Preeclampsia Prediction and Prophylaxis in Routine First-trimester Screening Services

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ABSTRACT

Prenatal screening confers benefits to the population served by that program. Screening programs that are poorly implemented can be misleading. Fetal Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13) have been routinely screened for in the practice of general obstetrics. Such screening is generally operated with a point-of-care service model called one-stop clinic for assessment of risk (OSCAR). First-trimester screenings for Down syndrome can be offered to singleton and twin pregnancies from 11 to 13 weeks of gestation. Risk of fetal Down syndrome is calculated from the algorithmic analysis of multiple parameters, including maternal characteristics, ultrasound parameters (nuchal translucency (NT) ± nasal bone), and serum biomarkers (pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG)).¹ Proprietary algorithms for calculating a pregnancy-specific risk have been offered by professional organizations and commercial laboratories. Confirmatory invasive prenatal diagnostic tests can be offered in those with high-risk screening result. Those with intermediate-risk result can be offered DNA-based noninvasive prenatal testing (NIPT) or integrated sequential screening to reduce false-positive screening.²

A different set of first-trimester parameters can be used to predict subsequent development of preeclampsia (PE) with a unique multivariate algorithm. Preeclampsia is a multisystem disorder that affects up to 5% of pregnancies. Those who require delivery at gestational age <34 weeks (early-onset PE) or <37 weeks (preterm PE) are more severe and more complicated than those who require delivery at gestational age ≥34 weeks (late-onset PE) or ≥37 weeks (term PE). The most common PE-related death is intracranial hemorrhage.³ Other serious PE-related complications include placental abruption, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, acute pulmonary edema, acute renal failure, and iatrogenic preterm delivery.⁴⁻⁷ Regional variation in mortalities of mothers and children contributed from PE is seen.⁸ The life expectancy of preterm PE survivors is shortened due to a higher risk of cardiovascular disease later in life.⁹ Prematurity is related with small for gestational age, thrombocytopenia, bronchopulmonary dysplasia, and cerebral palsy. Preeclampsia-related placental insufficiency may alter fetal organogenesis and increase risks of obesity, type 2 diabetes mellitus, coronary artery disease, and hypertension later in adult life. The short- and long-term consequences of preterm PE on the health of mother and child justify the effort for selective prophylactic intervention initiated in the first trimester of pregnancy.¹⁰ Recruitment for clinical research trials can also be guided by individualized risk identification.

Integration of maternal characteristics, biophysical (mean arterial pressure; MAP), Doppler (uterine artery pulsatility index; UtAPI), and biochemical profiles (serum placental growth factor; PlGF) at 11–13 weeks can achieve detection rates of preterm—and overall PE of 77 and 54%, respectively, with a fixed false-positive rate (FPR) of 10%. The efficacy of the multimarker screening model is higher than the prediction of PE using maternal characteristics alone.¹¹ First-trimester prediction of PE employing the multimarker screening model has recently been endorsed by International...
Federation of Gynecology and Obstetrics (FIGO). This article is aiming to outline components required for proper clinical instalment of PE prediction service, as an extension to the currently available fetal Down syndrome screening.

Maternal Characteristics
The traditional approach to predict subsequent development of PE is to identify risk factors from maternal characteristics (medical and obstetric history). Certain maternal characteristics are associated with development of PE, and have been utilized to produce risk of preterm PE in the multivariable competing risk model with multivariate logistic regression analysis adjusting for confounders. Recognition of maternal risk factors alone, although easily adopted in clinical practice, has low detection and high FPR for prediction of PE. Checklist, as provided in Table 1, should be employed for routine prenatal screening of PE.

Mean Arterial Pressure
The MAP is influenced by cardiac output and systemic vascular resistance. Endothelial cells mutually produce and respond to vasoactive substances. These vasoactive mediators, regulated by the autonomic nervous system, influence the diameter of the blood vessels and systemic vascular resistance. At rest, the proportion between systolic and diastolic periods of the cardiac cycle is about one-third and two-third, respectively. Therefore, an average systolic (SBP) and diastolic blood pressures (DBP) can be calculated from the following formula:

$$
\text{MAP} = \text{DBP} + 1/3 \ (\text{SBP} - \text{DBP})
$$

It is important that blood pressure is measured according to the National Heart Foundation of Australia (NHFA) protocol using automated devices. Women should be sitting with their arms well supported at the level of their heart, as shown in Figure 1. The size of adult cuff used depends on the mid-arm circumference (small <22 cm, normal 22–32 cm, or large 33–42 cm). After 5-minute rest, blood pressure is measured simultaneously in both arms. Two sets of recordings are made within 1 minute. The four sets of SBP and DBP measurements are input into the risk calculator to generate patient-specific risk of PE.

