of termination of pregnancy to facilitate investigation and treatment was discussed, as was an alternative option of conservative management after percutaneous drainage and then delivery of the fetus in late second trimester and then surgical treatment for the CCA. The possible delay to the maternal treatment, the potential for high estrogen levels in pregnancy to aggravate the CCA, and the risk of prematurity complications of the baby resulting from early delivery were also discussed. The family opted for termination of pregnancy at 22 weeks of gestation.

Percutaneous transhepatic biliary drainages were performed. Pus aspirated from the right intrahepatic

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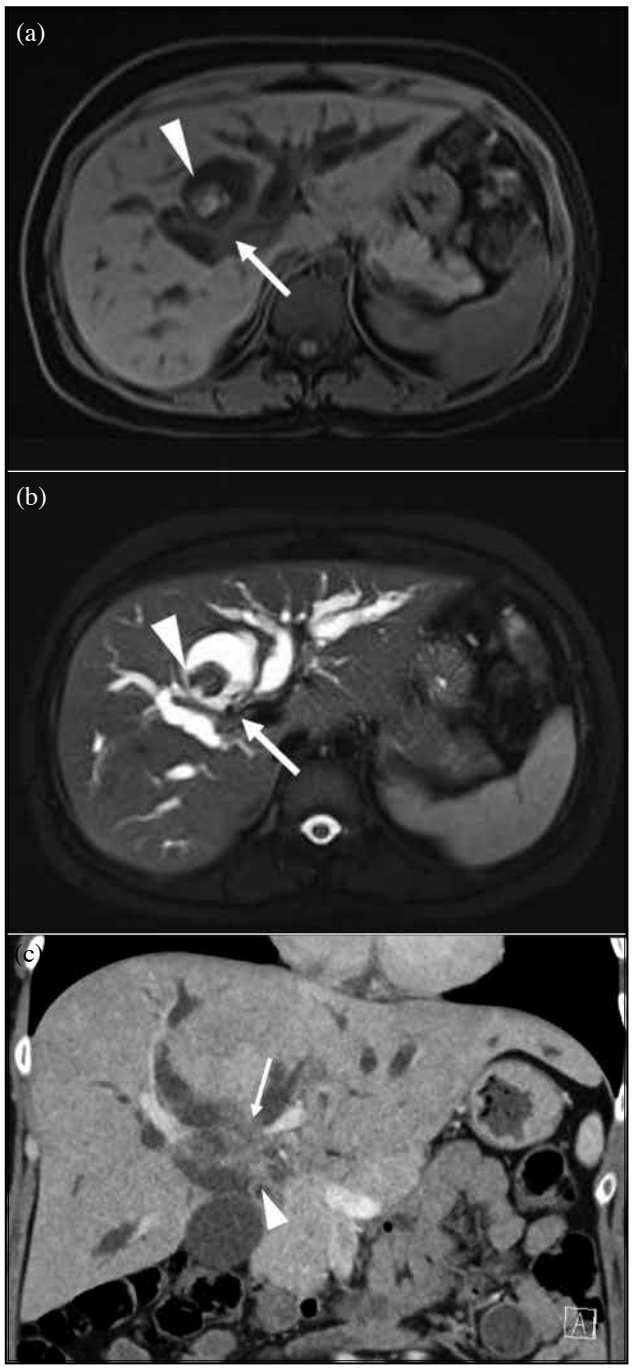

Figure. Transverse view of (a) T1-weighted and (b) T2-weighted magnetic resonance cholangiopancreatogram showing an abrupt change in calibre with tight stricture at the hilar region (arrows) causing severe bilobed intrahepatic ductal dilatation and a 2.5-cm stone (arrowheads) within a grossly dilated S8/4 intrahepatic duct. (c) Coronal view of contrast computed tomography showing an enhancing soft tissue tumour with irregular margin (arrowhead) leading to stricture at the hilar region (arrow).

duct yielded *Clonorchis sinensis* ovum and *Klebsiella pneumoniae*. Biliary sepsis was resolved. Positron emission tomography–computed tomography confirmed the metastatic CCA. A hepatobiliary surgeon was consulted, and surgery remained the only effective method to improve survival. The patient underwent resection of the liver lesion (right trisectionectomy, caudate lobectomy, and hepaticojejunostomy). A type-4 Klaskin tumour with multiple intrahepatic metastases in the right liver was confirmed intra-operatively. Histopathology showed a metastatic hilar mixed neuroendocrine carcinoma-CCA, with direct invasion to the liver and extensive lymphovascular invasion and perineural invasion. She underwent multiple courses of chemotherapy and immunotherapy, but the disease continued to progress. One year after the diagnosis, she died from hepatorenal failure with hepatic encephalopathy.

Discussion

CCA is a slow-growing heterogeneous group of malignancy arising from the biliary epithelium. It can be classified based on its anatomical location (extrahepatic, intrahepatic, and perihilar). It most commonly affects patients aged 50 to 70 years[1]. Most cases are asymptomatic at early stages, and presentation is usually delayed, with locally advanced or metastatic disease at the time of diagnosis[2]. CCA is the second most common hepatic malignancy, accounting for 3% of all gastrointestinal cancers and 10% to 15% of primary liver cancers[1-3]. Its incidence has been increasing in recent decades worldwide, with a much higher incidence in North Thailand and South Korea compared with the West[3]. In Hong Kong, the age-standardised incidence of CCA is 2.3 cases per 100 000 population[2,3]. The aetiology of CCA in Asian countries is mostly related to infection, especially with liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*. *Clonorchis sinensis* infects fish-eating mammals and is actively transmitted in Korea, China, and Vietnam[4]. A meta-analysis reported that the relative risks of CCA with infection of liver fluke was 4.8 (95% confidence interval, 2.8-8.4)[5].

Liver diseases complicate the courses of about 3% of all pregnancies and may have detrimental effects on the mother and fetus, but CCA during pregnancy is rare. In PubMed database, 14 such cases have been identified during 1975 to 2019[6-19]. Patients were aged 25 to 40 years, and no risk factor was identified in most patients. Common clinical manifestations include nausea, vomiting, abdominal pain, pruritus, jaundice, and hepatomegaly. For cases with laboratory results, liver enzymes (aspartate transaminase / ALT) and total bilirubin levels were either within normal range or elevated up to 2 to 3 times the upper limit for liver enzymes and up to 5 times the upper limit for bilirubin. Gamma-glutamyltransferase level was measured

in three cases only and all were markedly elevated. The symptoms of CCA mimic some pregnancy-specific conditions with abnormal liver function such as obstetric cholestasis, HELLP syndrome (haemolysis, elevated liver enzymes, and a low platelet count), and acute fatty liver of pregnancy (AFLP)[9,13,15]. In addition, differential diagnoses of deranged liver function not related to pregnancy include drug- or toxin-induced hepatitis and viral hepatitis[9]. Patients diagnosed with CCA usually portend poor prognosis given the delayed diagnosis and aggressive nature of disease[1,2]. Of the 14 cases, 8 died shortly (2 weeks to 6 months) after diagnosis. Pregnancy may adversely affect the prognosis of hepatocellular carcinoma, as gestational suppression of the immune system may aggravate tumour progression and aggression[9,14]. Pregnancy increases oestrogen levels and may aggravate a pre-existing malignant liver disease[12,14]. However, data for these rare conditions are lacking, and the effect of pregnancy on the progression and prognosis of CCA remains unclear.

Deranged liver function in pregnancy is related to pregnancy-specific conditions and primarily occurs in the third trimester, with incidence varying from 59.2% to 84%[20-22]. Common differential diagnoses include pre-eclampsia with hepatic impairment, HELLP syndrome, obstetric cholestasis, and AFLP[20-23]. The pattern of abnormal liver function differs in these differential diagnoses. In pre-eclampsia, liver function tests show a 2-to-5-fold increase in ALT level, with normal serum bile acids and total bilirubin level, whereas in HELLP syndrome, ALT level is more significantly elevated, with one case reporting a 30-fold increase[20]. HELLP syndrome is also associated with low haemoglobin level, low platelet counts, and raised lactate dehydrogenase level. In obstetric cholestasis, patients usually present with severe pruritus without rash in the third trimester, with moderately elevated (1.5- to 8-fold) transaminase level and increased total serum bile acid level[23]. In AFLP, the elevated transaminase level is wide (3- to 15-fold), with increased total bilirubin level[20]. Compared with HELLP syndrome, AFLP is associated with more severe hypoglycaemia (70%), hyperuricaemia (90%), coagulopathy (90%), and leukocytosis[23]. On the contrary, in CCA, liver function tests often show obstructive patterns, with normal aminotransferase levels, except in acute obstruction or cholangitis in which aminotransferase levels are markedly increased[21].

Surgical resection remains the only potentially curative option for CCA[24]. In most cases, babies are delivered prematurely to facilitate investigations and treatment when the diagnosis is suspected or confirmed. In only one case, the patient underwent extended left hepatectomy for intrahepatic CCA at 30 weeks of gestation while continuing the pregnancy and eventually had a normal vaginal delivery at 38 weeks of gestation[8]. In the management of malignancy, early treatment and long-term outcome should be prioritised[8]. An optimal management strategy is to balance between the risk of continuing pregnancy and the potential harm to fetus against the benefits of treatment to the mother. Decision should be made based on the gestational age and the extent of spread or staging of the disease and the recommended course of treatment in non-pregnant women[25,26]. Our patient was at 22 weeks of gestation at the time of diagnosis of CCA. The fetus was not viable and may have inevitable complications of prematurity had the patient decided to keep the pregnancy. Balancing the risk of disease progression and the risk of prematurity of the fetus, termination of pregnancy was the optimal decision.

Conclusion

CCA is a slow-growing disease and usually presents late with metastasis, with poor prognosis. CCA in pregnancy is rare and its diagnosis challenging. Treatment plan should take into account both maternal and fetal well-being and strike a balance between both.

