Accuracy of competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks’ gestation

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KEYWORDS: Bayes’ theorem; first-trimester screening; mean arterial pressure; placental growth factor; pre-eclampsia; pregnancy-associated plasma protein-A; pyramid of pregnancy care; survival model; uterine artery Doppler

ABSTRACT

Objective To examine the diagnostic accuracy of a previously developed model for prediction of pre-eclampsia (PE) by a combination of maternal factors and biomarkers at 11–13 weeks’ gestation.

Methods This was a prospective first-trimester multicenter study of screening for PE in 8775 singleton pregnancies. A previously published algorithm was used for the calculation of patient-specific risk of PE in each individual. The detection rates (DRs) and false-positive rates (FPRs) for delivery with PE < 32, < 37 and ≥ 37 weeks were estimated and compared with those for the dataset used for development of the algorithm.

Results In the study population, 239 (2.7%) cases developed PE, of which 17 (0.2%), 59 (0.7%) and 180 (2.1%) developed PE < 32, < 37 and ≥ 37 weeks, respectively. With combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor, the DR was 100% (95% CI, 80–100%) for PE < 32 weeks, 75% (95% CI, 62–85%) for PE < 37 weeks and 43% (95% CI, 35–50%) for PE ≥ 37 weeks, at a 10% FPR. These DRs were similar to the estimated rates for the dataset used for development of the algorithm.

Conclusion Assessment of a combination of maternal factors and biomarkers at 11–13 weeks provides effective first-trimester screening for preterm PE.

INTRODUCTION

Effective screening for preterm pre-eclampsia (PE) can be provided at 11–13 weeks’ gestation by assessment of a combination of maternal characteristics and medical history (maternal factors) with multiples of the median (MoM) values of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A). In a previous study, we used data from prospective screening in 35 948 singleton pregnancies at 11–13 weeks to develop an algorithm for the calculation of patient-specific risk of PE1. Bayes’ theorem was used to combine the a-priori risk from maternal factors2 with various combinations of MAP, UtA-PI, PAPP-A and PlGF1. In pregnancies with PE, the deviation from normal for each biomarker was inversely related to the gestational age at delivery and, consequently, the performance of screening was better for early than late PE. The performance of each biomarker in combination with maternal factors was superior to that of screening by maternal factors alone. Similarly, the performance of screening by a combination of two or more biomarkers was superior to that by
individual biomarkers. The only exception was serum PAPP-A, which did not provide significant improvement to any combination of biomarkers that included serum PI GF. With combined screening by maternal factors, MAP, UtA-PI and PI GF, the detection rate (DR) of delivery with PE < 32, < 37 and ≥ 37 weeks was 89%, 75% and 47%, respectively, at a false-positive rate (FPR) of 10%1. A limitation of the study is that the performance of screening by a model derived and tested using the same dataset may be overestimated.

The objective of this study was to determine the accuracy of the previously reported first-trimester screening model for PE1 in a prospective, non-intervention, multicenter study including 8775 singleton pregnancies. We hypothesize that the performance of screening would be similar to that estimated from the original model1.

METHODS

Study design and participants

This was a prospective, non-intervention, multicenter study in singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation in women booking for routine pregnancy care at: King’s College Hospital, London, UK; Medway Maritime Hospital, Gillingham, UK; Homerton University Hospital, London, UK; North Middlesex University Hospital, London, UK; Southend University Hospital, Essex, UK; Lewisham University Hospital, London, UK; Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, Spain; Hospital Universitario San Cecilio, Granada, Spain; Hospiten Sur, Tenerife, Spain; Centre Hospitalier Universitaire Brugmann, Brussels, Belgium; Attikon University Hospital, Athens, Greece; and Ospedale Maggiore Poli clinico, Milan, Italy. The women were screened between February and September 2015 and gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee in the UK and the Ethics Committee of each participating hospital in other countries. The Standards for Reporting Diagnostic Accuracy Studies (STARD)3 was adhered to.

Eligibility criteria for study inclusion were maternal age ≥ 18 years, no serious mental illness or learning difficulty, singleton pregnancy with live fetus demonstrated on 11–13-week ultrasound scan and subsequent delivery of a phenotypically normal live birth or stillbirth ≥ 24 weeks' gestation. Multiple pregnancies, those with aneuploidy or major fetal abnormality and those ending in termination or miscarriage were excluded.