Uterine Artery Doppler Pulsatility Index
Pulse-wave Doppler studies of the uterine arteries can noninvasively determine resistance of the uteroplacental circulation. In normal pregnancies, there is a significant decrease of resistance in the uterine arteries with advancing gestation. Persistent high impedance flow in the uterine arteries is an evidence of poor placentation. Histological examination of placental bed of pregnancies affected by PE has shown that absence of physiological changes of the uterine-spiral arteries corroborates with high UtAPI. Accurate measurement of UtAPI relies on appropriate training, certification, and audit of sonographers. Adherence to a standard ultrasound technique is important to achieve uniform results among different operators.

Transabdominal or transvaginal ultrasound examination at 11–13 weeks’ gestation (fetal crown–rump length (CRL) of 42–84 mm) should be performed with high-resolution equipment. The ultrasound scan should include a full structural survey to detect major fetal defects. The NT and UtAPI are measured according to established guidelines. Pulse-wave Doppler assessments are performed in accordance with the as low as reasonable achievable (ALARA) principle. Thermal and mechanical indices displayed on the monitor should be kept below 1.0 and 0.5, respectively. Video clips and images of the studies should be digitized for possible future reanalysis.

Measurement of UtAPI starts from identification of internal cervical os and cervical canal in a mid-sagittal section. The transducer is then gently tilted to the side to identify each uterine

Table 1: Checklists for maternal characteristics and medical history

| Parameters                              | Data                                      |
|-----------------------------------------|-------------------------------------------|
| Personal history                        | □ White, □ Black, □ South Asian, □ East Asian, □ Mixed/other |
| Maternal age (years)                    | □ Nulliparous, □ Parous without PE, □ Parous with PE |
| Maternal weight (kg)                    | □ Yes, □ No                               |
| Maternal height (cm)                    | □ Yes, □ No                               |
| Maternal ethnicity                      | □ Yes, □ No                               |
| Obstetric history                       | □ Yes, □ No                               |
| Past obstetric history                  | □ Yes, □ No                               |
| Interpregnancy interval (years)* > 10 years | □ Type 1, □ Type 2, □ Insulin dependent |
| Gestational age at previous delivery (weeks) | □ Yes, □ No                           |
| Birth weight of previous delivery (g)   | □ Yes, □ No                               |
| History of medical conditions           | □ Yes, □ No                               |
| Chronic hypertension                    | □ Yes, □ No                               |
| Diabetes mellitus                       | □ Yes, □ No                               |
| SLE or APS                              | □ Yes, □ No                               |
| Others                                  | □ Yes, □ No                               |
| Familial (mother) history of PE         | □ Yes, □ No                               |
| Method of conception                    | □ Yes, □ No                               |
| Smoker                                  | □ Yes, □ No                               |

kg, kilogram; cm, centimeter; g, gram; PE, preeclampsia; IVF, in vitro fertilization; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome

*Years between the birth of the last child
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artery on the side of the cervix at the level of the internal os with color flow Doppler mapping. Pulsed-wave Doppler is used with the sampling gate set at 2 mL to cover the whole vessel. Alternatively, the transverse approach for the measurement of UtAPI in the first trimester appears to be comparable with the sagittal approach in terms of reliability, reproducibility, and time required, and may be easier to perform. Care is taken to ensure that the angle of insonation is less than 30°. The UtAPI is measured when three similar consecutive waveforms are obtained, and the mean UtAPI of the insonation is less than 30°. The UtAPI is measured when three similar consecutive waveforms are obtained, and the mean UtAPI of the insonation is less than 30°. The UtAPI is measured when three similar consecutive waveforms are obtained, and the mean UtAPI of the insonation is less than 30°.