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Declaration

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Help-seeking behaviour among women with urinary incontinence: a cross-sectional study in two gynaecology clinics

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Introduction: This study aimed to assess the help-seeking behaviour of women with urinary incontinence (UI) and their knowledge on UI and to identify the barriers to seeking medical care among women in two gynaecology clinics.
Methods: Women who attended the gynaecology clinics of United Christian Hospital and Tseung Kwan O Hospital between May 2019 and May 2020 were invited to complete a questionnaire. The Urogenital Distress Inventory Short Form (UDI-6) was used to determine the prevalence and type of UI. The Incontinence Impact Questionnaire Short Form (IIQ-7) was used to assess the impact of UI on the quality of life in terms of physical, psychological, and social domains.
Results: 639 women (mean age, 43.6±11.5 years) were included for analysis. Of the 639 participants, 424 (66.4%) had symptoms of UI. Of them, 214 (50.4%) had mixed UI, 160 (37.7%) had stress UI, and 50 (11.8%) had urge UI. 45.8% of women with symptoms of UI had impairment in quality of life. 55.7% of women with symptoms of UI had consulted a doctor. Older women (p=0.005), women with more severe UI (p<0.001), and those with more severe impairment in quality of life (p=0.002) were more likely to consult a doctor. Inadequate knowledge on the treatment options (adjusted OR=0.35, p=0.002) and perception of not being bothered by UI (adjusted OR=0.51, p=0.038) were independent predictors for barriers to help-seeking behaviour, whereas the fear of having a serious condition was an independent predictor for seeking medical help (adjusted OR=2.18, p=0.014).
Conclusion: There is a need to improve public education on treatment options and preventive strategies for UI to encourage symptomatic women to seek medical help. Clinicians should be more proactive in asking for symptoms of UI during consultation.

Keywords: Help-seeking behaviour; Hong Kong; Surveys and questionnaires; Urinary incontinence

Introduction

Urinary incontinence (UI) is a common health problem among women, with a prevalence of 25% to 45%[1]. Stress UI is defined as involuntary loss of urine associated with effort/physical exertion or sneezing/coughing, whereas urge UI is associated with urgency and mixed UI is associated with urgency and effort/physical exertion or sneezing/coughing[2]. Similar to chronic medical diseases, UI impacts the quality of life in terms of limitation in physical activity, psychological distress, and social isolation[3]. Nonetheless, only a minority of symptomatic women seek medical advice, with a consultation rate of <40%[4-10]. Common barriers to help-seeking behaviour include inadequate knowledge on the nature and treatment of UI, not considering symptoms to be severe, regarding UI as a normal ageing process or normal consequence of childbirth, and embarrassment in talking about UI with doctors[1,4-6,11]. 40% to 75% of women agree to the misperception that UI is a normal ageing process[1]. Among Hong Kong Chinese women, knowledge on UI is poor, with 78.3% not knowing stress UI as a disease entity, 60.6% accepting UI as a normal ageing process, and only 25% of symptomatic women seeking medical advice[5]. Perceiving UI as a minor problem and feeling ashamed to ask for help are the most common barriers to seeking help[5].

Improvement in knowledge alone does not necessarily result in a positive change in help-seeking behaviour1. We aim to assess the help-seeking behaviour of women with UI and their knowledge on UI and to identify the barriers to seeking medical care in order to formulate better healthcare strategies and promote a more positive attitude for women with UI.

Methods

This cross-sectional study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-18-0265/ER-4). Women who attended the gynaecology clinics of United Christian Hospital and Tseung Kwan O Hospital between May 2019 and May 2020 were invited to complete a questionnaire.

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Those who already attended the urogynaecology subspecialty clinic were excluded, as were those who were aged <18 years, pregnant, non-Chinese ethnicity, or unable to understand Chinese.

The self-administered questionnaire consisted of five sections: (1) demographics, (2) knowledge and symptoms of UI, (3) impairment of quality of life (for symptomatic women), (4) whether they had consulted a doctor for any symptoms of UI, and (5) hypothesised barriers to seeking medical help. Nurses would provide assistance in completing the questionnaire if participants encountered problems. Knowledge of UI was assessed using five yes/no statements. The six-item Urogenital Distress Inventory Short Form (UDI-6) was used to determine the prevalence and type of UI, with scores ranging from 0 (asymptomatic) to 3 (severe) for symptoms of UI. The seven-item Incontinence Impact Questionnaire Short Form (IIQ-7) was used to assess the impact of UI on the quality of life in terms of physical, psychological, and social domains, using a four-point rating scale. The Chinese version of both questionnaires showed good internal consistency and test-retest reliability[12].

Statistical analysis was performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US).

Table 1. Associations between patient characteristics and consultation rate

Characteristic	No. of women	No (%) of women with urinary incontinence	Consultation rate in women with urinary incontinence, %	p Value
Total	639	424 (66.4)	55.7	
Age group, y				0.005
18-40	252	131 (52.0)	38.2	
41-50	206	141 (68.4)	36.2	
51-60	143	120 (83.9)	50.8	
61-80	38	32 (84.2)	65.6	
Body mass index, kg/m^2				0.027
<18.5	42	16 (38.1)	56.3	
18.5-22.9	281	172 (61.2)	40.1	
23-24.9	192	140 (72.9)	40.0	
≥25	124	96 (77.4)	51.0	
Parity				0.372
0	224	118 (52.7)	39.0	
1	198	137 (69.2)	40.9	
2	151	119 (78.8)	47.1	
3+	66	50 (75.8)	50.0	
Mode of delivery				0.738
Vaginal delivery	305	229 (75.1)	41.9	
Vacuum extraction	36	31 (86.1)	54.8	
Forceps delivery	8	6 (75.0)	50.0	
Caesarean section	68	39 (57.4)	51.3	
Education level				0.059
No formal	11	9 (81.8)	55.6	
Primary	54	42 (77.8)	61.9	
Secondary	390	275 (70.5)	40.7	
Tertiary	184	98 (53.3)	40.8	
Occupation				0.312
Housewives	243	177 (72.8)	48.0	
Manual workers	80	54 (67.5)	38.9	
Health care workers	51	26 (51.0)	42.3	
Professionals	31	17 (54.8)	52.9	
Others	234	150 (64.1)	38.0	

Associations between consultation rate and patient demographics were determined using the Chi-squared test or the z-test with a Bonferroni correction. Mann-Whitney *U* test was used to evaluate the association between consultation rate and severity of UI (UDI-6 score) and impact on the quality of life (IIQ-7 score). Logistic regression was used to assess the correlations between consultation rate and various barriers to seeking help. Variables with significant correlation were further analysed with binomial logistic regression to identify independent factor of help-seeking behaviour. The association between demographics and the level of knowledge was evaluated using the Kruskal-Wallis test. Pairwise comparison using the Dunn procedure with a Bonferroni correction for multiple comparisons was performed as post hoc analysis. A p value of <0.05 was considered statistically significant.

Results

Of approximately 8320 women attended the gynaecology clinics during the study period, 656 (7.9%) agreed to participate and completed the questionnaire. After excluding 17 questionnaires with missing data, 639 were analysed (Table 1). The mean patient age was 43.6±11.5 years and the mean body mass index was 23.9±5.2 kg/m^2. The most common reasons for attending the gynaecology clinics were menstrual disorder (28.5%) and uterine fibroids (16.1%). Of the 639 participants, 424 (66.4%) had symptoms of UI. Of them, 214 (50.5%) had mixed UI, 160 (37.7%) had stress UI, and 50 (11.8%) had urge UI. 45.8% of women with symptoms of UI had impairment in quality of life (Table 2).

Participants' knowledge on UI was good; majority of participants responded correctly to the statements, although 51.8% of them still perceived UI as a normal ageing process (Table 3). Women aged 18 to 40 years (p=0.001) and those with tertiary education (p<0.001) had higher level of knowledge of UI than the other groups. Healthcare workers and professionals had the highest level of knowledge of UI, but the difference to other occupations was not significant (p=0.092).

55.7% of women with symptoms of UI had consulted a doctor, most commonly a general practitioner (46.4%), followed by a gynaecologist (36.4%) and a urologist (14.2%). The consultation rate increased with age, especially for the age-group 61-80 years (p=0.005). Body mass index correlated with the consultation rate (p=0.027), but all pairwise comparisons were not significant after post hoc analysis. Women with more severe UI (p<0.001) and those with more severe impairment in quality of life (p=0.002) were more likely to consult a doctor. Type of UI (p=0.383), level of knowledge of UI (p=0.402), and awareness of the subspecialty of urogynaecology (p=0.325) did not correlate with the consultation rate.

Barriers to help-seeking behaviour that were predictive of a lower consultation rate were inadequate knowledge on the treatment options of UI (odds ratio [OR]=1.90, p=0.019), the perception of not being bothered by UI (OR=1.59, p=0.018), and the fear of being diagnosed with a serious condition (OR=2.73, p<0.001) [Table 4].

In binomial logistic regression analysis, inadequate knowledge on the treatment options (adjusted OR=0.35, p=0.002) and perception of not being bothered by UI (adjusted OR=0.51, p=0.038) were independent predictors for barriers to help-seeking behaviour, whereas the fear of having a serious condition was an independent predictor for seeking medical help (adjusted OR=2.18, p=0.014) [Table 5].

Discussion

The consultation rate among women with UI has been reported to be 10% to 31%[5-8,13-16]. In the present study, the consultation rate of 55.7% is likely a result of selection bias, as the recruitment was in a hospital setting, and these women may be more willing to consult a doctor for their symptoms. Only 25% of participants reported embarrassment as a barrier to seeking help, in contrast to 67% of women with UI opted not to mention their symptoms to their doctors a study in Turkey[16]. Our sample is not representative of the general population. Many participants attended the clinic for reasons other than UI. 52% of younger participants aged 18 to 40 years reported symptoms of UI. The relatively high incidence of UI is a result of selection bias and can be confounded by other gynaecological conditions. UI often coexists with other gynaecological conditions (such as uterine fibroids). Although most women had mild UI, nearly half had impairment in quality of life. This highlights the burden of UI and the importance of seeking medical help.

