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References: 1. MERCILON approved package insert, March 2013. **2.** Lammers P and Op Ten Berg M. Phase III clinical trial with a new oral contraceptive containing 150 µg desogestrel and 20 µg ethinylestradiol. *Acta Obstet Gynecol Scand.* 1991;70:497–500. **3.** Serfaty D and Vree ML. A comparison of the cycle control and tolerability of two ultra low-dose oral contraceptives containing 20 µg ethinylestradiol and either 150 µg desogestrel or 75 µg gestodene. *The European Journal of Contraception & Reproductive Health Care.* 1998;3(4):179–189. **4.** Anttila L, Kunz M, Marr J, et al. Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive. *Contraception.* 2009;80:445–451. **5.** Endrikat J, Cronin M, Gerlinger C. et al. Open, multicenter comparison of efficacy, cycle control, and tolerability of a 23-day oral contraceptive regimen with 20 µg ethinyl estradiol and 75 µg gestodene and a 21-day regimen with 20 µg ethinyl estradiol and 150 µg desogestrel. *Contraception.* 2001;64:201–207.

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The *Hong Kong Journal of Gynaecology, Obstetrics & Midwifery* publishes peer-reviewed articles on all aspects of gynaecology, obstetrics, midwifery and related fields, including original basic and clinical studies, review articles, case reports, perspective, and abstracts or reports presented at scientific meetings or seminars.

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

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Editorial
Brief review of our Journal

The *Hong Kong Journal of Gynaecology, Obstetrics and Midwifery* (HKJGOM) is the official publication of the Obstetrical & Gynaecological Society of Hong Kong (OGSHK) and the Hong Kong Midwives Association (HKMA). HKJGOM publishes peer-reviewed articles on all aspects of gynaecology, obstetrics, and midwifery fields, including basic sciences and clinical studies, in the form of original articles, case reports, review articles, and perspectives. The pink-coloured cover of the first edition was used from 2000 to 2002, whereas the current blue-coloured cover has been used since 2005. The Journal was published every half year between 2000 and 2002 under the auspices of our founding Editor-in-Chief, Dr Tang Chang Hung, Lawrence. After a hiatus of 2 years (2003 and 2004), it was published annually under the leadership of our second Editor-in-Chief, Dr Leung Kwok Yin, between 2005 and 2014. I have the great honour to be appointed the third Editor-in-Chief from 2015, and half-yearly issues have been resumed since then. Up to this current issue, the HKJGOM has published a total of 33 issues in the past 23 years and included around 216 original articles, 69 reviews, 24 case reports, and 28 editorials (editorial was introduced in 2005). Our readership includes not only members of the OGSHK and the HKMA, but also fellows, members, and trainees of the Hong Kong College of Obstetricians and Gynaecologists (HKCOG), as well as fellows and members of the Hong Kong College of Midwives. Although some memberships are overlapping, our readership covers all doctors and midwives in our specialties in public and private sectors.

Early issues of the HKJGOM included the historical accounts and reviews describing the milestones of our specialties. In the inaugural 2000 issue, Prof HK Ma wrote a detailed account of the development of the obstetrics and gynaecology specialty in Hong Kong titled "Obstetrics and Gynaecology in Hong Kong". In the second issue in 2000, Ms Anne WM Chow, then Principal of the School of Midwifery in Prince of Wales Hospital, published an equally important article titled "Metamorphosis of Hong Kong Midwifery" to highlight the development of midwifery training in Hong Kong and the changing roles of midwives. In the same issue, Prof Dennis YM Lo and Prof Rossa WK Chiu published a paper titled "Fetal DNA in maternal plasma: biological and diagnostic implications" as a prelude to the ground-breaking era of non-invasive prenatal testing in routine obstetric practice. Other milepost papers published were "The Family Planning Association of Hong Kong: history and development" in 2002 Issue 1 by Dr Susan YS Fan, then Director of the association, and "The birth of the Hong Kong College of Midwives" in 2013 Issue 1 by Dr Alice Sham, the founding President of the college.

With the consolidation of research training requirements for each HKCOG specialist trainee to publish an original paper as principal author in a peer-reviewed journal in 1997, the HKJGOM has served as a popular platform for trainees to publish their papers to fulfil their exit requirement. At one time, the increasing number of submissions resulted in a long delay from acceptance to publication. The reintroduction of half-yearly issues since 2015 has enabled timely publication and, as a corollary, has encouraged more trainees to submit their manuscripts to the HKJGOM. To facilitate trainees for their exit assessment, fast track peer review and processing, as well as support for English language, statistics, and data presentation are provided at the discretion of the Editorial Board.

To enrich the contents of the Journal, invited review articles have been reintroduced since 2015 to provide readers with up-to-date information on important new development and practice in our specialties. Landmark review articles include "Role of intrapartum ultrasound in modern obstetrics" by Dr Viola YT Chan et al in 2017 Issue 2, "Screening and prevention of pre-eclampsia: a review" by Dr Piya Chaemsaithong et al in 2019 Issue 1, "Enhanced recovery for gynaecological surgery: a review" by Dr Christopher F Yim et al in 2019 Issue 2, and "Expanded carrier screening for recessive genetic disorders: a review" by Dr Olivia YM Chan et al in 2020 Issue 1. The clinical protocols discussed in these reviews have increasingly become routine daily practice.

With the introduction of editorial in 2005, invited editorials on significant and controversial issues have been published to initiate discussion. Recent important editorials include "Would new medical graduates choose obstetrics and gynaecology as their future career anymore?" in 2017 Issue 1 by Dr WC Leung, then President of HKCOG, "Medical Indemnity: are we safe yet" in 2017 Issue 2 by Dr

Ares Leung, past president of HKCOG, "Genetic training for obstetricians and gynaecologists" in 2019 Issue 1 by Prof TY Leung, then president of HKCOG, and "How has COVID-19 impacted obstetrics?" in 2021 Issue 1 by Prof Liona Poon and her team. In this issue, the second editorial "Acute life support in obstetrics: the way forward" by Dr CW Kong describes the evolution of the courses of advanced life support in obstetrics in Hong Kong from its introduction two decades ago.

With the establishment of the HKJGOM website offering free downloads for all articles published from 2005 onwards (only abstracts are available for papers published between 2000 and 2002), papers of the HKJGOM are increasingly cited in other international journals. Although the HKJGOM is not indexed in PubMed, it is listed in Google scholar and Embase so that all articles in the Journal are searchable in Google. Future efforts to index the HKJGOM include increasing the number of issues per year, enhancing the quality of papers published, attracting more trainees and researchers to submit papers to HKJGOM, and applying indexing to other academic databases and platforms. All these targets are not easily achievable; nor can they be achieved by efforts of the Editorial Board or OGSHK or HKMA alone. Collaborated efforts of all parties are called for.

It has indeed been a great privilege for me to be one of the Editors-in-Chief of the HKJGOM in the past decade. Admittedly, due to the limited resources, a lot of the work in screening submissions, inviting reviewers, soliciting review articles and editorials, and editing and proofreading manuscripts have been manned by myself. However, the direct communications with authors, reviewers, and editors through these years have been most rewarding and gratifying. The process of reading and editing manuscripts in great depth has enhanced my professional learning. The connections with researchers and reviewers at all levels have greatly extended my professional circle and enriched my friendship and solidarity with many colleagues. I am most grateful to authors who revise their papers meticulously (and sometimes repeatedly) to meet the demands of reviewers, and to reviewers who agree to fast track the review process with a short notice. It is hoped that the upcoming Editor-in Chief will be in a better position in terms of support and resources available, and that the HKJGOM will continue to flourish and reach new heights in academic impact.

William WK TO, MBBS, MPH, MPhil, MD, Dip Med, FRCOG, FHKAM (O&G), Cert HKCOG (MFM)
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(This article is adapted and updated from "HKJGOM – a brief review" published in the Obstetrical and Gynaecological Society of Hong Kong 60th Anniversary Commemorative Book published in 2022.)

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Editorial
Acute life support in obstetrics: the way forward

Developed by the American Academy of Family Physicians, the Advanced Life Support in Obstetrics (ALSO) course is an evidence-based, inter-professional, and multidisciplinary training programme to equip the entire maternity care team with skills to effectively manage obstetric emergencies. The ALSO course aims to decrease mortality and morbidity of both the mother and baby by incorporating both didactic and practical hands on workstations with the use of manikins[1,2]. The ALSO course encourages a standardised team-based approach among doctors, nurses, midwives, and other members of the maternity care team to improve patient safety and maternal outcomes. Participants must pass a written test and a practical hands-on case management of a birth (mega-delivery) incorporating many elements learned throughout the course. One feature of ALSO is the use of ALSO mnemonics to 'immunise' learners against forgetting steps or details in handling obstetric emergencies[2].

Development of the original ALSO course was based on a vastly different clinical scenario from that in Hong Kong. At that time in the United States, pregnant women were commonly looked after by general practitioners in rural hospitals, often single-handedly. In 1991, Jim Damos and John Beasley from the Department of Family Medicine at the University of Wisconsin developed an obstetric emergency course to help standardise the care of these women[3]. The course was purchased by the American Academy of Family Physicians in 1993[4], and the ALSO course was launched as a national programme for all family physicians, registered nurses, and midwives. Since then, the ALSO course has been taught in more than 60 countries.

In 2001, the ALSO course was introduced to Hong Kong by Dr Chung Chin Hung who was then the Chief-of-Service of the Department of Emergency Medicine in North District Hospital. Since then, the course has been run annually, and over 2400 doctors, nurses, and midwives have participated. Hong Kong is one of the only places worldwide where ALSO is also taken up by emergency physicians. An early paper on ALSO specifically stated that "limited evidence suggests it can be effective and efficient in enhancing the knowledge and skills of prehospital and disaster medicine clinicians. Hong Kong provides a model in which emergency physicians have taken the lead in promoting the ALSO course"[1]. The first course was taught by four overseas instructors including Dr Charles Cox from Wolverhampton, UK and Dr Kim Hinshaw from Sunderland, UK (Figure 1). Dr Cox is also responsible for the development of the Management of Obstetric Emergencies and Trauma (MOET) courses. Dr Hinshaw subsequently returned to Hong Kong to teach the ALSO instructor courses in 2007 as well as the commissioned training programme of the Hospital Authority in 2008. He has been one of the overseas editors of our Journal since 2015.

In 2002, the Hong Kong College of Obstetricians and Gynaecologists (HKCOG) appointed Dr William To as the liaison officer to coordinate with the College of Emergency Medicine to organise the ALSO course. At that time, no local specialists had formally completed the ALSO instructor course yet to qualify as instructors and could only teach as guest instructors. Dr Mark Deutchmann, one of the founding members of the original ALSO board, participated in the 2002 courses as an overseas faculty (Figure 2). He did an excellent job to supervise and train the local faculty to teach using the ALSO mnemonics. In December 2003, the ALSO Board (Hong Kong) was established with Dr Chung as the founding chairman and Dr To as the honorary secretary. Since 2004, the ALSO has been jointly organised by the two colleges. A second instructor course was held in 2004, and specialists from our College were formally accredited as the first batch of

Figure 1. Participants of the first course of advanced life support in obstetrics in Hong Kong in 2001

Figure 2. Participants of the advanced life support in obstetrics instructor course in Hong Kong in 2002

bona fide instructors, along with emergency physicians, and midwives.

The Hong Kong ALSO has undergone many changes in the past years. Since Dr To's appointment as chairman of the board in 2006, it has been a tradition that the board is led by a chairman from our College, while the vice chairman is from the College of Emergency Medicine. In early years, the course was directly duplicated from the original course, comprising a 2-day programme with a mixture of formal lectures and hands-on skill sessions in the form of workstations. In 2007, case discussions and videos were introduced to replace some didactic lectures. In 2008, under the auspices of Dr To, the course was revamped by replacing more lectures with interactive case discussions and hands-on skill workstations and by introducing new modules such as breech delivery and neonatal resuscitation into the mega-delivery.

After I was appointed chairman of the board in 2021, with the support of other board members, I introduced maternal fetal resuscitation simulation training in the form of a scenario-based perimortem caesarean section drill using a manikin (Figure 3)[5]. In 2022, we evaluated the feedback of participants with regards to simulation training and published the results in the *Hong Kong Journal of Emergency Medicine*[6]. Among the participants, 97.8%, 98.5%, 97.0% agreed that the maternal fetal resuscitation simulation training could help their work, improve their knowledge and skills, and improve team training and co-ordination, respectively. 97.0% of participants felt more confident in managing maternal cardiac arrest, and 97.8% of participants felt that the perimortem caesarean section model was useful for such training.

In early days, most participants in the ALSO provider courses were residents, midwives, and registered

Figure 3. Perimortem caesarean section simulation training

nurses working in obstetrics and gynaecology units or accident and emergency departments in the public sector. As the ALSO becomes more well accepted and the ALSO mnemonics more popularly used, interested specialists from our College from both public and private sectors as well as midwives from private hospitals have also attended the ALSO courses. Faced with the pressure from non-entitled Mainland Chinese women in advanced pregnancy presenting to the accident and emergency department, emergency physicians have also eagerly attended the ALSO courses (Figure 4). Currently, the ALSO course is obligatory for all trainees in HKCOG. The Department of Health demands midwives working in private hospitals to have a valid ALSO (or other equivalent courses) provider status for re-accreditation of the hospital's obstetric practice. In addition, the ALSO board has run instructor courses in 2001, 2004, 2007, 2010, 2013, 2017, and 2019 to recruit obstetricians, emergency physicians, and midwives as instructors. In May 2023, an instructor course is scheduled to be held in parallel with the provider courses.

Apart from the ALSO and MOET, other courses with simulation training for obstetric emergencies include the Practical Obstetric Multi-Professional Training (PROMPT) and the Multidisciplinary Obstetric Simulated Emergency Scenarios (MOSES) from the UK. There are also short courses organised by the Royal College of Obstetricians and Gynaecologists or individual National Health Service Trusts focusing on certain clinical modules such as postpartum haemorrhage, instrumental delivery skills, or maternal resuscitation techniques[7]. The College

Figure 4. Participants of the advanced life support in obstetrics provider course

Table 1. Specialty and rank of participants of the advanced life support in obstetrics provider course in 2022

	No. of participants		
	Accident and emergency	**Obstetrics and gynaecology**	**Others**
Resident	33	13	0
Resident specialist	1	0	1
Associate consultant	2	0	0
Registered nurse	31	78	1
Registered midwife	1	7	0
Advanced practice nurse	7	0	0
Nurse officer	0	0	1
Total	**75**	**98**	**3**

of Family Physicians of Canada developed the Advanced Labour and Risk Management (ALARM), which serves the same purpose as the ALSO. The ALARM has also been taught in Australia. In Hong Kong in 2020, the Chinese University of Hong Kong under the auspice of Prof TY Leung launched the Safe Obstetrics Practice for High Risk and Emergency (SOPHIE). These various courses vary in scope and contents as well as the level of simulation training. For instance, the MOET and MOSES courses are generally considered to be more advanced than the ALSO, whereas the PROMPT course focuses more on team training than on individual skills training. The SOPHIE course is relevant to obstetric residents and midwives but is proved to be too sophisticated for emergency physicians or doctors or nurses not regularly practicing obstetrics or those with no foundation training in obstetrics. The ALSO remains to be the most acceptable and applicable to obstetric residents and midwives as well as to emergency physicians and nurses who handle obstetric emergencies.

With the onset of the COVID pandemic in early 2020, the ALSO course structure in the United States now features a 1-day online curriculum and a 1-day in-person hands-on skills workstation and a separate assessment session. Since 2022, the ALSO Board (Hong Kong) has adopted a hybrid programme with online lectures and a 1-day in-person skills training course. Participants are required to watch the recorded lectures and case discussions and read the training materials before attending the skills workstation. In May 2022, we conducted a survey of 178 participants in five provider courses. Of 176 participants responded, 55.7% were from obstetrics and gynaecology departments, 42.6% were from accident and emergency departments, and 1.7% were from other specialties, whereas 28.4% were doctors and 71.6% were nurses (Table 1). 69.9% of participants preferred the hybrid course ($p<0.001$, Table 2). Those who preferred the hybrid course reported that they had more preparation and watched more recorded lectures

Table 2. Factors associated with preference for hybrid course among participants in 2022 advanced life support in obstetrics (ALSO) course

	Preferring hybrid course (n=123)*	Preferring in-person course (n=53)*	p Value
Specialty			<0.001
Accident and emergency	41 (33.3)	34 (64.2)	
Obstetrics and gynaecology (O&G)	81 (65.9)	17 (32.0)	
Others	1 (0.8)	2 (3.8)	
Rank			0.73
Doctors	34 (27.6)	16 (30.2)	
Nurses	89 (72.4)	37 (69.8)	
Clinical experience in specialty, y	6.15±5.47	4.1±3.56	0.013†
Workplace support (for non-O&G only)	n=41	n=34	0.20
With on-site obstetric service	25 (61.0)	14 (41.2)	
Without on-site obstetric service	16 (39.0)	20 (58.8)	
Preparation before course			0.028
Nil	1	4	
Read <50% lectures	13	12	
Read 50% lectures	19	7	
Read >50% lectures	40	10	
Read 100% lectures	33	12	
Read ≥100% lectures	17	8	
Preparation before course >50%	90 (73.1)	30 (56.6)	0.03
Overall rating of recorded lectures			0.001
Excellent	24 (19.5)	8 (15.1)	
Good	86 (69.9)	26 (49.0)	
Fair	12 (9.8)	18 (34.0)	
Not satisfactory or poor	1 (0.8)	1 (1.9)	
Overall rating of practical workshops			0.77
Excellent	69 (56.1)	31 (58.5)	
Good	53 (43.1)	21 (39.6)	
Fair	1 (0.8)	1 (1.9)	
Not satisfactory or poor	0	0	
Overall rating of teaching materials			<0.001
Excellent	35 (28.5)	8 (15.1)	
Good	79 (64.2)	29 (54.7)	
Fair	9 (7.3)	16 (30.2)	
Not satisfactory or poor	0	0	
Achievement of the programme			
Improve obstetric management	105 (85.4)	38 (71.7)	0.033
Facilitate interactions between providers	94 (76.4)	33 (62.2)	0.054
Enhance care and abolish barriers	89 (72.4)	32 (60.4)	0.11
Format of ALSO course in future			<0.001
Keep current hybrid format	102 (82.9)	2 (3.8)	
Change to face to face	4 (3.3)	42 (79.2)	
Neutral	17 (13.8)	9 (17.0)	
Overall rating of ALSO course			0.011
Excellent	47 (38.2)	12 (22.7)	
Good	75 (61.0)	37 (69.8)	
Fair	1 (0.8)	4 (7.5)	
Not satisfactory or poor	0	0	

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

† Mean difference= -2.05, 95% confidence interval= -3.66 to -0.43

Table 3. Reasons for preferring recorded lectures versus face-to-face lectures

Reasons	No. (%) of participants
Preferring recorded lectures (n=123)	
Can watch beforehand	21 (17.1)
Can watch at convenient time	9 (7.3)
Can watch repeatedly	4 (3.3)
Can watch after course to revise on particular topics	2 (1.6)
All of the above	87 (70.7)
Preferring face-to-face lectures (n=53)	
Can allow demonstration of certain skills	14 (26.4)
Can memorise better	9 (17.0)
Can ask questions easier	4 (7.5)
Can have protected learning time	2 (3.8)
All of the above	24 (45.3)

Figure 5. Breech delivery and neonatal resuscitation workstations

before attending the workstations. They were more likely to consider the recorded lectures and teaching materials to be good quality. They could watch the pre-recorded lectures beforehand, at their convenient time, and repeatedly. Nonetheless, some participants considered that the in-person course may facilitate question-asking, memorisation of taught materials, and demonstration of skills (Table 3). Overall, 59.1% of participants preferred to keep the hybrid format, 14.8% were neutral, and 26.1% preferred in-person course. Over 90% of participants gave an overall rating as good or excellent. Most agreed that the ALSO courses could improve their obstetric management, interactions between providers, and utilisation of care and could abolish barriers. Based on these results, the ALSO board decided to keep the hybrid courses, which are more cost-effective and enable organisation of more courses as needed. The workstations in the coming ALSO courses will include instrumental delivery, shoulder dystocia, neonatal resuscitation, vaginal breech delivery, cord prolapse, postpartum haemorrhage, maternal resuscitation, and perimortem caesarean section simulation (Figure 5).

We hope that the ALSO (Hong Kong) Board continues to meet the needs of those who involve emergency obstetric care. We sincerely thank all board members, instructors, and participants for their support over these years.

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Predictors for poor maternal and neonatal outcomes in parturients with intrapartum fever: a case-control study

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Objective: This study aims to determine the predictors for intrapartum fever and for poor maternal and neonatal outcomes in parturients with intrapartum fever, and to evaluate the pathogens involved and their resistance to antibiotics.
Methods: Medical records of patients with intrapartum fever and singleton delivery at term in Tuen Mun Hospital, Hong Kong between 1 July 2020 and 31 June 2021 were retrieved. Each patient was matched with a consecutive healthy control by parity and gestational age. The case and control groups were compared in terms of composite adverse maternal and neonatal outcomes. Multivariate analyses were used to determine predictors for intrapartum fever and for poor maternal and neonatal composite outcomes. Pathogens isolated from maternal, placental, and neonatal specimens were evaluated, as was their resistance to antibiotics.
Results: The incidence of intrapartum fever was 4.4% (164/3729). In multivariate analysis, predictors for intrapartum fever were hypertensive disease (adjusted odds ratio [aOR]=7.42, p=0.015), epidural analgesia (aOR=6.22, p<0.001), and duration of ruptured membranes (aOR=1.07, p=0.044). Epidural analgesia was a predictor for composite adverse maternal outcome (aOR=2.65, p=0.007), whereas maternal temperature of ≥39°C was a predictor for composite adverse neonatal outcome (aOR=5.15, p=0.036). Positive bacterial culture was not associated with poor neonatal outcomes. Higher degrees of maternal temperature were associated with higher composite maternal and neonatal morbidity. 89 (54.3%) of febrile patients had positive culture results. *Enterococcus* was the most common gram-positive organism (48.1%) and *Escherichia coli* was the most common gram-negative bacteria (65.2%).
Conclusion: Intrapartum fever is associated with poor maternal and neonatal outcomes. Obstetricians should avoid long duration of labour and high maternal temperature. The choice of antibiotics for intrapartum fever/chorioamnionitis should be carefully selected, with consideration of efficacy, possible adverse effects, and antimicrobial resistance.

Keywords: Chorioamnionitis; Fever; Infant, newborn; Maternal health

Introduction

Intrapartum fever is defined as a maternal body temperature of ≥38°C during labour. Its prevalence ranges from 1.6% to 14.6% of deliveries[1]. Chorioamnionitis is suspected when the maternal temperature is ≥39°C alone or 38.0°C to 38.9°C plus presence of other risk factors[2]. Intrapartum fever/chorioamnionitis negatively affects obstetric and neonatal outcomes. Intrapartum fever can be caused by infections such as chorioamnionitis, pyelonephritis, respiratory infection, and viral infection[3]. It can also be triggered by non-infectious causes such as epidural analgesia, environment temperature changes, and prostaglandin use during induction of labour. The aetiology of most maternal fever cases is more likely to be non-infectious, particularly resulting from epidural analgesia[4]. Nevertheless, obstetricians usually start treatment once intrapartum fever is detected even when chorioamnionitis is not evident yet.

Intrapartum fever is highly associated with adverse maternal outcomes (postpartum haemorrhage, labour dystocia, operative vaginal delivery, caesarean delivery, endometritis, and sepsis) and increased risks of neonatal morbidities (low Apgar scores, respiratory distress, neonatal sepsis, meconium aspiration, and neonatal intensive care unit admission)[1,3,5-8]. This study aims to determine the predictors for intrapartum fever and clinical factors that lead to poor maternal and neonatal outcomes in parturients with intrapartum fever, and to evaluate the pathogens involved and their resistance to antibiotics.

Materials and methods

Medical records of patients with intrapartum fever and singleton delivery at term in Tuen Mun Hospital,

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Hong Kong between 1 July 2020 and 31 June 2021 were retrieved from the labour ward registry and cross-checked with neonatal ward registry. Intrapartum fever is defined as at least one measurement of ≥38°C during labour. Tympanic temperature was measured every 4 hours during intrapartum period, at the end of the second stage of labour, and at 1 hour after delivery. Elevated temperature was confirmed with repeated testing on another ear. Patients with fever were assessed by medical officers and treated with empirical intravenous antibiotics (ampicillin or clindamycin [if allergic to penicillin]). Basic septic workup included cultures of vaginal swabs and placental swabs. The placenta was examined histopathologically. Maternal blood was cultured for those with high fever or signs of acute chorioamnionitis. Prophylactic antibiotic (intravenous ampicillin 1 g every 6 hours) was given during labour for those with prolonged rupture of membranes (>18 hours) or known Group B *Streptococcus* carriers. Neonates of febrile women were assessed by paediatricians, and routine septic workup for neonates included ear swab, gastric lavage, and blood culture.