Test methods

The index test, or the test for which the accuracy was being evaluated, was the previously reported algorithm for first-trimester assessment of risk for PE by maternal factors and various combinations of MAP, UtA-PI, PAPP-A and PI GF1. Maternal factors were recorded2 and MAP was measured by a validated automated device following a standardized protocol4. Transabdominal color Doppler ultrasound was performed to measure the left and right UtA-PI and the average value was recorded5. Serum PAPP-A and PI GF concentrations were measured using an automated device (PAPP-A and PI GF 1-2-3TM kits, DELFIA® Xpress random access platform; PerkinElmer Inc., Wallac Oy, Turku, Finland). All operators performing Doppler assessment had received the appropriate Certificate of Competence from The Fetal Medicine Foundation. Measured values of MAP, UtA-PI, PAPP-A and PI GF were expressed as MoM, adjusting for those characteristics found to provide a substantive contribution to the log10-transformed value, including maternal factors, in the prior model6–9.

The index test was carried out prospectively in consecutive singleton pregnancies at 11 + 0 to 13 + 6 weeks' gestation; gestational age was determined from the measurement of fetal crown–rump length10. The results from screening were not made available to the patients or their physicians.

The target condition was PE, as defined by the International Society for the Study of Hypertension in Pregnancy11. PE was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least two occasions 4 hours apart, developing after 20 weeks of gestation in previously normotensive women. Hypertension was defined as proteinuria of ≥ 300 mg in 24 h or two readings of at least ++ on dipstick analysis of midstream or catheter urine specimens if no 24-h collection was available. PE superimposed on chronic hypertension was defined as significant proteinuria (as defined above) developing after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or presence of hypertension at booking visit before 20 weeks' gestation, in the absence of trophoblastic disease).

Data on pregnancy outcome were collected from the hospital maternity records of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was PE.

Statistical analysis

The previously described algorithm1 was used for calculation of patient-specific risk of delivery with PE < 32, < 37 and ≥ 37 weeks' gestation. The prespecified analyses for performance of screening by maternal factors and any combinations of maternal factors with MAP, UtA-PI, PAPP-A and PI GF were estimation of areas under the receiver–operating characteristics curve (AUC) and DR, with 95% CI, at FPRs of 5% and 10%. The statistical software package R was used for data analyses12.

RESULTS

Participants

During the study period, 9041 pregnancies met the inclusion criteria and underwent screening for PE. A
Table 1 Characteristics of women with normal singleton pregnancy and of those who developed pre-eclampsia (PE) with delivery < 32 weeks, < 37 weeks or ≥ 37 weeks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal (n = 8536)</th>
<th>&lt; 32 weeks (n = 17)</th>
<th>&lt; 37 weeks (n = 59)</th>
<th>≥ 37 weeks (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>31.5 (27.3–35.0)</td>
<td>29.8 (26.7–34.6)</td>
<td>30.6 (26.0–34.7)</td>
<td>31.2 (27.8–34.8)</td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>66.2 (58.8–76.9)</td>
<td>72.6 (65.6–86.0)</td>
<td>69.8 (63.0–87.8)</td>
<td>75.0 (64.9–84.0)</td>
</tr>
<tr>
<td>Maternal height (cm)</td>
<td>165 (160–169)</td>
<td>164 (161–166)</td>
<td>164 (160–169)</td>
<td>164 (159–168)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.5 (21.9–28.2)</td>
<td>27.3 (23.9–31.8)</td>
<td>27.1 (23.6–31.8)</td>
<td>27.8 (23.9–31.5)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>12.7 (12.3–13.1)</td>
<td>12.6 (12.3–12.7)</td>
<td>12.7 (12.4–13.0)</td>
<td>12.7 (12.3–13.2)</td>
</tr>
</tbody>
</table>

Racial origin

- Caucasian: 6716 (78.7%)
- Afro-Caribbean: 1040 (12.2%)
- East Asian: 153 (1.8%)
- South Asian: 447 (5.2%)
- Mixed: 180 (2.1%)

Medical history

- Chronic hypertension: 75 (0.9%)
- Diabetes mellitus: 63 (0.7%)
- APS/SLE: 32 (0.4%)
- Cigarette smoker: 717 (8.4%)
- Family history of PE: 434 (5.1%)

