Original Article

Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy

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Background: The aim of this study is to validate the Fetal Medicine Foundation (FMF) multiple logistic regression algorithm for prediction of risk of pre-eclampsia in an Australian population. This model, which predicts risk using the population rate of pre-eclampsia, a variety of demographic factors, mean maternal arterial blood pressure (MAP), uterine artery PI (UtA PI) and pregnancy-associated plasma protein A (PAPP-A), has been shown to predict early-onset pre-eclampsia (delivery prior to 34 weeks) in 95% of women at a 10% false-positive rate.

Methods: All women who attended first trimester screening at the Royal Prince Alfred Hospital had their body mass index (BMI), MAP and UtA PI assessed in addition to factors traditionally used to assess aneuploidy (including PAPP-A MoM). After delivery, risks of early-onset (delivery prior to 34 weeks) pre-eclampsia, late pre-eclampsia and gestational hypertension were calculated using the FMF risk algorithm.

Results: A total of 3099 women were screened and delivered locally. 3066 (98.9%) women had all data to perform pre-eclampsia screening available. This included 3014 (98.3%) women with a live birth, where risks of early pre-eclampsia were calculated. Twelve women were delivered before 34 weeks because of early pre-eclampsia with a prevalence of early pre-eclampsia of 1 in 256 pregnancies. Risks generated through the use of maternal history, MAP, UtA PI and PAPP-A detected 41.7 and 91.7% of early pre-eclampsia at a false-positive rate of 5 and 10%, respectively.

Conclusions: This study shows that the FMF early pre-eclampsia algorithm is effective in an Australian population.

Key words: first trimester screening, mean arterial pressure, pre-eclampsia, pregnancy-associated plasma protein-A, uterine artery doppler.

Introduction

Hypertensive disorders of pregnancy are common and are responsible for significant maternal and perinatal morbidity and mortality.[1–4] Traditionally, chronic and gestational hypertensions are defined in relation to gestation at diagnosis: being before or after 20 weeks gestation.[1,2] These conditions affect approximately 2 and 10% of pregnancies, respectively.[2] Pre-eclampsia, defined as proteinuric hypertension specific to pregnancy, affects approximately 3% of women and is more common in those women found to have chronic hypertension during early pregnancy.[1,2,5] Identification of women who develop pre-eclampsia is made difficult by the fact that the onset and severity of disease are unpredictable. It is therefore normal practice to review women antenatally with increasing frequency so that hypertension and pre-eclampsia can be recognised in a timely manner.[2]

Although many demographic, biophysical and biochemical risk factors for pre-eclampsia have been recognised, individually they perform poorly from a screening perspective.[6,7] Screening is only of value if there is a therapeutic intervention that can improve outcome. The prophylactic use of low-dose aspirin for the prevention of pre-eclampsia has been a focus of research for over thirty years. The initial observation that nulliparous women who had taken aspirin regularly during pregnancy were less likely to have pre-eclampsia than those who did not was subsequently examined in >50 trials.[8] A meta-analysis of these studies reported only a marginal (10%) benefit of low-dose aspirin in high-risk pregnancies.[9] Most studies reported onset of treatment >16 weeks' gestation. A recent

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meta-analysis focusing on treatment ≤16 weeks or earlier shows a significant reduction in the relative risk (RR) for pre-eclampsia (0.47, 95% confidence interval (CI) 0.34 – 0.65), whereas aspirin started >16 weeks had no significant benefit (RR 0.81, 95% CI: 0.63–1.03).[10] The most recent meta-analysis that has been published further demonstrates that low-dose aspirin started ≤16 weeks' gestation was particularly effective in preventing preterm pre-eclampsia rather than term pre-eclampsia (RR: 0.11, 95% CI: 0.04–0.33 vs RR: 0.98, 95% CI: 0.42–2.33).[11] Successful implementation of this intervention is therefore dependent on being able to screen effectively in early pregnancy.

