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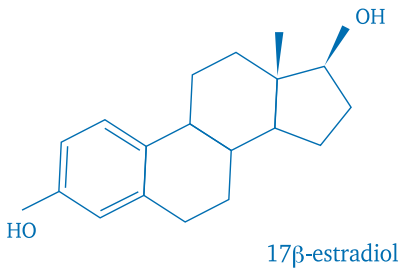

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OF

GYNAECOLOGY, OBSTETRICS & MIDWIFERY

July 2019, Volume 19, Number 2

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Books edited by other authors of the article

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

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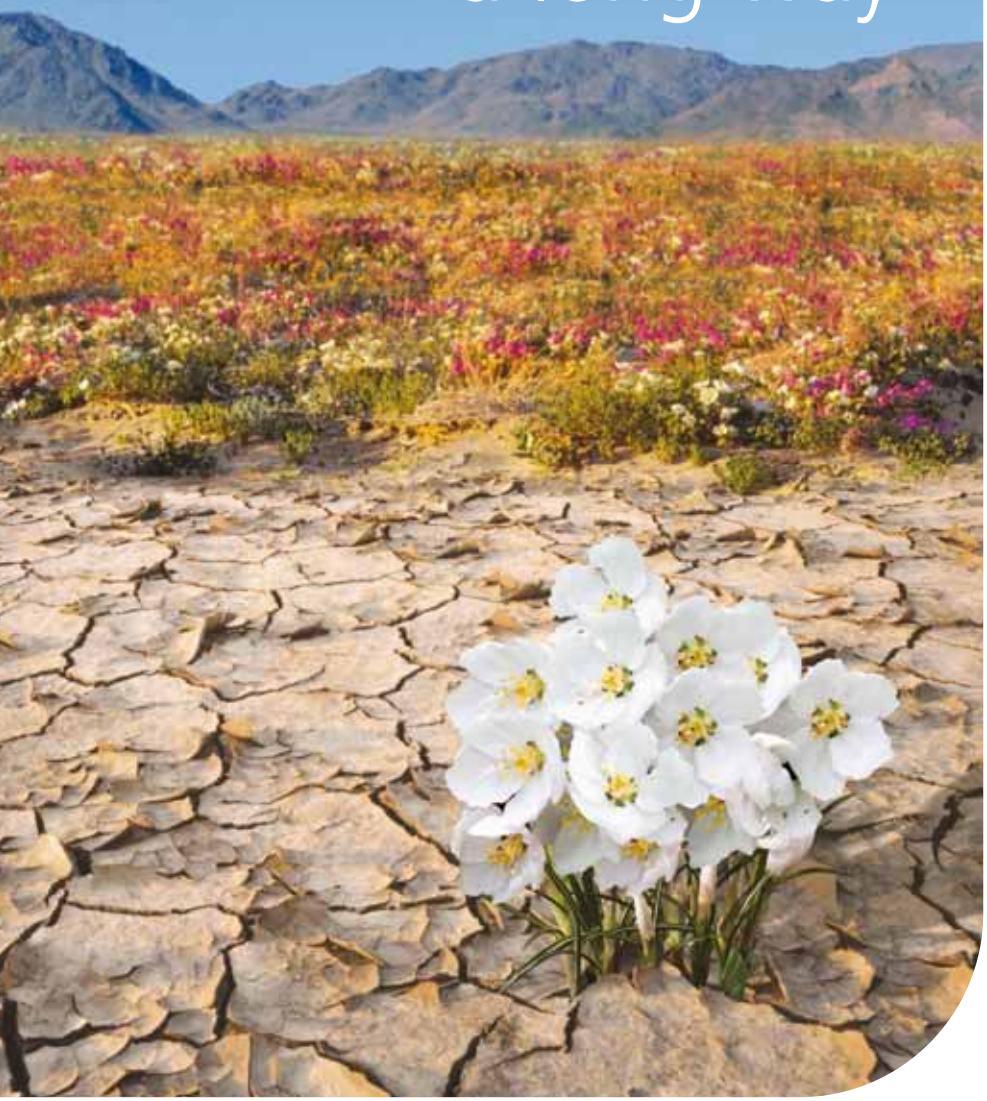

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Date of preparation: December 2018.

Reference:

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

2. Vagifem 10µg Summary of Product Characteristics.

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

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

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Hong Kong J Gynaecol Obstet Midwifery 2019;19(2):81-2 | https://doi.org/10.12809/hkjgom.19.2.00

Editorial
From Caesarean section to perioperative management to molecular genetics and beyond

I am most delighted to introduce this July 2019 issue as the 26th printed issue of the *Hong Kong Journal of Gynaecology, Obstetrics and Midwifery*. This is the fourth consecutive year that we have published two issues per year.

In this issue, we have a collection of original articles contributed mainly by young investigators in our specialty. With increasing use of intrapartum ultrasonography in the labour ward, Lau et al report the opinions of midwives and pregnant women on prelabour ultrasound examination in the labour ward and provide insights to the direction we should be advancing[1]. Many trainers would agree that teaching operative delivery skills to trainees has become more difficult in recent years owing to a variety of factors. Since 2008, the Hong Kong College of Obstetricians and Gynaecologists has stipulated the requirement of performing at least 30 forceps deliveries for specialist trainees. It came with no surprise that when secular trends in operative delivery rates were studied, such College requirements apparently have a profound impact on the number of instrumental deliveries performed. Chung et al report the intricate association between instrumental delivery and second-stage Caesarean section rates in a single training unit[2]. The Caesarean section rates of twin pregnancies have increased sharply in the past 20 years, partly as a result of less aggressive approaches at operative deliveries. Wong et al investigate the contributing factors associated with such an increase in a 20-year cohort study[3].

Patient blood management is an important issue in our speciality. The availability of new parenteral iron preparations with a greatly enhanced safety profile allows more liberal use of intravenous iron therapy in place of blood transfusion. Lau et al conducted a pilot study of intravenous iron therapy for menorrhagic patients with severe iron-deficiency anaemia and report on the great potential of this therapy[4].

Professor TY Leung, our College President, expressed his views on the need for genetics training in our specialty in an Editorial in the January 2019 issue of the Journal[5]. In the current issue, Lok et al report a case of whole exome sequencing for prenatal diagnosis of CHARGE syndrome and highlight the importance of genetics in prenatal diagnosis[6]. Traditionally, the diagnosis of CHARGE syndrome was based on clinical dysmorphology, but with the availability of advanced molecular genetic testing, the gold standard has shifted.

Lee et al report a case of acute colonic pseudo-obstruction (Ogilvie syndrome) after Caesarean section and highlight the need for early detection of such rare complications in order to avoid further complications such as multiple bowel perforations and severe sepsis[7]. This case is of particular medicolegal relevance as well, to be distinguished from iatrogenic surgical trauma to the bowels during Caesarean section.

Since 2016, we have published a number of review articles on key contemporary developments in our specialty. Enhanced recovery after surgery is a multimodal multidisciplinary approach to the care of patients undergoing surgery, and is relevant for patients undergoing major gynaecological surgery. Such protocols are usually managed jointly by anaesthetists and gynaecologists. It is therefore, most appropriate that an anaesthetist and a gynaecologist, Yim and Lam, co-authored a succinct review on enhanced recovery after surgery[8].

Finally, Chan et al of the prenatal diagnosis laboratory team at the Tsan Yuk Hospital review the most advanced developments in molecular genetic testing and their applications[9].

I hope you continue to enjoy and cherish the Journal as a platform for sharing new scientific developments and exchange of viewpoints and opinions in our specialty.

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Opinions of midwives and pregnant women on prelabour ultrasound examination

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Objectives: To survey the opinions of midwives and pregnant women on prelabour ultrasound examination.
Methods: Questionnaires on prelabour ultrasound examination were distributed to 40 midwives and 125 pregnant women in a regional hospital.
Results: 34 (85%) midwives and 125 (100%) pregnant women responded. Most midwives agreed or strongly agreed that prelabour ultrasound examination is acceptable with respect to workload (73.5%), enables labour ward beds to be utilised more efficiently (61.8%), should be encouraged for women not in labour (55.8%), and improves patient care (70.6%), and that most midwives are willing to learn and perform pre-labour ultrasound examination in future (85.3%). Subgroup analysis showed that the agree and non-agree groups did not differ significantly in terms of the number of prelabour ultrasound examination performed or years of labour ward experience. For pregnant women, 90.4% reported that it was their first ultrasound examination after admission for show or irregular contractions; 99.2% considered the study purpose clearly explained; 84.8% felt reassured that they were not yet in active labour after vaginal examination alone and 92.8% felt reassured with additional ultrasound examinations; 97.6% were satisfied with ultrasound examination and 95.2% would recommend it to others; and 72.8% reported no pain during ultrasound examination.
Conclusion: Most midwives support prelabour ultrasound examination and are willing to learn the technique. Prelabour ultrasound examination is well-tolerated by pregnant women. It should be introduced to midwives and pregnant women to improve intrapartum care.

Keywords: Midwifery; Patient satisfaction; Surveys and questionnaires; Ultrasonography

Introduction

The onset of labour is a diagnosis without a universally agreed definition[1,2]. It is a dilemma whether to admit women for early labour symptoms such as intermittent painful uterine contractions, as fast labour progress cannot be predicted[3]. Early hospital admission is associated with an increased risk of iatrogenic obstetric interventions including electronic fetal monitoring, epidural analgesia, augmentation, and Caesarean section[4-8]. It is unclear to women under what circumstances should they return to hospital again[9]. Therefore, providing information on labour progress may reduce the anxiety of women and their labour companions[10].

To assess labour progress, digital vaginal examination for cervical dilatation and length is traditionally used, but it is rather subjective and inaccurate, and uncomfortable to women[11,12]. Ultrasonography enables visualisation of fetal structures. Transperineal ultrasound can objectively assess fetal head position and station, with high inter- and intra-observer agreement[13-17]. The International Society of Ultrasound in Obstetrics and Gynaecology advocates the use of transperineal ultrasound in women with slow labour progress before instrumental delivery[18]. Transperineal ultrasound has been used to predict labour and delivery in situations of premature rupture of membranes at term[19], induction of labour[20], and first stage of labour[21] by measuring the head perineal distance, cervical length, fetal head position, and various maternal characteristics.

Since 2006, ultrasound examination has supplemented vaginal examination for labour examination on a case-by-case basis in our unit[22-26]. We studied 125 women from 2015 to 2017 to determine whether prelabour ultrasound examination could predict the time to delivery from the appearance of show or irregular contractions, using

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transabdominal scan for head position and transperineal scan for cervical length and head perineal distance[27-29]. The current study aimed to survey opinions of midwives and pregnant women on prelabour ultrasound examination.

Methods

This study was approved by the Kowloon West Cluster Research Ethics Committee (Reference: KW/FR-12-080 (86-15)). In January 2017, randomly coded questionnaires were distributed to midwives working in the labour ward and pregnant women who participated in the previous prelabour ultrasound study[30]. Consent was implied on returning the completed questionnaire.

Table 1. Demographics of midwives (n=34)

Variable	No. (%)
Age group, y	
20-29	9 (26.5)
30-39	12 (35.3)
40-49	12 (35.3)
≥50	1 (2.9)
Labour ward experience, y	
<1	8 (23.5)
1-5	4 (22.8)
6-10	9 (26.5)
>10	13 (38.2)
No. of prelabour ultrasound examinations performed	
0	8 (23.5)
1-5	3 (8.8)
6-10	5 (14.7)
>10	18 (52.9)

For the midwife questionnaire, there were three questions on demographics (age group, years of experience, and exposure of ultrasound examination) and five questions on their views and attitudes towards ultrasound examination. For the pregnant woman questionnaire, there were two questions asking whether this was their first ultrasound examination after the appearance of symptoms of labour, and whether the purpose of the study was clearly explained. In addition, there were five questions regarding whether they felt reassured with digital vaginal examination alone or with additional ultrasound examination, and whether they were satisfied with the ultrasound examination and would recommend it to others. They were then asked to give a pain score during prelabour ultrasound examination using a visual analogue scale of 0 to 10.

Statistical analysis was performed using SPSS (Windows version 22; IBM Corp, Armonk [NY], USA). The five responses were divided into agree (agree and strongly agree) and non-agree (neutral, disagree, and strongly disagree) groups. Subgroup analysis was performed to investigate the possible association between respondent characteristics and responses using Chi squared test or Fisher's exact test, as appropriate. A p value of <0.05 was considered statistically significant.

Results

Of 40 questionnaires distributed to midwives, 34 were returned (response rate, 85%). Most midwives agreed or strongly agreed that prelabour ultrasound examination is acceptable with respect to workload (73.5%), enables labour ward beds to be utilised more efficiently (61.8%), should be encouraged for women not in labour (55.8%), and improves patient care (70.6%), and that most midwives are willing to learn and perform pre-labour ultrasound

Table 2. Responses from midwives to questions on prelabour ultrasound examination (n=34)

Question	No. (%) of respondents				
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Q1: Prelabour ultrasound examination is acceptable with respect to staff workload	0	0	9 (26.5)	22 (64.7)	3 (8.8)
Q2: Prelabour ultrasound examination enables labour ward beds to be utilised more efficiently	0	4 (11.8)	9 (26.5)	17 (50.0)	4 (11.8)
Q3: Prelabour ultrasound examination should be encouraged for women not in labour	0	3 (8.8)	12 (35.3)	18 (52.9)	1 (2.9)
Q4: I am willing to learn and perform prelabour ultrasound in future	0	0	5 (14.7)	25 (73.5)	4 (11.8)
Q5: Prelabour ultrasound examination improves patient care	0	2 (5.9)	8 (23.5)	20 (58.8)	4 (11.8)

examination in future (85.3%) [Table 2]. Subgroup analysis showed that the agree and non-agree groups did not differ significantly in terms of the number of prelabour ultrasound examination performed or years of labour ward experience (Table 3).

Of 125 questionnaires distributed to pregnant women, all were returned (response rate, 100%). 90.4% reported that it was their first ultrasound examination after admission for show or irregular contractions; 99.2% considered the study purpose clearly explained; 84.8% felt reassured that they were not yet in active labour after vaginal examination alone and 92.8% felt reassured with additional ultrasound examinations; 97.6% were satisfied with ultrasound examination and 95.2% would recommend it to others; and 72.8% of women reported no pain during ultrasound examination (Table 4).

Discussion

This is the first local survey on opinions of midwives and pregnant women view on prelabour ultrasound examination in the labour ward. The overall positive response from midwives and pregnant women was encouraging for wider use of prelabour ultrasound examination. Traditional digital vaginal examination is fundamental for midwifery but it is subjective[30]. If midwives can perform ultrasound examination in the labour ward, the additional information may supplement vaginal examination and hence improve labour assessment. In addition, pregnant women should be empowered to make their own decision as to whether to have intrapartum sonographic assessment and do not regard it as excessive.

The survey was designed in conjunction with the prelabour ultrasound study[30] because most midwives had enough experience in prelabour ultrasound examination. It is likely that midwives are also supportive of prelabour ultrasound examination in the labour ward because they are familiar with the preparation and techniques.

In a study of the view of midwives after a 1-hour training course with slideshows and supervised measurement, although 63.6% agreed intrapartum ultrasound was advantageous to patient care, 90.9%

Table 3. Subgroup analysis of opinions of midwives

	Question 1		Question 2		Question 3		Question 4		Question 5	
	No. of agree : non-agree	p Value	No. of agree : non-agree	p Value	No. of agree : non-agree	p Value	No. of agree : non-agree	p Value	No. of agree : non-agree	p Value
Overall (n=34)	25:9		21:13		19:15		29:5		24:10	
No. of prelabour ultrasound examination performed		0.87		0.13		0.13		0.47		0.51
0	6:2		3:5		3:5		6:2		4:4	
1-5	2:1		3:0		2:1		2:1		2:1	
6-10	3:2		2:3		4:1		5:0		4:1	
>10	14:4		13:5		10:8		16:2		14:4	
0 vs ≥1	6:2 vs 19:7	1.00	3:5 vs 18:8	0.21	3:5 vs 16:10	0.42	6:2 vs 23:3	0.57	4:4 vs 20:6	0.20
≤5 vs >5	8:3 vs 17:6	1.00	6:5 vs 15:8	0.71	5:6 vs 14:8	0.48	8:3 vs 21:2	0.30	6:5 vs 18:5	0.23
≤10 vs >10	11:5 vs 14:4	0.70	8:8 vs 13:5	0.29	7:5 vs 12:10	1.00	13:3 vs 16:2	0.65	10:6 vs 14:4	0.46
Labour ward experience, y		0.60		0.13		0.13		0.69		0.84
0	7:1		7:1		5:3		6:2		6:2	
1-5	3:1		3:1		2:2		4:0		3:1	
6-10	7:2		3:6		4:5		8:1		7:2	
> 10	8:5		8:5		8:5		11:2		8:5	
≤5 vs >5	10:2 vs 15:7	0.44	10:2 vs 11:11	0.07	7:5 vs 12:10	1.00	10:2 vs 19:3	1.00	9:3 vs 15:7	1.00
≤10 vs >10	17:4 vs 8:5	0.25	13:8 vs 8:5	1.00	11:10 vs 8:5	0.73	18:3 vs 11:2	1.00	16:5 vs 8:5	0.45

Table 4. Responses from pregnant women to questions on prelabour ultrasound examination (n=125)

Question	No. (%) of respondents				
	Yes		No		Not answered
Q1: In this pregnancy, is this your first time to have ultrasound examination after having symptoms of labour (bleeding/pain)?	113 (90.4)		11 (8.8)		1 (0.8)
Q2: Have healthcare workers clearly explained to you the purpose of the study?	124 (99.2)		0 (0)		1 (0.8)
	Strongly agree	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**
Q3: I feel reassured that I am not yet in labour after vaginal examination alone	39 (31.2)	67 (53.6)	16 (12.8)	2 (1.6)	1 (0.8)
Q4: I feel more reassured that I am not yet in labour with both vaginal and ultrasound examination, rather than vaginal examination alone	55 (44)	61 (48.8)	8 (6.4)	0 (0)	1 (0.8)
Q5: Overall, I am satisfied with prelabour ultrasound examination	61 (48.8)	61 (48.8)	2 (1.6)	0 (0)	1 (0.8)
Q6: I will recommend prelabour ultrasound examination to other mothers-to-be	60 (48)	59 (47.2)	5 (4)	0 (0)	1 (0.8)
Q7: Do you experience any pain during prelabour ultrasound examination (visual analogue scale of 0-10)?	score 0=91 (72.8); score 1=7 (5.6); score 2=19 (15.2); score 3=2 (1.6); score 4=4 (3.2); score 5-9=0 (0); score 10=1 (0.8); not answered=1 (0.8)				

preferred standard digital vaginal examination over ultrasound[31]. Therefore, structured practical training is important to build midwives' confidence to perform intrapartum ultrasound. From our subgroup analysis, midwives' acceptance and willingness to learn were not associated with years of experience or previous exposure to ultrasound examination.

