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EDITORIAL

ORIGINAL ARTICLES (OBSTETRICS)

ORIGINAL ARTICLES (GYNAECOLOGY)

REVIEW ARTICLES

HealthBaby
生寶臍帶血庫

Most Professional Accreditations
Most Recommended by O&G Doctors[1]
>90% Market Share[2]

HealthBaby's
Cord Service Patented Technology

H.K. Patent

- H.K. FIRST cord storage service[3]
- Obtained H.K. patent
- Exclusively extracts the whole cord tissue
- Unique processing, storage and culturing techniques
- Enhances the cells' quantity and viability after thawing

Source: 1. IMS 2010 Cord Blood Bank Market Research in Hong Kong (with Private O&G physicians) 2. Ipsos Healthcare 2018 Cord Blood Bank Survey
3. Introduction to the Cord Tissue Market and Cord Tissue-Derived Mesenchymal Stem Cells (CT-MSCs)", BIOINFORMANT, Jun 2015

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Gestational Diabetes Mellitus Fact Sheet

Hyperglycemia is a common medical condition during pregnancy and over 80% of these cases are due to gestational diabetes mellitus (GDM) that is defined as "any degree of glucose intolerance with onset or first recognition during pregnancy"[1, 2].

Risk Factors of Hyperglycemia in Pregnancy[3, 4]

Medical history

- ☑ Polycystic ovarian syndrome
- ☑ Autoimmune disease
- ☑ Chronic hypertension
- ☑ Long-term use of medicines with diabetogenic

Personal/Family history

- ☑ Maternal age ≥ 35 years
- ☑ Obesity (BMI ≥ 25 kg/m^2 before pregnancy or at
- ☑ Family history of diabetes in 1st degree relative

Past pregnancy

- ☑ Previous macrosomic baby (≥ 4 kg/9 lbs)
- ☑ Previous GDM or diabetes during pregnancy

Present pregnancy

- ☑ Multiple pregnancy

In Hong Kong, it is speculated that at least 20% pregnant women have GDM as per figures in 2016[5]

Height and weight[6]

- Chinese women with height < 158 cm were at increased risk
- Overweight/obesity at the 1st antenatal visit further elevated the risk

Vitamin D

- Low vitamin D status may increase the risk of GDM[8, 9]
- Supplementing vitamin D helps ameliorate GDM conditions[8]

Latest Science on GDM

Exercise[7]

- Japanese women with GDM who walked ≥ 6,000 steps daily had significantly lower casual glucose level

Gut microbiome[10]

- Gut microbiota dysbiosis was associated with GDM

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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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WHO = World Health Organization; CDC = Centers For Disease Control and Prevention; ACOG =American College of Obstetricians and Gynecologists * In Hong Kong Market, as of Nov 2018

Reference:

1. Boostrix Hong Kong Full Prescribing Information 2018. **2.** Sanofi Tdap Hong Kong Full Prescribing Information 2017. **3.** CDC. Pertussis - Clinical Complications 2015. Available at: https://www.cdc.gov/ pertussis/clinical/complications.html (accessed Nov 2016). **4.** De Serres G, et al. Journal of Infectious Diseases 2000;182:174-179. **5.** ACOG Committee Opinion. Update on immunization and pregnancy: tetanus, diphtheria, and pertussis vaccination. Number 718, September 2017. [accessed June 2018]; Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Immunization-Infectious-Disease-and-Public-Health-Preparedness-Expert-Work-Group/Maternal-Immunization **6.** CDC. Pregnancy and Whooping Cough. Vaccinating pregnant patients. [accessed June 2018]; Available at: https://www.cdc.gov/pertussis/pregnant/hcp/pregnant-patients.html **7.** WHO. Pertussis vaccines: WHO position paper. Weekly epidemiological record. 2015;90(35):433-458.

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Editorial
Genetic training for obstetricians and gynaecologists

One of the major breakthroughs in obstetrics and gynaecology practice in the last decade is clinical application of advanced genomic technology. The advancement is multi-dimensional: from traditional cytogenetics to high-resolution molecular karyotyping using chromosomal microarray (CMA)[1] and whole exome sequencing (WES)[2]; from invasive prenatal diagnostic approach to non-invasive prenatal testing using circulating fetal cell-free DNA[3]; from prenatal genetic testing to pre-implantation genetic testing[4]; the scope of carrier screening is also expanded from a few individual hereditary diseases to a more comprehensive panel of multiple diseases using WES[5]. Advances in genetics and genomics have affected not only the practice of fetal medicine, but also reproductive medicine and gynae-oncology.

Genetic technology enables a more precise genetic diagnosis, a safer clinical approach, and a faster reporting time. However, this also brings medical, legal, and ethical concerns that should be carefully handled. Very often there are no straightforward or uncontroversial answers to these concerns. What practice is acceptable to society depends not only on the accuracy of the tests but also the cost and contemporary medical knowledge, which all change rapidly with time.

1. How far should we investigate on a genetic diagnosis for a suspected fetal abnormality?

When a fetal malformation is identified, we used to perform amniocentesis and karyotyping to look for any chromosomal abnormalities. Many fetal malformations are associated with a number of microdeletion syndromes that would be missed by karyotyping[6], so we often offer CMA for fetal diagnosis. The Hospital Authority is considering replacing karyotyping with CMA as the primary prenatal diagnostic test in 2019. If CMA results are normal, should we counsel the parents about the small chance of monogenic disorders, and advise further investigation? Sometimes the presence of specific ultrasonic phenotypes may guide us to do specific genetic tests (eg Noonan panel), but very often the prenatal phenotypes are unspecific[7]. A more comprehensive survey by WES may be useful. The positive yield of WES in abnormal fetal cases but normal karyotyping and CMA can be as high as 24%[8]. As prenatal WES is relatively more affordable and the reporting time is faster than before, parents have the right to know and make the choice, especially if they want to keep their fetus. However, such prenatal counselling to patients could be time consuming, anxiety-causing, and disheartening when the test is neither affordable nor covered by the public health care.

2. How much genetic information should we report to our clients?

Although CMA allows detection of fetal microdeletion syndromes[6], the resolution of CMA is so good that it can incidentally reveal copy number variants of unknown clinical significance, or those associated with largely variable and unpredictable phenotypes. Reporting these uncertain findings to the parents, could result in unnecessary anxiety, making prenatal counselling difficult and consequently leading to an innocent pregnancy termination. Nonetheless, if these uncertainties remain unreported and the fetus is born with birth defects or developmental disorders, clinicians may have to bear the medicolegal responsibility of the missed diagnosis, or deprive the parent of the right to know and a chance to consider termination of pregnancy. Vastly different from the postnatal setting, more but uncertain information could be troublesome in prenatal diagnosis and counselling[9].

3. To what extent should we screen for the parental carrier status of hereditary diseases?

In both public and private sectors, screening of parental thalassemia status is routinely offered in prenatal setting, because thalassemia trait is relatively prevalent in Chinese (5%-10%), and screening by taking peripheral blood for mean corpuscular volume of the parental red cells is simple, accurate, and inexpensive. The intervention option available to affected parents is termination of an abnormal pregnancy. However, carrier screening for other rarer hereditary diseases (autosomal recessive) may not be cost-effective in the public setting, unless there is a strong family history or other risk factors such as consanguineous marriage. Nonetheless, expanded carrier screening is readily available at an affordable price[10]. Multiple hereditary diseases can be screened by a single blood

sampling and sequencing test during antenatal check-up, before conception, or even before assisted reproductive treatment. Should married couples also be informed of the potential benefits of such test, and allow them to decide if it is worth to pay for the test[11]? Although the carrier rates of individual genetic diseases are usually lower than that of thalassemia (eg, spinal muscular atrophy: 1/50; fragile X disease: 1/1000 women)[12], preliminary data have shown that the chance of detecting at least one genetic disease in Hong Kong Chinese women using a commercially available panel could be as high as 40%, even after exclusion of thalassemia[13].

Practitioners should update their knowledge and skills on genetic and genomic technology to provide the best advice and management. Professional organisations should provide structured training to maintain the quality of care. The Hong Kong College of Paediatricians has established the subspecialty of genetics and genomics in 2017 (http://www.paediatrician.org.hk/index.php?option=com_content&view=article&id=277&Itemid=125), and accredited first five fellows of this subspecialty. A 3-year subspecialty training program has also been started. The Hong Kong College of Obstetricians and Gynaecologists has not set up a similar subspecialty or training program, although genetics is a component of the curriculum of maternal fetal medicine. As knowledge in genetics involving obstetrics and gynaecology has expanded quickly, it is time for our College to review the current curriculum to enhance the genetic training and to accredit relevant genetic qualification, in order to improve the quality of professional care and meet the needs of our society. In addition, our College may also draft clinical guidelines regarding the practice of genetic counselling and investigation. These are challenging tasks, as they require a lot of work by experts in the genetic field, which are in short supply in Hong Kong. Hence our College must work closely with the Hospital Authority and both universities in Hong Kong to complete the missions.

Unlike skill-based surgical training, clinical genetics requires a strong foundation of knowledge in a variety of rare diseases. The Hong Kong College of Paediatricians values the knowledge-based education in the 3-year genetic and genomic subspecialty training program. If a subspecialty trainee has completed a relevant Master of Science course in genetics, 6 months of clinical training can be exempted. Our College may also take this as a reference when we construct our training program. Of course, practical components such as clinical attachments and logbooks are mandatory. Both universities have Master of Science or diploma courses on clinical genetics, and a number of maternal fetal medicine subspecialists have completed the Master of Science in Medical Genetics at the Chinese University of Hong Kong, which is a quotable qualification approved by the Hong Kong Medical Council. However, our College has no consensus on how to position genetics in the training structure. Possible options include a separate subspecialty in genetics, or a combination of fetal medicine and genetics, or 'genetic counselling' as a special skill training and accreditation (similar to laparoscopy and colposcopy training). The last option has advantages that it is not confined to fetal medicine subspecialists, and the training program can be constructed independently from subspecialties.

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Skill retention at 6 versus 12 months after simulation training in singleton vaginal breech delivery: a randomised controlled study

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Introduction: Current evidence suggests that annual simulation training is adequate to maintain skills for management of vaginal breech delivery. This study aimed to investigate whether skill levels declined at 6 months and further declined at 12 months after training.
Methods: In this randomised single-blinded study, 12 obstetricians and 42 midwives were assigned at random to attend a 1-hour training session (lecture and simulation on singleton vaginal breech delivery) conducted at month 0 (control group) and at month 6 (intervention group). Their skill score was assessed before training (pre-test), immediately after training (at-test), and 12 months after training (post-test).
Results: Compared with the pre-test score, skill scores increased immediately after the simulation training (at-test) in the intervention group (7.98 vs 15.03, p<0.001) and in the control group (6.86 vs 14.92, p<0.001). Compared with the at-test score, skill scores decreased 6 months after the training (post-test) in the intervention group (15.03 vs 9.57, p<0.001) and 12 months after the training in the control group (14.92 vs 9.74, p<0.001). However, post-test skill scores were better than pre-test skill scores. The two groups were comparable in terms of the decline in skill score from at-test to post-test (-5.49 vs -4.90, p=0.606).
Conclusions: Simulation training results in short-term and long-term improvements in vaginal birth delivery skills. However, skill scores degrade over time and ongoing training at a minimum of 12-month interval is suggested for obstetricians and midwives.

Keywords: Breech presentation; Obstetrics; Simulation training

Introduction

Breech presentation occurs in 3% to 4% of all term deliveries and more commonly in premature deliveries. Perinatal mortality and morbidity is significantly higher in planned vaginal breech delivery than planned Caesarean sections[1], but the optimal mode of delivery remains controversial, especially when Caesarean section causes a significant mortality and morbidity risk to the mother[2,3]. Clinicians may encounter unavoidable vaginal breech delivery cases such as vaginal delivery upon maternal request, preterm delivery, multiple pregnancies, breech presentation when labour is well advanced, and risk of Caesarean section outweighs that of vaginal breech delivery.

Since the Term Breech Trial in 2000, the incidence of vaginal breech delivery has declined[4-8]. There are concerns that unless vaginal breech delivery is routinely practiced, skill transfer to young doctors and midwives will not be efficient and may affect patient safety[4,6]. Simulation training enables training in a safe and non-clinical environment without any risk to patients. Low- and high-fidelity training models and simulators have been shown effective to improve the technical performance of medical staff[9-11]. Simulation training improves resident performance in the management of vaginal breech delivery[12,13]. Nonetheless, knowledge and skills decline over time, and regular educational activities should be carried out to reinforce knowledge and skills[14].

The Clinical Negligence Scheme of Trust suggests annual training to maintain emergency obstetrics skills such as vaginal breech delivery[15]. We hypothesise that skills start to decline as early as 6 months after training and decline further by 12 months. This study aimed to evaluate the level of skill retention at 6 and 12 months after simulation training and to determine the optimal frequency of training required to maintain effective vaginal breech delivery skills.

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Methods

This randomised controlled single-blind study was approved by the Kowloon Central / Kowloon East research and ethics committee, Hospital Authority, Hong Kong (KC/KE-14-0081/ER-2). Oral informed consent was obtained from each participant. All obstetricians and midwives from the Department of Obstetrics and Gynaecology at Queen Elizabeth Hospital who had received simulation training at least 12 months earlier were invited to participate in simulation training for singleton vaginal breech delivery between August 2014 and September 2015. These participants had been included in our previous study on shoulder dystocia[16]. Those who had vaginal breech delivery training within the last 12 months were excluded.

Using an online research randomiser (http://www.randomizer.org/), obstetricians and midwives were each randomised to the intervention or control group to receive simulation training on singleton vaginal breech delivery at 6 months or 0 month later, respectively. Their skills were evaluated one week before training (pre-test), immediately after training (at-test), and 6 months (for intervention group) or 12 months (for control group) after training (re-test) [Figure 1]. Participants were unaware of the need for evaluation. Both groups were retested without prior notification to reduce bias. Those who failed to attend for re-testing were excluded from analysis. The obstetrician who assessed the outcome was not blinded to group assignment.

Participants attended a 60-minute lecture plus simulation training with multiple visual aids to explain the risk factors and complications of vaginal breech delivery. Manoeuvres for successful vaginal breech delivery were demonstrated. Participants then practiced the manoeuvres with the mannequin under supervision. Participant's skill to deliver a vaginal breech was tested using a birth simulator that included a mannequin pelvis and a mannequin baby. A scenario was simulated that a parous woman was admitted to the labour ward with a term singleton baby presented in extended breech position and in active labour. The cervix was fully dilated with the fetal sacrum at S+2 level (2 cm below the ischial spine of mother). Involuntary active pushing was ongoing and vaginal breech delivery was imminent and unavoidable. A 16-item marking scheme was used to score the participant's skills in all steps required for the vaginal breech delivery (Figure 2), based on courses of Advanced Life Support in Obstetrics[17] and Practical Obstetrics Multi-Professional Training[18]. Each item comprised both verbal and demonstrative components. No

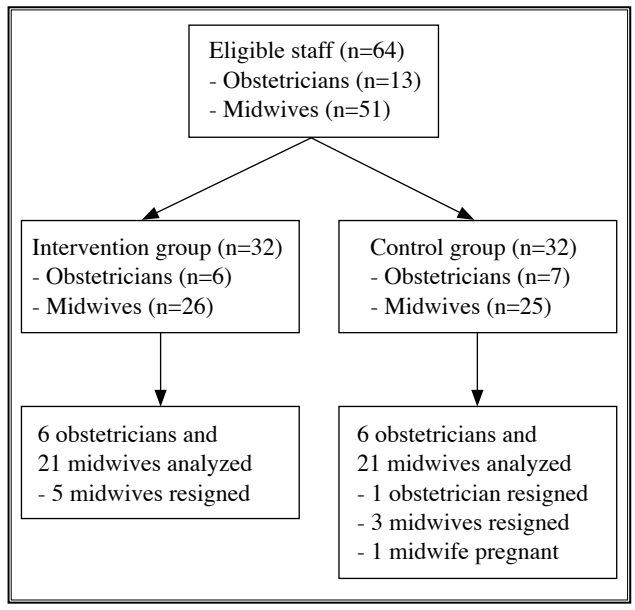

Figure 1. Flow diagram of participants

score was awarded when the participant failed to mention any of the required content. Half score was awarded when the answer was partially completed or when failure to demonstrate the correct manoeuvre despite correct verbal answer of the manoeuvre. The time required to complete the scenario was also assessed. Delivery of the mannequin baby was deemed successful when all the required steps were taken, with the use of the Mauriceau-Smellie-Veit or Burns-Marshall manoeuvre. Delivery of trapped fetal head was also discussed, including the use of forceps, cervical incision, and/or Caesarean section. The test was timed and automatically stopped at 500 s (30 s for each item and 20 s for scenario briefing). Testing, timing, and documenting the results were performed by a single independent obstetrician to prevent inter-observer bias.

Outcomes (score and time to complete the scenario) were compared between (1) pre-test and at-test, (2) at-test and post-test, and (3) pre-test and post-test. ANOVA, paired *t* test, and independent *t* test were used as appropriate. A p value of <0.05 was considered statistically significant. Subgroup analyses of obstetricians and midwives were also performed. In a similar study that investigated short- and long-term knowledge retention after a one-day simulation training for uncommon obstetrics emergencies (excluding vaginal breech delivery), the standard deviation for score in obstetrics emergency training was 6.6.[9] Assuming that skill scores at 6 months would be 5% higher than those at 12 months after simulating training, with one-sided difference and a power of 0.8, the minimal samples size was calculated to be 23 per arm.

Adequate staffing	
Senior midwife, senior obstetrician	
Neonatologist standby at delivery	
Inform anaesthetist	
Inform theatre staff for stand-by at delivery	
Preparation	
Continuous fetal heart monitoring	
Intravenous access, type, and screen	
Instrumental birth pack with forceps	
Procedures	
Delay active pushing until the breech is distending introitus (anus delivering)	
'Hands off' approach	
Avoid traction	
Pressure on non-bony prominences only	
Use correct manoeuvres for assisted breech delivery	
Back anterior and delivery of legs	
Lovset for delivery of arms	
Mauriceau-Smellie-Viet or Burns Marshall	
Forceps	
Work with assistant during Mauriceau-Smellie-Veit / forceps delivery	
Problem-solving skills	
Delay in descent of breech: avoid augmentation; book caesarean section	
Delivery of Nuchal arms	
Management of entrapped head	
Total score (1 mark each out of 16):	
Total delivery time (minutes):	

Figure 2. Marking scheme for management of singleton vaginal breech delivery

Results

A total of 13 obstetricians and 51 midwives were assigned at random to the intervention group (n=6+26) or control group (n=7+25). Five midwives from the intervention group and one obstetrician and four midwives from the control group were resigned or pregnant and hence excluded. Results of six obstetrician and 21 midwives in each group were analysed. The intervention and control groups were comparable in terms of years of working experience (14.05±7.15 vs 14.67±5.21) and the number of participants regularly working in the labour ward (17 vs 19).

Compared with the pre-test score, the at-test score increased and the time required to complete the scenario decreased immediately after the simulation training in the intervention group (7.98 vs 15.03, $p<0.001$; 348.09 vs 176.31 s, $p<0.001$) and the control group (6.86 vs 14.92, $p<0.001$; 369.34 vs 266.69 s, $p=0.003$), respectively (Tables 1 and 2). Compared with the at-test score, the post-test score decreased and the time required to complete the scenario increased 6 months after the training in the intervention group (15.03 vs 9.57, $p<0.001$; 176.31 vs 219.41 s, $p=0.06$) and 12 months after the training in the

Table 1. Skill score and time to complete the scenario before simulation training (pre-test), immediately after simulation training (at-test), and 6 months (for intervention group) or 12 months (for control group) after simulation training (post-test) for singleton vaginal breech delivery

Outcome	Pre-test	At-test	Post-test	P value (paired *t* test)		
				Pre-test vs test	At-test vs post-test	Pre-test vs post-test
Intervention group						
Skill score						
Overall	7.98±3.14	15.03±0.81	9.57±2.24	<0.001	<0.001	0.05
Obstetricians	8.29±5.67	15.43±0.79	11.88±2.47	0.01	0.003	0.029
Midwives	7.90±2.15	14.92±0.80	8.93±1.72	<0.001	<0.001	<0.064
Time, s						
Overall	348.09±105.78	176.31±63.94	219.41±58.74	<0.001	0.06	<0.001
Obstetricians	263.57±84.96	193.57±74.88	210.89±53.99	0.097	0.591	0.099
Midwives	371.76±99.91	171.48±61.39	221.79±60.84	<0.001	0.005	<0.001
Control group						
Skill score						
Overall	6.86±3.57	14.92±1.23	9.74±2.68	<0.001	<0.001	<0.001
Obstetricians	9.67±1.78	15.75±0.42	13.25±1.21	0.001	<0.004	<0.005
Midwives	6.21±3.58	14.73±1.28	8.93±2.23	<0.001	<0.001	0.001
Time, s						
Overall	369.34±130.85	266.69±104.02	213.00±53.97	0.003	0.018	<0.001
Obstetricians	261.00±52.58	307.17±105.37	154.17±42.64	0.444	0.007	0.027
Midwives	394.35±131.19	257.35±103.50	226.58±47.18	<0.001	0.194	<0.001

control group (14.92 vs 9.74, p< 0.001; 266.69 vs 213.00 s, p=0.018), respectively (Tables 1 and 2). Compared with the pre-test score, the post-test score increased and the time required to complete the scenario decreased at 6 months after the training in the intervention group (7.98 vs 9.57, p=0.05; 348.09 vs 219.41 s, p<0.001) and 12 months after the training in the control group (6.85 vs 9.74, p<0.001; 369.34 vs 213.00 s, p<0.001), respectively (Tables 1 and 2).

Both groups were comparable in terms of pre-test score (7.94 vs 6.86, p=0.185), at-test score (15.03 vs 14.92, p=0.677), and post-test score (9.57 vs 9.74, p=0.782). The two groups were comparable in terms of the decline in score from at-test to post-test (-5.49 vs -4.90, p=0.606). However, the change in the time to complete the scenario was longer for the intervention than control group (46.09 vs -50.56 s, p<0.001) [Tables 1 and 2]. Subgroup analyses for obstetricians and midwives showed similar trends.

Discussion

In most developed countries, in addition to external cephalic version, planned Caesarean section is a mode of delivery for a singleton breech presentation[19]. Expertise in vaginal birth delivery is difficult to acquire, and physicians may not gain enough experience during training. Simulation training in vaginal birth management is therefore important. Nonetheless, no conclusive practice recommendations are available, owing to the heterogeneity of studies[20]. Australia[21] and England[15] recommend annual drills for obstetrics skills including vaginal birth management. Self-assessed confidence and knowledge increase immediately after simulation training, but skills and knowledge levels may decrease as early as 72 hours or 6 weeks after training[13,22]. Annual training has been suggested because knowledge and skills declines as early as 4 months after training, but improvements are retained at both 4 and 12 months compared with the pre-test status[9].

Our study demonstrated that simulation training immediately improved skill levels in vaginal breech delivery, but these skill levels declined with time (at both 6 and 12 months after training). However, the skills level at 6

Table 2. Skill score and time to complete the scenario between intervention and control groups

Outcome	Intervention group	Control group	P value (ANOVA)
Skill score			
Pre-test			
Overall	7.98±3.14	6.86±3.57	0.185
Obstetricians	8.29±5.67	9.67±1.78	0.580
Midwives	7.90±2.15	6.21±3.58	0.048
At-test			
Overall	15.03±0.81	14.92±1.23	0.677
Obstetricians	15.43±0.79	15.75±0.42	0.390
Midwives	14.92±0.80	14.73±1.28	0.532
Post-test			
Overall	9.57±2.24	9.74±2.68	0.782
Obstetricians	11.88±2.47	13.25±1.21	0.244
Midwives	8.93±1.72	8.93±2.23	0.987
Pre-test vs at-test			
Overall	7.02	8.05	0.206
Obstetricians	7.14	5.75	0.540
Midwives	6.98	8.58	0.061
At-test vs post-test			
Overall	-5.49	-4.90	0.606
Obstetricians	-3.55	-0.49	0.282
Midwives	-6.03	-5.79	0.704
Pre-test vs post-test			
Overall	1.59	2.88	0.109
Obstetricians	3.59	3.58	0.994
Midwives	1.03	2.71	0.065
Time, s			
Pre-test			
Overall	348.09±105.78	369.34±130.85	0.478
Obstetricians	263.57±84.96	261.00±52.58	0.950
Midwives	371.76±99.91	394.35±131.19	0.494
At-test			
Overall	176.31±63.94	266.69±104.02	<0.001
Obstetricians	193.57±74.85	307.17±105.37	0.044
Midwives	171.48±61.39	257±103.50	0.494
Post-test			
Overall	219.4±58.74	213.00±53.97	0.651
Obstetricians	210.89±53.99	154.17±42.64	0.062
Midwives	221.79±60.84	226.58±47.18	0.754
Pre-test vs at-test			
Overall	-171.16	-99.84	0.063
Obstetricians	-14.69	46.17	0.103
Midwives	-200.28	-133.54	0.104
At-test vs post-test			
Overall	46.09	-50.56	<0.001
Obstetricians	17.31	-136.33	0.006
Midwives	-54.15	-30.77	0.004
Pre-test vs post-test			
Overall	-128.69	-156.34	0.322
Obstetricians	-52.69	-106.83	0.238
Midwives	-149.97	-167.77	0.567

months was maintained at 12 months. Despite the decline, the skill scores at 12 months remained significantly higher than those at pre-test. The intervention and control groups were comparable in terms doctor-to-midwife ratio, years of experience, and number of staff regularly working in the labour ward setting where exposure to vaginal delivery is more likely. Initial skills on vaginal breech delivery were suboptimal when >12 months had elapsed after last training and hence annual training was validated, as suggested by another study[15].

