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Editorial

# A century of academic obstetrics and gynaecology in Hong Kong: pioneering maternity and women's health

In Hong Kong, the formal academic discipline of obstetrics and gynaecology was established in 1925, exactly a hundred years ago, when Prof Richard Edwin Tottenham was appointed as the first Chair of Midwifery (Professor of Obstetrics and Gynaecology) at The University of Hong Kong (HKU). Over the past century, academic medicine has played a pivotal role in shaping remarkable transformations in healthcare, research, and development in obstetrics and gynaecology. HKU, and later The Chinese University of Hong Kong (CUHK) as well, have been at the forefront of advancing maternal and women's health through education, research, and clinical innovation. It is essential to recognise how academic obstetrics and gynaecology has shaped Hong Kong's medical landscape and led our way in reducing maternal morbidity and mortality, improving perinatal care, and setting high-quality standards in women's health.

## Maternity healthcare

Historical records indicated that Prof Tottenham performed the first Caesarean section in Tsan Yuk Hospital in June 1925. This exemplified that many procedures carried out today were first introduced by academic leaders. In the earlier years, maternal mortality was high. Prof Daphne Chun started obstetric audits in Tsan Yuk Hospital, setting in place the quality and safety activities that we nowadays pay more and more attention to. With this, Hong Kong excelled in achieving a low maternal mortality rate, which attracted international attention.

The first prenatal diagnosis laboratory in Hong Kong was established in 1981 at Tsan Yuk Hospital, which has since played a leading role in promoting the development of prenatal diagnosis of common conditions in our locality. In the 1980s, our HKU academics introduced ultrasonographic screening for fetuses affected by alpha-thalassaemia major in place of invasive tests, as well as strategies to prevent vertical transmission of hepatitis B. In the early 2000s, non-invasive prenatal testing for Down syndrome and other chromosomal abnormalities was introduced by academics from CUHK. These were examples of impactful pioneering work that improved obstetric care.

## Gynaecological care

Minimally invasive surgery was a major breakthrough in gynaecological treatment. The first laparoscopic gynaecological procedure in Hong Kong was carried out by Prof Daphne Chun and Prof Ho-Kei Ma in the late 1960s. More recently, robotic surgery has been introduced into gynaecological applications in Hong Kong, mainly in cancer surgeries, by the two university units.

Research interest in gestational trophoblastic diseases began in the 1950s, led by HKU professors over several successions. This put Hong Kong in a renowned position in the international arena. Prof Hextan Ngan was involved in the writing of a number of guidelines on gestational trophoblastic diseases and gynaecological cancers for the International Federation of Gynecology and Obstetrics.

## Reproductive health

Prof William Nixon founded the Hong Kong Eugenics League in 1936, succeeded by Prof Gordon King who re-established it as The Family Planning Association of Hong Kong in 1951. The subsequent HKU professors continued to preside over the governance of the association, which contributes enormously to the development of sexual and reproductive health in Hong Kong. Research work led by Prof Pak-Chung Ho, conducted both locally and in collaboration with the World Health Organization, has revolutionary impact on development of guidelines in medical abortion and emergency contraception.

The two universities were among the first to introduce in vitro fertilisation to Hong Kong, which revolutionised fertility treatment. They took the lead to expand the application of assisted reproduction technology for pre-implantation genetic testing and fertility preservation. In addition, our academics participated in the editorial work for the *Laboratory Manual for the Examination and Processing of Human Semen* published by the World Health Organization.

## Research and development

In addition to steering clinical excellence, clinical materials at the university teaching hospitals make an important contribution to supporting clinical studies as well as basic science and translational studies. Findings from the research studies can thus be translated into clinical applications to improve healthcare.

## Professional leadership and knowledge exchange

Throughout the years, our academics have held key positions in professional bodies locally, regionally, and internationally. Prof Ho-Kei Ma founded the Hong Kong College of Obstetricians and Gynaecologists, which was among the first constituent specialty colleges of the Hong Kong Academy of Medicine, and established a formal system for training specialists and subspecialists in Hong Kong. Prof Allan Chang, the founding Professor of Obstetrics and Gynaecology at CUHK, was intimately involved in the establishment of a conjoint examination between the Hong Kong and the UK Colleges. Through international collaboration, the two university units have bridged our academics with peers in other parts of the world to foster the exchange of academic and clinical knowledge.

## Conclusion

A century of academic obstetrics and gynaecology in Hong Kong has transformed women's healthcare from a rudimentary service to a world-class specialty. The contributions of the two university units and their affiliated hospitals have set the benchmarks in medical education, training, quality assurance, and innovation. As we look ahead, the next generation of academic specialists must continue this legacy and embrace the future with the same pioneering spirit that our predecessors have defined over the past 100 years. I am sure, with our academics, clinicians, and allied health staff working together closely, the next century will be just as transformative as the last.

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# Use of intrapartum ultrasound before assisted vaginal delivery in a single hospital in Hong Kong

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***Objectives:*** To investigate the use of intrapartum ultrasound (ITU) under different indications for assisted vaginal delivery, as well as the frequencies of assessment of various ITU parameters, by clinicians in a single hospital.
***Methods:*** Medical records of women who underwent assisted vaginal delivery at Kwong Wah Hospital between 3 January 2023 and 2 January 2024 were retrospectively reviewed. Seven ITU parameters were recorded: spine position, head position, angle of progression (AoP), head-perineum distance (HPD), head direction, asynclitism, and size of caput succedaneum.
***Results:*** In total, 113 assisted vaginal deliveries were included in the analysis, comprising ventouse extraction (n=94), forceps delivery (n=17), and sequential instrumental birth (n=2). There were no failed assisted vaginal deliveries. Of the 113 assisted vaginal deliveries, 70 (61.9%) had prior ITU for indications of prolonged second stage (n=46), fetal distress (n=20), and maternal medical conditions (n=4); the respective ITU use rates were 92.0%, 35.7%, and 57.1% (p<0.001). Among the 70 assisted vaginal deliveries with prior ITU, 29 (41.4%) had all seven sonographic parameters assessed before making the decision for assisted vaginal delivery. In terms of individual ITU parameters, HPD and AoP were assessed in all cases, followed by spine position (92.9%), size of caput succedaneum (80.0%), asynclitism (78.6%), head position (62.9%), and head direction (42.9%). The frequencies of assessment among parameters differed significantly (p<0.001). Asynclitism and size of caput succedaneum were assessed least frequently than head and spine positions, as well as station and descent (as measured by HPD, AoP, or head direction).
***Conclusion:*** The rate of using ITU to assess labour progress prior to assisted vaginal delivery for prolonged second stage was high at our hospital under the opt-out protocol. Sonographic assessment of fetal spine position and head station (via HPD and AoP) was most commonly performed. The opt-out protocol may encourage ITU use, particularly in cases of delayed second stage, while preserving clinicians' independent judgement.

*Keywords: Extraction, obstetrical; Labor stage, second; Ultrasonography*

## Introduction

Use of intrapartum ultrasound (ITU) before assisted vaginal delivery is gaining popularity. The Royal College of Obstetricians and Gynaecologists recommends using ultrasound to define fetal head position when there is uncertainty regarding clinical findings[1], whereas the International Society of Ultrasound in Obstetrics and Gynecology recommends ultrasound assessment of fetal head position and station before considering assisted vaginal delivery[2]. ITU provides a more objective and accurate assessment of labour progress, compared with digital vaginal examination. Ultrasound assessment before assisted vaginal delivery can reduce the incidence of incorrect diagnosis of head position without delaying delivery[3], as well as the incidence of deliveries in unexpected positions and associated neonatal morbidities[4]. Sonographic parameters of head station—such as angle of progression (AoP), head-perineum distance (HPD), and head direction—can predict the likelihood of success or failure of assisted vaginal delivery[5-9]. An algorithmic model incorporating both clinical and sonographic parameters can assist clinicians in deciding between assisted vaginal delivery and second-stage Caesarean section[10].

From the patient's perspective, ITU is better tolerated than digital vaginal examination for assessing labour progress[11-13]. Nevertheless, obstetricians are trained to monitor labour progress using digital vaginal examination, which remains essential in labour care. In a survey of Italian caregivers, ITU was most commonly used to assess fetal occiput position and less frequently for fetal head station and progression[14,15]. At our centre, ITU is highly recommended before making a decision regarding assisted vaginal delivery. In January 2023, an opt-out protocol was introduced, allowing clinicians to choose

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not to perform ITU before assisted vaginal delivery. This study aimed to investigate the use of ITU under different indications for assisted vaginal delivery, as well as the frequencies of assessment of various ITU parameters, by clinicians in a single hospital.

## Methods

Medical records of women who underwent assisted vaginal delivery at Kwong Wah Hospital between 3 January 2023 and 2 January 2024 were retrospectively reviewed through the Clinical Data Analysis and Reporting System. Women who had a spontaneous delivery after the obstetrician's decision to allow assisted vaginal delivery were excluded, as were those with intrauterine fetal demise. Prerequisites for assisted vaginal delivery were met in all cases. All trials of assisted vaginal delivery were conducted by either trainees under supervision or obstetricians. The decision not to perform ITU was made jointly by the trainee and supervising obstetrician. A portable two-dimensional ultrasound machine (Samsung Ultrasound System HS50, Korea) was used. Seven ITU parameters were recorded: spine position, head position, AoP, HPD, head direction, asynclitism, and size of caput succedaneum.

Statistical analysis was performed using SPSS (Windows version 29.0; IBM Corp, Armonk [NY], United States). Based on the indication for assisted vaginal delivery, ITU use prior to delivery was analysed in three groups: prolonged second stage, fetal distress, and maternal medical conditions (eg, pre-eclampsia). Comparisons were made using the Chi-squared test or Fisher's exact test. A p value of <0.05 was considered statistically significant.

## Results

During the study period, there were 1660 vaginal births and 809 Caesarean births in our obstetric unit. Of these, 113 (4.6% of all deliveries) were assisted vaginal deliveries, comprising ventouse extraction (n=94), forceps delivery (n=17), and sequential instrumental birth (n=2). There were no failed assisted vaginal deliveries. Three women underwent second-stage Caesarean section for cephalopelvic disproportion. Women with and without ITU were comparable in terms of baseline characteristics (Table 1).

Of the 113 assisted vaginal deliveries, 70 (61.9%) had prior ITU for indications of prolonged second stage (n=46), fetal distress (n=20), and maternal medical conditions (n=4); the respective ITU use rates were 92.0%, 35.7%, and 57.1% (p<0.001, Table 2). Among the 43 women who were opted out of ITU by obstetricians, the most common reason was the need for urgent delivery (n=31), whereas the remaining reasons were a busy labour ward (n=1), outlet delivery without perceived need for ultrasound assessment (n=1), maternal loss of consciousness (n=1), and no reason given (n=9).

**Table 1. Characteristics of patients.**

| Characteristic | Intrapartum ultrasound* | | p Value |
|---|---|---|---|
| | Performed (n=70) | Not performed (n=43) | |
| Age, y | 33.1±4.7 | 31.7±4.6 | 0.12 |
| Parity | | | 0.14 |
| Primigravida | 70 (100) | 41 (95.3) | |
| Multipara | 0 | 2 (4.7) | |
| Pregnancy order | | | 1.00 |
| Singleton | 69 (98.6) | 42 (97.7) | |
| Twins (first twins) | 1 (1.4) | 1 (2.3) | |
| Pre-pregnancy body mass index, kg/m$^2$ | 21.9±3.3 | 21.6±3.6 | 0.70 |
| Gestational age at birth, wk | 39.4±1.2 | 39.3±1.5 | 0.52 |
| Ethnicity | | | 0.67 |
| Chinese | 67 (95.7) | 40 (93.0) | |
| Non-Chinese Asian | 3 (4.3) | 3 (7.0) | |
| Use of synthetic oxytocin during labour | | | 0.44 |
| Yes | 33 (47.1) | 24 (55.8) | |
| No | 37 (52.9) | 19 (44.2) | |
| Head position at second stage | | | 0.28 |
| Occiput anterior | 57 (81.4) | 39 (90.7) | |
| Non-occiput anterior | 13 (18.6) | 4 (9.3) | |
| Head station at second stage | | | 0.12 |
| Mid-cavity | 0 | 1 (2.3) | |
| Low | 68 (97.1) | 38 (88.4) | |
| Outlet | 2 (2.9) | 4 (9.3) | |
| Mode of delivery | | | 0.11 |
| Ventouse extraction | 62 (88.6) | 32 (74.4) | |
| Forceps | 7 (10.0) | 10 (23.3) | |
| Sequential | 1 (1.4) | 1 (2.3) | |

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

Among the 70 assisted vaginal deliveries with prior ITU, 29 (41.4%) had all seven sonographic parameters assessed before making the decision for assisted vaginal delivery (Table 3). Based on the ISUOG Practice

**Table 2. Use of intrapartum ultrasound for different indications of assisted vaginal delivery.**

| | Indication of assisted vaginal delivery | | | p Value |
|---|---|---|---|---|
| | Prolonged second stage (n=50) | Fetal distress (n=56) | Maternal medical condition (n=7) | |
| Intrapartum ultrasound | | | | <0.001 |
| Performed | 46 (92.0) | 20 (35.7) | 4 (57.1) | |
| Not performed | 4 (8.0) | 36 (64.3) | 3 (42.9) | |
| Reasons | Not given (n=2), busy labour ward (n=1), outlet delivery (n=1) | Urgent delivery (n=30), not given (n=6) | Urgent delivery (n=1), maternal loss of consciousness (n=1), not given (n=1) | |

**Table 3. Assessment of intrapartum ultrasound parameters before assisted vaginal delivery.**

| Variable | All seven parameters assessed (n=29)* | p Value |
|---|---|---|
| Indication for assisted vaginal delivery | | 0.34 |
| Prolonged second stage (n=53) | 22 (41.5) | |
| Fetal distress (n=13) | 4 (30.8) | |
| Maternal medical condition (n=4) | 3 (75.0) | |
| Parameter assessed within three groups based on the ISUOG Practice Guidelines[2] | n=70 | <0.001 |
| Head and spine position | 65 (92.9) | |
| Station and descent (as measured by head-perineum distance, angle of progression, and head direction) | 70 (100.0) | |
| Asynclitism and size of caput succedaneum | 55 (78.6) | |

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

Guidelines[2], we classified the ITU parameters into three groups: head and spine position, station and descent (as measured by HPD, AoP, or head direction), and asynclitism and size of caput succedaneum. The latter was assessed less frequently than the other parameters (p<0.001). In terms of individual ITU parameters, HPD and AoP were assessed in all cases, followed by spine position (92.9%), size of caput succedaneum (80.0%), asynclitism (78.6%), head position (62.9%), and head direction (42.9%). The frequencies of assessment among parameters differed significantly (p<0.001).

## Discussion

The rates of ITU use before assisted vaginal delivery were 92.0% in cases of prolonged second stage and 35.7% in cases of fetal distress and 57.1% in cases of maternal medical conditions. The time required for ITU is approximately 10 minutes. The interval from decision of ultrasound assessment to delivery is not prolonged, compared with standard care, when ultrasound is used to assess fetal head position[3]. Measurement of HPD and/or AoP during rest and maternal pushing effort is typically completed within one or two uterine contractions. Therefore, ITU should not be considered unreasonable in cases of fetal distress, particularly when preparations for assisted vaginal delivery can be made simultaneously by supporting staff when urgent delivery is required. Clinicians may choose to assess specific ITU parameters based on findings from the vaginal examination to further reduce the ITU duration. Nevertheless, at our hospital, setting up the ultrasound machine in the delivery room may require additional minutes, which may not be preferable in the most urgent cases.

There were no cases of failed assisted vaginal delivery in our study. Failed instrumental delivery could increase the risk of neonatal morbidities, likely owing to delays in delivery and difficulty in delivery of the baby's head during Caesarean section[16]. In cases of high fetal head station in which the clinician is not confident in performing a mid-cavity delivery, ITU can provide objective information regarding labour progress and assist in the decision to attempt assisted vaginal delivery in the labour room or operating theatre, or to proceed directly to second-stage Caesarean section. This information is particularly relevant in cases of non-reassuring fetal status, in which the likelihood of successful assisted vaginal delivery must be carefully assessed to minimise neonatal morbidities.

Our hospital does not mandate the use of all seven ITU parameters, allowing flexibility. When ITU was performed prior to assisted vaginal delivery, head direction

was assessed in 42.9% of cases, whereas HPD and AoP were assessed in all cases. HPD and AoP have been found to predict failure of assisted vaginal delivery[5-9], although no consensus has been reached regarding definitive cut-off values[10]. They provide quantitative measurements and reduce errors during fetal head station assessment in the presence of a large caput succedaneum. Changes in HPD or AoP during maternal pushing also provide an objective estimation of head descent and facilitate communication among care providers. When the fetal head is in occiput posterior (OP) position, AoP increases during descent, whereas HPD remains high until flexion of the head occurs. These findings indicate that HPD and head direction might be more useful for assessing fetuses in OP position[17,18].

Head position was evaluated in 62.9% of cases when ITU was performed, probably because clinical suspicion of OP position is not common in practice. At our hospital, digital vaginal examinations to monitor labour progress are performed by obstetricians rather than midwives. The obstetrician making the decision of assisted vaginal delivery usually has assessed the woman during the first stage and is already aware of the head position. Moreover, OP position at the second stage is relatively uncommon[19]; the obstetrician may be confident confirming the head position by digital examination during the first stage alone, consistent with The Royal College of Obstetricians and Gynaecologists recommendations[1].

When occiput and spine positions are concordant, fetuses are mostly delivered in the same position without rotation, whereas when the occiput is posterior and the spine is anterior, no fetuses are delivered in the OP position[20]. Thus, ultrasound assessment of spine position alone can adequately reassure the OA position during vaginal examination. Spine position also predicts rotation of the fetal head during the delivery process and persistent OP position at delivery, which can guide the direction of traction during ventouse extraction[21]. In our study, spine position was checked in 92.9% of cases when ITU was performed. HPD, AoP, and spine position were most assessed during ITU, consistent with the International Society of Ultrasound in Obstetrics and Gynecology recommendations. In the five cases in which head position and spine position were not assessed, all were delivered in the OA position, consistent with findings from digital vaginal examinations.

Asynclitism is more prevalent in non-OA positions and can be associated with failed ventouse extraction secondary to incorrect vacuum cup placement[22,23]. However, extreme asynclitism is uncommon and usually evident on digital vaginal examination, although palpation of head position might be hindered. Correct cup placement may be aided by ultrasound confirmation of fetal head position. Similarly, the size of the caput succedaneum is conspicuous on digital examination. It is correlated with the duration of vacuum extraction but not with failure of assisted vaginal delivery[24]. When extensive caput succedaneum is present, forceps delivery is preferred over ventouse extraction to reduce cup slippage risk during traction.

Major limitations of our study included its retrospective design and single-centre setting. In our hospital, the frequent use of ITU facilitated the opt-out protocol. Most clinicians were familiar with ITU techniques and interpretation. Thus, our findings might not be generalisable to other hospitals without similar resources and expertise. Additionally, reasons for not performing ITU prior to assisted vaginal delivery were missing in some cases. Furthermore, maternal and neonatal outcomes were not investigated. Finally, we did not record whether clinicians were certain of the head position before performing ITU or proceeding with assisted vaginal delivery. Nonetheless, we examined clinicians' perspectives regarding the use of ITU under different indications before assisted vaginal delivery.

## Conclusion

The rate of using ITU to assess labour progress prior to assisted vaginal delivery for prolonged second stage was high at our hospital under the opt-out protocol. Sonographic assessment of fetal spine position and head station (via HPD and AoP) were most commonly assessed. The opt-out protocol may encourage ITU use, particularly in cases of delayed second stage, while preserving clinicians' independent judgement.

## Contributors

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

## Conflicts of interest

As an editor of the journal, WLL was not involved in the peer review process. Other authors have no conflict of interest to disclose.

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## Data availability

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

## Ethics approval

This study was approved by the Hospital Authority Central Research Ethics Committee (reference: CIRB-2024-581-5). All patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided informed consent for all treatments and procedures.

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# Characteristics and pregnancy outcomes of undetected fetal macrosomia

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***Objective:*** To identify antenatal characteristics associated with undetected macrosomia, as well as predictors for adverse maternal and neonatal outcomes.
***Methods:*** Medical records of women who gave birth to term macrosomic infants at Tuen Mun Hospital between 1 January 2019 and 31 December 2023 were retrospectively reviewed. Comparisons were made between women with antenatally detected macrosomia by ultrasound (estimated fetal weight ≥4000 g) within 1 week before delivery and women with antenatally undetected macrosomia. Logistic regression analysis was performed to determine independent predictors for Caesarean delivery, composite adverse maternal outcomes, and composite adverse neonatal outcomes.
***Results:*** Of the 360 macrosomic cases during the 5-year study period, 265 (73.6%) were undetected antenatally and 95 (26.4%) were detected antenatally. Compared with the undetected group, the detected group had a higher pre-pregnancy body mass index (24.8 vs 23.2 kg/m$^2$, p=0.024), a higher rate of elevated pre-pregnancy body mass index (48.4% vs 33.2%, p=0.008), a higher rate of shoulder dystocia in a previous pregnancy (3.2% vs 0%, p=0.018), a higher rate of polyhydramnios (11.6% vs 2.3%, p=0.001), a higher rate of pregnancy-related problems (45.3% vs 29.8%, p=0.006), and a greater number of ultrasound scans (2 vs 1, p<0.001). All cases of perineal traumas, shoulder dystocia, and birth injuries occurred in the undetected group. Antenatally detected macrosomia was independently associated with Caesarean delivery (adjusted odds ratio [aOR]=89.26, p<0.001), increased composite adverse maternal outcomes (aOR=2.73, p<0.001), and decreased composite adverse neonatal outcomes (aOR=0.32, p=0.001).
***Conclusion:*** Antenatal detection of macrosomia decreases neonatal complications but increases maternal complications and Caesarean delivery rates. Counselling regarding macrosomia should involve a shared decision-making process based on evidence-based recommendations.

*Keywords: Birth weight; Cesarean section; Fetal macrosomia; Shoulder dystocia*

## Introduction

Fetal macrosomia refers to an infant birth weight of >4000 g, irrespective of gestational age; its prevalence ranges from 3% to 15% worldwide[1]. Risk factors for macrosomia include pregestational or gestational diabetes mellitus, maternal obesity, and excessive gestational weight gain[2-4]. Macrosomia is associated with various maternal complications (Caesarean delivery, labour dystocia, anal sphincter injury, postpartum haemorrhage, and uterine rupture)[5-13] and fetal complications (shoulder dystocia, birth injuries including clavicular fracture, humeral fracture, and brachial plexus injury, and birth asphyxia)[14-16].

Both the American College of Obstetricians and Gynaecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommend consideration of Caesarean section in pregnancies with an estimated fetal weight (EFW) of ≥4500 g complicated by pregestational or gestational diabetes mellitus, and in pregnancies with an EFW of ≥5000 g without diabetes. Vaginal delivery is recommended for fetuses with an EFW of 4000 g to 4500 g. In a study of 12 229 singleton deliveries among Chinese and Southeast Asians[17] and a study of 80 953 singleton deliveries among Chinese women[18], the rate of all forms of complications increased when birth weight was ≥3600 g. Birth weight of ≥4200 g was the strongest independent risk factor for shoulder dystocia (adjusted odds ratio [aOR]=76.10), compared with birth weight of 4000 g to 4199 g (aOR=22.40)[18]. Other independent risk factors include instrumental delivery, maternal height <151 cm, maternal diabetes mellitus, and body mass index ≥25 kg/m$^2$ at delivery[18]. A cut-off value of 4000 g or 4200 g appears to achieve the optimal balance between the risk of shoulder dystocia and the need for Caesarean delivery. Thus, the current practice at our unit is to advise Caesarean delivery in pregnancies with an EFW of ≥4000 g complicated by diabetes and an EFW of ≥4500 g without diabetes.

Reduction of adverse perinatal outcomes remains a priority among obstetricians, partly owing to concerns over litigation risks, as highlighted by the Montgomery

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case[19]. Improvements in antenatal detection of macrosomia are therefore needed. However, antenatal detection of macrosomia by ultrasound is challenging. Among all macrosomic babies, 20% to 50% are undiagnosed prenatally[20]. A systematic review and meta-analysis found 56% sensitivity in diagnosing a macrosomic baby with an EFW of >4000 g and 80% sensitivity for an abdominal circumference of >35 cm[21].

This study aimed to identify antenatal characteristics associated with undetected macrosomia, as well as predictors for adverse maternal and neonatal outcomes.