Our survey did not aim to test the knowledge of midwives and did not include specific questions on knowledge. Currently, our institution provides a voluntary ultrasound training program in a labour ward that includes a 1-hour lecture and practical exercises with manikins[32], followed by a review of five ultrasound scans by the intrapartum team. Participants then perform 15 ultrasound examinations under the direct supervision of team doctors. Since 2017, eight midwives in our unit have been qualified and have performed intrapartum ultrasound scans to diagnose fetal head malposition so that alternative birthing posture may be adopted to enhance delivery progress[33].

Pregnant women were generally positive towards prelabour ultrasound examination. Most reported no pain during the examination, consistent with another study of intrapartum ultrasound[34]. Nonetheless, some women did not prefer prelabour ultrasound examination and reported discomfort as pressure was applied onto the perineum.

There were limitations to our study. The sample was small and involved only midwives working in the labour ward of a single centre and only pregnant women who participated in the prelabour ultrasound study; therefore the findings may not be representative of all midwives and pregnant women in Hong Kong. We aim to perform further surveys with more specific questions on intrapartum ultrasound examination after more midwives received such training and more pregnant women participated to determine which aspect of intrapartum ultrasound is most useful to midwifery practice and to identify potential barriers to its use.

Conclusion

Most midwives support prelabour ultrasound examination in the labour ward and are willing to learn the technique. Prelabour ultrasound examination is well tolerated by pregnant women. It should be introduced to midwives and pregnant women to improve intrapartum care.

Declaration

The authors have no conflict of interest to disclose.

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Association between rates of second-stage Caesarean section and instrumental delivery

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Objective: The increasing Caesarean section (CS) rate is a global public health concern, as is the second-stage CS rate at full cervical dilatation. This study aimed to study the temporal trends of the increased second-stage CS rate and the reduced instrumental delivery rate in a regional obstetric unit over 20 years.
Methods: Records of all CS and instrumental deliveries in a single obstetric unit between 1997 and 2016 were reviewed. Data were stratified into five 4-year intervals to analyse any significant trends.
Results: During the study period, there were a total of 87 413 deliveries, with 17 600 (20.1%) CS and 6502 (7.4%) instrumental deliveries. Although the overall CS rate increased modestly from 15.8% in 2001 to 24.6% in 2014, the rise in second-stage CS was significant ($p<0.001$) and culminated at 7.33% of all emergency CS in 2005-2008. Simultaneous to this increase was a trough in instrumental delivery rate of 5.3% ($p<0.001$) and a high failed instrumental delivery rate of 9.37% ($p<0.001$).
Conclusion: The increase in the second-stage CS rate was related to reluctance to attempt instrumental delivery together with failure of instrumental delivery. Introduction of training requirement in forceps delivery by Hong Kong College of Obstetricians and Gynaecologists resulted in an increasing use of forceps.

Keywords: Cesarean section; Delivery, obstetric; Labour stage, second

Introduction

The increasing Caesarean section (CS) rate is a global public health concern. From 1990 to 2014, the CS rate increased 12.4% globally, with an average annual rate increase of 4.4%, and in western European countries, it increased from 14.8% to 24.5%[1]. In Hong Kong, the secular trend of CS rates over 20 years also increased from 15.4% to 24.6%[2]. As the overall CS rate increases, so does the CS rate at full cervical dilatation, which is often coupled with a decline in the instrumental delivery rate. Up to 5% to 6% of intrapartum CS for singleton pregnancies were performed in the second stage of labour[3-5], and in 55% of these cases, no attempt was made to achieve vaginal birth with forceps or vacuum extraction[3]. There are concerns that resorting to second-stage CS after failed instrumental delivery is associated with increased risks of fetal trauma. Although failed instrumental delivery is a risk factor for birth trauma[6], the perception that second-stage CS is less traumatic to the mother and baby than a successful instrumental delivery is not supported by published data. Meta-analyses have demonstrated that second-stage CS is associated with a significant increase in maternal and fetal morbidity, including higher maternal admission to intensive care unit, transfusion rates, neonatal death rates, admission to neonatal unit, and rate of Apgar score of <7 in 5 minutes[6,7]. The rising number of CS at full dilatation not only increases the maternal risks for the delivery in question, but also has a negative impact on the woman's future pregnancies and deliveries[8]. Therefore, we aimed to study the temporal trends of the increased second-stage CS rate and the reduced instrumental delivery rate in a regional obstetric unit over 20 years.

Materials and Methods

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee. Data from the obstetric unit at United Christian Hospital from 1997 to 2016 were retrieved from the Hospital Authority Obstetrics Clinical Information System. Data on CS such as elective versus emergency CS, CS during the second stage of labour, and instrumental delivery (vacuum extraction versus forceps) were reviewed. Trends and changes in CS rates over the 20 years were examined.

The protocol for instrumental delivery was in accordance with Royal College of Obstetricians and

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Gynaecologists guidelines, and decision was made by obstetrician following evaluation of head station, position, and pelvis adequacy[9]. Prerequisites of instrumental delivery include vertex-presenting fetuses at full cervical dilatation and fully engaged head with no known suspicion of cephalopelvic disproportion. Forceps is preferred for deliveries <34 weeks of gestation. Indications for instrumental delivery include prolonged second stage of labour, fetal compromise, and shortening second stage for maternal benefit. Every detachment of the vacuum cup prior to delivery is considered as deviation from proper procedure and defined as slipped cup. Instrumental delivery is abandoned when no progression after three pulls of vacuum or forceps, or disengagement of vacuum cup for three times. The total number of failed instrumental deliveries was the summation of failed vacuum extraction or forceps. CS is performed within 30 minutes of failed instrumental delivery when further attempts at instrumental delivery were deemed inappropriate.

The proportions of those with advanced maternal age of >35 years, previous CS or other uterine scars, induction of labour, and multiple pregnancies were calculated. The total number of patients in each mode of delivery was stratified into five 4-year intervals, and the five intervals were compared using 5 × 2 contingency tables and Mantel-Haenszel Chi squared tests for linear trends for each category. A p valve of <0.05 was considered statistically significant.

Results

From January 1997 to December 2016, there were a total of 87 413 deliveries, with 17 600 (20.1%) CS and 6502 (7.4%) instrumental deliveries (Figure and Table 1). The annual number of deliveries ranged from 3371 in 1998 to 5648 in 2011. The CS rate increased modestly from 15.8% in 2001 to 24.6% in 2014. The rate of instrumental deliveries peaked at 10% in 1998-1999 and then troughed during 2005-2010, with the lowest rate of 4.92% in 2005, rising to 10% in 2015. Forceps delivery became more frequent after 2008, with the highest rate of 2.5% in 2013.

A total of 646 (3.67%) CSs were performed at full cervical dilatation, ranging from 19 cases in 1999 to 52 cases in 2008 (Table 1). The number of second-stage CS

Table 1. Major epidemiological risk factors and rates of Caesarean section (CS) and instrumental delivery from 1997 to 2016

	1997	1998	1999	2000	2001	2002	2003	2004
Total no. of deliveries	3501	3371	3534	3850	3522	3806	3787	4558
Crude perinatal mortality, %	3.16	3.25	3.56	3.87	3.68	2.59	3.98	3.63
Adjusted perinatal mortality, %	2.25	1.89	2.78	2.16	2.52	2.0	2.8	2.16
Women age >35 years, %	14.5	15.4	15.7	15.2	16.7	14.4	14.9	13.3
Previous CS, %	10.4	11.7	5.7	6.0	6.7	11.3	10.2	10.0
Induction, %	9.8	11.0	12.5	11.6	13.2	9.9	9.2	11.4
Multiple pregnancies, %	1.3	1.6	1.6	1.2	1.8	1.9	1.8	2.0
Total CS rate, %	18.1	19.5	16.6	16.5	15.8	17.4	18.2	19.5
No. (%) of emergency CS	424 (66.9)	384 (58.4)	437 (74.4)	457 (71.9)	389 (69.9)	387 (58.4)	421 (61.1)	596 (67)
No. (%) of second-stage CS	23 (5.42)	20 (5.20)	19 (4.34)	27 (5.90)	29 (7.45)	27 (6.97)	33 (7.83)	28 (4.69)
No. (%) of second-stage CS without trial of instrumental delivery	8 (35)	6 (30)	7 (36.8)	8 (29.6)	10 (34.5)	12 (44.4)	16 (48.5)	13 (46.4)
Instrumental delivery rate, %	8.99	10.3	10.5	10.2	8.88	8.14	7.26	6.34
No. of vacuum extraction	288	325	350	379	305	302	269	280
No. of forceps delivery	27	21	20	13	8	8	6	9
No. (%) of failed instrumental delivery	15 (4.76)	14 (4.04)	12 (3.24)	19 (4.84)	19 (6.07)	15 (4.84)	17 (6.18)	15 (5.19)
No. of failed vacuum extraction with slipped cup	8	10	6	14	15	8	13	10
No. of failed vacuum extraction with no slipped cup	6	4	6	5	4	7	4	5
No. of failed low forceps	1	0	0	0	0	0	0	0

peaked in 2005-2010, with a corresponding trough in the rate of instrumental deliveries, with the lowest at 4.85% in 2009. Of a total of 6502 attempted instrumental deliveries, 6139 (94.4%) were successful. The peak rate of failed instrumental delivery occurred in a period when fewer instrumental deliveries were performed, with the highest at 11.2% in 2008.

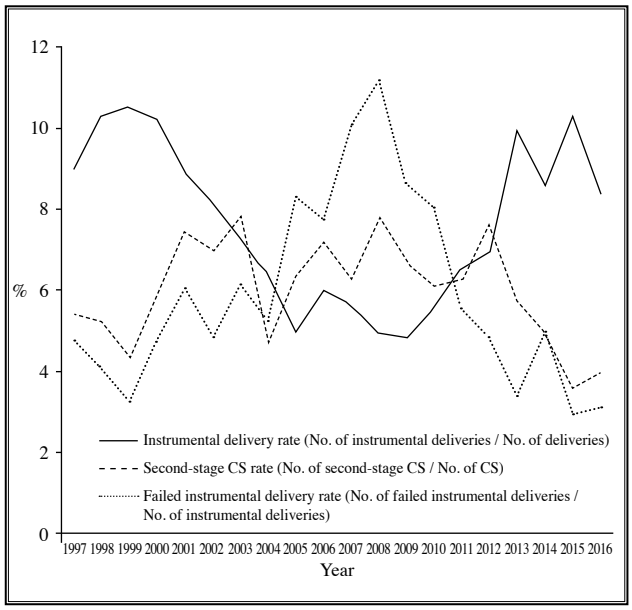

Figure. Rates of instrumental delivery, failed instrumental delivery, and second-stage Caesarean section (CS) from 1997 to 2016

The crude perinatal mortality rate ranged from 2.6 to 6 per 1000 deliveries; the adjusted perinatal mortality rate (excluding those with major congenital malformations and birth weight of <750 g) varied from 1.9 to 4.6 per 1000 deliveries. Owing to the small number of variations, no obvious trends were identified. The maternal mortality rate was <5 per 100 000 pregnancies, with many years recorded as zero so no trends could be observed. The incidence of significant birth trauma (including fractures and intracranial haemorrhage) and the incidence of maternal trauma (including third- and fourth-degree perineal tears) remained <0.5% of all deliveries and hence no obvious trends could be discerned.

Data were then stratified into five 4-year intervals for trend comparison (Table 2). The CS rate of 17.1% in 1997-2000 increased significantly to 22.9% in 2013-2016 ($p<0.001$). There was a progressive trend towards a higher

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
5122	4295	4754	5234	5009	5315	5648	5039	4128	4429	4253	4258
5.27	3.96	2.95	3.09	4.99	3.95	3.28	2.58	3.39	2.94	6	4.46
3.52	3.49	1.89	2.32	3.39	2.82	2.42	1.6	1.70	2.48	4.62	2.78
13.2	16.1	18.1	22.4	27.3	21.5	22.9	23.5	25.5	24.5	26.3	26.9
9.5	10.7	12.8	12.7	12.0	12.4	14.0	14.5	15.2	16.1	15.6	17.1
11.0	8.4	14.7	10.8	12.7	11.4	12.5	14.3	15.7	15.9	16.3	17.7
1.7	2.3	3.0	2.5	2.3	2.4	3.4	2.8	2.3	3.6	1.34	1.86
18.2	18.6	18.8	22.1	20.9	23.1	23.1	23.4	23.6	24.6	22.0	23.5
676 (72.5)	541 (67.7)	558 (59.5)	665 (60)	596 (59.9)	689 (58.6)	732 (57)	604 (55)	507 (54.8)	549 (53.7)	557 (55.7)	528 (54.9)
43 (6.36)	39 (7.20)	45 (6.27)	52 (7.81)	40 (6.7)	42 (6.09)	46 (6.28)	46 (7.61)	29 (5.72)	27 (4.92)	20 (3.59)	21 (3.97)
22 (51.1)	19 (48.7)	18 (45)	23 (44.2)	19 (47.5)	18 (42.8)	25 (54.3)	29 (63)	15 (51.7)	18 (66.7)	7 (35)	10 (47.6)
4.92	6.01	5.62	4.93	4.85	5.58	6.55	6.97	9.98	8.60	10.3	8.33
246	256	260	226	228	258	336	290	308	330	402	316
6	2	7	32	15	38	43	61	104	51	36	39
21 (8.33)	20 (7.75)	27 (10.1)	29 (11.2)	21 (8.64)	24 (8.05)	21 (5.54)	17 (4.84)	14 (3.39)	19 (4.98)	13 (2.96)	11 (3.09)
12	11	17	20	12	16	12	9	9	14	8	4
9	8	10	8	8	7	9	8	4	4	4	5
0	1	0	1	1	1	0	0	1	1	1	2

Table 2. Comparison of five 4-year intervals in terms of rates of total Caesareans section (CS), instrumental delivery, failed instrumental delivery, and second-stage CS

Variable	1997-2000	2001-2004	2005-2008	2009-2012	2013-2016	p Value (Mantel-Haenszel Chi square for linear trends)
Total no. of deliveries	14 256	15 673	19 405	21 011	17 068	
Total no. (%) CS	2444 (17.1)	2816 (18.0)	3884 (20)	4546 (21.6)	3910 (22.9)	<0.001
No. (%) of emergency CS	1702 (69.6)	1793 (63.7)	2440 (62.8)	2621 (57.6)	2141 (54.8)	<0.001
No. (%) of second-stage CS	89 (5.23)	117 (6.52)	169 (6.92)	174 (6.63)	97 (4.53)	<0.001
No. (%) of second stage CS without trial of instrumental delivery	29 (32.6)	51 (43.6)	82 (45.8)	91 (52.3)	50 (51.5)	<0.001
No. (%) of instrumental delivery	1423 (9.98)	1187 (7.57)	1035 (5.33)	1269 (6.04)	1586 (9.29)	<0.001
No. (%) of failed instrumental delivery	60 (4.21)	66 (5.56)	97 (9.37)	83 (6.54)	57 (3.59)	<0.001

proportion of elective CS as compared to emergency CS, probably related to the ever-increasing proportion of patients with elective repeat CS for previous CS. The rate of emergency CS among all CS dropped from 69.9% to 54.8%. Among all emergency CS, the proportion of second-stage CS increased from 5.23% in 1997-2000 to 7.33% in 2005-2008, and then decreased to 4.53% in 2013-2016 (p<0.001). Simultaneous to this increase in second-stage CS was a significant trough in the instrumental delivery rate of 5.3% in 2005-2008 (p<0.001), during which the rate of failed instrumental delivery was highest (9.37%). As instrumental delivery rates gradually rebounded to 9.29% in 2013-2016, the rate of failed instrumental delivery decreased to 3.59%. The proportion of women undergoing second-stage CS without a trail of instrumental delivery increased gradually from 32.6% in 1997-2000 to 60% in 2009-2012 and 50% in 2013-2016 (p<0.001).

Discussion

In our study, the CS rate increased modestly from 15.8% in 2001 to 24.6% in 2014. The second-stage CS rate reached 7.33% of all emergency CS during 2005-2008. Simultaneous to this increase in the second-stage CS rate was a significant trough in instrumental delivery rates. Even as instrumental delivery rates rebounded in later years, >50% of women who had a second-stage CS did not attempt at instrumental delivery.

The global CS rates increased 12.4% from 1990 to 2014[1]. Along with the rising CS rate, there is an increasing trend to CS at full cervical dilatation[4,10,11]. In a population-based study of US births, from 2005 to 2013 vacuum delivery reduced from 5.8% to 4.1% while forceps delivery decreased from 1.4% to 0.9%[12]. In 55% of second-stage CS, no attempt at instrumental delivery was made[3].

In our data, there was a close temporal relationship between rising second-stage CS rates, decreasing instrumental delivery rates, and increasing failed instrumental delivery rate. The decline in instrumental delivery was replaced, in whole or in part, by the increase in second-stage CS. This trend is multifactorial. First, junior doctors are better trained in performing CS than instrumental delivery. Junior doctors regularly perform elective CS under supervision, whereas instrumental deliveries are usually performed only under emergency settings. A lack of confidence could lead to reluctance to attempt instrumental delivery. Second, the medicolegal concerns over maternal and neonatal morbidities with failed instrumental delivery fuel earlier recourse to CS, which is perceived to be safer. Third, failed instrumental delivery may trigger a vicious cycle of reluctance to attempt instrumental delivery. Avoidance of primary CS may minimise risks in subsequent pregnancies and increase the chance of a normal vaginal birth thereafter. Women are more likely to aim for and to have vaginal delivery if they have a previous instrumental delivery rather than CS[13].

