Demographic factors that can be used to predict early-onset pre-eclampsia

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Abstract

Objective: To define the maternal demographic factors that predicts the risk of developing early-onset pre-eclampsia (requiring delivery before 34 weeks’ gestation) in an Australian population. These are compared to risk factors described in a British population to determine whether the Fetal Medicine Foundation (FMF) risk algorithm for predicting early-onset pre-eclampsia needs to be modified for an Australian population.

Methods: A secondary analysis of prospective cohorts in Australia and in the United Kingdom was conducted. Demographic details and past medical history were obtained. Odds ratios (ORs) for the development of early-onset pre-eclampsia were calculated for maternal factors in both populations. Forest plots were used to compare the two sets of odds ratios.

Results: In the Australian population, pre-existing hypertension (OR 19.89, 95% CI 4.17–94.93) and body mass index >40 kg/m² (OR 9.04, 95% CI 1.13–72.40) predicted risk of developing early-onset pre-eclampsia. There were no significant differences in the odds ratios for maternal factors in the two populations.

Conclusions: This study shows that the ORs used to describe risks associated with maternal characteristics in the FMF algorithm for early-onset pre-eclampsia are consistent with those found in our local population. There does not appear to be any value in changing the weighting of demographic factors included in the FMF algorithm for an Australian population.

Introduction

Hypertensive disorders of pregnancy are common, affecting 7.5% of pregnancies in New South Wales, Australia [1]. The World Health Organisation recognises hypertensive disease as a leading cause of maternal mortality in industrialised countries, accounting for 16% of maternal deaths [2]. It is also recognised as a significant risk factor for maternal cardiovascular morbidity later in life. Women with pre-eclampsia have a three- to four-fold increased risk of developing chronic hypertension and double the risk of ischaemic heart disease, stroke and venous thromboembolism [3]. Pre-eclampsia is also associated with significant risk of fetal mortality and morbidity [4]. Women who develop pre-eclampsia have a 35% higher risk of stillbirth and double the rate of neonatal mortality [5]. There is also an 80-fold increase in risk of iatrogenic preterm delivery before 33 weeks and a 40-fold increase in risk of delivery between 33 and 36 weeks [6]. Infants of pre-eclamptic women have a three- to four-fold increased risk of being small for gestational age (birth weight <10th percentile) [7].

Although the pathophysiology of pre-eclampsia is not completely described, the process involves abnormal development of the maternal component of the placental circulation. The trophoblast fails to invade the muscular wall of spiral arteries and the placental circulation maintains a high-resistance state [8]. The involvement of the placenta in this pathological process is important for two reasons. First, early delivery of the placenta, and therefore the fetus, is often required to end the disease [9]. Second, as trophoblast invasion is essentially complete by 16 weeks’ gestation, any therapeutic intervention designed to prevent the development of pre-eclampsia needs to be made before this time.

A number of studies have investigated the use of risk factors derived from maternal history, biochemistry and/or biophysical assessment as predictive tools for pre-eclampsia. Although a number of biomarkers have been found to have a clear association with pre-eclampsia, no single marker has proven to be efficient enough to act as a reliable clinical tool [10]. Some markers are indicative of secondary changes occurring in reaction to the disease process and are therefore more relevant to management of ongoing disease rather than...
to disease prevention [11]. The main biophysical parameters that have been assessed in relation to prediction of disease are maternal blood pressure and uterine artery Doppler pulsatility index [12,13]. Although, predictive algorithms that use a combination of demographic, biochemical and biophysical features seem to be effective [14–16] many obstetricians do not have ready access to such a comprehensive tool and define risk on the basis of maternal history alone. In a recent study designed to evaluate the effectiveness of a first trimester algorithm, the risk of early onset pre-eclampsia, the impact of screening by demographic features alone was disappointing, detecting 39.5% of cases for a 10% false positive rate [15] compared to 50.5% in the original paper [14]. In this study, we have compared the impact of individual risk factors in an attempt to determine whether risks previously attributed to demographic factors apply to our local Australian population, or whether alternative risk algorithms should be generated.