## Methods

Medical records of women who gave birth to term macrosomic infants at Tuen Mun Hospital between 1 January 2019 and 31 December 2023 were retrospectively reviewed. Women with multiple pregnancies, stillbirth, or incomplete data were excluded. Macrosomia was defined as birth weight of ≥4000 g and term pregnancy as gestational age of ≥37 weeks. Gestational age was calculated based on the last menstrual period; it was confirmed or adjusted by an early ultrasound scan. The gestational age of in vitro fertilisation pregnancies was calculated from the day of oocyte retrieval. Maternal demographics, maternal medical and obstetric history, intrapartum and delivery information, and pregnancy outcomes (both maternal and neonatal) were recorded.

All pregnant women were routinely offered a 12-week dating scan. Clinical evaluation of fetal growth was primarily based on abdominal palpation (Leopold's manoeuvre) and/or symphysis-fundal height measurement. When the uterine size was larger than expected for gestational age, a timely ultrasound examination for EFW was performed. Additional ultrasound scans were arranged for indications such as diabetes, malpresentation, antepartum haemorrhage, and uterine fibroids.

The ultrasound EFW was calculated using the Hadlock formula, which incorporates biparietal diameter, abdominal circumference, and femur length. Women with a large-for-gestational-age (LGA) fetus (defined as an ultrasound EFW of >90th percentile on the local chart) were screened for gestational diabetes using the 75 g oral glucose tolerance test[22]. The diagnosis of gestational diabetes was based on thresholds in the 2013 World Health Organization guideline[23]. Additionally, women with any identified risk factor were offered the 75 g oral glucose tolerance test at 24 to 28 weeks of gestation. In accordance with our departmental protocol, diabetic women with an LGA fetus were offered Caesarean delivery at 38 weeks, whereas women with macrosomia were advised to undergo Caesarean delivery at term. Non-diabetic women with suspected fetal macrosomia were offered options of expectant management, induction of labour, and Caesarean delivery beyond 38 weeks.

Comparisons were made between women with antenatally detected macrosomia by ultrasound (EFW ≥4000 g) within 1 week before delivery and women with antenatally undetected macrosomia (owing to a lack of growth scans or a final ultrasound EFW <4000 g). Excessive total weight gain was defined according to recommendations by the Institute of Medicine[24]. The accuracy of ultrasound EFW within 1 week before delivery relative to actual birth weight was calculated in terms of percentage error. A difference of <10% indicated an accurate estimation[25].

Maternal outcomes included induction of labour, mode of delivery, blood loss at delivery, postpartum haemorrhage, blood transfusion, perineal trauma (vaginal and cervical tears, obstetric anal sphincter injuries, and vaginal haematoma), uterine rupture, hysterectomy, length of hospitalisation, and maternal death. Non-progressive labour included prolonged first or second stage of labour. Interpretation of electronic fetal heart rate tracing was based on the 2022 National Institute for Health and Care Excellence guidelines[26]. Postpartum haemorrhage was defined as blood loss of ≥500 mL at delivery, and severe postpartum haemorrhage as blood loss of ≥1000 mL[27]. Composite adverse maternal outcomes included any of the following: postpartum haemorrhage, blood transfusion, and perineal trauma.

Neonatal outcomes included gestational age at delivery, birth weight, sex, shoulder dystocia, Apgar score at 1 and 5 minutes, arterial cord blood pH, resuscitation at birth, need for assisted ventilation, birth injury, convulsion, hypoxic-ischaemic encephalopathy, transient tachypnoea of newborn, respiratory distress syndrome, neonatal jaundice, phototherapy, polycythaemia, hypoglycaemia, neonatal intensive care unit admission, and early neonatal death. Shoulder dystocia was defined as vaginal delivery requiring an additional obstetric manoeuvre to deliver the fetal shoulder after delivery of the head and failure of gentle traction[16]. Birth injuries included subgaleal haematoma, cephalohaematoma, intracranial haemorrhage, intraventricular haemorrhage, bone fracture, and brachial plexus injury. Composite adverse neonatal outcomes included any of the following: resuscitation at birth, Apgar score of <7 at 5 minutes, arterial cord blood pH <7.1, neonatal intensive care unit stay >24 hours, shoulder dystocia, birth injury, transient tachypnoea of newborn, respiratory distress syndrome, neonatal jaundice requiring

phototherapy, hypoglycaemia, anaemia, polycythaemia, and convulsion.

Statistical analysis was performed using SPSS (Windows version 29.0; IBM Corp, Armonk [NY], United States). Women with or without antenatal detection of macrosomia were compared using the Student's *t* test or Mann-Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. A p value of <0.05 was considered statistically significant. Logistic regression analysis was performed to determine independent predictors for Caesarean delivery, composite adverse maternal outcomes, and composite adverse neonatal outcomes after exclusion of women with prescheduled Caesarean sections for reasons other than macrosomia, with adjustment for potential confounders.

## Results

During the 5-year study period, there were 16480 full-term singleton livebirths, of which 360 were macrosomic, yielding an incidence of 2.2%. Of the 360 macrosomic cases, 265 (73.6%) were undetected antenatally and 95 (26.4%) were detected antenatally.

Compared with women with antenatally undetected macrosomia, women with antenatally detected macrosomia had a higher pre-pregnancy body mass index (24.8 vs 23.2 kg/m$^2$, p=0.024), a higher rate of elevated pre-pregnancy body mass index (48.4% vs 33.2%, p=0.008), a higher rate of shoulder dystocia in a previous pregnancy (3.2% vs 0%, p=0.018), a higher rate of polyhydramnios (11.6% vs 2.3%, p=0.001), a higher rate of pregnancy-related problems (45.3% vs 29.8%, p=0.006), and a greater number of ultrasound scans (2 vs 1, p<0.001) [Table 1].

Among the 157 (43.6%) women who underwent ultrasound EFW measurement within 1 week before delivery, the percentage of accurate EFWs was higher in women with antenatally detected macrosomia (96.8% vs 43.5%, p<0.001) who also had higher clinical EFWs (3800 vs 3600 g, p<0.001). Their newborns were delivered earlier (39 vs 40 weeks, p=0.018), were less frequently delivered at or after 41 weeks (12.6% vs 22.6%, p=0.036), and had higher birth weights (4170 vs 4110 g, p<0.001).

After exclusion of 48 women with prescheduled Caesarean sections for reasons other than macrosomia, there were 226 women in the undetected group and 86 women in the detected group. Of the latter, 79 opted for Caesarean delivery and the remaining seven opted for labour induction (n=5) or expectant management (n=2), which resulted in normal vaginal delivery (n=6) or urgent Caesarean section (n=1) secondary to non-reassuring fetal heart rate during labour. Rates of induction of labour were similar between women with and without antenatal detection of macrosomia (p=0.455). Concerning abnormal labour progression, seven women required instrumental deliveries for prolonged second stage, and 37 (all in the undetected group) required Caesarean sections for non-progressive labour.

Women with antenatally detected macrosomia had a higher Caesarean delivery rate (93.0% vs 25.7%, p<0.001), greater blood loss at delivery (500 vs 300 mL, p<0.001), a higher rate of severe postpartum haemorrhage (11.6% vs 3.5%, p=0.012), a lower rate of perineal trauma (0% vs 8.4%, p=0.006), and a longer hospital stay (3 vs 2 days, p<0.001) [Table 2].

Compared with infants born to women with antenatally detected macrosomia, infants born to women with antenatally undetected macrosomia had a lower birth weight (4110 vs 4170 g, p<0.001), a lower rate of birth weight ≥4500 g (3.1% vs 10.5%, p=0.017), a higher rate of requiring resuscitation at birth (5.3% vs 0%, p=0.041), a lower Apgar score at 1 minute (8 vs 8, p=0.003), and a higher rate of neonatal intensive care unit admission (21.2% vs 10.5%, p=0.028) [Table 3].

All 19 cases of perineal traumas (including three cases of third-degree obstetric anal sphincter injuries, which were repaired and asymptomatic at 6 weeks) [8.4% vs 0%, p=0.006], nine cases of shoulder dystocia (4.0% vs 0%, p=0.068), and seven cases of birth injuries (3.1% vs 0%, p=0.196) occurred in the undetected group, compared with none in the detected group. All cases of perineal traumas, shoulder dystocia, and birth injuries resolved, except in two cases: one infant developed Erb's palsy related to shoulder dystocia after vacuum-assisted delivery for prolonged second stage; the other infant experienced seizures due to brain injury associated with impaction of the fetal head during Caesarean delivery. Two infants had persistent hyperinsulinaemic hypoglycaemia after birth: one was suspected to have Beckwith-Wiedemann syndrome with associated macroglossia and right hemihypertrophy; the other was diagnosed with paternally inherited type 1 maturity-onset diabetes.

On multivariate analysis, predictors for Caesarean delivery were antenatally detected macrosomia (aOR=89.26, p<0.001), nulliparity (aOR=17.83, p<0.001), and birth weight ≥4500 g (aOR=5.90, p=0.037). Predictors for composite adverse maternal outcomes were antenatally detected macrosomia (aOR=2.73, p<0.001), advanced maternal age (aOR=2.14, p=0.011), and

**Table 1. Maternal, antenatal, and ultrasound characteristics of women with or without antenatal detection of macrosomia.**

| Characteristic | All (n=360)* | Antenatally undetected macrosomia (n=265)* | Antenatally detected macrosomia (n=95)* | p Value |
|---|---|---|---|---|
| **Maternal characteristics** | | | | |
| Age at delivery, y | 31.8±5.4 | 31.6±5.3 | 32.5±5.8 | 0.164 |
| Advanced age (≥35 y) | 117 (32.5) | 83 (31.3) | 34 (35.8) | 0.425 |
| Ethnicity | | | | 1.000 |
| Asian | 352 (97.8) | 258 (97.4) | 94 (98.9) | |
| Others | 8 (2.2) | 7 (2.6) | 1 (1.1) | |
| Height, cm | 161 (157-165) | 161 (157-165) | 160.8 (157.1-165.0) | 0.997 |
| Pre-pregnancy body mass index, kg/m$^2$ | 23.5 (21.1-26.9) | 23.2 (21.0-26.1) | 24.8 (21.6-28.2) | 0.024 |
| <25 | 226 (62.8) | 177 (66.8) | 49 (51.6) | 0.008 |
| ≥25 | 134 (37.2) | 88 (33.2) | 46 (48.4) | |
| Gestational weight gain, kg | 16.0 (12.5-19.5) | 16.0 (12.5-19.5) | 16.8 (13.5-20.5) | 0.122 |
| Excessive gestational weight gain | 229 (63.6) | 163 (61.5) | 66 (69.5) | 0.166 |
| Tertiary education or above | 85 (23.6) | 66 (24.9) | 19 (20.0) | 0.334 |
| Smoking | 9 (2.5) | 9 (3.4) | 0 | 0.119 |
| Assisted conception | 10 (2.8) | 8 (3.0) | 2 (2.1) | 1.000 |
| Parity | 1 (0-2) | 1 (0-2) | 1 (0-1) | 0.132 |
| Nulliparity | 121 (33.6) | 82 (30.9) | 39 (41.1) | 0.074 |
| Previous Caesarean section | 42 (11.7) | 35 (13.2) | 7 (7.4) | 0.128 |
| Previous vaginal delivery | 202 (56.1) | 152 (57.4) | 50 (52.6) | 0.426 |
| Previous macrosomia | 42 (11.7) | 32 (12.1) | 10 (10.5) | 0.687 |
| Previous stillbirth | 1 (0.3) | 1 (0.4) | 0 | 1.000 |
| Previous shoulder dystocia | 3 (0.8) | 0 | 3 (3.2) | 0.018 |
| Previous operative delivery for labour arrest | 23 (6.4) | 17 (6.4) | 6 (6.3) | 0.973 |
| **Antenatal characteristics** | | | | |
| Antenatal complication | | | | |
| Hypertensive disorders of pregnancy | 16 (4.4) | 14 (5.3) | 2 (2.1) | 0.255 |
| Pregestational/gestational diabetes mellitus | 78 (21.7) | 53 (20.0) | 25 (26.3) | 0.200 |
| Antepartum haemorrhage | 9 (2.5) | 5 (1.9) | 4 (4.2) | 0.251 |
| Placenta previa | 1 (0.3) | 0 | 1 (1.1) | 0.264 |
| Polyhydramnios | 17 (4.7) | 6 (2.3) | 11 (11.6) | 0.001 |
| Oligohydramnios | 3 (0.8) | 1 (0.4) | 2 (2.1) | 0.171 |
| Malpresentation | 9 (2.5) | 6 (2.3) | 3 (3.2) | 0.703 |
| Uterine fibroids | 8 (2.2) | 6 (2.3) | 2 (2.1) | 1.000 |
| Any of the above | 122 (33.9) | 79 (29.8) | 43 (45.3) | 0.006 |
| **Ultrasound characteristics** | | | | |
| No. of third-trimester ultrasounds | 1 (0-2) | 1 (0-2) | 2 (1-3) | <0.001 |
| Ultrasound within 1 week before delivery | 157 (43.6) | 62 (23.4) | 95 (100) | <0.001 |
| Estimated fetal weight | 4050 (3756-4212) | 3706 (3486-3841) | 4166 (4067-4300) | <0.001 |
| Error | -4.1 (-9.7 to 0.8) | -10.6 (-14.9 to 7.4) | -0.5 (-4.1 to 3.2) | <0.001 |
| Error ≤10% | 119 (75.8) | 27 (43.5) | 92 (96.8) | <0.001 |
| Clinical estimated fetal weight (n=310) | 3600 (3400-3800) | 3600 (3400-3700) | 3800 (3800-4000) | <0.001 |
| Gestational age at delivery, wk | 40 (39-40) | 40 (39-40) | 39 (38-40) | 0.018 |
| Gestational age ≥41 wk | 72 (20.0) | 60 (22.6) | 12 (12.6) | 0.036 |
| Birth weight, g | 4120 (4052-4247) | 4110 (4050-4215) | 4170 (4080-4340) | <0.001 |

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

**Table 2. Maternal outcomes in women with or without antenatal detection of macrosomia.**

| Maternal outcome | Antenatally undetected macrosomia (n=226)* | Antenatally detected macrosomia (n=86)* | p Value |
|---|---|---|---|
| Induction of labour among women who attempted vaginal delivery | 120/226 (53.1) | 5/7 (71.4) | 0.455 |
| Indications | | | |
| Past term | 47 (39.2) | 1 (20.0) | |
| Large-for-gestational age | 3 (2.5) | 0 | |
| Macrosomia | - | 2 (40.0) | |
| Pregestational/gestational diabetes mellitus | 21 (17.5) | 1 (20.0) | |
| Hypertensive disorders of pregnancy | 5 (4.2) | 0 | |
| Prelabour rupture of membranes | 19 (15.8) | 0 | |
| Reduced fetal movement | 12 (10.0) | 0 | |
| History of neonatal death | 1 (0.8) | 0 | |
| Antepartum haemorrhage | 12 (10.0) | 1 (20.0) | |
| Mode of delivery | | | |
| Normal vaginal delivery | 147 (65.0) | 6 (7.0) | <0.001 |
| Instrumental delivery | 21 (9.3) | 0 | 0.003 |
| Prolonged second stage | 7 (33.3) | 0 | |
| Non-reassuring heart rate | 14 (66.7) | 0 | |
| Caesarean section | 58 (25.7) | 80 (93.0) | <0.001 |
| Non-progressive labour | 37 (63.8) | 0 | |
| Non-reassuring heart rate | 14 (24.1) | 1 (1.3) | |
| Suspected macrosomia | - | 79 (98.8) | |
| Cord prolapse | 1 (1.7) | 0 | |
| Placental abruption | 1 (1.7) | 0 | |
| Intrauterine infection | 1 (1.7) | 0 | |
| Severe pre-eclampsia | 4 (6.9) | 0 | |
| Estimated blood loss at delivery, mL | 300 (200-400) | 500 (350-700) | <0.001 |
| Postpartum haemorrhage (≥500 mL) | 48 (21.2) | 47 (54.7) | <0.001 |
| Severe postpartum haemorrhage (≥1000 mL) | 8 (3.5) | 10 (11.6) | 0.012 |
| Blood products transfusion | 4 (1.8) | 1 (1.2) | 1.000 |
| Uterine rupture | 0 | 0 | - |
| Hysterectomy | 0 | 0 | - |
| Perineal trauma | 19 (8.4) | 0 | 0.006 |
| Vaginal laceration or cervical tear | 17 (7.5) | 0 | |
| Obstetric anal sphincter injury | 3 (1.3) | 0 | |
| Vaginal haematoma | 1 (0.4) | 0 | |
| Maternal death | 0 | 0 | - |
| Length of hospital stay, d | 2 (1-3) | 3 (3-3) | <0.001 |

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

nulliparity (aOR=3.14, p<0.001). Predictors for composite adverse neonatal outcomes were antenatal detection of macrosomia (aOR=0.32, p=0.001), birth weight of ≥4500 g (aOR=4.64, p=0.007), and nulliparity (aOR=2.10, p=0.008) [Table 4].

## Discussion

The incidence of antenatally undetected macrosomia in our cohort was 73.6%, which is comparable to the 70% to 90% observed among Western populations in Europe and North America[28-31]. The higher incidences of polyhydramnios and previous pregnancies complicated by shoulder dystocia in the detected group may be attributed to polyhydramnios-induced uterine enlargement beyond the expected size—particularly when the fetus is also LGA—and to greater obstetrician vigilance regarding women with a poor obstetric history. Women with undiagnosed macrosomia may have undiagnosed diabetes if gestational diabetes screening is not universally practised; some of these women may develop late-onset gestational diabetes despite normal screening results at 24 to 28 weeks' gestation.

**Table 3. Neonatal outcomes in women with or without antenatal detection of macrosomia.**

| Neonatal outcome | Antenatally undetected macrosomia (n=226)* | Antenatally detected macrosomia (n=86)* | p Value |
|---|---|---|---|
| Gestational age at delivery, wk | 40 (39-41) | 39 (39-40) | 0.005 |
| Birth weight, g | 4110 (4045-4210) | 4170 (4080-4340) | <0.001 |
| Birth weight ≥4500 g | 7 (3.1) | 9 (10.5) | 0.017 |
| Male sex | 159 (70.4) | 58 (67.4) | 0.617 |
| Apgar score at 1 minute | 8 (8-8) | 8 (8-8) | 0.003 |
| Apgar score at 5 minutes | 9 (9-9) | 9 (9-9) | 0.785 |
| Apgar score <7 at 5 minutes | 1 (0.4) | 1 (1.2) | 0.476 |
| Arterial cord blood pH <7.1 | 1 (0.4) | 0 | 1.000 |
| Resuscitation at birth | 12 (5.3) | 0 | 0.041 |
| Assisted ventilation | 7 (3.1) | 1 (1.2) | 0.453 |
| Shoulder dystocia and/or birth injury | 15 (6.6) | 0 | 0.014 |
| Shoulder dystocia | 9 (4.0) | 0 | 0.068 |
| Birth injury | 7 (3.1) | 0 | 0.196 |
| Clavicle fracture | 4 (1.8) | 0 | |
| Brachial plexus injury | 1 (0.4) | 0 | |
| Cephalohematoma | 2 (0.9) | 0 | |
| Subgaleal haemorrhage | 2 (0.9) | 0 | |
| Intraventricular haemorrhage | 1 (0.4) | 0 | |
| Convulsion | 1 (0.4) | 0 | 1.000 |
| Hypoxic ischaemic encephalopathy | 0 | 0 | - |
| Meconium aspiration syndrome | 1 (0.4) | 0 | 1.000 |
| Transient tachypnoea of newborn | 8 (3.5) | 0 | 0.112 |
| Respiratory distress syndrome | 5 (2.2) | 2 (2.3) | 1.000 |
| Neonatal jaundice | 26 (11.5) | 8 (9.3) | 0.577 |
| Phototherapy | 23 (10.2) | 7 (8.1) | 0.585 |
| Polycythaemia | 1 (0.4) | 0 | 1.000 |
| Hypoglycaemia | 32 (14.2) | 12 (14.0) | 0.963 |
| Admission to neonatal intensive care unit | 48 (21.2) | 9 (10.5) | 0.028 |
| Early neonatal death | 0 | 0 | - |

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

Obstetricians rely on ultrasound-based fetal weight estimation to guide clinical decisions. There is no consensus on the implementation of universal third-trimester ultrasound scans in low-risk pregnancies for the screening of LGA or macrosomia, given the lack of high-quality evidence on improvement in perinatal outcomes[32,33]. In addition, potential errors in ultrasound estimation of fetal weight should be considered when interpreting results. Margins of error between 10% and 15% in sonographic fetal weight estimation have been reported[34,35]. In our cohort, approximately 25% of cases demonstrated an error >10%. Moreover, ultrasound estimation of fetal weight does not account for false-positive findings of macrosomia, which may further contribute to inaccuracy, unwarranted maternal anxiety, and unnecessary interventions. Women should therefore be informed about the limitations of ultrasound, potential for estimation error, and possible impact on clinical decisions.

In our study, antenatal diagnosis of macrosomia was associated with higher rates of Caesarean section and adverse maternal outcomes, as well as a lower rate of adverse neonatal outcomes. Overall, 93% of women with antenatal diagnosis of macrosomia opted for Caesarean section, consistent with findings from several other studies, although reported Caesarean delivery rates were much lower (25% to 50%)[28,31,32]. Similarly, a diagnosis of LGA is associated with increased risk of Caesarean delivery[36] because concerns about potential macrosomia-associated neonatal complications may lead patients to forgo a trial of vaginal delivery. Although previous studies failed to demonstrate a significant reduction in adverse maternal outcomes with predicted macrosomia[28,29,31], we observed higher rates of primary postpartum haemorrhage and longer hospital stay in cases of antenatally detected macrosomia. The higher rate of postpartum haemorrhage may be attributed to the increased rate of Caesarean

**Table 4. Predictors for Caesarean section, composite adverse maternal outcomes, and composite adverse neonatal outcomes.**

| Variable | Women with Caesarean section (n=138)* | Women without Caesarean section (n=174)* | Odds ratio (95% confidence interval) | p Value | Adjusted odds ratio (95% confidence interval) | p Value |
|---|---|---|---|---|---|---|
| Antenatal detection of macrosomia | 80 (58.0) | 6 (3.4) | 38.62 (15.99-93.27) | <0.001 | 89.26 (31.28-254.72) | <0.001 |
| Advanced maternal age | 42 (30.4) | 55 (31.6) | 0.95 (0.58-1.54) | 0.824 | 1.65 (0.71-3.88) | 0.247 |
| Nulliparity | 83 (60.1) | 35 (20.1) | 5.99 (3.62-9.92) | <0.001 | 17.83 (7.92-40.13) | <0.001 |
| Pregestational/gestational diabetes | 38 (27.5) | 33 (19.0) | 1.62 (0.95-2.76) | 0.073 | 0.85 (0.36-2.02) | 0.709 |
| Hypertensive disorders of pregnancy | 7 (5.1) | 5 (2.9) | 1.81 (0.56-5.82) | 0.316 | 2.21 (0.52-9.49) | 0.286 |
| Birth weight ≥4500 g | 12 (8.7) | 4 (2.3) | 4.05 (1.28-12.85) | 0.011 | 5.90 (1.11-31.25) | 0.037 |
| | **Women with composite adverse maternal outcomes (n=110)** | **Women without composite adverse maternal outcomes (n=202)** | | | | |
| Antenatal detection of macrosomia | 47 (42.7) | 39 (19.3) | 3.12 (1.86-5.22) | <0.001 | 2.73 (1.58-4.74) | <0.001 |
| Advanced maternal age | 42 (38.2) | 55 (27.2) | 1.65 (1.01-2.71) | 0.046 | 2.14 (1.19-3.85) | 0.011 |
| Nulliparity | 57 (51.8) | 61 (30.2) | 2.49 (1.54-4.02) | <0.001 | 3.14 (1.83-5.41) | <0.001 |
| Pregestational/gestational diabetes | 32 (29.1) | 39 (19.3) | 1.72 (1.00-2.94) | 0.049 | 1.29 (0.70-2.38) | 0.422 |
| Hypertensive disorders of pregnancy | 3 (2.7) | 9 (4.5) | 0.60 (0.16-2.27) | 0.550 | 0.45 (0.10-1.94) | 0.282 |
| Birth weight ≥4500 g | 7 (6.4) | 9 (4.5) | 1.46 (0.53-4.03) | 0.465 | 1.04 (0.33-3.24) | 0.951 |
| | **Infants with composite adverse neonatal outcomes (n=92)** | **Infants without composite adverse neonatal outcomes (n=220)** | | | | |
| Antenatal detection of macrosomia | 16 (17.4) | 70 (31.8) | 0.45 (0.25-0.83) | 0.009 | 0.32 (0.16-0.64) | 0.001 |
| Advanced maternal age | 31 (33.7) | 66 (30.0) | 1.19 (0.71-1.99) | 0.520 | 1.29 (0.71-2.34) | 0.411 |
| Nulliparity | 44 (47.8) | 74 (33.6) | 1.81 (1.10-2.97) | 0.018 | 2.10 (1.22-3.63) | 0.008 |
| Pregestational/gestational diabetes | 26 (28.3) | 45 (20.5) | 1.53 (0.88-2.68) | 0.134 | 1.64 (0.87-3.08) | 0.126 |
| Hypertensive disorders of pregnancy | 7 (7.6) | 5 (2.3) | 3.54 (1.09-11.46) | 0.046 | 1.84 (0.52-6.49) | 0.344 |
| Birth weight ≥4500 g | 9 (9.8) | 7 (3.2) | 3.30 (1.19-9.15) | 0.023 | 4.64 (1.51-14.26) | 0.007 |

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

sections. Unnecessary Caesarean deliveries remain a concern, especially given the rising Caesarean section rates worldwide[37]. Caesarean delivery has long-term implications for future pregnancies such as placenta accreta spectrum and uterine scar rupture[38]. Decision making in such situations is challenging; clinicians and women must balance the short- and long-term risks of Caesarean section against potential complications such as shoulder dystocia, which can lead to neonatal asphyxia.