In the United Kingdom, 10% to 13% of women underwent instrumental delivery[9]. In our cohort, the rate halved to 4.9% in 2008-2009. Unlike CS, the World Health Organization has not defined an optimal rate of

instrumental delivery. Nonetheless, instrumental delivery is one of seven basic emergency obstetric care services[14]; it potentially increases the expelling force, decreases resistance of birth canal such as soft tissue obstruction, and modifies the perimeter of fetal head in cases of malposition, asynclitism, or deflection. CS should be reserved for genuine cephalopelvic disproportion at the brim. Instrumental delivery has a role in optimising obstetric care and reducing the CS rate. Both the American College of Obstetricians and Gynecologists (ACOG) and Royal College of Obstetricians and Gynaecologists (RCOG) reiterated the need for better training for instrumental delivery. ACOG Obstetric Care Consensus 2014 recommends with moderate-quality evidence that: "Operative delivery in the second stage of labour by experienced and well-trained physicians should be considered as a safe, acceptable alternative to CS delivery. Training in, and ongoing maintenance of, practical skills related to operative vaginal delivery should be encouraged"[15]. In the RCOG curriculum, completion of Objective Structures Assessment of Technical Skills for operative vaginal delivery is one of the prerequisites to enter higher training[9]. Moreover, simulation and teamwork training in Advanced Life Support in Obstetrics course provides structured clinical training in a supportive environment. In Hong Kong, training in forceps delivery has decreased in the past 20 years. Since 2008, the Hong Kong College of Obstetricians and Gynaecologists has required all trainees to perform a minimum of 30 forceps deliveries under supervision within their 6-year specialist training[16]. This may have resulted in an increase in forceps delivery rates from 2008 onwards. Indeed, the need for adequate training in forceps delivery also encouraged trainees to perform more vacuum deliveries. Therefore, the overall instrumental delivery rate gradually returned from the trough years in 2005-2008 to that in 1997-2000.

Vacuum extraction is preferred over forceps because of lower incidence of maternal trauma. A Cochrane review supports the use of vacuum extraction as first-line method if there is no clear clinical indication for any specific instrument[17]. However, we found a trend that the vacuum-to-forceps ratio increased more than tenfold from 1:0.02 in 2001 to 1:0.34 in 2013. This shift closely reflects the re-introduction of forceps training by the Hong Kong College of Obstetricians and Gynaecologists[16]. The College saw the need to reinvigorate forceps training as forceps may be the safest option of delivery in certain clinical situations, such as delivery of a preterm baby <34 weeks' gestation, face presentation, poor maternal effort, expedient delivery for fetal distress, and after-coming head in vaginal breech delivery.

Deciding between a trial of instrumental delivery and a direct second-stage CS is a dilemma in obstetric practice. A UK study found that consultant assessment and decision is crucial in deciding whether a second-stage CS is the optimal mode of delivery[18]. There are substantial differences between consultant and specialist registrar opinions on factors affecting safe vaginal delivery such as the position of the fetal head and its proximity to the pelvic outlet. A consultant obstetrician is more likely to reverse the initial decision for CS and attempt instrumental delivery. In addition, intrapartum ultrasound can be used to assess labour progress. In particular, the angle of progression is an objective, accurate, and repeatable parameter to predict successful vaginal delivery and enable better decision-making on the optimal mode of delivery[19-21]. Furthermore, it provides an opportunity for experienced obstetricians to teach advanced skills such as manual rotation of fetal head. A retrospective study reported a vaginal delivery rate of 74% after successful manual rotation to occipital anterior position[22].

Instrumental deliveries are traditionally associated with increased risk of fetal trauma, ranging from brachial plexus injury to intracranial bleeding and skull fractures. Yet the risk of fetal trauma secondary to difficult disengagement of a deeply engaged head during CS should not be ignored. In 2012, the Cochrane Collaborative attempted to investigate outcomes of attempted instrumental delivery and direct CS for anticipated difficult births but failed to identify any randomised trials[23]. An observational cohort with 2531 women reported that in patients requiring second-stage delivery assistance with a station of +2 or below, attempted instrumental delivery was associated with fewer postpartum infection but more severe laceration than CS[24]. Another retrospective study of 2518 women demonstrated that a trial of forceps delivery from a low station was associated with decreased neonatal morbidity born to nulliparous women compared with CS[25]. These two studies examined the attempted (instead of ultimate) mode of delivery, thus minimising selection bias. Nonetheless, in the absence of randomised trials, the balance of risks between the two interventions remained unanswered.

When opting for a direct second-stage CS, obstetricians should be aware of the increased risk of massive postpartum haemorrhage requiring blood transfusion, and the impact of possible uterine tears on subsequent pregnancies[26]. Laparoelytrotomy (mistaking the upper vagina for lower uterine segment) is more common in second-stage CS[27]. CS at full dilatation is technically

challenging when the fetal head is deeply impacted into the maternal pelvis. The most common techniques for disengagement are the push and pull methods. In particular, the pull method may result in fewer hysterotomy extensions, lower blood loss, and shorter operating time[28]. Furthermore, second-stage CS is associated with a significant increase in the risk of spontaneous preterm birth <32 weeks of gestation in subsequent pregnancies[5,29].

Our overall rate of failed instrumental delivery was 5.5%, which is comparable to that reported in the Cochrane systematic review of 32 randomised controlled trials[17]. In our cohort, the peak of the failed instrumental delivery rate of 11.2% in 2008 coincided with one of the lowest instrumental delivery rates of 4.93%. Increasing failed instrumental delivery has been reported to be associated with reduced attempts at instrumental delivery (regression coefficient p=0.002)[4]. High instrumental delivery failure rate is often ascribed to malposition or erroneous assessment of fetal head position[23]. Defining fetal position is essential for appropriate choice of instrument and correct application. A large retrospective observational study involving 1291 full-term singleton cephalic birth with malposition of fetal head during second stage of labour suggested that in experienced hands, assisted vaginal birth by Kielland rotational forceps was the most effective and safe method. Births by Kielland forceps achieved comparable maternal and neonatal outcomes with rotational vacuum and primary emergency CS[30]. Therefore, phased re-introduction of rotational forceps should be considered should expertise and experience be available.

The strength of the current study is the large sample collected over 20 years for trend observance. However, data were limited to one single training centre. Although the trends should be similar in other centres, it would be interesting to extend the survey to include non-training private obstetric centres.

Conclusion

Instrumental delivery is important in optimising obstetric care and counteracting CS. It is imperative that residency training programmes continue to teach instrumental delivery skills as an alternative to CS. Experienced obstetricians should decide on the suitability and safety for trial instrumental delivery and provide supervision for technically challenging second-stage CS. The requirement from the Hong Kong College of Obstetricians and Gynaecologists for all trainees to perform a minimal number of forceps deliveries is the main reason to revive the forceps delivery rate. Our study highlights the need for continuous audits on instrumental delivery and second-stage CS as a useful measure of clinical standards.

Declaration

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Trends in Caesarean section rates for twin pregnancies: a 20-year cohort study

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Objective: To evaluate trends in Caesarean section (CS) rates for twin pregnancies over 20 years in a regional obstetric unit in Hong Kong.
Methods: Data on twin deliveries between 1998 and 2017 at United Christian Hospital were collected. CS rates were calculated for each calendar year, and data were stratified into four 5-year intervals to determine trends. Twins delivered vaginally or by CS were compared in terms of maternal epidemiological risk factors, pregnancy characteristics, and pregnancy outcome. A logistic regression model was used to determine significant risk factors associated with CS.
Results: From 1998 to 2017, 1083 (1.24%) of 87 480 deliveries were twin deliveries. The total CS rate for twins progressively increased from 58.9% in 1998-2002 to 84.1% in 2013-2017, particularly the CS rate for cephalic + cephalic twins from 41.7% in 1998-2002 to 74.7% in 2013-2017. The CS rate for non-cephalic first twin was close to 100% for all intervals. Logistic regression analysis showed that CS was positively associated with non-cephalic presentation of the first twin (odds ratio [OR]=13.1), previous CS (OR=4.19), and advanced maternal age (OR=1.7) and negatively associated with preterm delivery (OR=0.34), multiparity (OR=0.29), and induction of labour (OR=0.086). For perinatal outcome, CS was significantly associated with higher mean birthweight, lower incidence of adverse perinatal or neonatal outcome but higher risks of postpartum haemorrhage.
Conclusion: A progressive increase in CS rates for twins was observed over the past 20 years, particularly among cephalic-presenting twins, despite the lack of clear evidence on the preferred mode of delivery for such twin pregnancies.

Keywords: Caesarean section; Delivery, obstetric; Pregnancy, twins

Introduction

Twins account for 1% to 3% of all births[1-3]. There has been contradicting evidence concerning planned Caesarean section (CS) versus planned vaginal delivery (VD) for twin pregnancies. A retrospective cohort study in 2005 reported that CS reduced the risks of adverse perinatal outcome compared with VD[4]. However, the randomised controlled Twin Birth Study in 2013 reported no significant differences between CS and VD in neonatal morbidities or mortalities, particularly with the first twin being cephalic in presentation[5]. Based on such data, the 2014 American College of Obstetricians and Gynecologists guidelines on prevention of primary CS stated that women with cephalic-presenting twins should be counselled to attempt VD[6].

Although there remains no consensus on the optimal mode of twin delivery, the CS rates for twins have increased dramatically in many centres[7]. In an epidemiological study of trends in CS rates in a regional obstetric unit in Hong Kong from 1995 to 2014, the CS rate for multiple pregnancies increased from 48% in early years to 84% in later years, and among different Robson categories, ranked highest in the absolute percentage increase in CS rates[8].

This study aimed to review the trends of CS rates between 1998 and 2017 in a regional obstetric unit in Hong Kong, and to identify any associated risk factors for CS delivery in twin pregnancies.

Methods

This study was approved by the Kowloon Central/ Kowloon East Cluster Research Ethics Committee. Multiple deliveries at United Christian Hospital between 1998 and 2017 were identified from the Clinical Information System. Triplets or higher-order multiples were excluded. The CS and VD groups were compared in terms of maternal epidemiological risk factors (maternal age, parity, and induction of labour), pregnancy characteristics (presentation of the first and second twins, gestation, and mode of delivery), and pregnancy outcome parameters (birthweight, 5-minute Apgar score, and stillbirth or neonatal death). CS rates were calculated for each year to

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Table 1. Presentation of twins and mode of delivery

Presentation	No. (%) of cases		
	Vaginal delivery of both twins (n=227)	Caesarean section of both twins (n=839)	Combined delivery (vaginal delivery of first twin followed by Caesarean section of second twin) [n=17]
Cephalic + Cephalic	177 (31.9)	373 (67.2)	5 (0.9)
Cephalic + Breech	41 (16)	212 (83.1)	2 (0.8)
Cephalic + transverse/oblique	3 (4.5)	54 (80.5)	10 (15)
Breech + cephalic	5 (5.5)	85 (94.5)	0
Breech + transverse/oblique	1 (1)	92 (99)	0
Transverse/oblique + transverse/oblique	0	23 (100)	0

determine trends. The number of twin deliveries in different presentations was stratified into four 5-year intervals (1998-2002, 2003-2007, 2008-2012, and 2013-2017), and the four intervals were compared using a 4 × 2 contingency table using Mantel-Haenszel Chi square tests for linear trends. A logistic regression model was used to determine significant risk factors associated with twin delivery by CS. A p value of <0.05 was considered statistically significant.

Results

Among 87 480 deliveries from 1998 to 2017, 1083 (1.24%) were twin deliveries (2166 babies). Thirteen triplet deliveries were excluded. No maternal death concerning twin deliveries was recorded. Of the 1083 twin deliveries, 227 (21.0%) were by VD for both twins, 839 (77.4%) were by CS for both twins, and 17 (1.6%) were by VD for the first twin followed by CS for the second twin (combined delivery).

The first twin was cephalic presenting in 80.9% of the deliveries (Table 1). CS was performed in 67.2% of cephalic + cephalic twins, 83.1% of cephalic + breech twins, 80.5% of cephalic + transverse/oblique twins, 94.5% of breech + cephalic twins, and 99% of breech + transverse/oblique twins, and 100% (n=23) of transverse/oblique + transverse/oblique twins.

There was a progressive increase in total CS rates for twins, including cephalic + cephalic twins and cephalic + non-vertex twins (Figure). The CS rate for non-vertex first twin was close to 100% for all intervals. The CS rates increased significantly (p<0.001) for all presentations in total, with the greatest increase in cephalic + cephalic twins from 41.7% in 1998-2002 to 78% in 2008-2012 and to 74.7% in 2013-2017 (Table 2).

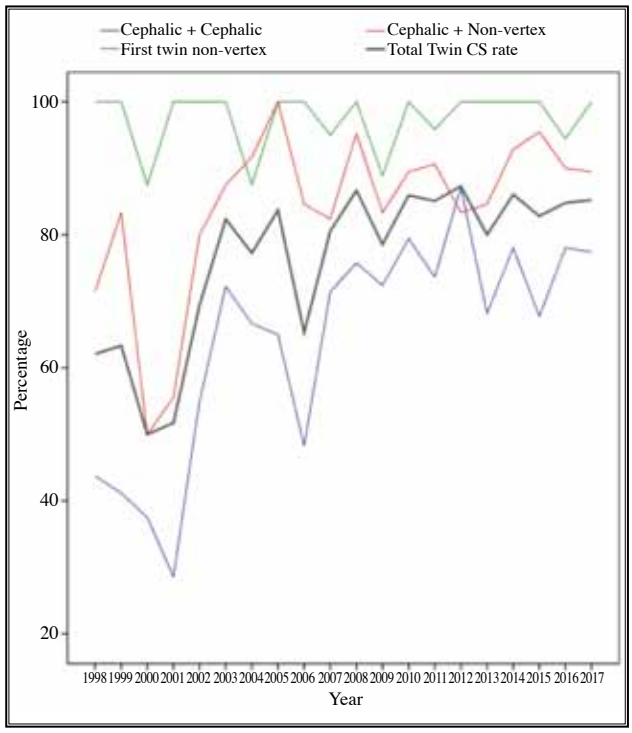

Figure. Total and different Caesarean section (CS) rates for twins with different presentations

Compared with the VD group, the CS group included more women with advanced maternal age (27.7% vs 38%, p=0.004), primiparity (42.3% vs 62.8%, p<0.001), gestational diabetes mellitus (9.25% vs 14.6%, p=0.038), and previous CS (6.6% vs 12.4%, p=0.013) [Table 3]. On the contrary, lower CS rates were associated with multiparity (57.7% vs 37.2%, p<0.001), preterm delivery <37 weeks (55% vs 41.3%, p<0.001), preterm delivery <32 weeks (16.7% vs 6.79%, p<0.001), and induction of labour (17.1% vs 1.8%, p<0.001) [Table 3]. In a logistic regression model, CS was positively associated with non-vertex presentation of first twin (odds ratio [OR]=13.1, p<0.001),

Table 2. Trends in the Caesarean section rate in different presentations

Presentation	Caesarean section rate, no. (%) of cases				p Value
	1998-2002 (n=168)	2003-2007 (n=242)	2008-2012 (n=345)	2013-2017 (n=328)	
Cephalic + cephalic	38/91 (41.7)	81/126 (64.3)	135/173 (78)	124/166 (74.7)	<0.001
Cephalic + non-vertex	29/44 (65.9)	55/62 (88.7)	101/114 (88.6)	93/102 (91.1)	<0.001
First twin non-vertex	32/33 (96.9)	52/54 (96.3)	57/59 (96.6)	59/60 (98.3)	0.91
Total	**99 (58.9)**	**188 (77.7)**	**293 (84.9)**	**276 (84.1)**	**<0.001**

Table 3. Comparison of pregnancy characteristics between vaginal delivery and Caesarean section groups

Characteristic	Vaginal delivery (n=227)*	Caesarean section for one or both twins (n=856)*	p Value
Maternal age, y	30.9±5.55	32.5±5.15	<0.001; mean difference= –1.59 (–2.36 to –0.82)
Advanced maternal age	63 (27.7)	326 (38)	0.004
Parity			<0.001
Primiparous	96 (42.3)	538 (62.8)	
Multiparous	131 (57.7)	318 (37.2)	
Gestation at delivery, weeks	35±4.03	36.1±2.5	<0.001; mean difference= –1.08 (–1.50 to –0.66)
Preterm delivery <37 weeks	125 (55)	354 (41.3)	<0.001
Preterm delivery <32 weeks	38 (16.7)	57 (6.79)	<0.001
Preterm delivery <28 weeks	17 (7.49)	6 (0.7)	<0.001
Gestational diabetes mellitus	21 (9.25)	125 (14.6)	0.038
Gestational hypertension/preeclampsia	19 (8.37)	104 (12.1)	0.13
Previous Caesarean section	15 (6.6)	106 (12.4)	0.013
Induction of labour	39 (17.1)	16 (1.8)	<0.001
Antepartum haemorrhage			0.075
Unknown origin	8 (3.5)	22 (2.57)	
Placenta abruption	0	15 (1.75)	
Placenta praevia	0	7 (0.82)	

* Data are presented as mean ± standard deviation or no. (%) of cases

previous CS (OR=4.19, p<0.001), and advanced maternal age (OR=1.7, p=0.005), whereas CS was negatively associated with preterm delivery (OR=0.34, p=0.001), multiparity (OR=0.29, p=0.001), and induction of labour (OR=0.086, p=0.001) [Table 4]. Gestational diabetes mellitus (OR=1.45, p=0.17) and gestational hypertension (OR=1.72, p=0.07) were not significant risk factors and thus excluded from the final equation.

For pregnancy outcome, compared with VD, CS was associated with higher mean birthweight (2193 g vs 2408 g, p<0.001), but the two groups did not differ significantly in mean birthweight of term babies (≥37 weeks) or the rate of fetal growth restriction in one or both twins (Table 5). CS was associated with lower incidence of adverse perinatal or neonatal outcome, including 5-minute Apgar score of <5 in livebirths (1.6% vs 0.29%, p=0.005), stillbirths (4.6% vs 0.29%, p<0.001), and neonatal deaths (2.2% vs 0.46%, p<0.001). However, CS was associated with higher risk of postpartum haemorrhage (9.69% vs 16.3%, p=0.012).