Factors PE have significantly lower maternal PlGF concentrations in the first trimester than pregnancies with normal outcomes. Factors PE have significantly lower maternal PlGF concentrations in the first trimester than pregnancies with normal outcomes. Factors PE have significantly lower maternal PlGF concentrations in the first trimester than pregnancies with normal outcomes. These factors need to be adjusted for algorithmic risk estimation of PE needs to be tailor accordingly to the population. These factors need to be adjusted for algorithmic risk estimation of PE needs to be tailor accordingly to the population. These factors need to be adjusted for algorithmic risk estimation of PE needs to be tailor accordingly to the population.

Measurement of Biochemical Markers

Trophoblastic injury from poor implantation may be the main origin of PE. Trophoblastic cells release vasoactive substances into maternal circulation. The most powerful first-trimester biochemical marker for prediction of preterm PE is PlGF. PlGF is a glycosylated dimeric glycoprotein secreted by trophoblastic cells. It is a vasoactive mediator that plays a role in normal pregnancy. Changes of circulating levels of PlGF have been implicated in the development of PE. Women who subsequently develop PE have significantly lower maternal PlGF concentrations in the first trimester than pregnancies with normal outcomes. Factors that affect the values of PlGF in pregnant women are gestational age, maternal age, weight, racial origin, cigarette smoking, PE in previous pregnancies, diabetes mellitus, and in vitro fertilization. These factors need to be adjusted for algorithmic risk estimation of preterm PE using PlGF.

Pregnancy-associated plasma protein-A is also useful if measurement of PlGF is not available. It is a metalloproteinase insulin-like growth factor (IGF) binding protein secreted by the syncytiotrophoblasts. It plays an important role in placental development through enhancement of the mitogenic function of the IGFs. Pregnancy-associated plasma protein-A is a well-established biochemical marker in prenatal screening of trisomies 21, 18, and 13. Some women who subsequently develop PE have significantly lower maternal PAPP-A concentrations in the first trimester than those with normal pregnancy outcomes. Soluble fms-like tyrosine kinase 1 (sFlt-1) is a tyrosine kinase protein with antiangiogenic properties. It reduces blood vessel growth through reduction of circulating vascular endothelial growth factor (VEGF) and PlGF concentrations. Abnormally high levels of sFlt-1 in the second and third trimester of pregnancy may predict imminent development of PE. Automated platforms for measurement of serum concentrations of these biomarkers are commercially available. Only 5 mL of blood sample is required. Written instructions for proper collection, handling, and transport of blood samples must be clear, easy to understand, and available in the appropriate language and literacy level for all health care providers and couriers. Clinical laboratory should obtain accreditation, i.e., International Organization for Standardization (ISO). No extra precautions need to be taken when PlGF is used for PE screening run alongside existing first-trimester aneuploidy screening programs that include PAPP-A and free β-hCG.

If immediate transport of the blood sample to the laboratory is not possible, blood samples can be kept in the clinic at room temperature for courier pick-up for a few hours without significant change in PlGF levels. If same-day pick-up is not possible, keeping blood samples refrigerated (4°C) can stabilize PlGF and sFlt-1 levels for at least 48 hours. Handling of blood samples for quantitation of PlGF in accordance with storage time is summarized in Table 2. Any significant deviation from these standards and guidelines, including specific clinical circumstances presented by the individual patient or specimen, that may affect the quality of test should be documented in the laboratory record.

Calculation for Risk of Preterm Preeclampsia

Validated algorithms can be used for converting the measured values of maternal characteristics, MAP, UtAPI, and PlGF into multiples of the median (MoMs). Individualized risk for preterm PE is calculated using the Bayes-based method. A risk calculation software is available free of charge on the web pages of professional organizations or from commercially available software, i.e., Predictor Software by PerkinElmer (Massachusetts, USA) and ViewPoint Software by GE Healthcare (Illinois, USA). These algorithms are similar but not identical. It depends on chosen cut-offs and test properties. It remains inconclusive as to which algorithm is the best. The calculated risk of ≥1 in 100 (high risk) detects 76.6% preterm PE cases at a fixed FPR of 10%. The algorithmic estimation of PE needs to be tailor accordingly to the population.