The ACOG and RCOG offer no recommendations for labour induction solely on the basis of LGA or suspected macrosomia[15,16]. The 2021 National Institute for Health and Care Excellence guidelines on inducing labour recommend a comprehensive discussion with women with suspected fetal macrosomia regarding options of expectant management, induction of labour, and Caesarean birth[39]. Although the risks and benefits of inducing labour compared with expectant management in non-diabetic

women remain uncertain, the risks of shoulder dystocia and third- or fourth-degree perineal tears increase with expectant management[39]. In the 2016 Cochrane review of induction of labour for suspected fetal macrosomia involving 1190 women, induction of labour resulted in fewer cases of birth fractures and shoulder dystocia, without a significant difference in the rates of Caesarean or instrumental delivery[40]. Further research is warranted to determine the optimal timing for induction, long-term maternal and neonatal outcomes, and cost-effectiveness.

The ACOG and RCOG guidelines are mostly intended for Western populations, who may exhibit different genetic predispositions and anthropometric characteristics, compared with Asian populations, potentially leading to variations in average birth weight[15,16]. For a given birth weight category, the incidence of shoulder dystocia is higher in Asian populations than in Western populations[18,41]. Among births complicated by shoulder dystocia, the rate is higher in Asian neonates than in Western neonates with a birth weight <4000 g (68% vs 38%)[18,42]. Apart from the EFW threshold, counselling on the mode of delivery should be individualised, considering diverse factors such as a history of shoulder dystocia, previous macrosomic deliveries, maternal height, and diabetes. Women should be informed about the fetal and maternal risks associated with vaginal birth, as well as the potential for error in clinical and ultrasound EFW. Further research concerning predictors for uncomplicated vaginal delivery in macrosomic infants is warranted to enhance prenatal counselling on the mode of delivery, potentially reducing rates of unnecessary Caesarean section.

The present study has some limitations. First, the sample size was small, and data were collected from a single institution. Thus, results may not be generalisable to other populations. Second, due to the retrospective nature of the study, only basic clinical data were collected. Advances in artificial intelligence and ultrasound technology may improve the accuracy of fetal biometric measurements, hence prediction and detection of macrosomia.

## Conclusion

Antenatal detection of macrosomia decreases neonatal complications but increases maternal complications and Caesarean delivery rates. Counselling regarding macrosomia should involve a shared decision-making process based on evidence-based recommendations. Patients should receive comprehensive information about potential risks and benefits to ensure informed consent. The mode of delivery should be individualised, considering diverse factors such as maternal history, fetal size, and potential complications. Future studies should focus on methods to improve the accuracy of macrosomia detection, while identifying predictors for uncomplicated vaginal delivery.

## Contributors

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

## Conflicts of interest

Both authors have no conflicts of interest to disclose.

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## Data availability

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

## Ethics approval

The study was approved by the Central Institutional Review Board of Hospital Authority (reference: CIRB-2023-170-1). Informed consent from patients was waived because of the retrospective nature of study.

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# Prenatal diagnosis of twins with thanatophoric dysplasia type I and Down syndrome: a case report

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We present a case of spontaneous dichorionic diamniotic twins, each affected by thanatophoric dysplasia type I and Down syndrome. Non-invasive prenatal screening revealed an increased level of chromosome 21 DNA. Ultrasound showed that twin A had short long bones and a bowed humerus, whereas twin B appeared phenotypically normal. Amniocentesis of twin A sent for quantitative fluorescent-polymerase chain reaction (QF-PCR), chromosome microarray, and sequence analysis of the fibroblast growth factor receptor 3 gene (*FGFR3*) identified a heterozygous variant in exon 7 of *FGFR3*, suggestive of autosomal dominant thanatophoric dysplasia type I (OMIM 187600). Amniocentesis of twin B sent for QF-PCR revealed trisomy 21, likely caused by meiotic nondisjunction, with normal chromosomes 13 and 18; karyotyping showed 47,XY,+21, suggestive of Down syndrome. At 22 weeks and 2 days of gestation, termination of pregnancy for both twins was performed.

*Keywords: Down syndrome; Prenatal diagnosis; Thanatophoric dysplasia*

## Case presentation

In December 2024, a 41-year-old Chinese woman with a natural pregnancy presented for prenatal diagnosis after a positive non-invasive prenatal screening (NIPS). The couple had no family history of congenital or hereditary abnormalities. The woman had undergone two surgical terminations of unwanted pregnancies and had no live births. At 11 weeks and 6 days of gestation, ultrasound showed dichorionic diamniotic twins. At 12 weeks, NIPS using safeT21express showed a total fetal fraction of 13.8%, with a borderline increase in DNA from chromosome 21, suggestive of trisomy 21. The possibility of one affected fetus or fetal mosaicism could not be excluded. Invasive diagnostic testing by amniocentesis for karyotyping was recommended to confirm the findings.

At 18 weeks and 2 days of gestation, ultrasound showed two viable fetuses with estimated fetal weights appropriate for gestational age. Twin A had short long bones, a bowed humerus, and macrocephaly (Figure 1). The femur length measured 2.38 cm (16th centile), and the humerus length measured 1.56 cm (below the 1st centile). The biparietal diameter was 4.76 cm and the head circumference was 16.87 cm (both above the 99th centile[1]). Twin B had normal parameters: the biparietal diameter was 4.26 cm (74th centile), the femur length was 2.35 cm (14th centile), the abdominal circumference was 13.01 cm (57th centile), and the head circumference was 15.59 cm (82nd centile). The estimated fetal weight was 215.9 g, which was appropriate for gestational age. A uterine fibroid was also noted.

At 19 weeks and 2 days of gestation, a morphology scan showed that twin A had short and bowed long bones, with all parameters below the 1st centile. The thoracic circumference measured 10.94 cm (7th centile). The femur length-to-abdominal circumference ratio was low at 0.143 (2.01/14.15), consistent with severe skeletal dysplasia. In twin B, the long bones appeared normal. No abnormal morphology was identified; however, the face and heart were not well visualised due to fetal position. Amniocentesis of both twins was performed without complications.

At 21 weeks of gestation, ultrasound showed that twin A had short and bowed long bones. The femur length measured 1.83 cm, and the humerus length measured 1.71 cm (both below the 1st centile). The thoracic circumference was 12.19 cm (5th centile). In twin B, the humerus measured 2.94 cm (2nd centile) and the femur length measured 3.0 cm (5th centile). The face and heart were re-examined and appeared normal.

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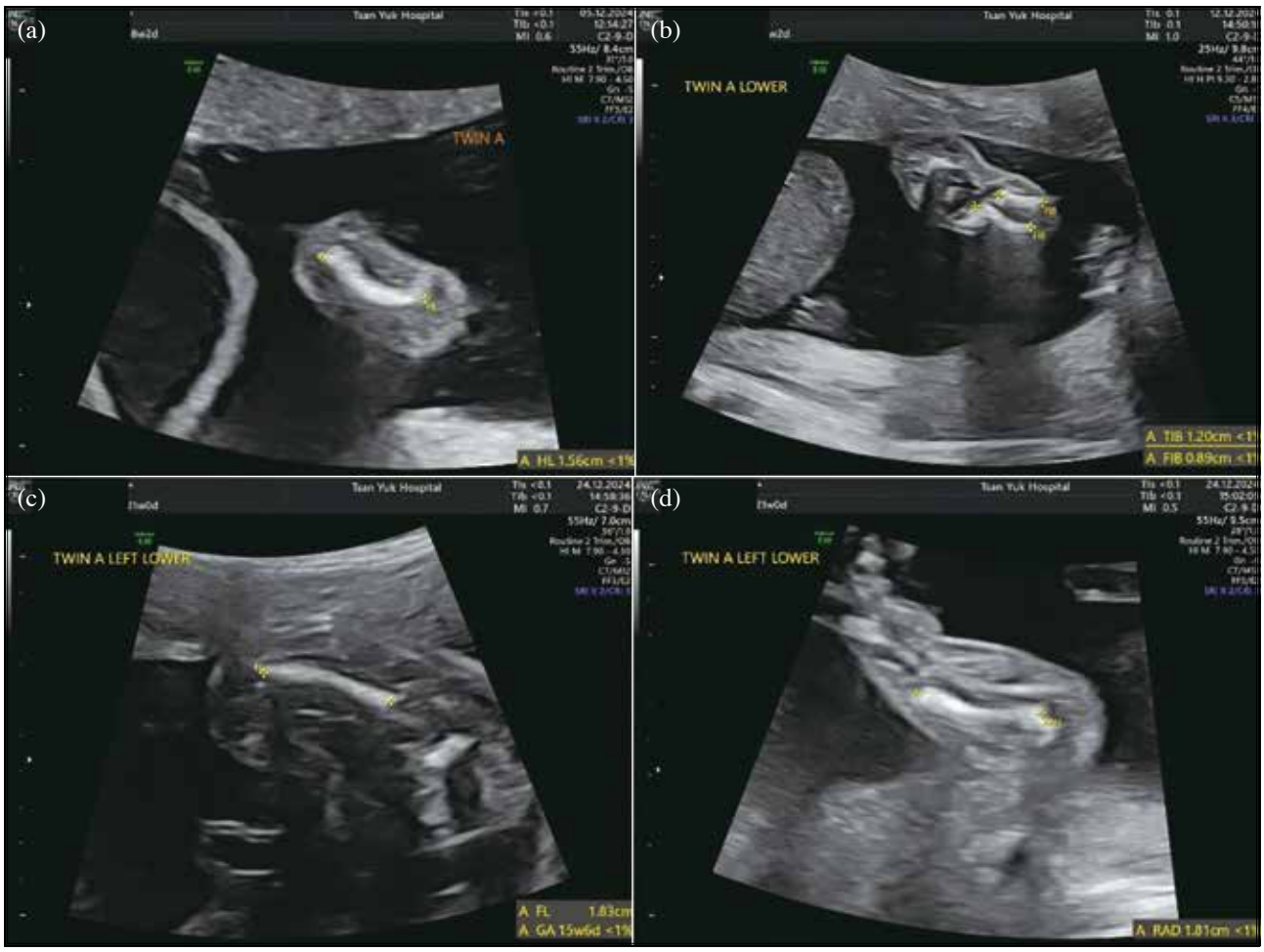


***Figure 1. Ultrasonography of twin A showing (a) the humerus at 18 weeks and 2 days, (b) the tibia and fibula at 19 weeks and 2 days, (c) the femur at 21 weeks, and (d) the radius at 21 weeks.***

Amniocentesis of twin A was sent for quantitative fluorescent-polymerase chain reaction (QF-PCR), chromosome microarray, and sequence analysis of the fibroblast growth factor receptor 3 gene (*FGFR3*). A heterozygous NM_000142.4:c.742C>T p.(Arg248Cys) variant in exon 7 of *FGFR3* was detected, suggestive of thanatophoric dysplasia (TD) type I (OMIM: 187600). The variant was considered pathogenic according to the American College of Medical Genetics and Genomics guidelines. The genetic findings were consistent with the phenotypic features of TD type I, an autosomal dominant disorder. Amniocentesis of twin B was sent for QF-PCR and revealed trisomy 21, likely caused by meiotic nondisjunction, with normal chromosomes 13 and 18. Karyotyping showed 47,XY,+21, suggestive of Down syndrome. The recurrence risk was low but would increase with maternal age.

Options of continuing the pregnancy or terminating the pregnancy for twin A or both twins were discussed. At 22 weeks and 2 days of gestation, the woman underwent termination of pregnancy for both twins.

Gross examination of twin A showed short and bowed limbs and a narrow thorax (Figure 2). A babygram showed markedly shortened, deformed, and bowed upper and lower limbs. The thoracic cage was narrow, and all vertebrae were markedly shortened. The skull was relatively large with frontal bossing. The overall findings were consistent with TD type I. Gross examination of twin B was unremarkable. A babygram showed that both upper and lower limbs were slightly short, without deformity or bowing. Vertebral pedicles were intact, and skull size was normal.

## Discussion

TD is the most common lethal skeletal dysplasia[2]. Babies with TD usually die during the early neonatal period due to pulmonary hypoplasia leading to respiratory distress, although some survive into childhood[3]. Features of TD include marked rhizomelic limb shortening with skin redundancy, a narrow thorax with short ribs but normal trunk

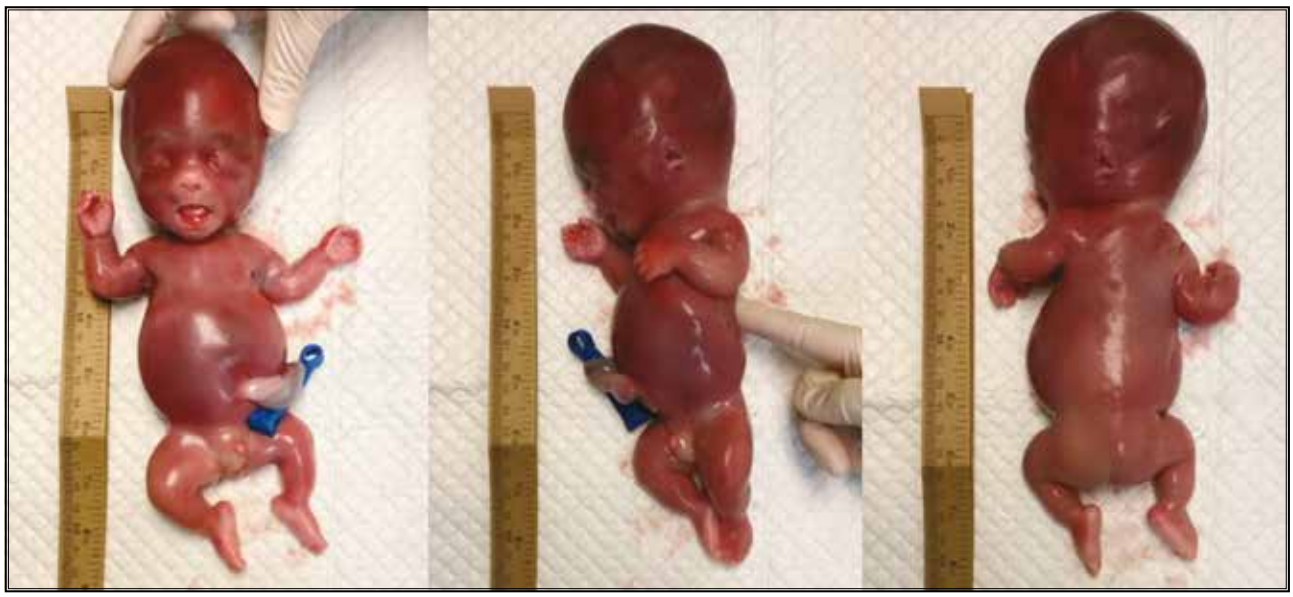

*Figure 2. Gross examination of twin A showing short and bowed limbs and a narrow thorax.*

length, flattened vertebral bodies, and macrocephaly with frontal bossing[4]. There are two major forms of TD, both caused by mutations in *FGFR3*. TD type I is characterised by curved femurs and variable craniosynostosis; the responsible mutations include p.Arg248Cys (55%), p.Tyr373Cys (24%), p.Ser249Cys (6%), and stop codon mutations (10%). TD type II is characterised by straight femurs and severe craniosynostosis, known as cloverleaf skull, and is associated with the p.Lys650Glu mutation[5].

Two-dimensional ultrasound is the primary imaging modality for prenatal diagnosis of TD type I[6]. Three-dimensional ultrasound can enhance visualisation of fetal structural abnormalities[7]. The most distinctive features of TD type I include shortening of the long bones (below the 5th centile), a narrow chest cavity with short ribs, bowed femurs, and platyspondyly[4]. Prenatal diagnosis of TD type I is based on ultrasound assessment and identification of a pathogenic or likely pathogenic variant in *FGFR3*, which should be confirmed by sequence analysis. If the phenotype is indistinguishable from other skeletal dysplasias, a multigene panel that includes *FGFR3* and other genes of interest can be used to identify the underlying genetic cause[8].

Our patient was initially referred for abnormal NIPS owing to increased chromosome 21. NIPS for trisomies 21, 13, and 18 has equivalent screening sensitivity and specificity in both twin and singleton pregnancies[9]. The American College of Medical Genetics and Genomics recommends NIPS over conventional trisomy screening in twin pregnancies[10]. Although NIPS is accurate in the detection of trisomies 21, 18, and 13, as well as sex chromosome aneuploidies, its performance in identifying rare autosomal trisomies and copy number variants is variable[9].

Next-generation sequencing panels to detect *FGFR3* mutations are available for pregnancies at risk of *FGFR3*-related skeletal dysplasia. Cases of NIPS for lethal skeletal dysplasia by targeted capture sequencing of maternal plasma have been reported[11]. Next-generation sequencing is accurate for detecting *de novo* and paternally inherited mutations in *FGFR3*-related skeletal dysplasia[12]. NIPS for *FGFR3*-related skeletal dysplasia is available in the United Kingdom for women carrying fetuses with suspected *FGFR3*-related skeletal dysplasia, for pregnancies at risk due to paternal *FGFR3*-related skeletal dysplasia, and for those with a previous pregnancy confirmed with *FGFR3*-related skeletal dysplasia. It can be performed after 8 weeks of gestation. It uses a next-generation sequencing panel and detects pathogenic variants of the *FGFR3* gene[13]. Given accurate sonographic phenotyping, the diagnostic yield of NIPS in fetuses with suspected *FGFR3*-related skeletal dysplasia can be maximised[14]. Although NIPS demonstrates high sensitivity and specificity for detecting *FGFR3* mutations, it is primarily used as a screening tool rather than a definitive diagnostic test[12]. A positive NIPS result typically warrants confirmation through invasive testing (amniocentesis or chorionic villus sampling)[15,16]. In patients exhibiting ultrasound abnormalities consistent with TD type I, the role of NIPS may be limited. The

primary diagnostic approach remains targeted ultrasound evaluation combined with invasive testing for molecular confirmation.

## Conclusion

This case report highlights the rarity of discordant genetic abnormalities in dichorionic diamniotic twins and the role of prenatal diagnosis in identifying genetic conditions. The combination of ultrasound findings and genetic testing facilitates decision making.

## Contributors

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

## Conflicts of interest

As an editor of the journal, PWH was not involved in the peer review process. Other authors have no conflict of interest to disclose.

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## Data availability

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

## Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki.

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# Extended follow-up of a single standardised dose of intravenous iron therapy for severe iron-deficiency anaemia in women with heavy menstrual bleeding: a single-centre retrospective study

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***Objective:*** To investigate the extended outcomes of a single standardised dose of intravenous (IV) iron therapy for severe iron-deficiency anaemia in women with heavy menstrual bleeding (HMB).
***Methods:*** Medical records were retrospectively reviewed in women with severe iron-deficiency anaemia (defined as a haemoglobin [Hb] level of 6-8 g/dL) secondary to HMB who received a single dose of 500 mg IV iron isomaltoside, followed by daily oral iron supplement for 10 weeks between January 2020 and June 2021 at Kwong Wah Hospital. Outcome measures included changes in Hb levels at different time points within 1 year and any hypersensitivity event.
***Results:*** In total, 155 women aged 21 to 55 years with a diagnosis of HMB without an identifiable structural cause (n=48), leiomyoma (n=75), adenomyosis (n=31), or endometrial hyperplasia (n=1) were included in the analysis. They received 159 infusions during the study period. The median Hb level was 7.1 g/dL before treatment and increased to 10.9 g/dL at 3 months and 10.7 g/dL at 6 months (p<0.001 for both). At the 1-year follow-up, the median Hb level was 9.8 g/dL among 25 patients (p<0.001) and 11 g/dL among 19 patients who complied with the treatment (p=0.001). Only 15 women had a recurrence of severe anaemia within 1 year. Moreover, 16 women experienced mild (n=13) or moderate (n=3) hypersensitivity to IV iron therapy, which presented as an urticarial rash and shortness of breath, respectively.
***Conclusion:*** IV iron therapy is an integral component of patient blood management among women with iron-deficiency anaemia secondary to HMB, effectively preventing recurrence of severe anaemia and maintaining Hb levels for up to 1 year. This provides a window for clinicians to investigate the underlying gynaecological conditions and to optimise definitive treatment.

*Keywords: Anemia, iron-deficiency; Iron isomaltoside 1000; Menorrhagia*

## Introduction

According to the World Health Organization in 2021, 29.9% of non-pregnant women aged 15 to 49 years have anaemia[1]. In Hong Kong, the prevalence of iron-deficiency anaemia is 10.6% among women of reproductive age (15 to 49 years)[2]. Iron-deficiency anaemia is common among gynaecology patients[3], especially those with heavy menstrual bleeding (HMB). Blood transfusion is a treatment option for severe anaemia in women with HMB. However, the supply, cost, and adverse events of blood transfusion raise an interest in alternative treatments[4]. Patient blood management is a patient-centred, multidisciplinary approach to optimise red cell mass and minimise blood loss. Intravenous (IV) iron therapy is an effective and safe treatment for severe iron-deficiency anaemia[5,6], including HMB[7-10]. IV iron increases haemoglobin (Hb) levels more quickly than oral iron supplementation[11]. Short-term effects of IV iron therapy in women with severe anaemia secondary to HMB have been well demonstrated[7-10]. This study aimed to investigate the extended outcomes of a single standardised dose of IV iron therapy for severe iron-deficiency anaemia in women with HMB.

## Methods

Medical records were retrospectively reviewed in women with severe iron-deficiency anaemia (defined as an Hb level of <8 g/dL and a ferritin level of <67 pmol/L) secondary to HMB who received a single dose of 500 mg IV iron isomaltoside (regardless of body weight), followed by ferrous sulphate 300 mg (or ferric hydroxide polymaltose complex 100 mg if ferrous sulphate was not tolerated) daily for 10 weeks between January 2020 and June 2021 at Kwong Wah Hospital. Women re-admitted for further infusions were recorded as separate sets of data. Patients were excluded if they were aged <18 years, had

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received a blood transfusion during the same admission, had other concomitant causes for iron-deficiency anaemia, did not complete the full dose of IV iron infusion, or had no post-treatment Hb level recorded.

The treatment protocol was based on a previous study in our unit, which demonstrated short-term effectiveness in women with HMB[7]. Patient compliance to treatment was assessed. Treatment plan was discussed with each patient before treatment. Patients were followed up at 3 and 6 months[12]; subsequent follow-ups were arranged on an individual basis. Outcome measures included changes in Hb levels at different time points within 1 year or until patients became hysterectomised or menopausal, along with any hypersensitivity events. Hypersensitivity reactions were classified into mild, moderate, and severe, according to the Hospital Authority protocol on iron therapy[13,14]. Mild reactions were defined as infusion reactions including itchiness, flushing, urticaria, slight chest tightness, hypertension, and back or joint pains. Moderate reactions were defined as transient cough, nausea, shortness of breath, tachycardia, and hypotension. Severe reactions were defined as anaphylactic reactions including sudden onset and rapid aggravation of symptoms with wheezing or stridor, periorbital oedema, cyanosis, loss of consciousness, and cardiac or respiratory arrest.

Statistical analysis was conducted using SPSS (Windows version 28.0; IBM Corp, Armonk [NY], US). Wilcoxon signed-rank test was used to compare the Hb levels at different time intervals. A p value of <0.05 was considered statistically significant.