Discussion

The increasing trend of CS rates for twin pregnancies in our cohort in the past 20 years echoed the findings in

Table 4. Logistic regression analysis of risk factors associated with Caesarean section for twins

Variable	B	Standard error	Wald	Odds ratio (95% confidence interval)	p Value
Non-vertex presentation of first twin	2.57	0.441	33.9	13.1 (5.51-31)	<0.001
Previous Caesarean section	1.43	0.32	19.7	4.19 (2.22-7.87)	<0.001
Advanced maternal age	0.5333	0.1858	8.058	1.7 (1.18-2.46)	0.005
Preterm delivery	-1.066	0.179	35.3	0.34 (0.24-0.48)	0.001
Multiparity	-1.23	0.181	46.4	0.29 (0.20-0.41)	0.001
Induction of labour	-2.45	0.339	52.5	0.086 (0.04-0.17)	0.001
Gestational diabetes	0.37	0.27	1.87	1.45 (0.85-2.46)	0.17
Gestational hypertension	0.544	0.302	3.24	1.72 (0.95-3.12)	0.07

Table 5. Comparison of pregnancy outcome between vaginal delivery and Caesarean section groups

Outcome	Vaginal delivery (n=454)*	Caesarean section for one or both twins (n=1712)*	p Value
Mean birthweight of all babies, g	2193±679	2408±508	<0.001; mean difference (confidence interval)= –214 (–294 to –133)
Mean birthweight of term babies ≥37 weeks, g	2649±366	2663±340	0.71; mean difference (confidence interval)= –14 (–87 to 59)
Fetal growth restriction in one or both twins (birthweight <10th centile according to gestation)	52 (22.9)	203 (23.7)	0.86
5-minute Apgar score <5 in livebirths	7 (1.6)	5 (0.29)	0.005
Stillbirth	21 (4.6)	5 (0.29)	<0.001
Neonatal death	10 (2.2)	8 (0.46)	0.001
Postpartum haemorrhage	22 (9.69)	140 (16.3)	0.012

* Data are presented as mean ± standard deviation or no. (%) of cases

other parts of the world The increase in the overall CS rate for twins was mainly the result of the increase in the CS rate for cephalic-presenting twins. In a cross-sectional study in United States from 1995 to 2008, the CS rate for twins increased from 53.4% to 75%[7], but the increase could not be fully explained by the increase in the CS rate for breech presentation. Despite no data for presentation according to the birth order of twins, it was suspected that the increase was contributed to a significant increase in the CS rate for vertex-vertex twins. This finding is consistent with that of the present study.

In another cross-sectional study in United States from 2006 to 2013, the CS rate for twins peaked at 75.3% in 2009 and remained static and then dropped to 74.8% in 2013[9]. There appeared to be a similar trend in our cohort, as the CS rate for cephalic + cephalic twins fell from 78% in 2008-2012 to 74.7% in 2013-2017. Such a trend could be due to the evidence confirming the safety of VD for twin pregnancies compared with CS[5,6]. Further data in subsequent years should confirm whether there is a genuine decreasing trend.

The CS rate for non-vertex first twins was close to 100% for all intervals, as the Term Breech Trial stated that planned CS was associated with a reduced risk of adverse perinatal outcome in term pregnancy with the fetus in breech presentation[10].

Presentation of the second twin and the mode of delivery

In the present study, the CS rate for cephalic + non-vertex twins increased significantly from 65.9% in

1998-2002 to 91.1% in 2013-2017. However, there is no evidence that CS achieves better neonatal outcomes than VD in delivering non-vertex second twins. In a systematic review in 2012 that included one high-quality clinical trial (60 twin pairs) and 16 moderate/low-quality observational studies (3167 twin pairs), there were no significant differences in neonatal outcome between VD and CS with first twin and/or second twin in non-cephalic presentation[11]. No final conclusion could be drawn because of the small sample size and statistical limitations of the included studies. A retrospective case-control cohort study in 2018 reported that non-cephalic presentation of second twin did not significantly influence the perinatal outcome after VD at or above 32 weeks of gestation[12]. In addition, a French study in 2019 reported that both non-cephalic and cephalic second twins at or above 32 weeks of gestation were associated with low composite neonatal mortalities and morbidities for VD[13]. However, other studies reported that non-vertex second twins had higher odds ratio for combined delivery compared with vertex second twins[14,15]. The odds ratio for combined delivery for breech second twins was 6.2 to 6.9 and that for transverse second twins was up to 177. This was due to a lack of experienced obstetricians in conducting vaginal breech extraction and internal podalic version. A Danish study also suggested that new-generation obstetricians were not sufficiently trained to perform internal podalic version and breech extraction[16], which is also the situation in our unit. Second twins with combined delivery had higher neonatal morbidities than those with successful vaginal delivery[17]. Women with combined delivery are subjected to risks of vaginal delivery and emergency second-stage CS, and therefore are associated with higher morbidities than direct CS of the twins[18]. Such arguments were likely the most important reasons for the increasing trend in CS rate for cephalic + non-vertex twins in our unit. We believe this is also the situation in other obstetric units in Hong Kong, as there is consistently only a very low incidence of vaginal breech deliveries in all training units after the publication of the Term Breech Trial in 2000[10]. There are very few opportunities for obstetricians to have training in internal podalic version and breech extraction. Obstetricians lacking actual experience in these vaginal delivery skills are more likely prefer to perform direct caesarean section on twin pregnancies.

The CS rate for cephalic-cephalic twins was also increasing significantly in our unit. More obstetricians opted for direct CS even for cephalic + cephalic twins, because many are concerned that they do not have enough experience to manage the non-engaged second twin after delivery of the first twin. Non-engaged vertex second twin is common after delivery of the first twin. If the second twin is still not engaged after a prolonged period of maternal pushing, many obstetricians choose to perform CS instead of internal podalic version of the second twin followed by breech extraction. In addition, in approximately 11% to 20% of these vertex second twins, the presentation can change to non-vertex after VD of the first twin[19,20]. Therefore, new-generation obstetricians are tempted to advise patients with twin pregnancies to have direct CS to avoid combined delivery and risks of complications.

Fetal outcomes and mode of delivery

In the present study, CS was associated with fewer adverse perinatal or neonatal outcomes, including 5-minute Apgar score of <5, stillbirth, and neonatal death. However, the poor perinatal outcome of VD twins may be explained by the larger proportion of very preterm twins. Compared with the CS group, the VD group had a significantly higher preterm delivery rate, including very preterm deliveries <32 weeks and <28 weeks, and significantly lower mean birthweight.

The literature showed contradicting evidence in perinatal outcome between CS and VD for twin pregnancies. The retrospective cohort study in 2005 with 8073 twin births reported that CS reduced the risk of perinatal death of twins by approximately 75%[4]. Afterwards, several studies also reported that CS reduced perinatal and neonatal morbidities and mortalities[21-23]. However, the Twin Birth Study in 2013 with 1398 women between 32+0 to 38+6 weeks of gestation and twins in vertex presentation reported no significant differences between planned CS and planned VD in neonatal morbidities and mortalities[5]. In 2017, a nationwide prospective cohort study in France with 5915 twin pregnancies reported that VD with a cephalic first twin at or above 32 weeks was associated with lower composite neonatal mortalities and morbidities, compared with planned CS[24]. Another nationwide cohort study in the Netherlands with 21 107 twin pregnancies reported that CS resulted in more perinatal mortalities before 36+6 weeks and there was no significant difference between CS and VD at or above 37 weeks in morbidities or mortalities[25]. The Cochrane review in 2015 found only two randomised controlled trials comparing planned CS with planned VD for twins[26]. One was the randomised controlled trial of 2013 mentioned above. The second had a small sample size of 60 women and insufficient power to assess neonatal mortalities and morbidities[27]. A prospective cohort study with 354 twins reported that VD was not associated with adverse childhood outcomes in children with an average

age of 5.9 years[28].

The American College of Obstetricians and Gynecologists guidelines in 2014 states that women with cephalic-presenting twins should be counselled to attempt VD[6]. In Hong Kong, there is no guideline or consensus for the mode of delivery in twin pregnancies. As the evidence of CS versus VD for cephalic-presenting twins remains conflicting, our unit provides both options to such cases with uncomplicated pregnancy, and risks of combined delivery were included in the counselling. As there is a general preference for CS even among low-risk patients, it is anticipated that a significant proportion of our twin pregnancy patients will opt for planned CS.

Maternal outcomes and mode of delivery

Our data showed that CS was significantly associated with postpartum haemorrhage. There were studies supporting our finding that mothers in the CS group were significantly more likely to have hemorrhage and surgical complications[23,29], whereas other studies showed that mothers were more likely to suffer from haemorrhage with VD[30]. There were also studies with neutral findings showing no significant differences in postpartum haemorrhage rates between CS and VD[31,32]. Further studies on maternal outcome in twin pregnancies are needed before any conclusion can be drawn.

Risk factors associated with CS

In the present study, compared with the VD group, the CS group were associated with advanced maternal age, primiparity, gestational diabetes mellitus, and previous CS. The logistic regression model identified non-vertex presentation of first twin, advanced maternal age, and previous CS as independent risk factors for CS. The higher CS rate for non-vertex first twins was likely due to the preference of obstetricians to perform CS for all breech-presenting fetuses following the recommendation of the Term Breech Trial[10]. Advanced maternal age was an independent risk factor for CS in both singleton and multiple pregnancies in a systematic review[33]. The increasing number of mothers with advanced maternal age may contribute to a further increase in the CS rates in twin pregnancies in coming years. The increasing rates of CS for those with previous CS have been evident in singletons (from 36.7% to 57% in a local 20-year cohort)[8]; so it came with no surprise that a large proportion of twin pregnancies with previous CS would be delivered by repeat CS.

CS for twin pregnancies was negatively associated with preterm delivery, multiparity, and induction of labour. Particularly for twin pregnancies with very preterm labour before 28 weeks, given the expected poor prognosis, VD would often be the preferred delivery mode. Multiparous women with previous VD likely preferred VD, whereas induction of labour preselected those pregnancies that aimed at planned VD.

Limitations

The limitation of this study is its retrospective design. A prospective cohort may provide better information on the reasons of choice of the mode of delivery from patients and obstetricians, as well as more detailed analysis of neonatal and maternal morbidities. Another limitation of our study is the generalisibility of our data to other centres in Hong Kong, as other service units may not offer the options of planned CS or VD equally to patients with uncomplicated twin pregnancies. On the other hand, theoretically, other centres with more obstetricians experienced in performing vaginal breech deliveries or internal podalic version may also counsel these patients differently, so that their CS rates could differ from our findings.

Conclusion

Despite the lack of consensus on a particular mode of delivery for twin pregnancies, a progressive increase in CS rates for twins was observed over the past 20 years, mainly as a result of an increase in the CS rate for cephalic-presenting twins. Key factors associated with CS for twins were non-vertex presentation of the first twin, advanced maternal age, and previous CS.

Declaration

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Intravenous iron therapy for menorrhagic patients with severe iron-deficiency anaemia: a retrospective cohort study

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Background: Patient blood management plays an increasingly important role in the management of menorrhagia. We have used a dose-standardised protocol for intravenous (IV) iron therapy for menorrhagic patients, without complicated dose calculation or prolonged hospitalisation. This study aims to evaluate the efficacy, safety, and patient acceptability of IV iron therapy followed by oral iron supplement based on a dose-standardised protocol for menorrhagic patients with severe iron-deficiency anaemia.
Methods: We retrospectively reviewed records of haemodynamically stable menorrhagic patients with severe iron-deficiency anaemia (haemoglobin level, 6-8 g/dL) who were admitted to Kwong Wah Hospital between October 2017 and October 2018. The IV iron therapy involved two doses of 200 mg iron (ferric hydroxide sucrose complex, Venofer) followed by oral iron supplement for at least 4 weeks. Outcome measures included haemoglobin (Hb) and ferritin levels and total iron binding capacity before treatment and 4 weeks after the first dose, and resolution of anaemic symptoms.
Results: Of 182 patients counselled with the option of IV iron therapy or blood transfusion, 138 (75.8%) opted for IV iron therapy. 24 of them were excluded. Of the 114 patients included, 52 (45.6%) had uterine fibroids, 23 (20.2%) had adenomyosis, and 39 (34.2%) had dysfunctional uterine bleeding. At 4 weeks after starting treatment, the mean Hb level increased significantly by 3.4 g/dL, the mean ferritin level increased significantly by 34.4 ng/mL, and the total iron binding capacity reduced significantly by 12.7 μmol/L. Before treatment, 103 (90.4%) patients reported anaemic symptoms. At 4 weeks after treatment started, anaemic symptoms had resolved in 102 (99.0%) patients. The increase in Hb level was not correlated with age, body weight, pre-treatment Hb level, or the interval between the two iron doses. One patient reported an adverse reaction with skin rash, which was treated with antihistamine. She had no anaphylaxis and her second dose was withheld.
Conclusion: IV iron therapy based on a dose-standardised protocol followed by oral iron supplement is a cost-effective, safe, well-accepted, and well-tolerated treatment for menorrhagic patients with severe iron-deficiency anaemia.

Keywords: Anemia, iron-deficiency; Iron; Menorrhagia

Introduction

Menorrhagia is estimated to affect 10% to 30% of women in reproductive age and can cause severe iron-deficiency anaemia[1-3]. Women with severe iron-deficiency anaemia secondary to menorrhagia constitute a distinct group from patients with severe iron-deficiency anaemia caused by renal problems or gastrointestinal bleeding, as these women suffer from cyclical blood loss.

Iron supplement is an effective treatment for anaemia. Oral iron supplement is the first-line treatment because it is convenient and relatively inexpensive. However, oral iron supplement has gastrointestinal side-effects[4,5], which may not be tolerated by patients, and thus intravenous (IV) iron therapy is suggested as second-line treatment. In patients with severe iron-deficiency anaemia secondary to general medical conditions, IV iron therapy has been shown to be effective in increasing the haemoglobin (Hb) level by 6.9 g/dL and reducing the need for allogenic blood transfusion[6]. However, IV iron therapy for menorrhagic women has been less studied. IV iron therapy for menorrhagic patients has reported to increase the Hb level by 2-4 g/dL at 4 weeks after treatment[7,8]. However, IV iron therapy may cause adverse drug reactions, especially anaphylaxis. Nonetheless, the second and third generations IV iron, such as iron sucrose, ferric carboxymaltose, and iron isomaltoside, have been associated with very low

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incidence of allergic reaction[7,9], compared with first-generation IV iron therapy that uses an anaphylactic-inducing Dextran conjugate[10,11]. Although proven to be safe, the wider use of IV iron therapy has been limited by the need for administration of multiple doses and/or multiple admissions, as well as complex dose calculation using the Ganzoni formula. Hence, this study aimed to investigate the efficacy, safety, and patient acceptability of IV iron therapy followed by oral iron supplement based on a dose-standardised protocol for menorrhagic patients.

Methods

This retrospective cohort study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee (Reference: KC/KE-18-0275/ER-1). Records of haemodynamically stable menorrhagic patients with severe iron-deficiency anaemia (Hb level, 6-8 g/dL) who were admitted to Kwong Wah Hospital between October 2017 and October 2018 were retrieved. Patients were given the choice of blood transfusion or IV iron therapy that involved two doses of 200 mg iron (ferric hydroxide sucrose complex, Venofer) followed by oral iron supplement for at least 4 weeks. In most patients, the second dose was given within 2 weeks of the first dose as day readmission. In patients required longer hospitalisation, the second dose was given 24 hours after the first dose during the same index admission. Patients were excluded if they (1) had vaginal bleeding secondary to malignant pathologies as confirmed by histology, (2) had received blood transfusion in the same index admission, (3) had not completed both doses of IV iron treatment, and/or (4) had incomplete blood tests data.

Table 1. Clinical characteristics of 114 patients

Characteristic	Mean±SD; median (range)
Age, y	44.0±7.9; 46 (16-54)
Body weight, kg	58.3±9.3; 57 (43.6-89.9)
Interval between two intravenous iron doses, d	12.8±4.4; 13 (1-14)
Uterine size, wks	8.0±5.2; 8 (4-26)

Outcome measures included Hb and ferritin levels and total iron binding capacity before treatment and 4 weeks after the first dose, and resolution of anaemic symptoms. Age, body weight, and uterine size were also recorded.

Hb and ferritin levels and total iron binding capacity before and after treatment were compared using the Wilcoxon signed-rank test or the paired-sample t-test as appropriate. Correlation between the increase in Hb level and clinical factors was assessed using one-way analysis of variance. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS (IBM Corp, Armonk [NY], USA).

Results

Of 182 patients with severe iron-deficiency anaemia secondary to menorrhagia, 138 (75.8%) opted for IV iron therapy. 24 of them were excluded according to the exclusion criteria. Of 114 patients included, 52 (45.6%) had uterine fibroids, 23 (20.2%) had adenomyosis, and 39 (34.2%) had dysfunctional uterine bleeding (Table 1). 19 (13.8%) patients had blood transfusion for menorrhagia or other causes prior to the index admission episode.

At 4 weeks after starting treatment, the mean Hb level increased significantly by 3.4 g/dL, the mean ferritin level increased significantly by 34.4 ng/mL, and the total iron binding capacity reduced significantly by 12.7 μmol/L (Table 2). Before treatment, 103 (90.4%) patients reported anaemic symptoms. At 4 weeks after treatment started, anaemic symptoms had resolved in 102 (99.0%) patients.

The increase in Hb level was not correlated with age, body weight, pre-treatment Hb level, or the interval between the two iron doses. One patient reported an adverse reaction with skin rash, which was treated with antihistamine. She had no anaphylaxis and her second dose was withheld.

