Accuracy of second trimester prediction of preterm preeclampsia by three different screening algorithms

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Abstract

Aim: To compare the performance of three different screening methods (NICE guidelines, ACOG recommendations and FMF algorithm) for second trimester prediction of preeclampsia.

Methods: This was a prospective non-intervention study in singleton pregnancies, including women attending for second trimester morphologic ultrasound at 19-22 weeks. Maternal characteristics, medical history, mean arterial pressure and mean uterine artery Doppler pulsatility index were recorded and used for risk assessment. Outcomes measured were preeclampsia with delivery before 34, before 37 and after 37 weeks' gestation. Detection rates, false positive rates and positive likelihood ratios were calculated, and ROC curves were produced.

Results: We screened 543 women during the study. The incidence of preeclampsia before 34, before 37 and after 37 weeks was 0.5%, 1.4% and 3.4%, respectively. Detection rates for prediction of preterm preeclampsia were 75% (95% CI 34.9-96.8), 87% (95% CI 47.3-99.6), 100% (95% CI 63.0-100), and 100% (95% CI 63.0-100) for NICE guidelines, ACOG recommendations, FMF algorithm with a 1:100 cut-off and FMF algorithm at 1:60 cut-off, respectively. False positive rates were, 22%, 67%, 19% and 12% for NICE guidelines, ACOG recommendations, FMF algorithm with a 1:100 cut-off and FMF algorithm at 1:60 cut-off, respectively.

Conclusion: Second trimester combined screening for preterm preeclampsia by maternal history, mean arterial pressure and mean uterine artery Doppler pulsatility index (FMF algorithm) was superior than screening by maternal factors alone (NICE guidelines and ACOG recommendations).

Introduction

Preeclampsia (PE) affects 2-8% of all pregnancies and constitutes one of the main causes of maternal and perinatal morbidity and mortality[1]. Identifying women at high risk in the first trimester allows preventive actions such as low-dose aspirin intake starting before 16 weeks[2-5]. In the last few decades, there has been a shift towards early screening for pregnancy complications[6]. However, the number of women attending their first antenatal visit after 16 weeks is often more than 50% and can be as high as 88.5% in developing countries, where avoiding complications of the disease remains as a significant challenge[7-9]. Screening for PE in the second trimester could still be of benefit, since close monitoring looking for early signs of PE permits timely treatment and delivery. Additionally, observational data have shown that women who develop PE are at increased lifetime risk of cardiovascular disease, which in turn is related to the severity and to the gestational age at onset of PE, and early identification of such group could facilitate the implementation of prevention strategies postnatally[10, 11].

Different methods of screening have been proposed and used in various healthcare systems. Most of them are based on maternal demographic characteristics and on medical and obstetric history (maternal factors)[12-15].

The current method of screening in the United Kingdom (UK) National Health System (NHS) is the National Institute for Health and Clinical Excellence (NICE) guidelines, that consider pregnant women to be at high-risk of developing PE if they have any one high-risk factor or any two moderate-risk factors; the high-risk factors are history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension and the moderate-risk factors are first pregnancy, age >40 years, inter-pregnancy interval >10 years, body mass index (BMI) at first visit of >35 kg/m^2 or family history of PE[15].

In the United States of America (USA), the American College of Obstetricians and Gynecologists (ACOG) states that taking a medical history to evaluate for risk factors is the best and only recommended screening approach for PE; the risk factors are nulliparity, age >40 years, body mass index >30 kg/m^2, conception by in vitro fertilization (IVF), history of previous pregnancy with PE, family history of PE, chronic hypertension, chronic renal disease, diabetes mellitus, systemic lupus erythematosus or thrombophilia[12].

However, these traditional methods have poor detection rate or high false positive rate[16, 17].

Other authors advocate an alternative method screening based on Bayes theorem, associating maternal history and characteristics with biomarkers such as measurement of mean arterial pressure, uterine artery Doppler pulsatility index (PI) and biochemical markers to generate an individual post-test probability of developing PE[18, 19].

Such algorithms have higher detection rates with an acceptable false positive rate both in the first and second trimesters for preterm PE prediction[18, 20, 21].

A recent study by O'Gorman et al compared the performance of these three methods of screening in the first trimester and reported a higher detection rate with a lower false positive rate when using a patient-specific risk approach[16]. Yet, the performance of individual risk estimation was rarely assessed in different populations in the second trimester.