## Results

Of 207 women with severe iron-deficiency anaemia who received a single standardised IV iron therapy, 52 were excluded owing to blood transfusion during the same admission (n=47) or incomplete IV iron infusion (n=5), whereas two women received three separate infusions during the study period and were counted as six separate sets of data. In total, 155 women (88 Chinese and 67 non-Chinese) aged 21 to 55 (median, 47) years, weighing 40 to 125 (median, 59) kg, with a diagnosis of HMB without an identifiable structural cause (n=48), leiomyoma (n=75), adenomyosis (n=31), or endometrial hyperplasia (n=1) were included in the analysis. They received 159 infusions during the study period, and 123 women were found to comply with treatment.

The median Hb level was 7.1 g/dL before treatment and increased to 10.9 g/dL at 3 months and 10.7 g/dL at 6 months (p<0.001 for both, Table 1). At the 1-year follow-up, the median Hb level was 9.8 g/dL among 25 women (p<0.001) and 11 g/dL among 19 women who complied with the treatment (p=0.001).

Change of treatment plans was discussed in 136 women. Of the treatment plans for 155 women, 19 were changed to an increased dosage of tranexamic acid, 51 to hormonal treatment, and 26 to surgical treatment (Table 2).

Of the 15 women who had recurrence of severe anaemia and required additional IV iron therapy or blood transfusion, three did not comply with treatment despite counselling, three declined definitive surgical treatment,

**Table 1. Increase in haemoglobin (Hb) levels at various time points after intravenous iron therapy.**

| Time | Hb level, g/dL* | Increase in Hb level, g/dL* | p Value |
|---|---|---|---|
| All patients | | | |
| Pre-treatment (n=159) | 7.1 (6.7-7.6) | - | - |
| Post-treatment <1 month (n=6) | 10.8 (10.4-11.9) | 3.4 (2.7-5.3) | 0.028 |
| Post-treatment 3 months (n=90) | 10.9 (9.5-12.4) | 3.7 (2.6-5.3) | <0.001 |
| Post-treatment 6 months (n=119) | 10.7 (8.8-12.3) | 3.7 (1.6-5.3) | <0.001 |
| Post-treatment 9 months (n=46) | 11.0 (9.0-12.5) | 3.8 (1.75-5.1) | <0.001 |
| Post-treatment 12 months (n=25) | 9.8 (8.7-12.4) | 2.7 (1.5-4.7) | <0.001 |
| Patients complied to treatment | | | |
| Pre-treatment (n=123) | 7.1 (6.7-7.5) | - | - |
| Post-treatment <1 month (n=5) | 10.8 (10.4-12.1) | 3.7 (2.6-5.4) | 0.043 |
| Post-treatment 3 months (n=70) | 10.9 (9.5-12.4) | 4.1 (2.6-5.5) | <0.001 |
| Post-treatment 6 months (n=90) | 11.0 (9.0-12.3) | 3.9 (1.7-5.4) | <0.001 |
| Post-treatment 9 months (n=36) | 10.8 (8.3-11.8) | 3.8 (1.5-5.0) | <0.001 |
| Post-treatment 12 months (n=19) | 11.0 (8.8-12.5) | 3.5 (1.6-4.9) | 0.001 |

* Data are presented as median (interquartile range)

**Table 2. Change of treatment plan after intravenous iron therapy***

| Treatment | Heavy menstrual bleeding without identifiable structural cause (n=48) | Leiomyoma (n=75) | Adenomyosis (n=31) | Endometrial hyperplasia (n=1) | Total (n=155) |
|---|---|---|---|---|---|
| Non-hormonal treatment | 48 (100) | 75 (100) | 31 (100) | 0 | 154 (99.4) |
| Hormones | 12 (25.0) | 20 (26.7) | 5 (16.1) | 1 (100) | 38 (24.5) |
| Long-acting hormones | 2 (4.2) | 5 (6.7) | 6 (19.4) | 0 | 13 (8.4) |
| Uterine artery embolisation | 0 | 0 | 0 | 0 | 0 |
| Surgical treatment | 0 | 23 (30.7) | 3 (9.7) | 0 | 26 (16.8) |

* Data are presented as No. (%) of patients. Patients can have more than one treatment modality

four relapsed while waiting for surgical management, and five failed the initial treatment and required further treatment. Two women received three separate doses of IV iron therapy within 1 year; they had large leiomyomas and refused either hormonal or surgical treatment.

Moreover, 16 women experienced mild (n=13) or moderate (n=3) hypersensitivity to IV iron therapy, which presented as an urticarial rash and shortness of breath, respectively, during (n=7) or after (n=9) infusion. Additionally, five women had hypersensitivity reactions and stopped IV iron therapy. The rate of hypersensitivity was 13% if these five women were included.

## Discussion

Of the 155 women with severe iron-deficiency anaemia secondary to HMB who received a single standardised dose of IV iron therapy followed by oral iron supplement, only 15 had a recurrence of severe anaemia within 1 year. The low recurrence rate is an unexpected finding. Although only 29% and 16% of patients were followed up for Hb levels at 9 and 12 months, respectively, their Hb levels could still be maintained at approximately 10 g/dL. This could be attributed not only to the IV iron therapy but also to a review of their treatment plan and their compliance with treatment, both of which help reduce the recurrence rate of severe anaemia after IV iron therapy. Early arrangement for surgical treatment of the underlying causes of HMB for suitable patients is of paramount importance to prevent recurrence of severe anaemia. It is recommended that the waiting time for operations in the public sector be shortened and prescription of a gonadotrophin-releasing hormone analogue be given to induce amenorrhoea and raise Hb levels before surgery[15]. However, owing to limited resources and constraints on arranging timely surgical slots in public settings, further IV iron therapy for recurrence can buy time before surgical treatment and reduce the more costly blood transfusions.

Patients received oral iron supplementation for 10 weeks immediately after IV iron therapy. There is concern about whether oral iron should be given immediately after IV iron therapy, because of the possible increase in the hepcidin level secondary to high iron load, which can affect oral iron absorption[16-18]. However, such an increase is transient. In patients requiring long-term maintenance secondary to cyclical bleeding, oral iron supplement given immediately after IV iron therapy may help maintain the Hb level among women with HMB.

In our study, no severe hypersensitivity reactions were reported and the rate of hypersensitivity reactions was 13%, which is similar to the 22.7% reported in a US multicentre study in 2016[5,8] and the 8.7% in a UK single-centre study in 2019[19]. Most cases involved mild reactions. This demonstrates that IV iron therapy with iron isomaltoside is safe for women with severe anaemia.

Our study had several limitations. The number of patients with Hb levels measured beyond 6 months was small, because regular blood taking for Hb levels was not included in the departmental protocol for management of HMB. Only 29% and 16% of patients had blood taken at 9 and 12 months, respectively. The patient cohort was heterogeneous, with various underlying causes of HMB. Our findings were confounded by patients' compliance with treatment, dietary modification, and treatment efficacy. Prospective studies on a larger scale and using standardised blood-taking schedules are warranted.

## Conclusion

IV iron therapy is an integral component of patient blood management among women with iron-deficiency

anaemia secondary to HMB, effectively preventing recurrence of severe anaemia and maintaining Hb levels for up to 1 year. This provides a window for clinicians to investigate the underlying gynaecological conditions and to optimise definitive treatment.

## Contributors

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

## Conflicts of interest

All authors have no conflicts of interest to disclose.

## Funding/support

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

## Data availability

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

## Ethics approval

The present study was approved by the Hong Kong Hospital Authority Kowloon Central / Kowloon East Cluster Research Ethics Committee (reference: KC/KE-23-0086/ER-3). All patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided informed consent for all treatments and procedures.

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# Predictors for adverse outcomes and recurrence of pyometra: a 10-year retrospective study

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***Objective:*** To identify predictors for adverse outcomes and recurrence in patients with pyometra.
***Methods:*** Medical records of patients with a diagnosis of pyometra admitted to Tuen Mun Hospital between 1 January 2014 and 31 December 2023 were retrospectively reviewed. Patients' clinical characteristics, laboratory findings, management options, and clinical outcomes (including treatment- and disease-related complications and recurrence) were collected. Patients with or without composite adverse outcomes were compared, as were patients with or without recurrence. Multivariate logistic regression was used to determine independent predictors for composite adverse outcomes and recurrence.
***Results:*** In total, 152 patients (median age, 79 years) were included in the analysis; the incidence of pyometra was 0.003%. Composite adverse outcome was more likely to occur in those with diabetes mellitus (adjusted odds ratio [aOR]=6.76, p=0.001) or congestive heart failure or a history of acute myocardial infarction (aOR=4.40, p=0.028), those with the longest diameter of the intrauterine pus collection (aOR=1.26, p=0.009), and those with extended-spectrum β-lactamase–positive bacteria (aOR=6.07, p=0.013), whereas composite adverse outcome was less likely to occur in those with vaginal bleeding (aOR=0.14, p=0.002). Of the patients, 24.0% had recurrence. The risk of recurrence increased with the presence of enterococci (aOR=3.31, p=0.022) and those with the longest diameter of the intrauterine pus collection (aOR=1.16, p=0.033).
***Conclusion:*** Pyometra is rare and often associated with malignancy and severe complications. Patients at risk of developing adverse outcomes include those with diabetes mellitus, congestive heart failure or a history of acute myocardial infarction, large pus collection, and infection with extended-spectrum β-lactamase–producing organisms. Patients at risk of recurrence include those with a large pus collection or the presence of enterococci. At-risk patients should be monitored vigilantly. Early diagnosis and intervention are crucial to improving clinical outcomes.

*Keywords: Bacteria; Pyometra; Recurrence*

## Introduction

Pyometra is the accumulation of pus in the uterine cavity caused by interference with its natural drainage[1,2]. The obstruction in the cervical canal can stem from a malignant or benign tumour, surgery, radiotherapy, or senile cervicitis[3]. Its incidence ranges from 0.01% to 0.5%[1,4,5]; it mainly occurs in postmenopausal women, with an incidence of 13.6%[5]. Pyometra has a possible association with malignancy; untreated cases may result in spontaneous uterine rupture, bacteraemia, pelvic abscess formation, generalised peritonitis, and septic shock[6-9].

Studies of pyometra primarily consist of case series and case reports. This study aimed to identify predictors for adverse outcomes and recurrence of pyometra and evaluate the microbial profile and antibiotic resistance of patients.

## Methods

Medical records of patients with a diagnosis of pyometra admitted to Tuen Mun Hospital between 1 January 2014 and 31 December 2023 were retrospectively reviewed. Pyometra was defined as a uterine pus collection confirmed by both pelvic ultrasound and drainage of purulent discharge from the cervix. Patients with haematometra or hydrometra were excluded.

Patients' clinical characteristics, laboratory findings, management options, and clinical outcomes (including treatment- and disease-related complications and recurrence) were collected. The composite adverse outcome was defined as the presence of any of the disease-related complications (uterine rupture, sepsis, septic shock, intensive care unit admission, organ derangement, disseminated intravascular coagulopathy, emergency hysterectomy for pyometra, all-cause mortality at 28 days,

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and prolonged hospitalisation of ≥21 days). Treatment-related complications entailed drainage-related perforation and failure to drain. Recurrence was defined as any readmission for pyometra within 1 year. Sepsis was defined as an infection leading to organ dysfunction, as reflected by a SOFA (sequential organ failure assessment) score of ≥2[10]. Septic shock was defined as a requirement for vasopressors to maintain a mean arterial pressure of ≥65 mmHg and a serum lactate level of >2 mmol/L (>18 mg/dL), despite adequate fluid resuscitation[11]. Sepsis-induced coagulopathy was defined as a SOFA score of ≥4, based on platelet count and prothrombin time[12].

Patients with or without composite adverse outcomes were compared using the Student's *t* test or Mann-Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. Similarly, patients with or without recurrence were compared. Variables with a p value of <0.05 in the univariate analysis were included in the multivariate logistic regression to determine independent predictors for composite adverse outcomes and recurrence. Statistical analyses were performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). A p value of <0.05 was considered statistically significant.

## Results

In total, 152 patients (median age, 79 years) were included in the analysis (Table 1). There were 43 959 gynaecological admissions during the study period, giving an incidence of 0.003%. Among the patients, 59.9% had impaired ambulation, 48.0% used incontinence pads regularly, and most had medical comorbidities.

Of 152 cultures, 55.9% grew ≥2 microorganisms (Table 2); 16.4% were extended-spectrum β-lactamase (ESBL)–producing bacteria, of which 96% were *Escherichia coli* and 4.0% were *Klebsiella* spp. Their isolate detection rates were 33.8% and 6.7%, respectively. Both ESBL-positive and -negative *E coli* strains had similar resistance rates to amoxicillin/clavulanic acid (co-amoxiclav) [7.1% and 6.4%, respectively, Table 3]. One ESBL-positive *E coli* isolate was resistant to second- and third-generation cephalosporins. Compared with ESBL-negative *E coli* isolates, ESBL-positive *E coli* isolates displayed higher antibiotic resistance against levofloxacin (56.5% vs 46.8%) and trimethoprim-sulfamethoxazole (41.7% vs 27.7%) and lower antibiotic resistance against gentamicin (16.7% vs 36.2%). ESBL-negative *Klebsiella* spp had a <20% resistance rate to most antibiotics, except for trimethoprim-sulfamethoxazole, whereas one ESBL-

**Table 1. Clinical characteristics of patients with pyometra (n=152).**

| Characteristic | Value* |
|---|---|
| Age, y | 79 (69-89) |
| Ethnicity | |
| Chinese | 151 (99.3) |
| Pakistani | 1 (0.7) |
| Menopause | 148 (97.4) |
| Impaired ambulation | 91 (59.9) |
| Incontinence pad use | 73 (48.0) |
| Living in nursing home | 63 (41.4) |
| Comorbidity | |
| Hypertension | 98 (64.5) |
| Stroke | 61 (40.1) |
| Diabetes mellitus | 56 (36.8) |
| Dementia | 44 (28.9) |
| Congestive heart failure / history of acute myocardial infarction | 29 (19.1) |
| Chronic kidney disease | 21 (13.8) |
| Osteoarthritis | 10 (6.6) |
| Long-term medication | |
| Steroid | 9 (5.9) |
| Other immunosuppressants | 4 (2.6) |
| Previous pyometra | 10 (6.6) |
| Intrauterine contraceptive device | 6 (3.9) |
| Endometrial polyp | 1 (0.7) |
| Submucosal fibroid | 18 (11.8) |
| Neighbouring infections: pyosalpinx or tubo-ovarian abscess | 6 (3.9) |
| Enteric or rectal fistula | 3 (2.0) |
| Malignancy | 37 (24.3) |
| Corpus | 12 (7.9) |
| Cervix | 21 (13.8) |
| Vagina | 1 (0.7) |
| Double primary (ovary and corpus) | 1 (0.7) |
| Colorectal | 2 (1.3) |
| Instrumentation (hysteroscopy, dilatation, or curettage of uterus) within 1 year | 3 (2.0) |
| History of loop electrosurgical excision procedure | 3 (2.0) |
| History of pelvic radiotherapy | 8 (5.3) |
| Any of the above | 61 (40.1) |
| Clinical presentation | |
| Asymptomatic | 9 (5.9) |
| Vaginal discharge | 58 (38.2) |
| Abdominal pain | 25 (16.4) |
| Fever | 25 (16.4) |
| Maximum temperature, ˚C (in 25 women with fever) | 38.3 (38-39) |
| Vaginal bleeding | 97 (63.8) |
| Duration, d (in 117 symptomatic women) | 10 (3-60) |
| Uterine size, wk | 6 (6-8) |

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

**Table 2. Laboratory findings of patients with pyometra (n=152).**

| Laboratory finding | Value* |
|---|---|
| Pyometra size on pelvic ultrasound | |
| Longest diameter, cm | 2.8 (2.1-4.6) |
| Shortest diameter, cm | 1.2 (1.0-2.3) |
| Laboratory parameters | |
| White cell count, $\times 10^9$/L (n=129) | 8.1 (6.5-12.3) |
| Platelet, $\times 10^9$/L (n=129) | 245 (187-323) |
| Urea, mmol/L (n=124) | 5.2 (3.9-7.3) |
| Creatinine, μmol/L (n=124) | 66 (57-83.8) |
| Alanine transaminase, U/L (n=119) | 12 (8-16) |
| Alkaline phosphatase, U/L (n=119) | 82 (70-101) |
| Bilirubin, μmol/L (n=119) | 8 (6-10) |
| Albumin, g/L (n=119) | 34 (31-38) |
| International normalised ratio (n=99) | 1.1 (1.0-1.2) |
| Prothrombin time, s (n=99) | 12.6 (11.8-13.7) |
| Activated partial thromboplastin time, s (n=99) | 25.5 (24.1-27.9) |
| C-reactive protein, mg/L (n=75) | 33 (3.7-107) |
| Positive culture | |
| Genital tract swab | 124 (81.6) |
| Blood | 4 (2.6) |
| Genital tract microorganisms | |
| Gram-positive bacteria | |
| Streptococci | 35 (23.0) |
| Enterococci | 19 (12.5) |
| Peptostreptococci | 14 (9.2) |
| *Peptoniphilus* spp | 14 (9.2) |
| *Actinomyces* spp | 12 (7.9) |
| Staphylococci | 8 (5.3) |
| Gram-negative bacteria | |
| *Escherichia coli* | 71 (46.7) |
| *Bacteroides* spp | 25 (16.4) |
| *Klebsiella pneumoniae* | 15 (9.9) |
| Extended-spectrum β-lactamase positive | 25 (16.4) |
| Fungus | |
| *Candida* spp | 18 (11.8) |
| Others† | 63 (41.4) |
| Polymicrobial (≥2 microorganisms) | 85 (55.9) |

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

† Diphtheroids (3.9%), *Proteus mirabilis* (3.9%), *Prevotella* spp (3.9%), *Lactobacillus* spp (3.9%), *Clostridium* spp (3.3%), *Fusobacterium* spp (2.6%), *Actinobaculum* spp (2.6%), *Morganella morganii* (2.0%), *Citrobacter* spp (2.0%), *Porphyromonas* spp (2.0%), methicillin-resistant *Staphylococcus aureus* (1.3%), *Gardnerella vaginalis* (1.3%), *Haemophilus parainfluenzae* (1.3%), *Dialister micraerophilus* (1.3%), *Pseudomonas aeruginosa* (0.7%), *Bifidobacterium* spp (0.7%), *Parvimonas micra* (0.7%), *Trueperella bernardiae* (0.7%), *Providencia stuartii* (0.7%), anaerococci (0.7%), *Burkholderia cepacia* complex (0.7%), group A streptococci (0.7%), and commensals (0.7%)

positive *Klebsiella* isolate was sensitive to gentamicin, levofloxacin, and trimethoprim-sulfamethoxazole. No streptococcal isolates displayed antibiotic resistance against penicillin. For enterococci, 22.2% showed resistance to ampicillin and none to vancomycin. The most frequently used antibiotic regimen was co-amoxiclav and levofloxacin (57.2%), followed by co-amoxiclav and metronidazole (24.3%), levofloxacin and metronidazole (13.8%), and cefuroxime and metronidazole (12.5%). The median duration of antibiotic use was 14 days; 25% of patients required change of antibiotics upon availability of culture results (Table 4).

With regard to clinical management, 88.8% of patients were treated with endometrial aspiration, followed by antibiotics alone (5.9%), Foley drainage (2.6%), emergency hysterectomy (2.0%), and laparotomy with drainage (0.7%) [Table 4]. For the three patients with emergency hysterectomy, the first one underwent staging laparotomy and hysterectomy for an infected uterine tumour, pyometra, and pyosalpinx; the histopathological outcome was carcinosarcoma. The second patient presented with septic shock and underwent staging laparotomy and hysterectomy for an infected ovarian tumour and pyometra; the histopathological outcome was endometrioid adenocarcinoma involving the endometrium and ovary. The third patient had uterine rupture and septic shock secondary to pyometra and pyosalpinx. In the patient who underwent laparotomy with drainage, she presented with urosepsis and septic shock secondary to pyometra, uterine rupture, and tubo-ovarian abscess. There were seven (4.6%) treatment-related complications including drainage-related uterine perforation (n=2) and drainage failure (n=5).

A total of 33 (21.7%) patients had disease-related complications, particularly organ derangement (n=24), sepsis (n=15), and prolonged hospitalisation (n=13) [Table 4]. The rate of all-cause mortality at 28 days was 2.0% (n=3); all three patients had multiple comorbidities before admission. One patient was admitted for drug-related acute kidney injury. Imaging examination incidentally revealed pyometra, and drainage was performed. The patient had cardiac arrest and died despite resuscitation. The remaining two patients died of sepsis resulting from pyometra and other coexisting infections (urinary tract infection, pneumonia, and right-leg infective collection).

Composite adverse outcome was more likely to occur in those with diabetes mellitus (adjusted odds ratio [aOR]=6.76, p=0.001) or congestive heart failure / a history of acute myocardial infarction (aOR=4.40, p=0.028), those

**Table 3. Antibiotic resistance of extended-spectrum β-lactamase (ESBL)–positive and –negative bacteria.**

| Antibiotic | Streptococci (n=35) | | Enterococci (n=19) | | ESBL-negative *Escherichia coli* (n=47) | | ESBL-positive *Escherichia coli* (n=24) | | ESBL-negative *Klebsiella Pneumoniae* (n=14) | | ESBL-positive *Klebsiella Pneumoniae* (n=1) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of patients | Drug resistance, % | No. of patients | Drug resistance, % | No. of patients | Drug resistance, % | No. of patients | Drug resistance, % | No. of patients | Drug resistance, % | No. of patients | Drug resistance, % |
| Ampicillin | - | - | 18 | 22.2 | - | - | - | - | - | - | - | - |
| Penicillin | 35 | 0 | 1 | 0 | - | - | - | - | - | - | - | - |
| Amoxicillin/clavulanic acid | - | - | 1 | 0 | 47 | 6.4 | 14 | 7.1 | 14 | 7.1 | - | - |
| Second-generation cephalosporin | - | - | 1 | 100 | 47 | 0 | 1 | 100 | 14 | 7.1 | - | - |
| Third-generation cephalosporin | - | - | - | - | 8 | 0 | 1 | 100 | 4 | 0 | - | - |
| Fourth-generation cephalosporin | - | - | - | - | 2 | 0 | - | - | 1 | 0 | - | - |
| Gentamicin | - | - | 1 | 100 | 47 | 36.2 | 24 | 16.7 | 14 | 7.1 | 1 | 0 |
| Levofloxacin | 2 | 0 | 1 | 0 | 47 | 46.8 | 23 | 56.5 | 14 | 14.3 | 1 | 0 |
| Erythromycin | 32 | 18.8 | 1 | 100 | - | - | - | - | - | - | - | - |
| Clindamycin | 14 | 28.6 | - | - | - | - | - | - | - | - | - | - |
| Ticarcillin/clavulanic acid | - | - | - | - | 47 | 0 | - | - | 14 | 7.1 | - | - |
| Trimethoprim-sulfamethoxazole | 21 | 4.8 | - | - | 47 | 27.7 | 24 | 41.7 | 14 | 21.4 | 1 | 0 |
| Piperacillin/tazobactam | - | - | 1 | 100 | 4 | 0 | - | - | 2 | 0 | - | - |
| Amikacin | - | - | - | - | 4 | 0 | 9 | 0 | 2 | 0 | - | - |
| Ertapenem | - | - | - | - | 1 | 0 | 4 | 25 | - | - | - | - |
| Imipenem | - | - | - | - | 2 | 0 | 5 | 0 | 1 | 0 | - | - |
| Meropenem | - | - | - | - | 2 | 0 | 4 | 0 | 1 | 0 | - | - |
| Vancomycin | - | - | 17 | 0 | 1 | 0 | - | - | - | - | - | - |
| Cefoperazone/sulbactam | - | - | - | - | 2 | 0 | - | - | 1 | 0 | - | |

with the longest diameter of the intrauterine pus collection (aOR=1.26, p=0.009), and those with ESBL-positive bacteria (aOR=6.07, p=0.013), whereas composite adverse outcome was less likely to occur in those with vaginal bleeding (aOR=0.14, p=0.002) [Table 5].

Of the patients, 24.0% had recurrence, and the median time interval from the index admission to recurrence was 1 (interquartile range, 0.6-2.8) month. The risk of recurrence increased with the presence of enterococci (aOR=3.31, p=0.022) and those with the longest diameter of the intrauterine pus collection (aOR=1.16, p=0.033) [Table 6].