Each patient was matched with a consecutive healthy control by parity and gestational age. Those with pregnancy complications (non-vertex presentation, multiple pregnancy, preterm delivery <37 weeks, known fetal chromosomal or structural anomalies, pre-labour fever on admission), contraindication for vaginal delivery, elective caesarean section, and 'born before arrival to hospital' were excluded, as were those without intrapartum fever but developed pyrexia just after delivery.

Composite adverse maternal outcomes included emergency caesarean delivery, postpartum haemorrhage (≥500 ml), blood transfusion, intensive care unit admission, prolonged hospitalisation (>3 days for vaginal delivery and >5 days for caesarean delivery), and hospital readmission within 6 weeks of delivery. Composite adverse neonatal outcomes included 1-min Apgar score of <4, 5-min Apgar score of <7, umbilical cord blood pH of <7.1, resuscitation at birth, neonatal intensive care unit admission, mechanical ventilation, meconium aspiration, transient tachypnoea of newborn, respiratory distress syndrome, haemodynamic instability, clinical sepsis, pneumonia, necrotising enterocolitis, and meningitis. The diagnosis of sepsis was made if signs of systemic infection (unstable body temperature, feeding intolerance, respiratory distress, acidosis, and increased C-reactive protein or white cell counts) were detected.

Data analysis was performed using the SPSS (Windows version 26; IBM Corp, Armonk [NY], United States). The case and control groups were compared using the *t* test and Mann-Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for discrete variables. Multivariate logistic regression model was used to determine predictors for intrapartum fever and adverse maternal and neonatal outcomes. A p value of <0.05 was considered statistically significant.

Results

During the study period, 3729 live babies were delivered, including 74 pairs of twins. The incidence of intrapartum fever was 4.4% (164/3729). The 164 patients with intrapartum fever were compared with controls matched for gestational age and parity (Table 1). The two groups were comparable in terms of ethnicity, smoker, Group B *Streptococcus* carrier, body mass index, and rates of diabetes in pregnancy and prelabour rupture of membranes. More patients with intrapartum fever had advanced maternal age (≥35 years) [22.0% vs 12.2%, p=0.019] and hypertensive disease in pregnancy (13.4% vs 1.2%, p<0.001). Patients with intrapartum fever had a longer duration of ruptured membranes (median, 12 vs 6 hours, p<0.001) and a longer labour duration (median, 8 vs 5 hours, p<0.001), were more likely to have epidural analgesia, induction of labour, emergency caesarean delivery, and intrapartum antibiotic use (all p<0.001), were less likely to deliver spontaneously (31.1% vs 59.1%, p<0.001), with a higher rate of caesarean delivery (40.9% vs 14.0%, p<0.001) owing to non-reassuring fetal heart rate (p=0.016) and failure of labour progress (p<0.001), a higher rate of postpartum haemorrhage (p<0.001), a longer duration of hospitalisation (p<0.001), and a higher rate of composite adverse maternal morbidity (67.7% vs 39.0%, p<0.001).

More neonates of febrile women were febrile at birth (21.3% vs 0%, p<0.001) and had a higher rate of neonatal complications including transient tachypnoea (7.3% vs 1.8%, p<0.017), clinical sepsis (17.7% vs 5.5%, p=0.001), longer length of hospitalisation (median, 5 vs 2 days, p<0.001), and a higher rate of composite adverse neonatal outcomes (24.4% vs 11.6%, p<0.003) [Table 2].

Significant risk factors found on univariate analysis were entered into multivariate logistic regression analysis. Predictors for intrapartum fever were hypertensive disease (adjusted odds ratio [aOR]=7.42, p=0.015), epidural analgesia (aOR=6.22, p<0.001), and duration of ruptured membranes (aOR=1.07, p=0.044) [Table 3]. Epidural analgesia was a predictor for composite adverse maternal outcome (aOR=2.65, p=0.007), whereas maternal

Table 1. Demographic, obstetric, and labour characteristics of patients with intrapartum fever and controls

Characteristic	Intrapartum fever cases (n=164)*	Controls (n=164)*	p Value
Maternal age, y	30.73±5.02	29.30±4.72	0.008
Advanced maternal age (≥35 y)	36 (22.0)	20 (12.2)	0.019
Body mass index, kg/m^2	22.39 (4.64)	21.53 (4.94)	0.083
Obesity (body mass index ≥25 kg/m^2)	36 (22.0)	35 (21.3)	0.893
Race			0.185
Chinese	150 (91.5)	156 (95.1)	
South Asian	14 (8.5)	8 (4.9)	
Smoker	21 (12.8)	24 (14.6)	0.630
Nulliparity	145 (88.4)	145 (88.4)	>0.99
Gestational age at delivery, wk	39 (2)	39 (2)	>0.99
Hypertensive disorders of pregnancy	22 (13.4)	2 (1.2)	<0.001
Diabetes in pregnancy	27 (16.5)	19 (11.6)	0.203
Group B *Streptococcus* carrier	35 (21.3)	45 (27.4)	0.199
Epidural analgesia	96 (58.5)	18 (11.0)	<0.001
Prelabour rupture of membranes	46 (28.0)	35 (21.3)	0.159
Induction of labour	126 (76.8)	75 (45.7)	<0.001
Meconium-stained amniotic fluid	22 (13.4)	19 (11.6)	0.616
Internal fetal monitoring	5 (3.0)	5 (3.0)	>0.99
Duration of rupture of membranes, h	12 (6)	6 (9)	<0.001
Total labour duration, h	8 (5)	5 (5)	<0.001
Intrapartum antibiotic use	158 (96.3)	36 (22.0)	<0.001
Mode of delivery			
Vaginal delivery	51 (31.1)	97 (59.1)	<0.001
Instrumental vaginal delivery	46 (28.0)	44 (26.8)	0.805
Caesarean delivery	67 (40.9)	23 (14.0)	<0.001
Caesarean section for non-reassuring fetal heart rate	26 (15.9)	12 (7.3)	0.016
Caesarean section for failure to progress	35 (21.3)	8 (4.9)	<0.001
Postpartum haemorrhage (blood loss ≥500 ml)	39 (23.8)	9 (5.5)	<0.001
Blood transfusion	1 (0.6)	1 (0.6)	>0.99
Intensive care unit admission	2 (1.2)	0	0.498
Hospitalisation, d	4±2	3±2	<0.001
Hospital readmission within 6 weeks of delivery	6 (3.7)	6 (3.7)	>0.99
Composite adverse maternal outcome	111 (67.7)	64 (39.0)	<0.001

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

temperature of ≥39°C was a predictor for composite adverse neonatal outcome (aOR=5.15, p=0.036) [Table 4]. Positive bacterial culture was not associated with poor neonatal outcomes. Higher degrees of maternal temperature were associated with higher composite maternal and neonatal morbidity (Table 5).

89 (54.3%) of febrile patients had positive culture results (either maternal/placenta or neonatal swabs), and 33 (20.1%) of febrile patients had more than one type of bacteria yielded. Although clinical chorioamnionitis was present in only 16 (9.8%) patients, histological chorioamnionitis was present in 121 (73.8%) patients. Gram-positive bacteria

Table 2. Neonatal outcomes of patients with intrapartum fever and controls

	Intrapartum fever cases (n=164)*	Controls (n=164)*	p Value
Male sex	84 (51.2)	81 (49.4)	0.740
Birthweight, g	3210.8±401.1	3155.9±368.6	0.197
Neonatal fever at birth (≥38°C)	35 (21.3)	0	<0.001
Apgar score <4 at 1 min	2 (1.2)	0	0.498
Apgar score <7 at 5 min	2 (1.2)	0	0.498
Umbilical cord blood pH <7.1	4/83 (4.8)	3/70 (4.3)	0.875
Resuscitation at birth	1 (0.6)	1 (0.6)	>0.99
Neonatal intensive care unit admission	9 (5.5)	4 (2.4)	0.157
Mechanical ventilation	8 (4.9)	5 (3.0)	0.396
Meconium aspiration	1 (0.6)	1 (0.6)	>0.99
Transient tachypnoea of newborn	12 (7.3)	3 (1.8)	0.017
Respiratory distress syndrome	1 (0.6)	2 (1.2)	>0.99
Haemodynamic instability	1 (0.6)	0	>0.99
Clinical sepsis	29 (17.7)	9 (5.5)	0.001
Pneumonia	2 (1.2)	2 (1.2)	>0.99
Meningitis	1 (0.6)	0	>0.99
Necrotising enterocolitis	1 (0.6)	0	>0.99
Hospitalisation, d	5 (2)	2 (2)	<0.001
Composite adverse neonatal outcome	40 (24.4)	19 (11.6)	0.003

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

Table 3. Multivariate logistic regression analysis for predictors of intrapartum fever

	Adjusted odds ratio (95% confidence interval)	p Value
Hypertensive disease	7.42 (1.48-37.10)	0.015
Epidural analgesia	6.22 (3.26-11.87)	<0.001
Advanced maternal age (≥35 y)	1.78 (0.87-3.61)	0.112
Induction of labour	1.27 (0.64-2.50)	0.491
Duration of ruptured membranes, h	1.07 (1.00-1.15)	0.044
Total labour duration, h	1.00 (0.99-1.00)	0.293

were found in 31.7% (n=52) of febrile patients. The most common was *Enterococcus* (48.1%), followed by Group B *Streptococcus* (15.4%), other *Streptococcus* (15.4%), *Staphylococcus* (15.4%), and *Diphtheroids* (5.8%). Gram-negative bacteria were found in 42.1% of febrile patients. The most common was *Escherichia coli* (65.2%), followed by extended-spectrum β-lactamases *E coli* (11.6%), *Proteus* (7.2%), *Bacteroides* (5.8%), *Prevotella* (4.3%), *Klebsiella* (2.9%), *Citrobacter* (1.4%), and *Morganella* (1.4%). Anaerobes (*Bifidobacterium*, *Peptoniphilus harei*, and *Ruminococcus*) were found in 3.0% of febrile patients. For Group B *Streptococcus*, all samples were sensitive to penicillin, but five of eight samples were resistant to clindamycin. Two samples of *Enterococcus* isolates were resistant to clindamycin or erythromycin. For *E coli* isolates, 2.2% were resistant to Augmentin, 15.6% were resistant to gentamicin, and 31.1% were resistant to trimethoprim/sulfamethoxazole, whereas 17.8% were sensitive to oral cefuroxime and all were sensitive to intravenous cefuroxime [Table 6].

Table 4. Multivariate logistic regression analysis for predictors of composite adverse maternal and neonatal outcomes

	Adjusted odds ratio (95% confidence interval)	p Value
Composite adverse maternal outcome		
Advanced maternal age (≥35 y)	1.52 (0.63-3.65)	0.348
Group B *Streptococcus* carrier	2.09 (0.82-5.34)	0.124
Parity	1.09 (0.62-1.90)	0.772
Epidural analgesia	2.65 (1.31-5.34)	0.007
Prolonged rupture of membranes (>18 h)	1.69 (0.44-6.52)	0.447
Maximal maternal temperature ≥39°C	1.14 (0.26-4.92)	0.862
Duration of intrapartum fever >4 h	1.44 (0.48-4.36)	0.517
Composite adverse neonatal outcome		
Advanced maternal age (≥35 y)	0.66 (0.25-1.77)	0.411
Group B *Streptococcus* carrier	0.57 (0.19-1.71)	0.316
Parity	0.31 (0.08-1.22)	0.093
Gestation at delivery	1.46 (1.00-2.14)	0.050
Epidural analgesia	1.60 (0.71-3.61)	0.261
Prolonged rupture of membranes (>18 h)	0.23 (0.03-1.92)	0.174
Maximal maternal temperature ≥39°C	5.15 (1.11-23.86)	0.036
Duration of intrapartum fever >4 h	0.39 (0.10-1.57)	0.183
Positive bacterial culture	1.32 (0.59-3.00)	0.501

Table 5. Higher maternal intrapartum temperature is associated with higher maternal and neonatal morbidity

Maternal intrapartum temperature, °C	Neonatal morbidity, %	Maternal morbidity, %
<38	11.6	39
38-39	22.1	68
>39	60	70

Discussion

To the best of our knowledge, this is the first study in Hong Kong evaluating the effects of intrapartum fever on both maternal and neonatal outcomes as well as the prevalence of microorganisms in patients with intrapartum fever and their rates of antibiotic resistance. These findings may guide future management of intrapartum fever.

The incidence of intrapartum fever in our hospital was 4.4%, which is within the range reported in the literature (1.6% to 14.6%)[1]. Predictors for intrapartum fever were hypertensive disease, epidural analgesia, and duration of ruptured membranes. Hypertensive disease is associated with intrapartum fever[9]. Pre-eclampsia is associated with a more vigorous systemic inflammatory response. Patients with pre-eclampsia have more remarkable systemic inflammatory response including leukocytic inflammatory markers and activity as well as inflammatory changes in endothelial or clotting function. This in turn triggers acute phase response such as fever[10].

Epidural anaesthesia is associated with intrapartum fever[4,11-13]. The rate of epidural analgesia-associated fever is approximately 20%[14]. In our cohort, almost 60% of patients with intrapartum fever received epidural analgesia. The underlying mechanism may be due to the change in the thermoregulation system[15], a decrease in heat-dissipating hyperventilation secondary to adequate pain relief[16] or possible inflammation state[17,18]. Compared with opioids, epidural analgesia is safe and effective to reduce labour pain[19] but is highly associated with intrapartum fever, which causes potential maternal and neonatal morbidity. In patients with both intrapartum fever and epidural analgesia, it is difficult to differentiate chorioamnionitis from non-infectious epidural analgesia–related fever. Hence, identifying predictors for poor maternal and neonatal outcomes is important.

Table 6. Gram-positive and -negative bacteria and their resistance to antibiotics*

	Penicillin	Erythromycin	Clindamycin	Augmentin	Cefuroxime (oral)	Cefuroxime (intravenous)	Gentamicin	Levofloxacin	Trimethoprim/ sulfamethoxazole
Gram-positive bacteria									
Group B *Streptococcus*	0/8	1/8 (12.5)	5/8 (62.5)	-	-	-	-	-	-
Other *Streptococcus*	0/8	0/8	1/8 (12.5)	-	-	-	-	-	-
Enterococcus	0/25	1/25 (4.0)	1/25 (4.0)	-	-	-	-	-	-
Staphyloccocus	2/8 (25.0)	1/8 (12.5)	-	-	-	-	-	-	-
Gram-negative bacteria									
Escherichia coli	-	-	-	1/45 (2.2)	8/45 (17.8)†	0/45	7/45 (15.6)	6/45 (13.3)	14/45 (31.1)
Extended-spectrum β-lactamases *E coli*	-	-	-	0/8	-	-	2/8 (25.0)	1/8 (12.5)	5/8 (62.5)
Bacteroides	-	-	-	0/4	0/4	0/4	0/4	0/4	1/4 (25.0)
Proteus	-	-	-	0/5	0/5	0/5	0/5	0/5	0/5
Klebsiella	-	-	-	0/2	0/2	0/2	0/2	0/2	0/2

* Data are presented as No. (%) of samples resistance to antibiotics
† Intermediate sensitivity to cefuroxime (oral)

Longer duration of ruptured membranes was associated with intrapartum fever. Prolonged ruptured membranes exacerbate the exposure of the uterine cavity or fetus to potential microbial threats[20]. In our practice, prophylactic antibiotics and septic workup are provided for parturients who have fever or prolonged ruptured membranes for >18 hours. For those with prelabour rupture of membranes, induction of labour is performed to shorten the duration of ruptured membranes and the first stage of labour. This practice is supported by a meta-analysis of 23 randomised trials of patients with prelabour rupture of membranes at ≥37 weeks of gestation[21]. Reduction in the time from membrane rupture to birth lowers the rates of chorioamnionitis/endometritis and admission to neonatal special care or intensive care unit. In a study analysing data from the TERMPROM trial, compared with expectant management, labour induction within the first 20 hours following prelabour rupture of membranes is associated with a reduction in the risk of the composite adverse neonatal outcome, whereas labour induction within the first 15 hours following prelabour rupture of membranes results in reduction in the rates of neonatal intensive care unit admission and maternal infectious morbidity[22]. Although early induction of labour may not prevent intrapartum fever, it acts as a precautionary way to reduce the duration labour and the occurrence of neonatal sepsis.

Epidural analgesia was a predictor for composite adverse maternal outcomes, whereas extremely high maternal temperature was a predictor for composite adverse neonatal outcomes. Epidural analgesia is associated with increased rates of instrumental delivery and caesarean section[23-25]. Increased rates of operative delivery in turn increase the risks of postpartum haemorrhage, blood transfusion, wound complications, hospital stay, and readmission secondary to complications. Therefore, it is important for obstetricians and anaesthetists to explain the risks and benefits of epidural anaesthesia and its associations with intrapartum fever and delivery modes.

Maternal intrapartum fever is associated with neonatal complications in a dose-dependent manner[7]. Extremely elevated intrapartum fever is an important indicator of severe neonatal morbidity, with increased rates of neonatal sepsis, low Apgar scores, and neonatal intensive care unit admission as well as higher risk of operative delivery[6]. In our study, higher maternal temperature was associated with poorer composite adverse neonatal outcomes. Although a high temperature of >39°C during labour is uncommon, it can cause adverse fetal outcomes. The mechanism of high temperature causing perinatal morbidities includes the inflammatory process, the lower threshold for hypoxic brain injury, and the higher fetal rate of metabolic expenditure[7]. To minimise the adverse impact of intrapartum fever, obstetricians should administer antipyretics in time, monitor the labour progress regularly, avoid prolonged labour, ensure adequate hydration, avoid unnecessary vaginal examinations and high environmental

temperature, avoid prolonged high body temperature, and alert paediatricians early to optimise neonatal evaluation and management.

In our study, intrapartum fever (≥38°C) was associated with increased maternal morbidity. Those with high temperature (≥39°C) did not significantly differ from those with moderately high temperature (38°C-38.9°C) in terms of composite adverse maternal outcomes. This may be due to the small sample size of the high fever group (4.9%).

Positive bacterial culture is associated with poor neonatal outcomes[8]. However, in our study, positive bacterial culture was not associated with poor composite adverse neonatal outcomes. This may be due to the small sample size, environmental contamination of some cultures (especially ear swab), and intrapartum antibiotic use (to inhibit bacterial growth).

All parturients with intrapartum fever received empirical antibiotics once fever was confirmed. The World Health Organization guideline recommends a simple regimen such as ampicillin and once-daily gentamicin as the first-line antibiotics for chorioamnionitis[26]. The American College of Obstetricians and Gynecologists guideline recommends that antibiotics should be considered in patients with isolated maternal fever unless causes other than intraamniotic infection are identified, and that the drug of choice should be a combination of ampicillin and gentamicin[2]. In Hong Kong, antibiotic regimens for intrapartum fever vary among hospitals. Some hospitals administer single antibiotics (benzyl-penicillin, ampicillin, Augmentin), whereas others use a combination of antibiotics (ampicillin plus metronidazole, ampicillin plus gentamicin, and Augmentin plus gentamicin). No one antibiotic is superior to another[27,28].

In our cohort, surprisingly, the most common gram-positive bacteria in both maternal and neonatal cultures were *Enterococcus faecalis* rather than Group B *Streptococcus*. *E coli* was the most common gram-negative bacteria. Similarly, in another study, the most common organisms cultured in fever patients were *E coli* (17%), Group B *Streptococcus* (4.4%), and *Enterococcus faecalis* (3.4%)[29]. In our cohort, the rate of resistance to gram-positive bacteria to penicillin was low. Therefore, the use of penicillin group antibiotics in febrile patients is justified. In our hospital, ampicillin was used empirically for intrapartum fever. Owing to the high prevalence of *E coli* and its likely resistance to ampicillin (resistance rate of 76% in the Hong Kong guideline IMPACT[30]), changing the antibiotics to Augmentin or intravenous cefuroxime is sensible. Broad-spectrum antibiotics should be used as chorioamnionitis is usually polymicrobial. Augmentin is easily available and possesses β-lactamase-inhibiting properties and covers a wide range of β-lactamase-producing pathogens. However, Augmentin is not recommended for patients with preterm/premature rupture of membranes because of its association with neonatal necrotising enterocolitis[31,32]. Gentamicin is widely used as the antibiotic of choice for intrapartum chorioamnionitis[33], but *E coli* has a relatively high rate of resistance to gentamicin (30% of *E coli* are resistant to gentamicin according to the IMPACT guideline[30] and 15.6% of *E coli* are resistant to gentamicin based on our data). It may not be appropriate to add gentamicin in the empirical antibiotic regimen in Hong Kong. In addition, there is no ground to add metronidazole owing to low culture rates of anaerobes. Future studies to compare Augmentin, intravenous cefuroxime with ampicillin, and a combination of antibiotics in managing chorioamnionitis are warranted.

Limitations to this study include the retrospective design and small sample size. In addition, our hospital's microbiology laboratory did not perform sensitivity testing of Gram-negative bacteria to ampicillin. This hindered our estimation of effectiveness of ampicillin to treatment of intrapartum fever.

Conclusion

Intrapartum fever is associated with poor maternal and neonatal outcomes. Obstetricians should avoid long duration of labour and high maternal temperature. The choice of antibiotics for intrapartum fever/chorioamnionitis should be carefully selected, with consideration of efficacy, possible adverse effects, and antimicrobial resistance.

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 New Territories West Research Ethics Committee (reference: NTWC/REC/22044). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Incidence, risk factors, and clinical outcomes of placental abruption in a tertiary hospital in Hong Kong: a retrospective case-control study

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Introduction: This study aims to identify risk factors for placental abruption and evaluate maternal and fetal outcomes of patients with placental abruption in a tertiary hospital in Hong Kong.
Methods: Medical records of patients with placental abruption treated at the Tuen Mun Hospital between January 2017 and December 2021 were retrospectively reviewed. Data retrieved included patient demographics, alcohol/substance abuse and smoking status, obstetric history, antenatal characteristics, body mass index at first antenatal visit, clinical presentation, intrapartum events, complications, and maternal and perinatal outcomes. Each patient was matched with a control who delivered just before the patient.
Results: Of 22 990 deliveries and 23 230 live births, there were 86 placental abruption cases; the incidence was 0.37%. After adjusting for confounders, the risk factor for placental abruption was a history of antepartum haemorrhage. Compared with controls, patients with placental abruption had higher rates of caesarean sections (91.9% vs 23.3%, p<0.001), postpartum haemorrhage (62.8% vs 15.1%, p<0.001), uterine atony (31.4% vs 3.5%, p<0.001), blood transfusion (25.6% vs 3.5%, p<0.001), and disseminated intravascular coagulopathy (7.0% vs 0%, p=0.029). Compared with controls, neonates complicated with placental abruption had lower Apgar score at 1 minute (7 vs 8, p<0.001), higher preterm birth rate (64.0% vs 9.3%, p<0.001), lower birth weight (2296.4 g vs 3088.8 g, p<0.001), and more perinatal morbidities. Patients with a Couvelaire uterus had higher rates of uterine atony (56.3% vs 27.0%, p=0.026), postpartum haemorrhage (93.8% vs 61.9%, p=0.014), disseminated intravascular coagulopathy (25.0% vs 3.2%, p=0.014), blood transfusion (68.8% vs 17.5%, p<0.001), and secondary intervention (25.0% vs 1.6%, p=0.005). Neonates born from patients with a Couvelaire uterus had higher rates of acidosis (umbilical cord blood pH <7.1) [53.3% vs 5.8%, p<0.001], lower Apgar score at 1 minute (25.0% vs 4.8%, p=0.028), and hypoxic-ischaemic encephalopathy (12.5% vs 0%, p=0.039).
Conclusion: Clinicians should be vigilant for placental abruption in patients with antepartum haemorrhage, especially in high-risk patients with a history of placental abruption, hypertension, or pre-eclampsia. Early and consistent antenatal care is imperative to identify those with risk factors. Proper education and timely preventive management should be provided to improve maternal and fetal outcomes.

Keywords: Abruptio placentae; Risk factors

Introduction

Placental abruption is defined as premature separation of the placenta from the decidua at or after 20 weeks of gestation and can result in maternal and fetal morbidity and mortality. Its incidence is higher in Canada and the United States and lower in Norway, Spain, Finland, Sweden, the Netherlands, and Denmark[1]. The overall incidence is approximately 3 to 10 per 1000 births[1,2]. Clinical presentation of placental abruption includes painful vaginal bleeding with uterine contraction and hypertonicity and a non-reassuring fetal heart rate pattern[3]. Progression of placental abruption can be rapid, especially in cases of severe abruption. Maternal complications include haemorrhagic shock, coagulopathy and disseminated intravascular coagulation, uterine rupture, renal failure, and ischaemic necrosis of distal organs[4,5]. Neonatal complications include death and neurodevelopmental issues[4,6].