Mode of conception

- Spontaneous: 8254 (96.7%)
- In-vitro fertilization: 218 (2.6%)
- Ovulation drugs: 64 (0.7%)

Parity

- Nulliparous: 3972 (46.5%)
- No previous PE: 4396 (51.5%)
- Previous PE: 168 (2.0%)

Interpregnancy interval (years)

- 2.7 (1.6–4.6)
- 5.4 (4.3–7.2)
- 4.1 (2.4–6.8)
- 3.4 (2.0–5.4)

Data are given as median (interquartile range) or n (%). Comparisons between outcome groups were by chi-square or Fisher’s exact tests for categorical variables and Mann–Whitney U-test for continuous variables. APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

Table 2 Performance of screening for delivery with pre-eclampsia (PE) < 32, < 37 or ≥ 37 weeks’ gestation in validation dataset of 8775 singleton pregnancies using previously developed algorithm based on maternal factors and combinations of biomarkers

<table>
<thead>
<tr>
<th>Screening method</th>
<th>PE with delivery &lt; 32 weeks (n = 17)</th>
<th>PE with delivery &lt; 37 weeks (n = 59)</th>
<th>PE with delivery ≥ 37 weeks (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DR (%) at:</td>
<td>DR (%) at:</td>
<td>DR (%) at:</td>
</tr>
<tr>
<td></td>
<td>AUC FPR = 5% FPR = 10%</td>
<td>AUC FPR = 5% FPR = 10%</td>
<td>AUC FPR = 5% FPR = 10%</td>
</tr>
<tr>
<td>Maternal factors</td>
<td>0.8045 41 (18–67) 53 (28–77)</td>
<td>0.7583 29 (18–42) 41 (28–54)</td>
<td>0.7449 18 (13–25) 37 (30–45)</td>
</tr>
<tr>
<td>Maternal factors plus:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>0.9071 59 (33–82) 71 (44–90)</td>
<td>0.8243 36 (24–49) 47 (34–61)</td>
<td>0.7789 26 (20–33) 37 (30–45)</td>
</tr>
<tr>
<td>UtA-PI</td>
<td>0.9309 71 (44–90) 82 (57–96)</td>
<td>0.8537 47 (34–61) 61 (47–73)</td>
<td>0.7539 22 (16–29) 39 (32–47)</td>
</tr>
<tr>
<td>PAPP-A</td>
<td>0.8546 47 (23–72) 59 (33–82)</td>
<td>0.7825 37 (25–51) 47 (34–61)</td>
<td>0.7504 21 (15–28) 34 (30–41)</td>
</tr>
<tr>
<td>PI GF</td>
<td>0.9506 65 (38–86) 88 (64–99)</td>
<td>0.8722 49 (36–63) 63 (49–75)</td>
<td>0.7578 20 (14–27) 39 (32–46)</td>
</tr>
<tr>
<td>MAP, UtA-PI</td>
<td>0.9677 82 (57–96) 94 (71–100)</td>
<td>0.8958 53 (39–66) 71 (58–82)</td>
<td>0.7875 27 (20–34) 41 (34–49)</td>
</tr>
<tr>
<td>MAP, PAPP-A</td>
<td>0.9133 65 (38–86) 76 (50–93)</td>
<td>0.8342 41 (28–54) 49 (36–63)</td>
<td>0.7827 28 (21–35) 40 (33–48)</td>
</tr>
<tr>
<td>MAP, PI GF</td>
<td>0.9674 76 (50–93) 86 (64–99)</td>
<td>0.8985 53 (39–66) 69 (56–81)</td>
<td>0.7870 29 (22–36) 43 (36–51)</td>
</tr>
<tr>
<td>MAP, UtA-PI, PAPP-A</td>
<td>0.9397 71 (44–90) 82 (57–96)</td>
<td>0.8538 49 (36–63) 66 (53–78)</td>
<td>0.7571 24 (18–31) 40 (33–48)</td>
</tr>
<tr>
<td>MAP, UtA-PI, PI GF</td>
<td>0.9772 82 (57–96) 100 (80–100)</td>
<td>0.9000 61 (47–73) 75 (62–85)</td>
<td>0.7619 22 (16–29) 39 (32–47)</td>
</tr>
<tr>
<td>MAP, PAPP-A, PI GF</td>
<td>0.9510 65 (38–86) 88 (64–99)</td>
<td>0.8741 51 (37–64) 66 (53–78)</td>
<td>0.7589 20 (14–27) 39 (32–47)</td>
</tr>
<tr>
<td>MAP, UtA-PI, PAPP-A, PI GF</td>
<td>0.9644 88 (64–99) 94 (71–100)</td>
<td>0.8856 61 (47–73) 69 (56–81)</td>
<td>0.7892 22 (16–29) 42 (35–50)</td>
</tr>
<tr>
<td>MAP, PAPP-A, PI GF</td>
<td>0.9672 76 (50–93) 88 (64–99)</td>
<td>0.8998 54 (41–67) 69 (56–81)</td>
<td>0.7882 29 (22–36) 43 (36–51)</td>
</tr>
<tr>
<td>MAP, UtA-PI, PI GF</td>
<td>0.9870 94 (71–100) 100 (80–100)</td>
<td>0.9242 66 (53–78) 75 (62–85)</td>
<td>0.7916 32 (25–39) 43 (35–50)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI. AUC, area under receiver–operating characteristics curve; DR, detection rate; FPR, false-positive rate; MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PI GF, placental growth factor; UtA-PI, uterine artery pulsatility index.