Discussion

To the best of our knowledge, this is the first local study of IV iron therapy for menorrhagic patients with

Table 2. Haemoglobin and ferritin levels and total iron binding capacity before and after treatment

Blood parameter	Pre-treatment	4 weeks after first dose of intravenous iron therapy	p Value
Mean±SD (median) haemoglobin, g/dL	7.1±0.7 (7.1)	10.5±1.2 (10.8)	<0.001
Mean±SD (median) ferritin, ng/mL	6.8±9.4 (3)	41.2±28.1 (45)	<0.001
Mean±SD (median) total iron binding capacity, μmol/L	75.2±10.6 (76.5)	62.5±9.2 (62)	<0.001

Table 3. Comparing the Ganzoni formula and the dose-standardised protocol in terms of intravenous iron dosage and drug cost in a sample with a body weight of 60 kg, a baseline haemoglobin (Hb) of 7 g/dL, and a treatment goal of Hb of 10.5 g/dL

	Ganzoni formula	Dose-standardised protocol
Intravenous iron dosage	IV iron needed = body weight × (target Hb - actual Hb) × 2.4 + iron store = 60 kg × (10.5-7 g/dL) × 2.4 + 500 mg = 1004 mg	IV iron 400 mg + oral iron supplement
Drug cost (based on Kwong Wah Hospital Pharmacy Prescription)	Venofer = HK$94.2/100 mg elemental iron × 10 = HK$942	Venofer = HK$94.2/100 mg elemental iron × 4 + ferrous sulphate = HK$0.26/tablet (60 mg elemental iron) × 30 days = HK$94.2 × 4 + HK$0.26 × 30 = HK$376.8 + HK$7.8 = HK$384.6

severe iron-deficiency anaemia. The dose-standardised protocol used was effective in raising both Hb and ferritin levels.

Currently there is no universally agreed guideline on calculating the optimal dosage of IV iron therapy. The Ganzoni formula is the most common method and has been reported to achieve an increase in Hb level of up to 4 g/dL 3 to 4 weeks after IV iron therapy in patients with menorrhagia[7,8]. Oral iron supplement is usually not recommended immediately after IV iron therapy because the intestinal epithelium cannot absorb anymore dietary iron, as the systemic iron store is at its full capacity[12,13].

In our dose-standardised protocol, a lower IV iron dose of 400 mg (rather than >1000 mg based on the Ganzoni formula) was given so that the iron store was not fully replenished and could be further replenished with oral iron supplement for at least 4 weeks. The post-treatment rise in Hb level in our patients was comparable to that reported in other studies using a more complicated dose calculation method. In addition, the treatment cost for each patient reduced by almost 60%. An example comparing the Ganzoni formula and the dose-standardised protocol in terms of IV iron dosage and drug cost is shown in Table 3.

There is a potential advantage for IV iron therapy followed by oral iron supplement for menorrhagic patients with severe iron-deficiency anaemia. We hypothesise that the initial IV iron dose quickly replenishes the extremely low iron store and kicks start the erythropoiesis at a faster rate, and then the erythropoiesis process is supported by the continuous oral iron supplement. This may be more cost-effective, as the cost of oral iron supplement is lower than the cost of IV iron therapy, and can avoid unnecessary blood transfusion, but it may not be effective in patients with poor tolerance or compliance to oral iron supplement. Further subgroup analysis is warranted to identify appropriate patients who can benefit from it.

Body weight is a significant independent variable in the Ganzoni formula calculation. Patients with different body weights respond differently in terms of Hb rise[14]. However, body weight was not correlated with Hb rise in the present study. This may be due to the use of oral iron supplement that gradually increased the iron store and Hb level.

The older generation of IV iron therapy may cause anaphylaxis and severe allergic reaction owing to the high molecular weight carbohydrate conjugate[12]. However, the risk of anaphylaxis is extremely low (1:10 000) for the ferric hydroxide sucrose complex (Venofer)[6,11,15]. In the present study, only one patient had mild allergic reaction with skin rash; no patients developed anaphylaxis or other severe adverse drug reactions. The present study confirmed that IV iron therapy with ferric sucrose is a safe treatment for patients with severe iron-deficiency anaemia. In addition, IV iron therapy is a well-accepted alternative to blood transfusion, as most patients chose IV iron therapy rather than blood transfusion. It is also a well-tolerated treatment, as no patient discontinued treatment except for one with mild drug allergy.

Conclusion

IV iron therapy based on a dose-standardised protocol followed by oral iron supplement is a cost-effective, safe, well-accepted, and well-tolerated treatment for menorrhagic patients with severe iron-deficiency anaemia. Further subgroup analysis is warranted to identify appropriate patients for this dose-standardised protocol.

Declaration

The authors have no conflict of interest to disclose.

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Enhanced recovery for gynaecological surgery: a review

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We review various aspects of enhanced recovery after surgery for gynaecological patients, including patient education and counselling, preoperative assessment and optimisation, preoperative fasting and nutrition, bowel preparation, thromboembolism prophylaxis, perioperative analgesia, peritoneal drains and urinary catheters, postoperative nausea and vomiting, hypothermia prevention, early feeding and early mobilisation, and implementation of enhanced recovery after surgery.

Keywords: Convalescence; Gynecologic surgical procedures

Introduction

Enhanced recovery after surgery (ERAS) is a multimodal, multidisciplinary, evidence-based approach to the care of patients undergoing surgery. It was developed by a group of surgeons and anaesthesiologists in Europe (mostly from Scandinavia, the Netherlands, and the United Kingdom) in the early 1990s. A Danish surgeon, Henrik Kehlet, introduced ERAS to wider recognition and broader application. In 1995, Kehlet and colleagues reported that hospital stay was reduced to 2 days in a group of elderly high-risk patients undergoing laparoscopic colonic surgery by early aggressive perioperative care such as early oral nutrition and mobilisation[1]. ERAS for patients with colorectal surgery results in improved patient satisfaction, less variation in the patient care, reduced postoperative complication rates, earlier mobilisation and resumption of normal diet, shorter length of stay in hospital, reduced readmission rates, while ensuring patient safety and cost-effectiveness[2-4]. ERAS has been used for many major operations across specialties including gastric/oesophageal, orthopaedics, urology, thoracic, etc. There is evidence that ERAS can be applied to gynaecological patients and lead to less postoperative nausea and vomiting (PONV), reduced length of hospital stay, shortened stay in postoperative ward, and hence reduced hospital costs[5,6].

Elements of ERAS

Surgery induces stress responses that can be immunological, endocrine, neural, and psychological[7]. ERAS can improve patient outcomes by reducing surgical stress responses and mitigating the potential associated negative consequences so as to expedite restoration of normal body functions[8,9]. ERAS interventions can be divided to preoperative, intraoperative, and postoperative interventions. Preoperative interventions include preoperative patient education and counselling, early optimisation of comorbidities, minimising preoperative fasting, avoiding mechanical bowel preparation and dehydration, and use of preemptive analgesia. Intraoperative interventions include the use of short acting anaesthetic agents and regional anaesthesia, prevention of PONV, goal directed fluid management, and maintenance of normothermia. Postoperative interventions include multimodal analgesia, avoidance of unnecessary drains and nasogastric tubes, early catheter removal, thromboembolic prophylaxis, early oral intake, and mobilisation.

ERAS is drastically different from traditional care pathways. A multimodal, evidence-based, protocol-driven approach should be adopted to achieve ERAS goals. A successful programme requires active engagement of all involved parties contributing to different elements of ERAS. Usually, a multidisciplinary team consists of surgeons, anaesthesiologists, nursing staff, allied health professionals such as physiotherapists, occupational therapists, and dietitians. They contribute to patient care as a team rather than segregations of input and expertise. ERAS care pathway entails a lot of interventions from various specialties. To assure quality and compliance, continuous auditing of the care pathway and patient outcomes is necessary[10].

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Patient education and counselling

An important principle of ERAS is to engage the patient as early as possible by providing education and counselling when surgery is planned. Patients should be informed about the care plan and pathway and the concepts of ERAS, for example perioperative pain management, PONV prophylaxis, early feeding, and mobilisation, as well as the rationale behind the practices and concepts. For example, pre-emptive analgesia and use of multimodal analgesic agents enable better pain control postoperatively so that one can mobilise earlier to achieve better outcomes. Earlier oral intake enables earlier return of bowel function and shorter hospital length of stay and thus reduced risks of developing associated complications. It is not uncommon that patients hesitate to mobilise because of pain and fear of wound disruption. Extended perioperative counselling allows patients to comply with the elements of ERAS and reduces the length of hospital stay[11]. Thus, a concise and clear approach is needed for patients of different age groups and backgrounds. It should also be patient-centred. Patients' own initiative and adherence to interventions such as oral carbohydrate loading, analgesics as premedication, and early mobilisation should be particularly focused upon. In addition, the rehabilitation protocols should encompass the journey from diagnosis to recovery at home. A Canadian study in 2017 reported that most patients, once understood the ERAS programme, wanted to take on an active, collaborative role throughout their surgical journey and were more likely to follow the expected protocols[12].

Surgery is a stressful experience; stressors can be emotional, psychological, and social. In gynaecological surgery, especially hysterectomy, it is not simply removal of an organ to treat a condition, but also a loss of fertility. Some women believe that uterus is important for sexuality and femininity, and hysterectomy may lead to negative body image and low self-esteem. Patients' expectations, fears, worries about surgery should be addressed because concerns or doubts with their postoperative care and condition may cause anxiety and impede recovery. Preoperative counselling helps to set expectations about the surgery and anaesthesia. Education materials such as pamphlets or audio-visual information containing description of the interventions and expected results should be provided. Occasionally, patients also require personalised care and appropriate adaptations within the standardised pathway.

Preoperative assessment and optimisation

ERAS emphasises early assessment and optimisation of chronic illness. Patients should have haemoglobin concentration measured before major elective surgery, and patients who are anaemic should be treated appropriately as preoperative anaemia is associated with postoperative morbidity and mortality[13]. Lower preoperative haemoglobin level is associated with longer hospital stay and a higher rate of allogeneic blood transfusion, which is associated with an increased risk of adverse effects[14]. The risks are increased with severity of anaemia[15]. Patient blood management is a multidisciplinary, evidence-based approach to optimise patient red cell mass and to improve clinical outcomes by avoiding unnecessary allogeneic blood transfusions. It should be an integral part of ERAS programme for patients undergoing major gynaecological surgery, because correcting even mild anaemia significantly reduces the need for transfusion and the resultant morbidity and mortality. Oral iron therapy is the first-line therapy for iron deficiency anaemia, and low-dose alternate-day oral iron therapy together with vitamin C optimises iron absorption. Intravenous iron therapy can be considered when oral therapy fails or intolerable, or when near the time of operation. The newer generation of intravenous iron preparations has fewer severe adverse events and allows a larger dose of iron in a shorter infusion time[16].

In Hong Kong, the prevalence of diabetes has increased significantly in both sexes and across all age groups. The overall prevalence of diabetes was 10.29% and that of pre-diabetes was 8.90%[17]. Elevated preoperative and perioperative glucose and glycated haemoglobin levels are associated with poor surgical outcomes; adverse outcomes include a >50% increase in mortality, a 2.4-fold increase in the incidence of postoperative respiratory infections, a threefold increase in postoperative urinary tract infections, a twofold increase of surgical site infections, a doubling in the incidence of myocardial infarction, and an almost twofold increase in acute kidney injury[18]. It is therefore important to ensure good glycemia control before proceeding to operation. Smoking and use of alcohol are associated with higher risks of perioperative complications and should be assessed routinely preoperatively.

Preoperative fasting and nutrition

Conventionally, fasting after midnight is adopted for elective surgery to avoid risks of aspiration and related problems. However, prolonged fasting can be associated with dehydration, patient discomfort and anxiety, caloric restriction, and metabolic changes such as impairment of glucose metabolism and increased insulin

resistance. Evidence has shown that intake of clear fluids 2 hours before surgery does not increase gastric content, reduce gastric fluid pH, or increase complication rates[19]. Minimising fasting times and maintaining nutrition reduce postoperative pain, nausea, perioperative insulin resistance, and muscle catabolism. Patients without conditions associated with delayed gastric emptying should be encouraged to drink clear fluids up to 2 hours before elective surgery; solid food should be avoided for at least 6 hours before elective surgery[20]. Carbohydrate loading before surgery is increasingly advocated to mitigate perioperative increase in insulin resistance and associated adverse effects and to improve perioperative wellbeing. In addition, it is associated with a small reduction in the length of hospital stay when compared with placebo or fasting in patients undergoing elective surgery but not associated with postoperative complication rates[21].

Bowel preparation

Mechanical bowel preparation was thought to reduce anastomotic breakdown in cases with bowel repair or resection. However, it is associated with discomfort and adverse effects such as dehydration and electrolyte imbalance, especially in elderly people with medical comorbidities. Moreover, there is no good evidence to support the routine use of mechanical bowel preparation. A Cochrane review of 18 randomised controlled trials reported that patients undergoing elective colorectal surgery did not show any significant benefit from mechanical bowel preparation or rectal enemas[22]. A systemic review of five randomised controlled trials for gynaecological surgery also did not show any benefits but reported an unpleasant patient experience. Its use in gynaecological laparoscopic surgery did not improve operative time or surgical field visualisation[23].

Thromboembolism prophylaxis

Prevention of venous thromboembolism is important in pelvic surgery especially for oncology patients. The risk of venous thromboembolism should be stratified according to individual risk factors. Hormone replacement therapy is a risk factor for venous thromboembolism, and the risk is higher for oral than transdermal preparations. Combined oral hormonal contraception is a common risk factor in gynaecological patients. The NICE guideline advised to consider stopping oestrogen-containing oral contraceptives or hormone replacement therapy 4 weeks before elective surgery. Medical prophylaxis should be commenced before operation in high risk cases, together with mechanical method such as pneumatic compression stockings during operation[24-26].

Perioperative analgesia

Multimodal analgesia (ie, administration of two or more drugs that act by different mechanisms for providing analgesia through additive or synergistic effects) is advocated in ERAS care plan, as poor pain control can impede postoperative rehabilitation, delay patient recovery, and affect patient outcomes. Long-acting opioids, particularly morphine, is traditionally used in perioperative pain control after major gynaecological surgery. However, adverse effects of opioids are common, including nausea and vomiting, sedation, pruritus, urinary retention, and respiratory suppression. These opioid-related adverse effects may lead to increased duration of immobilisation and length of hospital stay, total hospital costs, and rates of readmission[27]. A large cohort study in 2013 reported that patients with opioid-related adverse drug events had a 55% longer length of stay, 47% higher costs of care, 36% increased risk of readmission, and 3.4 times higher risk of inpatient mortality than those without[28]. High doses of opioids can induce hyperalgesia and acute tolerance. Thus, ERAS care pathway emphasises multimodal opioid-sparing analgesia to achieve earlier mobilisation and resumption of normal diet while maintaining effective pain control. Paracetamol is an effective analgesic agent and is commonly used perioperatively due to wide availability and accessibility of the intravenous form. When paracetamol is used as an adjunct to opioid analgesia, opioid requirements are reduced by 26% over 4 hours and by 16% over 6 hours[29]. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing pain and inflammation and are an integral component in multimodal analgesia[30]. A combination of paracetamol and NSAIDs offers superior analgesia than either paracetamol or NSAID alone, and should be administered to all patients unless contraindicated[31]. Gabapentinoid group such as gabapentin and pregabalin are commonly used. Preemptive administration of gabapentin or pregabalin can reduce postoperative pain score, opioid consumption, and rate of PONV[32,33].

Epidural analgesia is not a routine practice in gynaecological surgery, as the evidence is conflicting and controversial. Although epidural analgesia is superior to parenteral opioids such as intravenous patient-controlled analgesia in terms of pain control in patients undergoing major open gynaecological surgery, there is no significant difference in terms of return of bowel function or time to discharge[34]. Patient-controlled epidural analgesia provides good perioperative pain control but does not improve pain management in women undergoing gynaecological oncology surgery. In an Australian study of the effect

of epidural analgesia in patients undergoing abdominal hysterectomy, epidural analgesia was associated with an increase in postoperative complications and length of hospital stay[35]. A Cochrane review comparing epidural analgesia with patient-controlled intravenous analgesia following intra-abdominal surgery in adults reported that epidural analgesia provides better pain relief, but the benefit is small and may not be clinically important[36]. Problems associated with epidural analgesia include higher chance of failure to provide analgesia, increased likelihood of hypotension requiring intervention, and pruritus. It is important to balance the risks and benefits of epidural analgesia for postoperative pain control. Truncal blocks particularly transversus abdominis plane block are efficacious in terms of reduction in pain and opioid requirement up to 24 hours postoperatively for patients undergoing hysterectomy[37]. Wound infiltration using local anaesthetics is easy to perform and carries fewer complication risks. However, the pain efficacy is short-lived, limited, or even no opioid-sparing effect at all. There is no clinically significant difference between continuous wound infusion and intermittent epidural analgesia for postoperative analgesia in hysterectomy and myomectomy[38].

Peritoneal drains and urinary catheters

Peritoneal drains are used to prevent postoperative fluid or blood collection, and to help early detection of bleeding and anastomotic bowel leakage. In gynaecological oncology surgeries, drains are inserted to prevent formation of lymphocysts after lymphadenectomy. A Cochrane review of four randomised controlled trials concluded that placement of retroperitoneal drains is not effective in preventing lymphocysts[39]. There is no evidence that peritoneal drainage improves outcomes after gynaecological surgery, and therefore it is not recommended routinely after gynaecologic / oncology surgery including lymphadenectomy or bowel operation[40]. Nonetheless, its use can be considered in cases with increased risk of pelvic collection and bleeding, or very low anterior resection without concurrent temporary bowel diversion[41]. Urinary catheters are used to prevent urinary retention and to monitor urine output. In some urogynaecology or gynaeoncology cases, longer catheterisation is required due to higher bladder-related morbidity. For uncomplicated cases, urinary catheter should be used for a short period only, preferably <24 hours. Monitoring of voiding after catheter removal helps to detect voiding problems and prevent over distension of the bladder[40].

Postoperative nausea and vomiting

PONV is a common cause of patient dissatisfaction after surgery and anaesthesia. The average incidence of PONV is 30% in general post-surgical patients and up to 80% in high-risk groups[42]. Patients undergoing gynaecological surgery are among the high-risk populations. Female gender itself is a risk factor of PONV. Other risk factors include non-smoking status, history of motion sickness and/or PONV, use of opioids, and use of volatile anaesthetics or nitrous oxide. Gynaecological surgery is considered as a risk factor, but it remains controversial whether the increased risks are attributed to patient factors. A number of predictive risk scores are developed to stratify the risk of developing PONV. The Apfel simplified score is based on counting the number of risk factors that include female gender, non-smoking status, history of PONV and/or motion sickness, and use of opioids postoperatively[43]. When 0, 1, 2, 3, or 4 factors are present, the risk of PONV is 10%, 20%, 40%, 60%, or 80%, respectively. As most women in Hong Kong are nonsmokers (only 3.1% women smoke), they have at least two risk factors and the risk of PONV is at least 40%[44].