There are no reliable diagnostic tests or markers to predict or prevent the occurrence of placental abruption. Its risk factors include advanced maternal age, multiparity, smoking, cocaine and drug use, pre-eclampsia, chronic hypertension, premature rupture of membranes, trauma, polyhydramnios, structural uterine anomalies, and a history of placental abruption[7-10]. This study aims to identify risk factors for placental abruption and evaluate maternal and

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fetal outcomes of patients with placental abruption in a tertiary hospital in Hong Kong.

Materials and methods

This study was approved by the New Territories West Cluster Research Ethics Committee (reference: NTWC/REC/22071). Medical records of patients with placental abruption treated at the Tuen Mun Hospital between January 2017 and December 2021 were identified using the International Classification of Diseases codes. Tuen Mun Hospital is a public hospital in Hong Kong handling around 5000 live births per year. Data retrieved included patient demographics, alcohol/substance abuse and smoking status, obstetric history, antenatal characteristics, body mass index at first antenatal visit, clinical presentation, intrapartum events, complications, and maternal and perinatal outcomes. Each patient was matched with a control who delivered just before the patient.

The diagnostic criteria for placental abruption were: (1) presentation of signs of painful vaginal bleeding and at least one of the following: non-reassuring fetal status, severe abdominal pain, tetanic uterine contractions, and uterine hypertonicity; (2) a freshly delivered placenta showing clinically significant retroplacental bleeding or clots; and (3) a confirmation on prenatal ultrasound. Patients often had a combination of these diagnostic criteria.

Data analysis was performed using SPSS (Windows version 26; IBM Corp, Armonk [NY], United States). A p value of <0.05 was considered statistically significant. The case and control groups were compared using the Student's *t* test and Mann-Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was used to determine risk factors for placental abruption. Subgroup analysis was performed to determine association of Couvelaire uterus with maternal and fetal outcomes.

Results

Of 22 990 deliveries and 23 230 live births in Tuen Mun Hospital between 2017 and 2021, there were 86 placental abruption cases; the incidence was 0.37%. The most common symptom of placental abruption was a combination of vaginal bleeding and abdominal pain (38.4%), followed by a combination of vaginal bleeding, abdominal pain, and uterine hypertonicity (24.4%) and vaginal bleeding alone (19.8%) [Table 1]. The most common clinical presentation of placental abruption was retroplacental clot during delivery (96.5%), followed by blood-stained amniotic fluid during delivery (39.5%), a non-reassuring fetal heart rate pattern (38.4%), retroplacental clot on ultrasound (20.9%), and a Couvelaire uterus during caesarean section (18.6%).

As shown in Table 2, the case and control groups were comparable in terms of maternal age (32.4 vs 30.9 years, p=0.052) and the percentage of advanced maternal age (≥35 years) [34.9% vs 22.1%, p=0.063]. Compared with controls, patients with placental abruption had higher rates of pre-eclampsia (11.6% vs 3.5%, p=0.043), preterm prelabour rupture of membranes (16.3% vs 3.5%, p=0.005), a history of antepartum haemorrhage (20.9% vs 7.0%, p=0.008), and use of aspirin during the antenatal period (10.5% vs 0%, p=0.003). However, after adjusting for confounders, only a history of antepartum haemorrhage remained significant (p=0.013, Table 3).

Compared with controls, patients with placental abruption had higher rates of caesarean section (91.9% vs 23.3%, p<0.001), caesarean section for non-reassuring fetal heart rate (33.7% vs 7%, p<0.001), postpartum haemorrhage (blood loss ≥500 ml: 62.8% vs 15.1%, p<0.001; blood loss ≥1000 ml: 31.4% vs 3.5%, p<0.001), uterine atony (31.4% vs 3.5%, p<0.001), blood transfusion (25.6% vs 3.5%, p<0.001), disseminated intravascular coagulation (7.0% vs 0%, p=0.029), and prolonged hospital stay (>4 days) [30.2% vs 15.1%, p=0.018], and longer length of hospital stay (median, 4 vs 3 days, p<0.001) [Table 4]. Treatment performed for severe postpartum haemorrhage included compression sutures (n=4), bilateral uterine artery ligation (n=1), and hysterectomy (n=1).

As shown in Table 5, of 89 neonates (three sets of twins) in the placental abruption group, one was stillbirth. Compared with controls, neonates born from patients with placental abruption had higher rates of premature birth (before 37 weeks: 64.0% vs 9.3%, p<0.001; before 34 weeks: 37.1% vs 2.3%, p<0.001; and before 28 weeks: 11.2% vs 0%, p=0.002), lower birth weight (2296.4 g vs 3088.8 g, p<0.001), lower median Apgar score at 1 minute (7 vs 8, p<0.001), and higher rates of resuscitation care (18.2% vs 0%, p<0.001), mechanical ventilation (25.0% vs 1.2%, p<0.001), admission to neonatal intensive care unit (47.7% vs 1.2%, p<0.001), inotropes for management of haemodynamic instability (12.5% vs 0%, p=0.001), and blood transfusion (17.0% vs 0%, p<0.001). Neonates born from patients with placental abruption had higher complication rates in terms of respiratory distress syndrome (39.8% vs 0%, p<0.001), apnoea of prematurity (25.0% vs 0%, p<0.001), intraventricular haemorrhage (8.0% vs 0%,

Table 1. Symptoms, clinical presentations, and diagnostic criteria of placental abruption

	Patients with placental abruption (n=86)*
Symptom	
Vaginal bleeding alone	17 (19.8)
Abdominal pain alone	7 (8.1)
Uterine hypertonicity alone	1 (1.2)
Vaginal bleeding and abdominal pain	33 (38.4)
Abdominal pain and uterine hypertonicity	1 (1.2)
Vaginal bleeding and uterine hypertonicity	6 (7.0)
Vaginal bleeding, abdominal pain and uterine hypertonicity	21 (24.4)
Clinical presentation	
Non-reassuring fetal heart rate patterns	33 (38.4)
Retroplacental blood clot by ultrasound	18 (20.9)
Blood-stained amniotic fluid during delivery	34 (39.5)
Retroplacental clot/haemorrhage during delivery	83 (96.5)
Couvelaire uterus during caesarean section	16 (18.6)
Diagnostic criteria	
Retroplacental clots/haemorrhage	43 (50.0)
Ultrasound diagnosis	1 (1.2)
Ultrasound diagnosis and retroplacental clots/haemorrhage	12 (14.0)
Painful vaginal bleeding, uterine hypertonicity and non-reassuring fetal heart rate patterns	1 (1.2)
Painful vaginal bleeding, uterine hypertonicity and retroplacental clots/haemorrhage	7 (8.1)
Painful vaginal bleeding, uterine hypertonicity and ultrasound diagnosis	1 (1.2)
Painful vaginal bleeding, uterine hypertonicity, non-reassuring fetal heart rate patterns and retroplacental clots/haemorrhage	8 (9.3)
Painful vaginal bleeding, uterine hypertonicity, ultrasound diagnosis, non-reassuring fetal heart rate patterns and retroplacental clots/haemorrhage	2 (2.3)
Painful vaginal bleeding, uterine hypertonicity, ultrasound diagnosis and retroplacental clots/haemorrhage	2 (2.3)
Painful vaginal bleeding, non-reassuring fetal heart rate patterns and retroplacental clots/haemorrhage	9 (10.5)

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

p=0.014), chronic lung disease (8.0% vs 0%, p=0.014), retinopathy of prematurity (8.0% vs 0%, p=0.014), patent ductus arteriosus (12.5% vs 0%, p=0.001), neonatal hypoglycaemia (13.6% vs 3.5%, p=0.017), neonatal sepsis (11.4% vs 2.3%, p=0.019), and increased neonatal hospital stay (median, 7 vs 2 days, p<0.001). There were three (3.4%) early neonatal deaths because of prematurity in the placental abruption group but none in the control group.

15 of the patients had 17 subsequent pregnancies delivered beyond 24 weeks. Three of them had placental abruption; the incidence increased to 17.6% among women with a history of abruption. These three cases were not delivered in our hospital and therefore not included in our cohort.

16 of 79 patients were found to have a Couvelaire uterus intraoperatively by the operating surgeon through visual inspection. All four patients who needed secondary intervention for postpartum haemorrhage underwent compression sutures. Compared with patients without a Couvelaire uterus, patients with a Couvelaire uterus had higher rates of uterine atony (56.3% vs 27.0%, p=0.026), postpartum haemorrhage (93.8% vs 61.9%, p=0.014), disseminated intravascular coagulation (25.0% vs 3.2%, p=0.014), blood transfusion (68.8% vs 17.5%, p<0.001),

Table 2. Characteristics of patients with placental abruption and controls

Characteristic	Patients with placental abruption (n=86)*	Controls (n=86)*	p Value
Maternal age, y	32.4±5.0	30.9±5.4	0.052
Maternal age ≥35 y	30 (34.9)	19 (22.1)	0.063
Maternal age <20 y	1 (1.2)	1 (1.2)	>0.99
Body mass index, kg/m^2	22.7 (5)	22.6 (5)	0.930
Maternal ethnicity			0.496
Chinese	80 (93.0)	83 (96.5)	
South-Asian	6 (7.0)	3 (3.5)	
Tobacco use	6 (7.0)	3 (3.5)	0.496
Alcohol use	2 (2.3)	3 (3.5)	>0.99
Drug abuser	1 (1.2)	1 (1.2)	>0.99
Educational level			0.426
Tertiary or above	33 (38.4)	28 (32.6)	
Below tertiary	53 (61.6)	58 (67.4)	
Unmarried	12 (14.0)	17 (19.8)	0.309
Gravidity	2 (2)	2 (2)	0.266
Parity	1 (1)	1 (1)	0.594
Parity ≥3	6 (7.0)	4 (4.7)	0.515
Nulliparity	35 (40.7)	40 (46.5)	0.442
History of miscarriage/stillbirth	18 (20.9)	9 (10.5)	0.059
History of termination of pregnancy	18 (20.9)	21 (24.4)	0.585
History of caesarean section	21 (24.4)	11 (12.8)	0.050
History of placental abruption	4 (4.7)	0	0.121
Assisted conception	6 (7.0)	2 (2.3)	0.277
Twin pregnancy	3 (3.5)	0	0.246
No antenatal care	0	3 (3.5)	0.246
Hypertensive disorders	12 (14.0)	5 (5.8)	0.074
Chronic hypertension	5 (5.8)	1 (1.2)	0.210
Pregnancy induced hypertension	4 (4.7)	3 (3.5)	>0.99
Pre-eclampsia	10 (11.6)	3 (3.5)	0.043
Diabetes mellitus in pregnancy	13 (15.1)	9 (10.5)	0.361
Pre-existing diabetes mellitus	3 (3.5)	0	0.246
Gestational diabetes mellitus	10 (11.6)	9 (10.5)	0.808
Preterm premature rupture of membranes	14 (16.3)	3 (3.5)	0.005
Polyhydramnios	1 (1.2)	0	>0.99
Oligohydramnios	1 (1.2)	2 (2.3)	>0.99
Uterine anomaly	1 (1.2)	0	>0.99
Placental praevia	5 (5.8)	0	0.059
History of antepartum haemorrhage	18 (20.9)	6 (7.0)	0.008
History of abdominal trauma	1 (1.2)	0	>0.99
Use of aspirin	9 (10.5)	0	0.003
Anaemia	3 (3.5)	4 (4.7)	>0.99

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

Table 3. Risk factors for placental abruption

Variable	Adjusted odds ratio (95% confidence interval)	p Value
History of antepartum haemorrhage	3.59 (1.31-9.81)	0.013
Preterm premature rupture of membranes	3.51 (0.89-13.83)	0.072
Pre-eclampsia	2.44 (0.58-10.24)	0.222
Use of aspirin	-	>0.99

Table 4. Maternal outcomes of patients with placental abruption and controls

Maternal outcome	Patients with placental abruption (n=86)*	Controls (n=86)*	p Value
Mode of delivery			
Caesarean section	79 (91.9)	20 (23.3)	<0.001
Normal vaginal delivery	3 (3.5)	63 (73.3)	<0.001
Assisted vaginal delivery	4 (4.7)	3 (3.5)	>0.99
Caesarean section for non-reassuring fetal heart rate	29 (33.7)	6 (7.0)	<0.001
Blood loss, ml	700 (700)	200 (213)	<0.001
Postpartum haemorrhage of ≥500 ml	54 (62.8)	13 (15.1)	<0.001
Postpartum haemorrhage of ≥1000 ml	27 (31.4)	3 (3.5)	<0.001
Uterine atony	27 (31.4)	3 (3.5)	<0.001
Need for secondary intervention for postpartum haemorrhage	5 (5.8)†	0	0.059
Need for blood transfusion	22 (25.6)	3 (3.5)	<0.001
Hysterectomy	1 (1.2)	0	>0.99
Need for relaparotomy	0	0	-
Transfer to intensive care unit	4 (4.7)	0	0.121
Disseminated intravascular coagulation	6 (7.0)	0	0.029
Death	0	0	-
Length of maternal hospital stay, d	4 (2)	3 (2)	<0.001
Prolonged maternal hospitalisation of >4 d	26 (30.2)	13 (15.1)	0.018

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

† Compression sutures (n=4) and bilateral uterine artery ligation (n=1)

and secondary intervention (25.0% vs 1.6%, p=0.005) [Table 6]. Compared with neonates born from patients without a Couvelaire uterus, neonates born from patients with a Couvelaire uterus had higher rates of acidosis (umbilical cord blood pH <7.1) [53.3% vs 5.8%, p<0.001], lower Apgar score at 1 minute (25.0% vs 4.8%, p=0.028), and hypoxic-ischaemic encephalopathy (12.5% vs 0%, p=0.039) [Table 6].

Discussion

The worldwide incidence of placental abruption is 0.3% to 1%[11]; the incidence in our cohort was 0.37%. Having a previous placental abruption is the biggest risk factor, with 10- to 15-fold higher recurrence risk[12]. Recurrent placental abruption is associated with earlier gestational age at delivery, compared with first episodes, although perinatal mortality rates are similar[13]. In our cohort, the incidence of recurrence was 17.6%, but the number of patients with subsequent pregnancies was only 15.

Other risk factors for placental abruption include pre-eclampsia (5-fold increased risk[14]), fetal growth restriction, non-vertex presentations, polyhydramnios, advanced maternal age, multiparity, low body mass index, pregnancy following assisted reproductive techniques, intrauterine infection, preterm prelabour rupture of membranes, abdominal trauma, smoking and drug misuse

Table 5. Perinatal and neonatal outcomes of patients with placental abruption and controls

	Patients with placental abruption (n=89)*	Controls (n=86)*	p Value
Perinatal outcome			
Gestational age at birth, wk	35 (7)	39 (2)	<0.001
Birth before 37 weeks	57 (64.0)	8 (9.3)	<0.001
Birth before 34 weeks	33 (37.1)	2 (2.3)	<0.001
Birth before 28 weeks	10 (11.2)	0	0.002
Livebirth	85 (95.5)	86 (100)	0.121
Stillbirth	1 (1.1)	0	>0.99
Early neonatal death	3 (3.4)	0	0.246
Male sex	52 (58.4)	39 (45.3)	0.083
Birth weight, g	2296.4±835.7	3088.8±469.6	<0.001
Birth weight <10 centile	9 (10.1)	13 (15.1)	0.318
Neonatal outcome			
Apgar score at 1 min	7 (3)	8 (0)	<0.001
Apgar score at 1 min <4	7 (7.9)	0	0.014
Apgar score at 5 min	9 (2)	9 (0)	0.055
Apgar score at 5 min <7	7 (7.9)	1 (1.2)	0.064
Umbilical artery pH <7.1	11/73 (15.1)	-	-
Resuscitation at birth	16 (18.2)	0	<0.001
Mechanical ventilation	22 (25.0)	1 (1.2)	<0.001
Admission to neonatal intensive care unit	42 (47.7)	1 (1.2)	<0.001
Haemodynamic instability required inotropes	11 (12.5)	0	0.001
Need for blood transfusion	15 (17.0)	0	<0.001
Respiratory distress syndrome	35 (39.8)	0	<0.001
Apnoea of prematurity	22 (25.0)	0	<0.001
Transient tachypnoea of the newborn	7 (8.0)	3 (3.5)	0.330
Intraventricular haemorrhage	7 (8.0)	0	0.014
Hypoxic-ischaemic encephalopathy	2 (2.3)	0	0.497
Necrotising enterocolitis	3 (3.4)	0	0.246
Chronic lung disease	7 (8.0)	0	0.014
Retinopathy of prematurity	7 (8.0)	0	0.014
Patent ductus arteriosus	11 (12.5)	0	0.001
Hypoglycaemia	12 (13.6)	3 (3.5)	0.017
Jaundice-required phototherapy	21 (23.9)	18 (20.9)	0.643
Sepsis	10 (11.4)	2 (2.3)	0.019
Epilepsy	2 (2.3)	1 (1.2)	>0.99
Cerebral palsy	2 (2.3)	0	0.497
Length of hospital stay, d	7 (32)	2 (2)	<0.001
Early death	3 (3.4)	0	0.246

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

Table 6. Adverse maternal and neonatal outcomes in patients with placental abruption with or without a Couvelaire uterus

	% of patients		p Value
	Patients with Couvelaire uterus (n=16)	Patients without Couvelaire uterus (n=63)	
Adverse maternal outcomes			
Uterine atony	56.3	27.0	0.026
Disseminated intravascular coagulation	25.0	3.2	0.014
Postpartum haemorrhage	93.8	61.9	0.014
Blood transfusion	68.8	17.5	<0.001
Secondary intervention	25.0	1.6	0.005
Admission to intensive care unit	6.3	4.8	>0.99
Adverse neonatal outcomes			
Birth before 28 weeks	18.8	7.9	0.348
Early neonatal death	6.3	1.6	0.366
Umbilical cord blood pH <7.1	53.3	5.8	<0.001
1-minute Apgar score <4	25.0	4.8	0.028
5-minute Apgar score <7	18.8	6.3	0.143
Resuscitation at birth	31.3	15.9	0.171
Admission to neonatal intensive care unit	62.5	44.4	0.197
Hypoxic-ischaemic encephalopathy	12.5	0	0.039
Cerebral palsy	6.3	1.6	0.366
Epilepsy	6.3	1.6	0.366

(cocaine and amphetamines) during pregnancy[15]. In our cohort, other risk factors for placental abruption were pre-eclampsia, preterm prelabour rupture of membranes, antepartum haemorrhage, and the use of antenatal aspirin, but these became not significant after adjusting for confounders, except for a history of antepartum haemorrhage.

In a systematic review, patients with chronic hypertension with superimposed pre-eclampsia have 2.8-7.7-fold increased risk of placental abruption[16]. Severe pre-eclampsia is a strong risk factor for placental abruption, whereas transient hypertension in pregnancy and mild pre-eclampsia are associated with placental abruption. The common aetiology of placental abruption and pre-eclampsia is related to failed placentation in early pregnancy, which may lead to placental dysfunction and further increased risk of abruption. Among patients with preterm prelabour rupture of membranes, the incidence of placental abruption is 4% to 12%[16]. The association is due to either a sudden reduction of uterine volume or an ascending intrauterine infection.

Among patients who used antenatal low-dose aspirin, nine (10.5%) had placental abruption. In a meta-analysis, prophylactic low-dose aspirin (<100 mg per day) has no effect on the risk of placental abruption or antepartum haemorrhage, irrespective of the gestational age at onset of therapy[17]. However, when the dose is ≥100 mg per day, the risk of placental abruption is lower in women who started treatment before 16 weeks than after 16 weeks. Placental abruption and preeclampsia are due to impaired placentation; aspirin administration for women with an increased risk of impaired placentation may reduce the risk of placental abruption, as it does for preeclampsia. The ASPRE trial recommends that a daily dose of ≥100 mg before 16 weeks of gestation is effective in reducing the risk of preeclampsia[18]. However, the risk of placental abruption or antepartum haemorrhage may increase without reducing the risk of preeclampsia if treatment is started after 16 weeks of gestation, because placentation is mostly complete by 18 weeks of gestation. In patients with persistent abnormal placentation, the use of aspirin (through its antiplatelet properties) can increase the risk of haemorrhage and placental abruption. In our patients, all were on 80 mg aspirin daily started before 16 weeks, and antenatal aspirin use was not found to be a risk factor.

Smoking and drug abuse is a risk factor for placental abruption but was not significant in our study, probably owing to the small sample size and confounding factors. Of 172 patients in our study, only nine were smokers and only two were drug abusers, whereas only one had polyhydramnios and only one had abdominal trauma.

There are no universal diagnostic criteria for placental abruption. The most common clinical presentation leading to the diagnosis of placental abruption is the presence of retroplacental clot/haemorrhage during delivery[19]. 96.5% of our patients with placental abruption had this clinical presentation.

Ultrasound is useful to rule out other causes of antepartum haemorrhage and abdominal pain such as placenta previa and adnexal masses. It is useful in diagnosing retroplacental haematomas, with a positive predictive value of 88% and a sensitivity of 25% to 60%, as it is absent in many patients with placental abruption[20-23]. It is difficult to differentiate a concealed haemorrhage of the surrounding placental tissue during the acute phase of placental abruption, as the blood may be isoechoic. The locations of placental abruption can be subchorionic, retroplacental, and preplacental. Retroplacental haematomas with variable appearance is a common ultrasound finding (Figure 1). They may appear to be solid, complex, hypo-, hyper- or iso-echoic, compared with the placenta, depending on the severity and timing of the abruption. The absence of a positive ultrasound finding does not exclude the diagnosis of abruption.

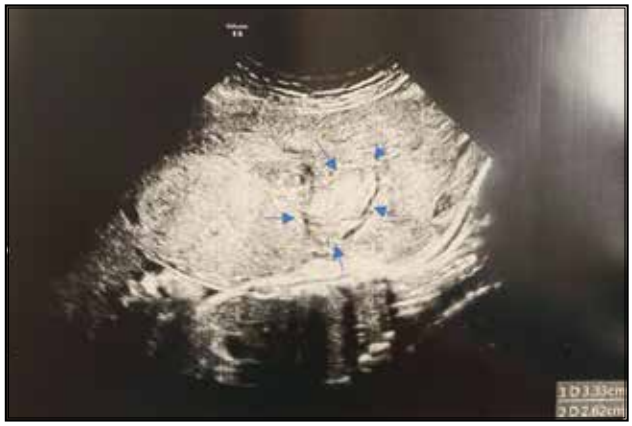

Figure 1. An ultrasound scan showing a retroplacental hematoma (outlined by arrows).

Placental abruption may lead to emergency caesarean birth for fetal or maternal indications, excessive blood loss, and disseminated intravascular coagulation, which can lead to hypovolaemic shock, acute kidney injury, multiorgan failure, respiratory distress syndrome, peripartum hysterectomy, and death[16,24]. In our study, placental abruption was associated with higher rates of caesarean sections, postpartum haemorrhage, uterine atony, blood transfusion, and disseminated intravascular coagulation.

16 of our patients with placental abruption were found to have a Couvelaire uterus intraoperatively (Figure 2), which occurs when a ruptured decidual spiral artery causing bleedings into the decidua basalis and the myometrium during a severe placental abruption. As blood permeates into the uterine serous layer, a blue-violet ecchymosis occurs[25]. The Couvelaire uterus is atonic and very prone to postpartum haemorrhage and thus aggressive and timely management of atony may prevent further worsening of conditions such as disseminated intravascular coagulation and exsanguination. Uterine atony in a

Figure 2. Intra-operative finding of Couvelaire uterus in two patients.

Couvelaire uterus responds less well to standard treatments and is at high risk of hysterectomy. In our patients with a Couvelaire uterus, the rates of uterine atony, postpartum haemorrhage, disseminated intravascular coagulation, and blood transfusion were all higher. Of the five patients who underwent secondary intervention, three of the four patients with compression sutures were those with a Couvelaire uterus. Therefore, it is crucial for surgeons to anticipate the risk of worsened outcomes when a Couvelaire uterus is noted intraoperatively and be proactive in the prevention of deterioration. The more severe the placental abruption, the worse the neonatal outcome.

In our study, there was no maternal death. This may be due to the timely diagnosis and prompt treatment of postpartum haemorrhage by a multidisciplinary team. High vigilance towards uterine atony and postpartum haemorrhage and timely involvement of other specialties (neonatologists, intensivists, anaesthesiologists, and haematologists) and massive transfusion protocol for expeditious transfusion and support are important.

Adverse perinatal outcomes of pregnancies complicated with placental abruption include low Apgar score, preterm birth, lower birth weight, and perinatal mortality[2,11,26-34]. 64% of our patients with placental abruption were delivered prematurely. The risk of preterm birth may be related to preterm labour or preterm prelabour rupture of membranes or a non-reassuring fetal or maternal condition. Neonatal morbidities are associated with both complications of placental abruption and prematurity[2]. In our cohort, neonates born from patients with placental abruption had an increased (but not significantly) risk of acidosis (15%) and cerebral palsy and hypoxic ischaemic encephalopathy. These problems are more likely to be attributable to the acute event of placental abruption leading to perinatal asphyxia than prematurity.