In the present study, older age, greater symptom severity, and quality of life impairment were predictors of help-seeking behaviour, consistent with results in previous studies[7,10,11,13,16-18]. The higher consultation rate among obese women could be explained by their higher prevalence of UI[19], but the consultation rate among underweight women was similarly high. None of these factors correlated with the consultation rate after logistic regression analysis. The

Table 2. Severity of urinary incontinence and impairment on quality of life

	Mean±SD	No*	Mild*	Moderate*	Severe*
Urogenital Distress Inventory Short Form total score	14.5±12.5				
Irritation	17.7±16.5				
Frequent urination		233 (36.5)	234 (36.6)	150 (23.5)	22 (3.4)
Urge incontinence		412 (64.5)	161 (25.2)	56 (8.8)	10 (1.6)
Stress	15.6±16.9				
Stress incontinence		294 (46)	240 (37.6)	78 (12.2)	27 (4.2)
Small amounts of leakage		383 (59.9)	201 (31.5)	45 (7.0)	10 (1.6)
Obstruction / discomfort	10.3±13.8				
Difficulty emptying bladder		486 (76.1)	114 (17.8)	32 (5.0)	7 (1.1)
Pain or discomfort in lower abdominal or genital area		384 (60.1)	194 (30.4)	48 (7.5)	13 (2.0)
Incontinence Impact Questionnaire Short Form total score	7.8±16.0				
Physical activity	7.7±17.0				
Ability to do household chores		553 (86.5)	62 (9.7)	22 (3.4)	2 (0.3)
Physical recreation		508 (79.5)	88 (13.8)	33 (5.2)	10 (1.6)
Travel	6.7±16.4				
Entertainment activities		551 (86.2)	60 (9.4)	24 (3.8)	4 (0.6)
Ability to travel by car or bus >30 minutes from home		537 (84.0)	69 (10.8)	30 (4.7)	3 (0.5)
Social / relationships					
Participation in social activities	7.4±18.2	532 (83.3)	79 (12.4)	22 (3.4)	6 (0.9)
Emotional health	9.2±18.9				
Emotional health		497 (77.8)	104 (16.3)	28 (4.4)	10 (1.6)
Feeling frustrated		509 (79.7)	103 (16.1)	20 (3.1)	7 (1.1)

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

Table 3. Knowledge on urinary incontinence

Statement	Yes*	No*
Urinary incontinence is a disease (yes)	436 (68.2)	203 (31.8)
Urinary incontinence is a normal ageing process (no)	331 (51.8)	307 (48)
Old age is a cause of urinary incontinence (yes)	482 (75.4)	157 (24.6)
Childbirth is a cause of urinary incontinence (yes)	378 (59.2)	261 (40.8)
Drinking excessive water is a cause of urinary incontinence (no)	81 (12.7)	558 (87.3)

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

results may be biased by the small proportion of women with severe UI or severe quality of life impairment.

In the present study, lack of awareness of treatment options for UI was a barrier to seeking help, consistent with a study that reported 30% to 63% of women unaware of the preventive strategies and treatment options for UI[1], and studies that reported learning about available treatment being a predictor for seeking help[11,20,21]. In the present study, 18.6% of participants thought that there was no treatment for UI; 29.7% did not know which specialty to consult; and 51.3% of participants and 27.4% of healthcare workers were not aware of the urogynaecology subspecialty. Although these observations did not correlate with the consultation rate, they reflect a need to improve public education on treatment options and preventive strategies for UI to encourage symptomatic women to seek medical help.

Women with different symptom severity face different barriers to help-seeking behaviour[7]. Women with

Table 4. Barriers to help-seeking behaviour

Barrier to help-seeking behaviour	% of participants with symptoms of urinary incontinence agreeing to the statement	Correlation with consultation rate, odds ratio (95% CI)	p Value
I do not understand the treatment options	36.6	1.90 (1.11-3.25)	0.019
The symptoms do not affect me	33.2	1.59 (1.08-2.34)	0.018
I do not want to take medication or have surgery	31.8	0.98 (0.60-1.59)	0.931
Urinary incontinence is a normal part of ageing	31.3	0.98 (0.68-1.39)	0.891
I do not know which doctor to consult	29.7	0.98 (0.61-1.58)	0.927
The doctors do not ask for symptoms of urinary incontinence	26.1	0.88 (0.53-1.45)	0.607
I was worried about being diagnosed with a serious condition	24.7	2.73 (1.7-4.3)	<0.001
I have more important diseases to deal with	23.9	0.65 (0.41-1.03)	0.066
I feel embarrassed to talk about urinary incontinence	20.8	1.30 (0.78-2.16)	0.311
There is no treatment for urinary incontinence	18.6	0.99 (0.59-1.65)	0.966
The doctors do not care about my symptoms	11.4	0.81 (0.43-1.53)	0.519

Table 5. Multivariate model for variables associated with consultation rate

Variable	Adjusted odds ratio (95% CI)	p Value
Age-group	0.82 (0.35-1.90)	0.639
Body mass index	1.08 (0.56-2.07)	0.829
Urogenital Distress Inventory Short Form score	0.78 (0.58-1.05)	0.105
Incontinence Impact Questionnaire Short Form score	1.03 (0.86-1.23)	0.770
Inadequate knowledge on treatment options	0.35 (0.18-0.68)	0.002
Symptoms not affecting the daily living	0.51 (0.27-0.96)	0.038
The fear of having a serious underlying condition	2.18 (1.17-4.04)	0.014

mild UI may not consider it a problem, and women with more severe UI may be hesitant to consult a doctor because of reluctance to take long-term medication or undergo surgery[7]. In the present study, the perception of UI as a relatively minor problem was a barrier to consultation, as most women had mild UI. 26.1% of participants did not seek help because they were not asked about the symptoms of UI, and 11.4% of participants thought that their doctors did not care about their symptoms of UI. Therefore, healthcare workers should take a more proactive role and ask for symptoms of UI and provide access to treatment for such women.

Participants' level of knowledge on UI was higher in the present study than in a local study in 2006[5]. More women regarded UI as a disease entity (68.2% vs 21.7%); fewer women agreed that UI is a normal ageing process (51.8% vs 60.6%) and that drinking excessive water causes urinary incontinence (12.7% vs 22.4%). In the present study, knowledge level on UI did not correlate with the consultation rate, consistent with a systematic review in 2018[1]. Help-seeking behaviour is a complex interaction of disease factors (severity and type of UI), patient factors (perception of UI, degree of quality-of-life impairment, knowledge and attitude toward UI), and social factors (healthcare system, cultural influence, socioeconomic backgrounds). Therefore, improvement in knowledge alone is not sufficient to change the help-seeking behaviour.

One limitation of this study was the selection bias. Participants were recruited from two regional hospitals in Hong Kong; women with poorer access to healthcare resources were not included. Our sample was not representative of the general population and thus our findings may not be generalised to the general population. In addition, the five statements used to assess the knowledge of UI and perceived barriers to help-seeking were not validated, and the knowledge on available treatment options was not assessed. Further studies on this aspect and the quality of existing public education programmes are warranted.

The Hong Kong Continence Society and the Hong Kong Urogynaecology Association have provided education on UI by organising public seminars and online platforms

with introductory videos on common urogynaecological problems. We shall continue our efforts in promoting the preventive strategies and treatment options for UI, and we shall be more proactive in asking for symptoms of UI during consultation.

Conclusion

There is a need to improve public education on treatment options and preventive strategies for UI to encourage symptomatic women to seek medical help. Clinicians should be more proactive in asking for symptoms of UI during consultation.

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Mucinous borderline ovarian tumour with torsion and micro-invasion and associated with high serum level of carbohydrate antigen 19-9: a case report

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Carbohydrate antigen 19-9 (CA19-9) is a tumour marker elevated in many gastrointestinal malignancies as well as in mucinous tumours of ovary, mature cystic teratomas and various other benign lesions. We present a case of mucinous borderline ovarian tumour with multifocal micro-invasion and torsion and associated with very high levels of serum CA19-9 in a 41-year-old woman. This report highlights that tumour markers and radiological findings may not be accurate in diagnosing the histological sub-type of ovarian tumour.

Keywords: Antigens, tumor-associated, carbohydrate; Necrosis; Ovarian neoplasms; Ovarian torsion

Introduction

Carbohydrate antigen 19-9 (CA19-9) is a tumour marker that is often elevated in gastrointestinal tract neoplasms of pancreatic, colorectal, and biliary origin as well as in ovarian mucinous neoplasms and many benign pathologies[1]. We present a case of mucinous borderline ovarian tumour with multifocal micro-invasion and torsion and associated with very high levels of serum CA19-9 in a 41-year-old woman. Tumour markers must be taken into consideration together with clinical presentation and findings of blood tests and imaging[2]. Careful clinical judgement is important when dealing with emergency admission to manage emergency complications such as torsion.

Case presentation

In November 2020, a 41-year-old woman was admitted to a gynaecological ward with a 2-day history of sudden onset abdominal pain and vomiting. She was severely obese (body mass index, 40 kg/m^2) and had regular monthly periods. She was para 3 with all normal vaginal deliveries. All her previous cervical smears were unremarkable. She had had an open appendicectomy. On examination, a solid mass was palpable in the left lower abdomen with associated rebound tenderness. Her pulse rate was 78/minute, systolic/diastolic blood pressure were 106/60, body temperature was 37.1°C, respiratory rate was 17/minute, and oxygen saturation was 98%. All were within normal ranges.

Computed tomography showed a 15-cm solid cystic mass arising from the left ovary highly suspicious of malignancy. There was no evidence of omental or peritoneal disease, and the abdominopelvic viscera were unremarkable, with no malignant ascites or pelvic, inguinal, or para-aortic lymphadenopathy (Figure 1). Serum level of CA125 was 179 U/mL (reference range, 0-35 U/mL) and serum level of CA19-9 was 17 350 U/mL (reference range, 0-37 U/mL). Haemoglobin levels had decreased from 124 g/L to 94 g/L over 2 days. The remaining blood test results and serum tumour markers were within normal limits: white blood cell count, 8 × 10^9/L; C-reactive protein, 2.60 mg/L; β-human chorionic gonadotropin, <5 IU/L; lactate dehydrogenase, 185 U/L; carcinoembryonic antigen, 2.9 ng/ml; and α-fetoprotein, <1.7 KIU/L.