At present, clinicians evaluate the risk of pre-eclampsia by taking a medical history at the 'booking' visit. This identifies approximately 30% of cases destined to develop early pre-eclampsia for a false-positive rate of 5%.[12] Recently, Poon *et al.* [13] suggested that when these demographic factors were analysed mathematically together with other biophysical and biochemical parameters, 95% of fetuses requiring delivery before 34 weeks gestation due to severe pre-eclampsia could be recognised at the time of the $11–13^{+6}$ week scan at a false-positive rate of 10%. This study reports the effectiveness of the multivariate screening algorithm reported by Poon *et al.* when applied to a population of Australian women attending for routine first trimester screening.

Materials and Methods

This is a retrospective analysis of a prospectively collected cohort of singleton pregnancies screened for chromosomal abnormality at $11–13^{+6}$ weeks' gestation. First trimester aneuploidy screening is offered to all patients booking for antenatal care within our unit. The study is based on an unselected cohort who opted for first trimester screening between 16th April 2010 and 9th March 2012 (23 months) and delivered at either Royal Prince Alfred Hospital or Canterbury Hospital. Women who presented with multiple pregnancies were excluded. Ethics approval was obtained from RPA Human Research Ethics Committee (HREC/11/RPAH/472).

Women were asked to complete a questionnaire identifying ethnicity, mode of conception, obstetric, past medical and family history, and smoking. They were specifically asked about hypertension, hypertension in a previous pregnancy and whether they had a family history of pre-eclampsia (affecting either their mother or sister). Women were not excluded on the basis of taking anti-hypertensive drugs, aspirin or any other medications that may affect the prevalence of pre-eclampsia. Maternal height and weight were measured and body mass index (BMI) was calculated. Maternal blood pressure was measured following a period of maternal rest for at least 10 min; this involved being seated and making two measurements at the level of the heart of systolic and diastolic blood pressure for each arm, and mean arterial pressure was then calculated.[14] Maternal blood pressure was recorded by trained staff using an automated devise (3BTO-A2; Microlife, Taipei, Taiwan) with an appropriately sized cuff. The Microlife 3BTO-A2 was chosen as it was the only automated device validated for use both in pregnancy and pre-eclampsia.[15,16] Calibration of the machine was performed at regular intervals during the study.

An ultrasound was performed as part of screening for aneuploidy in the first trimester. Gestational age was derived from the fetal crown-rump length (CRL). The fetal nuchal translucency, fetal heart rate and anatomic survey were completed. The uterine arteries were demonstrated by defining the cervix in the midline, then tilting the probe towards the lateral margin of the cervix and using colour Doppler to visualise the uterine artery ascending at the level of the internal cervical os.[17,18] Once a consistent uterine artery waveform was recorded, right and left uterine artery pulsatility indices were measured (over three cycles) and recorded.

Maternal serum PAPP-A was measured as part of the first trimester screening programme for aneuploidy. The samples were taken at the time of the first trimester ultrasound visit and analysed using a Siemens Immulite assay (Immulite XPi; Diagnostic products Corporation, Siemens Medical Solutions Diagnostic, Tarrytown, NY, USA). The raw data were converted to a Multiple of Median (MoM) value accounting for gestation (based on CRL) and maternal weight within the Department of Endocrinology (Using Prisca 4 software; Typolog Software Ltd & Co KG, Tomesch, Germany). The MoM values were then entered into the FMF software (Viewpoint Version 5.6.9.483; GE Healthcare, Sydney, NSW, Australia) for aneuploidy risk calculation.

Pregnancy outcome data were collated from the hospital records. Sources of data included the midwifery birth registry and the maternal and neonatal discharge summaries, which are all available electronically. The data were collated by three of the investigators (FP, CL and SR), initially working together to ensure uniformity in assessment. In addition, hospital records related to all obstetric admissions were reviewed when a diagnosis of a hypertensive disorder had been made to ensure that hypertension was appropriately categorised as pre-existing hypertension, gestational hypertension or pre-eclampsia. Gestational hypertension and pre-eclampsia were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy.[19] Hypertension in pregnancy is defined by a systolic BP >140 mgHg and/or diastolic BP >90 mmHg on two occasions more than four hours apart. Chronic hypertension is defined by a history of hypertension prior to conception or that is diagnosed <20 weeks' gestation. Gestational hypertension is defined as de novo hypertension, with no evidence of proteinuria, arising after 20 weeks gestation and returning to normal postpartum. Pre-eclampsia is defined as de novo hypertension arising after 20 weeks gestation, returning to normal postpartum, with proteinuria (24 h urine ≥300 mg or spot urine protein/creatinine ratio ≥30 mg protein/mmol creatinine).[19] Each woman was categorised at delivery as

having either no hypertensive disease of pregnancy, gestational hypertension, early pre-eclampsia (requiring delivery <34 weeks gestation) or late pre-eclampsia (requiring delivery ≥34 weeks). Women with chronic hypertension were not categorised as hypertensive disease of pregnancy unless they developed superimposed pre-eclampsia. Birth data, including gestation, mode of delivery and birth weight, were recorded.