Limitations of the present study include the retrospective nature and the small sample size. The incidence of placental abruption may be underestimated, as antepartum haemorrhage of unknown origin can be marginal bleeding of the placenta, which may be a type of very minor abruption that was not included. 64% of neonates born from patients with placental abruption were preterm, and the neonatal outcome was not controlled for gestation at delivery. Thus, the placental abruption group had higher neonatal morbidities that could be associated with prematurity (rather than placental abruption alone).

Conclusion

Clinicians should be vigilant for placental abruption in patients with antepartum haemorrhage, especially in high-risk patients with a history of placental abruption, hypertension, or pre-eclampsia. Early and consistent antenatal care is imperative to identify those with risk factors. Proper education and timely preventive management should be provided to improve maternal and fetal 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 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 upon reasonable request.

Ethics approval

The study was approved by the New Territories West Research Ethics Committee (reference: NTWC/REC/22071)). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

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Haemoperitoneum secondary to rupture of a superficial vein on a subserosal uterine fibroid: a case report

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Uterine leiomyomata are the most common pelvic tumours in women. Haemoperitoneum caused by bleeding from uterine leiomyomata is extremely rare and requires prompt diagnosis and surgical management. We report a case of massive haemoperitoneum in a 47-year-old woman who presented with abdominal pain and shock in the accident and emergency department. Contrast computed tomography showed a large (14 cm) subserosal fibroid, but there was no obvious cause for the haemoperitoneum. Emergency laparotomy was performed; the bleeding was due to spontaneous rupture of a superficial vein on the large fibroid and thus total hysterectomy was performed. Despite its rarity, bleeding from fibroid vessels should be included in the differential diagnosis for women presenting with a large fibroid and haemoperitoneum without obvious cause.

Introduction

Uterine leiomyomata, commonly known as fibroids, are benign smooth muscle neoplasms of the uterus. They are commonly found in women of reproductive age, and the incidence varies among different studies and ethnicities[1]. The life-time incidence of uterine fibroids in women can be as high as 70%[2]. Up to 70% of uterine fibroids are asymptomatic, but symptomatic fibroids can manifest with bulk or pressure symptoms, abnormal uterine bleeding, dysmenorrhea, bladder or bowel symptoms, and can be associated with infertility[1]. Haemoperitoneum associated with uterine fibroid is extremely rare and difficult to diagnose preoperatively[3,4]. We report a case of haemoperitoneum secondary to venous bleeding from superficial blood vessels overlying a large subserosal fibroid.

Case presentation

In November 2022, a 47-year-old Indonesian woman, parity 2, presented to the accident and emergency department with sudden onset of severe abdominal pain. She had no history of trauma, exercise, or coitus prior to the onset of the abdominal pain. The pain was initially on the right side and then progressed to generalised abdominal pain. She had been sexually inactive for 2 years, and her last menstrual period was around 2 weeks before admission. She had regular monthly menstrual cycles with normal menstrual flow lasting around 5 days. Since the previous 6 to 8 months, she had gradual abdominal distension and attributed it to gain in body weight. Upon admission, her blood pressure was 69/44 mmHg and her heart rate was >100 beats per minute. She was afebrile with a respiratory rate of 16 per minute. Physical examination revealed generalised tenderness over the abdomen with guarding and a 22-week gravid size firm pelvic mass. The urine pregnancy test was negative. Her haemoglobin level was 10.5 g/dL on admission. After fluid resuscitation, her blood pressure was 122/60 mmHg and her heart rate was 89 beats per minute. Contrast computed tomography (CT) of the abdomen and pelvis performed in the accident and emergency department showed haemoperitoneum with a 14-cm fibroid closely abutting the anterior wall of uterus, and a 1.6 cm left corpus luteal cyst. The patient was then transferred to the gynaecological ward for further investigation.

Pelvic ultrasound confirmed a large anterior subserosal fibroid measuring around 14 cm with moderate amount of free fluid in bilateral paracolic gutters, and the 1.6 cm left corpus luteal cyst. The provisional diagnosis was a ruptured corpus luteal cyst. As the patient complained of persistent abdominal pain and her haemoglobin level dropped to 8.9 g/dL 2 hours after admission, an exploratory laparotomy was performed and haemoperitoneum of 1650 mL blood was found. The left corpus luteal cyst showed no signs of rupture or bleeding, and the right ovary was normal. The uterus was enlarged with a 14-cm

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subserosal fibroid in the anterior fundal uterine wall. Both the anterior and posterior surface of the fibroid was covered by multiple large tortuous vessels (Figure 1). There was a small break point on one of the veins over the surface of the fibroid suspected to be the source of acute bleeding (Figure 2). Other causes of haemoperitoneum were ruled out by surgeons intraoperatively. Total abdominal hysterectomy and bilateral salpingectomy was performed

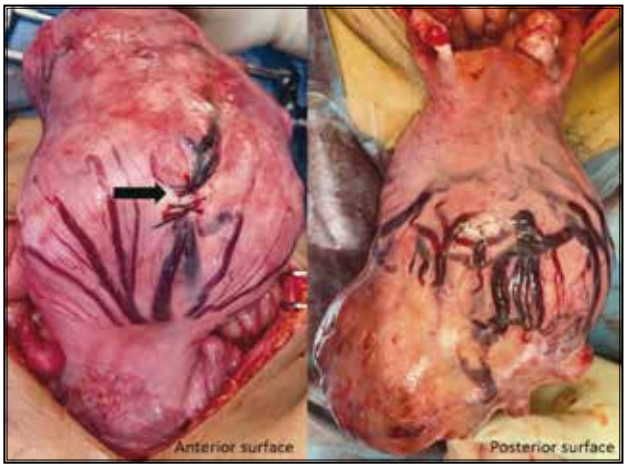

Figure 1. The anterior and posterior surface of the subserosal fibroid is covered by multiple large tortuous vessels. Haemostatic stitches (arrow) are applied on bleeding vessels during manipulation of the fibroid.

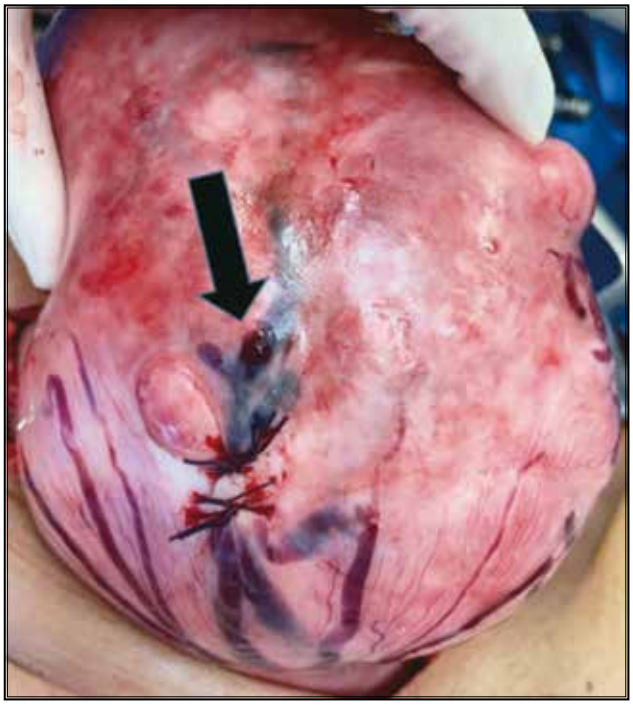

Figure 2. The source of acute bleeding is suspected to be the small break point (arrow) on a vein over the surface of the fibroid.

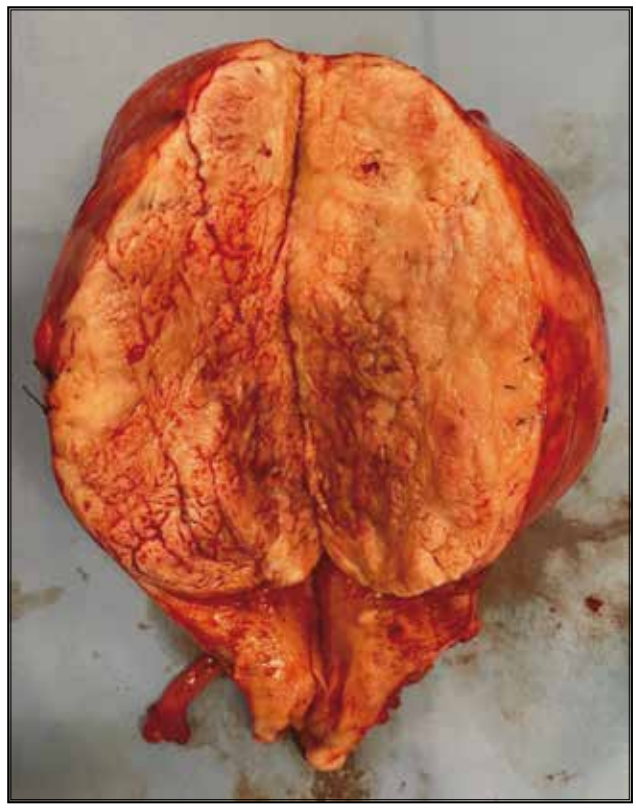

Figure 3. The uterus is cut open after hysterectomy showing the 14-cm fundal subserosal fibroid.

(Figure 3). The total amount of blood loss was 2100 mL and one unit of packed cell was transfused intraoperatively. The postoperative course was uneventful. Histopathology examination of the uterus and appendages confirmed the presence of a large benign uterine leiomyoma.

Discussion

In our patent, surgical cause for haemoperitoneum such as perforated peptic ulcer was ruled out by contrast CT of the abdomen performed in the accident and emergency department. The most common gynaecological causes for haemoperitoneum include ruptured ectopic pregnancy or ruptured corpus luteal cysts[5]. Ruptured ectopic pregnancy was also ruled out, as the patient was sexually inactive for >2 years and her pregnancy test result was negative. The most likely cause was ruptured corpus luteal cyst. However, intra-operatively, there was no evidence of bleeding from the left corpus luteal cyst, and the contralateral right ovary was normal with no evidence of ovarian cysts. The only positive finding was a very small venous rupture on one of the superficial blood vessels on the subserosal surface of the uterine fibroid.

Haemoperitoneum resulting from uterine fibroids

is extremely rare. Around 100 cases of haemoperitoneum caused by fibroids have been reported in the literature. Most were due to rupture of a degenerated fibroid or torsion of the fibroid leading to haemoperitoneum. Around 30 cases were resulted from rupture of a superficial vessel on the fibroid[6]. Haemoperitoneum caused by rupture of superficial vessels of fibroid can be spontaneous or traumatic and can occur secondary to rupture of a subserosal vein or superficial dilated vein and rarely as a result of rupture of an arterial aneurysm or arterial vessel arising from the uterine arteries[7]. Although most cases are due to venous rather than arterial rupture, a small venous rupture can still result in a tremendous amount of intra-abdominal bleeding as in our patient[6,8,9].

The size of fibroids complicated with haemoperitoneum varies from 4 cm to 16.3 cm[4]. Fibroids >10 cm are at higher risks for surface vein rupture[6]. Our patient had a large subserosal fibroid measuring 14 cm. The mechanism that precipitates the rupture of the vessels is unclear. In around half of patients, contributing causes leading to increased abdominal pressure and venous congestion include intense physical activity, trauma, defecation, violent coitus, pregnancy, and uterine contractions during menstruation[3,4]. Our patient denied any physical trauma, exercise, or coitus before onset of symptoms, nor was she menstruating at that time. We hypothesise that the rapid increase in size of the fibroid overgrew the extent of surface vascularisation and led to rupture of some surface vasculature[3]. This is supported by gradual abdominal distension in previous 6 to 8 months.

Preoperative diagnosis of rupture of the superficial vessels on the fibroids is difficult. Most cases are unexplained haemoperitoneum and necessitate exploratory laparotomy. In only one case, the diagnosis can be made preoperatively after visualisation of extravasation from dilated vessels on the fibroid in contrast CT scan of the abdomen[4]. In our patient, only portal venous phase images were taken and hence extravasation could not be identified. Arterial phase CT is not routinely performed even in trauma patients, unless the attending physician specifically orders it to investigate extravasation from bleeding vessels, as arterial phase requires higher radiation doses and slightly more time to perform[10]. Therefore, dual-phase CT (combined arterial and portal venous CT) should be ordered for patients with a large uterine fibroid presenting with unexplained haemoperitoneum when patients are haemodynamically stable to undergo CT of the abdomen and pelvis.

High suspicion of bleeding from uterine fibroids is crucial in making diagnosis preoperatively so that preoperative counselling for possible surgical procedures can be provided. Myomectomy is the preferred management for young patients with future fertility wish, whereas hysterectomy is the preferred management for post-menopausal women. However, myomectomy may not be feasible and depends on the number and site of the fibroids. Hysterectomy may be required if haemostasis is not achieved. Bleeding from fibroid vessels should be suspected in women presenting with a large fibroid and haemoperitoneum without other obvious cause. Dual-phase CT (rather than routine portal venous phase CT) should be performed. Possible surgical procedures including myomectomy and hysterectomy should be counselled to patients before operation.

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, CW Kong was not involved in the peer review process of this article. All other authors have disclosed no conflicts of interest.

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Data availability

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

Ethics approval

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

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Role of midwives in compassionate co-care for critically ill obstetric patients during the COVID-19 pandemic

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We report our experience in providing compassionate co-care for critically ill obstetric patients in the intensive care unit during the COVID-19 pandemic.

Background

After delivery, critically ill or medically indicated obstetric patients are transferred to the intensive care unit (ICU) for close monitoring, whereas newborns are transferred to the neonatal intensive care unit (NICU) or special baby care unit (SCBU) for monitoring and workup if medically indicated.

During the COVID-19 pandemic, visitors are not allowed in all acute wards. Refusal of visit requests from family members by the healthcare team becomes a moral dilemma, because postpartum women in critical condition are prone to develop postnatal depression[1].

This led to the use of telecommunication tools such as Skype, WhatsApp, and FaceTime to enable patients and family members to see and hear each other and babies in real-time through video conferencing, while keeping all parties free from the risks of COVID-19. Telecommunication tools are effective to provide psychological support to patients and their families, despite the physical seclusion imposed during the pandemic[2-5]. However, ICU staff have heavy workload during the pandemic. Thus, the midwifery team in the antenatal and labour ward stepped up and filled the service gap.

Compassionate care team

With the guidance from an obstetric consultant, Dr Meliza CW Kong, the midwifery ICU compassionate care team (CCT) was formed and comprised one obstetrics ward manager and three advanced practice midwives. The team aims to provide co-care to (1) enhance obstetric service to all critically ill obstetric patients transferred to ICU, (2) enhance communication between obstetricians, paediatricians, midwives, paediatric nurses, ICU nurses, patients, and patients' families, (3) decrease the emotional distress of patients and families, (4) provide postnatal and compassionate care, (5) strengthen the bonding between patients, newborns, and their families, and (6) develop good rapport between patients and midwives.

Workflow

When obstetric patients are transferred to ICU, labour ward midwives inform the CCT. The on-duty member records the patient information in a record book in the antenatal ward. The antenatal, labour, and postnatal progress is reviewed prior to visiting the patient. The assigned CCT midwife then visits the patient as soon as possible during office hours or shortly after delivery if the patient is admitted to the ICU postnatally. The CCT midwife usually first visits the newborn in NICU/SCBU/postnatal ward to get the updated condition of the baby from the paediatric nurse. With verbal permission from the paediatric nurse, the midwife takes photos and videos of the baby using the designated hospital smartphone. Then, the CCT midwife visits the patient in the ICU and ask the ICU nurse whether the patient is fit for telecommunication and whether the time is appropriate. If conditions are suitable, the CCT midwife approaches the patient. Most patients are admitted to the ICU shortly after delivery secondary to complicated caesarean section, peripartum hysterectomy, massive haemorrhage, or other critical conditions requiring

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Figure. A midwife from the compassionate care team shows photos and videos of the newborn and explains the updated condition to the mother in the intensive care unit through a designated hospital smartphone.

resuscitation. The CCT midwife briefly describes the delivery details to the patient because most patients do not recall what has happened to her and her baby. After that, photos and videos of her baby are shown through the hospital smartphone (Figure). The condition of her baby is explained to the patient. If the patient's condition is stable and can use her own smartphone, the CCT midwife then sends the photos and videos to her smartphone. The CCT midwife also provides postnatal care instructions to the patient such as expressing breastmilk if her condition allows. The CCT midwife then contacts the patient's husband by FaceTime and updates the condition of both the patient and baby to him. The couple are allowed personal time to chat. Photos and videos are also sent to the husband, but those in the hospital smartphone are deleted immediately because of privacy policy. This compassionate visit is then recorded in the medical progress notes, as are progress and follow-up items. All members of the CCT are aware of all current cases through internal communication, and appropriate colleagues are notified to follow up the progress of the patient and her baby when on duty. On the second day, the same procedure is repeated until the patient is transferred back to postnatal ward.

Case example

In particular, one case motivates the CCT a lot. While the husband was accompanying his wife in labour ward, the wife developed an eclamptic fit during the second stage of labour, and a crash caesarean section was carried out within a few minutes after the patient was stabilised. The patient was then transferred to the ICU with intubation, while the baby was transferred to NICU for respiratory distress. The husband was overwhelmed and helpless and could hardly give any response. He was not allowed to visit them and could just wait outside the ICU. The CCT updated him on the current condition of the patient and the baby and showed him photos and videos of the baby. He burst out in tears and thanked us for the help. We were happy to see that both the patient and the baby recovered uneventfully.

Experience gained

Since April 2020, the CCT has operated smoothly. The number of patients transferring to ICU has not been overwhelming. This CCT arrangement is welcomed by the patients who are satisfied that their babies' condition is updated, telecommunication with families is arranged, postnatal care is catered for, and their obstetrics concerns are addressed.

During the pandemic, the CCT eases the burden of frontline ICU nurses, improves communication with families of patients, and enables compassionate, patient-centred obstetric care. Telecommunication with loved ones provides psychological support to both patients and their families. Such interventions can be extended to regular labour ward and clinical work despite restrictions and uncertainties posed by the pandemic. We hope that the CCT can provide our nursing colleagues the impression that we are always with our patients. We try our best to offer any assistance to patients and their families when they are most in need and vulnerable.

Conclusion

The midwifery CCT aims to provide patient-centred care by enhancing communications between patients and their family members and by providing emotional and psychological support. We strive to take the initiative to serve our obstetric patients better during these difficult times.

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, CW Kong was not involved in the peer review process of this article. All other authors have disclosed no conflicts of interest.

Funding/support

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

Data availability

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

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Change in mode of feeding after ultrasonic therapy for lactating mothers with blocked mammary ducts

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Objectives: To retrospectively evaluate the effectiveness of ultrasonic therapy for severe breast engorgement or blocked mammary ducts, and to report the change in the mode of feeding after ultrasonic therapy and lactation consultation for mothers.
Methods: Medical records of mothers who underwent ultrasonic therapy for blocked milk ducts between November 2017 and 2020 at the Princess Margaret Hospital were retrieved. The physiotherapist assessed the visual analogue scale score for pain before and after therapy. The mode of feeding was recorded at the first consultation and at 2 weeks after the latest therapy.
Results: A total of 285 women aged 17 to 44 years underwent ultrasonic therapy for blocked milk ducts. 20.7% and 79.3% of women had one and both breasts affected, respectively. The total number of breasts included for analysis was 511. The number of ultrasonic therapies per breast varied from one to 13. After the first ultrasonic therapy, the mean pain score improved from 5.5 to 2.8, with a mean reduction of 2.7, which represented a mean of 54.7% reduction in pain score. Similarly, reduction of pain score was significant in subsequent ultrasonic therapy sessions ($p<0.001$). There was a trend towards association between the number of therapies and reduction in pain score ($r= -0.07$, $p=0.079$). At 2 weeks after the latest therapy, mothers who practised exclusive breastfeeding increased from 49.1% to 64.3%.
Conclusion: Ultrasonic therapy is effective for treatment of symptomatic postpartum breast engorgement and blocked milk ducts. It should be promulgated to all lactating mothers.

Keywords: Breast feeding; Mammary glands, human; Ultrasonic therapy

Introduction

Breastfeeding is the first step in promotion of health and wellbeing of infants and their families. The World Health Organization recommends that babies be exclusively breastfed for at least the first 6 months of their lives for optimal growth, development, and health[1]. The benefits of breastfeeding to both infants and mothers are well recognised[1,2].

Breastmilk provides optimal nutrition for newborn babies and protects against infectious disease such as otitis media, respiratory infection, diarrhoea, eczema, and allergy[3,4]. It also helps prevent future obesity and diabetes mellitus[5]. For mothers, breastfeeding reduces the risks of postpartum haemorrhage, anaemia, and breast and ovarian cancer[6,7]. Nonetheless, women may discontinue breastfeeding prematurely owing to biophysical, psychosocial, and sociodemographic factors[8,9]. Breast engorgement, despite a normal biological process during the immediate postpartum period, is a common cause of formula-milk supplementation and early cessation of breastfeeding. Within postpartum days 3 to 5, the breasts become swollen, hard, throbbing, aching, tender, and painful if emptying of breastmilk is insufficient. This may be due to improper positioning, infrequent nursing, and early or unnecessary supplementation with formula feeding. In severe cases, milk stasis occurs and may result in blocked ducts and further aggravation of the engorgement.

Two-thirds of breastfeeding mothers experience blocked ducts, which make lactation painful and difficult and cause anxiety and frustration to mothers and babies[10]. Conventional managements for difficult breastfeeding include watchful waiting (as blocked ducts often

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resolve within 24 hours), thermal therapy, cabbage leaf treatment, acupuncture, self-massage, use of herbal tea or pharmaceuticals, and ultrasonic therapy[11,12]. Ultrasonic therapy is a successful strategy to treat blocked milk ducts in lactating mothers[12-15]. It can reduce pain and inflammation and accelerate healing after soft tissue damage[16,17]. This study aims to retrospectively evaluate the effectiveness of ultrasonic therapy for severe breast engorgement or blocked mammary ducts, and to report the change in the mode of feeding after ultrasonic therapy and lactation consultation for mothers.

Methods

This study was approved by the Kowloon West Cluster Research Ethics Committee (reference: KW/EX-21-114(161-14)). Medical records of mothers who underwent ultrasonic therapy for blocked milk ducts between November 2017 and 2020 at the Princess Margaret Hospital were retrieved. In April 2016, a lactation consultation clinic was established to facilitate continuation of breastfeeding by reducing pain from blocked milk ducts through ultrasonic therapy by physiotherapists. Mothers with breastfeeding-related problem (mastitis, blocked ducts, and breast engorgement) with fever were assessed by a consultant and then referred to a physiotherapist for ultrasonic therapy. The physiotherapist assessed the visual analogue scale score for pain before and after therapy. The mode of feeding was recorded at the first consultation and at 2 weeks after the latest therapy. The mother was instructed to call back if symptoms persisted or recurred.

Data collected included mother age, parity, baby maturity at birth, mode of delivery, interval between delivery and therapy, number of therapy sessions received, pain score before and after ultrasonic therapy, mode of feeding, whether baby was separated from mother after delivery, and use of breast pump.

The Shapiro-Wilk normality test was used to examine the distribution of reduction in pain score after ultrasonic therapy. The pain score before and after ultrasonic therapy was compared using the paired *t* test or Wilcoxon signed-rank test for each ultrasonic therapy. Association between pain score reduction and the number of ultrasonic therapies was estimated using the linear mixed-effects model with random slope (number of ultrasonic therapies) and intercept (breast nested within subjects) and was adjusted by pre-therapy pain score, age, parity, and maturity. The mode of feeding before the first therapy and at 2 weeks after the latest therapy was compared using the McNemar-Bowker test. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using version 4.1.1 with 'Ime4', 'ggplot2', and 'ggpubr' packages.

Results

Between November 2017 and 2020, 285 women aged 17 to 44 (mean, 32.1) years underwent ultrasonic therapy for blocked milk ducts (Table 1). 16 (5.6%) women delivered their babies at <37 weeks of gestation. 189 women were primiparous and 96 women were multiparous. 105 (36.8%) women were separated from their infants who were admitted to neonatal units. The most common breastfeeding issue was breast refusal (22.8%), followed by milk insufficiency (11.6%) and sore nipples (14.0%). 20.7% and 79.3% of women had one and both breasts affected, respectively. The total number of breasts included for analysis was 511. The number of ultrasonic therapies per breast varied from one to 13.