Our study was limited by the fact that it was carried out in a single centre and with limited number of participants. Data involving larger numbers and multiple obstetric centres is preferable. The assessor of the participants was not blinded to the study aims. Some participants would have encountered real-life vaginal breech delivery and hence updated their knowledge and skills between tests. The time to complete the scenario during training was significantly faster in the control group, suggesting more receptive to the training. This is an incidental finding as the two groups were comparable in terms of work experience or ward settings. Nevertheless, the difference disappeared in the post-training test. Despite efforts to test all participants at the same time, it was unavoidable that participants may have informed others about the unannounced post-training test and this might have resulted in last-minute revision before the test.

Conclusions

Simulation training results in short-term and long-term improvements in vaginal birth delivery skills. However, knowledge and skills degrade over time. Ongoing training at a minimum of 12-month intervals is suggested for obstetricians and midwives.

Declaration

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Risk factors and pregnancy outcomes of term fetal growth restriction

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Objective: To evaluate the maternal risk factors associated with term fetal growth restriction (FGR) and immediate perinatal outcomes in these pregnancies.
Methods: This was a retrospective cohort study conducted at a regional obstetric unit in Hong Kong over a 6-year period. All singleton livebirths delivered at term (≥37 weeks of gestation) were analysed. Those with major congenital abnormalities were excluded. Maternal epidemiological and anthropometric characteristics, presence of antenatal complications (gestational diabetes and medical disorders), and pregnancy outcomes (need for labour induction, mode of delivery, Apgar scores, occurrence of shoulder dystocia, and birth trauma) were compared between those with FGR (defined as birthweight ≤10th percentile for gestation) and those with birthweight appropriate for gestational age. Logistic regression analysis was conducted to identify risk factors associated with FGR.
Results: From 2012 to 2017, 24 010 singleton term livebirths were stratified into FGR (n=2425, 10%), appropriate for gestational age (n=19 162, 80%), and large for gestational age. Those classified as FGR were compared with those appropriate for gestational age pregnancies. A logistic regression model confirmed that the key risk factors for FGR included maternal underweight (adjusted odds ratio [OR]=1.88), hypertensive disorders of pregnancy (adjusted OR=1.78), smoking (adjusted OR=2.02), and antenatal anaemia (adjusted OR=1.20), whereas multiparity, gestational diabetes, and hepatitis B antigen carrier status were apparently protective. Pregnancies with FGR were more likely to undergo induction of labour, but were less likely to have shoulder dystocia, Caesarean section, or postpartum haemorrhage.
Conclusion: Despite the inherent risks associated with FGR at term, the immediate perinatal outcomes of these pregnancies appeared to be comparable to those appropriate for gestational age.

Keywords: Fetal growth retardation; Pregnancy outcome; Risk factors

Introduction

Fetal growth restriction (FGR) is a common obstetric problem that confers a considerable risk of perinatal morbidity and mortality[1]. FGR is often referred as 'small for gestational age' or 'intrauterine growth restriction'[2]. Traditionally, an estimated fetal weight below the 10th percentile raises concerns over suboptimal intrauterine growth, although this distinction between normal and pathologic growth is arbitrary. It has been estimated that over 70% of fetuses below the 10th percentile have a normal perinatal outcome, particularly if the growth restriction occurs late in the pregnancy and the baby is born at term gestation[3,4]. FGR is likely a manifestation of various underlying maternal, placental, fetal, and environmental causes and therefore a heterogeneous condition. There are wide variations in the definition of FGR and in fetal weight standards. Ethnic, cultural, and epidemiological factors could affect fetal growth and hence different populations should develop their own reference values for FGR[5,6]. Within our own local population in Hong Kong, previous studies have reported that there could be secular changes, and that the birth weights in Hong Kong have been increasing in the past decades[6-8]. Antenatal detection of FGR is of particular concern, given that only one-third of such pregnancies are prenatally recognised[9,10]. Low detection rates of FGR can result in an increased risk of adverse perinatal outcomes for these pregnancies. Pregnancies with unrecognised FGR could carry an 8-fold increased risk of stillbirth when compared with normal pregnancies[11]. Antenatal recognition of such risk factors is therefore crucial for appropriate surveillance for fetal well-being[12].

This study aimed to assess the associations between different maternal and pregnancy characteristics with term FGR to determine risk factors for FGR and immediate neonatal outcomes.

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Methods

All singleton livebirths delivered at gestation ≥37 weeks over 6 years from 2012 to 2017 in the United Christian Hospital were retrospectively reviewed. Data were retrieved from the electronic antenatal record system, obstetrics clinical information system, and case records of the women, and neonates. Multiple pregnancies, stillbirths, and cases with known major congenital malformations were excluded. All included pregnancies had an early ultrasonographic scan for dating or Down syndrome screening, or a second-trimester morphology scan to exclude date problems.

Gestation at delivery was defined as the completed weeks of gestation according to the date of last menstrual period or ultrasonography. Admission to special care neonatal unit was defined as immediate admission until up to 28 days after birth. A body mass index of ≤18.5 kg/m^2 before pregnancy was considered as underweight. Antenatal anaemia was identified when the haemoglobin level dropped <10 g/dL any time during the pregnancy. The diagnosis of gestational diabetes or diabetes mellitus in pregnancy was based on the 75-g oral glucose tolerance test, according to the departmental protocol and the World Health Organization 2013 criteria. Hypertensive disorders in pregnancy were defined as blood pressure of >140/90 mmHg on two occasions at least 4 hours apart, and pre-eclampsia was diagnosed when pregnancy hypertension was associated with proteinuria defined as spot urine protein/creatinine ratio of ≥0.5, or 24-hour urine protein of ≥0.3 g.

Pregnancies with birthweight of ≤10th percentile were defined as FGR and those of ≥90th percentile were defined as large for gestational age. All eligible pregnancies were also re-categorised with available local and Southern Chinese birthweight percentile charts[5,6,8,13,14] published in the past three decades to evaluate whether the incidence of FGR would be different using different cut-off criteria. Maternal epidemiological and pregnancy characteristics, presence of antenatal complications, and immediate perinatal outcomes were then compared between pregnancies with FGR and pregnancies appropriate for gestational age. The management of term FGR was in accordance with standard departmental protocols. Ultrasonography was performed for monitoring serial growth and liquor volume, and umbilical artery Doppler measurements for fetal surveillance, and induction of labour was offered as indicated before 40 weeks.

A logistic regression model using the enter method was used to identify risk factors associated with term FGR, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all significant factors. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Windows version 23; IBM Corp, Armonk [NY], US).

Results

From 2012 to 2017, 24 010 singleton term livebirths were stratified into FGR (n=2425, 10%), appropriate for gestational age (n=19 162, 80%), and large for gestational age (Table 1). Using other local or Southern Chinese growth charts[5,6,8,13,14] with different cut-offs, the percentages of FGR varied widely from 1.7% to 10.2%, while using a single cut-off of 2.5 kg as the criteria for small for gestational age would only include 2.8% of all pregnancies. The percentiles of our current cohort correlated best with the New Territories cohort of Rogers et al[6] and the recent large Guangzhou cohort[14].

Comparing the FGR and the appropriate for gestational age groups, women with FGR were more likely to be nulliparous (60.8% vs 48.4%, p<0.001), shorter in height (155.8 vs 156.5 cm, p<0.001), have a lower early pregnancy weight (54.9 vs 56.5 kg, p<0.001) and body mass index (22.6 vs 23.1 kg/m^2), and were underweight (5.3% vs 3.3%, p<0.001) [Table 2]. In addition, women with FGR had a higher incidence of antenatal anaemia (9.7% vs 8.1%, p=0.01), smoking during pregnancy (2.0% vs 1.1%, p<0.001), and hypertensive disorders or pre-eclampsia (7.5% vs 4.2%, p<0.001). Furthermore, women with FGR were less likely to be ≥40 years old (5.9% vs 7.0%, p=0.035), have previous miscarriages (35.9% vs 39.8%, p<0.001), previous Caesarean section (12.3% vs

Table 1. Incidence of term fetal growth restriction (FGR) among singleton livebirths (n=24 010) varies in different growth charts

Database	No. (%) of cases
Our cohort	2425 (10)*
Woo et al[5]	1327 (5.5)*
Rogers et al[6]	2163 (9)*
Fok et al1[3]	413 (1.7)*
Fok et al[8]	529 (2.2)†
He et al[14]	2440 (10.2)*
Birthweight of <2.5 kg	670 (2.8)

* FGR defined as birthweight of ≤10th percentile

† FGR defined as two standard deviations below the mean birthweight (around the 3rd percentile)

Table 2. Maternal characteristics between fetal growth restriction (FGR) and appropriate for gestational age groups

Parameter	FGR (n=2425)*	Appropriate for gestational age (n=19 162)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	P value
Maternal age, years	32±5.36	31.9±5.1	-0.07 (-0.15 to 0.28)		0.53
Gestation at delivery, weeks	39±1.12	39±1.13	0.004 (-0.04 to 0.05)		0.86
Maternal age ≥35 years	572 (23.6)	4701 (24.5)		0.95 (0.86-1.05)	0.16
Maternal age ≥40 years	143 (5.9)	1354 (7)		0.82 (0.69-0.98)	0.035
Parity				0.60 (0.55-0.66)	<0.001
Nulliparous	1475 (60.8)	9288 (48.4)			
Multiparous	950 (39.2)	9874 (51.6)			
Maternal height, cm	155.8±5.52	156.5±5.46	-0.64 (-0.87 to -0.41)		<0.001
Early pregnancy weight, kg	54.9±8.61	56.5±8.38	-1.55 (-1.91 to -1.20)		<0.001
Body mass index (BMI), kg/cm^2	22.61±3.34	23.1±3.21	-0.45 (-0.58 to -0.31)		<0.001
Underweight (BMI of <18.5 kg/cm^2)	128 (5.27)	627 (3.27)		1.86 (1.53-2.26)	<0.001
Previous miscarriages	871 (35.9)	7627 (39.8)		0.16 (0.07-0.25)	<0.001
Previous Caesarean section	299 (12.3)	3462 (18)		0.64 (0.56-0.72)	<0.001
Post-term delivery (≥41 weeks)	259 (10.7)	2337 (12.2)		0.86 (0.75-0.98)	0.86
Antenatal anaemia (haemoglobin of <10 g/dL)	235 (9.69)	1560 (8.14)		1.21 (1.05-1.40)	0.01
Smoking during pregnancy	50 (2)	220 (1.1)		1.81 (1.33-2.41)	<0.001
Gestational diabetes / diabetes mellitus in pregnancy	220 (9)	2161 (11.2)		0.78 (0.68-0.91)	0.001
Hypertensive disorders / pre-eclampsia	183 (7.54)	798 (4.16)		1.87 (1.59-2.22)	<0.001
Hepatitis B Antigen carrier	144 (5.9)	1557 (8.1)		0.71 (0.60-0.85)	0.001
Other medical disorders (cardiac, thyroid, neurological, autoimmune, renal diseases)	303	2207		1.09 (0.96-1.25)	0.84

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

18.0%, p<0.001), gestational diabetes (9.0% vs 11.2%, p<0.001), or positive carrier status of hepatitis B (5.9% vs 8.1%, p<0.001).

In the logistic regression analysis, risk factors for FGR identified from univariate analysis that remained significant were hypertensive disorders in pregnancy (adjusted OR=1.78, 95% CI=1.51-2.12), maternal underweight (adjusted OR=1.88, 95% CI=1.54-2.30), smoking in pregnancy (adjusted OR=2.02, 95% CI=1.47-2.77), and antenatal anaemia (adjusted OR=1.20, 95% CI=1.04-1.39) [Table 3]. In addition, protective factors associated with a lower risk of FGR included multiparity (adjusted OR=0.64, 95% CI=0.58-0.69), hepatitis B antigen carrier status (adjusted OR=0.75, 95% CI=0.63-0.89), and gestational diabetes (adjusted OR=0.82, 95% CI=0.71-0.95) [Table 3]. Maternal age >40 years, previous miscarriages, and previous Caesarean section were not significant risk factors in the logistic regression analysis.

Regarding pregnancy outcomes, compared with pregnancies appropriate for gestational age, pregnancies with FGR were more likely to have induction of labour (24.0% vs 15.8%, OR=1.68, p<0.001) or normal vaginal delivery (72.6% vs 69.9%, OR=0.81, p<0.001) instead of Caesarean section (17.4% vs 20.6%), but more likely to require instrumental delivery (40.0% vs 29.7%, OR=1.62, p=0.015) or Caesarean section (17.0% vs 5.7%, OR=3.37, p<0.001) for fetal distress (Table 4). Pregnancies with FGR resulted in less blood loss at delivery (187 vs 234 mL, p<0.001) and lower incidence of postpartum haemorrhage (3.5% vs 8.8%, OR=0.38, p<0.001). None of the cases with FGR were complicated by shoulder dystocia. Pregnancies with FGR resulted in a higher rate of admission to special

Table 3. Logistic regression analysis on risk factors for fetal growth restriction

Variable	B	Standard error	Wald	Adjusted odds ratio (95% confidence interval)	p Value
Hypertensive disorders	0.581	0.086	45.6	1.78 (1.51-2.12)	<0.001
Underweight	0.634	0.101	39.0	1.88 (1.54 -2.30)	<0.001
Smoking in pregnancy	0.703	0.162	18.8	2.02 (1.47-2.77)	<0.001
Antenatal anaemia	0.186	0.074	6.29	1.20 (1.04-1.39)	0.012
Multiparity	-0.450	0.045	99.0	0.64 (0.58-0.69)	<0.001
Hepatitis B carrier status	-0.287	0.090	10.1	0.75 (0.63-0.89)	0.001
Gestational diabetes	-0.203	0.076	7.22	0.82 (0.71-0.95)	0.007
Maternal age >40 years	-0.046	0.093	0.24	0.95 (0.79-1.15)	0.62
Previous miscarriages	-0.047	0.051	0.84	0.95 (0.86-1.05)	0.36
Previous Caesarean section	-0.125	0.079	2.49	0.88 (0.76-1.03)	0.12

Table 4. Maternal and immediate neonatal outcomes between fetal growth restriction (FGR) and appropriate for gestational age groups

Variable	FGR (n=2425)*	Appropriate for gestational age ((n=19 162)*	Mean difference (95% confidence interval)	Odds ratio (95% confidence interval)	P Value
Birthweight, g	2600±210	3196±278	-596 (-607 to -584)		<0.001
Induction of labour	582 (24)	3027 (15.8)		1.68 (1.52-1.86)	<0.001
Mode of delivery				0.81 (0.73-0.91)†	0.001
Normal vaginal	1761 (72.6)	13391 (69.9)			
Instrumental	241 (10)	1816 (9.5)			
Caesarean section	423 (17.4)	3955 (20.6)			
Instrumental delivery for fetal distress	98 (40)	538 (29.7)		1.62 (1.23-2.13)	0.015
Caesarean section for fetal distress	72 (17)	227 (5.74)		3.37 (2.52-4.48)	<0.001
Blood loss at delivery, mL	187±152	234±181	-47 (-57 to -36)		<0.001
Postpartum haemorrhage	86 (3.54)	1682 (8.78)		0.38 (0.30-0.48)	0.001
Apgar score of ≤7 at 5 mins	6 (0.25)	21 (0.11)		2.26 (0.91-5.60)	0.07
Shoulder dystocia	0	58 (0.3)			-
Birth trauma	2 (0.08)	12 (0.06)		1.31 (0.29-5.89)	0.71
Admission to special care neonatal unit	1310 (54)	7250 (37.8)		1.93 (1.77-2.10)	0.001
Neonatal death	1 (0.04)	2 (0.01)		3.95 (0.35-43.6)	0.30

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

† Caesarean section versus vaginal delivery

care neonatal unit (54.0% vs 37.8%, OR=1.93, p<0.001). One baby in the FGR group died from persistent pulmonary hypertension, and two babies in the appropriate for gestational age group died: one from a massive subgaleal haemorrhage after vacuum extraction and another being born and succumbed to unknown causes before arrival to hospital.

Discussion

Before local charts are available, growth charts based on Western populations developed more than 50 years earlier were often referred to[15]. The first widely adopted local growth chart was published in 1986 based on 15 000 singleton births from two teaching hospital units[5], and subsequently, a number of similar datasets were published.

When we applied the cut-offs of previous local studies that used the 10th percentile to our dataset, the incidence of FGR varied from 1.7% to 10.2%. Similarly, when we compared our data with a previous cohort that used minus two standard deviations as the cut-off, the incidence of FGR was only 2.2%. The under-estimation of FGR with older growth charts could be explained by the trend of increasing birthweight in Hong Kong babies. Comparing a cohort of 10 339 babies from 1998 to 2001[8] with a cohort of 8445 babies from 1982 to 1986[13], the mean birthweight was significantly greater at each gestation after 34 weeks in the newer cohort, compared with the older cohort. However, in another study comparing birthweights of 10 512 deliveries between 1985 and 86 with those of 7857 deliveries between 1995 and 1996, the mean birthweights in the two periods were comparable, suggesting that birthweight has reached a plateau despite continuous improvements in socioeconomic status in Hong Kong[6]. Despite the conflicting findings, such studies showed the importance of having up-to-date data to produce standard growth charts relevant to a specific population.

To determine whether a single international standard for fetal growth can be applied to all populations, a retrospective study of 506 658 neonates from Guangzhou from 2009 to 2011 aimed to compare the birthweight reference with the global reference and the reference used in China[14]. The birthweight in the Guangzhou cohort was higher than the references used in both China and global models at advanced gestational ages. Recently, the World Health Organization conducted a multi-national prospective observational longitudinal study of fetal growth involving ten countries (two in South-East Asia), and showed wide variations in fetal growth standards across different parts of the world[16]. The authors concluded that the growth charts cannot be generalised owing to limited sample sizes for different populations[16], and the need for population-specific growth charts is highlighted. In addition, the smoothed birthweight percentiles from 37 weeks to 41 weeks of the Guangzhou study matched closely with our cohort. This could be explained by the fact that the Guangzhou study was also conducted within the past 10 years, and the ethnicity and socioeconomic characteristics are also similar to our cohort.

In our study, maternal underweight, hypertensive disorder, smoking, and anaemia were risk factors for FGR. Using the World Health Organization definition of maternal underweight (body mass index of <18.5 kg/m^2), a retrospective cohort study of 29 303 Chinese women reported that 9% of the cohort was underweight[17], which was higher than the 5.27% in our cohort. It remains controversial whether maternal underweight leads to FGR owing to nutritional deficiencies, and conversely, whether increasing pre-pregnancy weight or gestational weight gain is associated with better neonatal outcome[18]. Hypertensive disorders and pre-eclampsia have been reported to be associated with FGR. The pathogenesis of dysfunctional placental implantation in pre-eclampsia is hypothesised to lead to decreased uteroplacental flow and placental ischaemia, decreasing oxygen and nutritional supply to the fetus[18,19]. In our study, the incidence of hypertensive disorders or pre-eclampsia was 4.5%, which was comparable to the 5.2% reported in a large retrospective study of 112 386 Chinese women[20]. Further studies are needed to determine whether variations in the incidence of hypertensive disorders are associated with variations in birthweights in different populations.

In our study, smoking was a risk factor for FGR. In a retrospective cohort study of 13 661 non-malformed singleton deliveries in Spain[21], smoking during pregnancy was a risk factor for FGR, with an adjusted odds ratio of 1.9, which was comparable to the 2.0 in our logistic regression analysis. The effect of smoking on FGR is dose-dependent and is therefore modifiable. In a previous study of 18 816 pregnant women from our centre, the incidence of smoking in early pregnancy was 1.7%, of which 53.5% continued to smoke throughout pregnancy and 26.9%, 13.8%, and 5.8% quit smoking in the first, second, and third trimester, respectively[22]. According to the Royal College of Obstetricians and Gynaecologists guideline[1], women who stop smoking by 15 weeks of gestation can lower the risk to that of non-smokers. Therefore, it is vital to advocate the importance of smoking cessation in antenatal management.

Anaemia is a common antenatal problem. In a systemic review involving 341 832 mother-child dyads, moderate to severe anaemia was associated with increased risk for small for gestational age (birthweight ≤10th percentile)[23] babies, with the haemoglobin cut-off being 90 g/L or 80 g/L. In a randomised controlled trial of 1164 Hong Kong women, there were fewer small for gestational age babies born in the group with 60 mg iron supplement daily (OR=0.46) than in the placebo group[24]. However, a recent study suggested that giving too much iron to non-anaemic women can lead to haemoconcentration, which is associated with maternal hypertension, pre-eclampsia, or gestational diabetes[25]. Therefore, there is no consensus on giving prophylactic iron supplement in pregnancy, particularly in those with borderline anaemia.

In our study, multiparity, gestational diabetes, and hepatitis B infection were protective factors against FGR. No consensus could be drawn from previous studies on whether parity was a risk factor for FGR. Subsequent pregnancies are likely to have better weight gain owing to better trophoblast invasion and hence increased placental blood flow and nutrient supply to fetuses[14]. However, multiparity was associated with confounders such as increasing age and increasing risk of gestational diabetes, so it is difficult to deduce the true association between parity and FGR. A retrospective cohort study of 19 614 women in Hong Kong confirmed that multiparity was a risk factor for macrosomia (adjusted OR=1.50), as was diabetic complication in pregnancy (adjusted OR=3.90)[26]. This was consistent with our finding of gestational diabetes being a protective factor for FGR.

Hepatitis B infection is common in the Asian populations. The hepatitis B carrier status is negatively associated with pre-eclampsia[27]. In a meta-analysis of 11 566 Asian patients, chronic hepatitis B infection is associated with 23% decreased risk of pre-eclampsia and increased risks of gestational diabetes[28]. This is compatible with our finding of hepatitis B carrier status being a protective factor for FGR as pre-eclampsia is a risk factor for FGR.

In our study, those with term FGR were more likely to have induction of labour (OR=1.68) before due date to lower the risk of intrauterine death and other perinatal morbidities. In a retrospective cohort study of 2378 neonates small for gestational age, early term induction increased the risks of Caesarean delivery and neonatal metabolic and respiratory complications with no neonatal benefit[29]. A randomised trial comparing induction of labour with expectant monitoring for term FGR, the DIGITAT study, reported no important differences in adverse outcomes between both[30]. Therefore, it remains controversial whether a term fetus with FGR should be induced. In our study, smaller fetuses were less likely to encounter shoulder dystocia but were at higher risk of intrapartum hypoxia and acidosis, so that instrumental delivery and Caesarean section for fetal distress were more common than for fetuses appropriate for gestational age. Less blood loss and postpartum haemorrhage was predictable as FGR is inversely associated with risk factors for postpartum haemorrhage.

One limitation of our study was its retrospective nature. Regarding the management of term FGR, we were unable to verify the proportion of cases that were detected antenatally or that had additional fetal surveillance, which would have affected pregnancy management or outcome. Although we were unable to demonstrate significant perinatal morbidity associated with term FGR apart from the higher admission rate to special care neonatal unit, we were not able to analyse neonatal length of stay or incidence of other minor perinatal problems such as neonatal jaundice or weight-gain patterns.

Conclusion

Risk factors associated with term FGR include maternal underweight, hypertensive disorder, smoking, and antenatal anaemia. In contrast, multiparity, gestational diabetes, and hepatitis B carrier status were protective factors, which themselves are associated with adverse outcomes in pregnancy.

Declaration

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20-year trend in Caesarean section rates in primiparous women in a regional obstetric unit in Hong Kong

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Introduction: Using the Robson classification, we analysed the 20-year trend of Caesarean section (CS) rates among primiparous women in a regional obstetric unit in Hong Kong.
Methods: Deliveries over a 20-year period (1997-2016) from United Christian Hospital were classified into one of 10 categories according to the Robson classification. The annual CS rate was calculated for each category, and data were stratified into four 5-year intervals to determine any trends.
Results: A total of 86 908 deliveries from 1997 to 2016 were included for analysis. The overall CS rate increased from 17.5% to 23.5% over the period. However, the overall primiparous CS rate only increased modestly from 20.8% to 22.8%, with main contributors being breech presentation (category 6), multiple pregnancies (category 8), and preterm labour (category 10). Contrarily, the CS rate declined mildly among those with spontaneous and induced labour (category 1 and 2). These trends were significant ($p<0.001$) after stratification into four 5-year intervals.
Conclusion: Despite a sharper rise in overall CS rate over the past 20 years, the CS rates in primiparous women increased modestly, mainly because of modest increases in rates of breech presentation, multiple pregnancies, and preterm labour.

Keywords: Cesarean section; Obstetric labor complications; Parity

Introduction

Caesarean section (CS) is increasingly performed worldwide, especially in middle- and high-income countries[1]. The increasing trend has also been reported in Hong Kong[2,3]. In 1985, the World Health Organization stated that there was no justification for any region to have a CS rate higher than 10% to 15%[4]. Despite this, the CS rate continued to rise to as high as 47.6% in China[5]. The strive for an 'optimal' rate remains theoretical and controversial, as many factors have to be considered. In developing countries, a modest increase in the CS rate has been reported to be associated with significant improvement in maternal and neonatal morbidity and mortality[2,6]. This supports the argument that a rise in the CS rate is likely to improve pregnancy outcomes. However, in developed countries, a sharp increase in CS rate has not been shown to improve pregnancy outcomes and could be associated with increased adverse maternal complications[7-10].

The Robson classification is a systematic, all-inclusive, mutually exclusive, and replicable method to enable standardised comparisons between institutions[10,11]. It classifies pregnant women into 10 categories based on five parameters: gestational age (preterm or term), onset of labour (spontaneous, induced, or CS before onset of labour), fetal presentation and lie (cephalic, breech, transverse), parity (including previous CS), and number of foetuses (Table 1). Indications for CS are not required. Efforts have been made to audit and to reduce the CS rate using the Robson classification[1,5,11-13]. One of the main focuses is on the ever-increasing primary CS rates[14,15] and the vicious cycle of repeat CS. Previous CS has been reported to be one of the principal contributing factors to rising CS rates in Hong Kong[16]. As most primary CSs are performed on primiparous women with first delivery, this study aims to evaluate CS rate trends in primiparous women over a 20-year period in a regional obstetric unit and compare them with the overall CS rate trends. Applying the Robson classification to the data would allow identification of primiparous subgroups that had increasing CS rates.