The measured MAP and lowest UtAPI were converted to multiples of the expected normal median (MoM) corrected for fetal CRL, maternal age, BMI, smoking and racial origin.[20] The Fetal Medicine Foundation (FMF) risk algorithm was used to predict the development of early pre-eclampsia, late pre-eclampsia and gestational hypertension from first trimester parameters.[13,17,21–23] The algorithm was applied retrospectively to our study population and patient-specific risks of early pre-eclampsia, late pre-eclampsia and gestational hypertension generated, so this information was not reported to referring clinicians at the time of the first trimester scan. The algorithm used to define the risk of pre-eclampsia was Odds/(1 + odds) where odds = eY and where $Y = 0.154 + 2.546 \times \log(-3.657 + 1.592 \times \log$ maternal risk factor $+ 31.396 \times \log$ MAP MoM $+ 13.322 \times \log$ UtA L-PI MoM) $- 2.603 \times \log$ PAPP-A MoM. The maternal risk factor was −5.674 + (1.267 if African, 0 if other racial origin) + (2.193 if history of chronic hypertension, 0 if not) + (−1.184 if parous without previous PE, 1.362 if parous with previous PE, 0 if nulliparous) + (1.537 if conceived with ovulation induction, 0 if other method of conception). The categorisation of pregnancy outcome occurred prior to calculation of risk of hypertension in pregnancy.

The predictive performance of the algorithm was examined using the sensitivity and specificity of the test as well as the positive and negative predictive value in our population. Performance of screening was further examined by receiver operating characteristic (ROC) curve analysis. The expected number of cases of early- and late-onset pre-eclampsia and gestational hypertension was calculated as sums of risks of individual algorithm. Comparison between outcome groups by Mann–Whitney *U*-test with *post hoc* Bonferroni's correction and χ^2-test or Fisher's exact test for categorical variables (adjusted significance level $P < 0.0167$). The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp, Armonk, NY, USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for all data analyses.

Results

A total of 3099 women with a singleton pregnancy underwent first trimester screening for aneuploidy and delivered at Royal Prince Alfred or Canterbury Hospitals over this 23 month period. 3066 (98.9%) had sufficient data collected prospectively, at the time of first trimester screening, to calculate a risk for pre-eclampsia. In 33 cases, data were incomplete due to missing demographic history, maternal serum biochemistry (PAPP-A), maternal mean arterial pressure or uterine artery Doppler measurement. 3014 (98.3%) of the 3066 women who were screened had a live birth. This included 83 (2.8%) that developed pre-eclampsia; 12 (0.4%) that required delivery before 34 weeks (early pre-eclampsia) and 71 (2.4%) with late pre-eclampsia. 119 (3.9%) women developed gestational hypertension, whilst 2,812 (93.3%) cases were unaffected by either pre-eclampsia or gestational hypertension. 23 (0.8%) fetuses died in utero, 27 (0.9%) women had a termination of pregnancy, and two neonates died at early gestations (22 and 24 weeks) as the result of prematurity (Table 1).

Of 42 (4.0%) parous women reported a history of pre-eclampsia in a previous pregnancy; 142 (6.4%) women reported a maternal history of pre-eclampsia and 28 (1.3%) women had a history of pre-existing hypertension. The maternal and pregnancy characteristics of the hypertensive groups are compared with the normotensive group in Table 2. In the early pre-eclampsia group, when compared with the control group, there was a higher prevalence of women with chronic hypertension, the MAP MoM and UtAPI MoM were higher, the gestational age at delivery was earlier, and the neonatal birth weight was smaller. In the late pre-eclampsia group, when compared with the control group, there was a higher prevalence of nulliparous women and women with chronic hypertension, the BMI was higher, the MAP MoM was higher, the PAPP-A MoM was lower, the gestational age at delivery was earlier, and the neonatal birth weight was smaller. In the gestational hypertension group, when compared with the control group, there was a higher prevalence of Caucasian women and women with chronic hypertension and prior history of pre-eclampsia, the BMI was higher, the MAP MoM was higher, the PAPP-A MoM was lower, and the gestational age at delivery was earlier.