After the first ultrasonic therapy, the mean pain score improved from 5.5±2.4 to 2.8±2.2, with a mean reduction of 2.7, which represented a mean of 54.7% reduction in pain score (Table 2). Similarly, reduction of pain score

Table 1. Baseline characteristics of mothers with blocked milk ducts

Characteristic	Mothers with blocked milk ducts (n=285)*
Age, y	32.1±4.5
Maturity, wk	38 (38-39)
<34	14 (4.9)
34-36	2 (0.7)
≥37	269 (94.4)
Parity	
1	189 (66.3)
2	79 (27.7)
3	16 (5.6)
4	1 (0.4)
Mode of delivery	
Normal spontaneous delivery	150 (52.6)
Vacuum extractor/forceps delivery	29 (10.2)
Caesarean section	106 (37.2)
Breast affected	
Single	59 (20.7)
Both	226 (79.3)

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

was significant in subsequent ultrasonic therapy sessions (p<0.001). There was a trend towards association between the number of therapies and post-therapy pain score (*r*= -0.07, p=0.079, Table 3).

At 2 weeks after the latest therapy, 16 mothers were lost to follow-up, with the attrition rate being 5.6%. Before ultrasonic therapy, 49.1% of mothers breastfed exclusively, 50.6% supplemented with formula milk, and 0.4% formula-fed only. At 2 weeks after the latest therapy, the corresponding percentages were 64.3%, 31.2%, and 4.5%, respectively. 21.6% changed from mixed breast- and formula-feeding to exclusive breastfeeding, 8.9% changed from exclusive breastfeeding to mixed breast- and formula-feeding, and 69.5% did not change the mode of feeding (Table 4). The changes were significant (p<0.001, marginal homogeneity test).

Discussion

Blocked milk ducts are characterised by pain, swelling, heat, hardness of breast tissue, skin tightness, and discomfort, and are challenging for mothers physically and emotionally. In a survey performed in our hospital in 2015, 82.7% of mothers opted for breastfeeding, but the percentage dropped to 35.3% at 4 weeks after delivery, because 24% of mothers complained of blocked ducts that led to reduced milk production and difficult lactation[18]. Pain from blocked ducts is a major barrier to breastfeeding. In the present study, the percentage reduction in pain score after ultrasonic therapy ranged from 52.1% to 67.5%.

Ultrasonic waves generated from the piezoelectric crystal provide stable cavitation and acoustic streaming and enhance tissue fluid interchange and local blood flow. The improved local circulation facilitates removal of milk from the engorged breast and leads to less pain and congestion. The nursing mothers can continue to breastfeed once the drainage of breast milk and pain resolved[12,14]. Ultrasonic therapy enables faster resolution of pain and hardness in the breasts from the second therapy onwards[14].

Table 2. Pain score before and after ultrasonic therapy

Session	No. of breasts	Mean±standard deviation pain score		Mean (95% confidence interval)		p Value
		Before ultrasonic therapy	After ultrasonic therapy	Reduction in pain score	% Reduction in pain score	
1	511	5.5±2.4	2.8±2.2	2.7 (2.6-2.9)	54.7 (52.1-57.2)	<0.001
2	285	5.3±2.2	2.8±2.1	2.5 (2.4-2.7)	52.3 (49.1-55.4)	<0.001
3	105	5.0±2.3	2.6±2.1	2.4 (2.1-2.7)	52.1 (46.2-58.0)	<0.001
4	69	4.5±2.2	2.4±2.2	2.1 (1.8-2.4)	55.7 (48.0-63.4)	<0.001
5	43	5.0±2.3	2.7±2.1	2.3 (1.9-2.7)	54.5 (45.3-63.8)	<0.001
6	24	5.2±2.4	3.0±2.1	2.1 (1.5-2.7)	45.9 (34.0-57.8)	<0.001
7	23	3.8±2.6	1.7±2.2	2.1 (1.3-2.9)	67.5 (52.9-82.1)	<0.001
≥8	22	4.6±2.2	2.0±1.7	2.6 (2.1-3.2)	64.0 (52.3-75.7)	<0.001

Table 3. Multivariable mixed-effects model for association between the number of therapies and post-therapy pain score

Variable	Coefficient (95% confidence interval)	p Value
(Intercept)	1.74 (0.71-2.80)	0.002
No. of ultrasonic therapies	-0.07 (-0.14-0.01)	0.079
Pain score before ultrasonic therapy	0.30 (0.26-0.34)	<0.001
Mother age	-0.01 (-0.03-0.02)	0.527
Parity	-0.03 (-0.22-0.16)	0.793
Maturity, wk		
<34	Reference	-
34-36	-0.33 (-0.90-0.32)	0.296
≥37	-0.30 (-0.74-0.20)	0.232

Table 4. Mode of feeding before the first ultrasonic therapy and at 2 weeks after the latest therapy (n=269)*

Mode of feeding before the first ultrasonic therapy	Mode of feeding 2 weeks after latest therapy			Total
	Exclusive breastfeeding and/or expressed breastmilk feeding	Breastfeeding and/or expressed breastmilk feeding supplemented with formula feeding	Formula feeding	
Exclusive breastfeeding and/or expressed breastmilk feeding	115	13	4	132
Breastfeeding and/or expressed breastmilk feeding supplemented with formula feeding	58	71	7	136
Formula feeding	0	0	1	1
Total	**173**	**84**	**12**	**269**

* Data are presented as No. of mothers; p<0.001, marginal homogeneity test

Each recurrence of blocked ducts causes pain and lump formation and elevates the pain score back to 4.5 to 5.0[12]. In our patients, some received >8 ultrasonic therapies. Each ultrasonic therapy could reduce the pain score to 2.1 to 2.7, which represented 52.1% to 67.5% reduction in pain score. No adverse effect was reported.

In the present study, only a trend towards an association between the number of ultrasonic therapies and the post-therapy pain score was observed. Nevertheless, there was a significant change in the mode of feeding. The first ultrasonic therapy was performed at a mean of 56±22.6 postpartum days. This may be a reason for the change in the mode of feeding, as some mothers would have returned to work after maternity leave. Overall, the percentage of breastfeeding increased. However, 13 mothers changed from exclusive breastfeeding to mixed feeding; four mothers changed from exclusive breastfeeding to complete formula feeding; and seven mothers changed from mixed feeding to formula feeding. These changes may not result from the adverse effect of the ultrasonic therapy.

One limitation to the present study is the selection bias, owing to the nature of the retrospective study. There was no control group to adjust for confounders. There was no randomisation of patients. Nonetheless, the use of a control group without ultrasonic therapy is considered unethical. The 2-week follow-up after the latest therapy by phone should have been increased to 4 to 6 weeks.

Conclusion

Ultrasonic therapy is effective for treatment of symptomatic postpartum breast engorgement and blocked milk ducts. It should be promulgated to all lactating mothers.

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

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Pain relief in hysteroscopy

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Pain is a major barrier to successful outpatient hysteroscopy. Multiple factors can cause pain during the procedure including patient factors such as cervical stenosis and anxiety and procedural factors such as hysteroscope diameter and operative procedures. Pain relief strategies tailored to needs for Hong Kong women may enhance patient satisfaction and the success rate of outpatient hysteroscopic procedures.

Keywords: Hysteroscopy; Pain, procedural

Introduction

Outpatient hysteroscopy is a safe and well-accepted procedure for diagnostic and therapeutic purposes in ambulatory gynaecology care[1,2]. It is indicated for abnormal uterine bleeding, suspected uterine pathology, and subfertility. It enables visualisation of the uterine cavity and is more accurate than pelvic ultrasound in assessing the endometrial cavity[1-4]. It has a high diagnostic accuracy for endometrial cancer and is not associated with worse prognosis in early-stage endometrial cancer[5]. Performing hysteroscopic procedures in an outpatient setting reduces the need for operative theatres and hence healthcare costs[6-8]. This may translate to more efficient use of operative theatre sessions for other major gynaecological surgeries. Patients may also avoid the risk and morbidities associated with general anaesthesia.

Endometrial polyps are one of the most common pathologies diagnosed on hysteroscopy. In >80% of such cases, resection is feasible in an outpatient setting[9]. The risk of atypical lesion or malignancy of endometrial polyps in postmenopausal women ranges from 2% to 5%; the risk is higher in symptomatic cases[10,11]. The 'see-and-treat' approach in outpatient hysteroscopy facilitates early diagnosis and treatment of premalignancies and malignancies. This also reduces the need for patients to re-attend the hospital on another occasion. Moreover, patients need not suffer from symptoms arising from the uterine pathology (such as abnormal bleeding and recurrent anaemia secondary to submucosal fibroids) while awaiting the therapeutic procedure. Nonetheless, not all patients are suitable for outpatient procedures. Patient selection, patient counselling and expectation management, procedure time, type of uterine pathology, cervical priming, use of instruments, and surgical skills are important determinants.

Pain is a major factor that affects the success of outpatient operative hysteroscopic procedures and is a major component of patient satisfaction[12,13]. Pain may arise from genital tract instrumentation (use of a speculum or tenaculum, insertion of a hysteroscope, cervical dilatation), uterine cavity medium, and the operative procedure. Pain can be exacerbated by the patient's anxiety and vary in different types of procedures. Although patient acceptability for outpatient operative hysteroscopy is high, the pain score for operative hysteroscopy is higher than for diagnostic hysteroscopy[14,15]. In a study of >500 women with outpatient hysteroscopy under local anaesthesia, those with operative hysteroscopy had higher mean maximum pain scores than those with diagnostic hysteroscopy[16]. In a study of >5000 patients in the United Kingdom, the mean pain score was significantly higher during hysteroscopic myomectomy and endometrial ablation than during diagnostic hysteroscopy[17].

Although the Cochrane Database Systematic Review in 2017 concluded that there is limited evidence of the clinical difference in safety or effectiveness when comparing different types of pain relief methods or no treatment for hysteroscopy[18], it does not specifically address operative hysteroscopy, in which the procedure is longer and potentially needs cervical manipulation. Therefore, measures to reduce pain remain important in the context of outpatient operative hysteroscopy.

Reducing anxiety levels

Outpatient hysteroscopy is associated with pre-procedural anxiety, which affects pain during hysteroscopy. Higher anxiety levels are associated with a higher level of intraprocedural pain and thus an increased likelihood to

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need analgesics[19-21]. High levels of anxiety related to pain are a predictor for patients preferring future procedure to be performed under general anesthesia[22]. Longer duration of the procedure is associated with higher pain scores and anxiety levels[23]. Longer pre-procedural waiting time is positively correlated with pain during the procedure[24]. Special attention should be paid to patients with a history of dysmenorrhea, adenomyosis, chronic pain condition, or anxiety, as they may experience higher levels of pain.

General measures to reduce anxiety such as patient counselling, reduction of the waiting time and procedure time, and the use of a comfortable examination chair should be offered. Adequate surgeon experience plays a key role in this aspect. A 'vocal-local approach' during the procedure can reduce pain[25,26]. If the patient agrees, the surgeon and/or healthcare staff may explain to the patient what is happening and what the findings are, with a monitor showing the hysteroscopy view in real-time. Direct involvement of the patient provides emotional support to the patient and can reduce anxiety and pain.

Cervical preparation

Cervical stenosis can be present in up to 30% of hysteroscopy cases and is a major reason of failed outpatient hysteroscopy[12]. Cervical dilatation may increase the risk of uterine perforation and the need for cervical manipulation with dilators and tenaculum and hence the pain and discomfort. Examples of pharmacological preparation for cervical ripening include misoprostol, prostaglandin, and osmotic dilators. There is insufficient evidence to support routine use of misoprostol in outpatient hysteroscopy[1,2]. Misoprostol is associated with abdominal pain, fever, and vaginal bleeding, but these adverse effects are usually mild. Misoprostol is associated with a reduction of procedure duration and the need for cervical dilatation. The Cochrane Database Systematic Review in 2015 concluded that misoprostol is more effective in reducing the need for cervical dilatation and intraoperative complications than dinoprostone and osmotic dilators in a cohort of women in which 80% required mechanical cervical dilatation without cervical preparation[27].

Although the use of miniature scopes reduces the need for a larger diameter of the cervical os, misoprostol may still be useful for outpatient operative hysteroscopy where instruments of a larger size diameter are used, compared with diagnostic hysteroscopy. The American College of Obstetricians and Gynecologists (ACOG) guideline recommends the use of misoprostol for those with a higher risk of cervical stenosis and those undergoing operative hysteroscopy[1]. These may include nulliparous women, those with previous caesarean delivery, and those with a history of cervical stenosis or surgery. For postmenopausal women undergoing outpatient hysteroscopy, misoprostol plus 25 μg of vaginal oestrogen 14 days before the procedure is more effective than misoprostol alone in pain reduction[1,27]. There is no consensus on the optimal regimen for misoprostol. Various oral or vaginal regimens of misoprostol of 200 to 1000 μg administered up to 24 hours before the procedure have been reported[28-30]. In a randomised controlled trial of 120 nulliparous women, misoprostol administered 12 hours before outpatient hysteroscopy is more effective than misoprostol administered 3 hours before hysteroscopy[29]. Oral, sublingual, and vaginal regimens are all effective, although the vaginal regimen results in fewer side effects[30]. The vaginal regimen is usually self-administered and thus its effectiveness depends on whether the patient has administered the medication correctly. The route of administration should be discussed with the patient, as some women may not accept self-administration. Osmotic dilator is effective for cervical preparation but requires a separate visit for its application[31].

Uterine distension media

The distension medium pressure correlates with the level of pain experienced during hysteroscopy[32], but the use of lower intra-uterine pressure should be balanced with adequate visualisation of the uterine cavity. Lower intra-uterine pressure is associated with reduced intra-procedural pain and post-procedural pain[33,34]. In a systematic review in 2021, normal saline significantly reduces post-procedural pain but not intraprocedural pain, compared with carbon dioxide[33]. The Cochrane Database Systematic Review in 2021 concluded that normal saline results in fewer adverse events such as shoulder-tip pain and vasovagal reaction. Vaginoscopy is also easier with a fluid distension medium[35]. The use of warm saline (rather than room temperature saline) is a common practice, despite lacking evidence of pain reduction in outpatient hysteroscopy. Most studies show no difference in pain between warm saline and room temperature saline[33,36,37].

Music

Music has been widely used as a non-pharmacological method to reduce patient anxiety and perioperative pain and to increase patient satisfaction in surgery[38-40], labour[41,42], and endoscopy[43]. Music has been shown to reduce anxiety and enhance performance of surgeons during surgery[44]. In the context of outpatient hysteroscopy, there is a potential reduction of the duration

of the procedure. Music may distract the patient from the noise of operative instruments. Although music has been shown to be effective in reducing anxiety and pain scores[45,46], evidence of music as a stand-alone pain-relief strategy is lacking. Given its easy availability and non-invasive nature, music can be used as an adjunct to other pain-relief methods.

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation is widely used for acute and chronic pain conditions[47]. It is non-invasive, safe, easy to use, and well-tolerated. It is used during labour[48,49] and for symptomatic relief of primary dysmenorrhea[50,51]. A randomised, double-blinded, placebo-controlled trial of 138 women in 2017 has shown that transcutaneous electrical nerve stimulation has been associated with reduced pain and increased patient satisfaction in hysteroscopy[52].

Systemic analgesia

The joint guideline by the Royal College of Obstetricians and Gynaecologists (RCOG) and the British Society for Gynaecological Endoscopy (BSGE) on the best practice of outpatient hysteroscopy recommends the use of non-steroidal anti-inflammatory drugs around 1 hour before outpatient hysteroscopy[2]. In a systematic review of 22 studies and a meta-analysis of 16 studies, pre-procedural administration of anti-inflammatory drugs plus transcutaneous electrical nerve stimulation result in significant reduction in pain during outpatient hysteroscopy with no increase in adverse events, compared with controls[53]. Tramadol is effective in reducing pain but is associated with opioid adverse effects such as dizziness and vomiting[54,55]. Anti-spasmodic is associated with reduced pain but is also associated with more adverse effects[53].

Local analgesia

In a systematic review and meta-analysis in 2020, local analgesia results in a reduction in intraprocedural pain regardless of type or route of administration, although studies included in the analysis are heterogeneous and thus the role of local anaesthesia warrants further research[56]. Local anaesthesia given via the transcervical route has been shown to significantly reduce vagal effects during hysteroscopy. Both short-acting and long-acting anaesthetic agents are effective in reducing pain. Using the vaginoscopic approach (with minimal genital tract instrumentation) as the first-line approach requires further research[56]. Nonetheless, miniature operative hysteroscopes and instruments are still of a larger diameter than those for diagnostic hysteroscopy, local anaesthesia still has a role in outpatient operative hysteroscopy.

Local anaesthesia may be given topically, para-cervically, or intra-cervically. Topical anaesthesia such as lidocaine/prilocaine cream has been reported to reduce pain during endometrial biopsy and intrauterine device insertion.[57,58] It is easy to use and has low incidence of serious adverse effects and can be self-administered by patients. Lidocaine spray has been reported to reduce pain related to tenaculum use[59]. However, evidence on the effectiveness of these topical medications in pain control in hysteroscopy is limited. Topical anaesthesia requires time to work and its effectiveness wanes within a short time.

Intracervical injection of local anaesthesia can be administered at the 12 o'clock position of the cervix for pain relief, whereas paracervical anaesthesia administered into the vaginal mucosa at the cervicovaginal junction at the 3, 5, 7, and 9 o'clock positions is effective in cervical procedures and hysteroscopy[2,56]. Procedure should be started around 7 minutes after administration of local analgesia, during which the clinician may prepare the equipment for the procedure. Local anaesthesia is associated with pain during injection and takes time to work.

The use of intrauterine fundal anaesthesia for outpatient endometrial ablation and manual vacuum aspiration has been reported[60-65]. Anaesthesia is injected under direct visualisation by hysteroscopy into the myometrium medial to each tubal ostia. The rationale of uterine fundal anaesthesia is that the uterine fundus and the cervix differ in nerve innervation[66]. The uterine fundus sensory is primarily supplied from T10 to L1, whereas the sensory for the lower part of the uterus and cervix is through S2 to S4. Therefore, local paracervical anaesthesia may not be adequate for uterine interventions that involve the uterine fundus. Intrauterine fundal anaesthesia is safe and non-inferior to paracervical anaesthesia alone, but there is limited evidence of its use as a sole local anaesthesia.

Multimodal analgesia is commonly used for perioperative pain management[67], but there is limited evidence of this approach for outpatient hysteroscopy. In a study of a multimodal anaesthetic approach for both diagnostic and operative hysteroscopies that involve topical application of lidocaine gel on the speculum, use of intracervical and paracervical blocks, and application of lidocaine gel to the cervical canal, pain associated with application of anaesthesia was not higher than pain associated with operative procedures[16]. Serious adverse

effects of local anaesthesia for hysteroscopy are uncommon; vasovagal adverse effects include nausea, vomiting, dizziness, sweating, bradycardia, and hypotension[56]. The risk of serious adverse events can be reduced by using a standardised administration and dosage of local anaesthesia.

Vaginoscopic approach

Vaginoscopic approach to outpatient hysteroscopy is considered the standard approach by the RCOG[2], the ACOG[1], and the American Association of Gynecologic Laparoscopists[68], as it is associated with less pain, reduced incidence of vasovagal reaction, reduced procedural time, with similar efficacy[69,70]. Vaginoscopy enables a larger range of movement to facilitate procedures for an acutely anteverted or retroverted uterus. Cervical stenosis is the main reason for failure of vaginoscopy, and pain is the most common reason for failure of hysteroscopy[12]. Techniques of the vaginoscopic approach involve insertion of the hysteroscope to the posterior fornix of the vagina to enable gradual identification of external cervical os, which can guide the insertion of hysteroscopy into the endocervical canal[71]. Leakage of uterine distension media can be reduced by occluding the introitus manually or by balloon catheter. Suprapubic pressure and bladder filling may be applied to reduce anteflexion to facilitate the uterus to be in a more axial position. Similarly, digital pressure from the rectum can reduce retroflexion.

The vaginoscopic approach may be feasible when miniature operative hysteroscopes, such as resectoscopes and shavers, are used. However, it may not be practical for nulliparous or postmenopausal women, as operative instruments are still larger in diameter than diagnostic instruments. Evidence for the role of vaginoscopy in reducing pain during operative hysteroscopy is limited.

Miniaturised instruments

Miniaturised instruments may facilitate vaginoscopy and minimise pain. Hysteroscopic tissue removal systems enable simultaneous tissue removal and retrieval without applying electric energy to the endometrium, thereby reducing the need for reinsertion of instrument and thus reducing pain[72].

A systematic review of randomised controlled trials in 2021 has shown that medical technologies such as scissors and morcellators are associated with less pain experienced by patients than an electrical device[73].

Hysteroscopic electrosurgery has the advantage of controlling bleeding during operative procedures[74], but it may not be feasible to remove polyps and fibroids in one go (owing to the miniaturised instrument) and require further instrumentation for specimen retrieval. Hysteroscopic morcellators have the additional benefit of removing pathology specimens simultaneously with resection. This reduces the frequency of insertion and removal of instruments from the genital tract as well as the operation time. Intrauterine morcellators have been shown to have better outcomes in terms of shorter operation time and reduced risk of fluid deficit, compared with standard surgical procedures[75-77].

Quality and safety

Pre-procedure counselling and involvement of patients in making decisions on outpatient hysteroscopy are essential. In 2013, the National Health Service in the United Kingdom launched a campaign against inadequate pain relief during hysteroscopy for discussion by the Parliament[78]. In a study in 2020, disconnection between clinician- and patient-reporting resulted in negative correlation of patient self-rated pain with clinical estimates of pain[79]. Thus, patient-reported outcomes should be included when reviewing outpatient hysteroscopic services. An example of a pain relief protocol is shown in the Appendix.

The RCOG/BSGE joint guideline recommends auditable standards, which include items such as adverse events, failure rates, need for cervical dilatation, and patient satisfaction[2]. A national outpatient hysteroscopy service patient-centred survey in United Kingdom was conducted in 2019 to assess women's perspectives of their experience of outpatient hysteroscopy and to benchmark outpatient hysteroscopy practices[17]. This survey can help to identify problems in services and facilitate quality improvement initiatives in addressing service gaps.

Conclusion

Outpatient diagnostic and operative hysteroscopy is safe and effective. Major barriers to the success of outpatient hysteroscopic procedures are patient anxiety and pain. Thus, patient-reported outcomes should be considered. Although there is no standardised regimen for pain relief in outpatient hysteroscopy, pain-relief protocols comprising non-pharmacological and pharmacological options should be in place to minimise pain and anxiety, especially for operative procedures. Shared decision-making is essential when considering hysteroscopy as an outpatient or inpatient procedure.

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 takes responsibility for its accuracy and integrity.

Conflicts of interest

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Data availability

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

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Appendix.
Pain relief strategies

Before procedure
Patient counselling
Informed consent (including see-and-treat approach)
Manage expectations (duration of procedure, information sheet)
Answer any questions/concerns
Reduce waiting time in clinic
Pharmacological methods
Non-steroidal anti-inflammatory drugs (1 hour before procedure)
Use of vaginal misoprostol for those at higher risk of cervical stenosis
Use of oestrogen cream for postmenopausal women with a history of cervical stenosis
During procedure
Non-pharmacological pain-relief methods
Music
Transcutaneous electrical nerve stimulation
Techniques
Vaginoscopic approach as standard technique
Use hysteroscope of 12° to 30° optic angle
Avoid cervical dilatation
Avoid use of tenaculum on cervix
Use lowest pressure to distend the uterine cavity to obtain visualisation
Use warm normal saline as distension medium
Use of miniature equipment including scissors, resectoscope, and morcellator
Minimise procedure duration
Pharmacological strategies after discussion with patient
Topical anaesthesia
Intra-cervical block
Paracervical block
Multimodal anaesthesia
After procedure
Post-procedure analgesics

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Fetal neurosonographic phenotyping of inborn errors of metabolism

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Fetal central nervous system malformations are commonly encountered during routine fetal morphology scans. Fetal ventriculomegaly is among the most common prenatal neuroimaging findings including midline abnormalities, posterior fossa abnormalities, and cortical malformation. Their imaging features are often symptoms or part of the phenotypic features of the underlying disease. Collective information from targeted fetal neurosonography, magnetic resonance imaging, and genetic testing can help clinicians to make the diagnosis. We review various common and essential fetal neuroimaging features and highlight their association with inborn errors of metabolism.

Keywords: Brain; Genetic testing; Magnetic resonance imaging; Metabolism, inborn errors; Prenatal diagnosis; Ultrasonography, prenatal

Introduction

Fetal central nervous system malformations are commonly identified during routine fetal morphology scans. Fetal ventriculomegaly is among the most common prenatal neuroimaging findings including midline, posterior fossa, and cortical malformations. Their imaging features are often symptoms or part of the phenotypic features of the underlying disease. Collective information from targeted fetal neurosonography, magnetic resonance imaging (MRI), and laboratory testing can help clinicians to make the diagnosis. In this review, we discuss various common fetal central nervous system abnormalities and their linked to inborn errors of metabolism (IEM).