With a clinical suspicion of ovarian torsion, the patient was taken to the emergency theatre for laparoscopy and potential laparotomy. A twisted large necrotic left ovarian cyst was noted on the left abdominal cavity,

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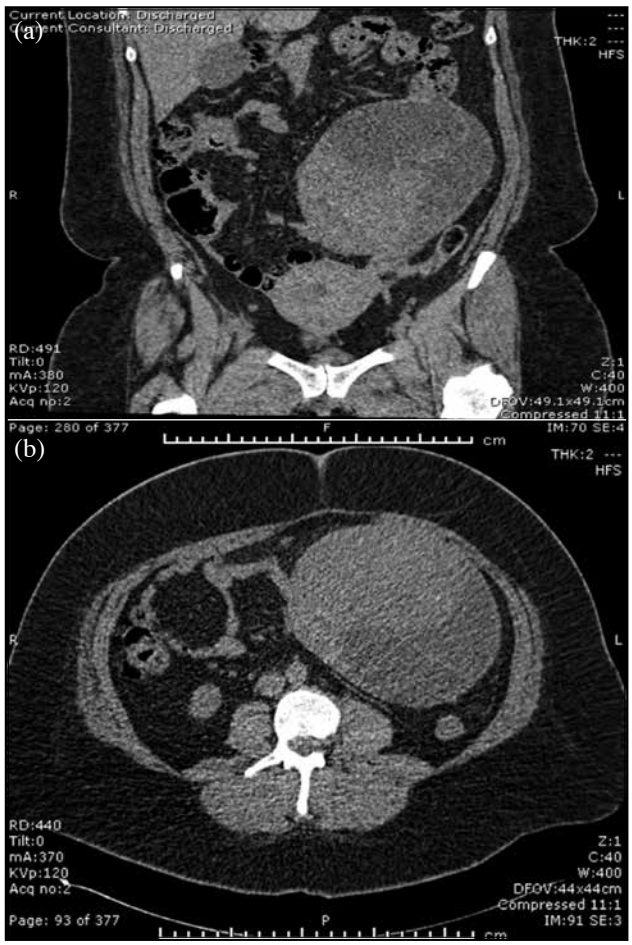

Figure 1. Computed tomography of the abdominopelvic area showing the left ovarian mass in (a) sagittal and (b) transverse view.

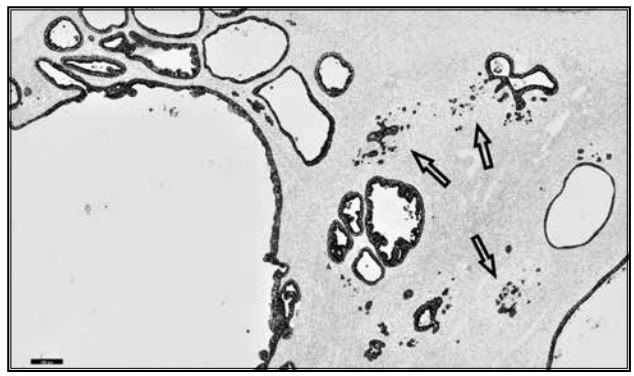

Figure 2. Cytokeratin 7 immunohistochemistry of the mucinous borderline tumour with multifocal micro-invasion: non-invasive borderline tumour is on the left and multiple foci of stromal invasion are on the right (arrows).

with spontaneous rupture resulting in about 200 mL of free haemorrhagic fluid in the pelvis. Fluid was aspirated laparoscopically and sent for cytology, followed by left salpingo-oophorectomy and omental biopsy through a transverse incision laparotomy. The right ovary and fallopian tube, omentum, peritoneum, liver, and diaphragm appeared to be unremarkable, with no signs of metastatic disease.

At 10 days after surgery, the CA125 level decreased to 91.7 U/mL and the CA19-9 level decreased to 289.5 U/mL, with a haemoglobin level of 107 g/L. Histology revealed a mucinous borderline tumour of the ovary with multifocal micro-invasion (Figure 2). Immunohistochemically, the tumour was strongly positive for CA19-9 and showed patchy ischaemic changes and infarction consistent with torsion. None of the invasive foci was >5 mm in linear extent. No tumour was identified in the omental biopsy or peritoneal fluid. The tumour was regarded as FIGO stage 1C2. The patient underwent total abdominal hysterectomy and right salpingo-oophorectomy with omental biopsy at a tertiary oncology centre. Biopsy result was unremarkable with no evidence of neoplasia.

Discussion

Epithelial ovarian cancers are considered the most common type of ovarian cancer, accounting for about 90% of cases. More than 75% of epithelial ovarian cancers are of the serous type, whereas mucinous, endometrioid, clear cell, Brenner, and undifferentiated lineage types are less common[3]. Failure in early detection can lead to high mortality rate[3].

Mucinous epithelial ovarian tumours are formed by cells that resemble those of the endocervical epithelium or, more frequently, those of the intestinal epithelium. Benign mucinous tumours are multiloculated cysts that are filled with opaque, dense, mucoid material and account for up to 25% of all benign ovarian neoplasms and 75% to 85% of all mucinous ovarian tumours[4]. Borderline mucinous tumours account for 10% to 15% of all ovarian mucinous tumours and are similar to benign mucinous tumours on gross pathological examination, but they may have solid regions and papillae projecting into the cyst locules[4]. These tumours are atypically proliferating and are intermediate in their nature with a low possibility of invasive transformation; they can occur in patients across a wide age range including paediatric patients and are the most common subtype of borderline tumour in Asia[4]. After surgical treatment, tumour recurrence and metastasis are rare, unless the tumours arise in a teratoma or are associated with pseudomyxoma peritonei; the prognosis is generally favourable[4]. Compared with borderline tumours, mucinous

carcinomas account for 5% to 10% of all malignant ovarian neoplasms and tend to contain more papillary projections within the cyst cavities, larger solid areas, and larger areas of necrosis and haemorrhage[4]. In contrast to serous tumours, for mucinous tumours, diagnosing benign type from borderline or malignant type is more challenging because of their typical large size and great variation in the degree of differentiation within individual tumours[5].

Mucinous borderline tumours with microinvasion are defined by stromal invasion measuring <5 mm in the greatest linear dimension and consisting of single cells, clusters, or small foci of confluent glandular or cribriform growth, regardless of the number of microinvasive foci[6]. Microinvasion has been reported in 4% to 18% of mucinous borderline tumours and has no adverse effect on prognosis[6]. Nonetheless, additional sampling and immunohistochemical testing are recommended to exclude frankly invasive adenocarcinoma[6]. Borderline ovarian tumours with microinvasion may lead to earlier relapses, but the overall incidence of relapses and overall survival do not differ significantly from those without microinvasion[7]. Fertility-sparing surgery is feasible, but strict follow-up is suggested[7].

Tumour markers have been used widely to determine therapeutic efficacy, detect recurrence, and predict prognosis in known cancers. Markers for ovarian cancer include CA125, CA15-3, CEA, and CA19-9[3]. CA125 contributes to early diagnosis of epithelial ovarian cancers by detecting an antigenic site on MUC16. However, CA125 is not frequently elevated in most primary ovarian mucinous neoplasms, and thus CA19-9 should be used instead[1,8]. In mucinous tumours, CA19-9 is more frequently elevated than CA125 or CEA (57% vs 15% vs 11%) and should be used for follow-up[9]. CA19-9 is a monosialoganglioside glycoprotein antigen related to Lewis blood group protein and is present in epithelial tissues of the pancreas and hepatobiliary tree and is often secreted by mucinous tumours of gastrointestinal tract including those of pancreas and biliary tree[1,2]. The reference range for CA19-9 is 0 to 37 U/mL. CA19-9 can be elevated in many conditions (Table)[10].

Compared with CA125 alone, CA19-9 and CA125 combined do not significantly improve detection of malignant adnexal masses[11]. Nonetheless, higher CA19-9 levels are helpful in differentiating metastatic tumours from primary ovarian malignancy[11]. Markedly raised CA19-9 levels of >10000 U/mL are almost exclusively seen in advanced stages of malignancy[12]. One study showed no correlation between serum CA19-9 levels and subtypes of primary ovarian mucinous tumours but a weak correlation between tumour size and serum CA19-9 levels[13]. In contrast, another study reported that CA19-9 was more frequently elevated in mucinous borderline and malignant tumours than in benign tumours, and therefore tumour pathology was the only independent factor for serum CA19-9 level elevation, regardless of tumour size or CA125 level elevation[8]. Nonetheless, there are case reports of high CA19-9 levels associated with benign mucinous cystadenoma[1].

In mature cystic teratomas, CA19-9 levels are also elevated[14], and this is correlated with larger tumour size and higher rate of ovarian torsion[15,16] but not with bilateral tumour involvement[16]. Nonetheless, one study reported correlation between tumour diameter and bilaterality and the highest CA19-9 level of 25590 U/mL in a case[17].

Table. Differential diagnoses in carbohydrate antigen 19-9 level elevation

Differential diagnosis
Hepatopancreaticobiliary malignancies
Cholangiocarcinoma
Pancreatic adenocarcinoma
Hepatocellular carcinoma
Other malignancies
Colorectal carcinoma
Gastric carcinoma
Bronchogenic carcinoma
Ovarian carcinoma
Non-malignant hepatopancreaticobiliary conditions
Acute and chronic pancreatitis
Cholecystitis
Cirrhosis
Chronic and alcoholic hepatitis
Acute hepatic necrosis
Gallstones
Non-malignant obstructive jaundice
Non-hepatobiliary conditions
Lung disorders (pneumonia, tuberculosis, cystic fibrosis)
Pelvic inflammatory disease
Hashimoto thyroiditis
Rheumatoid arthritis
Renal failure
Systemic lupus erythematosus

In dermoid cysts, elevated CA19-9 levels may be caused by rupture and leakage from the cyst wall into the blood stream or a weakened cyst wall in a larger diameter cyst[18], may be related to torsion of the ovary and to the extent of the necrosis[14], and may be an indicator for early surgical intervention owing to higher risks of torsion and larger cyst size[19].

