

Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort

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ABSTRACT

Objectives To develop a predictive model for pre-eclampsia based on clinical risk factors for nulliparous women and to identify a subgroup at increased risk, in whom specialist referral might be indicated.

Design Prospective multicentre cohort.

Setting Five centres in Auckland, New Zealand; Adelaide, Australia; Manchester and London, United Kingdom; and Cork, Republic of Ireland.

Participants 3572 "healthy" nulliparous women with a singleton pregnancy from a large international study; data on pregnancy outcome were available for 3529 (99%).

Main outcome measure Pre-eclampsia defined as ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or both, on at least two occasions four hours apart after 20 weeks' gestation but before the onset of labour, or postpartum, with either proteinuria or any multisystem complication. Preterm pre-eclampsia was defined as women with pre-eclampsia delivered before 37⁺⁰ weeks' gestation. In the stepwise logistic regression the comparison group was women without pre-eclampsia.

Results Of the 3529 women, 186 (5.3%) developed pre-eclampsia, including 47 (1.3%) with preterm pre-eclampsia. Clinical risk factors at 14-16 weeks' gestation were age, mean arterial blood pressure, body mass index (BMI), family history of pre-eclampsia, family history of coronary heart disease, maternal birth weight, and vaginal bleeding for at least five days. Factors associated with reduced risk were a previous single miscarriage with the same partner, taking at least 12 months to conceive, high intake of fruit, cigarette smoking, and alcohol use in the first trimester. The area under the receiver operating characteristics curve (AUC), under internal validation, was 0.71. Addition of uterine artery Doppler indices did not improve performance (internal validation AUC 0.71). A framework for specialist referral was developed based on a probability of pre-eclampsia generated by the model of at least 15% or an abnormal uterine artery Doppler waveform in a subset of women with single risk factors.

Nine per cent of nulliparous women would be referred for a specialist opinion, of whom 21% would develop pre-eclampsia. The relative risk for developing pre-eclampsia and preterm pre-eclampsia in women referred to a specialist compared with standard care was 5.5 and 12.2, respectively.

Conclusions The ability to predict pre-eclampsia in healthy nulliparous women using clinical phenotype is modest and requires external validation in other populations. If validated, it could provide a personalised clinical risk profile for nulliparous women to which biomarkers could be added.

Trial registration ACTRN12607000551493.

INTRODUCTION

Pre-eclampsia is a multisystem complication that occurs after 20 weeks of pregnancy and can cause considerable maternal and fetal morbidity and mortality.¹ This complex condition is characterised by suboptimal uteroplacental perfusion associated with a maternal inflammatory response and maternal vascular endothelial dysfunction.² One of the main reasons for serial clinical assessment in antenatal care is the early detection of signs (raised blood pressure and proteinuria) indicative of evolving pre-eclampsia.³ Recent guidelines from the National Institute for Health and Clinical Excellence (NICE) also recommend routine screening for specific risk factors for pre-eclampsia (nulliparity, older age, high body mass index (BMI), family history of pre-eclampsia, underlying renal disease or chronic hypertension, multiple pregnancy, more than 10 years between pregnancies, and a personal history of pre-eclampsia).³ The expected rate of pre-eclampsia when any one of these risk factors is present ranges from 3% to more than 30%, and many women have several risk factors.⁴⁻⁷ The absolute risk for an individual will be determined by the presence or absence of these and other predisposing or protective factors not incorporated in the NICE

guidelines.⁸⁻¹³ Currently, because of a paucity of large prospective studies, we cannot accurately estimate the risk of pre-eclampsia from combinations of clinical risk factors.^{4,14}

In prospective studies of general obstetric populations, the reported performance of a limited number of clinical risk factors to predict pre-eclampsia is modest, with an AUC (area under the curve) in the order of 0.66 to 0.79.^{15,16} These cohorts included high risk women and the best predictors of pre-eclampsia (underlying medical conditions that predispose to pre-eclampsia or a history of pre-eclampsia^{4,6,16}) are not applicable to healthy nulliparous women. Before preventive treatment and stratified antenatal care can be offered to nulliparous women, we need to identify those at high risk of pre-eclampsia.^{17,18} At present there is no method to accurately stratify healthy nulliparous women according to their risk profile for pre-eclampsia.