IEM is broadly defined as a congenital defect of metabolism including catabolism (breakdown of molecules) and anabolism (synthesis of molecules) in our body. Early identification of IEM can be life-saving and prevent irreversible damage to the body. The first screening of IEM was invented by Dr Robert Guthrie in the early 1960s who collected a capillary blood sample from a newborn heel prick on a card (the Guthrie card) to screen for phenylketonuria (PKU). PKU is characterised by abnormally elevated blood phenylalanine levels. Untreated or poorly controlled maternal PKU can cause fetal microcephaly, congenital heart disease, structural anomalies, and fetal growth restriction[1]. To date, the definition of IEM is further defined as any condition leading to the dysfunction of specific enzymes or disruption of biochemical pathways intrinsic to the pathomechanism[2,3]. Although IEM is rare individually, it is not uncommon collectively, with an estimated incidence ranging from one in every 800 to 2500 newborns[4]. Nevertheless, the true prevalence of IEM is difficult to estimate owing to various confounding factors and underdiagnosis.

The Society for the Study of Inborn Errors of Metabolism has described >600 different IEMs under 15 categories based on the affected biochemical pathways. IEMs are caused by genetic mutations that alter metabolism. However, the significance of genetic variants in their phenotypes remains uncertain. With the advancement of genomics and metabolomics technology, a combined metabolomics and genomics approach has been proposed[5]. There are 217 920 metabolites from 114 100 entries in the Human Metabolome Database (version 5.0). This information covers 132 335 metabolic pathways, 136 878 metabolites or xenobiotics, and 2153 proteins[6]. In-depth knowledge for interpreting genomics and metabolomics information and understanding the role of IEMs in different fetal neurodevelopmental disorders is essential to prenatal diagnostics, which may enable early intervention and immediate postnatal management.

Holoprosencephaly

Holoprosencephaly (HPE) is a common structural anomaly of the forebrain[7]. The prosencephalon (the most anterior brain vesicle) is the precursor of the forebrain. It divides into the telencephalon (ie, the cerebral hemisphere, commissural fibres, and basal ganglia) and the diencephalon

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(ie, the thalamus, posterior commissural fibres, and hypothalamus)[8]. Failure or incomplete separation of the prosencephalon by 8 weeks of gestation results in HPE and associated facial dysmorphism, neurological impairment, and endocrine abnormalities[9]. Four classical types have been proposed based on the degree of forebrain non-separation[10,11]. Alobar HPE, the most severe form, is readily seen on the first trimester ultrasound. It is characterised by loss of the midline falx and the absence of two distinct choroid plexuses (Figure 1)[12]. The less severe form involves non-separation of the frontal lobes in semi-lobar HPE (Figure 2), the basal aspect of the frontal lobes in

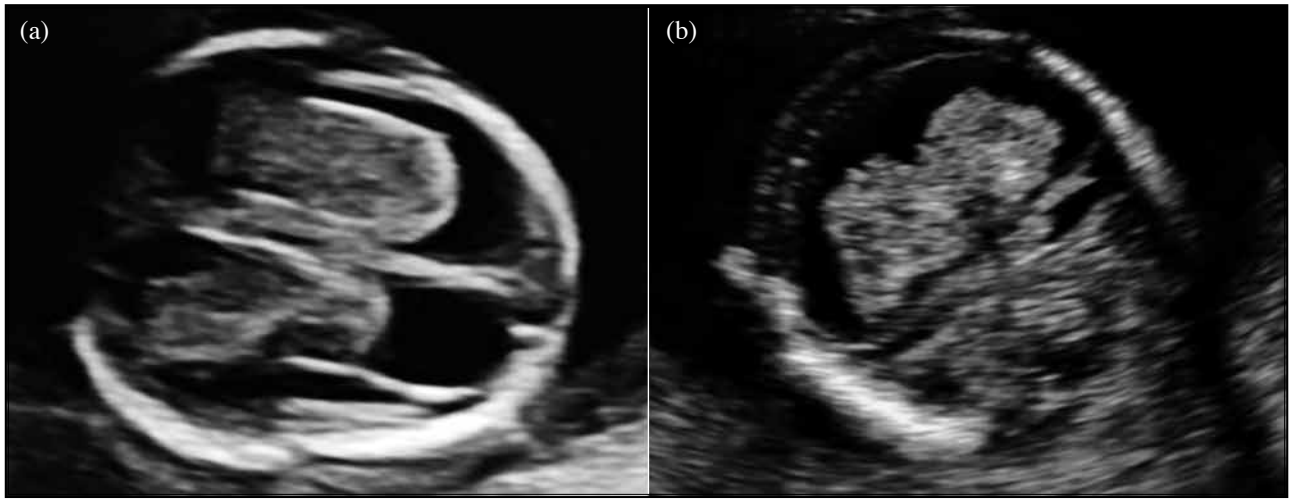

Figure 1. Fetal brain at 12 weeks of gestation: (a) a normal fetal brain showing a complete midline falx and each choroid plexus surrounded by fluid-filled cerebral ventricles, and (b) a fetal brain with alobar holoprosencephaly showing loss of the midline falx with a mono-ventricle and a fused choroid plexus at the coronal plane.

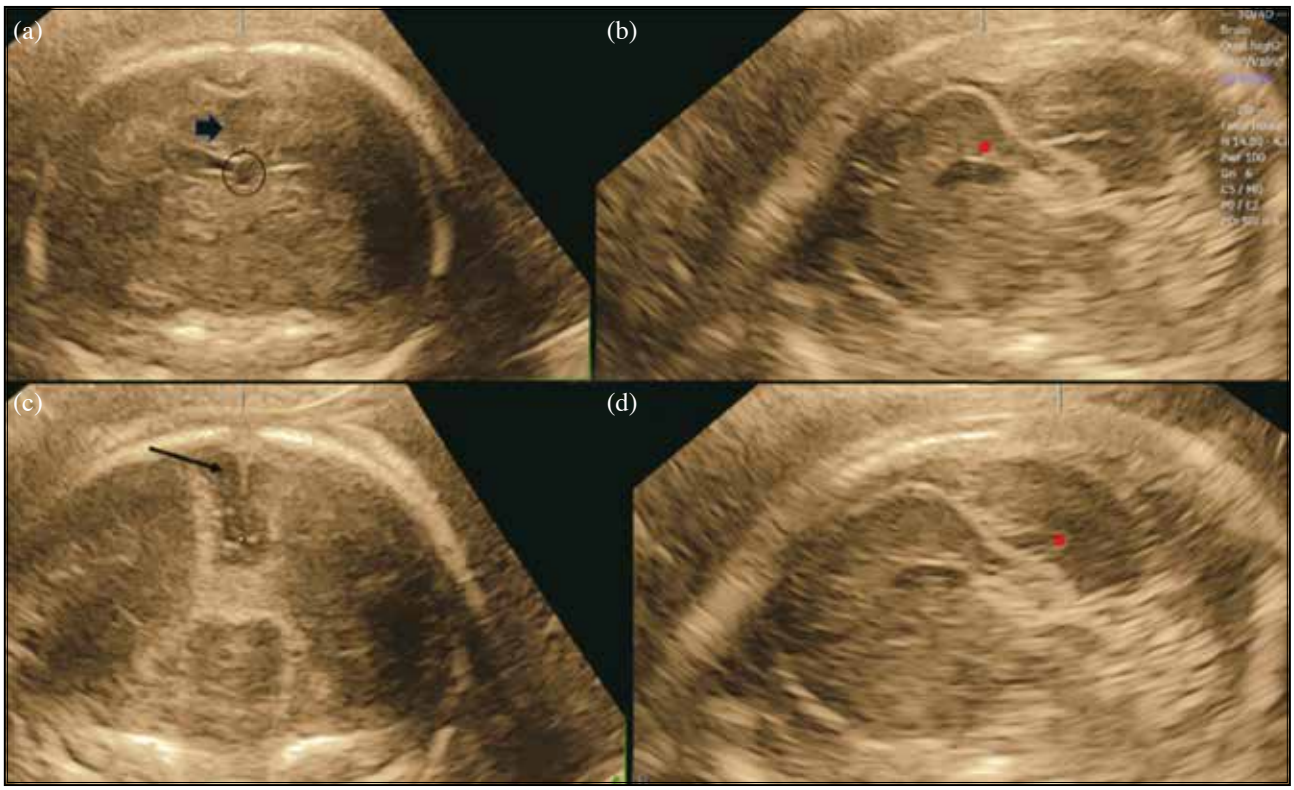

Figure 2. Three-dimensional neurosonography in the second trimester of a fetus affected by semi-lobar holoprosencephaly: the anterior (a) coronal and (b) sagittal planes showing a fused frontal lobe (arrow and dot) and the lack of a cavum septum pellucidum (circle). The posterior (c) coronal and (d) sagittal planes showing the presence of the midline falx (arrow and dot) indicating separation of the cerebral hemisphere at the parietal lobes.

lobar HPE, and the posterior frontal and parietal lobes in middle interhemispheric variant HPE.

Common neurosonography and/or MRI indications are absent in the cavum septum pellucidum during the second or third trimester. Common trisomies, namely 13 and 18, other chromosomal aberrations, and genetic abnormalities have been reported[13-16]. Smith-Lemli-Opitz syndrome (SLOS), a sterol metabolism disorder, is a known cause of HPE. Abnormalities such as microcephaly, corpus callosal agenesis, poly/syndactyly, polymicrogyria, ambiguous genitalia, and fetal growth restriction may be found in affected fetuses. In SLOS, the disease-causing variants in the *DHCR7* gene affect the enzyme 7-dehydrocholesterol reductase[17]. This enzyme is responsible for converting 7-dehydrocholesterol (7DHC) to cholesterol; thus, affected subjects have elevated circulating 7DHC (8-dehydrocholesterol) levels but low total cholesterol levels. 7DHC levels in the amniotic fluid were elevated among affected fetuses[18,19]. It remains unclear how this condition leads to fetal brain malformations. Nevertheless, myelin is rich in cholesterol, and the abnormal accumulation of 7DHC and a low-cholesterol environment may interfere with myelin synthesis[20].

In addition, Sonic Hedgehog (Shh) signalling defects are often associated with HPE. The Shh protein requires cholesterol as a modulator by covalently bonding with cholesterol and palmitic acid. Low-circulating cholesterol levels impact Shh signalling and causes HPE[17]. HPE is also observed in lathosterolosis (another IEM of cholesterol biosynthesis), which impairs the conversion of lathosterol to 7DHC. Interestingly, simvastatin, an HMG-CoA reductase inhibitor, has been reported to improve the biochemical phenotypes and various clinical features in some patients with lathosterolosis and SLOS[21-23]. However, more studies are required to substantiate the clinical significance of the finding[24].

Microcephaly

Fetal microcephaly is defined as a head circumference that is three standard deviations below the mean after correcting for gestational age[25-28]. Neuronal proliferative disorders causing reduced proliferation or excessive apoptosis of neuronal-glial progenitors can manifest early in the first and second trimesters of pregnancy. Migrational or post-migrational disorders affecting glial multiplication only manifest in the third trimester or become apparent after birth. The aetiology of autosomal recessive primary microcephaly is complex; at least 28 related genes are reportedly disease-causing or associated with severe microcephaly[29-31]. The causes of acquired microcephaly are beyond the context of the current review. Other factors that disrupt neuronal proliferation and migration (congenital infections, toxin exposure, ischaemic insults, and IEM) must be considered. Amino acid disorders (such as 3-phosphoglycerate dehydrogenase deficiency[32,33], asparagine synthetase deficiency[34], and maternal PKU[1]) have been described in cases of congenital and progressive microcephaly. Other IEMs linked to congenital microcephaly include SLOS[35] and pyruvate dehydrogenase deficiency[36]. High phenylalanine levels have potentially toxic effect on fetal neurodevelopment in maternal PKU. High phenylalanine levels compete with other neutral amino acids to facilitate transport across the blood-brain barrier. Relative depletion of non-phenylalanine neutral amino acids hinders cerebral enzyme activity or protein synthesis[37].

Macrocephaly

Macrocephaly was defined as head circumference that is two standard deviations above the mean after correcting for gestational age. Most cases are familial with normal developmental outcomes[38]. Macrocephaly secondary to underlying hydrocephalus or brain tumour and syndromic macrocephaly may result in abnormal neuropsychological development[39]. IEM cause prenatal macrocephaly and germinolysis cysts have been reported in glutaric aciduria type I[40,41], which is included in the current newborn screening in Hong Kong by analysing C5-DC carnitine in whole blood. Early metabolic treatment of newborns can prevent acute decompensation and irreversible neuronal damage[42,43]. Canavan disease, D-2-hydroxyglutaric aciduria, Hunter syndrome, Hurler syndrome, and Sly syndrome are often present as postnatal macrocephaly[44], which is beyond the scope of the current review.

Migrational disorder

Cortical development involves cerebral expansion and folding in three overlapping stages: neuronal proliferation, migration, and organisation. This highly complex fetal neurodevelopment is tightly regulated by cellular and molecular mechanisms that involve multiple genes and pathways[45]. The exact mechanisms of fetal brain development and neural migration are unclear. Nonetheless, *LIS1*, *DCX*, and *TUBA1A* were found in approximately 80% of patients with migrational disorders[46]. Neuronal migrational disorders are a spectrum of disease; the most severe form is schizencephaly and the agyria-pachygyria

Table. Brain disorders in different brain development phases[48]

Brain disorders in different brain development phases
Neuronal proliferation
Microcephaly
Megalencephaly
Neuronal migration
Heterotopia
Lissencephaly
Cobblestone malformation
Hemimegalencephaly
Neuronal organisation
Polymicrogyria
Schizencephaly

spectrum, whereas the milder form includes polymicrogyria and periventricular or subcortical heterotopia[47]. The Table shows brain disorders in different developmental phases[48].

Antenatal diagnosis of cortical development malformation is challenging. Standard screening in the second trimester includes assessments of fetal head size (by biparietal diameter), head circumference, and atrial width of the lateral ventricles[49]. Maturation of the Sylvian fissure is among the most readily identifiable hallmarks of cortical brain development. MRI can demonstrate continuous changes in the gyri and sulci that occur throughout gestation[8], with the Sylvian fissures being identified as early as 16 weeks of gestation. On ultrasound, the Sylvian fissure can be recognised at approximately 18 weeks of gestation, and the maturation of Sylvian fissure pattern is based on its shape[50-54].

Advances in high-resolution transvaginal fetal neurosonography have enhanced the precision of Sylvian fissure pattern evaluation[55-57]. Poon et al[58] pioneered a gestational age-specific reference chart of Sylvian fissure angle (SFA) development across 18 to 30 weeks of gestation based on 422 ultrasonographic data points from normal fetuses. The measurements were performed under a stringent and standardised protocol (Figure 3) that aims to minimise inter- and intra-observer variability. The SFA with respective to the gestational age and head circumference are expressed in a biometric chart to serve as a screening tool for fetal cortical malformations and enables early referral for further assessment.

Delayed cortical development

Classic lissencephaly (type 1), cobblestone lissencephaly (type 2), and lissencephaly secondary to tubulinopathy (type 3, also known as microlissencephaly) commonly present with ventriculomegaly and delayed or abnormal operculisation of the Sylvian fissure. In classic lissencephaly, the brain has broad or absent gyri and an abnormally thick cortex (Figure 4). Antenatal diagnosis of lissencephaly is largely made in the third trimester, with presentation of a slow-growing head circumference and ventriculomegaly. Clinical suspicion of lissencephaly in the second trimester is possible if the bilateral SFA is grossly delayed.

IEM-related lissencephaly mainly involves cobblestone lissencephaly. Cobblestone lissencephaly is characterised by over-migration of the neuroglial cell causing 'protrusions' of neurones over the brain surface that give rise to a cobblestone appearance on MRI. Cobblestone lissencephaly has been well reported in congenital glycosylation disorders. This category includes Walker-Warburg syndrome, muscle-eye-brain disease, and Fukuyama congenital muscular dystrophy, all of which share the clinical features of congenital muscular dystrophy. The presence of cobblestone lissencephaly together with cerebellar abnormalities (Z-shaped appearance of the brainstem), meningocele, and microphthalmia are pathognomonic of Walker-Warburg syndrome[59].

Microlissencephaly (type 3 lissencephaly) is characterised by microcephaly, lissencephaly, fetal growth restriction, polyhydramnios, micrognathia, and subcutaneous oedema secondary to fetal akinesia[60,61]. It is often associated with hypoplasia of the cerebellar vermis, with the anterior portion more severely affected. This subtype of lissencephaly encompasses genetic disorders that affect tubulin protein[62].

Polymicrogyria and heterotopia

Polymicrogyria is characterised by abnormal cortical migration. Many small plications are noted on the cortical surface that give rise to a wrinkled chestnut appearance over part or all the brain surface. Polymicrogyria primarily occurs during late neuronal migration or the early post-migrational period; therefore, it is often undetectable on second-trimester ultrasound. Heterotopia is characterised by arrested neuronal migration in the periventricular region (Figure 5) or subcortical white matter. Prenatally, heterotopia can present with an abnormally shaped Sylvian fissure, prominent subarachnoid space overlying the affected brain cortex, and ventricular wall irregularity.

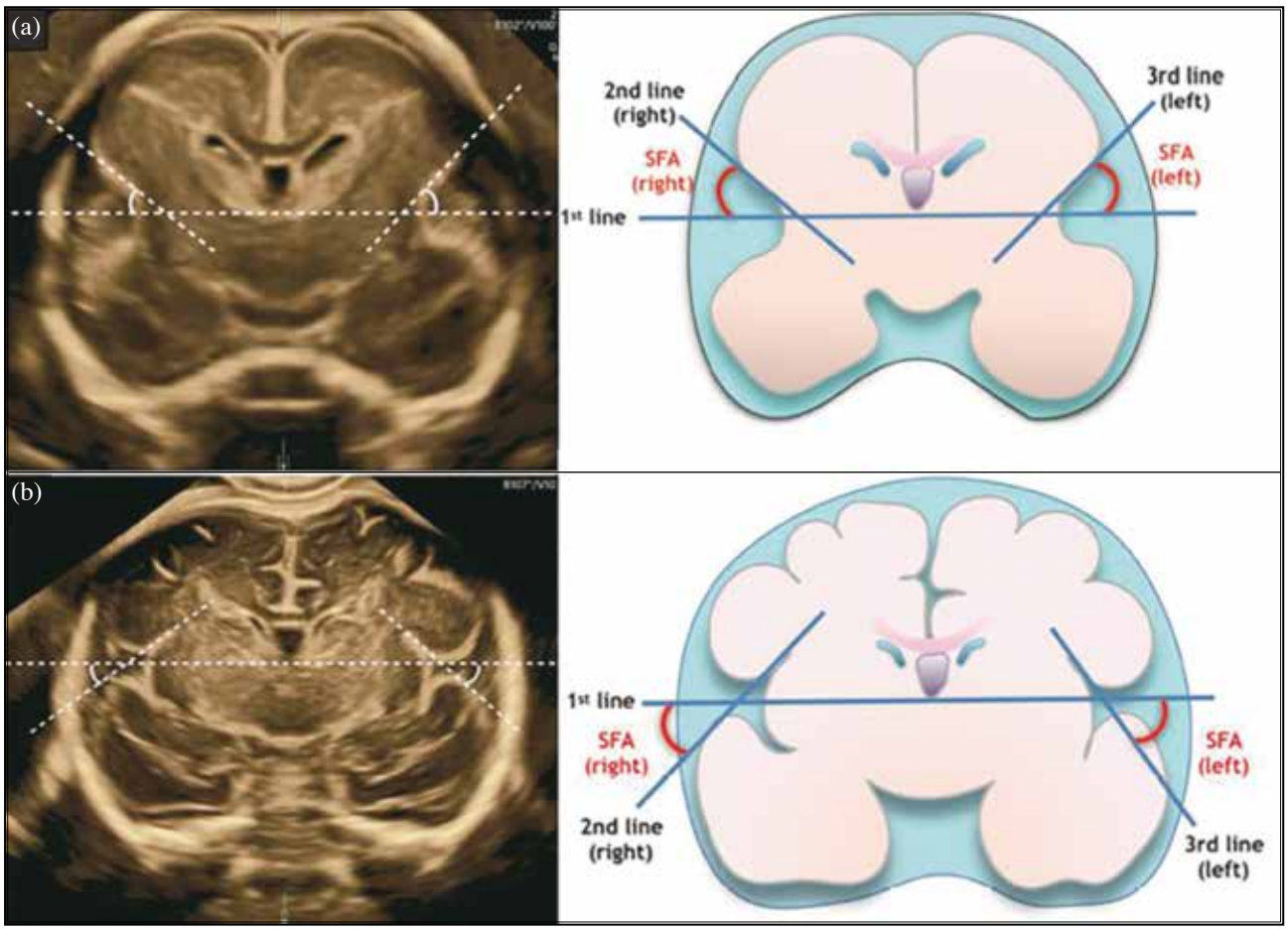

Figure 3. Measurement of (a) positive and (b) negative Sylvian fissure angle (SFA) on ultrasound images and corresponding schematic diagrams: the first line is drawn along the horizontal line and then the second and third lines are drawn along the upper sides of the right and left Sylvian fissures, respectively. The right and left SFA formed by these three lines are measured using the horizontal line as reference (0°). The angle above the horizontal line is deemed positive, whereas that below the horizontal line is deemed negative (adapted with permission from Poon LC, Sahota DS, Chaemsaithong P, et al. Transvaginal three-dimensional ultrasound assessment of Sylvian fissures at 18-30 weeks' gestation. Ultrasound Obstet Gynecol 2019;54:190-8.)

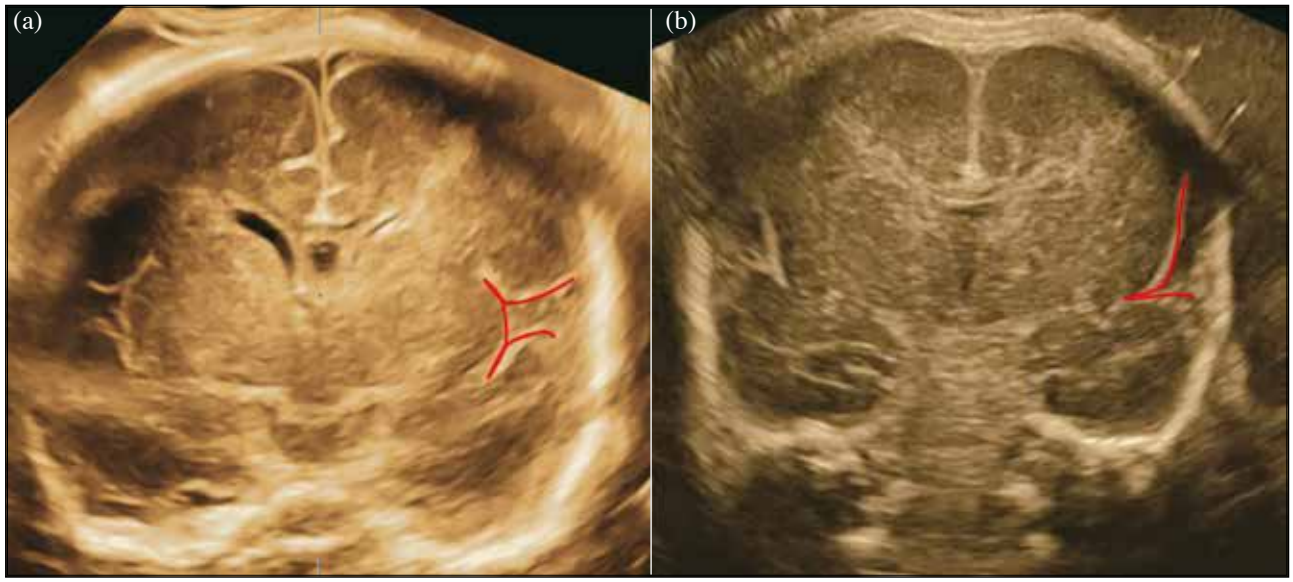

Figure 4. Fetal brains in coronal view at 30 weeks of gestation: (a) a normal fetal brain showing a normal quadrangular shape of the Sylvian fissure and (b) a fetal brain with Miller-Dieker lissencephaly showing abnormal development of the Sylvian fissure.

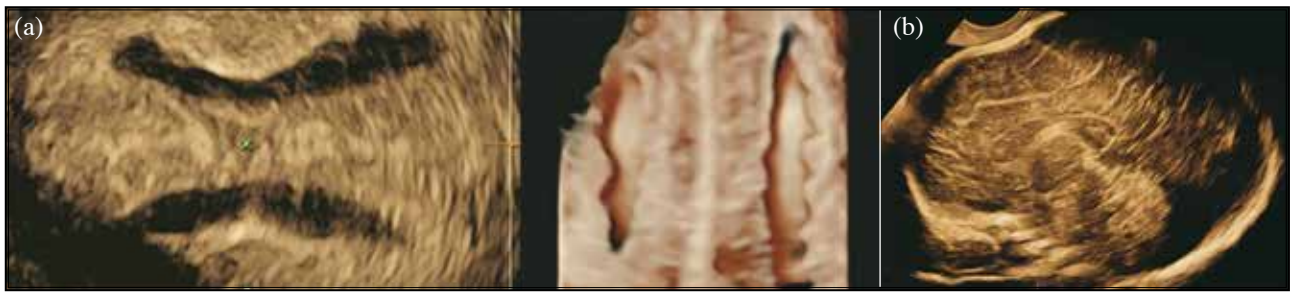

Figure 5. Ultrasound images of the fetal brain at 30 weeks of gestation showing (a) nodular irregularities at the ventricular wall in the ventricular view and (b) mega cisterna magna in the sagittal view.