In our patient, such high levels of CA19-9 raised suspicion of malignancy although it turned out to be a borderline mucinous tumour (rather than a frank mucinous adenocarcinoma) with torsion and multifocal micro-invasion. Immunohistochemistry revealed that the cyst epithelium was strongly positive for CA19-9. The cyst was quite large with a weakened cyst wall leading to rupture and had torsion and necrosis. We hypothesise that these could be the causes of extremely high levels of serum CA19-9. Clinically, ovarian torsion was not suspected initially owing to the abnormally high levels of serum CA19-9.

Serum tumour markers are helpful in initial diagnosis of cancer and can be used to flag further investigation of neoplasia. Nonetheless, the whole clinical picture should be taken into account, including symptoms and clinical and imaging findings, for accurate diagnoses and appropriate management.

Declaration

The authors have no conflicts of interest to disclose.

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Women's Health Initiative and menopausal hormone management

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This review discusses the findings of the Women's Health Initiative in 2002 and its updates in 2013. Risks and benefits of menopausal hormone therapy in terms of coronary heart disease, breast cancer, stroke, pulmonary embolism and venous thromboembolism, colorectal cancer, endometrial cancer, and hip fracture/osteoporosis are also discussed, as is prescription of menopausal hormone therapy to alleviate menopausal symptoms and optimise health.

Keywords: Breast neoplasms; Climacteric; Menopause

Women's Health Initiative in 2002

Since 1960s, the use of hormones in women to relieve menopausal symptoms and reduce mortality and incidence of coronary heart disease (CHD) has become popular[1-4]. The Women's Health Initiative (WHI) is a long-term health study funded by the National Heart, Lung, and Blood Institute of the United States[5]. It aims to assess the effect of hormonal use on CHD and invasive breast cancer in healthy postmenopausal women. In 2002, the WHI reported increased risks of invasive breast cancer, CHD, stroke, and pulmonary embolism in women on menopausal hormone therapy (MHT) [Table][6]. These results shook the media[7]. However, the 2002 WHI has limitations in terms of study design, interpretation[8], statistical analysis[9], and presentation of results to the public. It did not address the benefits of MHT to relieve menopausal symptoms. Nonetheless, the US Preventive Services Task Force recommended against MHT for preventing CHD[10], and the numbers of users and new users of MHT worldwide decreased significantly[11-13].

The clinical alert[14] of WHI drew widespread media attention. Some media misinterpreted 26% increase in relative risk (of invasive breast cancer) as 26% increase in absolute risk. To prevent misinterpretation, a short section on study results to the public is suggested[15].

In the 2002 WHI, the mean age of women in the MHT arm was 63.2 years. Only one third aged 50 to 59 years, and most women commenced on MHT after 60 years of age. In addition, one third of women were obese (body mass index ≥30 kg/m^2), one third were treated for hypertension, and only half were never-smokers. Age, obesity, hypertension, and smoking are risk factors for CHD[16], and these are confounding factors of the 2002 WHI. Although the sample was considered 'normal healthy population' in the US, the results may not be representative to other populations[17,18]. In addition, the high drop-out rate (42% from the MHT group and 38% from the placebo group) and the small absolute increase in invasive breast cancer (8 more per 10 000 women-years) render little clinical significance. Furthermore, the WHI was not designed to and did not have enough statistical power to assess the effect of MHT in younger peri-menopausal women[19]. The decision of early termination of MHT was based on unadjusted relative risks of CHD and invasive breast cancer; however, after taking into account the confounding factors, the adjusted relative risks were not significant[20].

In a 2012 study evaluating German patients' and gynaecologists' attitudes toward MHT before and after the 2002 WHI, 80% of patients became more critical about MHT after the WHI, but most of them were badly (43.9%) or moderately (44.5%) informed about WHI through the media[21]. MHT use decreased after the WHI; the decrease was smaller in women aged 60 to 69 years than in those aged 40 to 59 years[22]. Younger women with more vasomotor symptoms who are recommended to MHT showed the largest decrease in MHT initiation (owing to the risks of CHD and invasive breast cancer) and continuation (owing to doctor advice or media reports)[23]. Therefore, better education and understanding regarding the risks and benefits of MHT for patients and clinicians are needed, as is a more personalised treatment strategy. Without the option of MHT, peri- or early postmenopausal women may suffer from climacteric symptoms and lose the opportunity of cardio-protection and risk reduction of osteoporosis[24].

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Table. Findings of the 2002 Women's Health Initiative*

Adverse outcome	Estimated hazard ratio for the menopausal hormone therapy group	Absolute risk change per 10 000 women-years
Coronary heart disease	1.29	7 more
Invasive breast cancer	1.26	8 more
Stroke	1.41	8 more
Pulmonary embolism	2.13	8 more
Colorectal cancer	0.63	6 fewer
Endometrial cancer	0.83	Not significant
Hip fracture	0.66	5 fewer

* Compared with the placebo group, the menopausal hormone therapy group has an absolute excess risk of 19 adverse events per 10 000 women-years but no overall increase in mortality

The 2002 WHI also affected physicians' clinical practice, counselling, and prescription behaviours of MHT[25]. Physicians were concerned about the ambiguity of health information the WHI brought to women; they became less likely to prescribe MHT[25]. Compared with general gynaecologists, specialised gynaecologists reported a smaller decrease in MHT prescription[21].

Updates on Women's Health Initiative

Since the 2002 WHI, new evidence has resulted in updated consensus statements and recommendations in different societies. The North American Menopause Society published the evidence-based position statement in 2010 and updated it in 2012, recommending the initiation of MHT around menopause to treat climacteric symptoms and to prevent osteoporosis in high-risk patients[26]. It states that the absolute risk to healthy women aged 50 to 59 years is low. Similarly, the International Menopause Society updated its recommendations in 2011 and states that the potential benefits of MHT, if given for a clear clinical indication, outweighs the risks, which are low if MHT is initiated within a few years of menopause[27].

In 2013, cumulative 13-year follow-up data of WHI and subgroup analysis reported that the risk of CHD was neutral for MHT, but such risk increased significantly in women past 20 years of menopause, probably owing to other risk factors (age, hypertension, diabetes) rather than MHT[28]. The risks and benefits of MHT are complex.

Risks and benefits of menopausal hormone therapy

Coronary heart disease

The effect of MHT on CHD is associated with patient age and time since menopause when MHT is initiated[29]. Vascular response to oestrogen is affected by oestrogen receptor expression in artery[30,31]. Oestrogens are beneficial to younger women by delaying onset of atherosclerosis but are detrimental to older women who already have atherosclerosis[32]. The International Menopause Society and the North American Menopause Society updated their recommendations in 2016 and 2017, respectively[33,34], based on the 2015 Cochrane review[35] and the 2013 WHI[28]. Both societies considered that MHT is safe and effective to treat menopausal symptoms, provided that MHT is initiated in healthy postmenopausal women aged <60 years or within 10 years of onset of menopause. They also acknowledged the increased risk of CHD if MHT is initiated >10 years since menopause.

Breast cancer

Association between MHT and invasive breast cancer remains controversial. In the 2002 WHI, the absolute excess risk of invasive breast cancer was low (<0.1% per year), and the excess risk was affected by various confounding factors (body weight, alcohol intake, and physical inactivity)[36]. Therefore, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommended up to 5 years of combined MHT[37], after discussion with patients the potential small increased risk of breast cancer[34].

Stroke

The risk of stroke does not increase if MHT is initiated in women aged <60 years and/or within 10 years since menopause[28,35]. However, stroke incidence is increased if MHT is initiated after age 60 years.

Pulmonary embolism and venous thromboembolism

Oral oestrogens but not transdermal oestrogens increase the risk of recurrent venous thromboembolism[38].

Oral oestrogens may cause a significant increase in resistance to activated protein C and hence activating blood coagulation[39]. Such increase is much smaller in transdermal oestrogens. The International Menopause Society recommends the use of transdermal oestrogen therapy for obese women with menopausal symptoms and recommends against the use of oral oestrogen in women with a history of venous thromboembolism[33].

Colorectal cancer

A meta-analysis reported that MHT reduces the risk of colorectal cancer, with the benefit persisting up to 4 years of cessation of MHT[40]. In contrary, the 2013 WHI reported insignificant effect of MHT on colorectal cancer[28]. Thus, MHT should not be used solely as chemoprevention of colorectal cancer[33]. Rather than promoting MHT's benefit in reducing colorectal cancer risk, a healthy lifestyle together with more frequent colorectal cancer screening should be emphasised[41].

Endometrial cancer

The 2002 WHI reported a reduced risk of endometrial cancer after MHT; this benefit remains after 13 years[28]. However, oestrogen increases the risk of endometrial hyperplasia and cancer[42].

Hip fracture/osteoporosis

In the 2013 WHI, MHT reduces risks osteoporotic fracture at any age and is considered the most appropriate therapy in the early menopause for prevention of fractures[33]. The benefit of MHT in fracture prevention persists after 5 years of MHT discountinuation[43].

Prescription of menopausal hormone therapy

With better understanding of risks and benefits of MHT, comprehensive assessment of patients should be performed before prescription. This includes initial consultation to initiate check-up and identify risk factors. Toolkits with algorithms regarding patient assessment, hormonal therapy initiation, and review strategies are developed for clinicians[44]. Clinicians should help women make informed decisions on MHT by providing adequate information on their profiles and online resources for patient education. MHT is the most effective therapy in alleviating vasomotor symptoms, whereas complementary therapies have limited efficacy[33]. Thorough discussion with patients enables them to understand their own risk-and-benefit profile[45]. MHT should be customised regarding starting and stopping of MHT as well as dose and route of administration[46]. Patients become more involved in management of their menopausal transition, and menopause counselling provides an opportunity to reinforce key preventative health measures.