This study is part of the SCOPE (Screening for Pregnancy Endpoints) study, a prospective, multicentre cohort study of “healthy” nulliparous women with the primary aim of developing screening tests to predict pre-eclampsia, infants who are small for gestational age, and spontaneous preterm birth. The study design incorporates prospective collection of information on all known clinical risk factors for pre-eclampsia. The objectives are to develop multivariable predictive models for pre-eclampsia (based on clinical risk factors present in early pregnancy alone or in combination with ultrasound estimates of uteroplacental perfusion and fetal measurements at 19-21 weeks’ gestation) and determine their performance to predict pre-eclampsia as a baseline for future external validation; identify the rate of pre-eclampsia associated with specific combinations of clinical risk factors and ultrasound scan variables; and develop a proposal for risk stratification of “healthy” nulliparous women, based on combinations of key clinical risk factors and scan indices, to identify a subgroup at increased risk of pre-eclampsia for whom specialist referral might be indicated.

METHODS

Five centres (Auckland, New Zealand; Adelaide, Australia; London and Manchester, UK; and Cork, Ireland) recruited nulliparous women with singleton pregnancies to the SCOPE study between November 2004 and August 2008.¹⁹

Women (n=4961) attending hospital antenatal clinics, obstetricians, general practitioners, or community midwives before 15 weeks’ gestation were invited to participate. Exclusion criteria included recognised as high risk of pre-eclampsia, small for gestational age baby or spontaneous preterm birth because of underlying medical conditions (chronic hypertension requiring antihypertensive drugs, diabetes, renal disease, systemic lupus erythematosus, antiphospholipid syndrome, sickle cell disease, HIV), previous cervical knife cone biopsy, three or more abortions or three or more miscarriages, current ruptured membranes; known major fetal anomaly or abnormal karyotype;

or intervention that could modify the outcome of pregnancy (such as aspirin, cervical suture).¹⁹ A research midwife interviewed and examined women at 14-16 and 19-21 weeks’ gestation. Women underwent an ultrasound scan at 19-21 weeks. At the time of interview, data were entered on an internet accessed central database with a complete audit trail (MedSciNet).

At 14-16 weeks’ gestation the following data were collected: demographic information including age, ethnicity, immigration details, education, work, socioeconomic index, income level, living situation; the woman’s birth weight and gestation at delivery and whether it was a singleton or multiple pregnancy; previous miscarriages, abortions, or ectopic pregnancies and whether these pregnancies were with the same partner as the current pregnancy or not; history of infertility, use of assisted reproductive technologies, duration of sexual relationship, and exposure to partner’s sperm; gynaecological (including polycystic ovarian syndrome) and medical history, including hypertension while taking combined oral contraception, asthma, urinary tract infection, inflammatory bowel disease, thyroid disease, and thromboembolism; and family history (in mother and sisters) of obstetric complications (miscarriage, pre-eclampsia, eclampsia, gestational hypertension, spontaneous preterm birth, any preterm birth, gestational diabetes, stillbirth, and neonatal death) and family history (mother, father, sibling) of medical conditions (hypertension, coronary artery heart disease, cerebrovascular accident, type 1 and 2 diabetes, and venous thromboembolism).