The aim of this study is to compare the performance of the NICE guidelines[15], the ACOG recommendations[12] and a multimarker patient-specific risk assessment using the Fetal Medicine Foundation (FMF) previously published algorithm[18], including maternal history, MAP and mean uterine artery Doppler PI, in the second trimester (19-22 weeks) for the prediction of PE in the Australian population.

Materials and Methods

This was a prospective non-intervention study in singleton pregnancies. Women attending for their second trimester morphology ultrasound between 19 and 22 weeks' gestation at The Royal Women's Hospital in Melbourne, Australia, between June 2012 and January 2015 were offered participation in the study.

Maternal demographic characteristics and history were recorded, as well as mean arterial pressure after two measurements in each arm (following previously published technique)[22]. A standardised colour Doppler technique was used to measure the left and right uterine arteries pulsatility index by transabdominal ultrasound and the average value was recorded[23, 24]. Each patient was then classified as high or low risk for PE according to the NICE guidelines[15] and ACOG recommendations[12]. The individual risk for preterm PE according to the FMF algorithm was retrospectively calculated in the end of the study by one of the authors (DR), who was blinded to the outcomes, using a

previously published algorithm[18], available at The Fetal Medicine Foundation website (www.fetalmedicine.org).

Outcomes of the pregnancies were determined and the occurrence of PE was confirmed or ruled out by review of medical records. The main outcome measure was preterm PE, as defined by the International Society for the Study of Hypertension in Pregnancy[25].

Detection rates, false positive rates and positive likelihood ratios for detection of PE requiring delivery before 34 weeks, before 37 weeks and after 37 weeks were calculated and receiver operating characteristics (ROC) curves produced with the statistical software package IBM SPSS® for each method of screening.

The study was approved by the Royal Women's Hospital Research and Human Research Ethics Committees (Project approval number 11/23). All the patients involved in the study gave written informed consent.

Results

In total, 543 women were prospectively screened for PE and had complete outcome data. There were 516 pregnancies without PE and 27 cases (4.9%) with PE, including three cases (0.5%) of PE before 34 weeks, eight cases (1.4%) of preterm PE and 19 cases of PE at term (3.4%).

Baseline demographic and clinical characteristics of participants are shown in Table 1.

Detection rates (DR), false positive rates (FPR), areas under the curve and positive likelihood ratios for NICE, ACOG and FMF (at cut-off risks of 1:100 and 1:60 for PE before 37 weeks) screening methods are summarized in Table 2. The ROC curves are shown in figure 1.

PE screening by the NICE guidelines detected 33% (95% CI 0.84-90.5), 75% (95% CI 34.9-96.8) and 47.3% (95% CI 24.4-71.1) of PE before 34 weeks, preterm PE and term PE, respectively, with a FPR of 22.4%.

PE screening according to the ACOG recommendations detected 66.6% (95% CI 9.4-99.1), 87.5% (95% CI 47.3-99.6) and 89.4% (95% CI 66.6-98.7) of PE before 34 weeks, preterm PE and term PE, respectively, with a FPR of 67.8%.

Screening for PE using the FMF algorithm at a cut-off of 1:100 detected 100% of the cases of PE before 34 and 37 weeks (95% CI 29.2-100 and 63.0-100, respectively) and 42.1% of term PE cases (95% CI 20.2-66.5), with a FPR of 19.1%.

The FMF algorithm at a cut-off of 1:60 detected 100% of the cases of PE before 34 and 37 weeks (95% CI 29.2-100 and 63.0-100, respectively) and 26.3% of term PE cases (95% CI 9.1-51.2), with a FPR of 12.7%. A cut-off of 1:25 would detect 87.5% of the cases of preterm PE, with a 5% FPR.

All three methods had a high negative predictive value for preterm PE prediction (> 99%). There was a statistically significant association between screening positive and developing PE before 37 weeks for NICE guidelines and FMF algorithm ($p<0.01$), but not for ACOG recommendations ($p=0.44$).

Discussion

The results of this study demonstrate that combining MAP and mean uterine artery Doppler PI with maternal factors in the second trimester for the calculation of the individual risk of developing preterm preeclampsia is superior to the use of screening methods based only on maternal factors. While history-based methods lead to low detection rates (NICE guidelines) or very high false positive rates including more than half of the population in the high-risk group (ACOG recommendations), patient-specific risk assessment allows detection of a high proportion of the patients that will develop preterm preeclampsia with an acceptable false positive rate. Likelihood ratios were higher for the FMF algorithm than for NICE guidelines and ACOG recommendations, as well as the accuracy expressed by the area under the ROC curves.