Methods

This study is based on secondary analysis of a prospective cohort used to determine the accuracy of an algorithm predicting risk of early-onset pre-eclampsia in an Australian population [15]. In brief, the study included all women with a singleton pregnancy attending a metropolitan teaching hospital for combined first trimester screening at 11–13 + 6 weeks’ gestation who then booking for delivery in the same institution. The study population were collected over a two year period. Ethics approval was granted by the local hospital ethics committee (HREC/11/RPAH/472).

Demographic details were collected by asking women to complete a questionnaire whilst waiting for their ultrasound scan. Data collected included details of ethnicity (Caucasian, East Asian, South Asian, Afro-Caribbean or mixed), maternal age and smoking. Details of obstetric, past medical and family history were also obtained. These data were checked and entered into the computer database by the sonographer. Maternal height and weight were measured and body mass index was calculated.

Women were grouped according to whether they had no hypertensive disease of pregnancy, gestational hypertension, early-onset pre-eclampsia (requiring delivery <34 weeks gestation) or late-onset pre-eclampsia (requiring delivery ≥34 weeks). Women with chronic hypertension were not categorised as hypertensive disease of pregnancy unless they developed superimposed pre-eclampsia. Gestational hypertension and pre-eclampsia were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy [17]. Data on pregnancy outcome, including mode of delivery, gestation, and birth weight, were collated from hospital records.

Odds ratios (ORs) for the development of early (delivery <34 weeks) pre-eclampsia were calculated for maternal demographic factors. Covariates were entered as ethnicity (Afro-Caribbean, South Asian, East Asian or mixed), maternal age (<25, 26–30, 31–35, 36–40, >40), maternal BMI (<25, 26–30, 31–35, 36–40, >40), maternal BMI (<25, 26–30, 31–35, 36–40, >40), smoking (yes/no), method of conception spontaneous/clomiphene/IVF), nulliparity (yes/no), pre-existing hypertension (yes/no), mother with pre-eclampsia (yes/no) and parous women with a history of pre-eclampsia (yes/no). These findings were compared to ORs established in a UK-based population [14]. Forest plots were used to illustrate differences between ORs in these two populations. The potential between study heterogeneity was assessed by visually inspecting the forest plots and estimated by I-squared [18]. All analyses were performed using Stata version 11 (Stata Corporation, College Station, TX).

Results

Three thousand and ninety-nine women were screened at 11–13 + 6 weeks’ gestation. Data were incomplete in 33 (1.1%) cases which were excluded from subsequent analysis. A total of 3014 (98.3%) women subsequently had a live birth, 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, 83 (2.8%) women developed pre-eclampsia; 12 (0.4%) being delivered <34 weeks gestation, 119 (3.9%) women developed gestational hypertension and 2812 (93.3%) women had no evidence of hypertension during pregnancy.

ORs for each maternal factor associated with early-onset pre-eclampsia are described in Table 1. Pre-existing hypertension and increased BMI (>40 kg/m²) both showed a significant increase in risk for early-onset pre-eclampsia with ORs of 19.89 (95% CI: 4.17–94.93) and 9.04 (95% CI: 1.13–72.40) respectively. ORs are compared to those established in the UK study in Figure 1. These forest plots demonstrate that there were no significant differences in the ORs used to describe risks for early-onset pre-eclampsia in the two populations. I-squared values for East Asian ethnicity and BMI ≥25 kg/m² suggest there may be heterogeneity in these data; whilst the