Information was collected on vaginal bleeding early in pregnancy (gestation, severity and duration of bleeding, and recurrent bleeds), hyperemesis, and infections during pregnancy. Vegetarian status was recorded, and other dietary information before conception and during pregnancy was obtained from food frequency questions for fruit, green leafy vegetables, oily and other fish, and fast foods. Use of folate and multivitamins, cigarettes, alcohol (including binge drinking), and recreational drugs (including marijuana, amphetamine, cocaine, heroin, ecstasy, LSD (lysergide)) was recorded for before conception, first trimester, and at 15 weeks. A lifestyle questionnaire was completed on work, exercise and sedentary activities, snoring, domestic violence, and social supports. Psychological scales were completed to measure perceived stress,²⁰ depression,²¹ anxiety,²² and behavioural responses to pregnancy (adapted from the behavioural responses to illness questionnaire²³). Two consecutive manual blood pressure measurements (mercury or aneroid sphygmomanometer, with a large cuff if the arm circumference ≥ 33 cm and Korotkoff V for diastolic blood pressure) were recorded. Other maternal measurements included maternal height and weight and waist, hip, arm, and head circumference. Proteinuria in a midstream urine specimen was measured by dipstick or a protein:creatinine ratio. Random whole blood glucose and serum lipid concentrations (triglycerides, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, total

cholesterol:high density lipoprotein cholesterol ratio) were also measured.

Ultrasound examination at 19-21 weeks' gestation included measurements of the fetus (biparietal diameter, head circumference, abdominal circumference, and femur length) and Doppler studies of the umbilical and uterine arteries.²⁴ All fetal measurements were adjusted for gestational age by calculating the multiple of the median for each gestational week. Mean uterine resistance index (RI) was calculated from the left and right uterine resistance index. If only a left or right uterine resistance index was available, this was used as "mean resistance index" (n=20). Notching of each uterine artery was recorded. An abnormal uterine artery Doppler result was defined as a mean resistance index >90th centile (>0.695).

Participants were followed prospectively, and research midwives collected data on pregnancy outcome and measurements of the baby. Data monitoring included individual checks of all data for each participant, including checks for any transcription errors of the lifestyle questionnaire, and detection of illogical or inconsistent data and outliers with customised software.

Primary outcome

Our primary outcome was pre-eclampsia defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or both, on at least two occasions four hours apart after 20 weeks' gestation but before the onset of labour, or postpartum, with either proteinuria (24 hour urinary protein ≥ 300 mg or spot urine protein:creatinine ratio ≥ 30 mg/mmol creatinine or urine dipstick protein $\geq ++$) or any multi-system complication of pre-eclampsia.^{19,25} Multi-system complications included any of acute renal insufficiency defined as a new increase in serum creatinine concentration ≥ 100 $\mu\text{mol/L}$ antepartum or >130 $\mu\text{mol/L}$ postpartum; effects on liver, defined as raised aspartate transaminase or alanine transaminase concentration, or both, >45 IU/L and/or severe right upper quadrant or epigastric pain or liver rupture; neurological effects included eclampsia, imminent eclampsia (severe headache with hyper-reflexia and persistent visual disturbance), or cerebral haemorrhage; and haematological effects included thrombocytopenia (platelets $<100 \times 10^9/\text{L}$), disseminated intravascular coagulation, or haemolysis. The reference group was women who did not develop pre-eclampsia.

Other definitions

The estimated date of delivery was calculated as follows: if the woman was certain of the date of her last menstrual period (LMP), the estimated date of delivery was adjusted only if a scan at <16 weeks' gestation found a difference of seven or more days between the scan gestation and that calculated by the LMP or a scan at 20 ± 1 weeks found a difference of 10 or more days. If her date was uncertain, scan dates were used to calculate the estimated date of delivery. Preterm pre-eclampsia was pre-eclampsia resulting in delivery before 37⁺⁰

weeks' gestation. Small for gestational age was defined as a birth weight below the 10th customised centile, adjusted for maternal height, booking weight, ethnicity, and delivery gestation and infant's sex.^{26,27}

Power calculation

The number of women required to be screened was based on achieving suitable screening test characteristics and precise estimates of their values. Given a pre-test probability (prevalence) of pre-eclampsia of 5%, then a post-test probability of 30% or greater would make this a useful test, based on current clinical practice. The algorithm must therefore have sufficient ability such that it is unlikely the post-test probability will fall below 0.30 (30%) for pre-eclampsia. This can be attained, with a power of 80%, in a cohort of 3000 if the true positive likelihood ratio of the screening test is 9.2 to 10.0. Given a prevalence of 5%, if we observe a sensitivity of 90% this cohort size will give a 95% confidence interval for this sensitivity of 84.0 to 94.3, and a specificity of 91%.

