HKCOG Guidelines

Guidelines on Prediction of High Risk Pregnancies

1   INTRODUCTION

The objective of this guideline is to examine scientific evidence about capacities to predict high risk obstetric problems. Frontline clinicians may exercise their clinical judgment about risk-benefit appraisal in relation to individual needs and available support of the patient as well as capacity of the service provider.

This guideline would serve as an updated reference to summarize the current evidence on various risk assessment methods for high risk pregnancies, focusing on how accurate they are together with their limitations.

The information might be useful for triaging the management of pregnancies such as:
- appropriate & timely referrals of high risk pregnancies to tertiary centres
- shared care between Maternal and Child Health Centres & hospital-based Obstetrics Units
- midwifery vs. obstetrician-led antenatal care & deliveries
- determining the frequency of antenatal clinic visits based on risk assessment

This guideline is going to focus on four common types of high risk pregnancies:
1. Pre-eclampsia
2. Preterm deliveries
3. Gestational diabetes
4. Major placenta praevia and accreta

Twin or higher order multiple pregnancies are not included as they are already high risk to start with (HKCOG Guidelines No.11, Part I&II)[1,2]. Screening for fetal aneuploidies & fetal structural abnormalities, to which there are already good evidence based guidelines (HKCOG Guidelines No.12, Part II)[3], are also outside the scope of this guideline.

2   PREDICTION OF PRE-ECLAMPSIA

Pre-eclampsia, which affects 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality[4-6].

Maternal factors

The National Collaborating Centre for Women's and Children's Health (NCCWCH) in UK has issued guidelines on routine prenatal care recommending that at the first visit a woman's level of risk for Pre-eclampsia should be evaluated, by a series of maternal characteristics, such as maternal age, body mass index and previous and family history of Pre-eclampsia, so that a plan for her schedule of prenatal visits can be formulated[7]. The aim of such early identification of women at high risk is to allow intensive maternal and fetal monitoring, leading to an earlier diagnosis of Pre-eclampsia with the potential for preventing an adverse outcome. Additionally, there is evidence from randomised studies on the prophylactic use of aspirin that this may reduce the incidence of Pre-eclampsia by about 50%, provided treatment is initiated before 16 weeks[8].

The approach to screening recommended by NCCWCH (2008), which essentially treats each of the risk factors as a separate screening test, would falsely classify two thirds of the obstetric population as being at high risk and in need of intensive monitoring[9]. An alternative approach is to combine the maternal characteristics and previous history into an algorithm derived by multivariate analysis to estimate the individual patient-specific risk for Pre-eclampsia and with such an approach about one third of pregnancies developing Pre-eclampsia would be detected at a false positive rate (FPR) of 10%[9].

Biophysical and biochemical markers

The performance of screening can be improved by combining history with a series of biophysical and biochemical markers which are altered from

as early as the first trimester of pregnancy in cases that subsequently develop Pre-eclampsia. In the Pre-eclampsia group, compared with unaffected controls, at 11–13 weeks uterine artery pulsatility index (PI) and mean arterial pressure (MAP) and maternal serum or plasma levels of soluble endoglin (sEng), inhibin-A, activin-A, pentraxin-3 (PTX3) and P-selectin are increased, whereas serum pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PLGF) and placental protein-13 (PP13) are decreased[10-23]. These biophysical and biochemical markers are thought to be involved in placentation or in the cascade of events leading from impaired placentation to development of clinical symptoms of the Pre-eclampsia.

Early, intermediate and late Pre-eclampsia

There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short-term and long-term consequences of Pre-eclampsia are inversely related to the gestational age at onset of the disease[24-29]. Consequently, the endpoint in screening for Pre-eclampsia by first-trimester biophysical and biochemical markers should not be total Pre-eclampsia but the condition should be subdivided according to gestational age at delivery. This subdivision has so far been limited to early Pre-eclampsia, requiring delivery before 34 weeks and late Pre-eclampsia. Akolekar et al[30] recently showed that there are now sufficient data to allow further subdivision of the cases delivering at or after 34 weeks into intermediate Pre-eclampsia and late Pre-eclampsia groups, delivering at 34–37 weeks and after 37 weeks, respectively.