The performance of the FMF algorithm in predicting early- and late-onset pre-eclampsia and gestational hypertension is described in Table 3. Using all

Table 1 Description of cases that did not result in a live birth

Gestational age	Termination of pregnancy	Intrauterine death	Neonatal death
<20 weeks	Chromosomal abnormality: 18 Structural abnormality: 7 Genetic syndrome: 1 Maternal illness: 1	10	
20–23 weeks		4	1
24–33 weeks		1	1
34–36 weeks		4	
37–39 weeks		1	
≥40 weeks		3	1
Total	27	23	3

Table 2 Maternal and pregnancy characteristics by pregnancy outcome

Maternal variables	Unaffected (n = 2812)	Early PE (n = 12)	Late PE (n = 71)	GH (n = 119)
Maternal age in yrs, median (IQR)	33.3 (30.1–36.2)	34.1 (28.2–36.5)	31.4 (29.0–31.4)	33.4 (29.5–36.6)
Body mass index in Kg/m^2, median (IQR)	23.4 (21.3–26.2)	23.8 (23.1–26.3)	25.6 (22.4–28.8)*	26.1 (22.4–29.6)*
Racial origin				
Caucasian, *n* (%)	1,882 (66.9)	6 (50.0)	51 (71.8)	98 (82.4)*
Afro-Caribbean, *n* (%)	28 (1.0)	0 (0.0)	3 (4.2)	1 (0.8)
South Asian, *n* (%)	291 (10.3)	2 (16.7)	9 (12.7)	4 (3.4)
East Asian, *n* (%)	596 (21.2)	4 (33.3)	8 (11.3)	14 (11.8)*
Mixed, *n* (%)	15 (0.5)	0 (0.0)	0 (0.0)	2 (1.7)
Parity				
Nulliparous, *n* (%)	1,449 (51.5)	9 (75.0)	69 (97.2)*	72 (60.5)
Parous - no previous PET, *n* (%)	1,324 (47.1)	2 (16.7)	1 (1.4)*	33 (27.7)*
Parous - previous PET, *n* (%)	39 (1.4)	1 (8.3)	1 (1.4)	14 (11.8)*
Cigarette smoker, *n* (%)	86 (3.1)	0 (0.0)	3 (4.2)	2 (1.7)
Mother with PET, *n* (%)	198 (7.0)	1 (8.3)	7 (9.9)	14 (11.8)
Conception				
Spontaneous, *n* (%)	2,671 (95.0)	11 (91.7)	67 (94.4)	114 (95.8)
Ovulation induction, *n* (%)	54 (1.9)	1 (8.3)	3 (4.2)	2 (1.7)
In vitro fertilisation, *n* (%)	87 (3.1)	0 (0.0)	1 (1.4)	3 (2.5)
Chronic hypertension, *n* (%)	28 (1.0)	2 (16.7)*	6 (8.5)*	–
MAP MoM, median (IQR)	0.96 (0.90–1.02)	1.01 (0.99–1.10)*	1.03 (0.96–1.08)*	1.02 (0.97–1.11)*
Uterine artery PI MoM (lowest), median (IQR)	1.00 (0.79–1.25)	1.68 (1.19–1.78)*	1.12 (0.81–1.34)	1.00 (0.71–1.31)
PAPP-A MoM, median (IQR)	1.07 (0.73–1.53)	0.93 (0.50–1.41)	0.86 (0.58–1.38)*	0.95 (0.66–1.43)
Gestation at delivery in weeks, median (IQR)	39.7 (38.9–40.7)	31.4 (29.0–32.1)*	38.7 (37.9–39.9)*	39.0 (38.3–40.1)*
Birth weight (g), median (IQR)	3,420 (3,100–3,720)	1,203 (993–1,477)*	3,258 (2,768–3,570)*	3,360 (3,050–3,664)
Birth weight percentile[34] (Z score), mean (IQR)	0.09 (−0.58–0.68)	−0.88 (−1.43–0.47)	−0.09 (−0.95–0.59)	0.06 (−0.59–0.57)