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Methods

This study was approved by the Kowloon Central / Kowloon East Cluster Research Ethics Committee. Obstetric data from United Christian Hospital from 1997 to 2016 were obtained from the Clinical Information System. Pregnancies were then categorised into primiparous and multiparous according to the standard definition of previous delivery beyond 24 weeks of gestation. Maternal epidemiological risk factors (advanced maternal age, induction of labour) and pregnancy characteristics (multiple pregnancies, breech presentation, preterm deliveries, and induction of labour) were collected.

Table 1. The Robson classification for Caesarean section (CS)

Category	Characteristics
1	Primiparous women with a single cephalic pregnancy, ≥37 weeks' gestation, in spontaneous labour
2	Primiparous women with a single cephalic pregnancy, ≥37 weeks' gestation, who have induction of labour or CS prior to labour onset
3	Multiparous women without a previous uterine scar, with a single cephalic pregnancy of ≥37 weeks' gestation in spontaneous labour
4	Multiparous women without a previous uterine scar, with a single cephalic pregnancy of ≥37 weeks' gestation, with induction of labour or CS prior to labour onset
5	Multiparous women with one or more previous uterine scar(s) and a single cephalic pregnancy of ≥37 weeks' gestation
6	Primiparous women with a single breech pregnancy
7	Multiparous women with a single breech pregnancy, with/without previous uterine scar(s)
8	Women with multiple pregnancies with/without previous uterine scar(s)
9	Women with a single pregnancy with a transverse or oblique lie, with/without previous uterine scar(s)
10	Women with a single cephalic pregnancy at ≤36 weeks' gestation

Table 2. Annual rates of major epidemiological risk factors and primiparous Caesarean section (CS) in the relevant Robson categories from 1997 to 2016

	Year																			
	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
Total deliveries, n	3501	3371	3534	3850	3522	3844	3787	4558	5078	4244	4682	5169	4951	5251	5648	4968	4079	4350	4253	4258
Overall CS rate, %	18.1	19.1	16.6	16.5	15.8	17.4	18.2	19.5	18.2	18.6	18.8	22.1	20.9	23.1	23.1	23.4	23.6	24.6	22.3	23.8
Multiparous CS rate, %	15.1	18.0	15.5	13.3	13.4	16.0	17.3	18.1	17.1	1.5	16.9	22.8	21.7	24.6	26.4	26.2	25.3	26.6	22.8	23.8
Primiparous, %	47.3	47.4	50.2	50.2	50.5	51.5	49.6	52.4	50.7	48.2	47.5	48.4	47.7	49.0	47.1	48.1	50.2	49.0	49.4	48.5
Primiparous age >35 years, %	2.6	4.6	5.1	6.8	17.6	6.7	8.1	7.5	6.1	8.2	9.9	11.4	14.6	12.5	11.2	14.9	15.5	16.3	18.5	16.0
Primiparous with induction of labour, %	11.5	12.7	15.1	14.3	14.2	11.5	11.9	9.4	10.5	9.6	12.3	12.8	15.3	14.3	17.9	16.8	19.1	19.7	21.5	21.8
Primiparous with multiple pregnancies, %	0.49	0.87	0.79	0.88	0.73	2.57	1.33	1.00	0.89	1.17	1.97	1.63	1.52	1.28	1.94	1.84	1.61	2.20	1.85	2.76
Overall primiparous CS rate, %	21.6	20.3	20.6	19.6	18.1	18.7	19.1	20.8	19.3	18.7	20.9	21.4	20.0	21.3	19.4	20.4	21.9	22.5	21.7	23.8
Category 1 CS rate, %	12.8	12.6	14.8	13.4	10.3	11.6	11.4	14.7	12.3	11.0	13.4	13.3	11.8	11.8	10.6	10.9	12.3	12.1	12.0	13.1
Category 2 CS rate, %	39.1	35.6	29.1	30.1	35.1	32.0	33.1	35.9	37.4	31.8	36.5	35.1	35.5	41.9	31.5	29.6	37.0	35.1	20.4	26.9
Category 6 CS rate, %	82.5	86.9	77.9	89.5	95.6	95.4	91.5	94.6	97.2	97.0	93.0	97.4	96.7	97.3	95.9	94.2	96.4	96.9	98.8	97.8
Category 8 CS rate, %	62.5	64.3	71.4	58.8	61.5	78.4	84.0	87.5	82.6	79.1	86.4	85.3	96.7	84.8	86.5	95.5	84.8	89.4	81.6	89.4
Category 9 CS rate, %	100	100	100	100	100	94.4	100	91.6	92.3	100	100	95.6	93.7	100	93.3	92.8	100	100	100	100
Category 10 CS rate, %	21.3	24.4	17.2	17.3	17.1	27.3	21.2	23.1	19.1	25.6	24.1	19.2	23.3	27.9	29.3	29.7	26.9	25.8	29.5	29.5

All primiparous cases were classified into one of the Robson categories, and CS rates were calculated for each category in each year to observe for any trends and to compare with multiparous CS rates. The total number of patients in each category was then stratified into four 5-year intervals (1997-2001, 2002-2006, 2007-2011, and 2012-2016), and the four 5-year intervals were compared using a 4x2 contingency table and Mantel-Haenszel Chi squared tests for linear trends. A p value of <0.05 was taken as statistically significant.

Results

A total of 86 908 deliveries from 1997 to 2016 were included for analysis. The annual delivery rate increased steadily from 3501 in 1997 to 5648 in 2011, with a gradual decline to 4258 in 2016. The rate of primiparous delivery remained constant over the period, ranging from 47.3% to 52.4%. The primiparous CS rate varied between years; it was lowest at 18.1% in 2001 and gradually increased to 23.8% in 2016 (Table 2 and Figure 1). In contrast, the multiparous CS rate increased sharply from 15.1% in 1997 to 26.4% in 2011 and remained high at 23.8% in 2016.

The increase in the primiparous CS rate over the four 5-year intervals was significant, as were the increases of the rates of induction of labour (11.5% in 1997 to 21.8% in 2016), advanced maternal age of >35 years (2.6% in 1997 to 16% in 2016), and multiple pregnancies (0.49% in 1997 to 2.76% in 2016) among primiparous pregnancies (Table 3).

Using the Robson classification, among primiparous pregnancies, the increasing trend of CS was significant in category 6 (breech presentation) from lowest 77.9% in 1999 to highest 97.8% in 2016, category 8 (multiple pregnancies) from lowest 58.8% in 2000 to highest 96.7% in 2009 and remained high at 89.4% in 2016, and category 10 (preterm deliveries) from lowest 17.1% in 2001 to 29.5% in 2016 (Table 2). These increases were significant over the four 5-year intervals. From the first to the fourth 5-year interval, there were increases in category 6 (breech presentation) from 86.6% to 96.6% (p<0.001), category 8 (multiple pregnancies) from 63.6% to 88.6% (p<0.001), and category 10 (preterm deliveries) from 19.4% to 28.5% (p<0.001) [Table 3]. No specific trend was observed for category 1 (primiparous with term spontaneous labour),

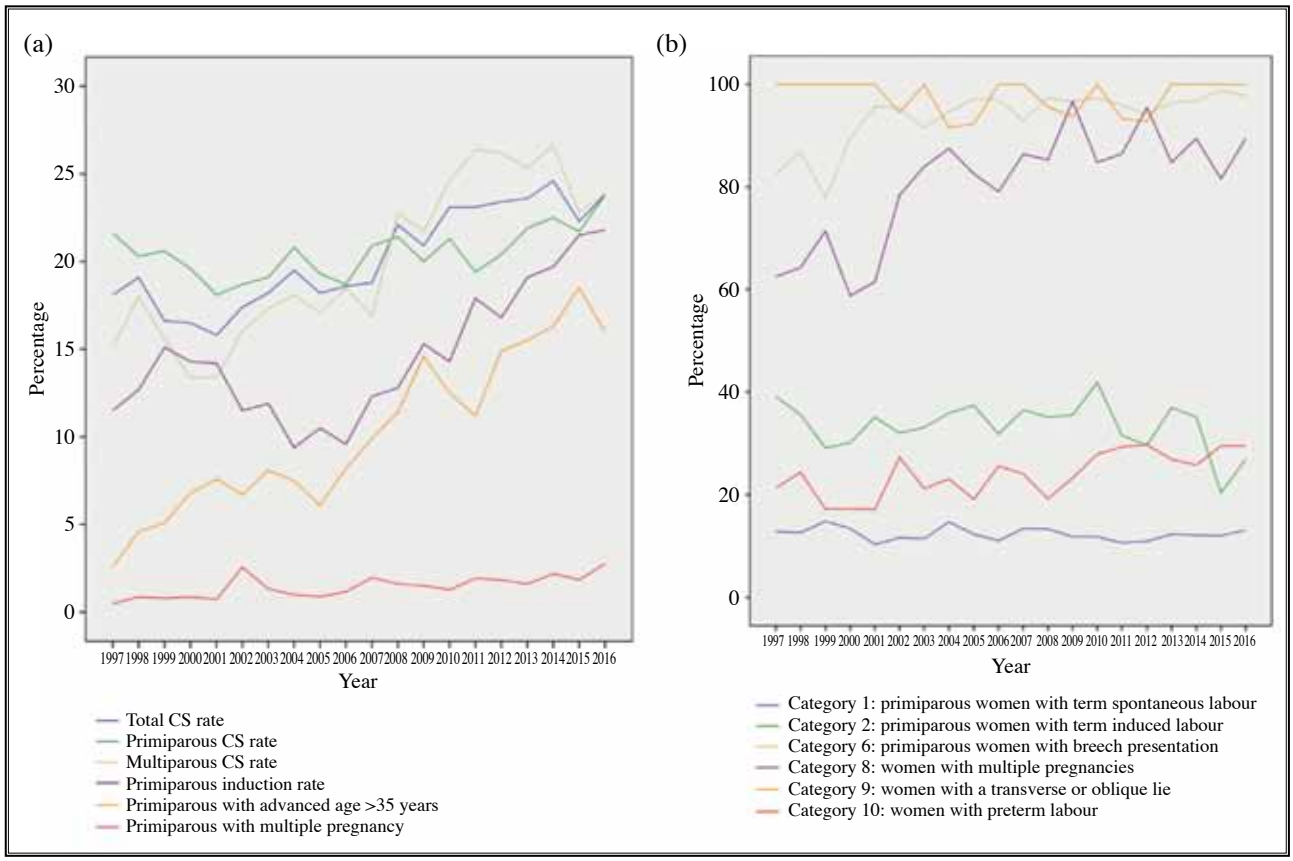

Figure 1. Comparison of (a) trends of total, multiparous, and primiparous Caesarean section (CS) rates and other epidemiological risk factors; and (b) trends of CS in primiparous women categorised by the Robson classification

Table 3. Comparison of Caesarean section (CS) rates in 5-year intervals for Robson categories for primiparous women

Characteristic	5-year interval				
	1997-2001	2002-2006	2007-2011	2012-2016	p value
Total deliveries, n	17 778	21 511	25 701	21 908	
Total CS, n (%)	3108 (17.5)	3960 (18.4)	5584 (21.7)	5158 (23.5)	<0.001
Primiparous total, n (%)	8702 (48.9)	10 868 (50.5)	12 348 (48.0)	10 732 (49.0)	<0.001
Primiparous age >35 years, n (%)	472 (5.4)	789 (7.3)	1472 (11.9)	1750 (16.3)	<0.001
Primiparous with induction of labour, n (%)	1189 (13.7)	1143 (10.5)	1804 (14.6)	2118 (19.7)	<0.001
Primiparous with multiple pregnancy, n (%)	66 (0.76)	147 (1.35)	206 (1.67)	230 (2.14)	<0.001
Multiparous CS rate, n (%)	1368/9076 (15.2)	1853/10 643 (17.4)	3085/13 395 (23.0)	2795/11 176 (25.0)	<0.001
Primiparous CS rate, n (%)	1811 (20.8)	2222 (20.4)	2726 (22.0)	2455 (22.8)	<0.001
Category 1 CS rate, n (%)	897/6985 (12.8)	1056/8569 (12.3)	1111/9107 (12.2)	881/7302 (12.1)	0.51
Category 2 CS rate, n (%)	399/1194 (33.4)	391/1192 (32.8)	661/1837 (35.9)	671/2314 (29.0)	<0.001
Category 6 CS rate, n (%)	298/344 (86.6)	452/474 (95.4)	519/540 (96.1)	459/475 (96.6)	<0.001
Category 8 CS rate, n (%)	42/66 (63.6)	120/147 (81.6)	175/206 (84.9)	194/219 (88.6)	<0.001
Category 9 CS rate, n (%)	82/82 (100)	66/69 (95.6)	81/84 (96.4)	57/58 (98.2)	-
Category 10 CS rate, n (%)	93/480 (19.4)	137/590 (23.2)	179/740 (24.2)	193/678 (28.5)	0.004

which remained stable over the period, ranging from 10.6% to 14.7% (mean, 12%), category 2 (primiparous with term induced labour), which showed a wider fluctuation between 29.1% and 41.9%, with the highest rate in the third 5-year interval (2007-2011) at 35.9% but the lowest in the fourth 5-year interval (2012-2016) at 29%, and category 9 (transverse lie), which remained high throughout the period at 98% to 100% (Table 3).

The absolute number of CS in each Robson category was then used to calculate the percentage contribution of each category to the total CS rates for each 5-year interval (Figure 2). For category 1 (primiparous with term spontaneous labour), the mean CS rate was around 12%, but it constituted over one third of all CSs. For category 2 (primiparous with term induced labour), the mean CS rate was around 30%, but it constituted over 20% of all CSs. Over the study period, contribution from category 1 gradually decreased while that from categories 2, 8, and 10 gradually increased (Figure 2). Although the absolute percentage change in categories 1 and 2 was small in comparison to that in other categories (Figure 2), these two categories carried overwhelming weighting on the total CS rate because of the large numbers. Specifically, the decrease in the percentage of CS in category 1 in the fourth 5-year interval significantly mitigated the overall increase in primiparous CS rate.

Discussion

Although the overall CS rate increased from 17.5% to 23.5% over the 20-year period, the primiparous CS rate only increased modestly from 20.8% to 22.8%. This is in line with our previous findings that the main contributor for the increase in the CS rate was from multiparous women with previous CS[16].

The World Health Organization global survey for 24 countries between 2004 and 2008 reported an overall CS rate of 26%[17], whereas the World Health Organization multi-country survey of maternal and newborn health from 2010 to 2011 reported an increase in the overall CS rate to 31%[18], of which a large proportion of the increase was attributed to previous CS[5,19]. In Hong Kong, a territory-wide audit performed by the Hong Kong College of Obstetricians and Gynaecologists in 2014 reported an increase in the overall CS rate from 27.1% in 1999 to 42.1% in 2009[20]. Our local CS figures aligned well with the ever-rising trends in CS observed in Asia as well as worldwide.

As the increase in the overall CS rate was strongly associated with previous CS, it is important to control primary CS. In China, a high CS rate of 54.5% among

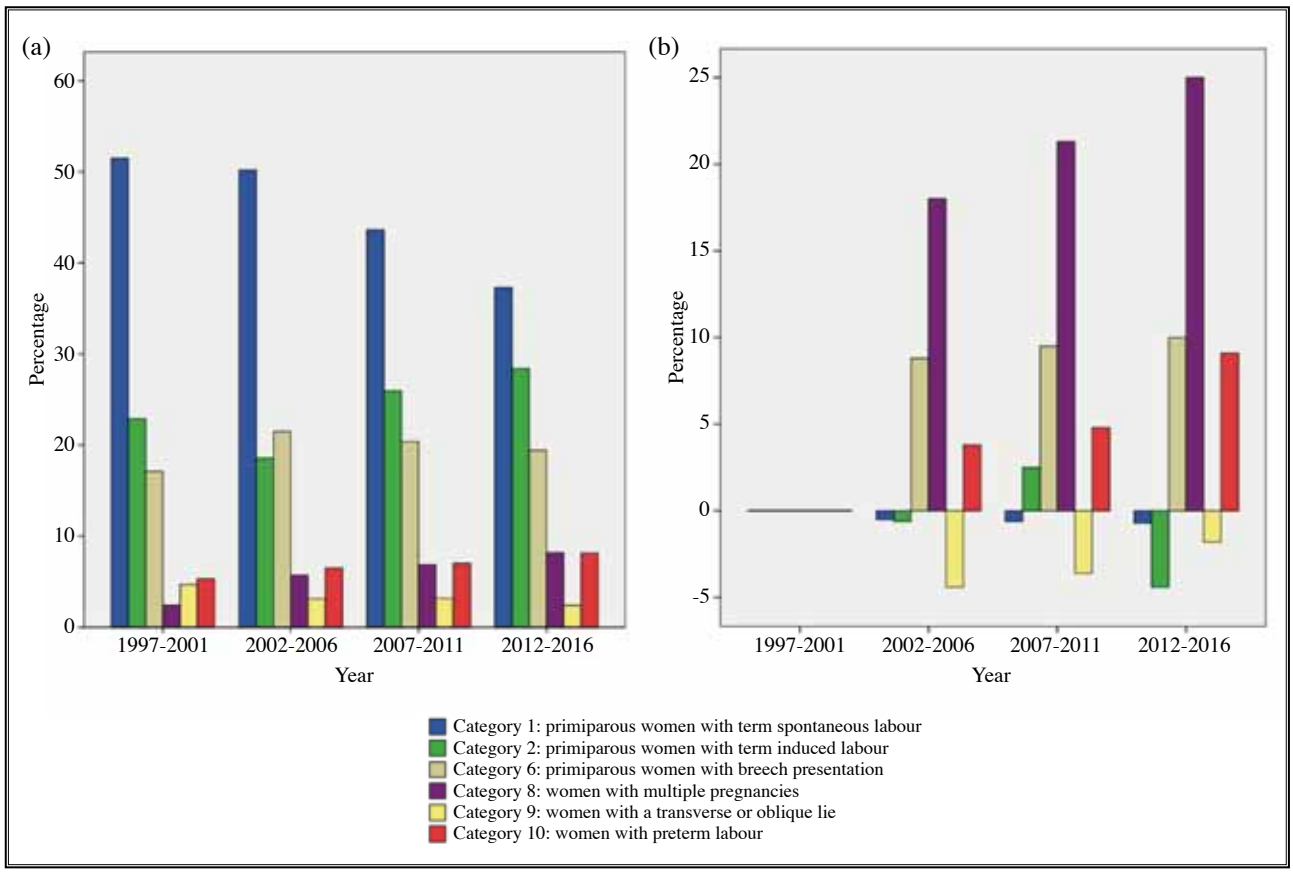

Figure 2. (a) Percentage contribution of Robson categories related to primiparous women to overall primiparous Caesarean section (CS) rate, and (b) percentage change in contribution of Robson categories related to primiparous women to overall primiparous CS rate

112 138 women has been reported, with non-indicated CS on maternal request constituting 38.4% of them and the majority of these being primary CS in primiparous women[21]. Women treated in the private sector have a higher risk of both elective and emergency CS compared with women treated in public sector[22,23]. In almost 30 000 nulliparous deliveries in Ireland where the practice settings and overall CS rate (26.1%) were similar to the Hong Kong system, a large excess 'private sector' effect remained even after adjusting for maternal, clinical, and hospital characteristics[24]. In Hong Kong, the prevalence of maternal preference for elective CS has been reported to be 17.2% at mid-trimester and 12.7% at term. Moreover, among women booked to deliver in the public sector, more women who preferred CS at term changed to deliver in the private sector than those who preferred vaginal delivery[25]. In public obstetric units, the incidence of non-indicated CS has been low, and this could be one of the key factors that contributed to controlling CS rates in our centre at reasonable levels. Practically, there is a need to avoid non-indicated CS in primiparous women in order to prevent the vicious cycle of CS in future pregnancies.

Categories 1 (term spontaneous labour) and 2 (term induced labour)

The CS rate was static for category 1 (spontaneous labour at term) but decreased for category 2 (induced labour at term). These encouraging trends are in sharp contrast to those reported in mainland China[21,26]. As these two categories constituted the largest absolute number of primiparous CS, controlling the CS rate in these two categories are important in primiparous women. The stable trend of CS reflects our adoption of evidence-based active management of labour, including close monitoring of intrapartum cardiotocography, use of partograms[14], early amniotomy with oxytocin augmentation[27,28], and regular clinical audits for CS indications within unit[13,29]. Originally aimed to shorten the labour duration, active management of labour resulted in reduced CS rates, better neonatal outcomes, and improved maternal satisfaction[30]. Later studies investigated the effects of individual interventions on reducing CS rates, and the conclusions were mixed[31,32]. In 2013, a meta-analysis of seven randomised trials reported that the CS rate was lower in those with active labour management, but the difference

was not significant[33]. Despite the controversies surrounding active labour management, reducing the CS rate in low-risk primiparous women with spontaneous labour appears safe and reasonable. In a study of nulliparous women with singleton cephalic livebirths at term in Australia from 2009 to 2010, the overall CS rate was 28.1%, and perinatal outcomes were similar despite significant variations in prelabour and intrapartum CS rates between different hospital centres. Although differences in case-mix and clinical practice were substantial contributors to variations in the CS rate, the CS rate in some hospitals can be safely lowered without adversely affecting pregnancy outcomes[34].

Although primiparous women with induced labour have a higher baseline CS rate than those in spontaneous labour, induction of labour per se has been demonstrated to decrease rather than increase the CS rate. A meta-analysis of 37 randomised controlled trials included 27 trials of uncomplicated term pregnancies and 10 trials evaluating induction versus expectant management in pregnancies with suspected macrosomia, diabetes in pregnancy, oligohydramnios, twins, intrauterine growth restriction, pregnancy-induced hypertension, and women with a high-risk score for Caesarean section[35]. This meta-analysis determined that a policy of induction was associated with a reduction in the risk of CS compared with expectant management (odds ratio=0.83)[35]. In a prospective randomised controlled trial of low-risk nulliparous women at 39 weeks (n=6000), routine labour induction did not result in a significantly lower frequency of a composite adverse perinatal outcome but demonstrated a significantly lower rate of CS delivery (18.6% vs 22.2%)[36]. Mathematical modelling revealed that elective induction of labour at 39 weeks resulted in lower population risks, specifically lower the rates of CS, maternal morbidity, and perinatal morbidity and mortality[37]. In our cohort, the labour induction rate in primiparous women increased from 11% in 1997 to 21% in 2016. This two-fold increase in labour induction could be a contributor for the modest but significant drop in the CS rate among primiparous women.

Category 6 (breech pregnancies)

The rate of CS for breech pregnancies showed a significant increase from the 86% in 1997-2001 to over 95% for the later three 5-year intervals, and the figure had remained relatively consistent over these 15 years. This is most likely due to the Term Breech Trial[38] published in 2000. This landmark paper involved 2088 women from 26 countries, and concluded that elective CS for the term breech reduced perinatal mortality, neonatal mortality and serious neonatal morbidity. International guidelines such as the RCOG Green-top guidelines[39] later incorporated these findings, and the data from this cohort reflected our compliance with these recommendations. A potential method of reducing CS in this category is indeed external cephalic version to enhance the chances for a successful vaginal delivery[40]. However, it should be noted that women who have a successful version will no longer remain in this category and will be assigned to category 1 or 2.

Category 8 (multiple pregnancies)

Category 8 increased the most in the CS rate among primiparous women from 63.6% to 88.6% across the four 5-year intervals. This trend is similar to that reported in other studies. The rate for twin CS in the United States has risen from 55% in 1995 to >75% in 2008; in Germany it has risen from 60% in 1990 to 77% in 2012[41]. Prior to the Twin Birth Study in 2005[42], CS was considered a safer delivery modality with a lower risk of mortality for both twins. A retrospective study of >8000 Scottish twin births from 1985 to 2001 with term gestations reported that planned CS might reduce the risk of perinatal death by 75% compared with planned vaginal delivery, by reducing the risk of death from intrapartum anoxia of the second twin. However, the Twin Birth Study in 2013 reported that there were no significant benefits in planned CS for uncomplicated twins pregnancies[43]. The JUMODA study confirmed that planned CS (compared with planned vaginal delivery) for twins could be associated with increased composite neonatal mortality and morbidity, particularly when delivery was before 37 weeks[44]. Nevertheless, there is a strong preference among mothers with twin pregnancies for planned CS, which is likely to be compounded by the clinician's lack of confidence in conducting complex vaginal deliveries[45]. The high CS rate for twin pregnancies is unlikely to be reduced in the future.

Category 10 (preterm labour)

Results for the optimal mode of delivery in this group were mixed, with no good evidence favouring CS[46]. A Cochrane review in 2012 reported no significant difference between CS and vaginal delivery with regards to birth injury, markers of possible birth asphyxia, or other complications of prematurity such as neonatal seizures, hypoxic ischaemic encephalopathy, and respiratory distress syndrome[47]. The National Institute for Health and Care Excellence guideline does not recommend CS over vaginal delivery for infants in preterm labour[48]. However, indications for CS in preterm deliveries were not studied in detail. In our cohort, a proportion of planned preterm CS were due to conditions such as early-onset fetal growth restriction or pre-eclampsia, frequently with evidence of

fetal compromise. Therefore, the modest increase in the preterm CS rate appeared to be iatrogenic. The prevalent medicolegal implications of delivering a compromised baby may have played a role in clinical decision on the mode of delivery.