Datasets

We used two datasets to construct the predictive models for pre-eclampsia. The first comprised clinical variables obtained at 16-16 weeks' gestation and the second comprised clinical data at 14-16 weeks combined with variables from the 19-21 week ultrasound scan. Of the 933 original and derived variables recorded, we excluded variables added after recruitment commenced (n=76), paternal variables (n=48), variables not applicable to prediction of pre-eclampsia (n=246), variables with more than 10% missing data (clinical laboratory data and work variables not applicable to women not working, n=27), and 402 variables with $P > 0.10$ on univariable comparison of women with and without pre-eclampsia. Of the remaining 134 variables, we selected 38 as candidate predictors on the following criteria: known potential risk factors for pre-eclampsia, ease of collection in the clinical setting, and potential applicability to future populations (see table A in appendix 1 on bmj.com for a full list of variables). With this approach the only established "risk" factor not included in the candidate predictors was cigarette smoking, as in our dataset this was not associated with pre-eclampsia. We added the number of cigarettes smoked a day at 15 weeks' gestation as a candidate predictor, giving a total of 39 variables for the multivariable analysis. Variables were not included as candidate predictors because of colinearity (n=61), a low cell count (≤ 5) in the χ^2 test (n=11), lack of a consistent relation with pre-eclampsia in literature (n=4), or not readily applicable to a future obstetric population (n=20).

Among the 39 candidate predictors, data were complete in 32, missing in $<1\%$ for six variables, and missing in 6% for participant's birth weight. We imputed missing continuous data (n=4) with expectation maximisation and used the median for three variables unrelated to other observed data. The expectation maximisation algorithm was implemented in the

Table 1 | Characteristics of participants at 14-16 weeks' gestation by pre-eclampsia status. Figures are numbers (percentages) unless stated otherwise

	No pre-eclampsia (n=3343)	Pre-eclampsia (n=186)	P value*
Mean (SD) maternal age (years)	28.2 (5.8)	27.0 (5.8)	0.004
Ethnicity:			
White	2903 (87)	158 (85)	0.50
Maori or Polynesian	106 (3)	9 (5)	
Asian	242 (7)	12 (6)	
Other	92 (3)	7 (4)	
Married/cohabiting	3080 (92)	172 (93)	0.87
Mean (SD) socioeconomic index	41 (17)	37 (16)	<0.001
<12 years' schooling	1581 (47)	98 (53)	0.15
Tertiary education	2670 (80)	140 (75)	0.13
Full/part time work	2798 (84)	148 (80)	0.16
Primigravida	2484 (74)	138 (74)	0.97
Previous miscarriage	487 (15)	28 (15)	0.83
Previous termination	463 (14)	22 (12)	0.51
Smoking status:			
Non-smoker	2600 (78)	146 (78)	0.81
Stopped during pregnancy	371 (11)	22 (12)	
Current smokers	372 (11)	18 (10)	
BMI:			
<20.0	58 (2)	1 (1)	<0.001
20.0-24.9	1830 (55)	70 (37)	
25.0-29.9	936 (28)	55 (30)	
≥30	519 (15)	60 (32)	
Mean (SD) blood pressure (mm Hg):			
Systolic	108 (11)	114 (11)	<0.001
Diastolic	64 (8)	69 (8)	<0.001

BMI=body mass index.

*For comparisons between groups with χ^2 or Student's *t* test.