PONV prevention is an integral part of ERAS. PONV may lead to increased risk of aspiration, patient distress, unanticipated hospital admission, and increased hospital length of stay. High-risk patients should be identified by calculating their baseline risks; volatile agents and nitrous oxide should be avoided, and total intravenous anaesthesia should be used. Newer antiemetic agents have been developed, and costs of antiemetic agents have decreased substantially because of more generic versions available. Combination of antiemetics is more effective than single antiemetic and should be used for high-risk patients[45]. Other strategies include use of regional anaesthesia and reducing use of opioids and neostigmine perioperatively.

Hypothermia prevention

Hypothermia not only causes patient discomfort, dissatisfaction, and postoperative shivering, but also is associated with coagulopathy and increased risk of bleeding, myocardial ischaemia, and higher risks of postoperative infection[46-49]. Hypothermia is associated with prolonged stay in post-anaesthesia care unit, increased intensive care unit admissions, and longer length of hospital stay. These consequences as well as cardiovascular, haemorrhagic, and infectious complications increase the costs. To avoid hypothermia, patient risks should be assessed and interventions should be commenced preoperatively.

High-risk factors include major or intermediate surgery, combined general and regional anaesthesia, ASA (American Society of Anesthesiologists) Class 2 or above, preoperative hypothermia (<36°C), and risk of cardiovascular complications. Core temperature should be monitored intraoperatively by direct measurement. Active prewarming should be started in the ward or preoperative unit if the patient's temperature is <36°C. Active warming techniques such as forced air warming device or heating mattress should be used intraoperatively from induction of anaesthesia[50]. Irrigation fluids should be warmed. Fluid warmer should be used if intravenous fluid or blood products are given. These active warming techniques should be continued if patients' temperature is still <36°C postoperatively.

Early feeding and early mobilisation

Early feeding is defined as resumption of oral fluid or solid food intake within the first 24 hours after surgery regardless of signs that indicate the return of bowel function. Feeding is encouraged as tolerated, but not forced. Systemic review showed that early feeding is safe, despite association with increased nausea; there is no evidence of increase in postoperative ileus, vomiting, or abdominal distension, instead the length of hospital stay is shorter in major abdominal gynaecologic surgery[51,52].

Early mobilisation reduces postoperative pulmonary complications, thromboembolism, ileus, metabolic imbalance, and cardiovascular events. With prior counselling about the benefits, use of multimodal analgesia to achieve better pain control, and removal of unnecessary drains and catheters that hinders movement, the practice of early mobilisation is more acceptable to patients. Compliance to other elements of ERAS helps to engage patients and remove barriers in implementation[53,54].

Implementation of ERAS

ERAS is a multimodal, multidisciplinary, evidence-based approach. Its implementation and success require inputs from all stakeholders. The pace of adoption and development differs in different specialties. Studies of ERAS in gynaecological surgeries for both benign and malignant conditions have reported improvement in patient satisfaction, length of hospital stay, and cost, while no difference in morbidity, mortality, and readmission rates[55,56]. Quality and safety are key drivers for changes in clinical interventions and systems. ERAS includes various elements; healthcare managers and practitioners can adopt suitable and feasible elements with a locally agreed pathway and protocol. Education helps the team to understand the concept, current services, and potential improvements. Audit with measurement of impact, clinical data collection, and outcome evaluation are important in implementation. Finally, the patient plays a central role. Enhanced recovery is a partnership between healthcare providers and patients, different improvement elements are informed and shared decisions. Engagement of patients is the key to success[57,58].

Declaration

The authors have no conflict of interest to disclose.

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Development of cytogenomics for prenatal diagnosis: from chromosomes to single nucleotides: a review

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Prenatal diagnosis encompasses traditional cytogenetics and molecular-based techniques. In the new era of genomics, challenge to prenatal diagnosis has led to revised diagnostic strategies. In this review, we discuss the application of chromosomal microarray and a new prenatal diagnosis workflow in the public setting in Hong Kong. Using this prenatal diagnosis workflow, up to 40% of fetuses with structural anomalies can be identified with an underlying genetic aetiology, leaving the majority of cases undiagnosed. With the advancement of next generation sequencing, we are able to tackle the challenge of investigating chromosomal changes to single nucleotide variant level. Therefore, we also discuss whole exome sequencing, whole genome sequencing, and long-read sequencing, as well as their limitations and prenatal applications. This DNA-based technology should be evaluated for prenatal clinical application in Hong Kong.

Keywords: Prenatal diagnosis; Whole exome sequencing; Whole genome sequencing

Introduction

Conventional G-banded karyotyping with a resolution of 5 to 10 Mb was the gold standard for detecting numerical and structural chromosomal abnormalities in prenatal diagnosis. It has a turnaround time of about 2 weeks, because it requires cell culture, metaphase preparation, and karyotyping by trained cytogeneticists. It is therefore mostly superseded by chromosomal microarray (CMA), which can examine DNA copy number variations (CNVs) at an increased resolution and detect microdeletion and micro-duplication on top of gross chromosomal imbalances. CMA can achieve higher diagnostic yield in both prenatal and postnatal settings. Since June 2019, CMA has been the first-line test for prenatal diagnosis in public hospitals in Hong Kong. Nonetheless, advancement in genomic analysis by next generation sequencing (NGS) [also known as massively parallel sequencing] and challenge to prenatal diagnosis have led to revised diagnostic strategies.

A definitive cytogenomic and genetic prenatal diagnosis by conventional cytogenetics and molecular-based techniques (including CMA and NGS) enables more informed choices and counselling of parents regarding prognosis, and hence empower parents in making pregnancy decisions. It provides reassurance of continuation of the pregnancy when the prognosis is good, and an option of termination of pregnancy when the prognosis is poor. Accurate and rapid cytogenomic and genetic diagnosis facilitates targeted in utero treatment and postnatal management, informs reproductive risk of future pregnancy, and has implications for other family members. In this review, we discuss the application of CMA, whole exome sequencing (WES), and whole genome sequencing (WGS) in prenatal diagnosis (Table).

Prenatal diagnosis workflow with CMA

CMA detects gain and loss of genomic regions by hybridization of fluorescently labelled test DNA from a patient (fetal sample) onto probe targets with known genomic coordinates, which are usually fixed on a glass slide. Depending on the type of CMA platform, there are oligonucleotide probes, single-nucleotide-polymorphism (SNP) probes, and a combination of two for detecting chromosomal abnormalities. Both oligonucleotide-based CMA and SNP-based CMA can determine CNVs, but only the latter can genotype SNPs on DNA target. The genotype information of the SNPs enables detection of maternal

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Table. Comparison of cytogenomic technologies

Molecular technology	Resolution	Detection of chromosomal change	Run time (turnaround time)	Throughput per test	Prenatal use in Hong Kong
Chromosomal microarray	100-200 kb	Copy number variants	2-3 days (7 working days)	1-8 samples per chip (depending on platform)	Yes
Whole exome sequencing	1 bp	Variants in exon	3-4 days (3-4 weeks)	6-12 samples (depending on the read-depth and gene coverage) per run on a medium throughput by next generation sequencing platform	Yes
Whole genome sequencing (low-coverage)	50-100 kb	Copy number variants	2-3 days (7 working days)	16-48 samples (depending on the read-depth and coverage) per run on a medium throughout by next generation sequencing platform	Yes
Long-reads sequencing	~10 bp accuracy	Structural variants and breakpoint mapping	Hours to 2 days (unknown)	Various (depending on purpose and region of interest)	No (yes for preimplantation genetic testing on chromosomal structural rearrangement)

cell contamination in the fetal sample, triploidy, and copy number neutral changes, namely absence of heterozygosity, uniparental isodisomy, and segmental iso/heterodisomy.

The limitations of CMA include inability to detect balanced structural rearrangement of chromosomes, low level mosaicism (sensitivity level is platform specific and ranges from 20% to 30%), polyploidy (except for triploidy by SNP-based CMA), CNVs not represented on the array design (such as supernumerary marker chromosomes that are of centromeric and heterochromatic origin where no probe can be designed from these repetitive sequence regions), and uniparental heterodisomy (unless trio analysis of SNP-based CMA is performed). Chorionic villus specimens with abnormal or mosaic findings should be interpreted with caution as there is a possibility of confined placental mosaicism, which should be excluded by confirmatory testing on amniotic fluid sample.

Chromosomal imbalances may suggest structural rearrangement. Unbalanced translocations can usually be inferred from having terminal deletion of one chromosome together with terminal duplication of another chromosome. Unbalanced translocations can be confirmed by karyotyping and/or fluorescence in-situ hybridization. Both of which are valuable tools and cannot be replaced by CMA alone in the study of structural chromosomal imbalances such as ring chromosome, marker chromosomes, isochromosomes, isodicentric chromosomes, and unbalanced translocations. Their corresponding quantitative gain or loss of chromosomal DNA can only be reflected in CMA results.

CMA is commonly used (in place of karyotyping) for prenatal diagnosis as supported by major professional societies in different countries[1-5]. Systematic reviews have shown an increased diagnostic yield of CMA of 3.5% to 10% for fetuses with ultrasound abnormality and normal karyotype, while the detection of variants of uncertain clinical significance remains low at around 1% to 2%[6-9]. Studies have demonstrated the clinical utilities of CMA[10,11], supporting its use as an adjunct diagnostic tool in prenatal cases with fetal ultrasound abnormalities[12-14]. It has been shown to be a cost-effective diagnostic test in pregnancies with fetal ultrasound anomalies[15,16]. A multicentre study in UK on array comparative genomic hybridisation in prenatal diagnosis of fetal anomalies concluded that CMA was a robust, acceptable, and probably cost-effective method to detect more clinically significant chromosomal imbalances in anomalous fetuses[17]. In Hong Kong, CMA has been accepted as a part of prenatal diagnosis to improve the prenatal care[18-21] and to investigate the underlying causes of fetal abnormalities[7, 22-33] that cannot be achieved by conventional cytogenetics alone.

Since June 2019, a new prenatal diagnostic workflow has been implemented in public hospitals in Hong Kong (Figure 1). It integrates CMA as a first-line test with quantitative fluorescent polymerase chain reaction

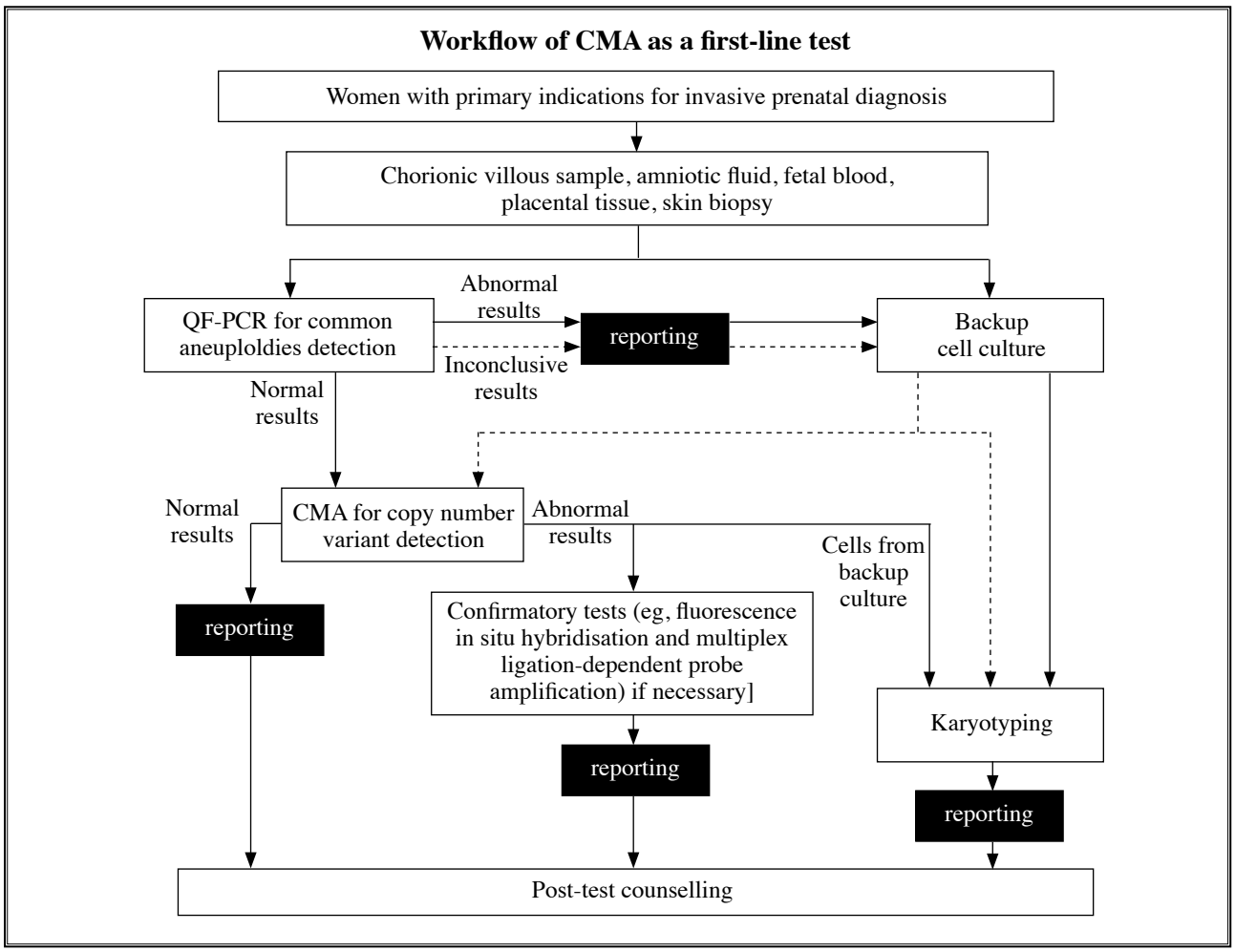

Figure 1. Workflow of chromosomal microarray (CMA) as a first-line test in prenatal diagnosis. Abnormal quantitative fluorescent polymerase chain reaction (QF-PCR) results include trisomies 13, 18, and 21, monosomy X, and triploidy. Inconclusive QF-PCR results indicate unable to conclude normal number of chromosomes 13, 18, 21 and inconclusive result for sex chromosomes. Dotted arrows indicate workflow for samples with inconclusive QF-PCR results.

(QF-PCR) for rapid common aneuploidies detection and conventional G-banded karyotyping. It is offered free to pregnant women with positive Down syndrome screening (including positive non-invasive prenatal test), fetal nuchal translucency ≥3.5 mm, structural abnormalities detected on ultrasound examination, and family history of chromosomal or genetic disorder. This workflow is also offered to women with second trimester miscarriage and stillbirth. These tests are performed by two accredited laboratories: the Prenatal Diagnostic Laboratory at Tsan Yuk Hospital using the Affymetrix CytoScan 750k SNP array and the Prenatal Genetic Diagnosis Centre at the Chinese University of Hong Kong using Fetal DNA Chip. Genetic counselling support is provided by the two clinical teams for complicated cases.

Regarding the new workflow, DNA extracted from fetal sample is subjected to rapid aneuploidies detection by QF-PCR while backup cell culture is set up. If QF-PCR shows normal results, CMA is performed. If QF-PCR shows abnormal results (trisomy 13, 18, 21, monosomy X, and triploidy), conventional karyotyping is performed. For samples with QF-PCR results showing XXX, XXY, and XYY, both CMA and conventional karyotyping are performed, as sex chromosome aneuploidy is unlikely to explain the ultrasound anomaly. CMA is performed using cultured or uncultured cells to rule out submicroscopic CNVs for samples with inconclusive QF-PCR that subsequently shows normal karyotyping results. In fetal samples with maternal cell contamination or inadequate amount of extracted DNA, CMA is performed on cultured cells after QF-PCR testing. Parental CMA is performed to clarify the inheritance of the CNVs detected in the fetal sample as indicated. G-banded karyotyping is performed

for cases with abnormal CMA to confirm the structural rearrangement and to inform future reproductive risk. Further testing such as uniparental disomy testing by short tandem repeat markers to rule out heterodisomy is arranged after discussion with referring doctor if it is clinically indicated.

For CNV interpretation, a 3-tier classification (benign, uncertain clinical significance, and pathogenic) is generally adopted in our laboratory instead of 5-tier (benign, likely benign, uncertain clinical significance, likely pathogenic, and pathogenic), as suggested by the American College of Medical Genetics and Genomics guideline[34]. It does not affect pathogenic variant classification and impact on the diagnostic yield[7]. Interpretation of CNV is more challenging in the prenatal setting than in the postnatal setting, because of the limited phenotype information from ultrasound examination. The clinical significance of CNV depends on its size, gene content, evidence on haploinsufficiency or triplosensitivity, inheritance of the CNV, any previous reports, and relevance between the disrupted gene and phenotype. In general, whole genome CMA enables detection of CNV at size of 100-200 kb on the backbone and at smaller sizes on disease-focused regions.

In accordance to the Royal College of Pathologists 2015 recommendation[35], certain low penetrance neuro-susceptibility CNVs are not reported in the public hospital setting, including proximal 1q21.1 duplications (overlapping RBMBA gene), 15q11.2 BP1-BP2 deletions or duplications (overlapping NIPA1 gene), 15q13.1q13.3 duplications, 16p13.11 deletions or duplications (overlapping MYH11 gene), 16p12.2 deletions (overlapping CDR2 gene), Xp22.31 duplications (overlapping STS gene), and Xp22.33 deletions (overlapping SHOX gene). They have no strong evidence of linking to potential phenotypes on the basis of genes involved for the pregnancy (future child) or have no clinically actionable consequence for that child or family in the future.

Next generation sequencing for CNV analysis

NGS enables analysis of nucleotides variation (using WES) and study of CNVs[36]. Compared with hybridisation technology in CMA, NGS generates sequencing reads that are mapped on chromosomes and quantitatively counted and segmented into region of an equal copy number. These features of NGS are used to developed low-pass (or low-coverage) WGS for CNV analysis. The degree of read depth of this low-pass WGS is approximately an average of 0.25× to 1× with respect to the whole human genome[37-39], meaning that a given nucleotide in a human genome is read once or less than that of an average, as not the whole genome is covered and sequenced. Low-pass WGS is most beneficial in terms of cost per sample, turnaround time, and sensitivity and resolution in CNV detection. Depending on the workflow, 6 to 28 million single end reads of 35 to 51 bp generated from each sample suffice for CNV analysis[36,37,40]. Such NGS-based analysis for CNV detection is referred to as CNV-seq[36,41] or low-pass (or low-coverage) WGS/NGS[37,40].