<table>
<thead>
<tr>
<th>Demographic feature</th>
<th>Australian cohort 2013</th>
<th>UK cohort 2012</th>
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<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
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</tr>
<tr>
<td>Afro–Caribbean</td>
<td>–</td>
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<tr>
<td>East Asian</td>
<td>1.86 (0.56–6.19)</td>
<td>0.36 (0.09–1.46)</td>
</tr>
<tr>
<td>South Asian</td>
<td>1.73 (0.38–7.95)</td>
<td>1.82 (1.12–2.96)</td>
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<tr>
<td>Mixed</td>
<td>–</td>
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<tr>
<td>Maternal age (year)</td>
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<tr>
<td>&lt;25</td>
<td>2.06 (0.26–16.07)</td>
<td>1.40 (1.00–1.96)</td>
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<td>26–30</td>
<td>0.80 (0.17–3.66)</td>
<td>1.05 (0.76–1.44)</td>
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<td>31–35</td>
<td>0.73 (0.22–2.44)</td>
<td>0.54 (0.39–0.75)</td>
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<td>36–40</td>
<td>1.12 (0.34–3.72)</td>
<td>1.13 (0.83–1.54)</td>
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<tr>
<td>&gt;40</td>
<td>2.02 (0.26–15.49)</td>
<td>1.83 (1.17–2.88)</td>
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<td>Maternal body mass index (kg/m²)</td>
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<tr>
<td>≤25</td>
<td>1.47 (0.40–5.44)</td>
<td>0.44 (0.34–0.59)</td>
</tr>
<tr>
<td>26–30</td>
<td>0.69 (0.15–3.14)</td>
<td>1.10 (0.81–1.48)</td>
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<tr>
<td>31–35</td>
<td>–</td>
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<tr>
<td>36–40</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>9.04 (1.13–72.40)</td>
<td>4.24 (2.45–7.31)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Method of conception</td>
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<tr>
<td>Clomiphene</td>
<td>4.64 (0.59–36.60)</td>
<td>1.99 (0.88–4.50)</td>
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<td>In vitro fertilisation</td>
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<tr>
<td>Nulliparity</td>
<td>2.82 (0.76–10.45)</td>
<td>1.60 (1.22–2.11)</td>
</tr>
<tr>
<td>Pre-existing hypertension</td>
<td>19.89 (4.17–94.93)</td>
<td>17.03 (11.47–25.27)</td>
</tr>
<tr>
<td>Mother with pre-eclampsia</td>
<td>1.20 (0.15–9.34)</td>
<td>2.01 (1.24–3.27)</td>
</tr>
<tr>
<td>Parous with a history of pre-eclampsia</td>
<td>6.46 (0.81–51.30)</td>
<td>7.93 (5.61–11.23)</td>
</tr>
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</table>
ORs for the two populations overlap, East Asian ethnicity is associated with an increased but non-significant risk of early onset pre-eclampsia in the Australian dataset; OR 1.86 (95% CI: 0.56–6.19) but a decreased risk; OR 0.36 (95% CI: 0.09–1.46) in the UK dataset. BMI >25 kg/m² was similarly associated with an increased, but non-significant OR 1.47 (95% CI: 0.40–5.44) in the Australian dataset but a decreased OR 0.44 (95% CI: 0.34–0.59) in the UK dataset.

Discussion
This study has shown that the ORs used to describe risks associated with various maternal demographic characteristics in the Fetal Medicine Foundation (FMF) algorithm for early-onset pre-eclampsia are consistent with those found in our local population. The only two factors found to be statistically significant in our dataset were maternal BMI >25 kg/m² and a medical history of pre-existing hypertension. There was some disparity between ORs calculated for East Asian ethnicity and for women with a BMI >25 kg/m², but these may have been due to the heterogeneity of the studies and the relatively small numbers of affected cases in these subgroups. There does not appear to be any value in changing the weighting of demographic factors included in the FMF algorithm for our local population.
Most studies describing an association between maternal demographic factors and pre-eclampsia have not discriminated between affected cases on the basis of gestational age. A systematic review of 52 studies published prior to 2003 found that nulliparity, high BMI, previous pre-eclampsia, pre-existing hypertension, family history, maternal age ≥40 years, pre-existing diabetes, antiphospholipid antibodies and multiple pregnancy are risk factors for pre-eclampsia [19]. A further 30 studies, reported more recently, also fail to discriminate between early- and late-onset disease but confirm the conclusions of the earlier meta-analysis. Risk factors described for pre-eclampsia include nulliparity [20–24], high BMI [20–22,25–33], previous pre-eclampsia [21], pre-existing hypertension [20–22,34], family history of pre-eclampsia [29,35–38], increasing maternal age [22,23,29,39–40], multiple pregnancy [21–23], pre-existing diabetes mellitus [20,23,24], gestational diabetes [22] and renal disease [24].