## Discussion

Pyometra is a rare condition that mainly affects older women; 74.1% of cases are idiopathic[1]. It probably results from genital atrophy, compounded by poor immunity and suboptimal hygiene[5]. In our study, malignancy was the most common predisposing factor, present in 24.3% of patients. Malignancy may distort intrauterine anatomy and obstruct outflow tract drainage; cervical cancer was the most frequently identified cancer.

In our study, 21.7% of patients had disease-related complications; 3.9% had septic shock, which is lower than the 14.6% reported in a study in South Korea, although it

**Table 4. Management and clinical outcomes of patients with pyometra (n=152).**

| Outcomes | Value* |
|---|---|
| Management | |
| Endometrial drainage | 135 (88.8) |
| Foley drainage | 4 (2.6) |
| Antibiotics alone | 9 (5.9) |
| Hysterectomy | 3 (2.0) |
| Laparotomy and drainage | 1 (0.7) |
| Antibiotic regimen | |
| Co-amoxiclav + metronidazole | 37 (24.3) |
| Levofloxacin + metronidazole | 21 (13.8) |
| Co-amoxiclav + levofloxacin | 87 (57.2) |
| Cefuroxime + metronidazole | 19 (12.5) |
| Ceftriaxone + metronidazole | 9 (5.9) |
| Piperacillin/tazobactam | 15 (9.9) |
| Vancomycin | 6 (3.9) |
| Carbapenem | 16 (10.5) |
| Pre-drainage antibiotics (n=140; excluding those with antibiotics alone and hysterectomy) | 124 (88.6) |
| Duration of antibiotics, d | 14 (14-14) |
| Disease-related complications | |
| Uterine rupture | 2 (1.3) |
| Sepsis | 15 (9.9) |
| Septic shock | 6 (3.9) |
| Intensive care unit admission | 2 (1.3) |
| Organ derangement | 24 (15.8) |
| Disseminated intravascular coagulopathy | 7 (4.6) |
| All-cause mortality at 28 days | 3 (2.0) |
| Emergency hysterectomy | 3 (2.0) |
| Prolonged hospitalisation | 13 (8.6) |
| Treatment-related complications | |
| Drainage-related perforation | 2 (1.3) |
| Failure to drain | 5 (3.3) |
| Recurrence (n=146; excluding those with mortality and hysterectomy) | 35 (24.0) |
| Time interval of recurrence from index admission, m | 1.0 (0.6-2.8) |

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

lacked a clear definition of septic shock[13]. In our study, four patients underwent emergency hysterectomy or laparotomy with drainage secondary to septic shock and/or uterine rupture. Such an association was also reported in the study in South Korea[13]. The morbidity and mortality rates were high when pyometra was complicated with uterine rupture and subsequent peritonitis[14,15]. The poor prognosis was partly attributed to the non-specific clinical presentations, leading to misdiagnosis and delayed management. Therefore, pyometra with uterine rupture should be considered in patients with haemodynamic instability and early intervention is imperative.

Cervical stenosis predisposes patients to recurrence. The incidence of recurrence has been reported to be 22% to 31.4%[4,16]. It was 24.6% in patients treated in a single hospital in South Korea between 2010 and 2021[17]. Similarly, our patients were predominantly treated with endometrial drainage, which yielded a recurrence rate of 24.0%. However, another South Korean study in 2024 reported a recurrence rate of 6.3%[13]. The lower recurrence rate can be attributed to the use of Foley catheter drainage[5,13]. Detection of recurrence can be affected by symptom severity, patient and caregiver awareness, and follow-up availability and duration.

Older women with chronic diseases and restricted mobility had an increased risk of pyometra[18]. Diabetes mellitus predisposes patients to immunosuppression, whereas congestive heart failure and a history of acute myocardial infarction reduce mobility. A Taiwanese study found that infection-related admissions in patients with heart failure were associated with higher mortality, decompensation, myocardial infarction, stroke, and worsened long-term prognosis[19]. Patients presenting with vaginal bleeding were less likely to experience adverse outcomes, because postmenopausal bleeding could prompt early medical attention and timely treatment, preventing complications. The longest diameter of the intrauterine pus collection was a predictor for both adverse outcomes and recurrence. Similarly, the incidence of septic shock increases with the longest diameter of pyometra, albeit not significantly in the multivariate analysis[13]. Pyometra size reflects disease severity, chronicity, and drainage interference; larger collections increase the risk of incomplete drainage and recurrence. We recommend monitoring with interval scans to ensure complete drainage and early detection of recurrence in patients with a large pyometra collection, thus improving outcomes and reducing complications.

Common causative organisms in the pus collection include *E coli*, *Bacteroides* spp, streptococci, peptostreptococci, and *Klebsiella pneumoniae*[5,13,17,18,20]. In a 2015 review in Hong Kong, *E coli*, *Bacteroides fragilis*, streptococci, and peptostreptococci were the most prevalent pathogens[5]. Our department does not routinely

**Table 5. Predictors for adverse outcomes in patients with pyometra.**

| Variable | Without adverse outcomes (n=119)* | With adverse outcomes (n=33)* | Odds ratio (95% confidence interval) | p Value | Adjusted odds ratio (95% confidence interval) | p Value |
|---|---|---|---|---|---|---|
| Age, y | 78 (68-88) | 84 (71-90.5) | - | 0.311 | - | - |
| Menopause | 116 (97.5) | 32 (97.0) | 0.83 (0.08-8.23) | >0.99 | - | - |
| Impaired ambulation | 66 (55.5) | 25 (75.8) | 2.51 (1.05-6.02) | 0.035 | 2.24 (0.62-8.04) | 0.217 |
| Incontinence pad use | 55 (46.2) | 18 (54.5) | 1.40 (0.64-3.03) | 0.397 | - | - |
| Living in nursing home | 47 (39.5) | 16 (48.5) | 1.44 (0.66-3.13) | 0.354 | - | - |
| Comorbidity | | | | | | |
| Hypertension | 75 (63.0) | 23 (69.7) | 1.35 (0.59-3.10) | 0.479 | - | - |
| Stroke | 49 (41.2) | 12 (36.4) | 0.82 (0.37-1.81) | 0.618 | - | - |
| Diabetes mellitus | 34 (28.6) | 22 (66.7) | 5.00 (2.19-11.42) | <0.001 | 6.76 (2.13-21.44) | 0.001 |
| Dementia | 33 (27.7) | 11 (33.3) | 1.30 (0.57-2.98) | 0.530 | - | - |
| Congestive heart failure / history of acute myocardial infarction | 18 (15.1) | 11 (33.3) | 2.81 (1.16-6.77) | 0.019 | 4.40 (1.18-16.44) | 0.028 |
| Chronic kidney disease | 15 (12.6) | 6 (18.2) | 1.54 (0.55-4.35) | 0.403 | - | - |
| Osteoarthritis | 8 (6.7) | 2 (6.1) | 0.90 (0.18-4.43) | >0.99 | - | - |
| Long-term medications | | | | | | |
| Steroid | 6 (5.0) | 3 (9.1) | 1.88 (0.45-7.97) | 0.408 | - | - |
| Other immunosuppressants | 4 (3.4) | 0 | - | 0.577 | - | - |
| Previous pyometra | 9 (7.6) | 1 (3.0) | 0.38 (0.05-3.13) | 0.691 | - | - |
| Presence of any predisposing factor | 46 (38.7) | 15 (45.5) | 1.33 (0.61-2.88) | 0.481 | - | - |
| Clinical presentation | | | | | | |
| Asymptomatic | 9 (7.6) | 0 | - | 0.207 | - | - |
| Vaginal discharge | 40 (33.6) | 18 (54.5) | 2.37 (1.08-5.19) | 0.029 | 3.23 (1.03-10.14) | 0.440 |
| Abdominal pain | 19 (16.0) | 6 (18.2) | 1.17 (0.43-3.22) | 0.761 | - | - |
| Fever | 12 (10.1) | 13 (39.4) | 5.80 (2.31-14.52) | <0.001 | 1.97 (0.53-7.37) | 0.314 |
| Maximum temperature, ˚C (in 25 women with fever) | 38.2 (37.7-38.6) | 38.5 (38.1-39) | 1.95 (0.68-5.64) | 0.155 | - | - |
| Vaginal bleeding | 84 (70.6) | 13 (39.4) | 0.27 (0.12-0.60) | <0.001 | 0.14 (0.04-0.49) | 0.002 |
| Uterine size, wk | 6 (6-8) | 6 (6-12) | - | 0.239 | - | - |
| Pyometra size | | | | | | |
| Longest diameter, cm | 2.8 (2.0-3.8) | 3.2 (2.2-8.9) | - | 0.043 | 1.26 (1.06-1.50) | 0.009 |
| Genital tract microorganisms | | | | | | |
| Gram-positive bacteria | | | | | | |
| Streptococci | 29 (24.4) | 6 (18.2) | 0.69 (0.26-1.84) | 0.455 | - | - |
| Enterococci | 12 (10.1) | 7 (21.2) | 2.40 (0.86-6.70) | 0.132 | - | - |
| Peptostreptococci | 9 (7.6) | 5 (15.2) | 2.18 (0.68-7.03) | 0.186 | - | - |
| *Peptoniphilus* spp | 12 (10.1) | 2 (6.1) | 0.58 (0.12-2.71) | 0.735 | - | - |
| *Actinomyces* spp | 8 (6.7) | 4 (12.1) | 1.91 (0.54-6.80) | 0.293 | - | - |
| Staphylococci | 6 (5.0) | 2 (6.1) | 1.22 (0.23-6.32) | 0.685 | - | - |
| Gram-negative bacteria | | | | | | |
| *Escherichia coli* | 52 (43.7) | 19 (57.6) | 1.75 (0.80-3.81) | 0.157 | - | - |
| *Bacteroides* spp | 18 (15.1) | 7 (21.2) | 1.51 (0.57-4.00) | 0.404 | - | - |
| *Klebsiella pneumoniae* | 10 (8.4) | 5 (15.2) | 1.95 (0.62-6.15) | 0.319 | - | - |
| Extended-spectrum β-lactamase positive | 15 (12.6) | 10 (30.3) | 3.01 (1.20-7.56) | 0.015 | 6.07 (1.45-25.34) | 0.013 |
| Fungus | | | | | | |
| *Candida* spp | 8 (6.7) | 10 (30.3) | 6.03 (2.15-16.94) | <0.001 | 4.05 (0.92-17.86) | 0.065 |
| Polymicrobial (≥2 microorganisms) | 62 (52.1) | 23 (69.7) | 2.12 (0.93-4.83) | 0.072 | - | - |

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

**Table 6. Predictors for recurrence in patients with pyometra.**

| Variable | Without recurrence (n=111)* | With recurrence (n=35)* | Odds ratio (95% confidence interval) | p Value | Adjusted odds ratio (95% confidence interval) | p Value |
|---|---|---|---|---|---|---|
| Age, y | 79 (69-88) | 84 (71-90) | - | 0.430 | - | - |
| Menopause | 108 (97.3) | 35 (100) | - | >0.99 | - | - |
| Impaired ambulation | 62 (55.9) | 25 (71.4) | 1.98 (0.87-4.50) | 0.102 | - | - |
| Incontinence pad use | 51 (45.9) | 19 (54.3) | 1.40 (0.65-3.00) | 0.389 | - | - |
| Living in nursing home | 44 (39.6) | 17 (48.6) | 1.44 (0.67-3.09) | 0.350 | - | - |
| Comorbidity | | | | | | |
| Hypertension | 73 (65.8) | 23 (65.7) | 1.00 (0.45-2.22) | 0.996 | - | - |
| Stroke | 40 (36.0) | 19 (54.3) | 2.11 (0.98-4.55) | 0.055 | - | - |
| Diabetes mellitus | 39 (35.1) | 14 (40.0) | 1.23 (0.56-2.69) | 0.602 | - | - |
| Dementia | 30 (27.0) | 13 (37.1) | 1.60 (0.71-3.56) | 0.252 | - | - |
| Congestive heart failure / history of acute myocardial infarction | 23 (20.7) | 3 (8.6) | 0.36 (0.10-1.28) | 0.101 | - | - |
| Chronic kidney disease | 15 (13.5) | 4 (11.4) | 0.83 (0.26-2.67) | >0.99 | - | - |
| Osteoarthritis | 5 (4.5) | 4 (11.4) | 2.74 (0.69-10.81) | 0.218 | - | - |
| Long-term medications | | | | | | |
| Steroid | 7 (6.3) | 2 (5.7) | 0.90 (0.18-4.55) | >0.99 | - | - |
| Immunosuppressants | 4 (3.6) | 0 | - | 0.573 | - | - |
| Previous pyometra | 7 (6.3) | 3 (8.6) | 1.39 (0.34-5.70) | 0.703 | - | - |
| Presence of any predisposing factor | 44 (39.6) | 13 (37.1) | 0.90 (0.41-1.97) | 0.792 | - | - |
| Uterine size, wk | 6 (6-8) | 6 (6-10) | - | 0.145 | - | - |
| Pyometra size | | | | | | |
| Longest diameter, cm | 2.8 (2.1-3.8) | 3.4 (2.3-7.1) | - | 0.045 | 1.16 (1.01-1.32) | 0.033 |
| Genital tract microorganisms | | | | | | |
| Gram-positive bacteria | | | | | | |
| Streptococci | 24 (21.6) | 10 (28.6) | 1.45 (0.61-3.43) | 0.396 | - | - |
| Enterococci | 10 (9.0) | 9 (25.7) | 3.50 (1.29-9.49) | 0.019 | 3.31 (1.19-9.20) | 0.022 |
| Peptostreptococci | 10 (9.0) | 4 (11.4) | 1.30 (0.38-4.45) | 0.743 | - | - |
| *Peptoniphilus* spp | 10 (9.0) | 4 (11.4) | 1.30 (0.38-4.45) | 0.743 | - | - |
| *Actinomyces* spp | 7 (6.3) | 5 (14.3) | 2.48 (0.73-8.37) | 0.160 | - | - |
| Staphylococci | 6 (5.4) | 2 (5.7) | 1.06 (0.20-5.51) | >0.99 | - | - |
| Gram-negative bacteria | | | | | | |
| *Escherichia coli* | 48 (43.2) | 20 (57.1) | 1.75 (0.81-3.77) | 0.151 | - | - |
| *Bacteroides* spp | 21 (18.9) | 4 (11.4) | 0.55 (0.18-1.74) | 0.305 | - | - |
| *Klebsiella pneumoniae* | 11 (9.9) | 4 (11.4) | 1.17 (0.35-3.95) | 0.757 | - | - |
| Extended spectrum β-lactamase positive | 20 (18.0) | 4 (11.4) | 0.59 (0.19-1.85) | 0.359 | - | - |
| Fungus | | | | | | |
| *Candida* spp. | 14 (12.6) | 2 (5.7) | 0.42 (0.09-1.95) | 0.359 | - | - |
| Polymicrobial (≥2 microorganisms) | 61 (55.0) | 23 (65.7) | 1.57 (0.71-3.47) | 0.262 | - | - |
| Management options | | | - | 0.483 | - | - |
| Endometrial drainage | 99 (89.2) | 34 (97.1) | | | | |
| Foley drainage | 3 (2.7) | 1 (2.9) | | | | |
| Antibiotics alone | 7 (6.3) | 0 | | | | |
| Laparotomy and drainage | 1 (0.9) | 0 | | | | |
| Composite adverse outcomes | 22 (19.8) | 5 (14.3) | 0.67 (0.24-1.94) | 0.462 | - | - |

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

test for sexually transmitted pathogens because most of our patients had impaired ambulation and lived in nursing facilities[13]. The microbial data of our patients suggest that the pyometras originate from gastrointestinal tract and urinary tract pathogens.

Infection with ESBL-producing Enterobacteriaceae is associated with adverse outcomes and thus higher mortality rate, treatment failure, longer hospital stays, and greater hospital expenses[21,22]. Correct empirical antibiotic use is a key contributor; treatment with carbapenem results in significantly lower mortality (3.7%), compared with quinolones (36.3%), cephalosporins (40%), and β-lactam/β-lactamase inhibitors (50%)[21]. The high efficacy of carbapenems against ESBL strains is the result of minimal hydrolysis by ESBL enzymes and reduced susceptibility to the inoculum effect[21,23]. In Hong Kong, the IMPACT guideline supports carbapenem as the preferred agent for serious ESBL-positive infections[24], as reflected in the low resistance rate in our study.

In our study, enterococci were associated with higher recurrence rates. As gut commensals and opportunistic pathogens, they exhibit resilience, antibiotic resistance, and biofilm formation, complicating treatment and leading to recurrent infections[25,26]. Risk factors for enterococcal overgrowth include prolonged hospitalisation, urinary catheterisation, and repeated antibiotic use[25,26], which were common in our patients. Efforts to reduce enterococcal colonisation should include judicious antibiotic use, enhanced surveillance, and preventive measures to minimise transmission[26].

In our study, polymicrobial cultures were present in 55.9% of our patients. Postmenopausal changes, including reduced lactobacilli and increased anaerobes, result in vaginal flora dysbiosis and predisposition to polymicrobial infections[27]. Therefore, broad-spectrum antibiotics should be prescribed to target common pathogens, particularly anaerobes. Co-amoxiclav, levofloxacin, cefuroxime, and metronidazole were the common antibiotics used in our patients. Co-amoxiclav provides good coverage for both Gram-positive and Gram-negative bacteria. Metronidazole primarily targets anaerobes, which are common in female genital tract infections[28]. High quinolone resistance among *E coli* (50% in our patients and 40% in Hong Kong[24]) raises concerns about levofloxacin as a viable option. Our study supports the suitability of cefuroxime for ESBL-negative infections, but it is ineffective against ESBL-positive strains, consistent with guidelines in Hong Kong[24].

In Hong Kong, co-amoxiclav and metronidazole would be a reasonable empirical regimen for pyometra, whereas carbapenem should be reserved for severe ESBL-positive infections. Duration of antibiotic use must be customised to individual needs. A microbiologist's input should be considered in patients with recurring pyometra or non-responders to antibiotics.

Our study has several limitations. Only inpatients were included; milder cases of pyometra managed in an outpatient setting were excluded. This selection bias potentially overestimates the severity and frequency of adverse outcomes. Consequently, generalisation of our findings to all pyometra cases is limited. Additionally, subgroup analysis for each adverse outcome was not feasible owing to the small sample size. The retrospective nature of the study is affected by missing data and loss to follow-up. Prospective randomised controlled trials are needed to determine the most optimal management strategies for improvement of clinical outcomes.

## Conclusion

Pyometra is rare and often associated with malignancy and severe complications. Patients at risk of developing adverse outcomes include those with diabetes mellitus, congestive heart failure or a history of acute myocardial infarction, large pus collection, and infection with ESBL-producing organisms. Patients at risk of recurrence include those with large pus collection or the presence of enterococci. At-risk patients should be monitored vigilantly. Early diagnosis and intervention are crucial to improving clinical outcomes.

## Contributors

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

## Conflicts of interest

All authors have no conflict of interest to disclose.

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## Data availability

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

## Ethics approval

The present study was approved by the Central Institutional Review Board of Hospital Authority (reference: IRB-2024-276). All patients were treated in accordance with the tenets of the Declaration of Helsinki.

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# Knowledge and attitudes regarding human papillomavirus vaccination and cervical cancer screening among pregnant women in Hong Kong: a cross-sectional study

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***Objectives:*** To evaluate the knowledge and attitudes regarding human papillomavirus (HPV) vaccination and cervical cancer screening among pregnant women in Hong Kong and to determine their associated factors. By identifying misconceptions and barriers, our findings could help formulate preventive strategies against HPV-related cancers.
***Methods:*** Pregnant women who attended antenatal clinics at Tuen Mun Hospital between June 2021 and May 2024 were invited to complete a questionnaire. The questionnaire explored pregnant women's knowledge about HPV (8 items) and cervical cancer (8 items), attitudes towards HPV vaccination and cervical cancer screening (15 items), experience and plan for HPV vaccination and cervical cancer screening (5 items), and demographic information (8 items). Responses to the knowledge questions were yes-or-no answers; obtaining >80% correct answers was defined as sufficient knowledge.
***Results:*** In total, 364 pregnant women completed the questionnaire. Of these, 126 (34.6%) had sufficient knowledge about HPV, and 82 (22.5%) had sufficient knowledge about cervical cancer. Among non-Chinese women, the percentages were 12.1% and 12.1%, respectively. Planning to receive HPV vaccination and to have regular cervical screening after pregnancy was more likely in pregnant women of Chinese ethnicity, with a family history of gynaecological malignancy, with cervical screening within 3 years, and with sufficient HPV knowledge.
***Conclusion:*** To increase the uptake of HPV vaccine and cervical screening, enhancement of knowledge and removal of misconceptions and stigma are crucial for health-seeking behaviours of both the mothers and their children.

*Keywords: Health knowledge, attitudes, practice; Papillomavirus vaccines; Pregnant people; Uterine cervical neoplasms*

## Introduction

Cervical cancer is the ninth most common cancer and cause of cancer death among women in Hong Kong, accounting for 2.9% of new cancer cases in women in 2022[1]. Persistent infections with high-risk human papillomavirus (HPV) can cause precancerous intraepithelial neoplasia and invasive cervical cancer[2]. HPV can also cause cancers and warts in the vagina, vulva, and anus. Therefore, prevention of HPV infection and cervical cancer remains an important public health initiative.

In 2004, the Department of Health in Hong Kong initiated a cervical screening programme (CSP) for women aged 25 to 64 years[3]. However, the CSP does not proactively include all eligible women but functions only as a database for women who have presented for screening. In 2008, a telephone survey in Hong Kong reported that 64% of eligible women had received cervical screening shortly after the CSP[4]. However, the 2023 annual report of the CSP showed that only 21.1% of women aged 25 to 64 years had registered with the CSP[5], suggesting inadequate screening coverage. Nonetheless, not all women who have received cervical screening are registered with the CSP because it is not mandatory.

HPV vaccination is a safe and effective preventive intervention for reducing the burden of HPV-related complications, and even women who have been exposed to some types of HPV can still benefit from sustained immunogenicity against other HPV types after vaccination[4,6]. A meta-analysis of prediction models suggests that high-risk HPV infection will be eliminated when 80% vaccination coverage is achieved[7]. However, the HPV vaccination coverage in Hong Kong remains low.

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Only 2.2% to 9.1% of schoolgirls and 0.6% of schoolboys had been vaccinated before the introduction of the no-cost Hong Kong Childhood Immunisation Programme in 2019/20, which provides HPV vaccine for girls in primary years 5 and 6[4,8]. In 2023, the HPV vaccination rate among schoolgirls rose to >80%[9], but uptake remained low among boys, because of barriers to acceptance of opportunistic vaccination among parents[4,10].

Women of reproductive age are most susceptible to HPV infections, and pregnant women represent the young, sexually active, female population. The awareness and attitudes of pregnant women regarding health issues can affect the health-seeking behaviour of their children. Parental awareness of HPV is closely related to HPV vaccine coverage in their children[4,11,12]. Pregnancy is often the first point of contact with regular health services, hence a good opportunity to promote health intervention. The postpartum period, in particular, is suitable for promoting opportunistic HPV vaccination, given the high acceptance of vaccines in the puerperium[6]. This study aimed to evaluate the knowledge and attitudes regarding HPV vaccination and cervical cancer screening among pregnant women in Hong Kong and to determine their associated factors. By identifying misconceptions and barriers, our findings could help formulate preventive strategies against HPV-related cancers.

## Methods

Pregnant women who attended antenatal clinics at Tuen Mun Hospital between June 2021 and May 2024 were invited to complete a questionnaire. There is no validated questionnaire to assess the knowledge and attitudes regarding cervical cancer and HPV vaccination. Thus, we designed the questionnaire based on findings in the literature, focusing on knowledge, attitudes, and practice (KAP) regarding cervical cancer and HPV vaccination in non-pregnant women[4,10,13,14]. The Chinese and English versions of the questionnaire were back translated, verified by an independent interpreter, and compared with the original version. There were no significant discrepancies between the original and the back-translated versions.

The questionnaire explored pregnant women's knowledge about HPV (8 items) and cervical cancer (8 items), attitudes towards HPV vaccination and cervical cancer screening (15 items), experience and plan for HPV vaccination and cervical cancer screening (5 items), and demographic information (8 items). Responses to the knowledge questions were yes-or-no answers; obtaining >80% correct answers was defined as sufficient knowledge, consistent with most KAP studies on knowledge of health issues[15]. Attitude was assessed on a five-point Likert scale ranging from strongly agree to strongly disagree. The questionnaire was pilot-tested with the first 10% of participants for clarity, and necessary modifications were made.