IQR, interquartile range; BMI, body mass index; PET, pre-eclampsia; MAP, mean arterial pressure; MoM, multiple of median; PI, pulsatility index; PAPP-A, pregnancy associated plasma protein-A.
Comparison between outcome groups by Mann–Whitney *U*-test with *post hoc* Bonferroni correction and χ^2-test or Fisher's exact test for categorical variables; Adjusted significance level *$P < 0.0167$.

demographic, biophysical and biochemical factors, screening at fixed 5 and 10% false-positive rates, the detection rates of early pre-eclampsia were 41.7% (95% CI 15.3–72.2) and 91.7% (95% CI 61.5–98.6), respectively. Using demographic and biophysical factors, screening at fixed 5 and 10% false-positive rates, the detection rates of late pre-eclampsia were 18.3% (95% CI 10.1–29.3) and 35.2% (95% CI 24.2–47.5), respectively. The respective detection rates for gestational hypertension were 27.6% (95% CI 27.6–36.2) and 37.8% (95% CI 29.3–46.8). Accuracy was measured by examining the area under the ROC curve (AUROC), with an area of 1 representing a perfect test and an area of 0.5 representing a worthless test. The AUROC for early pre-eclampsia calculated for the combined algorithm was 0.926 (95% CI 0.916–0.936) indicating good performance (Tables 3 and 4; Fig. 1).

Discussion

This study has demonstrated that the FMF algorithm that has been designed to predict early-onset pre-eclampsia is effective in an Australian population. The test had a sensitivity of 91.7% for 90% specificity. If this algorithm was applied to our population prospectively at 11–13^{+6} weeks' gestation, we would anticipate positive and negative predictive values of 3.6 and 99.9%, respectively. The high negative predictive value means the test could be used to define a group of women at very low risk of early-onset pre-eclampsia who could be managed within a low-risk care model. The positive predictive value remains relatively low, meaning that one in every 28 women placed in a high-risk group would actually develop early-onset pre-eclampsia and this would need to be taken under consideration when planning interventions for this group.

The findings of this study are similar to the data reported by Poon *et al.*[13]on the effectiveness of this multivariate screening algorithm. Poon *et al.* completed their study in a tertiary institution in the UK where there was a significant difference in ethnicity of women being examined, which included a large African population and few Asian women. Given these differences, it was important to demonstrate the effectiveness of the algorithm in a cohort of Australian women. Poon *et al.*[13]reported that

Table 3 Performance of screening for fixed 5 and 10% false positive rates for a range of different screening algorithms

	Area under receiver operating curve (95% CI)		
	Early PET (n = 12)	Late PET (n = 71)	GH (n = 119)
History	0.755 (0.739–0.771)	0.677 (0.660–0.694)	0.681 (0.664–0.698)
History with			
MAP	0.834 (0.819–0.847)	0.750 (0.734–0.766)	0.763 (0.747–0.778)
UtAPI	0.892 (0.880–0.903)	0.686 (0.668–0.703)	0.667 (0.649–0.684)
MAP + UtAPI	0.936 (0.926–0.945)	0.756 (0.740–0.771)	0.749 (0.733–0.764)
PAPP-A	0.741 (0.725–0.758)	0.695 (0.678–0.711)	–
PAPP-A + MAP	0.809 (0.794–0.823)	0.760 (0.744–0.776)	–
PAPP-A + UtAPI	0.873 (0.860–0.885)	–	–
PAPP-A + UtAPI + MAP	0.926 (0.916–0.936)	–	–