Conclusion

Most mainstream women's health regulatory and scientific bodies support appropriate use of MHT[33,34,37]. Future studies that compare different MHT regimens in terms of dose, route of administration, and duration of use are warranted. The second WHI extension study in 2020 may provide further insight into the health outcomes after long-term MHT[5]. A meta-analysis in 2019 concluded that MHT had at an excess risk of breast cancer even higher than that reported in the 2002 WHI[47]. However, the breast cancer risk under the current recommended MHT regimens is not addressed, as the regimens have changed substantially[48]. Further research is needed to address the impact of latest regimens.

Declaration

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Review Article

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Overview of fertility preservation

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Preserving fertility from damage by medical conditions or their treatments is increasingly popular. With the extended progression-free survival among young cancer survivors, oncofertility is an important subfield about preserving gonadal function and fertility among oncological patients. In this review, we discuss the gonadotoxicity of various anti-cancer treatments including radiotherapy and chemotherapy. We describe the current fertility preservation strategies including fertility-sparing surgery, radiation techniques, gonadal transposition, and assisted reproductive technology. We also discuss future trends including gonadal tissue cryopreservation and the current situation in Hong Kong. This review aims to promote the awareness, knowledge, and utilisation of fertility preservation so that more patients can benefit from it.

Keywords: Cryopreservation; Fertility Preservation; Infertility; Neoplasms; Quality of life

Introduction

Preserving fertility from damage by medical conditions or their treatments is increasingly popular. Cancer is the most common medical indication for fertility preservation (FP) [Table 1][1-4]. Oncofertility is an important subfield about preserving gonadal function and fertility among oncological patients. In patients with cancer during reproductive or pre-pubertal age, increasing efficacy of anti-cancer treatment and hence prolonged progression-free survival may result in subfertility and even infertility. Cancer management has shifted to a more holistic approach to consider the patients' quality of life, including fertility. In addition to FP for medical reasons, there is a trend of FP for social reasons including career planning, age-related fertility loss, and the absence of partners. The European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine include transgender patients as an indication for FP before sex transition[1,5]. To promote the awareness, knowledge, and utilisation of FP, this review discusses the gonadotoxic effect of anti-cancer treatment, FP strategies, future trends of FP, and the current situation of FP in Hong Kong.

Gonadotoxic effect of anti-cancer treatment

Gonads are vulnerable to anti-cancer treatments (surgery, radiotherapy, chemotherapy, and/or their combination), which may result in loss of endocrine and reproductive functions. The gonadotoxicity depends on disease, treatment, and patient factors (Table 2). Patients of reproductive or pre-pubertal age should be counselled about the gonadotoxic effect of the treatment. FP should be discussed as a part of the management in the early stage[1,6,7]. The window period for seeking FP advice between cancer diagnosis and treatment commencement varies. Timely referral to fertility specialists is crucial to maximise the future fertility potential.

Radiotherapy

In pelvic and abdominal cancers (eg, uterine, cervical, and rectal cancer) and some haematological malignancy requiring pelvic irradiation, unintentional irradiation to ovarian follicles inflicts DNA damage and leads to follicular atrophy and decreased follicular reserve[8]. The irradiation effect is dose-dependent and may lead to premature ovarian insufficiency[9]. Cranial radiotherapy inadvertently irradiates central neuroendocrine organs (such as the hypothalamus and the pituitary gland) and leads to endocrinopathy including central hypogonadism and hyperprolactinaemia. In addition, irradiation damages the uterine vasculature, the myometrium, and the endometrial epithelium[10]. Impaired ovarian function lowers the level of circulatory oestrogen and uterine function and hence increases the risks of miscarriage, preterm delivery,

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Table 1. Medical indications for fertility preservation

Medical indication for fertility preservation
Malignancy
Breast cancer
Gynaecological cancer (selective cases)
Testicular cancer
Childhood cancer (neuroblastoma, Ewing sarcoma, osteosarcoma, Wilms tumour)
Haematological malignancy (Hodgkin lymphoma, non-Hodgkin lymphoma, leukaemia)
Haematological diseases
Thalassemia major
Sickle cell anaemia
Other haematological diseases requiring bone-marrow transplantation
Autoimmune diseases
Systemic lupus erythematosus
Rheumatoid arthritis
Juvenile idiopathic arthritis
Other autoimmune diseases requiring chemotherapy
Genetic diseases
Mosaic Turner syndrome
Family history of premature ovarian failure
BRCA mutation carrier opting for prophylactic oophorectomy
Klinefelter syndrome
Gynaecological / urological diseases
Severe endometriosis
Recurrent ovarian cysts
Cryptorchidism

Table 2. Factors affecting fertility after anti-cancer treatment

Factors affecting fertility
Disease factors
Primary site of disease
Involvement of reproductive organs in systemic disease
Treatment factors
Type of treatment (surgery, chemotherapy, radiotherapy, immunotherapy, target therapy, or any combination)
Cumulative dose administered (depends on duration, dosage, number of cycles, fractionation)
Patient factors
Physical factors
Sex
Age
Comorbidity
Pre-treatment gonadal reserve
Psychosocial factors
Relationship status
Presence of a previous child
Religious background
Cultural background
Financial status
Educational level

low birth weight, and uterine rupture in future pregnancy. Vaginal stenosis and loss of vaginal lubrication after irradiation of the vagina contribute to sexual dysfunction and infertility[11].

In testicular cancers, cancer sites that are close to the testes (prostate, rectum, anus, and bladder), intracranial malignancy, and leukaemia requiring prophylactic cranial irradiation, radiotherapy may damage the testes and the hormonal axis[12]. Irradiation interferes with the process of spermatogenesis, particularly on the immature differentiating spermatogonia, and depletes the mature sperms[13]. Leydig cells that produce testosterone are also damaged[14]. Pelvic radiotherapy can result in erectile dysfunction[15]. Damage inflicted by irradiation can be transient or irreversible, and the risks vary in different dosages (Table 3)[3,16]. Irradiation

Table 3. Risks of prolonged azoospermia in men or amenorrhea in women after radiotherapy[3,16]

High-risk
Total body irradiation for bone marrow transplant or stem cell transplant
Pelvic or whole abdominal radiation dose
≥6 Gy in adult women
≥10 Gy in post-pubertal girls
≥15 Gy in pre-pubertal girls
Testicular radiation dose
>2.5 Gy in adult men
≥6 Gy in pre-pubertal boys
Intermediate risk
Craniospinal radiotherapy dose ≥25 Gy
Pelvic or whole abdominal radiation dose
5-10 Gy in post-pubertal girls
10-15 Gy in pre-pubertal girls
Testicular radiation dose
1-6 Gy from scattered pelvic or abdominal radiation

of 2 Gy to the female gonadal area can destroy up to 50% of the ovarian reserve[17]. The maximum dosage that ovaries can withstand before ovarian failure decreases with age[17,18]. Spermatogonia are sensitive to radiation damage, whereas Leydig cells are more radio-resistant after puberty[19]. Thus, hormonal function in post-pubertal men is less affected by radiotherapy.

Chemotherapy

Alkylating agents are the most gonadotoxic, as their cell-cycle non-specific property renders toxicity to primordial follicles. Damage to the follicle is immediate after exposure to cyclophosphamide, owing to the high sensitivity of the follicle to the agent[20]. Women with reduced primordial follicle reserve have a shortened reproductive lifespan[21]. For men, alkylating agents adversely affect spermatogenesis and can lead to azoospermia within 90 days of exposure, which can persist for years after treatment[22]. Other chemotherapeutic drugs are more target-specific and thus less gonadotoxic (Table 4)[23-26]. Nevertheless, toxicity accumulates when combining different chemotherapeutic agents; oncologists should prescribe regimens that are least gonadotoxic while ensuring adequate anti-cancer effects.

Table 4. Level of gonadotoxicity of chemotherapeutic drugs[23-26]

Drug	Risk level in women	Risk level in men
Alkylating agent		
Busulfan	High	High
Chlorambucil	High	High
Cyclophosphamide	High	High
Mechlorethamine	High	High
Melphalan	High	High
Platinum analogue		
Cisplatin	Intermediate	High (intermediate if <6g/m^2)
Carboplatin	Intermediate	Intermediate
Anthracycline antibiotic		
Doxorubicin	Intermediate	Intermediate
Daunorubicin	Low	Intermediate
Antimetabolite		
Cytarabine	Low	Intermediate
Methotrexate	Low	Low
Vinca alkaloid		
Vinblastine	Low	Low
Vincristine	Low	Low
Antitumor antibiotic		
Bleomycin	Low	Low
Purine analogue		
Fluorouracil	Low	Low
Immunotherapy	Unknown	Unknown
Monoclonal antibodies	Unknown	Unknown
Small-molecule targeted therapy	Unknown	Unknown

Fertility preservation strategies

Fertility preservation strategies for cancer patients depend on sex and pubertal status. For surgical treatment involving reproductive organs, fertility-sparing surgeries are alternatives for patients of reproductive age, but they are limited to early-stage diseases or tumours with low malignancy (Figure). Patient selection should balance the potential increased risk of recurrence versus the fertility potential. For cervical cancer, early-stage diseases can be treated with fertility-sparing surgery. Stage IA1 disease with no lymphovascular space invasion can be treated with cone biopsy[27]. Stage IA1 disease with lymphovascular space invasion, stage IA2 disease, and stage IB1 can be treated with additional radical trachelectomy (resection of the cervix, upper third of the vagina, and parametrial tissues) with bilateral pelvic lymphadenectomy. Stage IB1 disease can be treated with additional para-aortic lymph node dissection[28]. For ovarian cancer, early-stage unilateral disease and borderline epithelial ovarian tumours can be treated with unilateral salpingo-oophorectomy[11]. For atypical endometrial hyperplasia and very early-stage endometrial cancer, hysterectomy is the standard treatment, but conservative treatment with high-dose progesterone, followed by close monitoring, can be offered to those with fertility wish[29]. For testicular cancer, testicular-sparing surgery can be considered in cases of nonpalpable small masses (≤2 cm), a solitary mass, and bilateral tumours, without compromising oncological and functional outcomes[30]. Intraoperative frozen section should be performed to ensure a safe margin of malignant tissue.