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In the study population of 8775 pregnancies, 239 (2.7%) cases developed PE, of which 17 (0.2%), 59 (0.7%) and 180 (2.1%) developed PE $<$32, $<$37 and $\geq$37 weeks, respectively. Baseline demographic and clinical characteristics of the participants are shown in Table 1. In total, 12 maternity hospitals in five different countries were involved in patient recruitment, 127 doctors participated in the measurement of UtA-PI and 152 doctors or nurses were involved in the measurement of MAP.

Test results

The AUC and DR, at FPRs of 5% and 10%, of delivery with PE $<$32, $<$37 and $\geq$37 weeks' gestation with screening by maternal factors and biomarkers using the previously reported algorithm$^1$ are given in Table 2 and compared to previously reported values in Figure 1. The DRs in this validation dataset were similar to the estimated rates for the dataset used for development of the model.

The performance of screening for PE $<$37 weeks was superior to that of PE $\geq$37 weeks. The best performance of screening was achieved by a combination of maternal factors, MAP, UtA-PI and PlGF and this was not improved significantly by addition of PAPP-A.

DISCUSSION

Main findings

This prospective multicenter validation study demonstrates the feasibility of incorporating first-trimester screening for PE into routine clinical practice. The findings demonstrate that the performance of screening for PE at 11–13 weeks by a combination of maternal factors and biomarkers is similar to that estimated from the original model$^1$. The DR of screening by maternal factors, MAP, UtA-PI and PlGF, at 10% FPR, was 100% (95% CI, 80–100%) for PE $<$32 weeks, 75% (95% CI, 62–85%) for PE $<$37 weeks and 43% (95% CI, 35–50%) for PE $\geq$37 weeks; the estimated rates for the dataset used for development of the model were 89% (95% CI, 79–96%), 75% (95% CI, 70–80%) and 47% (95% CI, 44–51%), respectively$^1$.

Study limitations

The main limitation of the study relates to the low incidence of delivery with PE, with the inevitable wide CIs obtained for performance of screening. Nevertheless, the values obtained in the validation study are similar to those in the dataset of 35,948 pregnancies used for development of the algorithm.
Implications for practice

Screening and diagnosis of PE is traditionally based on the demonstration of elevated blood pressure and proteinuria during a routine clinical visit in the late second or third trimester of pregnancy. In a proposed new pyramid of pregnancy care, assessment of risk at 11–13 weeks’ gestation aims to identify pregnancies at high risk of developing PE and, through pharmacological intervention with such medications as low-dose aspirin, to reduce the prevalence of these complications.

The findings of this validation study confirm that screening at 11–13 weeks identifies a high proportion of cases that will develop PE < 37 weeks, but the performance of screening at this stage for those that will develop PE ≥ 37 weeks is poor. This is particularly important because the prophylactic use of low-dose aspirin is effective in the prevention of preterm PE rather than term PE. We reported previously that effective prediction of PE ≥ 37 weeks requires screening at 35–36 weeks.

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