	Detection rate (95% CI) at false positive rate					
	5%	10%	5%	10%	5%	10%
History	33.0 (6.5–72.5)	39.5 (10.0–75.5)	8.5 (3.2–17.5)	21.1 (12.3–32.4)	16.0 (9.9–23.8)	27.7(19.9–36.7)
History with						
MAP	25.0 (5.8–57.2)	58.3 (27.8–84.7)	21.1 (12.3–32.4)	31.0 (20.5–43.1)	22.7 (15.5–31.3)	37.0 (28.3–46.3)
UtAPI	66.7 (34.9–89.9)	75.0 (42.8–94.2)	9.9 (4.1–19.3)	22.5 (13.5–34.0)	19.3 (12.7–27.6)	26.9 (19.9–36.7)
MAP + UtAPI	66.7 (34.9–89.9)	91.7 (61.5–98.6)	18.3 (10.1–29.3)	35.2 (24.2–47.5)	27.7 (19.9–35.8)	36.1 (27.5–45.4)
PAPP-A	33.3 (10.1–65.1)	50.0 (21.2–78.8)	8.5 (3.2–17.5)	25.4 (15.8–37.1)	–	–
PAPP-A + MAP	41.7 (15.3–72.2)	41.7 (15.3–72.2)	19.7 (11.2–30.9)	32.4 (21.8–44.5)	–	–
PAPP-A + UtAPI	58.3 (27.8–84.7)	75.0 (42.8–94.2)	–	–	–	–
PAPP-A + UtAPI + MAP	41.7 (15.3–72.2)	91.7 (61.5–98.6)	–	–	–	–

PET, pre-eclampsia; GH, gestational hypertension; MAP, mean arterial pressure; UtAPI, uterine artery pulsatility index; PAPP-A, pregnancy associated plasma protein A.

Table 4 Performance of the full screening algorithm in detecting early pre-eclampsia. Performance rates are given for fixed 5 and 10% false positive rates

	False positive rate	
Testperformance	5%	10%
Sensitivity (95% CI)	41.7% (15.3–72.2)	91.7% (61.6–98.6)
Specificity	95.2% (93.5–95.2)	90.3% (89.7–91.8)
Positive predictive value	3.4% (1.3–8.6)	3.6% (2.0–7.0)
Negative predictive value	99.8% (99.4–99.9)	99.9% (99.7–99.9)

95% of early pre-eclampsia can be predicted through first trimester screening (at a 10% false-positive rate) which is comparable with the 91.7% detection rate that we have reported. It is interesting to note that in our population, inclusion of the serum measure of PAPP-A did not improve the predictive ability of the algorithm above what is achieved by the use of a combination of maternal factors, MAP and uterine artery PI. This is not the case for the study reported by Poon *et al.*[13] Possible explanations for this difference include the different patient population and the use of a different platform for measuring PAPP-A. The sample size was also smaller in this study and may not, therefore, have shown the small improvement previously reported with PAPP-A.

One limitation of this study is that despite recruiting >3000 pregnancies, only a small number of women developed early pre-eclampsia (n = 12). Consequently, confidence intervals describing test performance remain broad. A further limitation is that whilst the study population were unselected, they do represent a cohort of women who chose to have first trimester screening for aneuploidy. Also, the ethnic and socio-economic composition of this inner city population does not reflect that found in all Australian centres. Nevertheless, we have demonstrated that an algorithm developed in the UK appears to be sufficiently robust to be used in Australia.

The principle of first trimester screening is well established for the identification of pregnancies at increased risk of aneuploidy. First trimester screening could be expanded to include screening for hypertensive disorders of pregnancy, although systems need to be developed to ensure accurate recording of added demographic data, accurate measurement of weight and height, and accurate measurement of maternal blood pressure. Sonographers also need to be trained in the technique used for assessment of the uterine artery waveform, which is different to that traditionally described

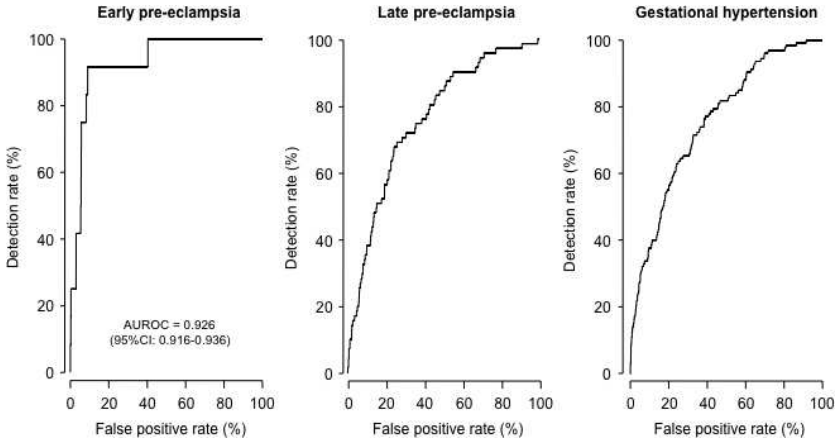

Figure 1 Receiver operator characteristic (ROC) curves for detection of early- and late-onset pre-eclampsia and gestational hypertension using the full screening algorithm.