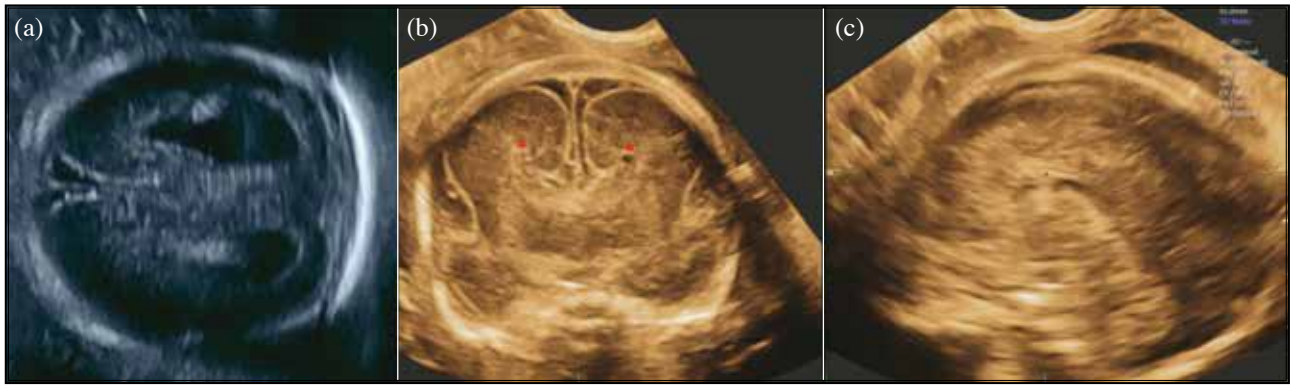

Figure 6. Ultrasound images of a 22-week fetal brain with complete agenesis of the corpus callosum: (a) axial plane showing tear drop–shaped lateral ventricles and (b) coronal and (c) midsagittal planes showing separation of the interhemispheric fissure and wide separation of the anterior frontal horns (asterisks) as well as complete absence of the corpus callosum.

These sonographic features are sometimes detectable on transvaginal ultrasonography[63]. Subcortical band heterotopia (double cortex) is essentially diagnosed by MRI.

Metabolic defects (such as the infantile form of pyruvate dehydrogenase deficiency, Zellweger syndrome, and SLOS) have been reported in cases of polymicrogyria and/or heterotopia. Pyruvate dehydrogenase deficiency is a potentially life-threatening mitochondrial disorder that can present with pachygyria, polymicrogyria, periventricular nodular heterotopias, and cerebellar and brainstem hypoplasia[36,64]. Zellweger spectrum disorder can present with migrational disorder and extracranial features such as renal cysts and bony stippling of the patella and long bones[65].

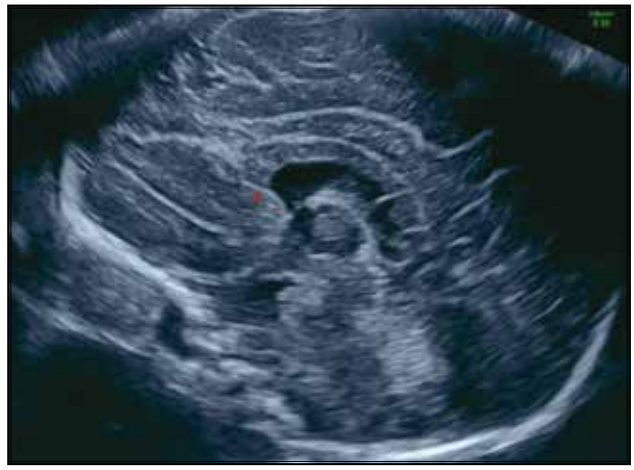

Figure 7. Ultrasound image of the sagittal plane of a fetal brain at 34 weeks of gestation showing a shortened and thickened corpus callosum with absence of the rostrum (asterisk).

Corpus callosum agenesis/ dysgenesis

The absence of the cavum septum pellucidum and the presence of a teardrop configuration of the lateral ventricle are common presentations of corpus callosum abnormalities (Figures 6 and 7). Complete agenesis of the corpus callosum is usually apparent on a second-trimester morphology scan. The mechanism of partial or complete agenesis of the corpus callosum is not entirely clear. Features of corpus callosum agenesis include midline axonal misguidance, decreased cortical neuron

numbers, a lack of long-range interhemispheric neurones, and a modified number of callosal axons[66,67]. The process is extremely dynamic, making the diagnosis of partial agenesis or dysgenesis extremely difficult, especially before the third trimester.

Corpus callosum abnormalities have been reported in various IEMs through neuroimaging and/or autopsy findings including pyridoxine-dependent epilepsy, 2,4-dienoyl-CoA reductase deficiency, argininosuccinate lyase deficiency, combined oxidative phosphorylation deficiency 12, complex I deficiency, cytochrome oxidase deficiency, fumaric aciduria, glutaric aciduria types I and II, Menkes disease, nonketotic hyperglycinaemia, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, and sulfite oxidase deficiency[67].

Anomalies of posterior fossa

The posterior fossa develops rapidly from the first to second trimester. The persistence of embryonic brain flexures after 15 weeks of gestation (ie, a Z-shaped appearance of the brainstem) is suggestive of severe cerebellar dysgenesis. This finding, together with cobblestone lissencephaly, is pathognomonic of Walker-Warburg syndrome[59].

Isolated cerebellar hypoplasia and, more commonly, progressive cerebellar and pons atrophy have been reported in congenital disorders of glycosylation such as PMM2 deficiency[68].

Conclusions

Prenatal ultrasound should be better be described as 'fetal sonographic phenotyping', which is a process of interpreting morphological findings with knowledge of physiology and pathomechanism. Because abnormal fetal neurosonographic features are usually a sign of an underlying disease, collective genomics and metabolomics information can supplement and substantiate sonographic phenotypes by providing a more specific and accurate aetiological diagnosis including IEM. Prenatal identification of IEM can improve antenatal and postnatal care through a multidisciplinary approach. We envision that making a diagnosis is not the end. Rather, it better prepares the family for the possible outcome and management. Novel therapeutic strategies are evolving with ongoing clinical trials to revitalise the defective biochemical pathways. These will shed light on the patients and their family regarding these previously unmanageable conditions.

Contributors

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

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

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

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Pregnancy outcomes after SARS-CoV-2 infection: the current evidence

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Many questions have been raised about SARS-CoV-2 infection complicating pregnancy such as whether pregnancy increases the susceptibility to SARS-CoV-2 infection, whether SARS-CoV-2 infection in pregnancy is associated with more severe disease and higher mortality, and whether SARS CoV-2 infection during various stages of pregnancy is associated with increased risks of adverse pregnancy and neonatal outcomes. Moreover, there are controversies on the association between SARS-CoV-2 infection and the development of pregnancy complications such as pre-eclampsia, preterm delivery, and fetal growth restriction. In addition to the direct impact of COVID-19 infection on pregnancy outcomes, social restriction measures and changes in healthcare system during the COVID pandemic are reported to lead to adverse pregnancy outcomes such as increased stillbirths. This review aims to summarise the current evidence in the literature on these issues.

Keywords: COVID-19; Pre-eclampsia; Pregnancy outcome; Preterm birth; SARS-CoV-2

Introduction

Clinical management for pregnant women with SARS-CoV-2 infection should be similar to that for women without pregnancy. The Royal College of Obstetricians and Gynaecologists[1], the National Institutes of Health[2], and the Society for Maternal and Fetal Medicine[3] regularly update their clinical guidelines for management of pregnant patients. Therefore, the management of SARS-CoV-2 infection in pregnancy is not discussed in this review, nor is the safety of COVID vaccines in pregnancy. This review aims to highlight the current evidence in the literature on pregnancy outcomes complicated by SARS-CoV-2 infection.

Does pregnancy increase susceptibility to COVID infection?

The physiological changes during pregnancy may create an immune-compromised state leading to a higher susceptibility to COVID infection during pregnancy. However, comparison between studies may not be feasible because of differences in vaccination rates among pregnant women and in the prevalence of COVID in the community. Data obtained in the early stages of the pandemic before the availability of COVID vaccines are more useful. According to the Centers for Diseases Control and Prevention, the incidence of laboratory-confirmed SARS-CoV-2 infection among women aged 15 to 44 years was 9% for pregnant women and 5% for non-pregnant women[4]. However, the study had a lot of missing data, and the testing and ascertainment rates differed between pregnant and non-pregnant women. The higher infection rate in pregnant women was likely the result of much more widespread screening of pregnant women. In another study in the United States, the infection rate was higher among pregnant women (13.9/1000 deliveries) than non-pregnant women (7.3/1000) aged 20 to 39 years[5]. However, the study was not controlled for various confounders such as exposure risks. Similar to the general population, the incidence of SARS-CoV-2 infection in pregnancy has been reported to be consistently higher among those living in socially and economically disadvantaged settings, those with lower household incomes, those with higher unemployment rates, those of minor ethnic groups, those lacking health insurance, and those in high-density neighbourhood[6,7]. Contrarily, in Hong Kong, people in lower social classes (the working poor and ethnic minorities) were more badly affected economically by the pandemic, but significantly higher infection rates in lower socioeconomic groups were not observed, nor were higher infection rates associated with underprivileged pregnant women[8,9].

Is SARS-CoV-2 infection more severe in pregnancy?

The 2003 SARS outbreak in Hong Kong resulted in three deaths among 12 pregnant women with the infection, giving a mortality rate of 25%[10]. SARS-CoV-2

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infection is of lower mortality than SARS infection but still causes more severe disease in pregnant women than non-pregnant women. In the early stage of the pandemic before vaccination was available, among over 400 000 women of reproductive age with symptomatic SARS-CoV-2 infection adjusted for age, race, ethnicity and underlying medical conditions, pregnant women had a three-fold increase in the risk for intensive care unit (ICU) admission (10.5 vs 3.9 per 1000 cases), 2.9-fold increase in the need for invasive ventilation (2.9 vs 1.1 per 1000 cases), 2.4-fold increase in the need for extracorporeal membrane oxygenation (0.7 vs 0.3 per 1000 cases), and 1.7-fold increase in death from the infection (1.5 vs 1.2 per 1000 cases), compared with non-pregnant women[11]. The increased morbidity and mortality in pregnancy are ascribed to physiological changes (such as decreased tidal volume as the uterus enlarges, immunological compromises) and increased risks for thromboembolism in pregnancy.

Using data from the national registry in Mexico that included admission data from 475 hospitals to compare 5183 pregnant women and 175 905 non-pregnant women of reproductive age (15-45 years) with COVID-19 infection confirmed by real-time reverse-transcription (RT-PCR), the crude rates of death, pneumonia, intubation, and ICU admission were 1.5% and 1.5%, 9.9% and 6.5%, 8.1% and 9.9%, and 13.0% and 6.9%, respectively[12]. After propensity score matching, pregnant women were still at higher risk of death (odds ratio [OR]=1.84), pneumonia (OR=1.86), and ICU admission (OR=1.86). Pregnancy is a risk factor for death and severe morbidity in women of reproductive age with SARS-CoV-2-infection, even after adjusting for demographic and medical factors.

In a multinational study conducted between March and October 2020 involving 706 pregnant women with or without SARS-CoV-2 infection in 43 institutions in 18 countries, women with SARS-CoV-2 infection were at higher risk for hypertensive disorders in pregnancy (relative risk [RR]=1.76), severe infections (RR=3.38), ICU admission (RR=5.04), spontaneous preterm delivery (RR=1.59), iatrogenic preterm delivery (RR=1.97), severe neonatal morbidity (RR=2.66), severe perinatal morbidity and mortality (RR=2.14), and maternal mortality (RR=22.3)[13]. Fever and shortness of breath was associated with increased risks of severe maternal complications (RR=2.56) and neonatal complications (RR=4.97), whereas asymptomatic women with COVID-19 infection were at higher risk for maternal morbidity (RR=1.24) and preeclampsia (RR=1.63) only. SARS-CoV-2 infection in pregnancy was associated with consistent and significant increases in severe maternal and neonatal morbidity and mortality.

In the CANCOVID-Preg study in Canada comparing 6012 pregnant women from six provinces with positive polymerase chain reaction (PCR) for SARS-CoV-2 and two age-matched control groups of uninfected pregnant women and non-pregnant women with SARS-CoV-2 infection between March 2020 and October 2021, pregnant women with infection were associated with an increased risk of SARS-CoV-2–related hospitalisation (7.75% vs 2.93%, RR=2.65) and ICU admission (2.01% vs 0.37%, RR=5.46), compared with non-pregnant women with infection[14]. Worse pregnancy outcomes were associated with increasing age, pre-existing hypertension, and more advanced gestation at diagnosis. Pregnant women with infection were at higher risk of preterm delivery (11.05% vs 6.76%, RR=1.63) even when hospitalisation was not needed, compared with uninfected pregnant women.

In a meta-analysis of 435 studies, 9% of pregnant or recently pregnant women attending or admitted to hospital for any reason were diagnosed as having SARS-CoV-2 infection[15]. The most common clinical manifestations were fever and cough (both around 36%). The risks of ICU admission (OR=2.61) and mechanical ventilation (OR=2.41) were higher in pregnant than non-pregnant women. The mortality rate of pregnant women with infection was 0.2% (970/179 981 women in 123 studies). Compared with pregnant women without infection, pregnant women with infection had increased odds of maternal death (OR=6.09), ICU admission (OR=5.41), caesarean section (OR=1.17), and preterm birth (OR=1.57). The odds of stillbirth (OR=1.8) and admission to the neonatal intensive care unit (OR=2.18) were also higher in babies born to women with infection, compared with those without infection. The updated version of this meta-analysis published in May 2022 is by far the largest and most comprehensive evaluation of pregnancy outcome after SARS-CoV-2 infection.

In other studies conducted in 2020 before vaccination was available, pregnant women with SARS-CoV-2 infection were reported to have more adverse outcome[16-20]. However, widespread community vaccination should probably attenuate the morbidity and mortality figures. Although infection is associated with a higher risk in pregnant women compared with non-pregnant women, risk factors for severe disease are similar among both groups. In a study in the United Kingdom, black ethnicity, advanced maternal age, and overweight or obesity were risk

factors for hospital admission among pregnant women[20]. Other studies confirmed that more severe SARS-CoV-2 disease during pregnancy was associated with non-white ethnicity, advanced maternal age, pre-existing medical conditions (obesity, asthma, chronic pulmonary diseases, hypertension, and diabetes mellitus), pregnancy-specific complications (gestational diabetes and pre-eclampsia), need for mechanical ventilation, and maternal death[15-18].

Maternal morbidity in different SARS-CoV-2 variants

In a multicentre study between March 2020 and January 2022, women with SARS-CoV-2 infection were propensity-matched with four control groups without infection during four periods based on the dominant strain of SARS-CoV-2 virus: March to December 2020 (wild type), January to June 2021 (Alpha [B.1.1.7]), July to November 2021 (Delta [B.1.617.2]), and December 2021 to January 2022 (Omicron [B.1.1.529]). Compared with 12 504 women without infection, 3129 women with infection had significantly higher rates of severe maternal morbidity events in all periods except for the Omicron period[21]. Compared with controls, the OR for any severe maternal morbidity was 2.74 for the wildtype strain, 2.57 for the Alpha variant, and 7.69 for the Delta variant (p for trend <0.01) but was not significant for the Omicron variant (OR=1.21). This trend was similar for respiratory and non-respiratory severe maternal morbidity. The Delta variant was associated with highest rates of maternal morbidity than other variants.

In a study of 1286 unvaccinated pregnant women in Turkey and the United Kingdom who were positive for SARS-CoV-2 by RT-PCR from April 2020 to February 2022 (870 during pre-Delta period, 339 during the Delta period, and 77 during the Omicron period), compared with infection during the pre-Delta period, infection during the Delta period was associated with increased need for nasal oxygen support (RR=2.53), high-flow oxygen or continuous positive airway pressure (RR=2.50), mechanical ventilation (RR=4.20), and extracorporeal membrane oxygenation (RR=11.0), as well as 3.6 times higher maternal mortality rate (5.3% vs 1.5%, p=0.01)[22]. However, the Omicron and pre-Delta periods showed similar rates for nasal oxygen treatment (RR=0.62), high-flow oxygen or continuous positive airway pressure (RR=1.07), artificial ventilation (RR=0.44), and maternal mortality rates (1.3% vs 1.3%, p=0.99). The need for nasal oxygen (RR=0.26) and preterm delivery before 34 weeks (15.4% vs 4.9%, p<0.001) were lower during the Omicron and pre-Delta periods than during the Delta period. This study included only unvaccinated pregnant women so that the full impact of different strains of SARS-CoV-2 could be compared. The results showed that the Delta strain was associated with higher maternal morbidity and mortality, whereas the Omicron and pre-Delta strains resulted in similar disease severity.

Transmission of SARS-CoV-2 to fetus

SARS-CoV-2 can transmit to the fetus as an intrauterine infection, an intrapartum infection (during labour and delivery), or a postpartum infection of the neonate (through breast feeding or close contact). However, only a few cases of intrauterine infection have been reported[23,24], whereas postpartum infection is the most common. Despite the risks of postnatal transmission, it is probably safe for an infected mother to continue to breastfeed, because replication competent virus has not been detected in breast milk although breast milk is positive for SARS-CoV-2 by PCR[25,26]. In a cohort of 1481 deliveries in New York, 8% of the mothers were tested positive for SARS-CoV-2[27]. The mothers were allowed to breastfeed provided that they consistently used surgical masks and practised hand hygiene and breast cleansing. All babies had negative PCR results at 5 to 7 days and 14 days of life. Therefore, perinatal transmission is unlikely if adequate hygiene measures are instituted. Direct breastfeeding should be safe when sufficient instructions on infant protection were given to parents.

In a meta-analysis of 206 cohort studies and 266 case series and case reports, 1.8% of 14 271 babies were born to mothers with SARS-CoV-2 infection by RT-PCR[28]. Of 592 babies positive for SARS-CoV-2 with exposure time and type, 14 were confirmed to have mother-to-child transmission: seven (of 448 cases) were in utero transmission, two (of 18 cases) were intrapartum transmission, and five (of 70 cases) were early postnatal transmission. Neonates positive for SARS-CoV-2 were associated with severe maternal infection (OR=2.4), maternal death (OR=14.1), maternal admission to ICU (OR=3.5), and maternal postnatal infection (OR=5.0). The data showed that vertical transmission of SARS-CoV-2 is rare but possible. The severity of maternal SARS-CoV-2 infection is the key risk factor associated with SARS-CoV-2 positivity in neonates.

In a meta-analysis of 176 cases of neonatal SARS-CoV-2 infections (confirmed by at least one positive nasopharyngeal swab and/or the presence of specific IgM), 70% and 30% of infections were due to environmental and vertical transmission, respectively[29]. 55% of infected

neonates developed symptoms including fever (44%), gastrointestinal symptoms (36%), respiratory symptoms (52%), neurological symptoms (18%), and abnormal lung imaging (64%). Late infection was associated with a lack of mother-neonate separation from birth (adjusted OR [aOR]=6.6, p<0.0001) but not with breastfeeding (aOR=2.2, p=0.148). Therefore, the risks of neonatal infection should be weighed against the benefits of breastfeeding and mother-infant bonding. Most guidelines support rooming in of the newborn with infected mother, particularly when the mother is afebrile and asymptomatic[1,2,30].

Gestation at the time of infection and obstetric complications

SARS-CoV-2 infection has been reported to be associated with various obstetric complications including preterm delivery, pre-eclampsia, fetal growth restriction, and postpartum haemorrhage[13-16]. However, impact of infection on different gestation stages remains controversial. In a multicentre study of 22483 women of whom 7.4% were tested positive for SARS-CoV-2 infection, women with infection were at an increased risk for severe obstetrical haemorrhage (1.1% vs 0.5%, aOR=1.78), pulmonary morbidity (2.0% vs 0.5%, aOR=3.90), and ICU admission (1.8% vs 0.5%, aOR=3.29), compared with women without infection[31]. However, the timing of infection (whether active or resolved at time of delivery) was not associated with the risk for severe obstetrical haemorrhage or hypertension-associated or neurologic morbidity.

In a multicentre study in the United States in 2020, among 2326 women tested positive for SARS-CoV-2 during pregnancy, 402 who were positive before 28 weeks of gestation had an increased risk of fetal or neonatal death (2.9% vs 1.5%, aRR=1.97), preterm birth at <37 weeks of gestation (19.6% vs 13.8%, aRR=1.29), and hypertensive disorders of pregnancy with delivery at <37 weeks of gestation (7.2% vs 4.1%, aRR=1.74), compared with 11705 women without infection[32]. Nonetheless, there was no difference in the rates of preterm birth at <34 weeks of gestation, any major congenital malformation, small or large for gestational age, and gestational hypertension or preeclampsia with severe features. The incidence of antenatal complications was similar between infections in the first and second trimesters and infections in the third trimester.

In a study in Italy, sero-molecular testing for SARS-CoV-2 at 12, 16, 21 weeks and at delivery identified 10.3% of women who were positive in the first trimester[33]. Composite adverse obstetric outcome was observed in 6.2% of positive women and 10.5% of negative women, whereas composite adverse neonatal outcome was noted in 12.5% of positive women and 7.6% of negative women. In newborns of women who developed IgG antibodies, the same antibodies were detected in arterial cord blood despite neonatal nasopharyngeal swab being negative. No maternal pneumonia or hospital admission secondary to COVID infection were recorded. Asymptomatic or mildly symptomatic women during the first trimester of pregnancy did not experience significantly more adverse events than negative women.

In a study in Turkey, 167 hospitalised pregnant women with confirmed COVID-19 infection were divided into three groups according to the trimester in which infection was diagnosed[34]. Of the women, 29.3% had an active infection at the time of delivery and 70.7% cleared of infection before giving birth. The three gestation groups were comparable in terms of the incidence of preterm birth (p=0.271), preeclampsia (p=0.394), fetal growth restriction (p=0.403), HELLP syndrome (p=0.763), and gestational diabetes mellitus (p=0.664). Four (2.39%) patients required ICU care and one patient died. The gestational age at the time of COVID-19 infection was not correlated with the frequency of adverse pregnancy outcomes among hospitalised pregnant women with severe disease.

Few studies have evaluated the pregnancy complications in women with active SARS-CoV-2 infection at the time of labour and delivery. In a study comparing 84 women who had active infection at the time of delivery and 92 women who had recovered for at least 10 days, the two groups were comparable in terms of the mean gestational age at delivery (39 weeks for both), the overall rate of caesarean delivery (26.2% vs 17.4%), and non-elective caesarean delivery (10.71% vs 4.34%)[35]. In the active-infection group, the rate of severe disease was 2.4% and the rate of critical disease (with ICU admission, mechanical ventilation, and extracorporeal membrane oxygen) was 3.6%, compared with 0% for both in the recovered group. The two groups were comparable in terms of adverse perinatal outcomes. Thus, delivery is safe in women with active infection despite a non-significant trend for more severe disease.

In the multicentre PregOuTCOV study to determine the effect of gestational age at time of infection on obstetric and neonatal outcomes, among 10 925 singleton pregnancies, 393 (3.60%) were infected with SARS CoV-2, of whom 11.7% developed pneumonia and 4% developed acute respiratory distress syndrome[36]. The infected group

had significant increases in composite adverse obstetric outcomes at >20 weeks' gestation (22.75% vs 19.25%, p<0.001) and composite adverse neonatal outcomes at >26 weeks' gestation (17.86% vs 14.28%, p<0.001) after adjusting for confounders. In Cox regression models, those with composite adverse obstetric outcomes were more likely to be infected after 20 weeks gestation (p<0.001), whereas those with composite adverse neonatal outcomes were more likely to be infected after 26 weeks gestation (p<0.001). The incidence of preeclampsia, eclampsia, and HELLP syndrome increased significantly (p=0.002) when infection was at >15 weeks gestation. The incidence of spontaneous preterm delivery at <37 weeks increased significantly (p<0.001) when infection was at >26 weeks. The incidence of preterm delivery at <32 weeks increased significantly (p<0.001) when infection was at >26 weeks. The incidence of NICU admission increased significantly (p<0.001) when infection was at >28 weeks. The incidence of respiratory distress increased significantly (p<0.001) when infection was at >28 weeks. Although the birthweight in the infected group was significantly lower (3129 vs 3228 g, p<0.001), the z-scores of birthweight in the two groups were similar. Although the effect of gestational age at the time of infection on adverse pregnancy outcomes remains controversial, there is a trend for more severe complications when the infection was acquired in the third trimester, compared with earlier trimesters.