The main advantage of NGS-based CNV analysis is the ability to adjust platform resolution by in silico manipulation of window size, which can be performed in data processing. This is not possible for CMA platform as its genomic resolution is fixed by the probe density and coordinate although the number of probes and the size of CNV can be defined in data analysis. The NGS-based method can adjust the resolution by altering the number of samples processed within the batch: fewer samples in a batch increase read-count per sample, hence increasing the resolution of imbalances to be detected. The NGS-based method requires relatively low amount of starting genetic material of 100 to 200 ng[36,37], depending on the sequencing platform and protocol. Low-pass NGS-based CNV analysis shares some of the limitations of CMA. It cannot detect polyploidy (except for 69,XXY)[40] and balanced structural rearrangement, unless by increasing sequencing read-depth, which in turn increases the cost per sample. At this low level of read-depth, it cannot detect uniparental disomy, compared with SNP-based CMA. In order to be cost-efficient, samples multiplexing (≥20 samples) is necessary.

Interpretation of CNV detected by low-pass NGS follows the same rules for CMA. Low-pass NGS is a reliable and robust alternative for CNV analysis with shorter turnaround time, higher resolution, capable of detecting lower level of mosaicism (by scaling up the sequencing depth), and improved detection of CNV, compared with CMA. Its clinical utility in prenatal setting has been demonstrated in prospective studies[36,42-44]. A large-scale prospective study in Mainland China involving 3429 women with amniocentesis reported detection of 2.83% pathogenic/likely pathogenic CNV, and 1.43% of variants of uncertain significance[43]. This led to expert recommendation in Mainland China to offer CNV-sequencing as first-line test for prenatal diagnosis under a confined context[45]. As large population scale projects such as the 100 K Genome Project are being conducted, more

data will be generated for NGS-based CNV interpretation, and hence NGS-based CNV analysis is likely to become a first-line test for prenatal diagnosis in the near future.

Whole exome sequencing

The human genome consists of about 3 billion base-pairs, and only 1% to 2% of DNA sequences encode for protein. Exomes refer to genome regions that contain exons, and it is estimated that 85% to 90% of all disease-causing mutations reside in the exome. WES is a type of NGS that focuses on gene exons. Basic workflow of WES starting from DNA extraction and library preparation to massively parallel sequencing on a sequencing instrument can be accomplished in <3-4 days. It is then followed by bioinformatics analysis of sequencing data, result interpretation, literature search, and if necessary, final result verification and inheritance analysis (when trio WES is not performed) using Sanger DNA sequencing. At the moment, the turnaround time of WES for prenatal diagnosis is around 3-4 weeks. In brief, DNA is extracted and fragmented into shorter pieces (200-400 bp) and ligated with adaptors for clonal amplification during sequencing reaction. To select and enrich for exonic regions, capture probes (short oligos that can hybridise to target DNA) are used. In commercially available exome capture kit, the total number of capture probes range from a few hundred thousands to millions to ensure broad and specific coverage of the exome. Once the target DNA is enriched and amplified, it becomes the 'library' for subsequent massively parallel sequencing to produce millions of short sequencing reads. For WES, an average of 100× read depth for proband or a lower threshold of average read depth of 70× for trios analysis is reliable to detect the single nucleotide change[46]. If a lower depth of coverage is obtained, Sanger sequencing should be performed for confirmation.

In prenatal diagnosis, trio WES (of parents and fetus) enables different inheritance analysis models, including de novo, autosomal recessive, autosomal dominant, X-linked recessive inheritance, mitochondrial, and imprinted gene variations (Figure 2). Advantages of trio WES with respect to the efficiency of variant detection and interpretation have been reported[47-49]. Targeted analysis of a gene panel is also plausible for a genetically heterogeneous condition with a clear clinical diagnosis. It has the advantage of focusing on known variants and genes related to the disease of interest, such as Noonan syndrome and skeletal dysplasia. Disease panels usually cover several to tens of genes; thus, the sequencing cost and result interpretation are not as demanding as WES[50].

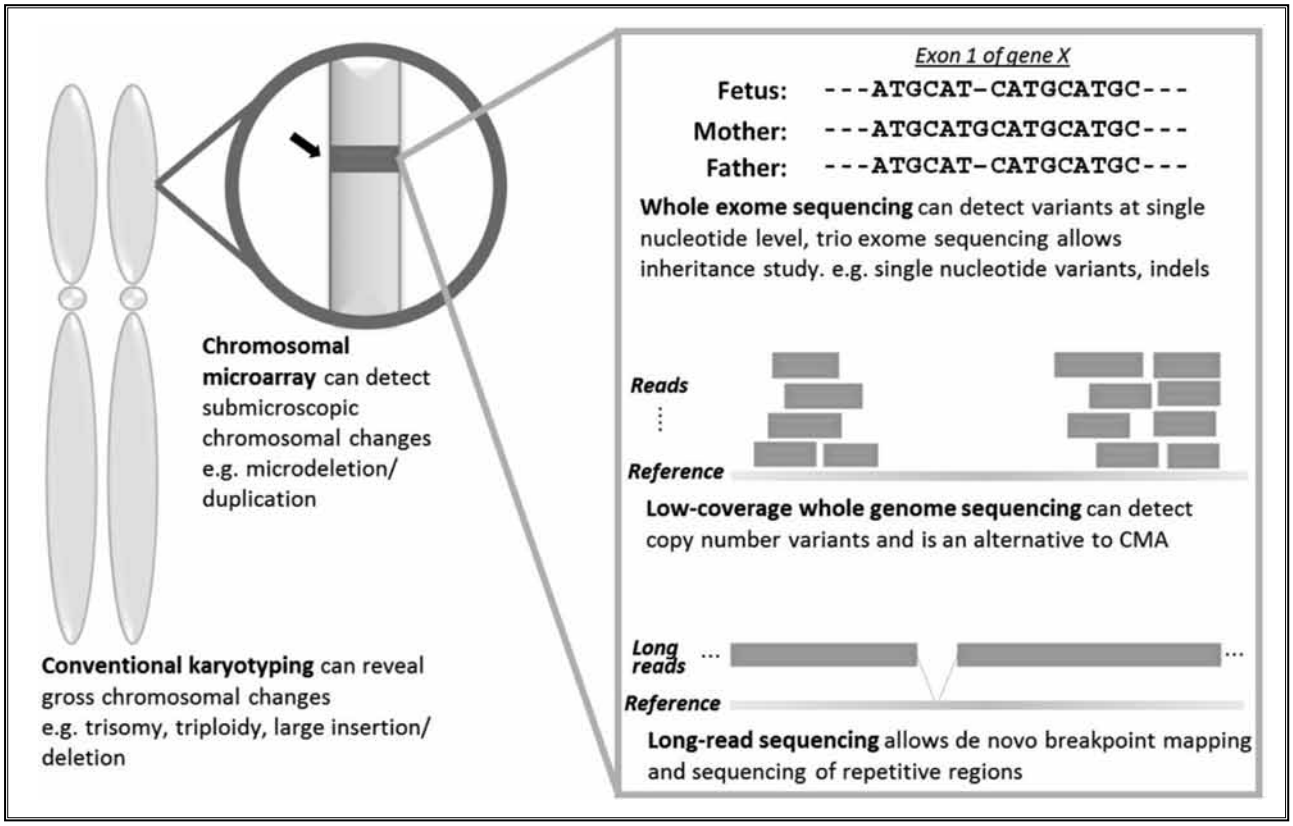

Figure 2. Advances in DNA-based technology in enhancing prenatal molecular diagnosis

Interpretation of WES findings varies among different laboratories and relies on multidisciplinary expertise from clinical scientist, geneticist, and clinicians. Classification of variants is based on the American College of Medical Genetics guidelines[51], and interpretation of the variant is highly evidence-based with reference to the literature, database, and matching clinical phenotypes. Challenges remain in understanding and reporting variants of uncertain clinical significance in the prenatal setting.

WES is mainly applied for prenatal diagnosis of monogenic disorders in fetuses with structural abnormalities. The PAGE study[52] in the UK analysing 610 trios reported an increased diagnostic yield of 8.5% of pathogenic variants and an additional 3.9% variants of uncertain significance that have potential clinical usefulness after exclusion of aneuploidy and large CNVs. Fetuses with multisystem or skeletal anomalies had the highest diagnostic yield of 15.4%. A study in US examining 234 consecutive fetuses using a similar approach reported diagnostic variants in overall 10.3% of fetuses[53]. Fetuses with multiorgan system involvement, skeletal, lymphatic or effusion, central nervous system, and renal anomalies had the highest diagnostic yield of 16% to 24%. Our recent study showed that WES could identify pathogenic variants in 9.1% and variants of uncertain clinical significance in 18.2% of fetuses with structural congenital anomalies that showed normal results in CMA and karyotyping[54]. The diagnostic yield for pathogenic variants in our study was consistent with that in the above studies[52,53].

However, there are limitations to its routine application, including requirement of rapid pipeline for analysis and a multidisciplinary team for timely interpretation of results preferably before 24 weeks' gestation, which is the legal limit of termination of pregnancy in Hong Kong. Other limitations include incomplete coverage of some genomic regions that are difficult to be enriched by the capture method and incomplete prenatal phenotyping by ultrasound examination alone as genotype-phenotype correlation can be weak. In addition, ethical issues include how to obtain adequate informed consent and reporting of incidental or secondary findings in parents' or fetus. Trios analysis may reveal non-paternity and consanguinity. There is also a possibility of reclassification of variants necessitating re-analysis or re-contact of patients. The position statement of the International Society of Prenatal Diagnosis states that diagnostic sequencing should best be offered for evaluation of fetuses under a research setting or in consultation with expert genetic professionals. Other points to consider include[55]: (1) trio approach is preferred for timeliness of result interpretation and pathogenicity assessment; (2) there is limited genotype-phenotype correlation in the fetal period and thus uncertainty on variant interpretation in the prenatal setting; and (3) involvement of a multidisciplinary team with expertise in both clinical and laboratory aspects for informed consent, pre and post-test counselling, and variant interpretation.

Whole genome sequencing for structural variant and chromosomal breakpoint discovery

Large structural variants (up to mega base-pair level) such as deletion, insertion, balanced or unbalanced translocations are studied by CMA (or traditionally by karyotyping). However, CMA is not capable of identifying chromosomal breakpoint at the nucleotide level. Several techniques have been developed to map chromosome breakpoints to the kilo base-pair (kb) level[56-62]. However, these techniques are time-consuming, expensive, and do not provide enough information of the breakpoint-linked SNPs for haplotyping analysis[63]. The advent of third-generation long-read sequencing has improved the definition of structural variants and their breakpoints, and there is growing interest in exploring the landscape of structural variants in the germline of a large number of genomes[64].

Third-generation long-read sequencing, or single molecule sequencing, refers to sequencing a DNA molecule continuously up to 80 kb (Figure 2). By mapping the long sequencing reads to the reference genome, large chromosomal changes can be detected, and their precise locations can be pinpointed to determine if any genes are involved. In highly repetitive regions of the genomes or GC-rich loci, long-read sequencing is feasible with a low error rate. Popular long-read sequencing platforms include single-molecule real-time technology by Pacific Biosciences and Oxford Nanopore sequencing technologies[65,66].

There are reports on single-molecule real-time long-read sequencing in detecting AGG interruptions in females with a FMR1 premutation for fragile X syndrome. The single-molecule real-time platform is the only technology so far that can separate the two repeats derived from different X-chromosomes, and hence is superior to PCR-based assays[67,68]. Long-read sequencing by Nanopore sequencing technologies on preimplantation genetic testing on chromosomal structural rearrangement can distinguish the balanced reciprocal translocation carrier embryos from

the euploid non-carrier embryos for transfer[63]. Library preparation for Nanopore sequencing can be completed in 90 minutes. The long-read sequencing results enable high-resolution breakpoint mapping, which can narrow down the region of interest for verification through Sanger sequencing, if necessary. There appears to be a lack of literature on using long-read sequencing and WGS on the study of structural variants and chromosomal breakpoints in the prenatal setting. A modified WGS 'jumping library' approach (a 13-day sequence and analysis pipeline) for genetic diagnosis of CHARGE syndrome in a single prenatal sample showed a direct disruption of CHD7 gene caused by a translocation breakpoint at 8q12.2[61]. It is technically feasible to generate whole fetal genome from cellular and cell-free DNA from amniotic fluid sample[69]. However, the high cost, turnaround time, and interpretation of high number of variant calls make such WGS difficult to be applied for clinical use in the near future.

Conclusion

Since June 2019, a new prenatal diagnostic workflow has been implemented in Hong Kong public hospitals, integrating CMA, QF-PCR, and conventional G-banded karyotyping. The next challenges are to accumulate experience in WES in terms of diagnostic workflow and result interpretation, and pre- and post-test counselling. Multidisciplinary input from clinical geneticists, obstetricians, clinical scientists, and genetic counsellors facilitates interpretation and understanding of WES results. However, application of long-read sequencing and WGS for structural variant and breakpoint analysis is limited, owing to the high cost and a lack of validated data analysis tools. Their potential utility in prenatal diagnosis remains to be explored.

Declaration

The authors have no conflicts of interest to disclose.

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Ogilvie syndrome following Caesarean section: a case report

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A 31-year-old woman with a previous Caesarean section developed distended abdomen 1 day after a repeat Caesarean section. Radiological images showed dilated large bowel with suspicious transition point posterior to the uterus, but without mechanical cause for the obstruction. Colonoscopy showed no stricture or tumour or extrinsic compression, and a diagnosis of acute colonic pseudoobstruction (Ogilvie syndrome) was made. Endoscopic decompression using a flatus tube was successful.

Keywords: Cesarean section; Colonic pseudo-obstruction; Intestinal pseudo-obstruction; Postpartum period

Case presentation

In January 2018, a 31-year-old woman with a previous Caesarean section underwent an elective lower segment Caesarean section under spinal anaesthesia at 38 weeks of twin pregnancy. There was no complication and the estimated blood loss was 200 mL.

At postoperative day 1, the patient had nausea and vomiting. On physical examination, distended abdomen and hyperactive bowel sounds were noted, with no bowel opening. Abdominal radiograph showed dilated large bowel but no rectal gas (Figure a). Large bowel obstruction[1] was suspected, and contrast computed tomography of the abdomen and pelvis was performed to exclude intestinal obstruction or bowel injury, with a nasogastric tube inserted. Computed tomography confirmed dilated large bowel of up to 6.2 cm at the transverse colon (Figure b), with suspicious transition point at the sigmoid colon posterior to uterus but no stricture or tumour or extrinsic tumour. In view of intestinal obstruction of unknown cause, emergency colonoscopy was performed by a surgeon to identify any mechanical or extrinsic causes of obstruction such as compression by the postpartum uterus. Colonoscopy showed dilated large bowel from caecum with rectum but no stricture or tumour or extrinsic compression. The diagnosis of acute pseudo-obstruction was made, and a flatus tube was inserted for decompression.

At postoperative day 2, distention decreased and nasogastric tube yielded minimal output. Radiographs showed reduced bowel distention, and the flatus tube was removed on day 3. Diet was resumed on day 4, and the patient was discharged on day 5.

Discussion

Acute colonic pseudo-obstruction (Ogilvie syndrome), characterised by massive dilatation of the colon in the absence of mechanical obstruction, is rare and potentially life-threatening. It often presents with abdominal distention and pain, and is associated with major surgeries, trauma, infection, and sepsis. Up to 5% of cases are associated with Caesarean section or pregnancy[2], with a reported incidence of up to 1 in 1500 deliveries[3]. Between 2002 and 2016, 66 postpartum cases were reported globally, and 28 (43%) of which resulted in bowel perforation or impending ischemic perforation[4]. To the best of our knowledge, this is the first confirmed postpartum case in Hong Kong[5].

The precise mechanism by which colonic dilatation occurs remains unknown, and the goal of management is to decompress the colon to minimize the risk of perforation and ischemia. Main modalities of decompression include neostigmine, colonoscopic decompression, percutaneous decompression, and surgical decompression.

In our patient, a suspected transition point posterior to the uterus was suggestive of mechanical obstruction. Emergency colonoscopy was performed by a surgeon to identify any mechanical or extrinsic obstruction. The diagnosis of pseudo-obstruction was made endoscopically, and a flatus tube was inserted for decompression. Medical

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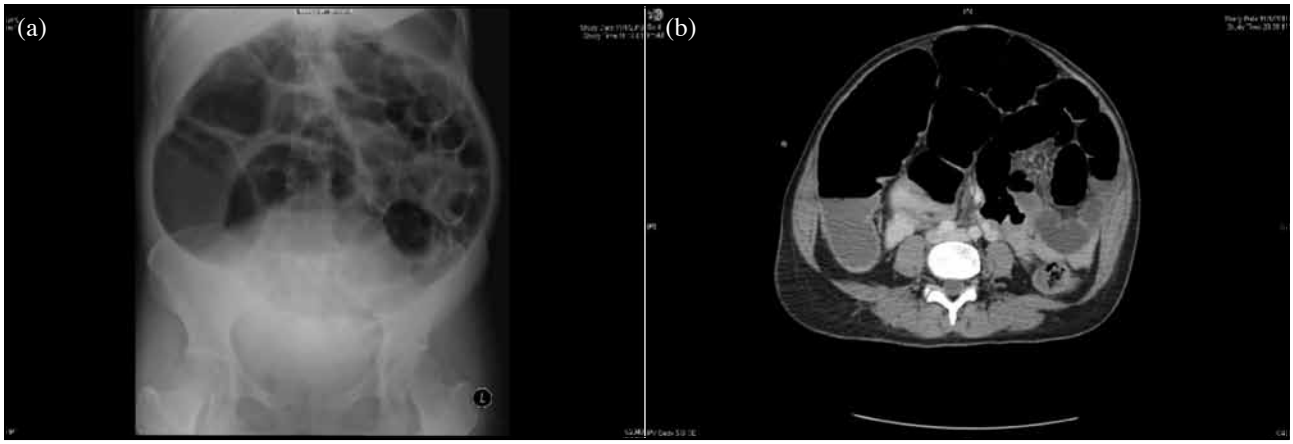

Figure. (a) Radiograph and (b) computed tomography image of the abdomen and pelvis showing dilated large bowel at the transverse colon, with suspected transition point at the sigmoid colon posterior to uterus.

therapy (neostigmine) was not considered, as mechanical obstruction was suspected and had to be ruled out[6].