Screening of Pre-eclampsia proposed by Fetal Medicine Foundation

This prospective screening study[30] in an UK heterogeneous population of about 35,000 singleton pregnancies has found that the prevalence of early, intermediate and late Pre-eclampsia is 0.3, 0.6 and 1.3%, respectively. Logistic regression analysis was used to derive the "a priori risk" for each of the Pre-eclampsia groups from maternal characteristics. The risk for Pre-eclampsia increased with maternal weight and decreased with height, it was higher in women of African and South Asian racial origin than in Caucasians, and increased in women conceiving after the use of ovulation induction drugs, in those with a personal or family history of Pre-eclampsia and in those with pre-existing chronic hypertension or diabetes mellitus. In parous women with no previous Pre-eclampsia, the risk of developing Pre-eclampsia in the current pregnancy was reduced by 60–70%. In general, the ORs for the factors in maternal history which defined the "a priori risk" for Pre-eclampsia were inversely proportional to the gestation at delivery, with higher ratios for early disease compared with those in intermediate and late Pre-eclampsia. Algorithms that combine the various maternal characteristics at 11–13 weeks could potentially identify 33, 28 and 25% of pregnancies that subsequently develop early, intermediate and late PE, at the FPR of 5%. The algorithm is freely accessible at the Fetal Medicine Foundation website www.fetalmedicine.com. The patient-specific a posteriori risk for early, intermediate and late Pre-eclampsia were calculated by multiplying the "a priori patient characteristics-derived risk" with the likelihood ratio of a series of biophysical and biochemical markers after appropriate adjustments for the intercorrelations between these markers. As in the cases of maternal factors, the differences in biophysical and biochemical markers of impaired placentation between the Pre-eclampsia and unaffected groups were, in general, more pronounced in those developing early disease compared with those in intermediate or late Pre-eclampsia. Algorithms which combine maternal characteristics and biophysical and biochemical tests at 11–13 weeks could potentially identify about 90, 80 and 60% of pregnancies that subsequently develop early, intermediate and late PE, at the FPR of 5%. Early estimation of patient specific risks for these pregnancy complications would improve pregnancy outcome by shifting prenatal care from a series of routine visits to a more individualized patient- and disease-specific approach both in terms of the schedule and content of such visits. In the case of Pre-eclampsia, effective early identification of the high risk group could potentially improve the outcome by directing such patients to specialist clinics for close surveillance and would be the basis for future studies investigating the potential role of pharmacological interventions, such as aspirin, starting from the first trimester to improve placentation and reduce the prevalence of the disease.

Local situation
However, this sort of comprehensive assessment at 11-13 weeks promoted by Fetal Medicine Foundation is not ready to be implemented in Hong Kong. Furthermore, even if we can offer this comprehensive assessment at 11-13 weeks, the efficacy & safety of this new antenatal care model in local pregnant women still require a prospective demonstration trail before clinical use.

3   PREDICTION OF PRETERM DELIVERIES

Preterm birth is the leading cause of perinatal death and handicap in children and the vast majority of mortality and morbidity relates to early delivery before 34 weeks which occurs in about 2% of singleton pregnancies. In two-thirds of the cases this is due to spontaneous onset of labour or preterm prelabour rupture of membranes and in the other one third it is iatrogenic, mainly due to preeclampsia[31].

We will focus on the risk assessment of spontaneous preterm delivery before 34 weeks in the following discussion.

The pathophysiologic events that trigger spontaneous preterm birth are largely unknown but include decidual hemorrhage (abruption), mechanical factors (uterine overdistention or cervical incompetence), and hormonal changes (perhaps mediated by fetal or maternal stress). In addition, several cervicovaginal infections have been associated with preterm labour[32].

Clinical history
Previous spontaneous preterm birth, second trimester miscarriage, advanced maternal age, smoking, previous cervical surgery (LLETZ/cone biopsy) and multiple pregnancies are the risk factors for spontaneous preterm delivery.

Therefore, traditional method of antenatal screening for spontaneous early preterm delivery is based on the above mentioned maternal characteristics, such as age, race and smoking status, and obstetric history.

Risk-scoring systems, which attempt to define women as being at high or low risk according to these maternal factors, have been shown to have a low detection rate and a high false-positive rate. Moreover, it is much less discriminating for primigravid than multigravid patients. Data

extracted from a recent systematic review of the literature demonstrated that with the most commonly used risk scoring system[33], the detection rate of spontaneous delivery before 37 weeks was 38% for a false-positive rate of 17%[34].

Sonographic cervical length at 20-24 weeks
The risk of spontaneous preterm birth is inversely related to cervical length measured by transvaginal sonography at 20 to 24 weeks[35-39]. A cervical length of 25mm or less had a sensitivity, specificity, positive predictive value, and negative predictive value of 76%, 68%, 20%, and 96%, respectively, to identify preterm singleton birth at less than 34 weeks of gestation[40].