We could only identify three studies that have attempted to define risk factors for early-onset pre-eclampsia (requiring delivery <34 weeks). In a prospective cohort of 8366 women, Poon et al. reported risk factors specific to early-onset pre-eclampsia in a UK population; these included a history of chronic hypertension, Afro-Caribbean ethnicity, and use of ovulation drugs. Increased maternal age, high BMI and family history of pre-eclampsia were significant risks for developing late-onset pre-eclampsia. Previous pre-eclampsia was a risk factor for both subtypes of pre-eclampsia [41]. A population-based study of 456,668 US-based women found chronic hypertension, African-American race and high BMI to be associated with late-onset pre-eclampsia and young maternal age (<20 years), nulliparity and diabetes to be more strongly associated with late-onset disease [42]. A Thai-based case-control study of 152 early-onset pre-eclamptics and 449 controls reported that chronic hypertension, previous pre-eclampsia, multiparity, diabetes (pre-existing or gestational) and a history of haemolysis or HELLP were all associated with early-onset pre-eclampsia and young maternal age (<20 years), nulliparity and diabetes to be more strongly associated with late-onset disease [43]. These studies, along with ours, are consistent in suggesting that chronic hypertension is an important risk factor for early-onset pre-eclampsia. There are, however, discrepancies in other factors that may be due to the differing characteristics of the cohorts. This underscores the need for clarification of risk factors in different populations.

Both East Asian ethnicity and BMI ≤25 kg/m² appear to be non-significant risk factors in our own population whilst these are protective factors in the British dataset. Whilst the odds ratios for these two factors are not statistically significant, they still represent a diverging trend from other populations. The risk of developing early-onset pre-eclampsia in our study with a BMI ≤25 kg/m² (OR 1.47; 95% CI 0.40–5.44) is contrary to a number of previous studies [20,22,26,44,45] and a meta-analysis [32] which showed that a low BMI is protective against pre-eclampsia. Interestingly, another meta-analysis of 36 studies involving 1,699,073 women reported that BMI <25 kg/m² was a weak, non-significant predictor of reduction of risk of pre-eclampsia with a the likelihood ratio of 0.73 (95% CI; 0.22–2.45) [46]. Our finding that East Asian ethnicity confers an increase in risk of early-onset pre-eclampsia in an Australian population (OR 1.86; 95% CI 0.56–6.19) also differs to reports in New Zealand and North American populations, where this appears to be protective [20,47]. Bramham et al. reported that Asian ethnicity was a risk factor for recurrent pre-eclampsia (OR 2.98; 95% CI, 1.33–6.59), but it is not clear whether these were East or South Asian women [48].

The limitations of this study include sample size and consequently a small number of early pre-eclamptic outcomes. The confidence intervals for odds ratios are therefore large. Maternal factors which were not included in this study (due to the small numbers of affected cases) were Type I/Type II diabetes, renal disease and autoimmune disease.

This study defines maternal demographic and medical risk factors for early-onset pre-eclampsia in an Australian population. As these risks are broadly similar to those described in the UK-based FMF population it appears reasonable to apply that risk algorithm for prediction of pre-eclampsia in Australian women.

Declaration of interest

The authors report no conflicts of interest.

References


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