Prophylactic Measures

Hypertension in Pregnancy Task Force Report previously recommends daily low-dose aspirin (81 mg per day) beginning in the late first trimester for women with a history of early-onset PE, or for women with more than one prior pregnancy complicated by PE. Low-dose (<300 mg per day) aspirin may prevent development of PE by inhibiting the biosynthesis of placental thromboxane A2, without affecting prostacyclin. Aspirin reversibly inhibits endothelial cyclooxygenase enzyme, but this process is irreversible in platelets. Results from the Combined Multi-marker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial provides definitive evidence that low-dose aspirin (150 mg per day) from 11 to 14 weeks of gestation until (1) 36 weeks of gestation, (2) delivery,
Model of the Service Flow

Counseling for the opportunity to receive PE screening and prophylaxis should be included in the first prenatal visit. Barriers for women and their partners to make an informed decision are complex concepts of risk and probability, lack of time, and limitations of choices of screening. An information leaflet can facilitate the counseling process. The OSCAR model can be applied for first-trimester screening of common fetal aneuploidies and early PE on a single visit. Maternal and obstetric histories are documented along with physical characteristics (height and weight). The SBP and DBP are recorded according to standard protocol to derive MAP. An ultrasound is performed to confirm the gestational age and number of fetus. The fetal NT and maternal left and right UtAPI are measured using standardized protocols. Blood is then taken from the mother for quantitation of PAPP-A, free β-hCG, and PlGF with a commercially available automated system. Turnaround time for the blood works is within a few hours. The software, customized

| Specimen collection | Nonheparinized tube for serum collection |
|---------------------|----------------------------------------|
| Collection tube     | Reject if the serum is hemolyzed, icteric (yellow), or lipemic (turbid) |
| Sample condition    | (1) Allow the sample to clot >30 minutes for optimal separation of the serum and reduction of fibrin plug in the separated serum portion after separation. |
| Serum separation    | (2) Centrifugation for 10 minutes at 1,800 g (1800RCF). |
|                     | (3) Decant serum sample in plain tube. Leave a small amount of serum above gel plug to ensure none of the gel plug is transferred to the plain tube. |

| Specimen analysis |
|-------------------|
| Immediate processing | Present to the analyzer for immediate measurement according to manufacturer’s instructions. |
| Processing within 24 hours | (1) Decant serum to a labeled clean plain tube within 1 hour of centrifugation. |
|                     | (2) Refrigerate at 2–8°C. |
|                     | (3) Remove from refrigerator and bring up to room temperature. |
|                     | (4) Place on roller for 30 minutes or invert tube 20 times to remix serum. |
|                     | (5) Present to analyzer. |
|                     | (6) Freeze excess serum at 80°C for long-term storage if needed in future. |
| Processing after 24 hours and within 7 days* | (1) Decant serum to a labeled clean plain tube within 1 hour of centrifugation. |
|                     | (2) Freeze at 20–30°C. |
|                     | (3) Remove from freezer, and refrigerate at 2–8°C overnight day before intended analysis. |
|                     | (4) Remove from refrigerator and bring up to room temperature. |
|                     | (5) Place on roller for 30 minutes or invert tube 20 times to remix serum. |
|                     | (6) Present to analyzer. |
|                     | (7) Freeze excess serum at 80°C for long-term storage if needed in future. |
| Processing after 7 days* | (1) Decant serum to a labelled clean plain tube within 1 hour of centrifugation. |
|                     | (2) Freeze at −80°C. |
|                     | (3) Defrost stage 1: remove from −80°C freezer, and freeze at −20 to −30°C. |
|                     | (4) Defrost stage 2: remove from freezer, and refrigerate at 2–8°C overnight day before intended analysis. |
|                     | (5) Remove from refrigerator and bring up to room temperature. |
|                     | (6) Place on roller for 30 minutes or invert tube 20 times to remix serum. |
|                     | (7) Present to analyzer. |
|                     | (8) Freeze excess serum at 80°C for long-term storage if needed in future. |

G, G-force; RCF, relative centrifugal force; °C, degree Celcius
*The sample should not be recentrifuged or revortexed as this creates a concentration gradient
Special Considerations