The detection rate of screening for preterm delivery before 32 weeks, at a fixed false-positive rate of 10%, was 38% for maternal factors, 55% for cervical length and 69% for combined testing. The detection rate of screening by a combination of maternal factors and the measurement of cervical length was substantially higher than that of screening by each method alone[38].

According to a recent systematic review and meta-analysis[41], a cervical length $\leq$20 mm at 20-24 weeks was the most accurate in predicting preterm birth <32 and <34 weeks in asymptomatic women with twin pregnancy. The pooled sensitivities, specificities, and positive and negative likelihood ratios were 39% and 29%, 96% and 97%, 10.1 and 9.0, and 0.64 and 0.74, respectively.

Biochemical markers
A growing body of evidence indicates that a positive fetal fibronectin (fFN) test between 24-36 weeks in cervical and/or vaginal fluids is associated with preterm delivery in the next 7 days both in patients with threatened preterm labour and in symptomatic patients, with a positive predictive value of 13-30%. However, its clinical usefulness may rest primarily with its high negative predictive value (99%)[42].

On the other hand, there are no other useful biophysical (such as uterine artery Doppler) or biochemical markers (such as maternal serum concentrations of pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotrophin (β-hCG), PlGF, placental protein 13 (PP13), a disintegrin and metalloprotease 12

(ADAM12), inhibin-A and activin-A) of spontaneous early delivery[43].

Future directions

The patient-specific risk for spontaneous delivery before 34 weeks might be determined by an algorithm combining maternal characteristics and obstetric history at 11-13 weeks[43]. There is some evidence that sonographic measurement of endocervical length at 11 to 13 weeks is inversely related to the likelihood for subsequent spontaneous early delivery[44]. Therefore, this "a priori risk" might be further modified by sonographic measurement of cervical length as early as 11 to 13 weeks gestation[31].

Further studies are also required to investigate whether a combination of biophysical (cervical length) and biochemical (fetal fibronectin) markers may better identify patients at risk for preterm delivery[45].

4   PREDICTION OF GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy[46]. It is common in Hong Kong with prevalence reported to be 14.2% based on the World Health Organization (WHO) 1998 diagnostic criteria[47]. In the past, GDM was divided into a less severe degree of glucose impairment, namely impaired glucose tolerance (IGT), and the more severe form of gestational diabetes mellitus. This definition was changed in the WHO 1998 report when GDM included both gestational IGT and the previous GDM. Pregnant women who meet WHO criteria for diabetes mellitus (DM) or IGT are both classified as having GDM. This is a reflection of the continuous relationship between maternal glycaemia and macrosomia-related perinatal risks without a biological threshold[48,49].

GDM has been associated with multiple perinatal complications[50], including macrosomia (21%), shoulder dystocia (3%), brachial plexus injury (0.6%) and neonatal hypoglycaemia (6.6%). Treatment of even mild degree of GDM has been shown to reduce the complications[50-52]. In addition, pregnant women with GDM are also at increased risk of development of type II diabetes mellitus (DM) in the future[53]. The diagnosis can increase the awareness among these patients to institute measures to reduce the development of type II DM, such as postnatal screening and modification of lifestyle[54].

Risk factor-based vs. universal screening

However, GDM is largely asymptomatic, unless there is maternal glycosuria or fetal complications such as large-for-gestational age or polyhydramnios. There are two approaches to achieve diagnosis: risk factor-based or universal screening[55]. Studies have identified several risk factors including older maternal age, high body mass index, previous birth of a large baby, a family history of DM, excessive weight gain and cigarette smoking[56]. In addition, there are marked differences in the prevalence of GDM in different ethnic groups, with South East Asians consistently shown to be of higher risk[57]. Because of this, The Hong Kong College of Obstetricians and Gynaecologists' guideline on GDM suggests universal screening, based on ethnicity, for Hong Kong Chinese pregnant women[58].

Screening and diagnostic tests

Various screening algorithms have been suggested by different professional bodies throughout the world[59]. There are differences on the gestation to perform the screening, the screening methods (random glucose or direct oral glucose tolerance test (OGTT) – 75 gram or 100 gram) and the cut-offs used. On the basis of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[49], the International Association of Diabetes and Pregnancy Study Groups (IADPSG) published a new set of screening algorithm, trying to offer a standardized platform for the diagnosis[60]. It encompasses the use of fasting, 1-hour and 2-hour 75 gram OGTT with any one value above the threshold (5.1, 10.0 and 8.5 mmol/l respectively) indicating a diagnosis. Random or fasting glucose is performed in the first prenatal visit to diagnose overt diabetes as early as possible. OGTT is performed at the second trimester (24 to 28 weeks) for the remaining. The American Diabetes Association has adopted this algorithm in autumn 2010[61]. It is anticipated that more studies will be performed to investigate if this translates to improved clinical outcome for both pregnant women and their offspring.