According to a study in the United States, 37.3% of pregnant women were found to be willing to receive the HPV vaccine[16]. Using the Cochran's formula and assuming a 37% positive response to the questions, a 5% margin of error, and a 95% confidence interval, a sample size of 359 women would be required for an infinite population[17]. Factors associated with planning to receive HPV vaccination after pregnancy and planning to have regular cervical screening after pregnancy were determined using univariable and multivariable logistic regression. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 25.0; IBM Corp, Armonk [NY], United States).

## Results

In total, 364 pregnant women completed the questionnaire (Table 1). Among these, 26.9% had completed HPV vaccination before pregnancy; and 25.7% (of those who had not completed HPV vaccination) planned to have HPV vaccination after pregnancy. In addition, 62.4% had received cervical screening within the previous 3 years; and 52.4% planned to have regular cervical screening after pregnancy.

Of the participants, 126 (34.6%) had sufficient knowledge about HPV, and 82 (22.5%) had sufficient knowledge about cervical cancer. The mean percentages of correct answers were 60.1% and 61.1% for knowledge about HPV and cervical cancer, respectively (Table 2).

Compared with non-Chinese women, Chinese women were more likely to have sufficient knowledge about HPV (40.1% vs 12.1%, p<0.001) and cervical cancer (26.5% vs 12.1%, p=0.018) [Table 3]. Sufficient knowledge about HPV was also associated with being married (p=0.005), being employed (p=0.002), higher education levels (p<0.001), higher monthly household income (p<0.001), having a family history of gynaecological malignancy (p=0.002), having completed HPV vaccination before pregnancy (p=0.001), and having cervical screening within 3 years (p<0.001), whereas sufficient knowledge about cervical cancer was also associated with higher education levels (p=0.002) and having cervical screening within 3 years (p<0.001).

**Table 1. Characteristics of participants (n=364).**

| Characteristic | No. (%) of participants |
|---|---|
| Age, y (n=314) | |
| <35 | 209 (66.6) |
| ≥35 | 105 (33.4) |
| Parity (n=314) | |
| Nulliparous | 113 (36.0) |
| Multiparous | 201 (64.0) |
| Ethnicity (n=337) | |
| Chinese | 279 (82.8) |
| Caucasian | 0 |
| Filipino | 13 (3.9) |
| Indian | 2 (0.6) |
| Nepalese | 13 (3.9) |
| Pakistani | 20 (5.9) |
| Others | 10 (3.0) |
| Marital status (n=331) | |
| Married | 299 (90.3) |
| Single/divorced/widowed | 32 (9.7) |
| Employment status (n=324) | |
| Employed | 157 (48.5) |
| Unemployed | 167 (51.5) |
| Education level (n=325) | |
| Primary | 11 (3.4) |
| Secondary | 188 (57.8) |
| Tertiary or above | 126 (38.8) |
| Monthly household income, HK$ (n=326) | |
| <10 000 | 14 (4.3) |
| 10 000-30 000 | 78 (23.9) |
| 30 001-50 000 | 67 (20.6) |
| 50 001-70 000 | 72 (22.1) |
| ≥70 001 | 15 (4.6) |
| Unknown | 80 (24.5) |
| Family history of gynaecological malignancy (n=344) | |
| Yes | 49 (14.2) |
| No | 226 (65.7) |
| Unsure | 69 (20.1) |
| Completed human papillomavirus vaccination before pregnancy (n=360) | |
| Yes | 97 (26.9) |
| No | 263 (73.1) |
| Experience of cervical screening (n=362) | |
| Never | 92 (25.4) |
| Within 3 years | 226 (62.4) |
| Beyond 3 years | 44 (12.2) |
| Plan to have human papillomavirus vaccination after pregnancy (excluding those who completed vaccination) [n=257] | |
| Yes | 66 (25.7) |
| No/unsure | 191 (74.3) |
| Plan to have cervical screening after pregnancy (n=359) | |
| Yes | 188 (52.4) |
| No/unsure | 171 (47.6) |

Among the pregnant women, about one-third had negative attitudes towards HPV vaccination and cervical cancer screening. For example, 27.7% were worried that having cervical screening would affect relationship with their partner; 37.6% were embarrassed to have cervical screening; 36.5% needed more time and information to decide because the HPV vaccine was too new to them; 34.6% and 33.8% were worried that HPV vaccine would affect their potential to conceive and their breastfeeding, respectively; 29.4% preferred to have cervical screening alone without HPV vaccination; 27.5% thought that HPV vaccine was not necessary if their partner had been vaccinated; and 31.3% and 47.8% considered that cervical screening and HPV vaccine, respectively, were too expensive (Table 4).

Planning to receive HPV vaccination after pregnancy was more likely in pregnant women of Chinese ethnicity (aOR=4.78, p=0.014), with a family history of gynaecological malignancy (aOR=2.54, p=0.007), with cervical screening within 3 years (aOR=2.27, p=0.014), and with sufficient HPV knowledge (aOR=2.07, p=0.038), whereas planning to have regular cervical screening after pregnancy was more likely in pregnant women of Chinese ethnicity (aOR=3.45, p<0.001), being married (aOR=3.53, p=0.019), with secondary education (aOR=5.39, p=0.018) or tertiary education or above (aOR=1.98, p=0.008), with a family history of gynaecological malignancy (aOR=3.63, p=0.007), having completed HPV vaccination (aOR=2.90, p<0.001), with cervical screening within 3 years (aOR=3.72, p=0.014), with sufficient HPV knowledge (aOR=2.15, p<0.001), and with sufficient cervical cancer knowledge (aOR=2.28, p=0.004) [Table 5].

Pregnant women preferred multiple channels to obtain information about HPV vaccination including discussion with healthcare professionals during consultation (29.8%), internet or social media platforms (29.6%), and television or radio (25.7%), information pamphlets or letters (14.2%), and through friends (0.7%).

## Discussion

HPV vaccination and cervical screening can be very cost-effective in diminishing the HPV-related healthcare burden in areas where screening coverage is low[4,18-21]. Vaccination coverage is a crucial element and hinges on parental acceptance and practice. In Hong Kong, the uptake of HPV vaccination by female adolescents has been surveyed among mothers and their adolescent children[4,10]. However, factors associated with mothers' practice to

**Table 2. Knowledge about human papillomavirus (HPV) and cervical cancer among participants (n=364).**

| Knowledge | Correct answer | No. (%) of participants with correct response |
|---|---|---|
| HPV | | |
| Is HPV a sexually transmissible infection? | Yes | 239 (65.7) |
| Can HPV cause cervical cancer? | Yes | 243 (66.8) |
| Can HPV cause genital warts? | Yes | 209 (57.4) |
| Can HPV infection cause abnormal cervical smear (pap smear)? | Yes | 243 (66.8) |
| Can HPV infection occur without visible symptoms? | Yes | 199 (54.7) |
| Do only women acquire HPV infection? | No | 226 (62.1) |
| Do only those with multiple sexual partners acquire HPV infection? | No | 217 (59.6) |
| Can HPV vaccination cure HPV infection? | No | 173 (47.5) |
| Cervical cancer | | |
| Is cervical cancer rare in Hong Kong? | No | 192 (52.7) |
| Would infection with high-risk HPV increase the risk of cervical cancer? | Yes | 252 (69.2) |
| Is cervical screening (pap smear) advised after sexual exposure? | Yes | 277 (76.1) |
| Is cervical cancer curable in early stage? | Yes | 262 (72.0) |
| Does HPV vaccine protect against all types of HPV infection? | No | 134 (36.8) |
| Is HPV vaccine included in the government routine vaccination programme? | Yes | 153 (42.0) |
| Can HPV vaccine still offer protection for women with previous sexual exposure? | Yes | 249 (68.4) |
| Is regular screening with cervical smear (pap smear) still advised after vaccination against HPV? | Yes | 260 (71.4) |

prevent HPV and cervical cancer have not been well evaluated. Our study targeted pregnant women and explored factors associated with higher rates of HPV vaccine uptake and cervical screening. Raising HPV awareness is essential, particularly among parents, to increase vaccine uptake[10]. Under the Hong Kong Childhood Immunisation Programme, HPV vaccination is provided via schools for girls in primary years 5 and 6, rather than via healthcare clinics for all eligible women. Thus, information about HPV vaccine and misconceptions may not be directly addressed. Promoting HPV and cervical cancer education to pregnant women during the antepartum and postpartum periods could increase the vaccine uptake of both the mothers and their children.

Knowledge about HPV and cervical cancer was insufficient among pregnant women in Hong Kong, particularly among non-Chinese, of whom only 12.1% had sufficient knowledge about HPV and cervical cancer. Possible explanations include language barriers, lack of awareness of services, and cultural stigmas over gynaecological check-ups. Most information leaflets in Hong Kong are in Chinese or English, which may not be comprehensible for some ethnic minorities. Language barriers also impede communication with healthcare professionals or access to healthcare services. Cultural stigmas may lead to embarrassment when receiving HPV vaccine or cervical screening. Therefore, resources should be made more accessible to women of all ethnicities.

In our study, higher education levels were associated with better knowledge about HPV and cervical cancer. A possible explanation is that more educated parents would be more willing to support HPV vaccination and cervical screening for their children. Promoting HPV and cervical cancer education to pregnant women would influence health-seeking practices in their children. Having a family history of gynaecological malignancy was also associated with better knowledge about HPV. These women may have higher health awareness and are more likely to learn about gynaecological malignancies.

Pregnant women with better knowledge about HPV were more likely to plan for both HPV vaccination and cervical screening in the future. However, having better knowledge about cervical cancer increased the likelihood

**Table 3. Stratified distribution of different bacterial species in subjects with uncomplicated urinary tract infection.**

| Characteristic | Insufficient HPV knowledge (n=238) | Sufficient HPV knowledge (n=126) | p Value | Insufficient cervical cancer knowledge (n=282) | Sufficient cervical cancer knowledge (n=82) | p Value |
|---|---|---|---|---|---|---|
| Age, y (n=314) | | | 0.762 | | | 0.154 |
| <35 (n=209) | 135 (64.6) | 74 (35.4) | | 154 (73.7) | 55 (26.3) | |
| ≥35 (n=105) | 66 (62.9) | 39 (37.1) | | 85 (81.0) | 20 (19.1) | |
| Parity (n=314) | | | 0.224 | | | 0.573 |
| Nulliparous (n=113) | 78 (69.0) | 35 (31.0) | | 87 (77.0) | 26 (23.0) | |
| Multiparous (n=201) | 125 (62.2) | 76 (37.8) | | 149 (74.1) | 52 (25.9) | |
| Ethnicity (n=337) | | | <0.001 | | | 0.018 |
| Chinese (n=279) | 167 (59.9) | 112 (40.1) | | 205 (73.5) | 74 (26.5) | |
| Non-Chinese (n=58) | 51 (87.9) | 7 (12.1) | | 51 (87.9) | 7 (12.1) | |
| Marital status (n=331) | | | 0.005 | | | 0.097 |
| Married (n=299) | 188 (62.9) | 111 (37.1) | | 222 (74.3) | 77 (25.8) | |
| Single/divorced/widowed (n=32) | 28 (87.5) | 4 (12.5) | | 28 (87.5) | 4 (12.5) | |
| Employment status (n=324) | | | 0.002 | | | 0.107 |
| Employed (n=157) | 89 (56.7) | 68 (43.3) | | 113 (72.0) | 44 (28.0) | |
| Unemployed (n=167) | 122 (73.1) | 45 (27.0) | | 133 (79.6) | 34 (20.4) | |
| Education level (n=325) | | | <0.001 | | | 0.002 |
| Primary (n=11) | 11 (100.0) | 0 | | 9 (81.8) | 2 (18.2) | |
| Secondary (n=188) | 140 (74.5) | 48 (25.5) | | 156 (83.0) | 32 (17.0) | |
| Tertiary or above (n=126) | 59 (46.8) | 67 (53.2) | | 83 (65.9) | 43 (34.1) | |
| Monthly household income, HK$ (n=246) | | | <0.001 | | | 0.357 |
| <10 000 (n=14) | 12 (85.7) | 2 (14.3) | | 12 (85.7) | 2 (14.3) | |
| 10 000-30 000 (n=78) | 62 (79.5) | 16 (20.5) | | 61 (78.2) | 17 (21.8) | |
| 30 001-50 000 (n=67) | 42 (62.7) | 25 (37.3) | | 48 (71.6) | 19 (28.4) | |
| 50 001-70 000 (n=72) | 34 (47.2) | 38 (52.8) | | 49 (68.1) | 23 (31.9) | |
| ≥70 001 (n=15) | 4 (26.7) | 11 (73.3) | | 9 (60.0) | 6 (40.0) | |
| Family history of gynaecological malignancy (n=344) | | | 0.002 | | | 0.208 |
| Yes (n=49) | 22 (44.9) | 27 (55.1) | | 34 (69.4) | 15 (30.6) | |
| No/unsure (n=295) | 201 (68.1) | 94 (31.9) | | 229 (77.6) | 66 (22.4) | |
| Completed HPV vaccination before pregnancy (n=360) | | | 0.001 | | | 0.757 |
| Yes (n=97) | 50 (51.6) | 47 (48.5) | | 76 (78.4) | 21 (21.7) | |
| No (n=263) | 184 (70.0) | 79 (30.0) | | 202 (76.8) | 61 (23.2) | |
| Cervical screening within 3 years (n=362) | | | <0.001 | | | <0.001 |
| Yes (n=226) | 126 (55.8) | 100 (44.3) | | 161 (71.2) | 65 (28.8) | |
| No (n=136) | 111 (81.6) | 25 (18.4) | | 119 (87.5) | 17 (12.5) | |

**Table 4. Attitude towards human papillomavirus (HPV) vaccination and cervical cancer screening among participants (n=364).**

| Attitude | No. (%) of participants (n=364) | | | | | |
|---|---|---|---|---|---|---|
| | Strongly agree | Agree | Neutral or not sure | Disagree | Strongly disagree | No response |
| HPV infection is a serious disease | 13 (3.6) | 207 (56.9) | 111 (30.5) | 22 (6.0) | 1 (0.3) | 10 (2.7) |
| Preventing cervical cancer is better than treating it | 92 (25.3) | 200 (54.9) | 34 (9.3) | 10 (2.7) | 1 (0.3) | 27 (7.4) |
| Regular cervical screening (pap smears) is an important health practice for all women | 76 (20.9) | 213 (58.5) | 40 (11.0) | 9 (2.5) | 4 (1.1) | 22 (6.0) |
| Only high-risk women need regular cervical screening (pap smear) | 11 (3.0) | 99 (27.2) | 53 (14.6) | 134 (36.8) | 53 (14.6) | 14 (3.8) |
| Cervical smear (pap smear) is too expensive for me | 17 (4.7) | 97 (26.6) | 130 (35.7) | 101 (27.7) | 7 (1.9) | 12 (3.3) |
| Cervical smear is effective in prevention of cervical cancer | 25 (6.9) | 175 (48.1) | 92 (25.3) | 47 (12.9) | 1 (0.3) | 24 (6.6) |
| HPV vaccine is safe and effective | 29 (8.0) | 198 (54.4) | 91 (25.0) | 33 (9.1) | 0 | 13 (3.6) |
| HPV vaccine is too expensive for me | 22 (6.0) | 152 (41.8) | 123 (33.8) | 45 (12.4) | 2 (0.5) | 20 (5.5) |
| I am embarrassed to have cervical screening (pap smear) | 16 (4.4) | 121 (33.2) | 90 (24.7) | 102 (28.0) | 18 (4.9) | 17 (4.7) |
| Having cervical screening will affect my relationship with my partner | 12 (3.3) | 89 (24.5) | 70 (19.2) | 132 (36.3) | 48 (13.2) | 13 (3.6) |
| I need more time and information before making a decision because the HPV vaccine is too new to me | 20 (5.5) | 113 (31.0) | 98 (26.9) | 110 (30.2) | 16 (4.4) | 7 (1.9) |
| I prefer to have cervical screening only rather than HPV vaccination | 11 (3.0) | 96 (26.4) | 117 (32.1) | 116 (31.9) | 16 (4.4) | 8 (2.2) |
| I am worried that HPV vaccine will affect my potential for conceiving | 13 (3.6) | 113 (31.0) | 83 (22.8) | 115 (31.6) | 33 (9.1) | 7 (1.9) |
| I am worried that HPV vaccine will affect my breastfeeding | 13 (3.6) | 110 (30.2) | 93 (25.5) | 106 (29.1) | 28 (7.7) | 14 (3.8) |
| HPV vaccine is not necessary if my partner has been vaccinated | 12 (3.3) | 88 (24.2) | 70 (19.2) | 139 (38.2) | 39 (10.7) | 16 (4.4) |

to plan for cervical screening only. This finding suggests that the prevention of cervical cancer by HPV vaccination may not be fully understood by these women, when 36.6% considered the HPV vaccine too new and 29.4% preferred cervical screening alone rather than together with HPV vaccination. Education on the role of the HPV vaccine in cervical cancer prevention should be strengthened.

To eliminate cervical cancer, the World Health Organization proposed that 90% of girls be fully vaccinated with HPV vaccine by the age of 15 years and 70% of women undergo cervical screening by age 35 years and again by age 45 years[22]. In our cohort, rates of HPV vaccine and cervical screening uptake were low at the time of survey (26.9% and 62.4%, respectively) and in future planning (25.7% and 52.4%, respectively). Misconceptions, incorrect attitudes, and possible social stigma should be addressed. Among our participants, 27.7% considered that having cervical screening would affect their relationship with their partner, and 27.5% considered that HPV vaccination was not needed if their partner had been vaccinated. These misconceptions could have a negative impact on cervical cancer prevention. Furthermore, pregnant women should be educated on the safety of the HPV vaccine during breastfeeding[23]. Although 62.4% agreed that the HPV vaccine was safe and effective, 34.6% and 33.8% were worried about any impact on conception and breastfeeding, respectively. Worries and embarrassment lower the likelihood of receiving cervical screening.[24-26]. The procedure of cervical screening should be elaborated, and worries and embarrassment sensitively

**Table 5. Factors associated with planning to receive human papillomavirus (HPV) vaccination and to have regular cervical screening after pregnancy.**

| Factors | Plan to receive HPV vaccination after pregnancy (excluding those who completed HPV vaccination) | | | | Plan to have regular cervical screening after pregnancy | | | |
|---|---|---|---|---|---|---|---|---|
| | Crude odds ratio (95% confidence interval) | p Value | Adjusted odds ratio (95% confidence interval) | p Value | Crude odds ratio (95% confidence interval) | p Value | Adjusted odds ratio (95% confidence interval) | p Value |
| Age, y | | | | | | | | |
| <35 | Reference | | - | | Reference | | - | |
| ≥35 | 0.70 (0.37-1.34) | 0.287 | - | - | 1.03 (0.62-1.71) | 0.635 | - | - |
| Parity | | | | | | | | |
| Nulliparous | Reference | | - | | Reference | | - | |
| Multiparous | 0.67 (0.31-1.47) | 0.242 | - | - | 0.91 (0.57-1.47) | 0.624 | - | - |
| Ethnicity | | | | | | | | |
| Chinese | 3.89 (1.13-13.33) | 0.024 | 4.78 (1.37-16.67) | 0.014 | 3.50 (1.88-6.55) | <0.001 | 3.45 (1.81-6.56) | <0.001 |
| Non-Chinese | Reference | | Reference | | Reference | | Reference | |
| Marital status | | | | | | | | |
| Married | 0.64 (0.15-2.81) | 0.246 | - | - | 4.16 (1.81-9.57) | 0.001 | 3.53 (1.42-8.82) | 0.019 |
| Single/divorced/widowed | Reference | | - | | Reference | | Reference | |
| Employment status | | | | | | | | |
| Employed | 0.81 (0.38-1.76) | 0.357 | - | - | 0.50 (0.32-0.78) | 0.003 | 0.86 (0.50-1.48) | 0.582 |
| Unemployed | Reference | | - | | Reference | | Reference | |
| Education level | | | | | | | | |
| Primary | Reference | | - | | Reference | | Reference | |
| Secondary | 0.99 (0.21-4.81) | 0.785 | - | - | 5.60 (1.41-22.24) | 0.014 | 5.39 (1.34-21.70) | 0.018 |
| Tertiary or above | 0.80 (0.16-3.99) | 0.486 | - | - | 2.31 (1.44-3.71) | 0.001 | 1.98 (1.20-3.27) | 0.008 |
| Monthly household income, HK$ | | | | | | | | |
| <10 000 | Reference | | - | | Reference | | Reference | |
| 10 000-30 000 | 0.72 (0.17-3.01) | 0.814 | - | - | 0.31 (0.16-0.61) | <0.001 | 0.45 (0.05-4.03) | 0.452 |
| 30 001-50 000 | 1.05 (0.26-4.22) | 0.211 | - | - | 0.21 (0.10-0.42) | 0.001 | 0.50 (0.41-1.48) | 0.476 |
| 50 001-70 000 | 0.92 (0.15-5.53) | 0.712 | - | - | 0.18 (0.09-0.36) | <0.001 | 0.73 (0.45-1.71) | 0.388 |
| ≥70 001 | 0.85 (0.21-3.41) | 0.596 | - | - | 0.14 (0.04-0.49) | <0.001 | 0.37 (0.10-1.79) | 0.058 |
| Family history of gynaecological malignancy | | | | | | | | |
| Yes | 3.78 (1.46-9.83) | 0.002 | 2.54 (1.28-5.01) | 0.007 | 3.48 (1.71-7.07) | 0.001 | 3.63 (1.67-7.88) | 0.007 |
| No/unsure | Reference | | Reference | | Reference | | Reference | |
| Completed HPV vaccination before pregnancy | | | | | | | | |
| Yes | - | - | - | - | 4.54 (2.41-8.56) | <0.001 | 2.90 (1.83-4.50) | <0.001 |
| No | - | | - | | Reference | | Reference | |
| Cervical screening within 3 years | | | | | | | | |
| Yes | 2.60 (1.38-4.91) | 0.003 | 2.27 (1.18-4.35) | 0.014 | 7.14 (4.03-12.50) | <0.001 | 3.72 (1.89-7.30) | 0.014 |
| No | Reference | | Reference | | Reference | | Reference | |
| Sufficient HPV knowledge | | | | | | | | |
| Yes | 2.59 (1.15-5.83) | 0.010 | 2.07 (1.14-3.74) | 0.038 | 2.51 (1.59-3.95) | <0.001 | 2.15 (1.32-3.49) | <0.001 |
| No | Reference | | Reference | | Reference | | Reference | |
| Sufficient cervical cancer knowledge | | | | | | | | |
| Yes | 1.05 (0.46-2.40) | 0.180 | - | - | 2.08 (1.21-3.58) | 0.001 | 2.28 (1.30-4.01) | 0.004 |
| No | Reference | | - | | Reference | | Reference | |

addressed. Of the participants, 31.4% and 47.8% considered that the prices of cervical screening and the HPV vaccine, respectively, were too expensive, consistent with findings from other studies[4,27-29]. Organisations that provide affordable cervical screening services and HPV vaccination should be introduced to these women.

Nowadays, health information can be acquired via the internet and social media platforms. Government agencies can help raise mothers' awareness about HPV vaccination and cervical screening through online resources, because these were preferred channels among our participants. Online platforms allow updates and translations more easily, and the latest evidence can be made easily available to all ethnicities. The vaccine uptake may remain low if preventive measures for cervical cancer in Hong Kong remain opportunistic. Campaigns to promote prevention should involve proactive initiation. Information pamphlets for HPV vaccination and cervical screening should be distributed to pregnant women during antenatal and postnatal check-ups, during which women should discuss their concerns with healthcare professionals. Interactions with health professionals may help eliminate patients' misinformation as well as social and cultural stigma, which have a negative impact on cervical cancer prevention.[14]

This study had some limitations. First, it was a cross-sectional study, which is less effective than a longitudinal survey in assessing the temporal association between acceptance and practice of HPV vaccination and cervical cancer prevention. Second, it was conducted in a single centre, and the sample size was small; our results may not be generalised to all pregnant women in Hong Kong. Third, our questionnaire has not been validated, but it incorporated various KAP studies about HPV and was adequately pilot-tested. We followed most KAP studies to use 80% as the cut-off for sufficient knowledge[15]. Last, ethnic minorities were under-represented, and non-participants were not assessed (participation bias). Nonetheless, our study had several strengths. The proportion of missing responses was relatively small. Pregnant women represent the young, sexually active, female population in Hong Kong; thus, our findings may be generalised to this population. Our results can help inform policy makers and healthcare providers to formulate preventive strategies.

## Conclusion

Among pregnant women in Hong Kong, 34.6% had sufficient knowledge about HPV and 22.5% had sufficient knowledge about cervical cancer. Among non-Chinese women, the percentages were 12.1% and 12.1%, respectively. To increase the uptake of HPV vaccine and cervical screening, enhancement of knowledge and removal of misconceptions and stigma are crucial for health-seeking behaviours of both the mothers and their children.