Strengths and limitations

As the study was based on a single centre, the temporal effects of changes in clinical protocols in line with international recommendations on the CS rate could be readily traced and audited. The large sample size over the 20-year period enable observation of trends. Nonetheless, one might question whether our findings would be generalisable to other public obstetric units or private hospitals. According to the Hospital Authority annual obstetric reports, similar increases in the CS rates have been observed in all other obstetric units, with variable extents. As practices and policies within the Hospital Authority are similar, it is reasonable to conclude that our findings may reflect the overall trend in the CS rate among public hospitals. In private obstetric units, the CS rate has all along been much higher[3]. With the prevalence of non-indicated CS due to maternal preference in recent years, the trends from private hospital settings would be anticipated to be very different from our findings. We look forward to similar analyses from other public and private obstetric units to compare with our data.

Conclusion

The increase in the CS rate is a global phenomenon and is also observed in our unit. However, the CS rate in primiparous women has remained fairly stable over the past 20 years. The modest increase was mainly associated with mild increases in the CS rate in those with breech presentation, multiple pregnancies, or preterm labour. Future efforts should continue to be focused on maintaining a static CS rate in primiparous women to avoid the escalating CS rates in multiparous women due to previous CS.

Declaration

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Single fetal demise in monochorionic twins: a case report and literature review

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We report a case of single fetal demise in an apparently uncomplicated monochorionic twin pregnancy at 29 weeks of gestation. The surviving co-twin was delivered within 2 days based on ultrasound features of acute fetal anaemia. The baby had neurological damage and renal failure and progressively deteriorated to death. We review the literature on management of single fetal demise in monochorionic twin pregnancy and discuss the controversies in management.

Keywords: Fetal death; Fetofetal transfusion; Pregnancy, twin

Case presentation

A 31-year-old woman, para 3, naturally conceived a twin pregnancy. Ultrasound at 12 weeks of gestation showed monochorionic diamniotic twins. The nuchal translucency of both fetuses was normal and the first trimester combined biochemical screening showed low risk for Down syndrome. Morphology scan at 20 weeks was unremarkable. Serial ultrasound scans at 16, 20, 23, and 26 weeks of gestation showed normal growth and liquor volume of both fetuses (Figure 1). There were no growth discrepancies between the two fetuses and there was no evidence of twin-twin transfusion syndrome (TTTS).

In August 2018, she was admitted to our hospital at 29+1 weeks of gestation for decreased fetal movement of one day. Ultrasound showed that the first twin had died while the other was viable. Parameters of both fetuses were within normal range with no significant growth discrepancy (Figure 1). The liquor volume of both fetuses was normal with the deepest pocket 2.8 cm in first twin and 3.6 cm in second twin. There were no hydropic changes in the demised fetus. The umbilical artery and ductus venosus Doppler waveforms of the surviving fetus were normal, and peak systolic velocity of the middle cerebral artery Doppler was 53 cm/s, which was just below 1.5 MoM for gestation (Figure 2). Cardiotocogram tracing was unremarkable. The patient was afebrile with normal blood pressure and urine analysis. She did not have any symptoms and signs of labour. There was no evidence of pre-eclampsia or placental abruption. The maternal blood test showed no coagulopathy. With the presence of single fetal demise in a monochorionic twin pair, the risks of intrauterine death and neurological damage of the co-twin were explained to the patient. Balancing these risks with the risks of prematurity

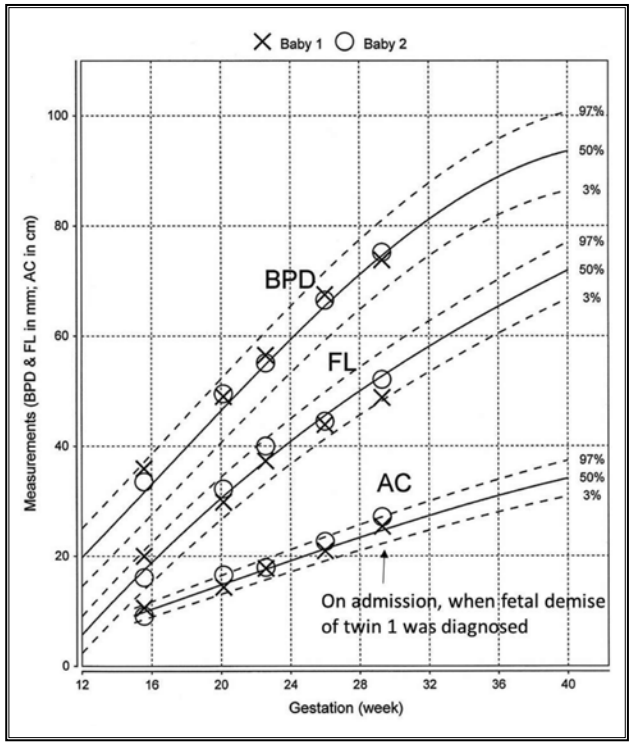

Figure 1. Ultrasonographic chart showing no significant growth discrepancies between the two fetuses

to deliver the surviving co-twin at 29 weeks of gestation, it was decided to adopt conservative management with close surveillance of the co-twin. Antenatal steroid therapy was started to enhance fetal lung maturity.

On the next day, the maternal condition was stable and the cardiotocogram of the surviving fetus showed

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reactive pattern. However, 1 day later, ultrasound scan showed the peak systolic velocity of the middle cerebral artery in the surviving fetus was 65 cm/s, exceeding 1.5 MoM signifying significant fetal anaemia (Figure 2). The umbilical artery Doppler and ductus venous Doppler remained normal, and cardiotocogram continued to show a reactive fetal heart rate pattern (Figure 3). The course of steroids was completed. The risks of progressive fetal anaemia of the surviving fetus and possible deterioration with sudden intrauterine death were explained to the patient and her family. They strongly requested delivery instead of conservative management. Maternal magnesium sulphate was given for neuroprotection before delivery. Emergency caesarean section was performed. Twin 1 was stillbirth with birthweight of 1376 g. Twin 2 was delivered with birthweight of 1690 g. The Apgar score was 5 at 1 minute and 9 at 5 minutes of life. The cord arterial pH was 7.34 with base excess -0.2.

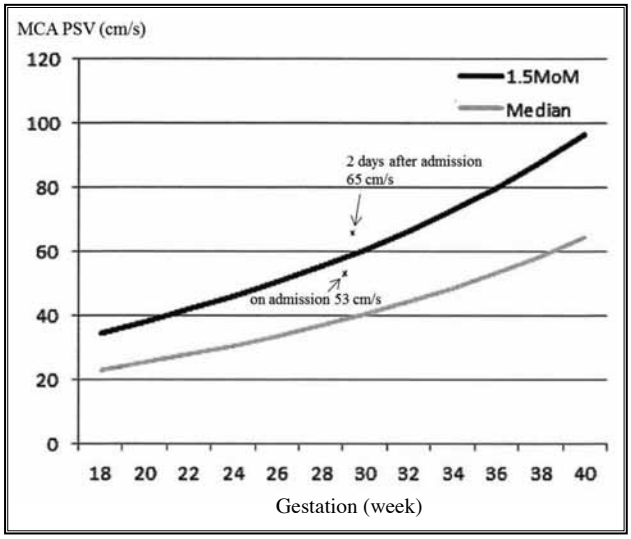

Figure 2. Peak systolic velocity (PSV) of the middle cerebral artery (MCA) of the surviving twin on admission and on day 2
The median and 1.5 MoM values were adopted from: Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunisation. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000;342:9-14.

Twin 2 was born with weak crying. He was put on continuous positive airway pressure but was subsequently intubated at 1 hour of life due to respiratory distress. Blood test showed his haemoglobin level was 5.8 g/dL, and blood transfusion was performed. He developed seizure at 3 hours of life. Anti-convulsant therapy was started. Computed tomography of the brain showed diffuse cerebral oedema with generalised hypo-attenuation of brain parenchyma, intraventricular haemorrhage, and petechial haemorrhages in both frontal lobes (Figure 4), suggestive of significant hypoxic ischemic encephalopathy. The baby developed renal failure with no urine output since birth despite trial of diuretics. The creatinine level rose from 59 (on the day of birth) to 143 (on day 2 of life) and to 326 μmol/L (on day 7 of life). The baby was deemed not suitable for haemodialysis due to his low birthweight. In

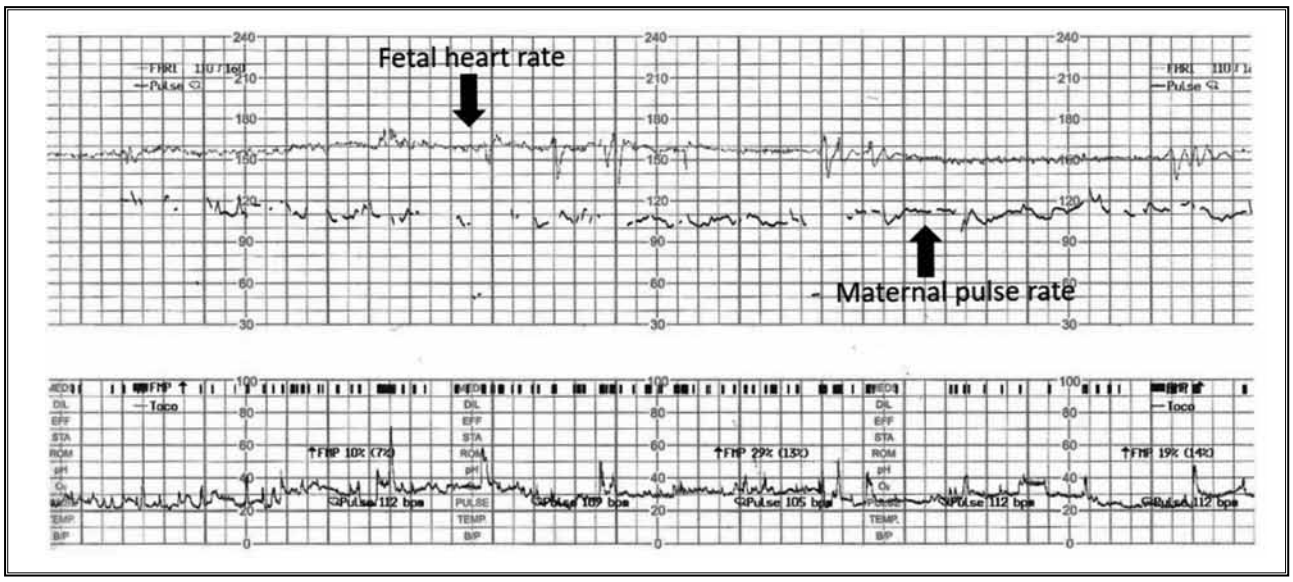

Figure 3. Cardiotocogram of the surviving twin showing reactive fetal heart rate pattern even when Doppler ultrasonography of the middle cerebral artery showed fetal anaemia

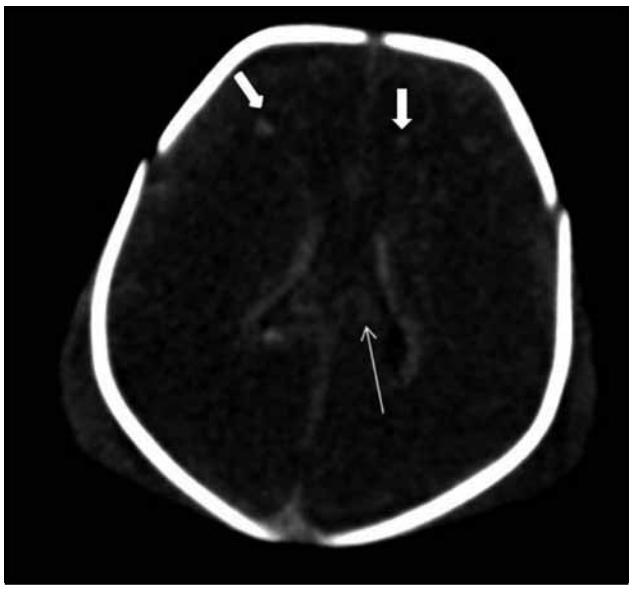

Figure 4. Computed tomography of the brain of the surviving twin 2 days after birth showing diffuse cerebral oedema with generalised hypo-attenuation of brain parenchyma, intraventricular haemorrhage (thin arrow), and petechial haemorrhages in both frontal lobes (bold arrows)

view of the poor prognosis, the couple opted for extubation on day 18 and the baby succumbed. The histology of the placenta showed monochorionic placenta with mild acute subchorionitis. The placenta karyotype was normal. The postmortem examination of twin 1 was unremarkable. The parents refused postmortem examination of twin 2.

Discussion

The incidence of single fetal demise in twin pregnancy is around 0.5% to 6.8% in all twin pregnancies during the second and third trimesters[1]. The incidence of single fetal demise in a regional unit in Hong Kong is 3.8%[2]. The causes of single fetal demise in twin pregnancy can be similar to singleton pregnancy including fetal causes such as chromosomal or genetic abnormalities, structural abnormalities, fetal infection, and placental causes such as placental insufficiency, placental abruption, and maternal causes such as pre-eclampsia. In addition, there are other specific causes for twin pregnancy with single fetal demise such as TTTS in monochorionic twins and cord entanglement in monochorionic monoamniotic twins. However, no specific cause for the intrauterine death of twin 1 was identified. The karyotype and postmortem examination were normal. There was no evidence of placental abruption and maternal pre-eclampsia. Serial ultrasound did not find any evidence of TTTS or selective intrauterine growth restriction of the demised fetus. In a systematic review and meta-analysis of 1747 pairs of monochorionic twin pregnancies who were not complicated with TTTS, intrauterine growth restriction, or major anomalies[3], the rate of stillbirth was consistently higher in monochorionic twins than dichorionic twins at all gestations. The rate of stillbirth in uncomplicated monochorionic twins was 3.1 per 1000 pregnancies at 28-29 weeks of gestation and the prospective risk of any fetal death per uncomplicated monochorionic twin pregnancy at 28-29 week of gestation was 2.1%[3]. Therefore, single fetal demise in uncomplicated monochorionic twins is not rare.

For single fetal demise in twin pregnancy, the outcome of the co-twin is poorer in monochorionic twins than dichorionic twins. In the 2011 systematic review and meta-analysis of 20 studies on co-twin prognosis after single fetal demise[4], the rate of co-twin death after single fetal demise was 15% in monochorionic twins, compared with 3% in dichorionic twins. The rate of neurodevelopmental impairment in the co-twin after single fetal demise was 26% in monochorionic twins, compared with 2% in dichorionic twins[4]. There are two theories for the poorer prognosis for monochorionic twins. The first theory is haemodynamic fluctuations in monochorionic twins. The death of one fetus results in low pressure in that fetal vascular tree, leading to transfer of blood from the surviving fetus 'back-bleed' through placental anastomoses to the demised fetus. This leads to hypoperfusion, hypotension, and fetal anaemia in the surviving fetus. If the hypotension is severe, this can result in tissue hypoxia, acidosis, and damage in fetal systems, particularly in the central nervous system, and possibly death of the co-twin[5-7]. The second theory is that the demised fetus produces thromboplastic material that passes from the demised fetus to the co-twin via placental vascular anastomoses, which then induces disseminated intravascular coagulopathy in the co-twin. However, there is doubt as to whether these thrombi arise from the dead twin or as a result of haemodynamic changes in the co-twin. As intracranial ultrasound anomalies had been detected in the surviving co-twin as early as 7 days, it is unclear whether disseminated intravascular coagulopathy can arise so quickly. The second theory is not supported by recent studies[5-7].

There are three patterns of brain pathology in surviving co-twins. The first is hypoxic ischaemic lesions of white matter, especially over areas supplied by the middle cerebral artery. The second is haemorrhagic lesions which may lead to post-haemorrhagic hydrocephalus. The third is anomalies secondary to a vascular disturbance including neural tube defects and optic nerve hypoplasia[6]. A study

reported that single fetal demise before 28 weeks of gestation was significantly less likely to lead to neurological damage in the co-twin than after 28 weeks of gestation (3.6% vs 20.0%, p=0.02)[8]. However, a case of single fetal demise as early as 13 weeks leading to neurological injury of the co-twin has been reported[9]. Therefore, there is no definite cut-off value as to the gestation at which the co-twin is safe from neurological damage. Our surviving co-twin was found to have neurological damage, which manifested as seizures in the early neonatal period, and lesions were discernable from computed tomography of the brain within the first week of life. The cause of neonatal death of the co-twin was due to renal failure, which was likely caused by hypoperfusion to the co-twin's kidneys after the fetal demise. When counselling patients on the prognosis of the co-twin after single fetal demise in monochorionic twin pregnancy, we usually focus on the incidence of intrauterine death and the risk of neurological damage of the surviving co-twin, and seldom refer to complications in other organ systems. Renal cortical necrosis, small bowel atresia, gastroschisis, aplasia cutis, and terminal limb infarction have all been reported in the surviving co-twin as a result from fetal anaemia[7]. Therefore, we should provide more comprehensive counselling on these possible complications, in addition to neurological damage.

There are no guidelines or gold standard for management of single fetal demise in monochorionic twin pregnancy. Recommendations are mainly based on case reports, case series, or expert opinions. In a local case series of six cases of single fetal demise in monochorionic twins, four had immediate delivery of the co-twin when the fetal demise occurred after 35 weeks of gestation, whereas two had conservative management when the fetal demise occurred at 19 and 21 weeks of gestation[2]. Management remains controversial when the fetal demise occurs in late second trimester or early third trimester, as in our patient. Some proposed a more aggressive management to deliver the surviving co-twin instead of conservative management, as there are major potential risks of leaving the co-twin in the hostile intrauterine environment that have already led to the death of one fetus[10]. In a case series of immediate delivery of the co-twin in 13 cases of twins with single fetal demise, two were found to have subsequent neurological damage, one being the results from prematurity[11]. In a retrospective study of 38 cases of twins with single fetal demise (79% were monozygotic pairs), those co-twin survivors with abnormal neurological outcomes had fetal demise at later gestations than those co-twins with normal neurological outcomes (31 vs 16.5 weeks). The former also had a shorter interval between the fetal demise and delivery (2.5 vs 21 weeks) and were delivered earlier in gestation (36.5 vs 39.5 weeks). A more conservative approach is advocated, because the ischemic brain damage in the co-twin likely occurs during or soon after the fetal demise; thus, immediate delivery would not prevent this damage but would add to the complications of prematurity[6]. Prematurity and low birthweight are the main risk factors for poor neurological outcome of the surviving co-twin[12].

As the complications of the surviving co-twin in a monochorionic twin pair are largely related to hypoperfusion and fetal anaemia, intrauterine transfusion of the surviving co-twin is suggested. In two case series on 22 pairs of twin pregnancies, fetal blood sampling was performed after single fetal demise[13,14]. Nine surviving co-twins were non-anaemic and had normal outcomes, whereas the remaining 13 were anaemic and underwent in-utero blood transfusion. Of the latter, six had normal neurological outcomes, three had abnormal brain scan on follow-up and were terminated, two had intrauterine death at 24 hours after transfusion, one was delivered at 34 weeks with neurological damage, and one was delivered at 29 weeks with subsequent neonatal death[13,14]. Intrauterine blood transfusion may prevent death of the co-twin but whether it can prevent neurological damage is controversial, as the damage may have already occurred shortly after twin fetal demise and before intrauterine transfusion. In our patient, if intrauterine blood transfusion was performed instead of delivery when Doppler parameters showed signs of fetal anaemia, the pregnancy might be prolonged to a later gestation for the baby to gain sufficient birthweight and maturity for renal dialysis after delivery. However, it is unknown whether the neurological outcome and renal failure of the surviving co-twin could be improved by intrauterine transfusion. Nevertheless, if the surviving co-twin was suspected to have anaemia on ultrasound, the option of intrauterine blood transfusion could be offered while pointing out the limited evidence supporting such treatment, and the patient could be referred to a quaternary centre where intrauterine transfusion could be arranged.

After single fetal demise in twin pregnancy, spontaneous labour may occur. However, some women may develop pre-eclampsia and placental abruption and necessitate immediate delivery of the co-twin. In the systematic review and meta-analysis of co-twin prognosis after single fetal demise, the risk of preterm delivery of the surviving co-twin was 68% in monochorionic twins, which included spontaneous labour and intragenic delivery[4]. Most reviews advocate regular surveillance of the surviving co-twin by ultrasound for fetal signs of anaemia, fetal growth

and liquor volume and by cardiotocogram for fetal well being[1,2,5,6]. In our patient, the peak systolic velocity of the middle cerebral artery can reflect the anaemic status of the surviving co-twin, but the cardiotocogram was not useful. The cardiotocogram pattern was still reactive immediately before delivery, even when the baby was found to be severely anaemic after birth. Therefore, a reactive cardiotocogram pattern alone should not be regarded as normal fetal well-being without consideration of other ultrasound parameters. For prediction of neurological damage in the surviving co-twin, apart from regular ultrasonography of the brain, magnetic resonance imaging of the brain is regarded as 'routine' imaging for such cases, and can be performed around 2-3 weeks after the fetal demise to detect any structural evidence of neurological damage. The sensitivity of such imaging remains unknown[1,5-7].

Conclusion

The prognosis of the co-twin in single fetal demise in monochorionic twin pregnancy is poorer than dichorionic twin pregnancy. Accurate determination of chorionicity in early gestation is crucial for all twin pregnancies, as the subsequent monitoring and management is different. Regular ultrasound surveillance and appropriate intervention to avoid single fetal demise in monochorionic twins such as in those with TTTS or selective intrauterine growth restriction is a more effective way to prevent adverse outcome of the co-twin, compared with close surveillance after single fetal demise, which cannot guarantee good outcome of the surviving co-twin. There is no gold standard for the optimal management of the surviving co-twin, but the current evidence favours conservative management before 34 weeks of gestation. The role of intrauterine transfusion is controversial, and treatment should be individualised.

Declaration

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Risk factors for failure of antibiotic therapy for tubo-ovarian abscess

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Objective: To assess the risk factors for antibiotic therapy failure and to predict which patients will require surgical drainage for tubo-ovarian abscess.
Methods: We collected data from patients by ICD-9 codes starting with 614.2. We extracted data regarding background information, clinical presentation, laboratory parameters, and ultrasonographic findings. Patients responded to antibiotics alone were compared with patients required surgical drainage. Relative risk of surgical drainage was estimated with logistic regression model.
Result: A total of 126 cases of tubo-ovarian abscess were evaluated, of which 92 were successfully managed with antibiotic therapy alone and 34 required surgical drainage. Age, multiparity, intrauterine device use, fever, maximal white cell count and abscess size were identified to be significant risk factors associated with the need for surgical drainage. The adjusted relative risks of surgical drainage were 2.250 for abscess size ≥8 cm, and 3.162 for fever on admission. The duration of hospitalisation was increased by 23.8% for abscess size ≥8 cm and by 23.7% for fever on admission.
Conclusion: Larger abscesses are associated with increased risk of surgical drainage. However, additional research is required to determine the optimal treatment for large abscesses. It is reasonable to try antibiotic therapy in clinically stable patients irrespective of abscess size.

Keywords: Abscess; Anti-bacterial agents; Drainage; Fallopian tube diseases; Ovarian diseases

Introduction

Tubo-ovarian abscess (TOA) is a severe form of pelvic inflammatory disease and can involve the fallopian tubes, ovaries, and occasionally adjacent pelvic organs (eg, the bowel, bladder, and omentum). The mortality rate of TOA could approach 50% before the era of broad-spectrum antibiotics and modern surgical drainage[1]. Mortality is rare for uncomplicated TOA, but if TOA is complicated with systemic sepsis or rupture of abscess, the mortality rate can be as high as 5% to 10%[2]. Management options for TOA include antibiotics with or without surgical drainage that is performed immediately or subsequently after suboptimal response to antibiotics. Antibiotic therapy is commonly used; the rate of surgical drainage is 25%. Abscess size, white cell count (WCC), fever, and age are common predictors of surgical drainage[3,4]. In critically ill patients (with signs of sepsis and peritonitis), prompt surgical drainage and antibiotics and appropriate resuscitation are preferable. In clinically stable patients, a combined regimen of broad-spectrum antibiotics is the primary treatment option and is effective in up to 70% of cases[3]. The chosen antibiotics should cover the commonest causative pathogens, have high abscess cavity penetration power, and have a low local resistance rate. The British Association for Sexual Health and HIV provides guidance on possible antibiotic choices, but the local units should develop their own protocols with input from microbiologists.

In the gynaecology unit of Tuen Mun Hospital, patients with suspected TOA are examined by ultrasonography of the pelvis, and diagnosis is made when an infected complex adnexal mass is observed. All such patients are treated as inpatients initially: unstable patients undergo surgical drainage immediately, whereas stable patients are treated with intravenous antibiotics, most commonly (80%) with intravenous levofloxacin and metronidazole, which is recommended by gynaecology

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consultants and local microbiologists in Tuen Mun Hospital, based on previous treatment performance and the bacterial resistance profile. Additional antibiotics or alteration to the regimen is based on clinical response and sensitivity results. Patients are closely monitored for vital signs and laboratory parameters (especially WCC) for 48 hours after treatment. Surgical drainage by laparoscopy or laparotomy is considered if no significant clinical improvement. Image-guided drainage is seldom performed in our unit, owing to limited support from interventional radiology services. For patients with significant clinical improvement after 48 hours, antibiotics are switched to oral route and patients can be discharged from the hospital according to their progress. A ward follow-up session is arranged within 4 to 6 weeks to confirm resolution of the TOA with ultrasonography.

Local data in TOA treatment outcomes are lacking. This retrospective study aimed to identify the risk factors of failed antibiotic therapy in a local population so as to predict which patients require surgical drainage and which factors affect treatment success.

Methods

Case notes of women diagnosed with TOA admitted to Tuen Mun Hospital from 1 January 2012 to 31 December 2016 were retrospectively reviewed. Potential subjects were selected based on ICD-9 codes starting from 614.2 (ie, salpingitis and oophoritis not specified as acute, subacute, or chronic). Only clinically stable patients treated initially with antibiotics were included. Critically ill patients who underwent immediate surgical drainage were excluded, as were those who were initially misdiagnosed as having other diseases and later correctly diagnosed as having TOA during operation. A total of 126 patients with TOA were included in the final analysis.