Association of infection with pre-eclampsia, preterm delivery, and fetal growth restriction

Epidemiological studies have demonstrated an increased incidence of pre-eclampsia in women with SARS-CoV-2 infection[13,15,16]. In a systematic review and meta-analysis of 42 studies involving over 438 548 pregnant women, SARS-CoV-2 infection was positively associated with preeclampsia (OR=1.33)[37]. Compared with mild infection, severe infection was strongly associated with preeclampsia (OR=4.16), preterm birth (OR=4.29), gestational diabetes (OR=1.99), and low birth weight (OR=1.89).

In a systematic review and meta-analysis of 28 studies comprising 790 954 pregnant women, 15 524 (1.96%) of them were diagnosed with SARS-CoV-2 infection[38]. Infection during pregnancy increased the odds of preeclampsia (pooled aOR=1.58, p<0.0001, 11 studies). Pregnant women with infection had increased odds of preeclampsia severe features (pooled aOR=1.76, 7 studies), eclampsia (pooled aOR=1.97, 3 studies), and HELLP syndrome (pooled aOR=2.10, 1 study), compared with those without infection. Both asymptomatic and symptomatic infections significantly increased the odds of developing preeclampsia, with odds higher in symptomatic patients (OR=2.11) than asymptomatic patients (OR=1.59). However, the meta-analysis was dominated by two large cross-sectional studies (one from the United Kingdom[39] and the other from the United States[40]). The former study included white (76.3%), Asian (12.2%), and black (4.6%) pregnant women; association between infection and pre-eclampsia persisted even after adjusting for maternal age, ethnicity, parity, pre-existing diabetes mellitus, pre-existing hypertension, and socioeconomic deprivation (by the index of multiple deprivation 2019)[41].

Based on these findings, it is recommended that obstetricians should be aware of this and closely monitor pregnant women with infection for early detection of preeclampsia. However, this association was not consistently seen[42,43], and biases have been identified. For instance, in the absence of prospective cohort studies of pregnant women with and without infection to evaluate subsequent development of pre-eclampsia, there is likely to be under-reporting of women who had infection but were relatively asymptomatic and did not go on to develop pre-eclampsia. In addition, most studies made the diagnosis of SARS-CoV-2 infection in the third trimester. Given that the pathophysiology of pre-eclampsia is supposed to originate in the first and early second trimesters, any causal relationship with infection would be more readily established with those having infection at earlier gestational ages. Therefore, the current evidence does not support such a temporal relationship between infection and pre-eclampsia. Moreover, the 1.5 times increased risk of pre-eclampsia in pregnant women with infection (compared with those without infection) is too small to prove causal relationship. Epidemiologically, it should be explained by other underlying confounding or contributing factors. Furthermore, the direct pathophysiology for SARS-CoV-2 infection to pre-eclampsia is still unknown. Possible mechanisms including downregulation of the angiotensin-converting enzyme 2 receptor ACE2 in the placenta by SARS-CoV-2 spike proteins, and upregulation of sFlt-1 and endoglin and other antiangiogenic factors that cause vasoconstriction remains to be proven[41].

The association of SARS-CoV-2 infection with preterm birth is less consistent, compared to pre-eclampsia. Studies of preterm delivery often did not specify the gestation at infection or the difference between spontaneous or iatrogenic preterm births. In a study of 5893 women from 77 countries with pregnancy gestation beyond 20 weeks,

symptomatic SARS-CoV-2 infection before 20 weeks did not increase the risk of preterm delivery, compared with no infection or mild infection after 20 weeks. However, severe infection in late pregnancy significantly increased the risk of preterm delivery (compared with no infection), primarily due to an increase in medically indicated preterm deliveries (including preterm caesarean sections) while the increase in spontaneous preterm delivery was mild. Overall, mild or moderate infection conferred minimal risk, as did severe disease in early pregnancy[44].

Although medically indicated preterm birth appears to be a logical sequalae of severe SARS-CoV-2 infection in the third trimester, the association of earlier infection in the first or second trimester to subsequent preterm birth remains controversial. In the registry of the Maccabi Healthcare Services of Israel, 2753 pregnant women with infection between February 2020 and July 2021 were identified and matched with non-infected pregnant women according to age, last menstruation date, sector, and socioeconomic status[45]. 17.4% and 48.4% of pregnant women were infected during the first and third trimesters, respectively. Infection during the first and second trimester was not associated with preterm labour ($p>0.8$), whereas infection during the third trimester had a greater risk of preterm birth (aOR=2.76), particularly after 34 weeks of gestation (aOR=7.10). Preterm birth risk was higher in symptomatic third trimester infections (OR=4.28). Pregnancy loss incidence was similar in both groups (aOR=1.16). Only infection during late pregnancy was associated with increased risk of preterm birth, particularly among symptomatic women.

In a study using live births documented by California Vital Statistics between July 2020 and January 2021 (n=240 147), births were classified as very preterm (<32 weeks), preterm (<37 weeks), early term (37-38 weeks), and term (39-44 weeks)[46]. The joint effects of SARS-CoV-2 diagnosis, hypertension, diabetes, and obesity on preterm, and very preterm births were calculated. SARS-CoV-2 diagnosis was associated with an increased risk of very preterm birth (aRR= -1.6), preterm birth (aRR= -1.4), and early term birth (aRR= -1.1), and was associated with elevated risks in women with hypertension, diabetes, and/or obesity. It was argued that in this large population-based study, medical comorbidities were contributed by preterm birth rather than SARS-CoV-2 infection per se.

To determine the real impact of asymptomatic/mild SARS-CoV-2 infection on preterm birth not caused by maternal respiratory failure, a case-control study was conducted to compare a preterm birth group of 102 women and a full-term control group of 127 women in Turin[47]. Only women with spontaneous or medically indicated preterm birth because of placental vascular malperfusion were included. Current or past SARS-CoV-2 infection was determined by nasopharyngeal swab testing and detection of IgM/IgG antibodies in blood samples. There was no significant difference in the cumulative incidence of SARS-CoV-2 between the preterm and term groups (20.5% vs 25.1%), although the preterm group was burdened by a higher prevalence of comorbid risk factors including body mass index of >24.9 kg/m^2, asthma, and chronic hypertension. Logistic regression analysis showed that asymptomatic/mild SARS-CoV-2 infection was not an independent predictor for spontaneous and medically indicated preterm birth secondary to pregnancy-related hypertension and its complications. Thus, women without comorbidities should be reassured that asymptomatic/mild SARS-CoV-2 infection does not increase the risk of preterm delivery. Preterm birth and severe SARS-CoV-9 infection shared common comorbidity risk factors, which may explain the high rate of preterm birth secondary to maternal conditions rather than SARS-CoV-2 infection.

Early epidemiological studies have associated SARS-CoV-2 infection with increased incidences of fetal growth restriction. There have been case reports that link SARS-CoV-2–induced placental infarcts with fetal growth restriction[48]. To compare fetal growth velocity and fetal haemodynamics in pregnancies complicated and in those not complicated by severe acute SARS-CoV-2, 49 consecutive pregnancies complicated by SARS-CoV-2 during the second half of pregnancy was prospectively matched with 98 unaffected women[49]. General baseline and pregnancy characteristics were similar. There were no differences between the two groups at the second and third trimesters in terms of head circumference, abdominal circumference, femur length, and estimated fetal weight z-scores as well as growth velocity of all these body parameters and the pulsatility index of both maternal and fetal Doppler scans throughout gestation. Thus, increased fetal growth surveillance is not supported in pregnancies complicated by SARS-CoV-2[49].

In a Japanese study that reviewed the medical records of infants born and admitted to the neonatal intensive care unit and growth care unit of Shiga University of Medical Science Hospital before the COVID-19 pandemic (April to September 2019) and during the pandemic (April to September 2020), apart from fewer preterm babies, there

were fewer infants born with fetal growth restriction during the pandemic period than the pre-pandemic period (12 vs 31, p=0.0002)[50]. There were no significant differences in any infant or maternal factors associated with fetal growth restriction. It was concluded that there was a paradoxical reduction in the number of infants with fetal growth restriction during the COVID-19 pandemic. Therefore, evidence is not consistent on association of SARS-CoV-2 infection with fetal growth restriction.

Social impact of COVID-19 pandemic on obstetric care

In addition to the direct impacts of SARS-CoV-2 infection on pregnant women and pregnancy outcomes, the pandemic itself has negative impacts on healthcare delivery and accessibility and leads to adverse outcomes even among women not infected with SARS-CoV-2. Particularly in the early stages in 2020, the pandemic had profound impacts on healthcare systems and social economic structure worldwide. Extensive lockdowns, disruption of healthcare services, and fear of attending healthcare facilities might also have brought about adverse effects on patient care.

In a retrospective, multicentre cohort study of perinatal outcomes in Melbourne before and during the COVID-19 lockdown (from March 2020 to March 2021), 24817 births exposed to lockdown were compared to 50017 births before the pandemic[51]. There was a higher risk of preterm stillbirth in the exposed group than the control group (0.26% vs 0.18%, aOR=1.49, p=0.015). There was also a significant reduction in the preterm birth of live infants <37 weeks (5.68% vs 6.07%, aOR=0.93, p=0.02), which was largely mediated by a significant reduction in iatrogenic preterm birth (3.01% vs 3.27%, aOR=0.91, p=0.03) including iatrogenic preterm birth for fetal compromise (1.25% vs 1.51%, aOR=0.82). These observations raised concerns that the pandemic in 2020 may have led to a failure to identify and appropriately care for pregnant women at an increased risk of antepartum stillbirth.

In a similar study on the effect of restriction measures to mitigate SARS-CoV-2 transmission during the pandemic on preterm labour, 3150 women who were exposed to restriction measures during pregnancy and 3175 unexposed controls were compared[52]. Preterm birth before 34 weeks or stillbirth occurred in 3.0% exposed pregnancies and in 4.1% controls (RR=0.74, p=0.021). Preterm birth before 34 weeks occurred in 2.4% of women in the exposed group and in 3.4% of women in the control group (RR=0.71, p=0.022), without evidence of an increase in the rate of stillbirth in the exposed group (0.7% vs 0.9%, RR=0.83, p=0.515). Competing-risks regression analysis showed that the effect of the restriction measures on spontaneous preterm birth was stronger and started earlier than the effect on medically indicated preterm birth. The effect was stronger in women with a previous preterm birth (RR=0.42, p=0.008) than in parous women without a previous preterm birth (RR=0.93, p=0.714) [p for interaction=0.044]. Composite adverse perinatal outcome was less frequent in the lockdown exposed group than in controls (2.1% vs 2.9%, RR=0.73, p=0.042). It was concluded that restriction measures to mitigate SARS-CoV-2 transmission were associated with a reduced rate of preterm birth before 34 weeks, which was mainly due to a lower rate of spontaneous prematurity. The effect was more substantial in women with a previous preterm birth and was not associated with an increased stillbirth rate.

In a study of singleton births in United Kingdom National Health Service hospitals conducted between March 2020 to February 2021 comparing 451727 births during the pandemic and corresponding births 1 year earlier, maternal characteristics were similar in the pre-pandemic and pandemic periods[53]. Stillbirth rates remained similar (0.36% vs 0.37%, p=0.16), but the rates of preterm birth (6.0% vs 6.1%, aOR=0.96, p<0.001) and small for gestational age (5.6% vs 5.8, aOR=0.95, p<0.001) were lower during the pandemic, whereas the rates of obstetric intervention were higher during the pandemic (induction of labour: 40.4% vs 39.1%, aOR=1.04; elective caesarean section: 13.9% vs 12.9%, aOR=1.13; emergency caesarean section: 18.4% vs 17.0%, aOR=1.07; all p<0.001). The small changes in obstetric intervention rates and pregnancy outcomes could be associated with women's behaviour, environmental exposure, changes in maternity practice, and reduced staffing levels. The COVID-19 pandemic was not associated with overall worse pregnancy outcomes, and the overall impact on outcome was small.

In a study in the United Kingdom investigating whether the COVID-19 pandemic affected the decision-to-delivery interval and neonatal outcomes in women who underwent category-1 (crash) caesarean section, 562 patients who underwent emergency caesarean section in the pre-COVID-19 period in seven hospitals were compared with 577 patients who underwent emergency caesarean sections during the COVID-19 pandemic from April 2020 to July 2020[54]. The use of general anaesthesia decreased significantly between the two groups (RR=0.48, p<0.0001). Compared with the pre-COVID group, the COVID group had an increase in median decision-to-delivery interval (26

[18-32] vs 27 [20-33] minutes, p=0.043) and a decrease in the number of caesarean sections meeting the decision-to-delivery interval target of <30 min (66.5% vs 60.5%, p=0.02). However, the incidence of adverse neonatal outcomes was similar in the two groups (24.6% vs 24.0%, p=0.85). Thus, the small increase in decision-to-delivery interval during the COVID-19 pandemic did not adversely affect neonatal outcomes.

In a meta-analysis of 40 studies, significant increase in stillbirth (pooled OR=1.28, 12 studies) and maternal death (OR=1.37, two studies) were identified during the pandemic, compared with pre-pandemic[55]. Preterm births before 37 weeks' gestation were not significantly changed overall (OR=0·94, 15 studies) but were decreased in high-income countries (OR=0.91, 12 studies) where spontaneous preterm birth was also decreased (OR=0.81, two studies). The mean Edinburgh Postnatal Depression Scale scores were higher, which indicated poorer mental health, during the pandemic (pooled mean difference=0.42, three studies), but no overall significant effects were identified for other major parameters such as postpartum haemorrhage and neonatal outcome. Owing to the considerable disparity between high-resource and low-resource settings, there is an urgent need to prioritise safe, accessible, and equitable maternity care during the pandemic. Therefore, the evidence suggesting substantial increase in the rates of stillbirth and preterm birth during the pandemic remains controversial. The increasing vaccination rates in most communities to achieve a reasonable degree of herd immunity and a reduction in severe disease and mortality should mean that extensive lockdown measures can be abolished in most countries. Therefore, major interruptions in healthcare delivery and suspension of services in hospitals seen earlier in the pandemic should not reappear. The impact of the pandemic on the overall provision of obstetric services and thus pregnancy outcome should not be a major concern anymore.

Conclusion

Pregnancy increases the risk of having severe disease after COVID-19 infection, but intrauterine transmission of SARS-CoV-2 is rare. Adverse pregnancy and neonatal outcomes are more common among women with severe SARSCoV-2 during pregnancy, whereas comorbid conditions are the main risk factors for developing severe disease. The association of SARS-CoV-2 with pregnancy complications including pre-eclampsia, preterm birth, and fetal growth restriction remains controversial. The negative effects of the pandemic on obstetric outcome secondary to lockdowns and healthcare disruptions should no longer exist, as most communities have abandoned social restrictions with the alleviation of pressure on healthcare systems. With increasing vaccination rates and herd immunity, predominance of SARS-CoV-2 variants with attenuated virulence, and enhanced treatment modalities, it is anticipated that mortality and morbidity associated with SARS-CoV-2 infection should progressively be mitigated. Nevertheless, we should make every effort to enhance our knowledge about SARS-CoV-2 infection in pregnancy as the virus will likely remain with us for a considerable period of time in future.

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 editors of the journal, WWK To and CW Kong were not involved in the peer review process of this article.

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Data availability

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

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Advanced Endometrial Cancer

A Combination Treatment To Help You To Fight Advanced Endometrial Cancer

Consider **KEYTRUDA + LENVIMA** for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation [1,2]

KEYTRUDA + LENVIMA

KEYTRUDA + LENVIMA achieved superiority across PFS, OS, and ORR vs doxorubicin or paclitaxel in previously treated advanced endometrial cancer patients with pMMR status **as shown in KEYNOTE-775/Study 309** [3,4]

	KEYTRUDA + LENVIMA	DOXORUBICIN OR PACLITAXEL	
Median PFS	**6.6 months** HR=0.60 *(p<0.001)* 95% CI, 0.50–0.72	**3.8 months**	**40%** reduction in risk of disease progression or death
Median OS	**17.4 months** HR=0.68 *(p<0.001)* 95% CI, 0.56–0.84	**12.0 months**	**32%** reduction in risk of death
ORR	**30.3% ORR** 25.1% PR + 5.2% CR n=346 *(p<0.001)* 95% CI, 25.5%–35.5%	**15.1% ORR** 12.5% PR + 2.6% CR n=351	**2x** the ORR vs doxorubicin or paclitaxel

Follow up duration: 12.2 months

CI=confidence interval; dMMR=mismatch repair deficient; HR=hazard ratio; MSI-H=microsatellite instability-high; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pMMR=mismatch repair proficient.

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LENVIMA® (lenvatinib) Abbreviated Prescribing Information

Indications: Endometrial Carcinoma: LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. **Differentiated Thyroid Cancer:** LENVIMA is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer (DTC). **Hepatocellular Carcinoma:** LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). **Renal Cell Carcinoma:** LENVIMA is indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti- angiogenic therapy. **Presentation:** Hard capsules 4mg and 10mg. **Dosage and administration: EC:** The recommended daily dose is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression. Refer to the pembrolizumab prescribing information for other pembrolizumab dosing information. **DTC:** The recommended daily dose is 24 mg as lenvatinib administered orally once a day. **HCC:** The recommended daily dose is 12 mg for patients ≥ 60 kg or 8 mg for patients < 60 kg as lenvatinib administered orally once a day. **RCC:** The recommended daily dose is 18mg as lenvatinib in combination with 5mg everolimus administered orally once a day. LENVIMA capsules can be swallowed whole or dissolved in a small glass of liquid. To dissolve in liquid, put capsules into 1 tablespoon of water or apple juice without breaking or crushing the capsules. Leave the capsules in the water or apple juice for at least 10 minutes. Stir for at least 3 minutes. After drinking the mixture, add 1 tablespoon of water or apple juice to the glass, swirl the contents a few times and swallow the water or apple juice. **Warnings and precautions:** Hypertension. Cardiac dysfunction. Arterial thromboembolic events. Hepatotoxicity. Renal failure or impairment. Proteinuria. Diarrhea. Fistula formation and gastrointestinal perforation. QT interval prolongation. Hypocalcemia. Reversible posterior leukoencephalopathy syndrome (RPLS). Hemorrhagic events. Impairment of thyroid stimulating hormone suppression/thyroid dysfunction. Impaired wound healing. Embryo-fetal toxicity. Pregnancy and lactation. For detailed precautions, please consult the full prescribing information. **Contraindications:** None. **Adverse events:** The most common adverse reactions (>20%) observed in LENVIMA with pembrolizumab in patients treated for EC include: fatigue, musculoskeletal pain, hypertension, hemorrhagic events, diarrhea, nausea, stomatitis, vomiting, abdominal pain, constipation, decrease appetite, hypomagnesaemia, hypothyroidism, decreased weight, headache, urinary tract infection, dysphonia, dyspnea, cough, palmar-plantar erythrodysesthesia syndrome and rash. The most common adverse reactions (>30%) observed in LENVIMA in patients treated for DTC include: hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight decreased, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar serythrodysesthesia syndrome, abdominal pain, and dysphonia. The most common adverse reactions (>20%) observed in LENVIMA in patients treated for HCC include: hypertension, fatigue, diarrhea, decrease appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. The most common adverse reactions (>30%) observed in LENVIMA with everolimus in patients treated for RCC include: diarrhea, fatigue, arthralgia/myalgia, decreased appetite, vomiting, nausea, stomatitis/oral inflammation, hypertension, peripheral edema, abdominal pain, dyspnea, rash, decreased weight, hemorrhagic events and proteinuria. **Storage:** To be stored under 30°C. Store in the original blister in order to protect from moisture. **Packaging:** LENVIMA capsules are supplied in cartons of 2 blister cards. Each carton contains a 20 capsules of LENVIMA in 4mg or 10mg capsule. Please refer to the Full Prescribing Information for details. Further information is available upon request.

Selected Safety Information for KEYTRUDA (pembrolizumab): **Contraindications:** None **Precautions:** •Immune-mediated pneumonitis •Immune-mediated colitis •Immune-mediated hepatitis and hepatotoxicity •Immune-mediated endocrinopathies •Immune-mediated nephritis and renal dysfunction •Immune-mediated Dermatologic Adverse Reactions •Other immune-mediated adverse reactions •Infusion-related reactions (including hypersensitivity and anaphylaxis) •Complications of allogeneic HSCT in patients after or prior to treatment with KEYTRUDA treatment •Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone •Embryo-fetal toxicity **Adverse Events:** Most common adverse reactions (reported in ≥20% of patients) were: •Keytruda as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. •Keytruda in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis. •Keytruda in combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. •KEYTRUDA in combination with lenvatinib: fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, weight loss, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. **For detailed precautions and adverse events, please consult the full prescribing information.**

To access to full SSI for KEYTRUDA, please scan the QR code below:

KEYTRUDA® (pembrolizumab) Injection 100 mg

LENVIMA® (lenvatinib) capsules | 10 mg and 4 mg

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MSD

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Eisai

Eisai (Hong Kong) Company Limited
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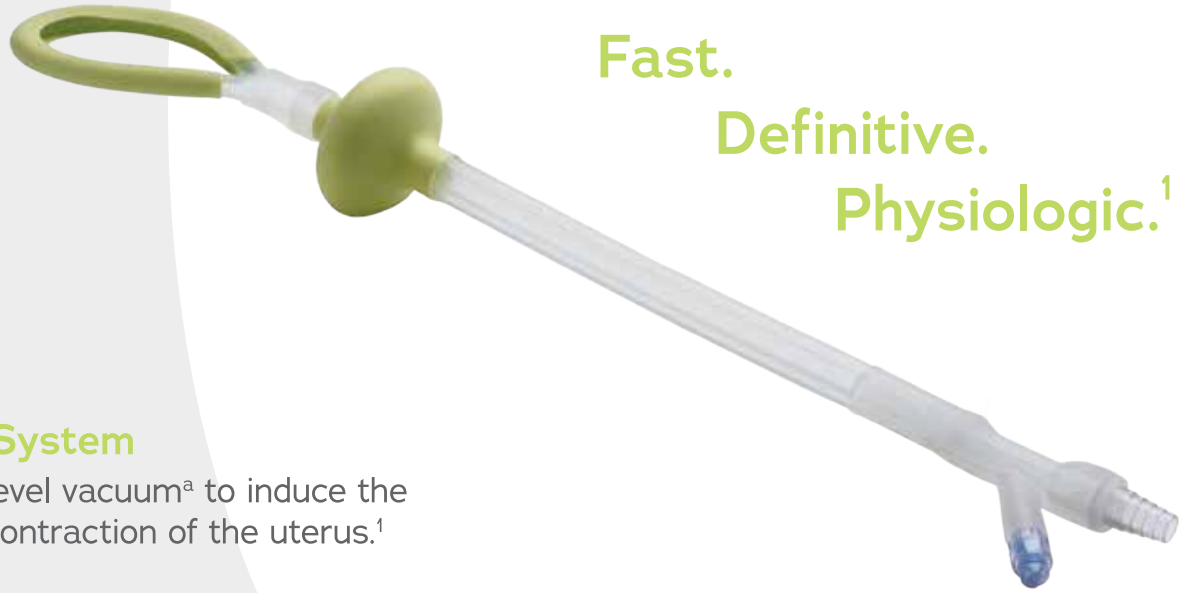
Jada®

The Jada® System is intended to provide control and treatment of abnormal postpartum uterine bleeding or hemorrhage when conservative management is warranted.



Fast. Definitive. Physiologic.[1]

The Jada System

utilizes low-level vacuum[a] to induce the physiologic contraction of the uterus.[1]

94% Effectiveness

94% (n=100/106) of participants treated successfully in the PEARLE study with the Jada System (*P*<0.001).[1,b]

Low-level vacuum[a] induces collapse of the atonic postpartum uterus[1]

Contraction of the myometrium provides physiologic control of bleeding[1]

[a] 80 mm Hg +/- 10 mm Hg. The maximum vacuum pressure is 90 mm Hg. Do not increase the vacuum pressure higher than 90 mm Hg or tissue trauma may occur.

[b] Primary effectiveness was the control of postpartum hemorrhage, defined as the avoidance of non-surgical, second-line, or surgical intervention to control uterine hemorrhage.[1]

Reference: 1. D'Alton ME, Rood KM, Smid MC, et al. Intrauterine vacuum-induced hemorrhage-control device for rapid treatment of postpartum hemorrhage. *Obstet Gynecol.* 2020;136(5):882-891. doi:10.1097/AOG.0000000000004138

Please refer to the Jada System Instructions for Use for the indications, contraindications, warnings, precautions, and other important information at thejadasystem.com/ifu.

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