in the second trimester of pregnancy. Attributes of a good screening test for pre-eclampsia include a test that is simple, rapid, non-invasive, inexpensive, easy to perform and does not expose patients to risk of significant discomfort.[24] We have found implementation of the additional parameters required for pre-eclampsia screening at 11–13^{+6} weeks to be straightforward although we would emphasise the need for appropriate training in uterine artery Doppler measurement and the need for ongoing quality assurance.

Screening is only of value if there is a therapeutic intervention that can improve outcome. Low-dose aspirin given to women at increased risk of pre-eclampsia has been examined extensively. Large reviews report a small but significant reduction in risk of pre-eclampsia with low-dose aspirin.[9,25] A recent meta-analysis that examined the effectiveness of low-dose aspirin for the prevention of pre-eclampsia showed a 50% reduction in prevalence at all, and 90% reduction in prevalence at early (<34 weeks) gestations in high-risk women.[10] These improvements were reliant on aspirin therapy being started <16 weeks' gestation – this requires early screening. These data have confirmed that screening for pre-eclampsia at 11–13^{+6} weeks is highly predictive of early-onset disease. If 1 in 28 women who are high risk would have an affected pregnancy and there is a 90% reduction through early intervention with low-dose aspirin, then we would anticipate that 31 women would need to be treated to prevent one case of pre-eclampsia requiring delivery <34 weeks. As low-dose aspirin has been shown to be safe for the fetus, this seems to be an acceptable treatment for high-risk women.[26] We recognise that women who screen positive may experience concern and anxiety about their pregnancy outcome.[27] We anticipate that this can be minimised with pre- and post-test counselling and the implementation of a plan of monitoring during the pregnancy for women who screen positive, although this requires further evaluation. We also recognise that women should be given an opportunity to decline screening.

Each measurement used in calculating an individual woman's risk of the development of pre-eclampsia required training, implementation and review of the accuracy of the measurement for quality assurance of the risk calculation generated. This was particularly relevant for uterine artery Doppler measurement. The importance of this principle is well understood for aneuploidy risk assessment in the first trimester with nuchal translucency measurement requiring annual audit for clinicians to maintain their accreditation, ensuring that the performance of this screening test remains high. Quality assurance of risk components, including uterine artery Doppler assessment, needs to be considered. Although the data for risk assessment were collected prospectively in this study, risks were not calculated until the pregnancy was complete, avoiding any bias that may have been introduced through changes in clinician management of these pregnancies.

The performance of the multivariate screening algorithm may be further improved. Akolekar *et al.* [28] have published an algorithm, including an additional biochemical marker that reduced the false-positive rate to 5% while maintaining detection rate at 91% for early-onset pre-eclampsia. Whilst this algorithm is predictive of late-onset pre-eclampsia and gestational hypertension, it is less sensitive for these conditions. The difference in predictive performance for early- and late-onset disease may reflect differences in the underlying pathologies. There is a evidence that suggests that the morphological changes seen in the placenta in early-/severe- or late-onset pre-eclampsia are significantly different.[29,30] An alternative screening strategy for late-onset disease may involve two step screening, using either the same markers in a multiple measures model or additional markers indicative of risk of pre-eclampsia.[31–33]

This study supports the multivariate screening algorithm published by the Maternal Fetal Medicine Foundation for the prediction of pre-eclampsia between 11 and 13^{+6} weeks when applied to an Australian population.

While a full cost-benefit analysis needs to be undertaken, the introduction of routine first trimester screening for severe pre-eclampsia, which can be performed at the same time as defining risks of aneuploidy, merits further consideration.

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