Clinical characteristics were extracted and categorised into background information, clinical presentation, laboratory parameters, and ultrasonographic findings. Background information included age, parity, presence of immunocompromised condition (eg, diabetes mellitus, autoimmune disease, or long-term steroid use), history of pelvic inflammatory disease, history of hydrosalpinx or ovarian cyst, history of major abdominal surgery, presence of intrauterine device, condom usage, and history of invasive gynaecological procedure within 6 weeks (eg, hysteroscopy or endometrial aspiration). Clinical presentation included presenting symptoms (ie, fever, vomiting or nausea, pain, or vaginal discharge) and duration of symptoms. Laboratory parameters included WCC on admission, maximal WCC during hospitalisation, and presence of positive culture. Pelvic ultrasonography by transvaginal and transabdominal route was the major imaging modality used in our unit. Ultrasonography was performed to quantify abscess size and any bilateral lesions. Abscess size was defined as the maximal dimension of the mass on ultrasonography. If bilateral abscesses were present, the larger of the two was used to quantify abscess size.

Outcome measures included the success rate with antibiotics alone and the duration of hospitalisation. Successful antibiotic treatment was defined as no emergency surgical procedures for TOA were needed within 12 weeks of presentation.

Non-parametric methods were used owing to the non-normal nature of the data and small sample size. Fisher's exact test was used for categorical variables for comparing the distribution of surgical drainage and antibiotics alone group. Wilcoxon rank-sum test was used for continuous variables for comparing the two groups. Relative risks (RRs) and 95% confidence intervals (CIs) of variables were estimated from the logistic regression of surgical drainage with robust error variance[5]. Poisson regression with robust error variance was used to estimate the regression coefficients for length of hospitalisation.

Results

Of 126 patients, 92 (73.0%) responded to antibiotics alone and 34 (27.0%) required surgical drainage. Of 126 patients, 104 (82.5%) were initially treated with intravenous levofloxacin and metronidazole: 31 of 34 patients in the surgical drainage group and 73 of 92 patients in the antibiotics group (91% vs 79.3%, p=0.1851, Table 1). 22 patients were treated with other antibiotic regimens, including intravenous cefuroxime, metronidazole, and doxycycline (n=12), intravenous Augmentin and metronidazole (n=5), and intravenous cefuroxime and metronidazole (n=2).

In total, 34 patients had suboptimal response to initial antibiotics treatment, necessitating surgical drainage through laparotomy (n=16) or laparoscopy (n=17). Only one patient underwent computed tomography–guided drainage performed by an interventional radiologist.

Table 1. Antibiotic regimen*

	All patients (n=126)	Patient responded to antibiotics alone (n=92)	Patient required surgical drainage (n=34)
Levofloxacin + metronidazole	104 (82.5)	73 (79.3)	31 (91)
Other regimens	22 (17.5)	19 (20.7)	3 (9)
Cefuroxime + metronidazole + doxycycline	12	12	0
Augmentin + metronidazole	5	5	0
Cefuroxime + metronidazole	2	2	0
Taxobactam + piperacillin	1	0	1
Ceftriaxone + doxycycline	1	0	1
Clindamycin + metronidazole	1	0	1

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

The mean time interval between diagnosis and drainage was 4.3 days (median, 3 days); 33 patients underwent drainage during the same admission. The remaining one patient was discharged from the hospital after a 14-day course of antibiotics with good response, but she later complained of persistent pelvic pain. Ultrasonography during the ward follow-up session showed persistent TOA. Laparoscopic drainage was performed 26 days after the initial presentation.

The mean age of patients was 40.8±10.7 years; 42 (33%) patients were nulliparous; 9 (7%) patients were considered to have an immunocompromised condition; 26 (20.6%) patients had a history of pelvic inflammatory disease; 50 (39.7%) patients had major abdominal operations before; 17 (13.5%) patients were using intrauterine device for contraception; and 10 (7.9%) patients had invasive gynaecological procedures within 6 weeks prior to presentation. The most common symptom on presentation was abdominal pain (100%), followed by fever (50.8%). The mean maximal WCC was 14.7±6.2 per mm^3. The mean abscess size was 6.2±1.9 cm; 48 (35.7%) patients had bilateral abscesses. The mean duration of hospitalisation was 6.5±3.4 days.

Of 36 (28%) patients with positive culture results, the most common pathogen yielded was *Escherichia coli* (n=14), followed by *Staphylococcus aureus* (n=6), chlamydia (n=5), *Streptococcus milleri* (n=4), and *Streptococcus agalactiae* (n=4). Four (11.1%) cultures showed resistance to antibiotics (three in the surgical drainage group from peritoneal swabs and one in the antibiotics group, in which the regimen was changed to Augmentin and metronidazole.

Compared with the surgical drainage group, the antibiotic group were younger (39.4±11.0 years vs 44.3±9.5 years, p=0.0156) and had a higher prevalence of nulliparity (39% vs 17.6%, p=0.0323), a lower (not significantly) prevalence of intrauterine device use (9.8% vs 23.5%, p=0.074), a lower prevalence of fever on admission (35.9% vs 91.2%, p<0.0001), a lower maximal WCC during hospitalisation (13.9±5.7 vs 17.0±7.0, p=0.0108) but similar WCC on admission (13.6±5.7 vs 14.3±6.5, p=0.7312), smaller abscesses (5.7±1.8 cm vs 7.5±1.8 cm, p<0.0001) but similar in the prevalence of bilateral abscesses (32.6% vs 44.1%, p=0.2953), and a shorter duration of hospitalisation (5.2±2.5 days vs 9.9±3.2 days, p<0.0001) [Table 2].

The adjusted RR of surgical drainage of each clinical variable was estimated in a logistic regression model, with abscess size dichotomised to ≥8 cm and <8 cm. Surgical drainage was associated with abscess size ≥8 cm (adjusted RR=2.250, 95% CI=1.149-3.119) and fever on admission (adjusted RR=3.162, 95% CI=2.002-3.581).

Table 2. Patient characteristics, presenting symptoms, blood parameters, and ultrasonographic features*

	All patients (n=126)	Patient responded to antibiotics alone (n=92)	Patient required surgical drainage (n=34)	P value
Mean age, years	40.8±10.7	39.4±11.0	44.3±9.5	0.0156
Nulliparous	42 (33.3)	36 (39)	6 (17.6)	0.0323
With immunocompromised condition	9 (7.1)	6 (6.5)	3 (8.8)	0.7015
History of pelvic inflammatory disease	26 (20.6)	22 (23.9)	4 (11.8)	0.2137
History of hydrosalpinx	10 (7.9)	8 (8.7)	2 (5.9)	0.7279
History of ovarian cyst	12 (9.5)	6 (6.5)	6 (17.6)	0.0845
History of major abdominal surgery	50 (39.7)	34 (37.0)	16 (47.1)	0.3136
Presence of intrauterine device	17 (13.5)	9 (9.8)	8 (23.5)	0.074
Not using condom	109 (86.5)	77 (83.7)	32 (94.1)	0.1535
Having invasive gynaecological procedure within 6 weeks	10 (7.9)	6 (6.5)	4 (11.8)	0.4569
Fever >38°C on admission	64 (50.8)	33 (35.9)	31 (91.2)	<0.0001
Vomit/nausea	12 (9.5)	7 (7.6)	5 (14.7)	0.3035
Abdominal pain	126 (100)	92 (100)	34 (100)	1.0000
Vaginal discharge	31 (24.6)	24 (26.1)	7 (20.6)	0.6437
Duration of symptoms before admission, days	5.5±7.98	5.0±6.3	6.9±11.4	0.5962
White cell count on admission, per mm^3	13.8±5.9	13.6±5.7	14.3±6.5	0.7312
Maximal white cell count during hospitalisation, per mm^3	14.7±6.2	13.9±5.7	17.0±7.0	0.0108
Positive pathogen culture	36 (28)	22 (23.9)	14 (41.2)	0.0754
Abscess size, cm	6.2±1.9	5.7±1.8	7.5±1.8	<0.0001
Bilateral involvement	45 (35.7)	30 (32.6)	15 (44.1)	0.2953
Hospitalisation stay, days	6.5±3.4	5.2±2.5	9.9±3.2	<0.0001

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

The association between clinical variables and duration of hospitalisation was estimated using the Poisson regression model. After controlling for confounders, the duration of hospitalisation increased by 23.8% for abscess size ≥8 cm (p=0.045), by 0.86% for 1 year older (p=0.02), by 23.7% for fever on admission (p=0.01), and by 1.2% for 1 day longer duration of symptoms (p=0.01).

Discussion

Results of our study are consistent with those in other studies[6-8]. In a retrospective review of TOA, 65.6% of patients responded to antibiotics and 34.4% of patients required surgical or image-guided drainage; the mean TOA size was larger in those with surgical drainage (4.4 cm vs 7.3 cm, p<0.0001); and a higher risk of surgery was associated with higher maximal leukocyte count, older age, and more parity[6]. In a cross-sectional study of TOA, 74% of patients responded to antibiotic treatment; compared with patients with surgical drainage, those with antibiotic treatment had shorter hospitalisation (6.32 days vs 12.75

days, p=0.021) and smaller TOA (53.6 mm vs 67.9 mm, p=0.036)[7]. In a retrospective review, 69% of patients responded to antibiotic treatment and 31% of patients required surgical drainage; the mean TOA size was larger in those with surgical drainage (6.3 cm vs 7.7 cm, p=0.02); a 1-cm increment in abscess size was associated with an increase in hospitalisation of 0.4 days (p=0.01)[8].

In our study, 73% of patients responded to antibiotic treatment and 27% of patients required surgical drainage. Patients requiring surgery were older; were more likely to be multiparous, having a higher maximal WCC, having a bigger abscess, having longer duration of hospitalization, and more likely to use intrauterine device for contraception.

Larger abscesses and surgical drainage lead to a longer hospitalisation[7,8]. In a retrospective study, patients with TOA of ≥8 cm were hospitalised longer than those with TOA of <8 cm (7.71 days vs 5.97 days, p<0.029)[9]. In our study, hospitalisation was longer in surgical drainage group than antibiotic group (9.9 days vs 5.2 days, p<0.0001). Duration of hospitalisation was 23.8% longer for patients with abscess size ≥8 cm (p=0.01). In addition, older age and longer duration of symptoms also increased length of hospitalisation.

Abscess size is a risk factor of surgical drainage. A management algorithm proposed that patients with TOA of ≥8 cm should receive ultrasound-guided drainage or surgery with concomitant intravenous antibiotics to shorten hospitalisation and decrease hospital costs[9]. Nonetheless, surgical complications, readmission rate, and fertility preservation should be considered. Surgical drainage should be offered when medical treatment fails. In our study, 45% (10/22) of patients with abscess size ≥8 cm responded to antibiotic treatment. We suggest primary treatment with antibiotics for all clinically stable patients with TOA provided that patients are closely monitored for TOA complications and surgical drainage is promptly performed when indicated.

Limitations of our study include an inability to completely control confounders such as virulence of pathogens, and no study of long-term complications (recurrence, chronic pelvic pain, fertility) of antibiotic treatment and surgical drainage. Randomised controlled trials are needed to provide evidence regarding optimal treatment of TOA patients with different risk factors. Nonetheless, the sample size of our study was large (n=126) despite TOA being an infrequent pelvic inflammatory disease complication. Relative risks of the clinical variables were estimated with a regression model.

Conclusion

Larger abscesses are associated with increased risk of surgical drainage. However, additional research is required to determine the optimal treatment for large abscesses. It is reasonable to try antibiotic therapy in clinically stable patients irrespective of abscess size.

Declaration

The authors have no conflict of interest to disclose.

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Genetic loci associated with age at menopause and bone mineral density in Southern Chinese women: a replication study

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Purpose: A meta-analysis of genome-wide association studies in Europeans identified 19 loci associated with age at menopause. This study aimed to validate these loci in Southern Chinese women and their association with bone mineral density.
Methods: This was a replication study on 609 women who had participated in the Hong Kong Osteoporosis Study. Archived DNA was genotyped using the Sequenom iPLEX platform. 14 single-nucleotide polymorphisms that had been reported to be associated with age at menopause or bone mineral density in European populations were examined using univariate linear and logistic regression analyses.
Results: Of the 14 genotyped loci, only rs11668344, rs365132, and rs10183486 were associated with age at menopause in Southern Chinese women, with effect sizes of -0.847 (p=0.014), 0.524 (p=0.008), and -1.300 (p=0.028), respectively. Two of them (rs11668344 and rs365132) were associated with early menopause, with the odds ratio being 1.975 (p=0.048) and 0.639 (p=0.032), respectively. Each unit increase in the genetic risk score composed of these two single nucleotide polymorphisms was associated with an odds ratio of 1.62 (p=0.006) for early menopause. rs10183486 was also associated with bone mineral density at the lumbar spine (p=0.048) and femoral neck (p=0.039).
Conclusions: rs11668344, rs365132, and rs10183486 are associated with age at menopause and bone mineral density in Southern Chinese women.

Keywords: Bone density; Menopause; Menopause, premature; Polymorphism, single nucleotide

Introduction

Menopause is a major life event of women that marks the end of a reproductive life. The age at menopause (AAM) varies widely across different populations, with a median of 49 to 52 years. Premature or early menopause can be associated with health implications such as increased risks of cardiovascular diseases[1-4], cardiovascular death[5], stroke[3,6], osteoporosis[4], and all-cause mortality[7], with shortened life expectancy in general. Later AAM is associated with increased risks of cancers of the breast, endometrium, and ovary[8,9].

AAM is a complex trait determined by intricate interactions between a number of genetic and environmental factors. Heritability estimates ranging from 31% to 87% have been reported[10]. Identification of the genetic factors influencing AAM can contribute to understanding of the underlying mechanisms of the ovarian ageing process and the pathogenetic linkage to other health conditions that are associated with early or late AAM.

A meta-analysis of 22 genome-wide association studies (GWASs) in women of European descent identified 19 loci that were associated with AAM[11]. Whether these loci are associated with AAM in the Southern Chinese

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population remains unknown. The current study aimed to validate these loci in Southern Chinese women.

Methods

This study was a secondary analysis of the Hong Kong Osteoporosis Study[12]. In brief, women of Southern Chinese ethnicity who were not receiving medical treatment for osteoporosis or other medications that might affect bone mineral metabolism were recruited from roadshows and health talks in various districts in Hong Kong between 1995 and 2010. The recruitment procedure, inclusion and exclusion criteria have been reported previously[12,13]. This study and the original study were approved by the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster. Those who were post-menopausal at recruitment with archived DNA and data on AAM and bone mineral density (BMD) were included in this secondary study.

Early menopause was defined as AAM <45 years. Women with early menopause were compared with those with AAM ≥50 years, which was the median AAM in our cohort.

The archived DNA samples were genotyped for the 20 genetic loci (Table 1), using the Sequenom iPLEX system (Sequenom, San Diego, CA, USA). For quality control, we included single nucleotide polymorphisms (SNPs) with minor allele frequency of ≥0.01, Hardy-Weinberg equilibrium p value of ≥0.0025, and call rate of ≥90%. Of the SNPs, one failed in minor allele frequency (rs16991615), three failed in Hardy-Weinberg equilibrium (rs4246511, rs12294104, rs2307449), and four failed in call rate (rs4246511, rs12294104, rs4886238, rs2307449); these were excluded from analysis.

BMD was measured at the L1 to L4 lumbar spine and femoral neck using dual-energy X-ray absorptiometry, which was calibrated daily, with in vivo precision of 1.2% at the lumbar spine and 1.5% at the femoral neck.

Associations of the minor allele of the GWAS-significant loci with AAM and BMD at baseline were analysed using the univariate linear regression model. Association of the minor allele of the GWAS-significant loci with occurrence of early menopause was analysed using the univariate logistic regression model. Additive genetic model was used in the analyses. A one-sided p value of <0.05 was considered statistically significant if the direction of association was the same. The unweighted genetic risk score was calculated by summing the number of significant at-risk alleles associated with early menopause (ie, the minor allele of rs10183486 and rs11668344, and the major allele of rs365132), or the number of significant at-

Table 1. Significant single-nucleotide polymorphisms (SNP) in genome-wide association study

Chr	SNP	Physical position	Nearest gene(s)	Major/minor allele		Beta (European studies)[11]	Missingness	Minor allele frequency
				This study	European studies[11]			
1	rs1635501	240107398	*EXO1*	T/C	T/C	-0.164	0.003	0.192
2	rs2303369	27568920	*FNDC4*	C/T	C/T	-0.175	0.002	0.161
2	rs10183486	171699217	*TLK1*	C/T	C/T	-0.196	0.062	0.017
2	rs7606918	172603695		A/G	A/G	-0.228	0.007	0.118
4	rs4693089	84592646	*HEL308*	G/A	A/G*	0.228	0.011	0.329
5	rs890835	175888877	*RNF44*	C/A	C/A	0.177	0.009	0.201
5	rs365132	176311180	*UIMC1*	G/T	G/T	0.287	0.007	0.478
6	rs2153157	11005474	*SYCP2L*	A/G	G/A*	0.165	0.01	0.346
8	rs2517388	38096889	*ASH2L*	G/T	T/G*	0.262	0.005	0.379
12	rs2277339	55432336	*PRIM1*	T/G	T/G	-0.380	0.001	0.199
13	rs3736830	49204222	*KPNA3*	G/C	C/G*	-0.180	0.011	0.426
16	rs10852344	11924420	*TNFRSF17, RUNDC2A, GSPT1*	C/T	T/C*	0.168	0.007	0.212
19	rs11668344	60525476	*TMEM150B*	A/G	A/G	-0.416	0.012	0.083
19	rs12461110	61012475	*NLRP11*	G/A	G/A	-0.158	0.007	0.327

* Minor allele was different between data from Stolk et al[11] and our cohort

risk alleles associated with early menopause (ie, the minor allele of rs11668344 and the major allele of rs365132). Statistical analysis was carried out using PLINK v1.07 and SPSS (Windows version 22; IBM Corp, Armonk [NY], US). Power calculation confirmed that our study was well-powered (≥80%) to detect SNP with an effect size of 1% with an additive genetic model, assuming the alpha was 0.05 (1-sided).

Results

A total of 609 participants were included, with median age 63 years (25th to 75th percentile, 57-70 years), median height 1.52 m (25th to 75th percentile, 1.48-1.57 m), median weight 53.6 kg (25th to 75th percentile, 47.5-61 kg), and median AAM 50 years (25th to 75th percentile, 47-52 years).

The studied SNPs were not in linkage disequilibrium. Three of the genotyped loci, namely rs10183486, rs11668344, and rs365132, showed significant association with AAM, with effect sizes (beta) of the minor allele being -1.300 (p=0.028), -0.847 (p=0.014), and 0.524 (p=0.008), respectively (Table 1). The unweighted genetic risk score of these three loci explained 2.4% of the variance in AAM, and each unit increase in genetic risk score was associated with a beta of -0.699 (SE=0.188, p<0.001).

The GWAS-significant loci were compared between those with early AAM (n=55) and those with AAM ≥50 years (n=353). The minor alleles of rs11668344 and rs365132 were associated with increased odds of 1.98 (95% CI=1.01-3.88, p=0.048) and decreased odds of 0.64 (95% CI=0.42-0.96, p=0.032) of early menopause, respectively (Table 2). The genetic risk score composed of these two SNPs showed a significant association with early menopause; each unit increase in genetic risk score was associated with an odds ratio of 1.62 (95% CI=1.15-2.28, p=0.006).

Of the three significantly replicated loci, only rs10183486 was associated with BMD at the lumbar spine and femoral neck, with a beta of -0.044 (SE=0.022, p=0.048) and -0.031 (SE=0.015, p=0.039), respectively (Table 3).

Discussion

To our knowledge, this is the first report on the replication of the genetic loci in association with AAM in

Table 2. Association between significant single-nucleotide polymorphisms (SNP) with age at menopause in Hong Kong Chinese

SNP	Age at menopause			Age at menopause of <45 vs ≥50 years (reference)	
	Beta	SE	p value	Odds ratio (95% confidence interval)	p value
rs1635501	-0.227	0.281	0.21	1.181 (0.706-1.976)	0.526
rs2303369	-0.216	0.302	0.237	1.294 (0.773-2.168)	0.327
rs10183486	-1.300	0.677	0.028	2.490 (0.897-6.915)	0.080
rs7606918	-0.342	0.336	0.154	1.679 (0.952-2.961)	0.073
rs4693089	-0.105	0.232	0.325	1.047 (0.691-1.584)	0.829
rs890835	0.163	0.269	0.273	0.855 (0.513-1.424)	0.547
rs365132	0.524	0.218	0.008	0.639 (0.424-0.963)	0.032
rs2153157	-0.113	0.224	0.308	1.001 (0.666-1.505)	0.997
rs2517388	0.072	0.225	0.375	0.932 (0.610-1.423)	0.744
rs2277339	0.074	0.261	0.389	0.974 (0.608-1.562)	0.913
rs3736830	-0.105	0.226	0.321	1.297 (0.858-1.959)	0.218
rs10852344	0.248	0.261	0.171	0.607 (0.347-1.061)	0.080
rs11668344	-0.847	0.383	0.014	1.975 (1.005-3.882)	0.048
rs12461110	0.229	0.237	0.168	1.028 (0.669-1.577)	0.901
Genetic risk score*	-0.699	0.188	<0.001	1.62 (1.15-2.28)	0.006

* Refers to the number of significant at-risk alleles associated with early age at menopause (ie, the minor allele of rs10183486 and rs11668344, and the major allele of rs365132), or the number of significant at-risk alleles associated with occurrence of early menopause (ie, the minor allele of rs11668344 and the major allele of rs365132) of individual subjects

Table 3. Association between significantly replicated single-nucleotide polymorphisms (SNP) with bone mineral density (BMD) after adjusting for age, sex, height, and weight

SNP	Lumber spine BMD			Femoral neck BMD		
	B	SE	p value	B	SE	p value
rs10183486	-0.044	0.022	0.048	-0.031	0.015	0.039
rs365132	0.002	0.006	0.708	-0.002	0.004	0.670
rs11668344	-0.011	0.011	0.291	-0.007	0.007	0.353

the Southern Chinese population. Our results demonstrated considerable disparity between the genetic factors that determine AAM in the European and Southern Chinese populations. Only three of the genetic loci, namely rs11668344, rs365132, and rs10183486, were common determinants in the two populations. In a replication study on the GWAS-identified SNPs for AAM conducted in Shanghai, only two of our replicated genetic loci, namely rs11668344 and rs365132, were common determinants, and another SNP (rs7246479) related to the former (*TMEM150B*) gene was reported instead.[14] In the Shanghai study, six other significant SNPs were reported but they were not significant in our cohort. Another replication study using GWAS data in the Shanghai and Korean populations replicated five of the loci, namely rs365132, rs11668344, rs4246511, rs2307449, and rs12461110[15]; the first two concurred with our findings in Southern Chinese.

The rs10183486 and rs11668344 loci had the largest effect sizes among those studied. The rs10183486 locus is in the intron of the *TLK1* gene, which codes for a nuclear serine-threonine kinase involved in DNA repair mechanisms and regulation of chromatin assembly[16]. The rs11668344 locus is in the intron region of the *TMEM150B* gene, which encodes a transmembrane protein called DRAM-3 which is ubiquitously expressed in all tissues and may modulate damage-related autophagy[17]. The rs365132 loci is associated with the *UIMC1* gene, which encodes a protein that interacts with BRCA1 and oestrogen receptor-alpha and regulates G2/M phase check-point control of the cell cycle. This protein is hence involved in DNA damage repair and replication[18]. Apart from association with AAM[11], these three SNPs have not been associated with any direct actions on physiological processes in the human ovary. Their underlying mechanisms associated with AAM are unknown. It is possible that the actions of these genetic factors in modulating DNA repair, cell cycle control, and inflammatory processes may interact synergistically to influence ovarian ageing processes.

The absolute effect size of each gene locus in our Southern Chinese population was much smaller than that in European populations[11]. The difference probably arises from ethnic difference in the minor allele frequency and different exposure to various environmental factors. Despite the small effect size of these gene loci and that each unit increase in the unweighted genetic risk score only explained 2.4% of the variance in AAM, the presence of one of the three at-risk alleles resulted in a 62% increase in the odds of early menopause. The synergy of these loci in interaction with various environmental factors is expected to modulate the AAM of each woman.

Only one replicated SNP, rs10183486, was significantly associated with BMD at both the lumbar spine and femoral neck. The minor allele of rs10183486 was associated with both early AAM and lower BMD, conforming with the common understanding that early AAM is considered a predisposing factor to accelerated loss in BMD. Nonetheless, further longitudinal studies with osteoporosis as the outcome measure are needed for validation. Genetic diversity between Southern Chinese and Europeans was great, because allele frequencies of most the SNPs in our population differed from those reported in the European populations[11], and some SNPs in the minor allele in one population was the major allele in the other.

The main limitation of our study was the small sample size. We preliminarily explored how the genetic loci in the European populations were replicated in our population. Larger-scale studies are needed because of the considerable difference between our population and both the European and Shanghai populations. In addition, data were lacking on environmental factors (such as smoking, diet) and past medical history (such as previous ovarian surgery or gonadotoxic treatments), which might interact with the genetic factors in determining AAM. Such gene-environment interactions are worth exploring in larger studies. Furthermore, this study was designed

as a replication study, and hence could not address other significant SNPs in our population that were not significant in Europeans.

Conclusion

Three of the genotyped loci (rs11668344, rs365132, and rs10183486) are associated with AAM in Southern Chinese women. Further investigation is needed to determine the mechanisms of how these associated genes act towards ovarian ageing, the occurrence of menopause, and the association with postmenopausal osteoporosis.

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Declaration

The authors have no conflict of interest to disclose.