Pelvic shielding and transposition of gonads

For radiotherapy, to minimise the gonadotoxic effect, shielding the pelvic organs is an easy and non-invasive way. For men, gonadal shielding effectively lowers the irradiation dose the gonads received unintentionally by >60%[31]. When shielding is not feasible, the gonads can be transposed surgically out of the irradiation field. Ovarian transposition enables preservation of ovarian function in 90% of the cases[32]. Lateral transposition by laparoscopic surgery is more common; the utero-ovarian ligament and tubes are divided, and the ovary is placed 3 cm above the

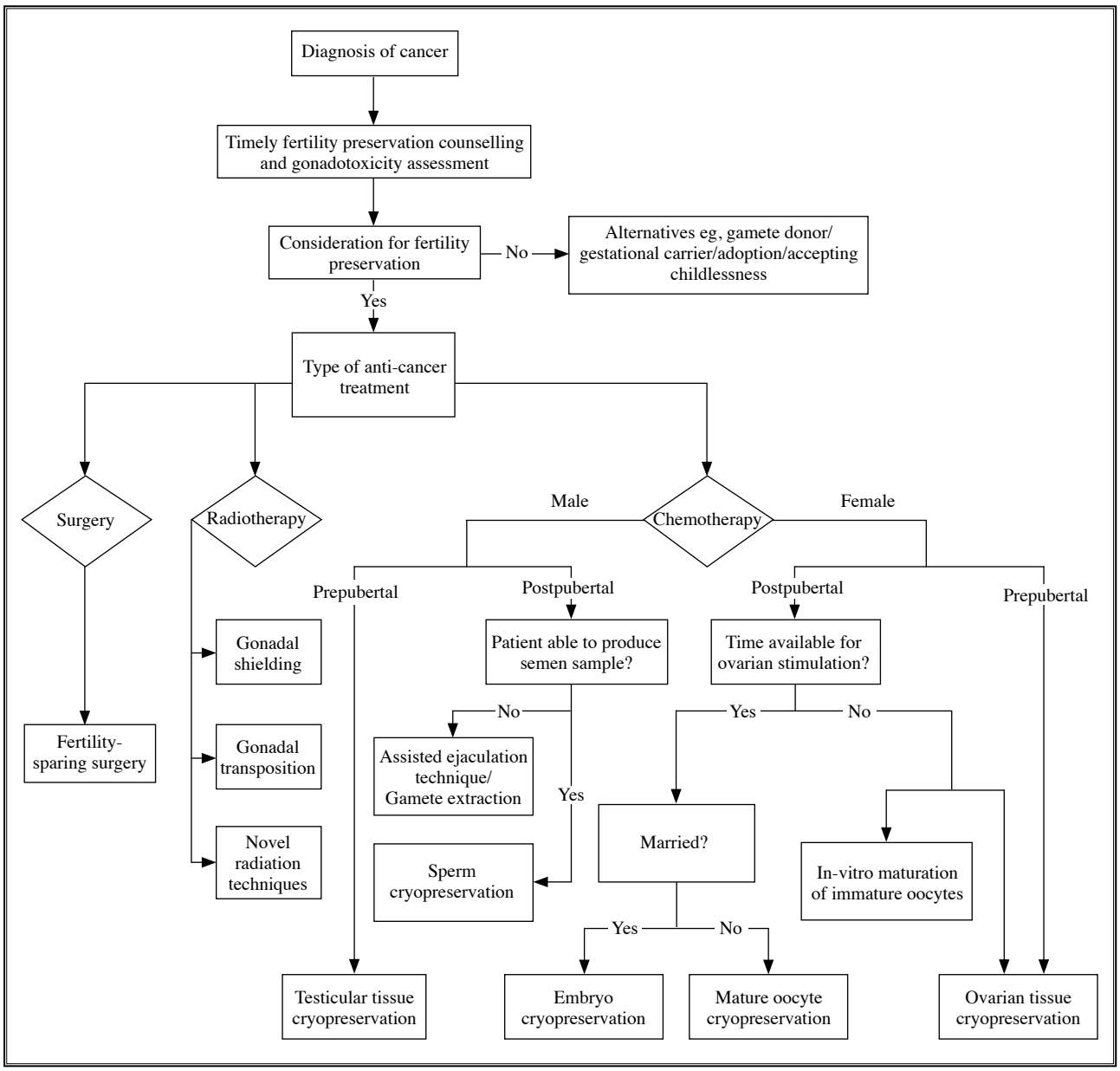

Figure. Fertility preservation strategies

radiation field. However, women with reduced ovarian reserve and risk of ovarian metastasis are not suitable for ovarian transposition. As radiation scatters, ovaries are not completely protected from radiation. There is also a risk of remigration of ovaries; thus, ovarian transposition should be performed close to the time of radiotherapy[6]. In testicular transposition, the spermatic cord is moved up to the external inguinal ring, the gubernaculum attachments at the scrotum are released, and the testes are transposed under the abdominal skin. Testicular transposition can lower the radiation dose received by the testes during scrotal or pelvic irradiation[33]. After radiotherapy, the testes are relocated back to the scrotum[34].

Intensity-modulated radiation therapy and proton radiotherapy

In conventional radiotherapy, the X-ray passes the body, through the tumour, and comes out at the other side. This 'exit dose' of radiation affects healthy tissue in the field. In contrast, intensity-modulated radiation therapy manipulates proton beams to precisely irradiate the target tumour, minimising radiation dose to neighbouring healthy tissue. Proton radiotherapy can deliver energy more precisely to the tumour. Protons release more energy within the tumour and cease to penetrate healthy tissues, reducing radiation exposure and potential damage to healthy tissue[35,36].

Strategy for chemotherapy

For women, gonadotropin-releasing hormone agonist (GnRHa) is used to create a state similar to menopause. However, GnRHa can cause hypo-estrogenic symptoms and irreversible bone loss after long-term use. Although a meta-analysis reported a benefit of GnRHa in the prevention of chemotherapy-induced premature ovarian failure, the American Society of Clinical Oncology and the European Society of Medical Oncology do not recommend GnRHa as a sole FP strategy[6]. The former suggests GnRHa in young women with breast cancer only when other FP strategies are not feasible. For men, GnRHa shows efficacy in animal models only but not in humans[37]. Therefore, chemical shielding is not recommended in male patients.

Assisted reproductive technology

Sperm cryopreservation can be offered to post-pubertal patients. Ejaculation through masturbation does not delay cancer treatment. Phosphodiesterase type-5 inhibitors can be used to facilitate ejaculation in those with or without ejaculating difficulty or erectile dysfunction[38]. Assisted ejaculation techniques (vibratory or electro-ejaculatory stimulation) can be used in pre-pubertal patients or patients unable to ejaculate. For azoospermic patients, urological procedures (percutaneous epididymal sperm aspiration, microsurgical epididymal sperm aspiration, and testicular sperm extraction) can be used for sperm acquisition[39]. For patients with testicular cancer who failed to ejaculate, oncological testicular sperm extraction can be performed immediately after orchiectomy[40], followed by intracytoplasmic sperm injection (injection of a single sperm into an oocyte using a micropipette under the microscope), which is beneficial for those with oligospermia or cryopreserved sperms in whom in vitro fertilisation may be less effective.

Testicular tissue and spermatogonial stem cells cryopreservation through biopsy is performed under general anaesthesia for pre-pubertal boys who have no mature sperm or cannot ejaculate. In patients aged 13 to 14 years, sperm cells might be present and thus can be cryopreserved[41]. For younger patients, only spermatogonial stem cells can be isolated and cryopreserved. As spermatogenesis originates from spermatogonial stem cells, auto-transplantation of these stem cells into the testes may restore fertility[17]. This technology also preserves other testicular cells, including Sertoli cells, which is postulated to maintain crucial cell-cell interactions and account for improved spermatogonial stem cell survival. It can be performed in patients in whom chemotherapy cannot be delayed. However, success has been reported in animal model only but not yet in humans[42]. Similar to ovarian tissue cryopreservation (OTC), testicular tissue cryopreservation carries both surgical risk and the risk of reseeding malignancy during auto-transplantation.

FP is more complicated in females than in males and depends on pubertal stage, time availability before anti-cancer treatment, and marital status. False reassurance should not be given[43]. Women should attempt to conceive soon after remission of disease when they are physically fit for pregnancy, as their fertility decreases with age.

Embryo cryopreservation is the optimal choice of FP for married women with adequate time for ovarian stimulation[44]. It involves ovarian stimulation to produce mature oocytes for retrieval and then in vitro fertilisation. Embryos are cryopreserved and thawed for use when the patient is ready for a pregnancy. Embryos are more resistant to cryo-damage than oocytes, as oocytes have a higher susceptibility to meiotic spindle damage[44]. However, ovarian stimulation takes at least 2 to 3 weeks, rendering a delay in anti-cancer treatment. There is also a risk of a transient increase in oestradiol levels, leading to regrowth of tumour cells in hormone-sensitive cancer.

Mature oocyte cryopreservation is the most common strategy and is used for post-pubertal women who are single and have adequate time for ovarian stimulation. It involves controlled ovarian stimulation, harvesting of mature oocytes, and freezing of unfertilised eggs. Vitrification is a relatively new cryopreservation technology; it rapidly freezes the oocyte using a high concentration of cryoprotectant to prevent crystallisation of water content, thus lowering the cryo-damage. Slow freezing is the conventional cryopreservation technique; it freezes the oocyte at a lower rate (2°C/minute) with a low cryoprotectant concentration. A systemic review reported that vitrification is superior to slow-freezing in terms of post-thaw viability of the oocyte and clinical pregnancy[45,46]. Intracytoplasmic sperm injection is suggested to increase the success rate, as cryopreservation of the oocytes leads to hardening of the outer shell (zona pellucida) and potentially reduces the fertilisation rate[47]. Mature oocyte cryopreservation provides greater flexibility and autonomy on fertility decision. It is an alternative to married women, especially in case of potential change of future marital status[48]. Women can decide the timing and partner to start a family[48]. Legally, women are prohibited to use cryopreserved embryos in situations such as divorce and decease of the partner. Mature oocyte cryopreservation is also an alternative for patients with religious or ethical

concern over embryo cryopreservation. However, it temporarily increases oestradiol level and thus the risk of hormone-sensitive cancer progression. The rate of a cryopreserved oocyte translating to live birth is about 5% to 7% in well-established units. 15 to 20 oocytes are needed to secure a 70% to 80% probability of having one live birth in women under 38 years old[49]. As only 8 to 12 oocytes can be harvested in each ovarian stimulation cycle, more than one cycle is needed to harvest adequate oocytes, and the anti-cancer treatment may be further delay[48].