## Contributors

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

## Conflicts of interest

All authors have disclosed no conflicts of interest.

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## Data availability

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

## Ethics approval

This study was approved by the Central Institutional Review Board of Hospital Authority, Hong Kong (reference: NTWC/REC/21032). Participants were treated in accordance with the Declaration of Helsinki. All participants provided written informed consent for all treatments and procedures and for publication.

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# Menstruation: the fifth vital sign in women of reproductive age: a perspective

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Menstruation is a vital sign of women's health; every woman typically experiences 400 to 450 ovulations and 7 years of menstruation over her lifetime. Abnormal uterine bleeding (AUB) affects up to one-third of women during their reproductive years, impacting quality of life, but menstrual complaints are frequently under-reported. Healthy menstruation is determined by non-modifiable factors (age, ethnicity, and genetics) and modifiable factors (smoking, diet and nutrition, exercise, body weight, stress, gynaecological disorders, and systemic disorders). Healthy menstruation encompasses regularity, normal flow and duration, and the absence of dysmenorrhoea. These characteristics are indicators of a healthy reproductive system and overall well-being. AUB is a leading cause of iron deficiency and anaemia, particularly in women of reproductive age. In Hong Kong, 17.5% of women of reproductive age have iron deficiency. Comprehensive evaluation of menstruation is crucial in managing anaemia. Femtech (female technology) facilitates menstrual education and personalised health management. Recognition of menstruation as the fifth vital sign in women of reproductive age is important to overall health assessment. Early detection and management of AUB, along with related complications, namely iron-deficiency anaemia, can optimise women's health outcomes.

*Keywords: Anemia, iron deficiency; Menstruation; Metrorrhagia; Women's health*

## Introduction

Approximately half of the female population worldwide are of reproductive age[1]. Each day, approximately 800 million women aged 15 to 49 years are menstruating[2]. Based on the average menarche age of 12.5 years and the average menopause age of 50.5 years, every woman experiences 400 to 450 ovulations and 7 years of menstruation over her lifetime. Abnormal uterine bleeding (AUB) affects up to one-third of women during their reproductive years, impacting quality of life[3]. Although menstrual abnormalities are increasingly recognised, menstrual complaints remain under-reported[4].

The International Federation of Gynecology and Obstetrics (FIGO) has developed two systems. FIGO AUB System 1 defines the bleeding pattern using four descriptors: frequency, duration, regularity, and flow volume, whereas FIGO AUB System 2 (PALM-COEIN) classifies causes of AUB in terms of structural (polyp, adenomyosis, leiomyoma, malignancy), non-structural (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic), and causes not otherwise specified[5]. AUB symptoms may present at any reproductive age, with certain conditions being more common at particular ages. For instance, Müllerian anomalies typically present in early pubertal years, whereas endometrial hyperplasia and malignancy mainly present in mature, perimenopausal, or even postmenopausal women. Clinicians can streamline the investigations and determine the pathogenesis of underlying causes of AUB by applying the FIGO systems. Although a woman may have one or more causes of AUB, these may or may not contribute to the chief menstrual complaint. A woman may also be asymptomatic despite having structural lesions.

## Determinants of healthy menstruation

Healthy menstruation is determined by non-modifiable factors (age, ethnicity, and genetics) and modifiable factors (smoking, diet and nutrition, exercise, body weight, stress, gynaecological disorders, and systemic disorders). Menstrual regularity increases with age and stabilises in the prime reproductive years. AUB caused by ovulatory dysfunction is common in the pubertal and perimenopausal years[6]. Ethnicity is associated with age at menarche and menstrual blood flow[6]. Menstrual patterns may be heritable because the follicle-stimulating hormone β-subunit locus is associated with the length of menstrual cycles and menopause timing[7]. Smoking, especially starting at an early age, is associated with more menstrual irregularities[8,9]. Smoking cessation is strongly recommended to enhance menstrual regularity and overall health. The Mediterranean diet is associated with a lower likelihood of heavy menstrual bleeding, whereas alcohol consumption is associated with longer cycle lengths[10]. Low-carbohydrate and ketogenic diets have been found to increase menstrual dysfunction, particularly amenorrhoea[11]. Eating disorders (anorexia nervosa, binge eating, and bulimia) can result in significant weight loss and

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anovulation, which often emerge during adolescence[12-15]. Incorporating a menstrual review for patients with these conditions facilitates comprehensive care. Physical training and excessive exercise can result in functional hypothalamic amenorrhoea, leading to the classic female athlete triad. Women with a history of eating disorders, significant weight loss, or underweight status have a higher prevalence of anovulation. Low physical activity levels are associated with irregular cycles, particularly in those who are obese (body mass index >35 kg/m$^2$) and have a sedentary lifestyle[11]. In addition, obesity is associated with longer cycles[16]. Major life changes, high-intensity work environment, depressive mood, and stress increase the risk of irregular menstruation, leading to heavier, prolonged flow[17]. Systemic disorders such as thyroid dysfunction, hyperprolactinaemia, inflammation, infection, and haematological and oncological conditions can trigger disturbance of the hypothalamic-pituitary-ovarian axis, resulting in AUB. In fact, AUB may be the presenting symptom of a major medical illness.

## Changes in menstruation and COVID-19 vaccination

Changes in menstruation after COVID-19 vaccination or infection have been reported. Postulated causes include pandemic-associated stress and behavioural changes, as well as increased reporting of menstrual disturbances[18]. Causes of AUB associated with COVID-19 infection or vaccination are more likely to be non-structural. From a pathophysiological perspective, anovulation, coagulopathy, inflammation and tissue hypoxia, and iatrogenic factors have been postulated to disrupt endometrial shedding and repair, resulting in AUB. Studies examining the endometrium in women suggest that a direct impact of COVID-19 infection on the endometrium is unlikely. Nonetheless, indirect effects on endometrial function may occur, because the endometrium is sensitive to systemic inflammation and immune responses. The influx of circulating immune cells and altered endometrial inflammation may be implicated in the AUB. Treatment of COVID-19 may have off-target effects that lead to menstrual disturbances. For instance, the antiviral medication—ritonavir—is a cytochrome P450 inhibitor, which can interact with hormonal contraception and heighten adverse effects. Hospitalised patients may receive low-dose steroids and anticoagulants to reduce mortality. Endogenous glucocorticoids can inhibit endometrial angiogenesis; therefore, proper haemostatic function is essential to minimise endometrial bleeding and menstrual blood loss[18]. The impact of COVID-19 on menstruation is bidirectional; symptoms of long COVID can be influenced by menstrual cycles. Sex differences in infection and fatality also affect menstruation and ovarian sex hormone levels, which may modulate disease susceptibility[18,19].

## Impacts of abnormal uterine bleeding

AUB can lead to anaemia; 30% of women with AUB are anaemic, and the percentage increases to 60% in South Asia[20], possibly compounded by dietary deficiency. Iron deficiency is the commonest micronutrient deficiency and a major cause of anaemia[21]. Iron-deficiency anaemia is a public health issue that is under-recognised and under-reported across social and economic backgrounds.

According to the Population Health Survey 2020-2022 in Hong Kong[22], the prevalence of iron deficiency among the population aged 15 to 84 years was 5.7%, whereas that among women of reproductive age (15 to 49 years) was 17.5%. The prevalence was 0.7% among men, 10.2% among women, and 2.7% among postmenopausal women. The prevalence of iron-deficiency anaemia was also higher among women of reproductive age than among postmenopausal women (10.6% vs 2.1%), probably because of regular and heavy menstrual blood loss. These findings are consistent with those reported in high-income countries[22].

Reduction in anaemia is one of the six nutrition targets endorsed by the World Health Assembly, and combating anaemia in women of reproductive age is one of the targets for the United Nations 2030 Agenda for Sustainable Development[21]. The Hong Kong College of Obstetricians and Gynaecologists is a member of the Working Group on Prevention of Iron Deficiency of the Department of Health. Joint recommendations are made on iron intake, including consumption of iron-rich foods, adequate consumption of vegetables and fruits, and reduction in tea and/or coffee intake with meals. Management of health conditions and iron supplementation should be considered for those at risk of iron deficiency.

The mental health effects of AUB are often overlooked. The health-related quality of life score is <25th percentile in women with AUB, compared with the general female population of the same age[3]. Of women with heavy menstrual bleeding and mental health concerns, 50% reported heavy menstrual bleeding as the cause of their anxiety and depression[23]. Menstrual symptoms affect interpersonal relationships, school and work performance, and job and financial prospects, incurring healthcare burdens and loss of opportunities.

## Menstruation as a vital sign

Healthy menstruation encompasses regularity, normal flow and duration, and the absence of dysmenorrhoea. These characteristics are indicators of a healthy reproductive system and overall well-being. The concept and advocacy of menstruation being the fifth vital

sign was first brought up by the Society for Menstrual Cycle Research in 2004. The committee opinion of The American College of Obstetricians and Gynecologists (published in 2006, updated in 2015, and reaffirmed in 2020) recommended including an evaluation of the menstrual cycle as an additional vital sign in girls and adolescents[24]. It was endorsed by the American Academy of Pediatrics[25]. This approach highlights the importance of menstruation in assessing overall health status for patients and caregivers. Similar to how abnormalities in blood pressure, heart rate, or respiratory rate can signal serious health conditions, identifying irregular menstrual patterns during adolescence (such as menarche, changes of cycle interval, flow length, and menstrual product use) can facilitate early detection of potential health concerns for adulthood.

Charting menstrual symptoms is more than planning for vacations or beach trips; it is as informative as monitoring blood pressure. Assessment of menstrual blood flow is useful for clinical practice and research. However, self-perception of menstrual blood loss has limitations, as subjective assessment of menstrual blood loss does not always correspond to the actual volume. Nonetheless, it may prompt women to seek medical attention to improve their quality of life[6].

## Practical insights for clinicians

Clinicians should (1) recognise menstruation as a vital sign in women of reproductive age because menstrual health is a key indicator of overall and reproductive well-being; (2) integrate menstrual history as part of routine evaluations by reviewing menarche, changes in menstrual patterns including cycle regularity, flow, and duration, as well as symptoms of AUB (refer to the FIGO System 1); (3) evaluate the underlying causes of AUB based on the FIGO System 2 and treat the underlying causes accordingly; (4) address complications of AUB, identify, treat, and prevent iron deficiency and anaemia in reproductive-age women, and raise public awareness about the recommendations on adequate iron intake; and (5) educate patients on menstrual health by offering guidance on what constitutes a healthy menstrual cycle and when to seek medical attention for AUB, empowering individuals to engage in personalised health management.

## Famtech

Famtech (female technology) includes fertility solutions, pregnancy and nursing care, women's sexual wellness, and reproductive system health care, focusing on menstrual care through period-tracking apps[26]. In August 2024, the Hospital Authority of Hong Kong added the Menstrual Chart, under MyHealth section of the HAGo app, for recording menstrual symptoms, medication use, cycle dates, flow volume, and other conditions, facilitating personalised health management and patient involvement.

A survey on women's experiences of using menstrual tracking applications found user distribution across the reproductive lifespan, despite mainly teenagers and young women. Increased menstrual literacy, anticipatory management, and participation in personalised healthcare are the main reasons for using the apps. Most users considered that the tracker predicted periods correctly most of the time; one in four users reported heavy menstrual flow. Most reported that the tracking applications provided a sense of preparedness and empowerment, although some reported anxiety and stress[27].

General public knowledge about menstruation remains poor. Famtech empowers women to make decisions about their own bodies and reproductive health, although there are concerns about data sharing. Some applications may share data with social media for fertility- or pregnancy-related products. The sensitivity and intimate nature of menstruation may still be a cultural taboo and cause societal stigma related to women's health, body, and sexuality. Mishandling of data has implications for privacy, safety, reputation, and overall well-being. The overturning of the Roe v Wade case in the United States highlighted concerns that data collected by apps could potentially be used as criminal evidence[28]. Securing privacy and proper handling of sensitive data are therefore of paramount importance. Practically, it would be difficult to comply with a wide range of laws and data privacy regulations in different countries. Womanhood and women's health are not a one-size-fits-all experience. In low-income regions, access to femtech is not guaranteed[27].

## Conclusion

Menstruation is a vital sign for women. Assessment of AUB is essential, because it reflects underlying health status. The high prevalence of iron deficiency and iron-deficiency anaemia in women of reproductive age must not be overlooked. Monitoring menstrual symptoms with femtech can facilitate personalised health management and enhance women's health and well-being.

## Contributors

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

## Conflicts of interest

The author has no conflicts of interest to disclose.

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## Data availability

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

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# Medical management and minimally invasive interventions for uterine fibroids: a perspective

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Uterine fibroids are found in up to 70% of women by the age of 50 years, of whom up to 40% experience symptoms including heavy menstrual bleeding, urinary or bowel dysfunction, pelvic discomfort, pressure symptoms, reproductive dysfunction, and mood disturbances. Uterine fibroids have a detrimental effect on quality of life and cause a large proportion of gynaecological hospitalisations. Although hysterectomy is the definitive treatment, up to 3% and 4% of patients experience intra- and post-operative complications, respectively. Moreover, hysterectomy is unacceptable in women who wish to preserve their fertility. Medical management of uterine fibroids includes hormonal and non-hormonal (tranexamic acid) medications. Commonly used hormonal medications include combined oral contraceptives and progestogens, levonorgestrel-releasing intrauterine devices, selective progesterone receptor modulators, and gonadotrophin-releasing hormone agonists and antagonists. Other less commonly used agents include androgens, selective oestrogen receptor modulators, and aromatase inhibitors. Minimally invasive interventions include uterine artery embolisation, high-intensity focused ultrasound, and radiofrequency ablation. Treatment should be personalised to suit each woman's needs without compromising fertility, reproductive, or obstetric outcomes. Surgery must still be considered when symptoms are intractable, malignancy is suspected, or in an emergency setting in which fibroid-related complications such as torsion or obstructive uropathy arise. Shared decision making is essential, particularly in women of reproductive age, to balance efficacy, fertility goals, and treatment risks.

*Keywords: Leiomyoma; Uterus*

## Introduction

Uterine leiomyomata (also known as fibroids) are steroid hormone-responsive, benign, smooth muscle tumours found in up to 70% of women by the age of 50 years, of whom up to 40% experience symptoms[1,2]. Fibroids may present with a variety of symptoms including heavy menstrual bleeding, urinary or bowel dysfunction, pelvic discomfort, pressure symptoms, reproductive dysfunction, and mood problems such as depression. Moreover, fibroids account for up to 29% of gynaecological hospitalisations[3,4] and significantly affect the quality of life[5]. In a Hong Kong study in 2023, fibroids attributed to an increase in disability-adjusted life-years from 90 389 in 1990 to 159 558 in 2019[5]. In the US, fibroids were estimated to incur US$4.1 to US$9.4 billion in direct annual costs, US$1.55 to US$17.2 billion in lost work costs, and US$238 million to US$7.76 billion in associated obstetric outcome costs[3,4]. Thus, given the ever-increasing health and economic burden of fibroids, prompt and effective treatment is imperative.

The definitive treatment of uterine fibroids is a hysterectomy. A 2014 audit of obstetric and gynaecological services in Hong Kong revealed that 56.3% of abdominal and 48.6% of laparoscopic hysterectomies were performed for uterine fibroids[6]. Among these hysterectomies, the blood loss ranged from 100 to 400 mL, and the hospital stay ranged from 3 to 5 days. Nearly 2% of open hysterectomies and >3% of laparoscopic hysterectomies had intraoperative complications, with the most common being haemorrhage requiring transfusion (1.25% of open hysterectomies) and visceral injury (0.7% of open and laparoscopic hysterectomies). Indeed, postoperative complications occurred in 3.86% of open hysterectomies, 1.50% of laparoscopic hysterectomies, and 4.19% of vaginal hysterectomies. Hysterectomy is associated with significant risks of intra- and post-operative complications. Moreover, most women experience symptomatic fibroids before the menopause, and hysterectomy is unacceptable for women who wish to preserve fertility. Thus, non-surgical management for uterine fibroids is warranted.

## Medical management

Medical management of uterine fibroids includes hormonal and non-hormonal medications. Leiomyoma cells demonstrate a dependency on steroid hormones such as oestrogen; thus, the disruption of the hypothalamic-

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pituitary-ovarian axis with hormonal medication can lead to a decrease in the production of steroid hormones and subsequent symptomatic relief.

***Non-hormonal medications***

Tranexamic acid, which inhibits fibrinolysis and stabilises blood clots, is the most prescribed non-hormonal agent for treating fibroids, because up to 40% of women with uterine fibroids present with heavy menstrual bleeding[7]. A Cochrane systematic review in 2018 demonstrated that, compared with placebo, tranexamic acid led to a reduction in mean blood loss of 53.20 mL per cycle and higher rates of symptom improvement in 43% to 63% of women[8]. The finding of reduction in menstrual blood loss was supported by a randomised controlled trial (RCT)[9]. Moreover, tranexamic acid was superior to progestogens and non-steroidal anti-inflammatory drugs in terms of symptom improvement and reduction in mean blood loss per cycle. Nevertheless, contraindications to tranexamic acid include previous or current thromboembolic disease, epilepsy, severe renal impairment, subarachnoid haemorrhage, and active variceal bleeding. Tranexamic acid should not be used in pregnancy. It must be noted that tranexamic acid does not ameliorate pressure symptoms or reduce the size of uterine fibroids.

***Hormonal medications***

Hormonal medications for treating uterine fibroids include combined oral contraceptives and progestogens (COCP), levonorgestrel-releasing intrauterine devices, aromatase inhibitors, androgens, selective oestrogen receptor modulators, selective progesterone receptor modulators, and gonadotrophin receptor agonists and antagonists (Table).

***Combined oral contraceptives and progestogens***

COCPs contain varying levels of oestrogen and progesterone that disrupt the hypothalamic-pituitary-ovarian axis and reduce the amount of endogenous oestrogen and progesterone, resulting in reduction of menstrual blood loss by up to 53.5%[10], but they have limited efficacy in reducing fibroid volume or uterine size. A meta-analysis showed that COCPs have a role in prevention of uterine fibroids; the risk reduced by 57% in current users and by 17% in those who have ever used COCPs (a persistent effect even after cessation of treatment)[11]. The use of COCPs may, however, be limited by age and contraindications such as obesity, smoking, hypertension, and migraines. COCPs, unlike progestogens, cannot be used together with tranexamic acid owing to an increased risk of venous thromboembolism.

Progestogens are structurally similar to progesterone and often used in the treatment of abnormal uterine bleeding through an oral (ie, norethisterone acetate) or intramuscular (ie, depot medroxyprogesterone acetate) route. A RCT comparing norethisterone acetate and leuprolin showed a 7.3% reduction in uterine fibroid volume 16 weeks after treatment[12]; however, the study quality was low. Another study comparing promegestrone, nomegestrol acetate, and depot medroxyprogesterone acetate did not demonstrate significant reductions in menstrual bleeding or fibroid size[13]. Indeed, a Cochrane review concluded that there is insufficient evidence to support the efficacy of progestogen treatment for uterine fibroids[14].

***Levonorgestrel-releasing intrauterine device***

The levonorgestrel-releasing intrauterine device is a T-shaped thermoplastic device inserted into the uterus through the cervix; it releases levonorgestrel to thin the endometrium and induce endometrial decidualisation, thus inhibiting the proliferation of leiomyoma cells. The National Institute for Health and Care Excellence recommends it as first-line treatment for women with heavy menstrual bleeding, except in those with fibroids >3 cm and uterine cavity distortion. However, its overall effect is mixed; compared with COCPs and other progestins, the device has no strong evidence of benefit in premenopausal women, with inconsistent results in change of uterine and fibroid volumes[14,15].

***Gonadotrophin-releasing hormone agonists and antagonists***

Gonadotrophin-releasing hormone (GnRH) agonists have demonstrated efficacy in treating symptomatic fibroids. They are structurally akin to endogenous GnRH and, after an initial flare effect that elevates follicle-stimulating hormone and luteinising hormone levels, induce receptor downregulation, leading to a hypogonadotrophic hypogonadal (ie, hypo-oestrogenic) state. GnRH agonists are well established for preoperative preparations; a Cochrane review demonstrated improvements in pre- and post-operative haemoglobin levels and reductions in uterine and fibroid volumes, uterine size, and duration of hospitalisation[16]. Patients undergoing GnRH agonist injection before surgery have better perioperative outcomes including a lower rate of midline laparotomy, less blood loss and blood transfusion, and reduced operative time and difficulty. However, GnRH agonists are not used for prolonged periods owing to a significant and rapid loss of bone mineral density of up to 6% annually, secondary to the ensuing hypo-oestrogenic state, which may not recover after discontinuation[17].

**Table. Hormonal medications and minimally invasive interventions for uterine fibroids.**

| Treatment | Mechanism | Reduction in bleeding, % | Reduction in fibroid size, % | Reduction in uterine size, % | Improvement in quality of life | Sustained response | Reproductive outcome | Adverse effects |
|---|---|---|---|---|---|---|---|---|
| **Commonly used hormonal medications** | | | | | | | | |
| Tranexamic acid | Antifibrinolytic | 40-60 | No | No | Yes (reduced heavy menstrual bleeding) | Recurrence after cessation | - | Mild (gastrointestinal tract symptoms, thrombosis risk in high doses) |
| Combined oral contraceptives and progestogens | Disrupt hypothalamic-pituitary-ovarian axis, reduce endogenous oestrogen and progesterone | 30-40 | Minimal (low-quality evidence) | No | Limited | Recurrence after cessation | - | Moderate (venous thromboembolism risk, headaches, breast tenderness, weight gain, acne, mood changes) |
| Progestogens | Inhibit endometrial proliferation | 30-50 | Minimal (low-quality evidence) | No | Limited | Recurrence after cessation | - | Mild (weight gain, bloating, mood changes) |
| Levonorgestrel-releasing intra-uterine device | Localised progestin effect, inhibits endometrial proliferation | 70-90 (for heavy menstrual bleeding in those without uterine fibroids) | Minimal (low-quality evidence) | No | Yes (reduced heavy menstrual bleeding) | Effective for 5 years | - | Mild (irregular bleeding, amenorrhoea) |
| Gonadotrophin-releasing hormone agonists | Induces hypo-oestrogenic state | 80-90 | 30-60 | 30-50 | Significant | Fibroid regrowth after cessation | - | Major (vasomotor symptoms, accelerated loss in bone mineral density) |
| Gonadotrophin-releasing hormone agonists + add-back therapy | Induces hypo-oestrogenic state Replenishes steroid hormones to prevent bone loss | 70-90 | 10-30 | 10-30 | Significant | Fibroid regrowth after cessation | - | Mild (vasomotor symptoms) |
| Selective progesterone receptor modulators | Direct reduction in fibroid proliferation | 70-90 | 30-70 | 30-40 | Significant | Yes | - | Major (benign endometrial changes, rare liver toxicity) |
| **Less commonly used hormonal medications** | | | | | | | | |
| Aromatase inhibitors | Inhibit local aromatase activity | Yes | Up to 46 | Up to 21 | - | - | - | Moderate (arthralgia, vasomotor symptoms, follicular hormonal profile over study period) |
| Androgens | Binds to and decreases sex hormone-binding globulin, suppresses hypothalamic-pituitary-ovarian axis | 69 (in amenorrhoea) | 23.6-37.6 | - | - | - | - | Moderate (acne, weight gain, permanent voice changes, muscle cramps, oily skin) |
| Selective oestrogen receptor modulators | Oestrogen receptor agonist/antagonist effect | No | 9.1-31 greater shrinkage than gonadotrophin-releasing hormone | - | - | - | - | Mild (vasomotor symptoms) |
| **Minimally invasive interventions** | | | | | | | | |
| Uterine artery embolisation | Direct occlusion of blood supply | 85-90 | 35-60 | 30-50 | Significant | Yes | Worse, compared with myomectomy | Moderate (post-embolisation syndrome, ovarian failure, pelvic pain) |
| High-intensity focused ultrasound | Direct thermal ablation with ultrasound waves | 70-80 | 30-50 | 20-40 | Moderate to significant | Yes, but higher reintervention rate. | Better, compared with uterine artery embolisation | Moderate (skin burns, pelvic pain, visceral and nerve injury) |
| Radiofrequency ablation | Direct thermal ablation with radio waves | 75-85 | 40-60 | 30-50 | Significant | Yes | Better, compared with uterine artery embolisation | Mild (pain, infection, visceral injury) |

In 2021, oral GnRH antagonists such as relugolix and elagolix were approved for the treatment of fibroid-induced abnormal uterine bleeding by the US Food and Drug Administration (FDA). Oral GnRH antagonists have a faster onset of action and can avoid the initial flare effect[17-20]. Loss in bone mineral density can be mitigated with oestrogen and progestogen add-back therapy. Multiple RCTs (namely ELARIS UF-I, UF-II, UF-EXTEND, LIBERTY I, II, and III, Extended LIBERTY, and LIBERTY randomised withdrawal) have demonstrated significant reductions in menstrual blood loss, increase in haemoglobin levels, decrease in fibroid numbers and volume, and improvement in quality-of-life scores.