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Iron therapy in obstetrics and gynaecology: a review

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There are three problems in managing iron deficiency anaemia in child-bearing-age women: lack of awareness of the condition by both patient and clinician, inexperience in the diagnosis, and lack of familiarity with available oral and intravenous iron therapy. Iron deficiency is common in women, from menarche, through growth spurt in puberty, pregnancy, and postpartum, and until menopause. To screen for underlying iron deficiency, a haemoglobin cut-off for anaemia is used. Iron deficiency anaemia must be excluded for patients with haemoglobin level below the cut-off. Oral iron therapy is effective in treating iron deficiency anaemia. Low-dose alternate-day oral iron therapy is recommended (rather than daily iron dose). It is crucial to accompany oral iron therapy with vitamin C. Intravenous iron therapy, particularly with third-generation iron compounds, is safe, effective, and faster acting than oral iron therapy.

Keywords: Anemia, iron-deficiency; Ferritins; Postpartum period; Pregnancy

Introduction

Iron is vital for bodily functions. Women typically have 2000-3000 mg elemental iron in the body (about 40 mg/kg). Two-thirds of the body's iron is embedded in red blood cells facilitating oxygen transfer, whereas 10% is in skeletal muscle and the myocardium carrying out oxidative metabolism or in iron-containing enzymes and proteins all over the body involved in adenosine triphosphate formation, DNA synthesis, hormonal synthesis, signal-controlling functions in neurotransmitters, and detoxification in the liver. The remaining iron is stored in the reticuloendothelial system. Well-nourished child-bearing-age women retain around 300-600 mg (5-10 mg/kg) iron in this reticuloendothelial system. A normal pregnancy requires around 1000 mg elemental iron[1,2]. This requirement would be challenging for women with low iron reserve because of inadequate dietary iron intake and/or high menstrual flow.

Epidemiology

Iron deficiency anaemia affects one-sixth of the global population (ie around 1.24 billion people)[3]. It ranks the fourth in the leading causes of disability worldwide[3]. In Hong Kong, there are no epidemiological data about anaemia, iron deficiency, or iron deficiency anaemia in child-bearing-age women. According to data from new blood donors, the anaemic rate among reproductive age women increased from 21.6% in adolescents aged 16-20 years to 26.9% in women aged 41-50 years (Table 1). According to data from local hospitals, 16.3% of women are anaemic at term and 22.3% of women are anaemic post-delivery (Table 2).

Clinical consequences of iron deficiency

Iron deficiency anaemia markedly impairs the quality of life in child-bearing-age women and may result in fatigue, reduced exercise tolerance, reduced concentration, and impaired emotional control manifesting as depression, anxiety, stress or irritability, restless leg syndrome, and hair loss[4-6]. During pregnancy there may be additional detrimental effects on maternal and fetal outcomes. In a retrospective study of 75 660 singleton pregnancies, 7977 women were diagnosed with iron deficiency anaemia at delivery. Compared with pregnant women without iron deficiency, the presence of iron deficiency increased the risks of blood transfusion (odds ratio [OR]=5.48, 95% confidence interval [CI]=4.57-6.58), preterm delivery (OR=1.54, 95% CI=1.36-1.76), Caesarean delivery (OR=1.30, 95% CI=1.13-1.49), 5-minute Apgar score <7 (OR=2.21, 95% CI=1.84-2.64), and intensive care unit admission (OR=1.28, 95% CI=1.20-1.39)[2,7]. In a meta-analysis of 26 studies, maternal anaemia (mostly iron deficiency anaemia) was associated with higher risks of low birthweight (relative risk [RR]=1.31, 95% CI=1.13-1.51), preterm birth (RR=1.63, 95% CI=1.33-2.01), perinatal mortality (RR=1.51, 95% CI=1.30-1.76), and neonatal mortality (RR=2.72, 95% CI=1.19-6.25)[2,8].

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Table 1. Anaemia rate in new female blood donors in 2016 and 2017 (n=57 312)

Anaemia (haemoglobin level, g/dL)	Anaemia rate in new female blood donors, %			
	Age 16-20 years	Age 21-30 years	Age 31-40 years	Age 41-50 years
Severe (<8.0)	0.2	0.2	0.3	0.6
Moderate (8.0-10.9)	6.8	6.8	8.1	10.4
Mild (11.0-12.0)	14.6	15.8	16.0	15.9
Total	**21.6**	**22.8**	**24.4**	**26.9**

Table 2. Anaemia rate at admission and at discharge in women who deliver in Hospital Authority hospitals in September 2018 (n=2668)

Haemoglobin level, g/dL	No. (%) of women	
	At admission	At discharge
<7.0	4 (0.1)	3 (0.1)
7.0-7.9	15 (0.6)	62 (2.3)
8.0-8.9	57 (2.1)	197 (7.4)
9.0-9.9	195 (7.3)	333 (12.5)
10.0-10.5	163 (6.1)	-
Total	**434 (16.3)**	**595 (22.3)**

Diagnosis

To screen for underlying iron deficiency, different haemoglobin level cut-offs for anaemia at different stages of women's life have been defined[9]. The cut-off of <12 g/dL in non-pregnant women is widely accepted[9]. However, cut-offs in pregnant women are diverse: <11 g/dL is suggested by the World Health Organization (WHO)[9]; <11 g/dL in the first trimester and <10.5 g/dL in second and third trimesters are suggested by the British Committee for Standards in Haematology (BCSH)[10], the Royal College of Obstetricians and Gynaecologists (RCOG)[11], the National Institute for Health and Care Excellence (NICE)[12], the American College of Obstetricians and Gynecologists (ACOG)[13], and in South Australia[14]. For the postpartum period, BCSH defines anaemia as <10.0 g/dL[10], whereas Milman defined anaemia as <10 g/dL within 24-48 hour after delivery, <11 g/dL at first week postpartum, and <12 g/dL at 8 weeks postpartum and beyond[15,16].

To exclude iron deficiency in women with haemoglobin level below cut-offs, oral iron therapy trial is recommended for confirmation of iron deficiency anaemia[10,11,13,14,17]. Serum ferritin should be measured, as it is the most reliable indicator of iron deficiency in the absence of inflammation. The WHO defines iron deficiency as serum ferritin of <15 ng/mL[18]; however, the BCSH definition of <30 ng/mL is more widely accepted, improves sensitivity from 25% to 92%, and maintains specificity at 98%[10]. To accurately assess the maternal iron store, measuring serum ferritin at the first prenatal visit and at the beginning of the third trimester in addition to the usual haemoglobin checking is recommended[2]. Iron therapy is recommended if serum ferritin <40 ng/mL in the presence of anaemia or serum ferritin <15 ng/mL in the absence of anaemia[2]. In women with or suspected to have thalassemia trait or other haemoglobinopathy, concomitant iron deficiency can be diagnosed by either oral iron therapy trial or measurement of serum ferritin levels if haemoglobin levels are below cut-off[2].

Oral iron therapy

Prophylactic oral iron therapy is recommended throughout child-bearing age (by the WHO)[19,20], during pregnancy (by the WHO[21], Centers for Disease Control and Prevention [CDC][17], Network for the Advancement of Transfusion Alternatives [NATA][22]), and during postpartum (by the WHO[5] and NATA[22]). Oral iron therapy trial in the presence of anaemia is recommended as confirmation for iron deficiency anaemia (by the CDC[17], BCSH[10], RCOG[11], ACOG[13], and in South Australia[14]). Most international clinical guidelines agree that oral iron therapy is the first-line therapy for confirmed iron deficiency anaemia, except in some clinical scenarios in which oral iron therapy fails. Haemoglobin level should be rechecked after 4 weeks to confirm the response; a haemoglobin rise of at least 1 g/dL is considered optimal. Oral iron therapy should be continued until the haemoglobin level is normalised and continued for a few more months to restore the body iron reserve.

Recently, an important change in practice has been emphasised: to stop using daily iron dosing and start using low-dose alternate-day oral iron therapy[2]. This is based on the latest absorption studies that maximal absorption of iron occurs with a dose in the range of 40-80 mg of elemental iron daily and that greater doses do not result in more iron

absorption and are associated with more side effects[23,24]. Once-daily and twice-daily regimens are comparable in terms of fractional (day 1-3 geometric mean: 11.8% [range, 7.1%-19.4%] once daily vs 13.1% [range, 8.2%-20.7%] twice daily, p=0.33) or total iron absorption (day 1-3: 44.3 mg [range, 29.4-66.7 mg] once daily vs 49.4 mg [range, 35.2-69.4 mg] twice daily, p=0.33)[25]. Twice-daily divided doses resulted in a higher serum hepcidin concentration than once-daily dosing (p=0.013) and reduces iron absorption; iron supplements on alternate days and in single doses optimise iron absorption[25].

In addition, administration of 250 mg of vitamin C with low-dose oral iron therapy increases oral iron absorption by 4-6 times[1,2,26-30]. The effect of vitamin C on iron absorption is so significant that it can be considered one of the physiological roles of vitamin C[1]. Nonetheless, multivitamins that contain both calcium and iron should never be used as iron therapy, because calcium inhibits most iron absorption in this setting[31].

Intravenous iron therapy

The wider application of intravenous (IV) iron therapy has reshaped management of iron deficiency anaemia in gynaecology and obstetrics settings. Blood transfusion was previously regarded as inevitable for patients in whom oral iron therapy was ineffective. However, each unit of red cell contains only around 200 mg of elemental iron, 0.5 mg elemental iron per 1 mL blood, which means a large volume of blood is required to replenish the total body iron deficit. First-generation IV iron therapies (iron saccharide, high-molecular-weight dextran iron) are effective treatments for iron deficiency, but the dextran-induced anaphylactic reaction hampers wider use. Second-generation IV iron therapies (iron gluconate, iron sucrose) result in markedly fewer severe adverse events by replacing the dextran component with other non-dextran carbohydrates. Third-generation IV iron compounds (ferric carboxymaltose, iron isomaltoside, ferumoxytol) allow a larger dose of iron in a shorter infusion time owing to advancement in the carbohydrate moiety compounding the core iron[32]. These IV iron compounds behave as prodrugs and retain ionic iron until the iron–carbohydrate complex is metabolised[32].

Efficacy

In a meta-analysis of 10 605 patients treated with IV iron in 72 randomised controlled trials (19 of them related to obstetrics), intravenous iron therapy was associated with an increase in haemoglobin concentration (standardised mean difference=6.5 g/L, 95% CI=5.1-7.9 g/L) and a reduced risk of requirement for red blood cell transfusion (risk ratio=0.74, 95% CI=0.62-0.88) and could have broad applicability in acute care settings[33]. In another meta-analysis of 10 randomised controlled trials comparing IV iron with oral iron in treatment of iron deficiency anaemia in pregnancy, pregnant women were more likely to achieve target haemoglobin level with IV iron than prophylactic oral iron in seven studies (summary OR=2.7, 95% CI=2.0-3.6, p<0.001); haemoglobin levels increased more at 4 weeks with IV iron in eight studies (mean difference=1.2 g/dL, 95% CI=1.0-1.3 g/dL, p<0.001); and adverse reactions were lower with IV than prophylactic oral iron in 10 studies (summary OR=0.54, 95% CI=0.41-0.72, p<0.001)[34]. IV iron therapy is superior to oral iron therapy for iron deficiency anaemia in pregnancy; women receiving IV iron therapy achieve desired target haemoglobin levels, more frequently, faster, and with fewer side effects[34]. Within bone marrow, IV iron therapy results in 4.5-7.8 times the normal production of erythrocytes, compared with the 2.5-3.5 times in oral iron therapy[35].

Safety

In a study of 688 183 recipients of IV iron therapy under Medicare from January 2003 to December 2013, the risk for anaphylaxis at first exposure was 68 (95% CI=57.8-78.7) per 100 000 persons for iron dextran and 24 (95% CI=20.0-29.5) per 100 000 persons for all non-dextran IV iron products combined (iron sucrose, gluconate, and ferumoxytol), with an adjusted OR of 2.6 (95% CI=2.0-3.3, p<0.001)[36]. In another meta-analysis of 10 390 patients treated with IV iron in 103 trials (27 of them related to obstetrics and gynaecology), IV iron therapy was associated with an estimated severe adverse reaction incidence of <1 in 200 000 when high-molecular-weight dextran iron was avoided[37]. However, red blood cell transfusion was associated with events that cause major morbidity in 1 in 21 413 components issued according to the Serious Hazards of Transfusion 2012 data[37]. There was no increased risk of infections with IV iron therapy; IV iron formulations are safe and can be an alternative to red blood cell transfusions[37]. A placental perfusion study reported that ferric carboxymaltose did not pass to the fetus via the placenta[38].

Cost-effectiveness

In a study comparing the cost-effectiveness of IV iron with prophylactic oral iron in treating severe iron deficiency anaemia, the cost of IV iron therapy was 29.30% lower than that of oral iron therapy; in patients with severe iron deficiency anaemia (haemoglobin of <8.0 g/dL), IV iron therapy is an effective, safe, and overall less expensive

iron delivery[39]. In another study comparing IV iron therapy with allogeneic blood transfusion for severely anaemic gynaecologic patients, the net saving was US$782 per capita for IV iron therapy[40]. A study in Greece comparing the cost-effectiveness of second- and third-generation IV iron therapies reported that the total cost of ferric carboxymaltose was 113% and 15.4% lower than that of iron sucrose and low-molecular-weight dextran iron, respectively, in an inpatient analysis, and was 201.1% and 151.8% lower in an outpatient analysis[41]. Ferric carboxymaltose is a cost-saving option compared with second-generation IV iron[41]. A study in Switzerland on the cost-effectiveness of various IV iron therapies reported that the third-generation IV iron (ferric carboxymaltose) was associated with cost savings of 30% to 44% per patient per treatment cycle, compared with second-generation IV iron (iron sucrose).[42] Costs per 200/500/1000 mg total dosage treatment cycle were reported to be US$101/210/420 for ferric carboxymaltose and US$144/375/721 for iron sucrose; substituting iron sucrose with ferric carboxymaltose results in cost savings of US$22-31 million across all indications in 2009[42].

Stratification

IV iron therapy in obstetrics and gynaecology is recommended in United Kingdom, Germany, Switzerland, Scandinavia, Spain, Eastern Europe, Russia, Pakistan, India, Malaysia, Singapore, Indonesia, China, Thailand, Peru, Argentina, Chile, Australia, and the United States[2,4,6,10-14,22,40,43-51]. IV iron therapy is considered when oral iron therapy fails or is expected to fail in the following clinical scenarios: oral iron therapy intolerance[2,4,6,10-14,22,40,43-47,49,50], oral iron therapy unresponsiveness[2,4,6,10-14,22,40,43-47,49,50], oral iron therapy non-compliance[2,4,6,10-14,22,40,43-47,49,50], known conditions causing absorption problems[2,4,6,10,11,13,14,40,43,47,49,50], excessive blood loss exceeding the rate of oral absorption capacity[4,45], severe anaemia[6,13,22,40,44,46,47,50,51], iron deficiency anaemia in the presence of risk factors such as coagulation disorders, placenta previa[6], third trimester[2,22,44], and close proximity to term or obstetric/gynaecological operations[4,6,11,14,22,43,44,49].

Although clinical scenarios vary individually, different regions have different recommendations for oral and IV iron therapy in pregnancy and postpartum (Table 3)[6,22,40,44,46,47].

Administration and dosage

Two preparations allow total dose infusion. Premedication is not necessary prior to IV iron therapy in patients without a history of asthma or drug allergy. In patients with asthma or more than one drug allergy who are at increased risk of allergic or infusion reaction, corticosteroid (eg intravenous hydrocortisone 100-500 mg) should be administered prior to IV iron therapy. In patients with a history of inflammatory arthritis, IV corticosteroid, followed by a short course of prednisone (1 mg/kg per day orally for 4 days), is suggested. These recommendations avoid adverse events secondary to premedications for IV iron therapy, especially diphenhydramine. Premedication with diphenhydramine may cause hypotension, somnolence, flushing, dizziness, irritability, nasal congestion, wheezing, and supraventricular tachycardia[52]. Patients should be monitored for adverse effects for at least 30 minutes following injection.

Iron isomaltoside is added to maximum 500 mL sterile 0.9% sodium chloride. Doses <1000 mg and >1000 mg must be infused for >15 minutes and >30 minutes, respectively. The maximum single dose is 20 mg/kg bodyweight. If split dose is required, 20 mg/kg bodyweight is given in the first dose and the second dose is given at least 1 week apart. In patients with bodyweight of 50-69

Table 3. Different recommendations for oral and intravenous (IV) iron therapy in pregnancy and postpartum[6,22,40,44,46,47]

Region	Haemoglobin level, g/dL	
	Oral iron therapy	IV iron therapy
Switzerland[40]		
Pregnancy	9-10.5	≤9
Postpartum	10-11.5	≤10
Germany[47]		
Pregnancy	9-11.5	≤9
Postpartum	8-10	≤8
Turkey[6]		
Pregnancy	9-11 (1st & 3rd trimesters); 9-10.5 (2nd trimester)	≤9
Postpartum	9-11	≤9
Asia-Pacific[46]		
Pregnancy	10-10.5	≤10
Postpartum	10-10.5	≤10
Network for the Advancement of Transfusion Alternatives[22,44]		
Pregnancy	≤11 (2nd trimester)	≤11 (3rd trimester)
Postpartum	-	≤10

kg and ≥70 kg, iron isomaltoside of 1500 mg and 2000 mg, respectively, is needed for haemoglobin of <10 g/dL, whereas 1000 mg and 1500 mg, respectively, is needed for haemoglobin of ≥10 g/dL[53].

Ferric carboxymaltose is added to maximum 250 mL sterile 0.9% sodium chloride. Its dilution and infusion time are similar to that of iron isomaltoside. The maximum single dose is 1000 mg. If split dose is required, 1000 mg is given in the first dose and the second dose is given at least 1 week apart. In patients with bodyweight of <35 kg, 35-69 kg, and ≥70 kg, ferric carboxymaltose of 500 mg, 1500 mg, and 2000 mg, respectively, is needed for haemoglobin of <10 g/dL; 500 mg, 1000 mg, and 1500 mg, respectively, is needed for haemoglobin of 10-13 g/dL; and 500 mg, 500 mg, and 500 mg, respectively, is needed for haemoglobin of ≥14 g/dL[54].

Contraindications

Contraindications include hypersensitivity to the intended intravenous iron, known serious hypersensitivity to other intravenous iron products, first trimester of pregnancy, non-iron deficiency anaemia (eg haemolytic anaemia), iron overload or disturbances in utilisation of iron (eg haemochromatosis, haemosiderosis), active infection, and decompensated liver disease[53,54].

Response monitoring

Haemoglobin level and iron parameters should be measured 4 to 8 weeks after IV iron therapy[55].

Conclusion

Iron deficiency anaemia should be managed by addressing the underlying cause of the iron deficiency and replenishing the iron store. Both oral and IV routes of iron therapy are safe and efficacious, even in complicated clinical scenarios.

Declaration

The author has no conflicts of interest to disclose.

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Screening and prevention of pre-eclampsia: a review

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Pre-eclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality. Early-onset PE requiring preterm delivery is associated with a higher risk of complications in both mothers and babies. It is important to identify pregnant women who are at high risk of developing PE in the first trimester, so that preventive measures can be initiated early to improve placentation and reduce the prevalence and severity of the disorder. This review illustrates that effective screening for early-onset PE can be performed in the first trimester of pregnancy by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler ultrasonography, and placental growth factor. This prediction algorithm has detection rates of 90%, 75%, and 41% for very-early (delivery <32 weeks), preterm (delivery <37 weeks), and term (delivery ≥37 weeks) PE at 10% false positive rate, respectively. This model has been validated in several populations. Recent evidence has demonstrated that administration of low-dose aspirin (150 mg/nightly) starting at 11-14 weeks of gestation to high-risk women is effective in reducing the risk of preterm PE and the length of stay in neonatal intensive care unit.

Introduction

Pre-eclampsia (PE) is a multisystem disorder of pregnancy characterised by new onset of hypertension and significant proteinuria after 20 weeks of gestation[1-7]. It affects 2% to 5% of pregnant women and is a leading cause of maternal and perinatal morbidity and mortality. Worldwide, 76 000 women and 500 000 babies die yearly from this disorder[8]. PE can be divided into early onset (with delivery at <34 weeks of gestation), late onset (with delivery at ≥34 weeks of gestation), preterm (with delivery at <37 weeks of gestation), and term (with delivery at ≥37 weeks of gestation). Early-onset or preterm PE is associated with a higher risk of adverse maternal and perinatal outcomes than late-onset or term PE[9,10].

PE is a two-stage process in which the first stage is caused by inadequate trophoblast invasion, resulting in failure of physiologic transformation of spiral arteries[1,11]. The second stage is characterised by placental dysfunction, followed by production of oxidative stress, inflammatory cytokines, angiotensin 1 autoantibodies, and imbalance in angiogenic/anti-angiogenic factors, causing widespread endothelial dysfunction and clinical features of this disorder[12].

It is important to identify pregnant women who are at high risk of developing PE in the first trimester, so that preventive measures can be initiated early to improve placentation and reduce the prevalence and severity of the disorder[13,14]. In addition, high-risk women can benefit from increased antenatal surveillance, thus allowing detection of PE at the earliest for appropriate management in order to minimise the risk of associated complications to both the women and babies[14]. Recent advances have made it possible to predict and prevent PE in the first trimester of pregnancy, but effective prediction and prevention of PE is limited to early-onset PE.

First trimester screening for pre-eclampsia

Maternal history

According to the National Institute for Health and Care Excellence (NICE)[15] in 2010, the presence of any one of the following high risk factors (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus or autoimmune disease) or any two or more moderate risk factors (nulliparity, age >40 years, body mass index [BMI] ≥35 kg/m^2, family history

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of PE, or inter-pregnancy interval >10 years) is considered high risk for PE (Table 1).

According to the American College of Obstetricians and Gynecologists (ACOG)[16-18] in 2013, women are classified as high risk if they have: (1) a history of early-onset PE and preterm delivery at <34 weeks of gestation, or (2) a history of recurrent PE (Table 1).

In 2014, the US Preventive Services Task Force expanded the indications for the use of low-dose aspirin for the prevention of PE[17]. Low-dose aspirin (81 mg/day, starting after 12 weeks) should be given to women with one or more high risk factor (history of PE, renal disease, autoimmune disease, type 1 or type 2 diabetes mellitus, or chronic hypertension) or two or more moderate risk factors (first pregnancy, age >35 years, BMI >30 kg/m^2, family history of PE, sociodemographic characteristics, and personal history factors)[17].

In 2018, ACOG endorsed these indications for the use of low-dose aspirin for the prevention of PE[18]. High risk women are recommended to commence daily low-dose aspirin (81 mg/day) starting between 12-28 weeks (optimally before 16 weeks) and continue until delivery (Table 1). The approach recommended by the NICE and ACOG essentially treats each risk factor as a separate screening test with additive detection rate (DR) and screen positive rate. Evidence supporting these recommendations is mainly based on retrospective epidemiological studies of associations between individual risk factor and the development of PE; and most studies have not differentiated between preterm and term PE.

A first trimester screening study of 9149 singleton pregnancies evaluated maternal risk factors profile according to the severity of PE using multivariable regression analysis[19]. An increased risk of early-onset PE was associated with women of Afro-Caribbean origin (adjusted odds ratio [OR]=3.64, 95% confidence interval [CI]=1.84-7.21, p<0.001), a history of PE (adjusted OR=4.02, 95% CI=1.58-10.24, p<0.001), chronic hypertension (adjusted OR=8.70, 95% CI=2.77-27.33, p<0.001), and those who conceived with ovulation induction (adjusted OR=4.75, 95% CI=1.55-14.53, p<0.001). For late-onset PE, the risk increased with maternal

Table 1. Women at risk for pre-eclampsia (PE) according to professional organisations

National Institute for Health and Care Excellence, 2010[15]	American College of Obstetrics and Gynecology, 2013[16]	American College of Obstetrics and Gynecology, 2018[17,18]
Any one of the high risk factors: • Hypertensive disease in a previous pregnancy • Chronic kidney disease • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome • Type 1 or 2 diabetes mellitus • Chronic hypertension Or Any two of the moderate risk factors: • First pregnancy • Age >40 years • Pregnancy interval >10 years • Body mass index of ≥35 kg/m^2 at first prenatal visit • Family history of PE	Any one of the following: • Primiparity • Previous preeclamptic pregnancy • Chronic hypertension • Chronic renal disease • History of thrombophilia • In vitro fertilisation • Family history of PE • Type 1 or 2 diabetes mellitus • Body mass index of >30 kg/m^2 • Systemic lupus erythematosus • Age >40 years Aspirin (60-80 mg/day beginning in the late first trimester) is recommended if having: (1) history of early-onset PE and preterm delivery at <34 weeks of gestation, or (2) >1 previous history of PE	High risk factors: • History of PE, especially when accompanied by an adverse outcome • Chronic hypertension • Type 1 or 2 diabetes mellitus • Renal disease • Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome) Moderate risk factors: • Nulliparity • Body mass index of >30 kg/m^2 • Family history of PE (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age ≥35 years • Personal history factors (low birthweight or small for gestational age, previous pregnancy outcome, >10-year pregnancy interval) Aspirin (81 mg/day beginning between 12- 28 weeks) is recommended if the patient has ≥1 high risk factors or ≥2 moderate risk factors

age (adjusted OR=1.04, 95% CI=1.00-1.07, p<0.001), BMI (adjusted OR=1.10, 95% CI=1.07-1.13, p<0.001), family history (adjusted OR=2.91, 95% CI=1.63-5.21, p<0.001), and a history of PE (adjusted OR=2.18, 95% CI=1.24-3.83, p<0.001). Additionally, late-onset PE was more common in Afro-Caribbean and South Asian women (adjusted OR=2.66-3.31). Maternal risk factors alone yielded a detection rate of 37% for early-onset PE and 29% for late-onset PE at 5% false-positive rate (FPR)[19].