In the last decade, there has been promising result from the use of biomarkers in the first trimester, combined with maternal characteristics, to predict the development of GDM in the latter part of gestation[62]. More prospective, large-scale studies are required to verify the results before clinical use.

5 PREDICTION OF MAJOR PLACENTA PRAEVIA AND ACCRETA

The RCOG and the National Institute for Health and Clinical Excellence support placental localization in routine ultrasound scanning at around 20 weeks of gestation[63].

Transvaginal scan is safe and should be used to improve the accuracy of the diagnosis of low lying placenta at 20 weeks of gestation[64].

Table 1. Risk of Placenta Praevia (PP) with ultrasound findings of low lying placenta at 18-23 weeks of gestation

	No of patients	Gestational age (wks)	Type of USG/Distance of placenta overlapping cervical os	Incidence at USG	Positive predictive value for final PP	Overall incidence of PP
Taipale et al 1988[65](Finland)	3696	18-23	Transvaginal			
			>0mm	1.5%	8.8%	0.14%
			>15mm	0.68%	18.5%	0.14%
			>25mm	0.27%	40%	0.11%
Becker et al 2001[66](Germany)	8650	20-23	Transvaginal			
			>0mm	0.48%	67%	0.32%
			>25mm	0.14%	100%	0.14%
Fung et al 2011[67] (Hong Kong)	16236	2nd trimester (Mainly 20 wks)	Transabdominal /overlapping cervical os	3.75%	22.7%	1.1%

0 mm = placenta reaching cervical os

Significant migration to allow vaginal delivery is unlikely if the placenta substantially overlaps the internal os by over 25 mm at 20–23 weeks of gestation.

Time of follow up scan
Women who bleed should be managed individually according to their needs. In cases of asymptomatic women with suspected minor praevia, follow-up imaging can be left until 36 weeks of gestation. In cases with asymptomatic suspected major placenta praevia or a question of placenta accreta, imaging should be performed at around 32 weeks of gestation to clarify the diagnosis and allow planning for third-trimester management, further imaging and delivery[63].

Risk of Placenta Accreta
Incidence of placenta accreta in patients with placenta praevia increased with the number of previous Caesarean sections: 1.9%, 15.6%, 23.5%, 29.4%, 33.3%, and 50.0% after 0, 1, 2, 3, 4, and 5 previous Caesarean sections, respectively[68].

Women with both anterior or central placenta praevia and two or more previous Caesarean deliveries have a 40% risk of placenta accreta[69].

In those patients with previous Caesarean section and anterior / central placenta praevia, one should look out for placenta accreta. Between 15 to 20 weeks, about 1.6% of the patients will be suspected to have placenta accreta. Visualization of lacunae had the highest sensitivity of 79% with positive predicative value of 93%[70].

Recommendation
Ultrasound at 20 weeks (with the help of transvaginal scan) to detect the placenta site is recommended. If the placenta overlaps the internal os more than 25mm, the risk of placenta praevia is 40 to 100%. Follow up ultrasound scan at 32 weeks is necessary to confirm the diagnosis.

Patients with anterior & low lying placenta and previous Caesarean section should have ultrasound scan to look for placenta accreta.

If major placenta praevia or placenta accreta is suspected, inpatient management should be offered after 34 weeks of pregnancy. Even there are no symptoms before, there is a small risk that the patient can bleed suddenly and severely, which may mean an urgent Caesarean section. If there is low-lying placenta after 20 weeks without bleeding, the patient may be able to have

care at home. However, she should be able to get to the hospital quickly and easily at any time[71].

6 CONCLUSION

Many high risk pregnancies such as (1) pre-eclampsia & (2) preterm deliveries that we deal with in clinical practice are not discrete entities, but are syndromes with more than one cause. It thus explains the disappointing results when we tried to predict and prevent high risk pregnancies. Therefore, no single test would be able to predict this group of high risk pregnancies with heterogeneous etiology.

A new set of screening algorithm for (3) gestational diabetes has been proposed by IADPSG, but note that the screening would not be completed by 28 weeks.

(4) Major placenta praevia & accreta is probably the only high risk obstetric condition (out of the four described in this guideline) which can be predicted by an ultrasound assessment at 20 weeks with reasonable accuracy, especially with history of previous Caesarean section.

Future research to further improve the performance of various algorithms to predict high risk pregnancies, especially in early gestation, is necessary before the traditional standard regular antenatal care could be replaced.

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.