It is important to highlight that the addition of MAP and mean uterine artery Doppler PI to maternal factors at the time of 19-22 weeks' foetal assessment, at minimal extra cost and without the addition of biochemical markers to the predictive model, still detected all cases of early-onset and preterm preeclampsia.

Recording maternal history and measurement of blood pressure are widely carried out as part of routine antenatal care; measurement of MAP requires adherence to a specific technique but can easily be performed by healthcare professionals after minimal training and using inexpensive blood pressure devices[22]. Measurement of mean uterine artery Doppler PI requires specific training by sonographers and auditing, but can be done within a few minutes by sonographers during routine second trimester scan ultrasound[24].

The multimarker screening did not perform well for the detection of term preeclampsia. On the contrary, the ACOG recommendations detected most of the term preeclampsia

cases, but at the expense of a very high FPR, identifying two thirds of the population as being at increased risk.

Similar findings were recently reported in the first trimester screening for preeclampsia[16].

Furthermore, risk calculation using Bayes theorem gives clinicians and healthcare systems the opportunity to opt for the best cut-off value in their settings.

Park et al, in 2013, performed a validation of the first trimester FMF multiple logistic regression algorithm for prediction of risk of preeclampsia in an Australian population[26]. However, to our knowledge, this is the first study to evaluate the performance of different methods of screening in Australia and to externally validate the FMF algorithm for second trimester prediction of preeclampsia in our population. The incidence of preeclampsia was equal that reported for the Australian population in previously published studies[27].

The main limitation of this study was the small number of cases of early-onset and preterm PE, with consequent large 95% confidence intervals. Nevertheless, the incidence of PE in our population and the detection and false positive rates obtained were very similar to those previously reported[16, 19, 21, 26], and all cases delivering before 37 weeks were detected by the multimarker algorithm.

In conclusion, screening for preterm preeclampsia in the second trimester by individual risk calculation using maternal factors, MAP and uterine artery Doppler pulsatility index (FMF algorithm) performs better than screening by maternal factors alone using the NICE guidelines and the ACOG recommendations.

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Table 1. Characteristics of study population.

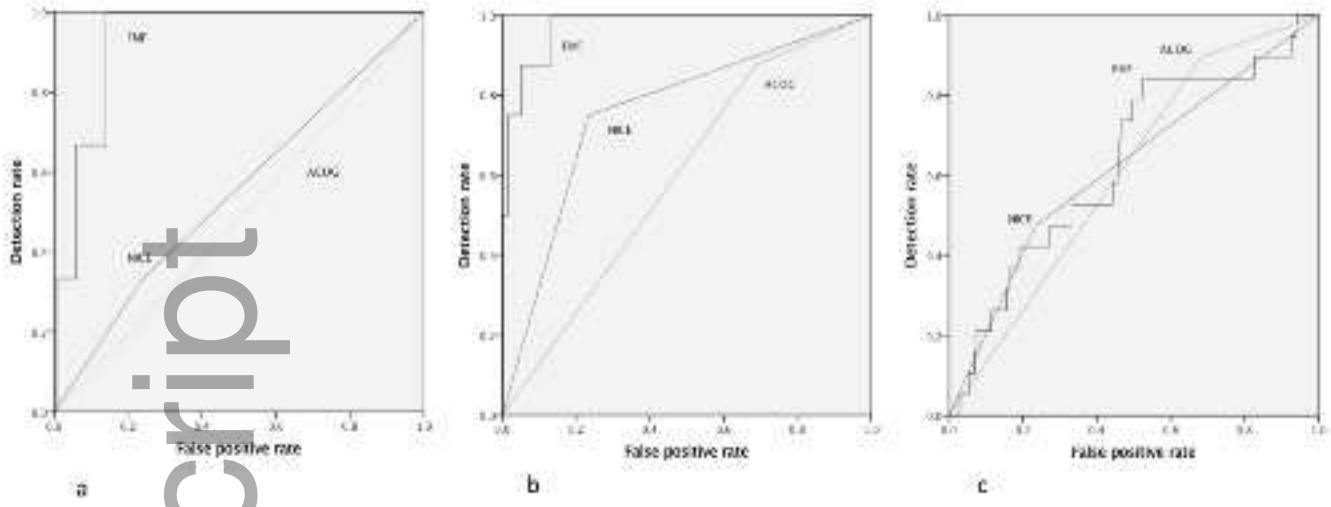
Maternal characteristics	No PE (n=516)	PE < 34 weeks (n=3)	PE < 37 weeks (n=8)	PE >37 weeks (n=19)
Maternal age in years, median (IQR)	35 (28, 42)	36 (32,40)	34 (27, 41)	32 (26, 38)
GA in weeks, median (IQR)	20.3 (19.3, 21.3)	20.7 (20.0, 21.4)	20.3 (19.3, 21.3)	20.4 (19.4, 21.4)
Weight in Kg, median (IQR)	69 (53, 85)	88.6 (72.4, 102.8) *	85.5 (57.5, 113.5) *	69.9 (38.9, 100.9)
Height in cm, median (IQR)	165 (156,174)	164 (157, 171)	163.2 (151.2, 175.2)	164 (158, 170)
BMI, median (IQR)	25.3 (19.3, 31.3)	33.7 (27.4, 40) *	32 (24, 40) *	28.4 (17.4, 39.4)
Racial origin, n (%)				
Caucasian	389 (75.4)	2 (66.7)	5 (62.5)	17 (89.5)
Afro-Caribbean	19 (3.7)	0	1 (12.5)	0
East Asian	42 (8.1)	1 (33.3)	1 (12.5)	2 (10.5)
South Asian	43 (8.3)	0	1 (12.5)	0
Mixed	23 (4.5)	0	0	0
Medical history, n (%)				
Chronic hypertension	18 (3.5)	1 (33.3)	3 (37.5) *	0
Diabetes	23 (4.4)	1 (33.3)	2 (25.0)	3 (15.8)
SLE or APS	5 (0.9)	0	0	1 (5.3)
Cigarette smoking, n (%)	33 (6.4)	0	1 (12.5)	2 (10.5)
Family history of PE, n (%)	28 (5.4)	0	0	0
Conception, n (%)				
Spontaneous	483 (93.6)	2 (66.7)	7 (87.5)	16 (84.2)
Ovulation drugs	6 (1.2)	0	0	0
IVF	27 (5.2)	1 (33.3)	1 (12.5)	3 (15.8)
Parity, n (%)				
Nulliparous	222 (43.0)	1 (33.3)	1 (12.5)	13 (68.4) *
Parous: no previous PE	260 (50.4)	2 (66.7)	4 (50.0)	4 (21.1) *
Parous: previous PE	34 (6.6)	0	3 (37.5) *	2 (10.5)