Conventional ovarian stimulation starts during the follicular phase of the menstrual cycle. For patients with limited time between diagnosis and commencement of anti-cancer treatment and those who seek FP consultation during non-follicular phase, random-start ovarian stimulation (initiation of ovarian stimulation at any point of the menstrual cycle) enables harvesting oocytes in a short time[50]. Its effectiveness is similar to conventional protocols in terms of oocyte yield and fertilisation rate[51]. Double stimulation combines conventional stimulation at the follicular phase with luteal phase stimulation; thus, oocyte can be retrieved twice in the same cycle[52]. For breast cancer sensitive to oestrogen, protocols that lower the circulating oestrogen level increase the safety margin of ovarian stimulation and prevent recurrence and progression. Letrozole is an aromatase inhibitor that suppresses circulating oestrogen level. It releases the negative feedback by oestrogen on the hypothalamic-pituitary axis, promoting the follicle-stimulating hormone secretion. During ovarian stimulation, co-administration of letrozole suppresses oestradiol levels without significantly affecting the oocyte yield or shortening the disease-free survival rates[53]. Tamoxifen is a selective oestrogen receptor modulator used in hormone-sensitive breast cancer. In addition to the anti-oestrogen effect on the breast tissue, its antagonist effect on the central nervous system releases the negative feedback of oestrogen on the hypothalamic-pituitary axis, resulting in increased GnRH secretion and hence follicle-stimulating hormone for follicle development[21,54]. Co-administration of tamoxifen lowers the ovarian stimulation dose, but a comparable or larger number of oocytes can still be collected[54].

Immature oocyte cryopreservation is used for women requiring immediate anti-cancer treatment or those with polycystic ovarian syndrome who are not candidates for embryo or mature oocyte cryopreservation. It does not require mature oocyte or ovarian stimulation. This alternative has shown success and may be the standard of treatment in future. The collected immature oocytes are matured inside the culture medium, ie in vitro maturation. The matured oocytes can then be preserved or fertilised with sperms to form embryos for cryopreservation. Immature oocyte cryopreservation with in vitro maturation has a lower risk of ovarian hyperstimulation syndrome than does conventional ovarian stimulation[55]. However, compared with conventional IVF, in vitro maturation has a lower live birth and cumulative ongoing pregnancy rate[56].

Ovarian tissue cryopreservation (OTC) uses cortical biopsies to obtain multiple primordial follicles from each ovary. The tissue is then reimplanted in the orthotopic region (eg, pelvis) or heterotopically in the subcutaneous space of the forearm or abdomen when the patient desires for pregnancy[57]. The first live birth after OTC is reported in 2004, and >170 live births have been reported since then[58]. OTC is no longer considered experimental according to the American Society for Reproductive Medicine[59,60]. It is the only FP strategy for pre-pubertal girls. OTC is beneficial to patients with limited time before anti-cancer therapy such as those with leukaemia. Without the need for ovarian stimulation, cortical biopsies can be performed immediately before anti-cancer therapy. Risks related to ovarian stimulation are avoided. The live birth rate in patients with OTC after anti-cancer treatment is comparable to that in patients with OTC before the treatment[61]. OTC restores not only fertility but also gonadal function. OTC and reimplantation can act as a physiological hormone replacement therapy after menopause; this is known as cell/tissue-based hormone replacement therapy[62]. However, this may be limited by the lifespan of graft tissue and thus requires repeated implantation[63]. It is unknown whether OTC itself leads to earlier menopause[64]. However, OTC involves both surgical biopsy for cryopreservation and auto-transplantation. The transplanted tissue may carry malignant cells, particularly in cancers with high gonadal metastasis risk such as haematological cancers (leukaemia and non-Hodgkin lymphoma) and paediatric cancers (neuroblastoma and Ewing sarcoma)[65]. The risk of reintroduction of malignant cells at the time of auto-transplantation can be minimised by meticulous examination of a representative biopsy in terms of histology, immunohistochemistry, and molecular biology[66]. Optic coherence tomography can also be used to screen malignant cells in the ovarian tissue before transplantation[67].

Future trends

Artificial ovary can solve the potential malignancy implantation risk of OTC. Preantral follicles are obtained through an ovarian tissue biopsy and are subsequently

isolated and cryopreserved. Other non-germ cells of the ovaries are then harvested from the pre-treatment ovarian tissue or from a second biopsy after cancer remission, which minimises the risk of carrying cancerous cells[68]. The follicles and other ovarian cells are contained by using a scaffold made from biological or synthetic materials[69]. The artificial ovary remains at a primitive stage of development; more studies are warranted.

In-vitro growth and maturation of primordial follicles and immature oocytes from cryopreserved ovarian tissue is an alternative to mature oocyte cryopreservation. This method is useful in whom ovarian auto-transplantation is not possible or in women with blood-borne leukaemia or cancers with high risk of ovarian metastasis[70].

Alternatives to FP such as donor gametes and gestational carriers can be discussed with suitable patients who are in clinical remission and fit for parenting. Donor gametes are suitable for those who are not suitable for gamete retrieval, including those with ovarian malignancy or those who cannot produce gametes after anti-cancer treatments (eg, bilateral oophorectomy or orchiectomy). Gestational carrier, or gestational surrogacy, refers to a woman who gestates an embryo with no biological relationship for a couple or an individual and has to relinquish the child to them after its birth[71]. Gametes are from the couple with fertility needs and form an embryo in vitro before transplantation into the gestational carrier's uterus. Gestational carrier differs from traditional surrogacy, in which the woman has a biological link to the foetus, as the fertilisation is completed with the oocyte from the surrogate mother. These solutions are suitable for those who cannot have intrauterine pregnancy such as those with hysterectomy.

Adoption is another solution that does not require ART. Medical social workers can be referred to those who are interested. If all the above options fail, the patient may have to be counselled to accept the fact of not having children.

Current situation in Hong Kong

In Hong Kong, fertility-sparing surgeries and pelvic shielding are frequently practised. Oocyte cryopreservation and embryo cryopreservation are widely used. Ovarian and testicular tissue cryopreservation are not currently available. Hopefully, they will be FP options for pre-pubertal patients and those in need in future. Although FP is an essential part of cancer treatment, the awareness and utilisation of FP in Hong Kong are low. In a cross-sectional study of clinicians, only 45.6% were familiar with FP[72]. In a study of medical students, 77.8% did not know where to seek FP service providers in Hong Kong[73]. The awareness of FP among the general public is inadequate, with about 50% of respondents not aware of any FP strategies and about 80% not knowing where to seek FP advice or service[74]. Respondents with higher education and income have significantly higher awareness and knowledge of FP[74]. Inadequate understanding and awareness of FP result in low utilisation of FP in Hong Kong. Between 1995 and 2012, only 125 cases of sperm cryopreservation were performed in a university hospital in Hong Kong[75]. Both medical students and the general public (64.3%) acquire the FP knowledge mainly from the traditional and/or social media, followed by medical schools (among medical students) and healthcare providers (among the general public). The mass media has a major role in promoting FP. Medical professionals should provide correct concepts of FP during teaching to medical students or consultation with patients and through mass media, especially social media. Other channels for patient education include public talks, television programmes, newspaper articles, and printed information/pamphlets. All these help promote awareness and knowledge of FP among the general public.

In Hong Kong, ART is regulated by the Human Reproductive Technology Ordinance (Cap. 561). The Council on Human Reproductive Technology sets up the Code of Practice on Reproductive Technology and Embryo Research. Cryopreserved oocytes and sperms can only be used when the patient is married at the time of using ART. The storage duration for frozen gametes is limited to 10 years or until the patient reaches the age of 55 years, whichever longer. The storage duration for frozen embryos is also limited to 10 years. The cryopreserved gametes and embryos can only be used when the patients have sufficiently recovered from illnesses and are legally married. It is a clinical judgement made by the appropriate experts of the relevant discipline. In addition, posthumous use of the cryopreserved gametes and embryos is prohibited in order to protect the welfare of the future child[76].

Conclusion

Anti-cancer treatment adversely affects one's fertility. FP is a vital component of quality of life in cancer survivors, especially those with fertility wish. Oncofertility is an emerging field aimed at preserving gonadal function and fertility among oncological patients. This review discussed the risks of fertility impairment after anti-cancer therapies and the FP strategies to enable live birth after gonadotoxic procedures. Each FP strategy has certain

limitations and is not suitable for all patients; the FP plan should be customised for each patient. FP counselling should be conducted promptly after the diagnosis to shorten the time between diagnosis and treatment. In Hong Kong, FP services are underutilised, owing to technological limitations and financial concerns as well as lack of awareness and understanding of FP among the public, even among medical students and physicians. Patient education, research, and campaigns are required to promote the awareness and utilisation of FP, as are establishment of FP centres to provide medical professionals training, FP management, and comprehensive bio-psycho-social care to patients.

Declaration

The authors have no conflicts of interest to disclose.

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Visanne®

The LONG TERM TARGETED treatment for Endometriosis

There's a way out of the pain

Visanne® offers :

(2mg dienogest)

- Long-term, Favourable Safety Profile for use beyond 5 Years [4,5]
- Proven Reduction in Lesion Severity & Cyst Size [2,3,6,7]
- Effective Pain Relief [1,2,6]
- Significant Prevention of Post-operative Recurrence [4,8]

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Visanne Abbreviated Prescribing Information

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

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資料來源: 1. Center for Disease Control and Prevention. Genital HPV Infection-CDC Fact Sheet. Available at: https://www.cdc.gov/std/hpv/HPV-FS-July-2017.pdf. Accessed on 19 Mar 2021.
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