A large systematic review and meta-analysis of 92 studies, including 25 356 688 pregnancies, was conducted to determine the association between clinical risk factors identified before 16 weeks of gestations and the risk of PE[20]. The most significant risk factors for PE were women with a history of PE (relative risks [RR]=8.4, 95% CI=7.1-9.9) and chronic hypertension (RR=5.1, 95% CI=4.0-6.5). Other clinical risk factors for PE included nulliparity (RR=2.1, 95% CI=1.9-2.4), maternal age >35 years (RR=1.2, 95% CI=1.1-1.3), chronic kidney disease (RR=1.8, 95% CI=1.5-2.1), conception by assisted reproductive technology (RR=1.8, 95% CI=1.6-2.1), pre-pregnancy BMI of >30 kg/m^2 (RR=2.8, 95% CI=2.6-3.1), and pregestational diabetes mellitus (RR=3.7, 95% CI=3.1-4.3)[20].

The performance of NICE and ACOG recommendations in screening was evaluated in about 9000 singleton pregnancies at 11-13 weeks of gestation. Screening by NICE recommendation detected 41% (95% CI=62-85) of preterm PE and 34% (95% CI=27-41) of term PE at 10% FPR[21]. Screening by 2013 ACOG recommendation detected 5% (95% CI=2-14) of preterm PE and 2% (95% CI=0.3-5) of term PE at 0.2% FPR[21]. Screening by 2018 ACOG recommendation detected 90% (95% CI=79-96) of preterm PE and 89% (95% CI=84-94) of term PE at a FPR of 64%[21]. Although recognition of maternal risk factors is useful in identifying at risk women in clinical practice, it is not sufficient for effective prediction of PE[22].

Biomarkers

Biomarkers can be used to predict PE in the first trimester of pregnancy. Combination of biomarkers has better predictive performance than single biomarker[13]. Thus, the combination of maternal risk factors, biophysical (mean arterial pressure [MAP] and uterine artery Doppler measurement) and biochemical (maternal serum placental growth factor [PLGF]) markers in a multivariable model is the best approach for PE screening in the first trimester of pregnancy.

Mean arterial pressure

Accurate measurement of maternal blood pressure (BP) antenatally is the mainstay for early detection and diagnosis of PE. Women who develop PE typically have an elevated BP in the first and second trimesters of pregnancy[23-26]. In a systematic review of 60 599 women including 3341 cases with PE, MAP predicted PE with a moderate area under the receiver-operating characteristic curve (AUC) of 0.76 (95% CI=0.70-0.82), whereas systolic and diastolic BP are less effective in predicting PE, with an AUC of <0.70[27]. The systematic review identified considerable heterogeneity between studies in terms of study design, study populations, sample size, and types of BP devices. Standardisation of BP measurement is essential for accurate prediction of PE, and thus it is important to use validated automated BP devices and apply a standard protocol for BP measurement.

The use of mercury sphygmomanometers for BP monitoring has been phased out owing to concerns about clinical performance and safety[28,29]. Methodological problems include inter-observer error, terminal digit preference, and inconsistent cuff deflation rates[30,31]. Automated BP monitors allow standardised measurements to be taken, but accurate measurements still require correct cuff size and patient positioning.

There is a need for specific guidelines for BP measurement in pregnancy. According to the National Heart Foundation of Australia (NHFA)[32], patients are asked to rest for 5 minutes in the sitting position with their backs leaning against the seat, their arms supported at the level of the heart, and legs uncrossed as well as the use of correct cuff size (Figure 1). BP is measured in both arms simultaneously and a minimum of two recordings are made at 1-minute intervals until variations between consecutive reading fall to within 10 mmHg in systolic BP and 6 mmHg in diastolic BP in both arms[32]. When this point of stability is achieved, the average of the last two stable measurements of the left and right arms is calculated and the highest of these two measurements from the two arms is used[33]. However, to achieve BP stability, it is necessary to perform two measurements in both arms in about 50% of cases, three measurements in 25% of cases, and four measurements in 25%[34]. In a prospective study of 5435 healthy women with singleton pregnancy, the prevalence of significant BP inter-arm difference (defined as >10 mmHg) of systolic BP and diastolic BP was 8.3% and 2.3%, respectively, supporting the need to measure BP in both arms[35].

A simplified protocol for BP measurement was

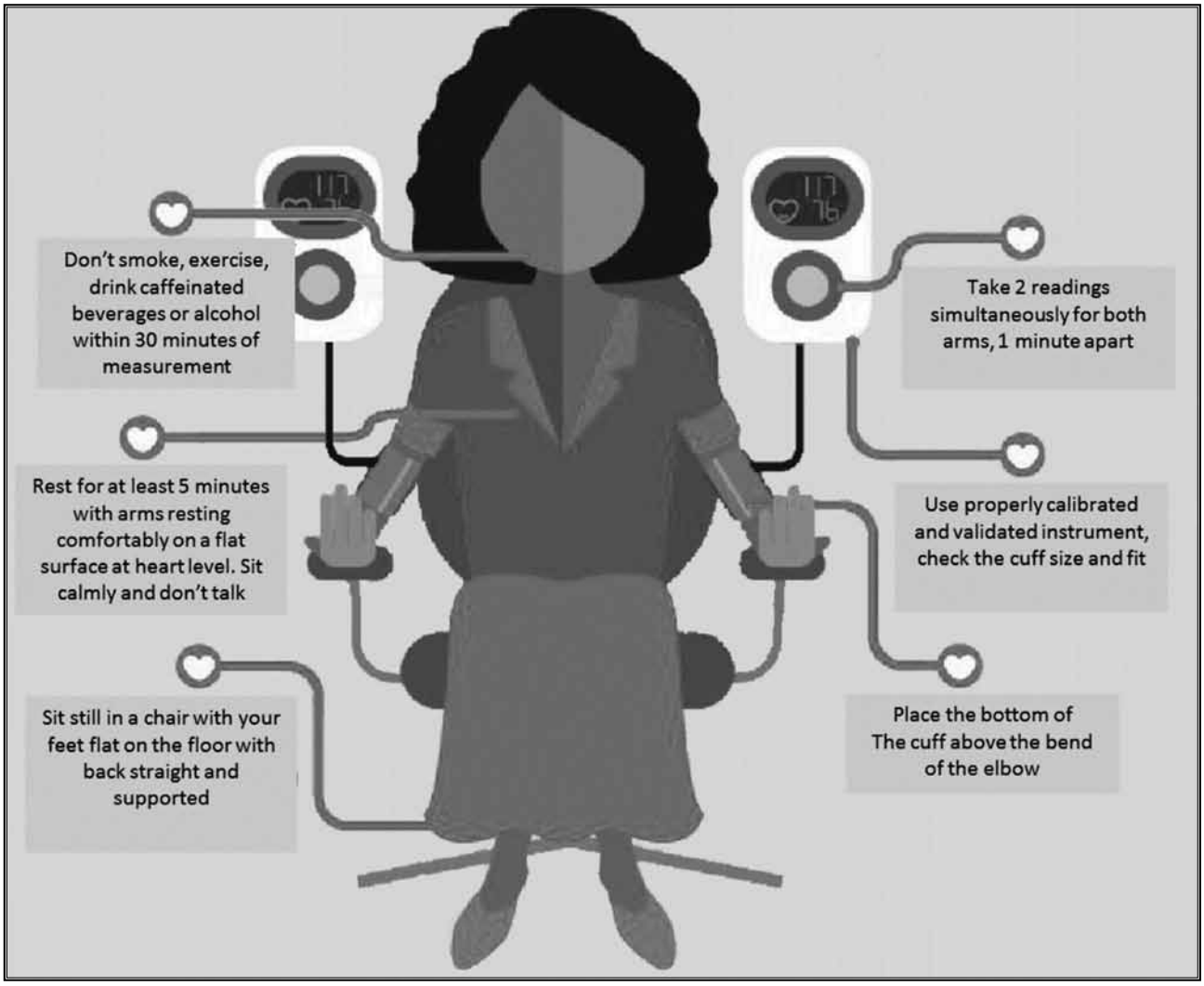

Figure 1. Correct position for blood pressure measurement.

developed in a study of 25505 women with singleton pregnancy where BP measurements were made at 11-13 weeks of gestation with the use of validated automatic devices[34]. The performance of screening for PE with the average of a minimum of two BP measurements from both arms was comparable to that of BP measurement according to the NHFA protocol. Thus, BP should be measured in both arms simultaneously with the correct positioning of patients and the final MAP is calculated from the average of the four measurements.

The measurement of MAP is affected by gestational age at screening, maternal age, racial origin, BMI, smoking, family history of PE, prior history of PE, and history of chronic hypertension and diabetes mellitus[36]. The MAP should be converted to multiple of median (MoM) adjusted for these variables in a multivariable prediction model. In a study of 5590 pregnant women with singleton pregnancy, detection rates for PE at 10% FPR were 43%, 38%, and 63% for maternal history alone, MAP alone, and combination of both, respectively[25]. In a study of >9000 singleton pregnancies screened at 11-13 weeks of gestation to compare the screening performance of systolic BP, diastolic BP, and MAP[26], the MAP performed best, with a detection rate of 76% for early-onset PE, which increased from 47% (based on maternal factors alone) at a FPR of 10%.

Uterine artery pulsatility index

Abnormal uteroplacental circulation can be observed as abnormal uterine arteries by Doppler velocimetry as early as the first trimester of pregnancy. To achieve reproducible, consistent, and accurate screening performance, standardisation for the measurement of uterine artery pulsatility index (PI) is required. According to the Fetal Medicine Foundation (FMF), transabdominal ultrasound is used to obtain a sagittal section of the uterus and to locate the internal cervical os. Then, ultrasound

transducer is kept in the midline and tilted to the lateral sides of the cervix. Colour Doppler flow mapping is used to identify the uterine arteries at the level of the internal cervical os. Pulsed wave Doppler is then performed with the sampling gate set at 2 mm to cover the vessel. The uterine artery PI and peak systolic velocity are measured by the ultrasound machine to obtain three similar consecutive waveforms. The peak systolic velocity must be >60 cm/s to ensure measurement of the uterine artery PI is performed at the level of the internal os (Figure 2)[37]. Evidence suggests that the uterine artery PI measurement taken at the level of internal os is more reproducible than that obtained at the level of external iliac vessels crossover[38]. The FMF provides a process of accreditation for sonographers to indicate uterine artery PI measurement competency. The measurement of uterine artery PI is associated with gestational age at screening, maternal age and weight, racial origin, history of PE, gestational age at birth of the last pregnancy, and birthweight Z-score[39]. The uterine artery PI needs to be adjusted for these variables by conversion to MoMs before comparing the values between affected and unaffected groups.

In a prospective PE-screening study evaluating the predictive value of the measurement of uterine artery Doppler at 11-13 weeks of gestation in 3107 singleton pregnancies that included 22 cases (0.7%) of early-onset PE and 71 cases (2.3%) of late-onset PE[40], the uterine artery PI MoM was significantly higher in women with PE than in unaffected women. The detection rates by uterine artery PI were 77% (95% CI=55-92) for early-onset PE and 27% (95% CI=17-39) for late-onset PE at a 10% FPR. These findings were confirmed in a follow-up study of 8366 women including 165 cases of PE[41].

In a meta-analysis of first trimester uterine artery Doppler measurement for the prediction of PE that included eight studies (n=41 692) for the prediction of early-onset PE and eleven studies (n=39 179) for prediction of PE of any gestations[42], the first trimester abnormal uterine artery Doppler was defined as the resistance index or PI ≥90th centile, with a pooled detection rate of 48% (95% CI=39-57) at 8% (95% CI=5-11) FPR for early-onset PE, and 22% (95% CI=18-25) at 10% (95% CI=9-10) FPR for late-onset PE. However, measurement of uterine artery PI is under scrutiny because of its methodological challenges and moderate reproducibility[43,44]. An alternative measurement approach through visualisation of the cervix in a transverse plane obtains the uterine artery PI comparable with that obtained through the conventional sagittal approach in terms of reliability, reproducibility, and time required, and is easier to perform[45].

Serum biochemical markers

Maternal serum PLGF has shown promising results in early prediction of PE. It can be measured by several commercially available automated analysers that provide reproducible results within 20-40 minutes of sampling. Similar to measurements of MAP and uterine artery PI, certain maternal and pregnancy characteristics affect the crude serum concentration of PLGF. It is therefore necessary to express the MoM values that adjust for confounders as well as analyser and reagents used[46].

PLGF is a glycosylated dimeric glycoprotein secreted by trophoblastic cells and is part of the angiogenic

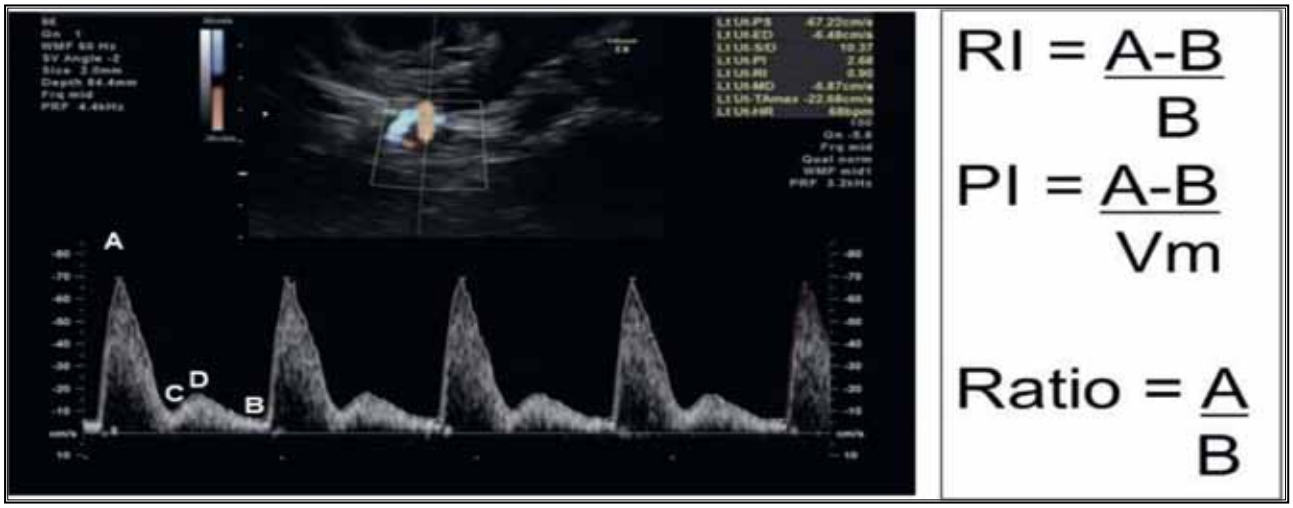

Figure 2: Measurement of uterine artery resistance indices in the first trimester: RI=resistance index, PI=pulsatility index, Vm=mean velocity, A=systolic peak; B=end-diastole, C=start of diastole, and D=maximum diastole

vascular endothelial growth factor family. It binds to vascular endothelial growth factor receptor-1, which increases in pregnancy. PLGF is synthesised in villous and extravillous cytotrophoblasts and has both vasculogenesis and angiogenetic functions. Its angiogenetic abilities may play a role in normal pregnancy, and changes in PLGF levels or its inhibitory receptors have been implicated in the development of PE[47-49].

PLGF can be detected in the maternal circulation from as early as 6 weeks of gestation[50]. Its concentrations increase with gestational age, peaking at 29-32 weeks of gestation and decrease thereafter[49]. Women who subsequently develop PE have significantly lower serum PLGF concentrations in the first trimester than those with unaffected pregnancy[50-53]. In a case-control study of 127 pregnant women with PE and 609 controls, PLGF has a detection rate of 55% (95% CI=33-71) for early-onset PE and 33% (95% CI=24-43) for late-onset PE at a 10% FPR[54]. Similar findings have been observed in larger studies[55,56]. In a systematic review and meta-analysis of performance of maternal serum pregnancy associated plasma protein-A (PAPP-A), human chorionic gonadotropin (hCG), PLGF, and placental protein-13 in the first trimester for the prediction of PE[57], PLGF is superior to the other biochemical markers for predicting PE. Specifically, serum PLGF concentrations alone achieve a detection rate of 40% at 10% FPR, with positive and negative likelihood ratios of 4.01 and 0.67, respectively[57]. The predictive performance is greater for early-onset PE, with a detection rate of 56% (95% CI=52-61), FPR of 9% (95% CI=8-41), positive likelihood ratio of 6.05 (95% CI=5.55-6.55), and negative likelihood ratio of 0.48 (95% CI=0.43-0.52)[57]. The addition of PLGF to maternal factors and uterine artery PI increases the detection rate for early-onset PE from 76% (95% CI=57-90) to 90% (95% CI=73-98) at 10% FPR[54]. Unlike PLGF, the significant increase in levels of soluble fms-like tyrosine kinase-1, an anti-angiogenic protein also binding vascular endothelial growth factor, is only apparent approximately 5 weeks prior to the onset of the condition[49]. Therefore, its contribution to the first trimester prediction algorithm is limited[55].

Pre-eclampsia prediction algorithms

In a systematic review comparing the performance between simple risk models (maternal characteristics only) and specialised models (measurements of MAP, uterine artery PI, and/or biochemical markers) for the prediction of PE[58], 70 models (from 29 studies) were identified: 17 to predict PE of any gestation, 31 to predict early-onset PE, and 22 to predict late-onset PE. Of the 70 models, 22 were simple risk models and 48 were specialised models. The latter performed better in predicting both early- and late-onset PE, with an additional detection rate of 18% (95% CI=0-56) for identification of PE at a FPR of 5% or 10%[58]. Therefore, a combination of various tests rather than a single test is recommended for the prediction of PE.

In a prospective PE-screening study by FMF of 7797 singleton pregnancies that included 157 (2%) cases of PE[59], a combination approach (of maternal factors, MAP, uterine artery PI, serum PAPP-A, and PLGF at 11-13 weeks of gestation) was superior to the traditional checklist-based approach that relies on maternal factors only in detecting PE. Using the first trimester combined test with four biomarkers, the detection rates of early- and late-onset PE at 5% FPR were 93% and 36%, respectively[59].

The first trimester combined test incorporates a novel analytical approach and evolves to the FMF 'competing risk model', which is based on a survival time model for the time of delivery for PE[60,61]. It hypothesised that all women would develop PE if pregnancy were to continue indefinitely. There is a competition between delivery before or after the development of PE. A model that represents the distribution of gestational age at delivery with PE is applied (Figure 3).

The largest study to date for the development of the first trimester PE prediction algorithm using the competing risk model included 61 174 mixed European pregnant women, with 1770 (2.9%) cases of PE[46]. A combination of maternal factors, MAP, uterine artery PI, and maternal serum PLGF yielded the best predictive performance, with detection rates of 90%, 75%, and 41% for very-early (delivery <32 weeks), preterm, and term PE, respectively, at 10% FPR. The incorporation of PAPP-A to the model did not improve the detection rate of PE of any gestational age at delivery[46]. These findings are in line with previous studies[21,55,56].

In a secondary analysis of data from the Aspirin for Evidence-Based Preeclampsia Prevention study that included 34 573 pregnant women, of which 239 (0.7%) cases developed preterm PE[62], at least one of the ACOG criteria was found in 22 287 (64.5%) pregnancies and the incidence of preterm PE was 0.97% (95% CI=0.9-1.1). The incidence of preterm PE increased substantially in those who were positive in the FMF test (4.8%, 95% CI=4.1%-5.6%). When screen negative by the FMF test, the incidence reduced to within or below background levels (0.3%, 95% CI=0.2%-0.3%). The relative incidence in FMF

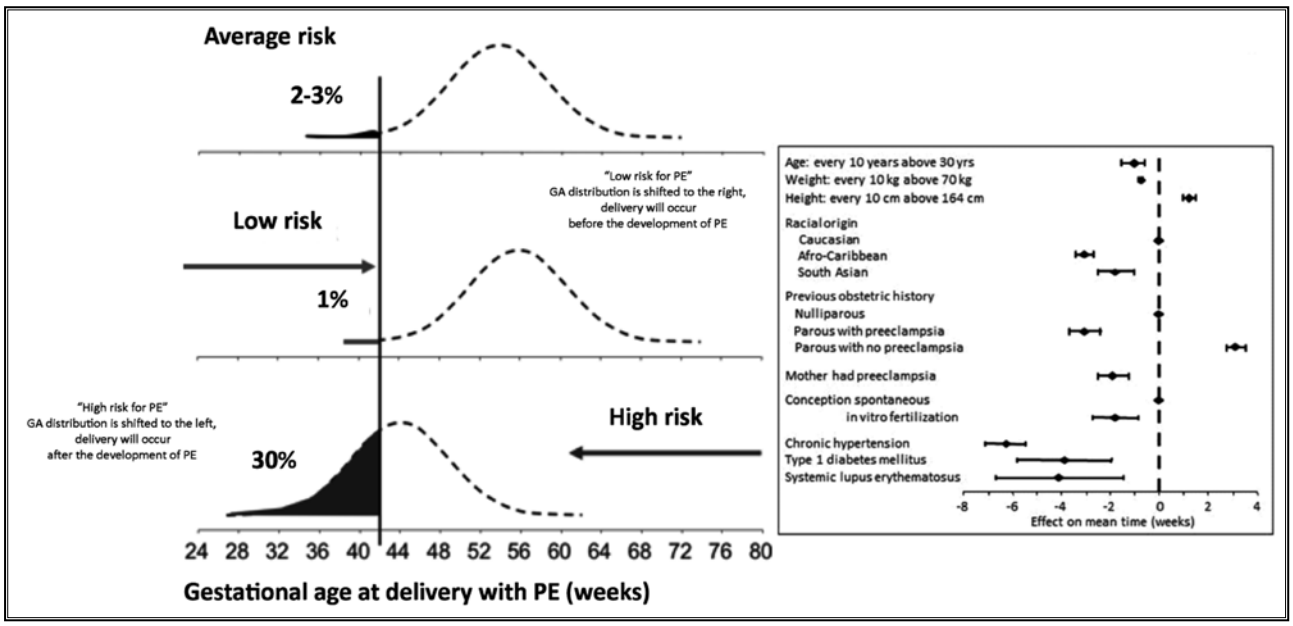

Figure 3: The competing risk model represents the distribution of gestational age at delivery with pre-eclampsia (PE). In women with a low risk for PE, the gestational age distribution is shifted to the right indicating that the gestational age for development of PE will be after delivery. In women with a high risk for PE, the gestational age distribution is shifted to the left indicating that the gestational age for development of PE will occur before delivery. The distribution of gestational age at delivery with PE is defined by two components: (1) the prior distribution based on maternal characteristics, and (2) the distribution of MoM biomarker values with gestational age in pregnancies affected by PE. (Modified from Wright D, Akolekar R, Syngelaki A, Poon LC, Nicolaides KH. A competing risks model in early screening for pre-eclampsia. Fetal Diagn Ther 2012;32:171-8.)

screen negative to FMF screen positive was 0.05% (95% CI=0.04%-0.07%). Similarly, in women fulfilling any of the NICE high risk criteria, the incidence of preterm PE in the subgroup of FMF negative pregnancies was 92% lower than in the positive group (8.7% [95% CI=6.9%-10.9%] vs 0.3% [95% CI=0.3%-1.7%]), and for those with any two or more moderate-risk factors the reduction was 91% (4.9% [95% CI=3.5%-6.8%] vs 0.4% [95% CI=0.2%-0.9%]). Hence, in pregnant women with ACOG/NICE-recognised risk factors who are negative by the FMF test, the risk of preterm PE is decreased to or below background levels[62].

Other first trimester combined prediction models have been developed in different populations (Table 2). Specifically, two Spanish cohort studies developed models that included maternal risk factors, uterine artery PI, MAP, and biochemical markers reported similar predictive performance with that derived from the FMF test[63,64]. In contrast, three combined PE prediction algorithms based on cohort studies in American populations demonstrated lower predictive performance than that from the FMF test[65-67].

Validation studies of existing pre-eclampsia prediction models

The prevalence of the disease, characteristics of the population (ie, low vs high risk, race, height, weight), and variations in biomarkers can influence the effectiveness of screening tests. Specifically, detection rate and FPR are characteristics of a screening test and are only influenced by the test characteristics and the criterion of screen positivity. In contrast, positive predictive value of a screening test is dependent on the prevalence of the disease in the population tested. It is necessary to validate prediction models that have been developed in specific study populations in different populations prospectively (Table 3). External validation is considered the optimal approach for evaluating a prediction model, which should be tested in independent validation samples with patients from a different but 'plausibly related' population[68] and it reflects generalisability of the prediction model[69].

In a systematic review[70] evaluating the benefits and harms of 16 PE-screening models that were validated in four studies (n=7123)[71-75], five models were considered good or better discrimination determined by C statistic score >0.8 (Table 4)[60,76-79]. Although all models had low positive predictive value, effective prediction of preterm PE, followed by prevention, was demonstrated in the Aspirin for Evidence-Based Preeclampsia Prevention trial[70].