PE: preeclampsia; IQR: interquartile range; GA: gestational age; BMI: body mass index; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; IVF: in vitro fertilization. * $p<0.05$ when compared to the unaffected group.

Table 2. Screening performance according to NICE guidelines, ACOG guidelines and FMF algorithm (at cut-offs of 1:60 and 1:100) for preeclampsia delivering before 34, before 37 and after 37 weeks.

Method of screening	PE < 34 weeks			PE < 37 weeks			PE > 37 weeks			
	DR (%) (95% CI)	AUC (95% CI)	LR+ (95% CI)	DR (%) (95% CI)	AUC (95% CI)	LR+ (95% CI)	DR (%) (95% CI)	AUC (95% CI)	LR+ (95% CI)	FPR (%)
NICE guidelines	33.3 (0.8-90.5)	0.546 (0.20-0.88)	1.38 (0.28-6.91)	75.0 (34.9-96.8)	0.758 (0.58-0.93)	3.21 (2.09-4.93)	47.3 (24.4-71.1)	0.620 (0.48-0.75)	2.03 (1.24-3.35)	22.4
ACOG recommendations	66.6 (9.4-99.1)	0.489 (0.15-0.81)	0.97 (0.43-2.16)	87.5 (47.3-99.6)	0.595 (0.41-0.77)	1.28 (0.98-1.67)	89.4 (66.8-98.7)	0.607 (0.49-0.71)	1.31 (1.11-1.55)	67.8
FMF (cut-off 1:100)	100.0 (29.2-100)	0.931 (0.86-0.99)	4.82 (4.0-5.6)	100.0 (63.0-100)	0.973 (0.94-1.0)	5.00 (4.22-5.92)	42.1 (20.2-66.5)	0.632 (0.50-0.76)	2.06 (1.19-3.59)	19.1
FMF (cut-off 1:60)	100.0 (29.2-100)	0.931 (0.86-0.99)	7.11 (5.7-8.7)	100.0 (63.0-100)	0.973 (0.94-1.00)	7.54 (6.07-9.36)	26.3 (9.1-51.2)	0.632 (0.50-0.76)	1.86 (0.85-4.07	12.7

PE: Preeclampsia. DR: detection rate. FPR: False positive rate. AUC: Area under the curve. LR+: positive likelihood ratio. 95% CI: 95% confidence interval.



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