In LIBERTY I and LIBERTY II double-blinded phase III trials, patients with fibroid-associated heavy menstrual bleeding were randomised to receive daily relugolix combination therapy (ie, add-back therapy of 1 mg of oestradiol and 0.5 mg of norethindrone acetate daily), relugolix with delayed combination therapy (relugolix alone for 12 weeks and then combined with add-back therapy for the remaining 12 weeks), or placebo[20]. At 6 months, 73% of patients with relugolix combination therapy attained a reduction in menstrual bleeding ≥50% and a total volume of menstrual blood loss <80 mL, whereas 80% of patients with a delayed relugolix combination achieved the same outcomes. Bone mineral density loss in the respective groups was 0.4% and 1.9% to 2.4% at the lumbar spine and 0.1% to 0.5% and 1.1% to 1.6% at the hip. Patients with relugolix combination therapy had an 84.3% to 89.4% decrease in menstrual blood loss volume from baseline; 50% to 61% of those with anaemia had an increase in haemoglobin levels of >2 g/dL; the volume of the primary fibroid reduced 12.4% to 30.2%; and the Bleeding and Pelvic Discomfort scores improved 28.9% to 33.4%. When the treatment was extended to 76 and 104 weeks, 78.4% and 69.8% of patients maintained a menstrual blood loss of <80 mL, respectively[21]. The mean loss in bone mineral density from week 52 to week 104 of treatment was 0.8% at the lumbar spine and 0.3% at the hip. Thus, a combination of relugolix and add-back therapy is effective for treating symptomatic uterine fibroids.

***Selective progesterone receptor modulators***

Selective progesterone receptor modulators such as ulipristal acetate (UPA) exhibit variable agonist and antagonist activities on progesterone receptors, decreasing endogenous oestrogen through inhibition of the hypothalamic-pituitary-ovarian axis, resulting in antiproliferative, proapoptotic, and antifibrotic changes in leiomyomata. RCTs have shown significant decreases in fibroid and uterine volumes and menstrual blood loss; the effects and improvement in quality-of-life scores and serum oestradiol levels in the mid-follicular range were maintained 6 months after cessation, thereby negating the hypo-oestrogenic state of GnRH agonist drugs[22].

The PEARL trials evaluated the efficacy and safety of UPA in the treatment of symptomatic uterine fibroids. PEARL I demonstrated the efficacy of UPA in controlling heavy menstrual bleeding and pain, without significant adverse effects[23]. PEARL II compared UPA with a GnRH agonist (leuprolide acetate); patients with UPA achieved amenorrhoea 2 weeks earlier, with better pain control and fewer adverse effects[24]. Only 10% to 11% of those with UPA experienced moderate to severe hot flashes, compared with up to 40% in those with leuprolide acetate. The mean serum oestradiol was maintained at 70 to 79 pg/mL in those with UPA, compared with 24 pg/mL in those with leuprolide acetate. PEARL III showed that long-term (18 months) UPA resulted in shrinkage of uterine leiomyomata by up to 72% and an amenorrhoea rate of nearly 90%[25]. At 3 months after cessation of UPA, the volume of the three largest leiomyomata decreased by 60%, and up to 45% of patients experienced a reduction in uterine volume by ≥25%. Fibroid-specific quality-of-life scores improved from 22.7 to 31.4 and were maintained even after treatment cessation. The PEARL IV compared two doses of UPA (5 and 10 mg) given as two 12-week courses separated by two menstrual cycles and showed reductions in fibroid volume by 54% and 58%, respectively, with no increase in adverse effects[26]. UPA can, therefore, maintain amenorrhoea and fibroid and uterine volume reduction, with superior adverse effect profile and quality of life, compared with GnRH agonist alone. In a case series of 47 women (mean age, 36 years) with pregnancy after UPA (75% were nulliparous), 85% conceived spontaneously, and 64% resulted in live births after a mean gestational age of 38 weeks[27]. There were no fetal malformations, and 43% of patients did not require myomectomy after UPA treatment.

Up to 12% of patients treated with UPA had thickened endometria (>16 mm) and progesterone receptor modulator–associated endometrial changes. Long-term follow-up with endometrial sampling showed no atypia in any patients, and these endometrial changes were reversible 1 to 2 months after treatment cessation. However, the European Medicines Agency recommends restricting UPA use due to cases of serious liver injury[28]. It stipulates that UPA can only be used to treat uterine fibroids in premenopausal women for whom surgical procedures (including embolisation) fail or are not appropriate; UPA

must not be used to control symptoms of uterine fibroids while awaiting surgical treatment[29]. It is argued, however, that the associations between UPA and acute liver injury are overblown. According to the FDA's Drug-Induced Liver Injury Guidance[30], indicators of drug-induced liver injury (ie, Hy's law) include tripling or more of alanine aminotransferase or aspartate aminotransferase levels compared with the upper limit of normal (ULN), and doubling or more of total bilirubin levels in such patients without evidence of cholestasis, underlying liver disease, or any other explanation for the deranged liver function other than exposure to the drug. In the phase I trials for UPA, 160 patients received up to 50 mg of UPA daily for up to 10 days—up to ten times the marketed dose—and none showed any derangement of liver function. In the phase II trials, 152 patients (excluding those with alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, or bilirubin more than double the ULN, and those with alcohol abuse) received up to 20 mg of UPA daily for 3 months and none experienced any elevation of liver transaminases more than double the ULN or a total bilirubin >1.5 times the ULN. In the phase III trials, 1556 patients received 5 and 10 mg UPA daily for up to eight 3-month courses; only eight patients had liver transaminase levels more than three times the ULN[31].

***Other medical treatments***

Other less commonly used agents include androgens, selective oestrogen receptor modulators, and aromatase inhibitors (Table). Androgens such as danazol (a synthetic testosterone derivative that binds to and decreases sex hormone-binding globulin production) and gestrinone (a synthetic steroidal hormone with androgenic and anti-oestrogenic properties) have been used with some efficacy. Studies have shown a reduction in fibroid volume of up to 38% and amenorrhoea in up to 69% of women[32-35]. However, persistent androgenic adverse effects such as weight gain, permanent voice deepening, oily skin, and acne limit widespread use of androgens. Raloxifene is a selective oestrogen receptor modulator that binds to oestrogen receptors with varying degrees of agonist and antagonist effects; it has an antiproliferative effect on leiomyoma cells and hence reduces fibroid size. A Cochrane review reported that selective oestrogen receptor modulators did not significantly reduce the duration or severity of uterine bleeding or improve haemoglobin levels, despite being effective in reducing the mean leiomyoma size[36], but existing data are limited and of low quality. Aromatase inhibitors, which block local aromatase activity and prevent extragonadal and intratumoural oestrogen conversion, are effective in fibroid size reduction and symptom improvement[37-39]. An RCT comparing aromatase inhibitors and GnRH agonists demonstrated a reduction in mean fibroid volume of up to 45.6% without any adverse effects or changes in bone mineral density, follicle-stimulating hormone, or oestrogen levels. Additionally, prospective studies have shown a reduction in mean fibroid and uterine volumes by approximately 47% and 22%, respectively, and a decrease in mean blood loss from 315 to 151 mL[37-39]. However, the evidence is limited, and none shows whether treatment response is sustained after cessation.

## Minimally invasive interventions

***Uterine artery embolisation***

Uterine artery embolisation (UAE) is a minimally invasive, interventional radiological procedure, in which microparticles (made of tris-acryl gelatin or polyvinyl alcohol) are delivered to the uterine arteries under image guidance via a catheter through the common femoral artery. Occlusion of one or both uterine arteries leads to ischaemia with subsequent necrosis and shrinkage of the uterine fibroids.

According to the Society of Interventional Radiology guidelines, noticeable reductions in uterine and fibroid volumes occur weeks after UAE and continue for 3 to 12 months after treatment; the rates of leiomyoma size reduction were 50% to 60%; there were 88% to 92% reduction of bulk symptoms, >90% elimination of abnormal uterine bleeding, and up to 75% elimination of symptoms[40].

A systematic review and meta-analysis in 2024 comparing UAE and myomectomy for symptomatic uterine fibroids reported that UAE had superior post-procedural outcomes including fewer major complications (infection, pulmonary embolism, uterine ischaemia, fibroid expulsion, and sepsis) within 30 days of discharge (odds ratio [OR]=0.44), fewer readmissions due to complications (OR=1.16), and shorter hospital stay (mean difference [MD]= -47.07)[41]. UAE was not inferior to myomectomy in terms of obstetric outcomes, with comparable rates of amenorrhoea, pregnancy, live birth, and miscarriage. However, the quality-of-life scores did not improve significantly at 2 or 4 years of follow-up. At 1, 2, and 4 years of follow-up, UAE was associated with higher rates of reintervention (OR=1.77, 3.44, and 1.84, respectively) and greater risks of hysterectomy (OR=2.67, 4.06, and 4.04, respectively). Common post-procedural adverse effects include pain, nausea, groin haematoma, fever, and post-embolisation syndrome (fever, pain, and nausea).

***High-intensity focused ultrasound***

High-intensity focused ultrasound (HIFU) guided by ultrasound or magnetic resonance imaging transmits energy to a targeted lesion, raising its temperature to >60°C and leading to localised coagulative necrosis within 1 to 3 mm of boundaries of the lesion without damaging surrounding tissue[42].

In a meta-analysis of 10 studies involving 4450 women comparing outcomes of HIFU with myomectomy[43], HIFU showed better fibroid symptom control, with significant improvements in uterine fibroid symptom–related quality-of-life scores at 6 months (MD= -4.16, 95% confidence interval [CI]= -7.39 to -0.94) and 12 months (MD= -2.44, 95% CI= -3.67 to -1.20) and in overall quality-of-life scores at 6 months (MD=2.13, 95% CI=0.86-3.14) and 12 months (MD=2.34, 95% CI=0.82-3.85). HIFU showed significantly shorter duration of hospital stay (MD= -3.41 days, 95% CI= -5.11 to -1.70 days) and time to return to work (MD= -11.61 days, 95% CI= -19.73 to -3.50 days), as well as a significantly lower incidence of severe complications (including fever, transfusion, and re-hospitalisation) within 42 days (risk ratio=0.33, 95% CI=0.13-0.81). The rate of reintervention at 60 months, however, was 53.9% after HIFU, compared with 12.2% after myomectomy and 14.4% after UAE[44].

In a systematic review of 14 studies assessing reproductive outcomes after magnetic resonance imaging–guided HIFU (n=124) or ultrasound-guided HIFU (n=366)[28], in the respective groups, pregnancy rates were 7% to 36% and 10% to 69%; live birth rates were 73% to 84% and 91%; conception occurred within 0 to 36 months and 4 to 16 months of treatment; miscarriage rates were 30% to 50% and 4% to 15%; and rates of Caesarean section were 36% to 64% and 72% to 80% (although most were performed for social reasons). Overall, the pregnancy rates were lower after HIFU than after myomectomy, but live birth rates were comparable. There were eight cases of placenta praevia without any invasive placentation but no reports of uterine rupture.

HIFU is generally safe; absolute contraindications include pregnancy, malignant or suspected malignant pelvic masses, active pelvic infections, intrauterine contraceptive device in situ, severe abdominal adhesions, interposed bowel/bladder, and submucosal fibroids with a significant intracavity component, whereas relative contraindications include pedunculated fibroids, fibroids >10 cm, numerous or diffuse fibroids, previous uterine surgery, and very thick abdominal walls. With appropriate patient selection, HIFU can deliver effective treatment of uterine fibroids.

***Radiofrequency ablation***

Radiofrequency ablation (RFA) applies an alternating current in the radiofrequency range of 450 to 500 kHz, through a transvaginal, transcervical, percutaneous, or laparoscopic approach. It induces local tissue destruction, coagulative necrosis, and hence fibroid shrinkage.

In a systematic review and meta-analysis of 30 studies that evaluated clinical outcomes after RFA, the mean fibroid volume reduced by 46% at 3 months and 65.4% at 12 months, with substantial improvement in abnormal menstrual bleeding within the first 3 months, which was maintained up to 24 months[45]. Uterine fibroid symptom–related quality-of-life scores peaked at 6 months after RFA (88.0, 95% CI=83.0-92.9; 11 studies), with a significant increase in quality-of-life scores (53.4, 95% CI=48.2-58.5; 20 studies) and a significant decrease in symptom severity scores (52.2, 95% CI=46.2-58.1; 17 studies). The symptom severity scores were lowest at 12 months (12.8, 95% CI=7.0-18.6; 11 studies) and were sustained for up to 5 years. The mean hospital stay was 2.5 to 12 hours; the mean time for return to normal activity was 2.2 to 16.3 days, averaging 5.8 days; and the rates of secondary hysterectomy were 1% to 24.1%, with the longest follow-up being 74 months.

A systematic review of 10 studies involving 923 patients with RFA reported a total of 50 pregnancies[46]. The mean age of patients ranged from 27 to 46 years; conception occurred within 3.5 to 33 months of RFA; 44 of the pregnancies were full term and delivered vaginally (55%) or through Caesarean section (45%); the spontaneous miscarriage rate was 12%. There were no reports of uterine rupture, placental abruption, or invasive placentation. Nevertheless, RFA has not yet been approved by the FDA for women seeking future fertility.

RFA is generally safe and well tolerated. Absolute contraindications include pregnancy, malignant or suspected malignant pelvic masses, active pelvic infections, intratubal or other metal implants, and intrauterine contraceptive device in situ. Relative contraindications include nickel allergy, coagulopathy, numerous or diffuse fibroids, interposed bowel or bladder, and significant abdominal adhesions. With appropriate patient selection, RFA can be effective treatment for uterine fibroids.

## Conclusion

Treatment for uterine fibroids should be personalised to suit each woman's needs with minimal compromise to

fertility, reproductive, or obstetric outcomes. Leiomyomata, however, do not exist in isolation and are commonly found as a constellation of gynaecological pathologies including endometriosis, adenomyosis, and endometrial hyperplasia or even malignancy. Surgery must still be considered when symptoms cannot be adequately controlled or in an emergency setting in which fibroid-related complications such as torsion or obstructive uropathy arise. Malignancy should be suspected in cases of rapidly growing fibroids (particularly in postmenopausal women), when suspicious features (irregular margins, intralesional vascularity, central necrosis, or haemorrhage) are seen on imaging or when there are associated symptoms. Prompt surgical evaluation to exclude leiomyosarcoma is warranted. Although minimally invasive techniques preserve fertility and avoid surgical morbidity, myomectomy or hysterectomy remains the definitive treatment. Shared decision making is essential, particularly in women of reproductive age, aiming at balancing efficacy, fertility goals, and procedural risks.

## Contributors

JL designed the study, acquired and analysed the data, drafted the manuscript, and critically revised the manuscript. MC critically revised the manuscript. Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy.

## Conflicts of interest

Both authors have no conflicts of interest to disclose.

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## Data availability

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

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With Monofer®, your patients need ONE IV infusion when their required iron is up to 20 mg/kg body weight[1,2,4,5]

## Rapidly improves fatigue†[6]

In the PHOSPHARE-IBD# study, Monofer® was associated with a greater improvement in patient-reported fatigue score at Day 35, compared with ferric carboxymaltose (p=0.005)[6]

## Robust safety profile[1,3]

Well tolerated across patient groups with an uncommon incidence of hypophosphataemia (0.1% to 1% of patients)[1,3]

†In the PHOSPHARE-IBD# study, Monofer® was associated with greater improvement in patient-reported fatigue scores at Days 35 and 49, compared with ferric carboxymaltose (p=0.005 and 0.009 respectively).[6]

#A multicentre, randomised, head-to-head comparison of IV Monofer® and ferric carboxymaltose in patients with both IBD and IDA. The primary endpoint for this study was the incidence of hypophosphataemia (serum phosphate < 2.0 mg/dL) at any time, Day 0-35 (SAS). Change in FACIT-Fatigue Scale score (prespecified exploratory outcome; ITT) was a secondary endpoint in this study. A greater improvement in fatigue scores was observed among Monofer®-treated patients compared to ferric carboxymaltose-treated patients at Day 35 ($p=0.005$) and Day 49 ($p=0.009$), despite the difference not being significant at Day 70.[1]

*Hypophosphataemia is an uncommon adverse drug reaction observed during clinical trials and post-marketing experience.

Abbreviations: IV, intravenous; IBD, inflammatory bowel disease; IDA, iron deficiency anaemia; FACIT, Functional Assessment of Chronic Illness Therapy; ITT, intention to treat; SAS, statistical analysis system.

**Monofer® 100 mg/ml solution for injection/infusion**

**Composition:** 1 ml contains 100 mg iron as iron(III) isomaltoside 1000. Available in vials/ampoules of 1 ml and 5 ml. **Indications:** Monofer® is indicated for the treatment of iron deficiency in the following conditions: (1) Oral iron preparations are ineffective or cannot be used. (2) There is a clinical need to deliver iron rapidly. The diagnosis must be based on laboratory tests. **Dosage and Administration:** Monitor patients for hypersensitivity reactions during and following each administration. Administer only when staff trained to evaluate and manage anaphylactic reactions is available. Calculate iron need using the Simplified Table or Ganzoni formula. Do not exceed 20 mg iron/kg body weight per week. Not recommended for children and adolescents <18 years. **IV bolus injection:** up to 500 mg up to three times a week, administered undiluted or diluted in max. 20 ml sterile 0.9% NaCl at a rate of up to 250 mg iron/min. **IV infusion:** up to 20 mg iron/kg body weight, administered undiluted or diluted in max 500 ml sterile 0.9% NaCl (to no less than 1 mg iron/ml). **Contraindications:** Hypersensitivity to the active substance or any excipients. Known serious hypersensitivity to other parenteral iron products. Non-iron deficiency anaemia. Iron overload or disturbances in iron utilisation. Decompensated liver disease. **Precautions:** Hypersensitivity reactions, including serious and potentially fatal anaphylactic/anaphylactoid reactions. Increased risk in patients with known allergies including drug allergies, including patients with a history of severe asthma, eczema or other atopic allergy, and patients with immune inflammatory conditions. Each patient should be observed for adverse effects for at least 30 minutes following each Monofer injection. Avoid in patients with hepatic dysfunction where iron overload is a precipitating factor and patients with ongoing bacteraemia. Absorption of oral iron is reduced when administered concomitantly. **Fertility, Pregnancy, and Lactation:** Pregnancy: Limited data from use in pregnant women. Treatment should be confined to second and third trimester if the benefit outweighs the potential risk for both the mother and the foetus. Breast-feeding: At therapeutic doses, no effects on the breastfeed newborns/infants are anticipated. Fertility: No data on human fertility. **Effects on ability to drive and use machines:** No studies on have been performed. **Undesirable Effects:** Acute severe hypersensitivity reactions may occur. In pregnancy, associated foetal bradycardia may occur. Distant skin discolouration has been reported. Common ADRs (≥1/100 to <1/10): Nausea; Rash; Injection site reactions. Uncommon ADRs (≥1/1000 to <1/100): Hypersensitivity, Headache, paraesthesia, dysgeusia, blurred vision, loss of consciousness, dizziness, fatigue; Tachycardia; Hypotension; hypertension; Chest pain, dyspnea, bronchospasm; Abdominal pain, vomiting, dyspepsia, constipation, diarrhoea; Pruritus, urticaria, flushing, sweating, dermatitis; Hypophosphataemia; Back pain, myalgia, arthralgia, muscle spasms; Pyrexia, chills/shivering, infection; local phlebitis reaction, skin exfoliation; Hepatic enzyme increase. For further information consult full prescribing information. [July 2022]

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**VEOZA is indicated for the treatment of moderate to severe Vasomotor Symptoms (VMS) associated with menopause, *also known as hot flashes & night sweats.*[1,6]**

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LARC: Long-acting reversible contraception
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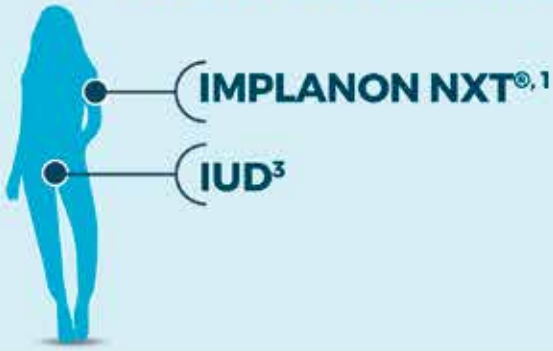


Provides up to **3 years** of pregnancy prevention without depending on daily adherence

**3**
Lasts for 3 years without any daily, weekly, or monthly dosing[2]

Over **99%** effective[1,*]
>99.9% effective[2]

Reversible[2]
Rapid return to normal menstrual cycle upon removal

**30**
Mean insertion time was <30 seconds[1]

* Placed subdermally just under the skin in the inner non-dominant upper arm.

**References: 1.** Implanon NXT® CCDS, Organon Inc., February 22, 2022. **2.** Implanon NXT® Prescribing Information. Organon Hong Kong, Dec 2023. **3.** American College of Obstetricians and Gynecologists. Long-acting reversible contraception (LARC): intrauterine device (IUD) and implant. Accessed 17 Jun, 2024. https://www.acog.org/womens-health/faqs/long-acting-reversible-contraception-iud-and-implant

**Selected Safety Information of Implanon NXT®**

**Therapeutic indications** Contraception. Safety and efficacy have been established in women between 18 and 40 years of age. **Posology** 1 implant, which can be left in place for three years. **Method of administration** Pregnancy should be excluded before insertion of Implanon NXT. It is strongly recommended that Implanon NXT be inserted and removed only by physicians who have completed training for the use of the Implanon NXT applicator and the techniques for insertion and removal of the Implanon NXT implant, and, where appropriate, that supervision be requested prior to inserting or removing the implant. Before inserting the implant, carefully read and follow the instructions for insertion and removal of the implant in section 4.2 How to insert Implanon NXT and How to remove Implanon NXT. <Videos demonstrating insertion and removal of the implant are available online www.nexplanonvideos.com> If you are unsure of the necessary steps to safely insert and/or remove Implanon NXT, do not attempt the procedure.

**Selective Safety Information**

**Contraindications** • Active venous thromboembolic disorder. • Known or suspected sex steroid sensitive malignancies. • Presence or history of liver tumours (benign or malignant). • Presence or history of severe hepatic disease as long as liver function values have not returned to normal. • Undiagnosed vaginal bleeding. • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of prescribing information. **Special warnings and precautions for use** If any of the conditions / risk factors mentioned below is present, the benefits of progestagen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with Implanon NXT. In the event of aggravation, exacerbation or first appearance of any of these conditions, the woman should contact her HCP. The HCP should then decide on whether the use of Implanon NXT should be discontinued. • Carcinoma of the Breast • Liver Disease • Thrombotic and Other Vascular Events • Elevated Blood Pressure • Carbohydrate Metabolic Effect • Chloasma • Body Weight • Complications of Insertion • Ovarian Cysts • Ectopic Pregnancies • Psychiatric Disorders • Others: The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestagens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss and (hereditary) angioedema. **Undesirable effects Related undesirable effects reported in clinical trials** Very Common (>1/10): vaginal infection; Headache; Acne; breast tenderness; breast pain; menstruation irregular; weight increased Common (< 1/10 ≥ 1/100): increased appetite; affect lability; depressed mood; nervousness; libido decreased; Dizziness; hot flush; abdominal pain; nausea; flatulence; Alopecia; Dysmenorrhoea; ovarian cyst; implant site pain; implant site reaction; fatigue, influenza like illness; pain; weight decreased; Uncommon (< 1/100 ≥ 1/1000): pharyngitis, rhinitis, urinary tract infection; Hypersensitivity; Anxiety; insomnia; Migraine; somnolence; Vomiting; constipation; diarrhoea; hypertrichosis, rash; pruritus; back pain; arthralgia; myalgia, musculoskeletal pain; Dysuria; genital discharge; vulvovaginal discomfort; galactorrhoea; breast; enlargement; pruritus genital; Pyrexia; oedema; For detailed side effects, please refer to the full prescribing information.

**Before prescribing, please consult the full prescribing information.**

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