Table 2. First trimester combined pre-eclampsia (PE) prediction models

Study	Populations	Pre-valence of PE	Model	Detection rate
Poon et al, 2009[59]	Total (n=7797), control (n=7504), PE (n=157), gestational hypertension (n=136)	2.0%	Maternal factors, uterine artery PI, MAP, serum PAPP-A and PLGF	At 5% FPR, 82.8% for early-onset PE, 35.7% for late-onset PE, 18.3% for gestational hypertension
Audibert et al, 2010[123]	Nulliparous women only, total (n=893), early-onset PE (n=9), late-onset PE (n=31), gestational hypertension (n=20)	4.5%	Maternal factors, PAPP-A, inhibin-A, PLGF	At 10% FPR, 31.8% for all PE, 75% for early-onset PE
Goetzinger et al, 2010[124]	Total (n=3716), control (n=3423), PE (n=293)	7.9%	Maternal factors, PAPP-A	At 10% FPR, 36.4% at 86.8% specificity for score of >2, positive likelihood ratio of 2.8, negative likelihood ratio of 0.73
Akolekar et al, 2011[125]	Total (n=33 602), control (n=32 850), PE (n=752)	2.2%	Maternal factors, uterine artery PI, MAP PAPP-A, PLGF, Inhibin-A, activin-A, soluble endoglin	At 10% FPR, 95.2% (95% CI=89.1%-98%) for early-onset PE, 88.3% (95% CI=80.5%-93.2%) for intermediate PE (delivery 34-37 weeks), and 71.1% (95% CI=61.6%-79.1%) for late-onset PE
Odibo et al, 2011[65]	Control (n=410), PE (n=42), early-onset PE (n=12)	9.3%	Placental protein-13, PAPP-A, mean uterine artery PI	At 10% FPR, 45%-50% for all PE by each individual biomarker; combinations of markers do not improve
Wright et al, 2012[60]	Control (n=57 458), PE (n=1426)	2.4%	Maternal factors, mean uterine artery PI, MAP	89.7% for early-onset PE, 71.5% for preterm PE, 56.6% for all PE
Akolekar et al, 2013[79]	Total (n=58 884), control (n=57 458), (n=1426)	2.4%	Maternal factors, uterine artery PI, MAP, PAPP-A and PLGF	At 10% FPR, 96.3% for early-onset PE, 76.6% for preterm PE, 53.6% for all PE
Scazzocchi et al, 2013[63]	Total (n=5170), PE (n=136), early-onset PE (n=26), late onset PE (n=110)	2.6%	Maternal factors, uterine artery PI, MAP, PAPP-A	At 10% FPR, 80.8% for early-onset PE, 39.6% for late-onset PE
Baschat et al, 2014[66]	Total (n=2441), PE (n=108), early- onset PE (n=18)	4.4%	Maternal factors, MAP, and PAPP-A	At 10% FPR, 55% for early-onset PE, 49% for all PE
Crovetto et al, 2015[64]	Total (n=9462), early-onset PE (n=57), late-onset PE (n=246) A subset of women had PLGF and soluble fms-like tyrosine kinase-1 (n=853)	3.2%	Maternal factors, MAP, uterine artery PI, PLGF, soluble fms-like tyrosine kinase-1	At 10% FPR, 91.2% for early-onset PE, 76.4% for late-onset PE
Gabbay-Benziv et al, 2016[126]	Total (n=2433), PE (n=108), early-onset PE (n=18)	4.4%	Maternal factor, diastolic blood pressure, PLGF	At 60% FPR, 90% for all PE
O'Gorman, et al, 2016[55]	Total (n=35 948), PE (n=1058), early-onset PE (n=18)	2.9%	Maternal factors, uterine artery PI, MAP, and PLGF	At 10% FPR, 75% (95% CI=70%-80%) for preterm PE, 47% (95% CI=44%-51%) for term PE
Yucel et al, 2016[127]	Total (n=490), PE (n=41)	8.37%	Uterine artery PI, placental volume, PAPP-A	92.68% at specificity of 85.2% for one abnormal parameter, 85.37% at specificity of 98.89% for 2 abnormal parameters
Sonek et al, 2018[67]	Total (n=1068), Total PE (n=46), early-onset PE (n=13), late-onset PE (n=33)	4.3%	Maternal characteristics, MAP, PLGF, PAPP-A, uterine artery PI and estimated placental volume	At 10% FPR, combination of maternal characteristics, PLGF, and PAPP-A had the best detection rate for PE: 85% for early-onset PE, 60% for preterm PE, 41% for all PE; addition of MAP, uterine artery PI, and estimated placental volume did not improve predictive performance.
Tan et al, 2018[46]	Total (n=61 174), Total PE (n=1770), early-onset PE (<32 weeks) (n=493), preterm PE (n=493), term PE (n=1277)	2.9%	Maternal factors, uterine artery PI, MAP and PLGF	At 10% FPR, 89.5% (95% CI=83%-94%) for early-onset PE, 74.8% (95% CI=71%-79%) for preterm PE, 41% (95% CI=38%-44%) for term PE

Abbreviations: CI=confidence interval, FPR=false-positive rate, MAP=mean arterial pressure, PAPP-A=pregnancy-associated plasma protein A, PI=pulsatility index, and PLGF=placental growth factor

Table 3. External validation studies of the first trimester pre-eclampsia (PE) prediction models

Study	Population	Sample size	Original models	Performance of validation studies (detection rate at 10% false-positive rate)	Performance of original studies (detection rate at 10% false-positive rate)
Farina et al, 2011[71]	Bologna, Italy	n=554, late-onset PE=7% (n=39)	Plasencia et al, 2008	41%	47%
			Plasencia et al, 2007	54%	52%
			Onwudiwe et al, 2008	74%	50%
			Poon et al, 2009	39%	45%
			Poon et al, 2009	41%	47%
			Poon et al, 2009	44%	46%
			Poon et al, 2009	36%	41%
			Poon et al, 2010	85%	57%
Park et al, 2013[72]	Sydney, Australia	n=3066, PE=2.8% (n=83), early-onset PE=0.4% (n=12)	Poon et al, 2010	92% for early-onset PE	95%
Oliveira et al, 2014[73]	Baltimore, Maryland	n=871-2962, early onset PE=1%-1.2%		Early-onset PE:	
			Parra-Cordero et al, 2013	29%	47%
			Scazzocchio et al, 2013	43%	81%
			Poon et al, 2009	53%	89%
			Poon et al, 2010	52%	95%
			Odibo et al, 2011	80%	68%
			Caradeux et al, 2013	30%	63%
				Late-onset PE:	
			Parra-Cordero et al, 2013	18%	29%
			Scazzocchio et al, 2013	31%	40%
Skrastad et al, 2015[75]	Throndheim, Norway	n=541, PE=3.9% (n=21), preterm PE=0.9% (n=5)	Akolekar et al, 2013	80% for preterm PE, 30% for late-onset PE	96% for early-onset PE, 54% for all PE
Allen et al, 2017[81]	Royal London Hospital, UK	n=2500, PE=2.4% (n=60		**Area under the curve**	**Area under the curve**
				Early-onset PE:	Early-onset PE:
			Akolekar et al, 2008	0.718	0.941
			DiLorenzo et al, 2012	0.504	0.893
			Plasencia et al, 2008	0.706	0.931
			Poon et al, 2009	0.765	0.905
			Poon et al, 2009	0.833	0.954
			Poon et al, 2009	0.824	Not reported
			Parra-Cordero et al, 2012	0.702	Not reported
			Scazzochio et al, 2013	0.831	0.960
			Baschat et al, 2014	0.624	0.830
				Late-onset PE:	Early-onset PE:
			Akolekar et al, 2008	0.737	0.941
			DiLorenzo et al, 2012	0.504	0.893
			Plasencia et al, 2008	0.659	0.779
			Poon et al, 2009	0.691	0.790
			Poon et al, 2009	0.828	0.863
			Poon et al, 2009	0.811	Not reported
			Parra-Cordero et al, 2012	0.644	Not reported
			Scazzochio et al, 2013	0.699	0.710
			Baschat et al, 2014	0.631	0.820
Guizani et al, 2017[82]	Brussels, Belgium	n=3239, PE=2.5%, preterm PE=1.1% (n=36), term PE=1.4% (n=44)	O'Gorman et al, 2016	83% for early-onset PE, 81% for preterm PE, 32% for term PE	89% for early-onset PE, 75% for preterm PE, 48% for term PE
Scazzocchio et al, 2017[128]	Barcelona, Spain	n=4203, PE=4% (n=169)	Scazzocchio et al, 2013	86% for early-onset PE, 43% for late-onset PE	75% for early-onset PE, 53% for late-onset PE
Lobo et al, 2017[80]	Sao Paulo, Brazil	n=617, PE=5.5% (n=34)	Akolekar et al, 2013	86% for early-onset PE, 67% for preterm PE, 53% for all PE	96% for early-onset PE, 77% for preterm PE, 53% for all PE
O'Gorman et al, 2017[21]	European populations	n=8775, PE=0.2% (n=17), preterm PE=0.7% (n=59), term PE=2.1% (n=180)	O'Gorman et al, 2016	100% for PE <32 weeks, 80% for preterm PE, 43% for term PE	82% for PE <32 weeks, 75% for preterm PE, 47% for term PE
Tan et al, 2018[85]	European populations	n=16 747, all PE=2.8% (n=473), preterm PE=0.8% (n=142)	O'Gorman et al, 2016	90% for early-onset PE, 82% for preterm PE, 43% for term PE	82% for early-onset PE, 75% for preterm PE, 47% for term PE

Table 4. Summary of five first trimester pre-eclampsia (PE) prediction models and their external validation (Modified from Henderson JT, Thompson JH, Burda BU, Cantor A. Preeclampsia screening: evidence report and systematic review for the US Preventive Services Task Force. JAMA 2017;317:1668-83.)

	PE <34weeks			PE <37weeks	PE ≥34weeks	
Model	Poon et al, 2010	Poon et al, 2010	Odibo et al, 2011	Akolekar et al, 2013	Onwudiwe et al, 2008	Poon et al, 2010
Model variables	Maternal factors, MAP, PAPP-A, uterine artery PI	Maternal factors, MAP, PAPP-A, uterine artery PI	Chronic hypertension, PAPP-A, placental protein-13, uterine artery PI	Maternal factors, MAP, PAPP-A, PLGF, uterine artery PI	Maternal factors, MAP, uterine artery PI	Maternal factors, MAP, uterine artery PI
External validation study	Oliveira et al, 2014	Park et al, 2013	Oliveira et al, 2014	Skrastad et al, 2014	Farina et al, 2011	Farina et al, 2011
Population tested	United States of America	Australia	United States of America	Norway	Italy	Italy
No. (%)	2833 (1.0)	3014 (0.4)	871 (1.1)	541 (0.9)	554 (7.0)	554 (7.0)
C statistic (95% CI)	0.8 (0.7-0.9)	0.93 (0.92-0.94)	0.86 (0.73-0.99)	0.94 (0.86-1.00)	0.85 (0.78-0.93)	0.93 (0.88-0.98)
Detection rate, % (95% CI)	52	91.7 (61.5-98.6)	80	80 (28.4-99.5)	74.4 (60.7-88.1)	84.6 (73.3-95.9)
Positive predictive value	4.2 (2.6-6.5)	3.6 (2-7)	11.3 (5.3-21.5)	6.8 (1.9-16.5)	36.3	39.3
Negative predictive value	99.6 (99-100)	99.9 (99.7-99.9)	99.8 (99-100)	99.8 (98.8-100)	97.9	98.7

Abbreviations: MAP=mean arterial pressure, PAPP-A=Pregnancy associated plasma protein-A, PI=pulsatility index, PLGF=placental growth factor

Several FMF prediction models have been evaluated in different populations, including Italian[71], Australian[72], American[73], Brazilian[80], mixed European[21,56,75,81-83], and South Chinese[84]. Some validation studies have reported comparable predictive performance corresponding to the original studies[55,56,72,75,82], but some have not[71,73,84]. In a European-wide multicentre, prospective non-intervention study to validate the FMF prediction model that included 8775 pregnant women with 239 (2.7%) having PE[56], the screening performance was comparable to that obtained from the original study and reported detection rates of 100%, 75%, and 43% at 10% FPR for very-early, preterm, and term PE, respectively. In a validation study of the FMF test conducted in a multicentre UK population that included 16747 singleton pregnancies with 473 (2.9%) of cases developing PE[85], predictive performance was similar to the original study in which detection rates were 90% (95% CI=80-96) for early-onset PE, 82% (95% CI=59-75) for preterm PE, and 43% (95% CI=37-48) for term PE at a FPR of 10%.

On contrary, a validation study performed in the American population demonstrated discrepancies of prediction algorithms between validated and original studies[73]. Predictive performance of six first trimester algorithms in 2969 women was evaluated, with rates of early-onset PE being 1.0% to 1.2% and late-onset PE being 4.1% to 5.0%. Maternal characteristics, MAP, and uterine artery PI were recorded in all patients, whereas maternal blood samples for PAPP-A (n=2833), free β-hCG (n=2833), PLGF (n=1565), and placental protein-13 (n=957) were available in subsets of patients. For the prediction of early-onset PE, detection rates (range, 29%-80%) of all models except one[65] at a fixed 10% FPR were lower than those derived from the original studies. Similar observations were reported for the prediction of late-onset PE, with a detection rate of 18% to 31%[73].

First trimester pre-eclampsia prediction in Chinese populations

Biomarker values differ between Chinese and non-Chinese populations[84,86-88]. Specifically, Chinese women have higher median serum PAPP-A, PLGF, β-hCG concentrations in the first trimester of pregnancy than Caucasian women, after adjusting for weight and gestational age[84,89-91]. These variations can affect the screening performance.

In a case-control study of 3330 South Chinese women (3000 in control group, 30 in PE group) evaluated

in the first trimester PE prediction test[84], MAP was measured once from each woman's left arm using a non-pregnancy specific automated BP monitor, uterine artery PI was measured according to the FMF protocol[37,92], and maternal serum PLGF concentrations were measured using the AutoDELFIA platform. Biomarker values were transformed to MoMs and adjusted for maternal and pregnancy characteristics with the use of published expected values from the FMF[79]. The MoM values of MAP and uterine artery PI in the control group based on the FMF model were significantly lower than the original values (mean log10 MAP=0.04, mean log10 uterine artery PI= -0.03, p<0.0001 for both)[84]. Using published models from the FMF and from Spain, predictive performance derived from the South Chinese population was lower than those obtained from the original studies. The poor performance of screening may be due to the lower rate of PE in Chinese population and under measurement of the MAP and uterine artery PI[84]. An Asia-wide prospective validation study of the FMF test is underway and results are expected in early 2019 (ClinicalTrials.gov Identifier: NCT03554681).

Quality assessment

Tools to access quality control include the sequential probability ratio test, cumulative sum[93,94], and target plot. Cumulative sum assesses changes in means or slopes of trend of sequential data (Figure 4)[95]. Target plot evaluates central tendency (deviation from expected median MoM) and dispersion (deviation from expected median standard deviation) [Figure 5]. Cumulative sum is sensitive to detect small shifts over time and the point of shift can be easily visualised[96]. However, its design is more complicated than target plot, which is easy to construct and visualised but requires large datasets and is insensitive.

Quality assessment is relevant in the context of screening for PE, as each biomarker is susceptible to inaccurate measurements, thus affecting performance of screening[97]. The biophysical markers MAP and uterine artery PI are susceptible to significant variability in measurements, mainly as a result from poor adherence to well-defined protocols. Quality control of the uterine artery PI Doppler by using cumulative sum and target

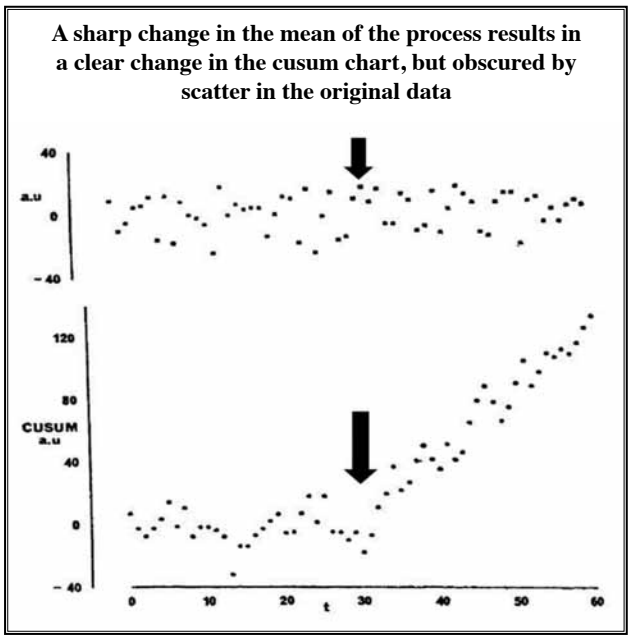

Figure 4: Cumulative sum: the reference value (mean or common reference point) is selected and this value is subtracted from each data point in succession. The successive deviations of the data from the reference value are then added to the previous sum. Changes in the cumulative sum indicate changes in the mean or trend of data from the baseline (mean or reference point), which allow the detection of small but sustained changes that are obscured by conventional methods or original data (Modified from Chaput de Saintonge DM, Vere DW. Why don't doctors use cusums? Lancet 1974;1:120-1.)

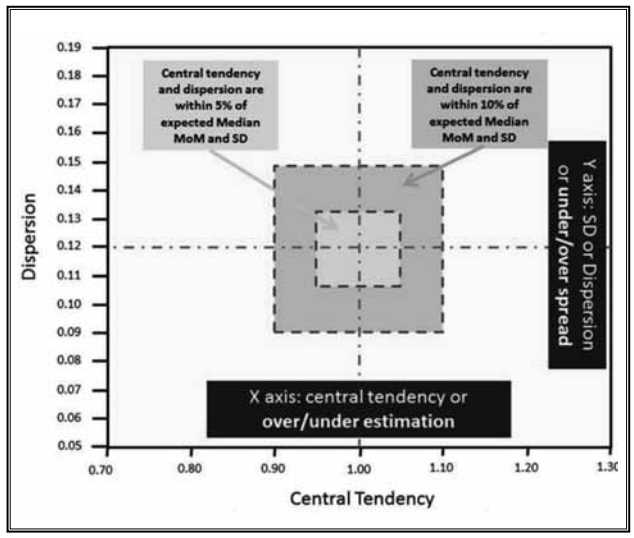

Figure 5: Target plot is a common tool to evaluate central tendency (deviation from expected median multiple of median [MoM]) and dispersion (deviation from expected median standard deviation [SD]). Central tendency is plotted against the X-axis and dispersion is plotted against the Y-axis. Acceptable performance is considered if the central tendency and dispersion are within 10% of the expected median MoM and SD (represented as outer square box, light grey). The inner square box (dark grey) represents that central tendency and dispersion that are within 5% of the expected median MoM and SD. (Modified from Ridding G, Hyett JA, Sahota D, McLennan AC. Assessing quality standards in measurement of uterine artery pulsatility index at 11 to 13 + 6 weeks of gestation. Ultrasound Obstet Gynecol 2015;46:299-305.)

plot demonstrated that detection rates of early-onset PE improved in ultrasonographers who received feedback on their performance than those without any feedback (screen positive rate for early-onset PE, 10% vs 2.7%)[43]. Furthermore, a retrospective cohort study of 21010 first trimester pregnant women showed that overall uterine artery PI MoM was 1.042 (interquartile range=0.85-1.26). Of 46 operators, 42 (91.3%) had more than 50 examinations; 24 (57.1%) of 42 had mean values in the ideal range of 0.95 to 1.05 MoM and 41 (97.6%) of 42 had mean values within the acceptable limits of 0.90 and 1.10 MoM. Ultrasonographers measuring PI <0.95 MoM and >1.05 MoM had, respectively, lower and higher screen positive rates when compared to those with measurements within the 0.95-1.05 MoM range (7.2% vs 13.2% vs 11.2%, p<0.001)[97]. Similarly, inaccurate biochemical marker results may occur because of changes in batch of reagent used, changes in temperature[98], and deviation from the manufacturer's protocol, and failure to implement a continuous quality control process. Therefore, a process for quality control must be performed regularly to ensure data standardisation, reliability, and accuracy. Any deviations of screening values should be promptly investigated for the causes and retraining of the measurement may be required.

Prevention of pre-eclampsia

Effective screening to identify women at risk of developing preterm PE allows early prophylactic treatment and therapeutic intervention. Approaches to prevent PE include administration of low-dose aspirin, heparin, anti-oxidants, calcium supplementation, proton pump inhibitor or metformin. The only proven effective preventive strategy is administration of low-dose aspirin to high-risk women for preterm PE at <16 weeks of gestation[99,100].

Prostacyclin-thromboxane imbalance contributes to vasospasm and coagulation abnormalities and is an underlying mechanism for development of PE. Aspirin is a potential prophylactic agent because it targets prostaglandin pathways and modifies the imbalance between thromboxane A2 and prostacyclin. In 1978, a patient with recurrent PE and thrombocytopenia was reported to benefit from aspirin prophylaxis[101]. Nulliparous women who took aspirin or aspirin-containing compounds for more than once a fortnight throughout pregnancy had a lower risk of PE than those with no aspirin consumption[102]. A randomised, open-labelled trial showed that women at risk of PE or fetal growth restriction, based on obstetric history, who received 300 mg of dipyridamole and 150 mg of aspirin since 12 weeks of gestation until delivery was not complicated by PE, fetal loss, or severe fetal growth restriction, compared to those in the non-intervention group[103].

In an individual patient data meta-analysis of 32217 women including 31 randomised trials of PE prevention, patients who received anti-platelet agents especially aspirin for prevention of PE had a 10% reduction in the rates of PE (RR=0.90, 95% CI=0.84-0.97), preterm birth at <34 weeks of gestation, and serious adverse pregnancy outcomes (a composite of PE, delivery at <34 weeks of gestation, small for gestational age neonates, fetal or maternal death), irrespective of aspirin dosage, starting time and indications[104]. Low-dose aspirin started at 16 weeks or earlier in patients at risk of PE substantially reduced the rate of PE (RR=0.47, 95% CI=0.34-0.65); however, aspirin started after 16 weeks of gestation did not decrease the rate of PE (RR=0.81, 95% CI=0.87-1.10)[105]. Subsequent meta-analyses consistently demonstrated that the administration of low-dose aspirin (50-150 mg/day) to women at risk of PE prior to 16 weeks of gestation significantly reduced the risk of PE[106,107], especially for severe PE with a 78% risk reduction (RR=0.22, 95% CI=0.080-0.567)[106]. Early aspirin was associated with a 50% reduction in the rate of fetal growth restriction and 60% reduction in the rate of perinatal death[100,105].

In a retrospective study comparing a non-intervention cohort with an intervention cohort of women at high risk for PE in the first trimester, the rates of early-onset PE (p<0.01) and preterm PE (p=0.03) significantly reduced in the intervention cohort who were prescribed 150 mg of aspirin[74]. The effect of aspirin is most pronounced in those who are at high risk of early-onset or preterm PE, as a consequence of improved placentation. However, a triple blinded randomised controlled trial of 150 mg of aspirin or placebo to women with abnormal uterine artery Doppler in the first trimester of pregnancy reported no improvement in placentation as represented by the mean value of uterine artery PI at 28 weeks of gestation[108]. Nonetheless, this study excluded women with high risk factors for PE.

In the Aspirin for Evidence-Based Preeclampsia Prevention trial that compared placebo with low-dose (150 mg per night) aspirin started at 11-14 until 36 weeks of gestation, the rate of preterm PE can be reduced by >60% by low-dose aspirin started in high-risk women identified by the FMF prediction model[99]. In this multicentre, double-blind, placebo-controlled trial, 1776 women with singleton pregnancies at high risk of preterm PE were randomly assigned to receive aspirin at a dose of 150 mg per night or placebo from 11 to 14 weeks of gestation until 36 weeks. According to the intention-to-treat principle, logistic

regression analysis was used to determine differences in the incidence of preterm PE between the aspirin and placebo groups, adjusting for the effect of the estimated risk for PE at the screening and participating centres. Excluding those withdrawn and lost to follow-up, 798 participants in the aspirin group and 822 participants in the placebo group were included for analysis. Preterm PE occurred in 13 (1.6%) and 35 (4.3%) participants in the respective groups (OR=0.38, 95% CI=0.20-0.74, p=0.004). Adherence was good with a reported intake of ≥85% of the required number of tablets in 80% of the participants. Low-dose aspirin was safe, with no significant between-group differences in adverse events and serious adverse events. In a secondary analysis of data of 1620 participants with 1571 liveborn neonates, the total (1696 vs 531 days) and mean (31.4 vs 11.1 days) length of stay in neonatal intensive care unit was significantly longer in the placebo than aspirin group[109]. Overall, including those not admitted to the neonatal intensive care unit, the mean length of stay was longer in the placebo than aspirin group (2.06 vs 0.66 days), corresponding a reduction of 68%[109].

In the latest meta-analysis of 16 randomised controlled trials with 18 907 participants[100], administration of aspirin was associated with a reduction in the preterm PE rate (RR=0.62, 95% CI=0.45-0.87) but not with term PE (RR=0.92, 95% CI=0.70-1.21). Only when aspirin was started at ≤16 weeks of gestation at a dose of ≥100 mg/day was associated with a reduction in the frequency of preterm PE (RR=0.33, 95% CI=0.19-0.57, p=0.0001); initiation of aspirin at >16 weeks or the daily dose of <100 mg was not associated with a reduction in preterm or term PE[100].

Evidence is not well established in other potential prophylaxes such as exercise[110,111], heparin[112,113], vitamin C and E[114-117], magnesium[118], folate[119], metformin[120], statin[121], and proton pump inhibitor[122].

Conclusion

Traditional PE screening based on maternal risk factors as proposed by the NICE or ACOG has limited predictive performance. The most promising PE prediction model is the first trimester combined test developed by the FMF that comprises maternal risk factors, MAP, uterine artery PI, and maternal serum PLGF concentration. Measurement of biomarkers can be performed in the same setting for routine screening of common trisomies. The first trimester combined test can identify a high proportion of women that will develop preterm PE, but the performance of screening for term PE is suboptimal[21,46,55,59,60,63-67,71-73,75,80-82,85,123-128]. The first trimester combined test is clinically useful because prophylactic low-dose aspirin (150 mg starting at <16 weeks, nightly) is effective in preventing preterm PE rather than term PE. Low-dose aspirin is safe for both the mother and fetus. Appropriate pre- and post-test counselling and surveillance throughout pregnancy should be provided to high risk women. Further studies are needed to evaluate whether the same PE screening and prevention program is effective in both developing and developed regions of Asia.

Declaration

All authors have no conflicts of interest to disclose.

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