Ogilvie syndrome should be considered a differential diagnosis for abdominal pain and distention following Caesarean section. Physical examination and abdominal radiography are important in early detection.

Declaration

This case report has been presented as a poster at Hong Kong College of Obstetricians and Gynaecologists 30th Anniversary Symposium in June 2018

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Whole exome sequencing for prenatal diagnosis of CHARGE syndrome: a case report

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We report a prenatal case of CHARGE syndrome with multiple fetal structural abnormalities detected on ultrasonography despite normal karyotype and chromosomal microarray results. Whole exome sequencing of the fetus identified a pathogenic, *de novo* mutation in *CHD7*, and hence CHARGE syndrome was molecularly confirmed. The challenges in prenatal diagnosis of CHARGE syndrome by clinical features are discussed, as are the usefulness and limitations of whole exome sequencing in prenatal diagnosis.

Keywords: CHARGE syndrome; Prenatal diagnosis; Whole exome sequencing

Case presentation

In October 2018, a 34-year-old Chinese woman was referred to United Christian Hospital for multiple fetal structural abnormalities detected on morphology scan. She was gravida 2 with one previous normal full-term vaginal delivery. Her family history was unremarkable. Her second-trimester biochemical Down syndrome screening was negative, with a calculated risk of 1 in 49 000. Ultrasonography at 22 weeks detected multiple fetal abnormalities, including Dandy walker variant anomaly, median cleft lip, hypoplastic left heart syndrome, and absent stomach bubble (Figure 1). Amniocentesis followed by rapid aneuploidy detection by quantitative fluorescent polymerase chain reaction showed normal copy numbers of chromosomes 13, 18, and 21. The patient opted for termination of pregnancy at 22 weeks and 4 days of gestation in view of fetal multiple congenital anomalies before karyotype and chromosomal microarray results were available. The termination was uneventful.

Karyotyping showed 46,XY but chromosomal microarray result was normal. Autopsy of the fetus revealed cerebellar vermis hypoplasia, median cleft lip and palate, aorta isthmic hypoplasia, absent right brachiocephalic vein and artery, and clinodactyly of right fifth finger (Figure 2). The heart valves and the four cardiac chambers were unremarkable. Chona were patent and the oesophagus and stomach were normal. In view of multiple fetal abnormalities despite negative karyotype and chromosomal microarray results, whole exome sequencing (WES) was performed, and a NM_017780.4:c.2959C>T:p.(Arg987Ter) mutation in exon 12 of *CHD7* was identified. Parental analysis showed that neither parent carried the variant, indicating the variant was *de novo* in origin. According to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for interpretation of sequence variants[1], the mutation was pathogenic and indicated CHARGE syndrome. Sanger sequencing was performed for validation. The risk of recurrence in future pregnancy was 1% to 2% owing to the risk of gonadic mosaicism[2].

Discussion

CHARGE syndrome (OMIM number 214800) is a rare, usually sporadic disorder caused by loss-of-function mutations in *CHD7*, which is of autosomal dominant inheritance[3]. Loss-of-function mutation refers to mutation that results in a premature stop of the transcription of the gene and a non-functional truncated protein. The CHARGE acronym summarises the features commonly found postnatally: Coloboma of eye, Heart defects, Atresia choanae, Retardation of growth, Genital abnormalities,

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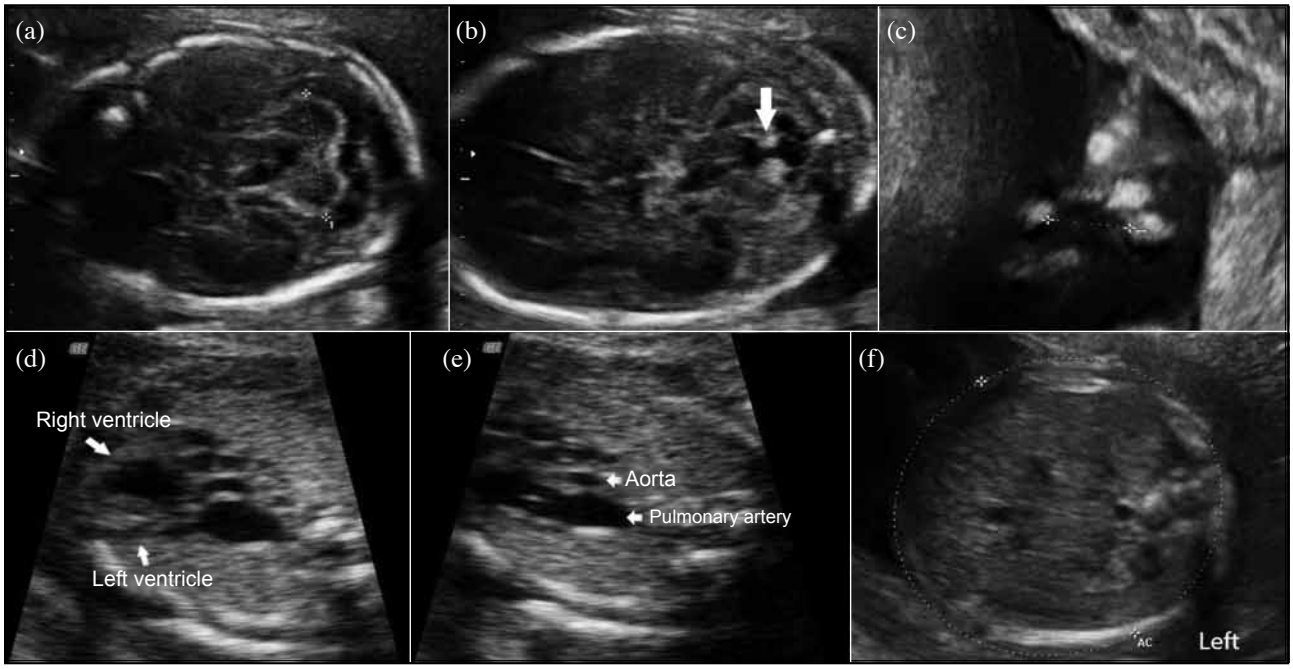

Figure 1. Prenatal ultrasound at 22 weeks' gestation showing (a) normal cerebellar hemispheres and posterior fossa (transcerebellar diameter=2.28 cm), (b) a defect in the inferior cerebellar vermis (arrow) that communicates with the 4th ventricle signifying Dandy walker variant anomaly, (c) median cleft lip (size=1.00 cm). (d) Four-chamber view and (e) three-vessel view showing hypoplastic left heart with narrow aorta and (f) absent stomach bubble on transverse view of the abdomen.

Figure 2. Abortus showing (a) median cleft lip and palate, (b) external ear abnormality, (c) clinodactyly of right fifth finger.

and Ear abnormalities/deafness. Its incidence ranges from 1 in 8500 to 10000 live births[4,5]. The phenotypic presentations are highly variable and involve multi-organ systems. Orofacial cleft, oesophageal atresia, and limb defects are common features. Based on the frequency and specificity of a distinct set of anomalies, all four major criteria (coloboma, choanal atresia, characteristic ear abnormalities, cranial nerve dysfunction) or three major and three minor criteria (genital hypoplasia, developmental delay, cardiovascular malformations, growth deficiency, orofacial cleft, tracheoesophageal fistula, distinctive face) must be exhibited in order to fulfil the diagnosis of CHARGE syndrome[5]. Major criteria also include cranial nerve anomalies, including weak chewing or sucking, facial palsy, sensorineural hearing loss, balance vestibular problems, and swallowing problems. Among patients with CHARGE syndrome, 92% exhibit at least one cranial nerve anomaly and 72% more than one. Isolated cranial nerve involvement is rare[6].

Prenatal diagnosis of CHARGE syndrome is challenging as prenatal ultrasound may not be able to diagnose coloboma or choanal atresia, and growth retardation only arises postnatally. Moreover, cranial nerve dysfunction and mental retardation cannot be assessed before birth. A case series identified three constant features in all 10 fetuses: bilateral and asymmetric external ear abnormalities, semicircular canal hypoplasia or agenesis, and arhinencephaly (lack of olfactory tracts); intrauterine growth retardation was never observed[7]. The case series subsequently expanded to include 40 cases and identified some novel features in fetuses that differed from living affected patients. Features such as coloboma, developmental delay, genital anomalies, and growth retardation were uncommon or missed in fetuses, and 16 of the 40 cases would have been missed if postnatal

CHARGE diagnostic criteria were used. Thus, criteria for diagnosing fetal CHARGE syndrome should include at least four of the six major criteria (external ear anomalies, heart defects, semicircular canal agenesis/hypoplasia, arhinencephaly, coloboma, and choanal atresia or cleft) or three major and two of eight minor criteria (central nervous system anomalies, limb anomaly, genital anomalies, thymic hypoplasia/agenesis, polyhydramnios, renal anomaly, skeletal anomaly, and oesophageal anomalies), and absence of intrauterine growth retardation[8].

Establishing the diagnostic criteria for fetal CHARGE syndrome aids prenatal detection and hence proper counselling. Although our case had some major features (cleft lip/palate and congenital heart defect) and minor features (vermis hypoplasia and limb anomalies), neither the clinical nor the pathological features documented were sufficient to fulfil the diagnostic criteria of fetal CHARGE syndrome. One reason is that major features such as arhinencephaly and semicircular canal agenesis are not routinely examined histopathologically. This highlights the importance of detailed fetal autopsy including neuropathological examination for diagnosis. Focused ultrasonography and fetal magnetic resonance imaging are recommended for assessment of external ear abnormalities, choanal atresia, semicircular canal agenesis, and arhinencephaly. However, expertise is often not readily available in routine practice.

Next-generation sequencing is a high-throughput sequencing technology that sequences DNA in a massively parallel manner. It can be classified into three categories: targeted gene panels, WES, and whole genome sequencing (WGS). WES sequences the protein-coding part of the genome, which represents 1.5% to 2% of the genome (about 30 megabases). WGS sequences every nucleotide in the whole genome, which is equivalent to approximately 3.3 gigabases, and covers non-coding and inter-genic regions. Next-generation sequencing is widely used for diagnosing complex diseases that involve a large number of genes. WES/WGS is more cost-effective than sequencing individual genes sequentially. Over 85% of known disease-causing mutations are found in exome, and therefore WES is a reasonable approach for diagnosing some diseases to reduce cost and data storage. However, WES may miss a pathogenic variant in a non-coding region of the genome. WGS may be preferable to WES when the cost decreases and more information about the role of non-coding DNA in human diseases becomes available. However, WGS may unexpectedly cover many variants of uncertain significance that makes clinical interpretation more challenging. Sanger sequencing, which is first-generation DNA sequencing technology, has >99.99% accuracy for most genes sequenced and remains the gold standard for diagnosis. Therefore, Sanger sequencing is generally performed to confirm any variant reported as pathogenic by WES or WGS as secondary validation[9,10].

Conventional prenatal cytogenetic test of karyotype allows low-resolution detection of chromosomal abnormalities. Although chromosomal microarray analysis offers higher detection rate of copy number variants, it still cannot detect point mutations and small insertion-deletion mutations that cause >4600 known single gene disorders and others yet to be characterised. Some phenotypes can be caused by mutations in different genes. Our case is an example of CHARGE syndrome overlapping with DiGeorge syndrome, VACTERL association, renal coloboma, and Feingold or anophthalmia-oesophageal-genital syndromes. Owing to limitations of prenatal imaging and the fact that intellectual disability, minor birth defects, and dysmorphic features can only be ascertained after birth, comprehensive, unbiased genetic diagnosis prenatally using next-generation sequencing is needed[11].

Although WES is an invaluable tool for genetic diagnosis in paediatrics, it is still not widely adopted in prenatal diagnosis. WES is useful in prenatal cases with multiple fetal anomalies identified by ultrasound but without a particular syndrome being diagnosed. A local study evaluated the usefulness of WES in prenatal diagnosis of fetuses with structural anomalies detected on ultrasound but with normal chromosomal microarray results[12]. 33 families were recruited to undergo trio-based WES. Pathogenic mutations were identified in 9.1% of fetuses, including mutations in *DNAH11*, *RAF1*, and *CHD7* genes, which were associated with primary ciliary dyskinesia, Noonan syndrome, and CHARGE syndrome, respectively. Variants of uncertain significance were detected in 18.2% of fetuses. In a prospective multicentre study of 34 units in the United Kingdoms, 610 fetuses with structural anomalies after exclusion of aneuploidy and large copy number variants were analysed by trio-based WES[13]. A pathogenic genetic variant was identified in 8.5% of fetuses; the variant was present in 15.4% of fetuses with multisystem anomalies, 11.1% of fetuses with cardiac anomalies, and 15.4% of fetuses with skeletal anomalies. And 3.9% of fetuses were found to have a variant of uncertain significance. WES is useful to diagnose monogenetic disease in fetuses with structural anomalies despite normal cytogenetic findings. In 2018, the International Society for Prenatal Diagnosis, the Society for Maternal Fetal Medicine, and the Perinatal

Quality Foundation published a joint position statement and recommended the use of diagnostic genome wide sequencing for evaluation of fetuses with single major anomaly or with multiple organ system anomalies that are suggestive of a possible genetic aetiology, but with uninformative chromosomal microarray results. Nevertheless, the routine use of diagnostic prenatal sequencing cannot be supported until more validation studies are available. Currently, WES and WGS are ideally performed in the research setting[14].

WES aids a definite genetic diagnosis so that proper counselling on fetal prognosis can be provided and appropriate management plan can be arranged. In addition, WES enables estimation of the risk of recurrence in future pregnancy so that future reproductive decision including preimplantation genetic testing and early prenatal diagnosis can be discussed. However, there are limitations and ethical considerations for prenatal WES. The cost of WES may be a financial burden to parents. There are time constraints from sample retrieval to obtaining genetic results and the time limit on gestation for termination of pregnancy. Women may have unrealistically high expectations of test performance and may be disappointed or falsely reassured conversely when no causative mutations are discovered. WES may incidentally reveal gene mutations that are unrelated to the initial indications for the test including unexpected childhood disorders, cancer-susceptibility genes, and adult-onset disorders. Variants of uncertain significance is also found at relatively high incidence and their significance on the future outcome of the baby can be difficult to determine[15]. Therefore, comprehensive pre- and post-test counselling from an expert in genetics is crucial when offering the test.

Conclusion

WES is useful to aid in prenatal diagnosis of CHARGE syndrome. WES has an increased diagnostic yield for the genetic diagnosis of fetal structural anomalies when cytogenetics or chromosomal microarray analysis showed normal results. However, the cost and turnaround time of WES is a concern. Variants of uncertain significance and incidental findings of other genetic diseases are major challenges for applying WES in prenatal diagnosis. Appropriate case selection is crucial to maximise its benefit in prenatal diagnosis.

Declaration

The authors have no conflict of interest to disclose.

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WNSC HK expert interview with Dr Jose Hurtado

The emerging science behind the role of the microbiota in mastitis

Dr Jose Hurtado

Section Chief of Paediatrics Service, Hospital Universitario Virgen de las Nieves, Granada, Spain

How does mastitis arise and how is the human milk microbiome implicated?

Dr Hurtado: **Lactational mastitis is an inflammation of the breast tissue during lactation and may be triggered by mammary dysbiosis – a disruption in the natural balance of the mammary microbiota** due to a proliferation of pathogenic bacteria.[1] When mastitis occurs, an overall decrease in the diversity of the human milk microbiota may be observed,[2] with an overgrowth of certain bacterial species such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, with a decrease in the population of lactobacilli.[3,4]

Mammary dysbiosis and subsequently mastitis is primarily caused by milk stasis, which can result from poor breastfeeding techniques such as incorrect latching of the infant or inadequate emptying of the breast.[5] **The overgrowth of staphylococci in breast tissue can lead to the formation of biofilms which progressively obstruct the milk ducts, causing increased pressure in the glands, breast pain and engorgement.**[6] Women who are at heightened risk of mastitis include those who have received antibiotics around the time of childbirth, women who wear tight fitting clothes or bras, women inexperienced with breastfeeding (first-time mothers), women with an oversupply of milk (second-time mothers), and those with a previous history of mastitis.

Other sharing from Dr Hurtado:

- What is the composition, origin and functional significance of the microbiota in human milk?
- With human milk as the primary source of nutrition for many infants, what are the implications of an imbalanced human milk microbiota on an infant's health and development?
- Which interventions can modulate a healthy microbiome in human milk, and what data is available to support its use?
- Are there any safety concerns with the use of probiotics during lactation?
- Practical tips for healthcare professionals

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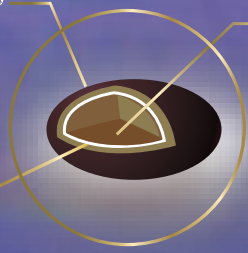
1 Gastro-Protective Technology

2 Softgel Coating



3 Iron with patented Technology

Iron protected by patented chelation technology (Ferrous Bisglycinate) and stays intact in the stomach with reduced GI intolerance^

BRAND CHOICE**
Among private O&G HCPS
One capsule a day containing DHA + Multi Vitamins & Minerals
Perinatal multi-nutritional supplement

Nestlé
Start Healthy Stay Healthy™
1st 1000 Days Allergy Prevention Program

For pre-pregnant, pregnant and lactating women. Need to accommodate with a balanced diet and moderate exercise. #Each capsule contains 200 mg DHA meeting 100% of the WHO/ FAO recommended daily requirements during pregnancy and lactation *Source: IQVIA 2018 HCP tracking study among healthcare professionals with specialty in obstetrics/gynecology/pediatrics in HONG KONG. Sample size is 80. (For the category of perinatal multi-nutritional supplement containing DHA + multi vitamins & minerals) ^Pineda, O., et al. (1994). Effectiveness of iron amino acid chelate on the treatment of iron deficiency anemia in adolescents. Journal of Applied Nutrition, 46(1), 2-13. INFORMATION FOR THE MEDICAL PROFESSION ONLY. NAN 201906 - 020 HKG