Prediction of preterm PE should not be based on maternal factors alone. Routine screening for preterm PE should at least consist of maternal and ultrasound markers and MAP (first-tier test). Maternal serum PAPP-A routinely measured for first-trimester screening of aneuploidies can be included for PE risk assessment. The UtAPI and PIGF can be reserved for those who are screened positive (second-tier test).\(^{50,51}\) Community outreach strategies such as mobile clinics may increase access to prenatal care in the resource-constraint setting. Quality of prenatal screening in these settings remains to be evaluated. Underresourced practices should prioritize the availability of accurate devices for measuring blood pressure and proteinuria, training of on-site sonographers, reliable supply of medications (i.e., aspirin, antihypertensive medications, and magnesium sulfate), and access to necessary (maternal and neonatal) critical care and laboratory services.\(^{52}\)

The incidence of PE in monochorionic and dichorionic twin pregnancies is increased by three and fourfolds, respectively. There are elevation of MAP and UtAPI, and decrease of serum PIGF and PAPP-A in twin pregnancies subsequently develops PE.\(^{53}\) A multimarker screening model for PE in low-risk twin pregnancies, using a modified version of predictors in singletons, is available. At a cut-off of 1 in 75, the model can detect 99% of preterm PE in twin pregnancies at much higher screen positive rate of 75%. The addition of PAPP-A does not improve the performance of screening for preterm PE in twin pregnancies.\(^{53}\) The UtAPI is of little value in screening for PE in low-risk twin pregnancies.\(^{54}\)

Vaginal spotting must be duly assessed but does not necessitate stopping aspirin prophylaxis.\(^{10}\) The use of low-dose aspirin during pregnancy is not associated with major bleeding complications, i.e., placental abruption or postpartum hemorrhage.\(^{55}\) Aspirin is contraindicated in those with bleeding tendencies, i.e., peptic ulcers or bleeding disorders. In high-risk women who are allergic to aspirin, expectant management with frequent (home or clinic) blood pressure monitoring to ensure early diagnosis of PE is appropriate. Heparin, vitamins C and E, magnesium, folate, metformin, and statin have not been proven to prevent preterm PE. Low-dose aspirin may prevent preterm PE in multiple pregnancies, although its real efficacy remains elusive.\(^{56}\)

Research Agenda

Early PE prediction and prevention substantially saves cost in high-income countries.\(^{57}\) It is a constant challenge for middle- and low-income countries to implement and sustain early PE prediction with a sophisticated approach. Basic devices such as blood pressure monitors and urine dipsticks for use in low-resource settings have shown to be cost-effective in early diagnosis of PE.\(^{52}\) Alternatively, two-stage screening and biomarker testing for only part of the population may have financial benefits over conducting the test for the entire population.\(^{58}\) More work is required to evaluate the cost-effectiveness balance between the ability to early diagnose PE and ability to predict and prevent early PE in a low-income setting.

The UtAPI, measured in the first or second trimester of pregnancy, can also identify a high proportion of women who develop early-onset fetal growth restriction. However, the value of prophylactic pharmacologic intervention in those with exceptionally high UtAPI is less remarkable.\(^{59,60}\)

It is possible that another round of screening with MAP, UtAPI, and serum biomarkers at 30–34 or 35–37 weeks’ gestation may effectively predict imminent development of pregnancy complications during the third trimester.\(^{61,62}\) The potential value of such approach is to improve the perinatal outcome by rationalizing and individualizing the timing and content of subsequent visits for selection of the best time for delivery. Prompt interventions could alleviate the progression to eclampsia, placental abruption, and HELLP syndrome.\(^{53}\)

If agreed by the women, excess serum samples from first-trimester screening can be archived at −80°C for future research, i.e., novel biomarkers, possible genetic predisposition of PE, etc.
PIGF and sFlt-1 are stable for at least 3 years when serum samples are stored at −80°C.

**Conclusion**

Early prenatal visit is important to achieve the goal of prediction and prevention of preterm PE, especially in low-resource countries. Self-monitoring, together with increased awareness of healthcare professionals, would enable an active action to improve pregnancy outcomes. Given the resource constraints in low- and middle-income countries, variations of the first-trimester combined test should be considered but the most basic test should be maternal risk factors combined with MAP. Early access to prenatal services must be encouraged so that the PE screening strategies can be adapted. The initiation of PE screening service needs to consider the level of acceptability, feasibility, and ease of implementation in different resource settings.

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