“mix” package in R, version 2.9.1.^{28,29} To evaluate its imputation, we used a permutation technique on the complete dataset. For each variable, we systematically removed each data point and imputed the “missing” value using expectation maximisation. We calculated the ratio of mean absolute error between imputed and original values to the mean value for that variable. The mean ratio for the variables imputed with expectation maximisation was 10.8%.

Statistical methods

We used SAS (version 9.1) for univariable data analysis and to generate a multivariable logistic regression model. We used Student's *t* test, Wilcoxon rank sum test, or χ^2 test for comparing characteristics in the study population and pregnancy outcomes between women who did and did not develop pre-eclampsia. Stepwise logistic regression was used to determine independent risk factors for pre-eclampsia in both datasets. The order of variable selection was determined by the χ^2 statistic for each potential variable and the forward selection step could be followed by removal of variables in one or more backward elimination steps. We calculated receiver operating characteristics curves and determined screening test characteristics at a 25%, 10%, and 5% false positive rate. For internal

validation we evaluated the calibration and discrimination (10-fold cross validation) of the model using methods described by Altman et al.³⁰ Calibration was assessed by plotting the observed proportion of events against the predicted probabilities. For the cross validation, participants were stratified by region (New Zealand, Australia, Ireland, and UK), pre-eclampsia status (positive or negative), and gestation (<260 days or ≥260 days) and randomly allocated to one of 10 groups. Tenfold cross validation was then performed, with 90% of the data used to generate a model, and estimation of disease risk was performed in the 10% remaining. These predicted values were then combined across the 10 runs and summarised by the C statistic (AUC). This entire procedure was repeated 10 times.

To determine the variables most consistently retained in the prediction models, we generated the 10 “best models,” based on the proportion of variance explained, by calculating all possible logistic regression models retaining 10 variables. We determined the frequency of each variable present in the 10 highest scoring models and identified key risk factors. We then calculated the proportion of women with specific combinations of key clinical risk factors and abnormal uterine artery Doppler at 20 weeks' gestation who developed pre-eclampsia.

RESULTS

Of the nulliparous women (n=4961) invited to participate in the study, 3780 (76%) agreed but a further 208 were excluded before or at the 15 week interview (fig 1). Among the 3572 women recruited into the study, we had data on pregnancy outcome for 3529 (99%). When we compared the women who declined to participate (n=1202) with the 3529 women in the study population there were minor but significant differences in the ethnicity mix (79% v 87% white, 4% v 3% Maori or Pacific Islander, 11% v 7% Asian, 6% v 3% other, P<0.001) and age (mean 28.8 (SD 5.7) v 28.1 (SD 5.8), P=0.001). A further 182 women were excluded

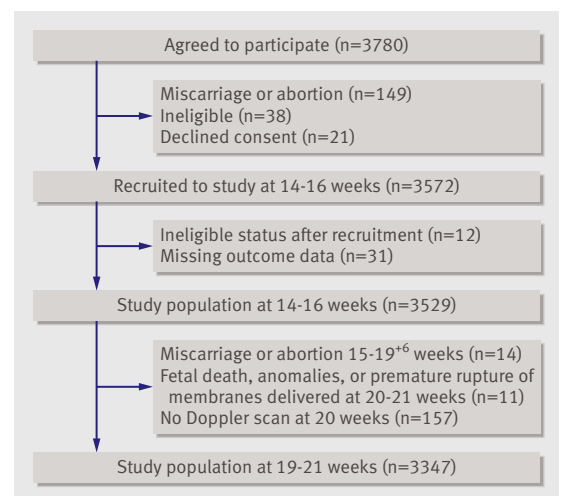
**Fig 1** | Recruitment and flow of participants through study

Table 2 Characteristics of pregnancy outcomes by pre-eclampsia status. Figures are numbers (percentages) unless stated otherwise

	No pre-eclampsia (n=3343)	Pre-eclampsia (n=186)	P value*
Maternal			
Mean (SD) blood pressure (mm Hg):			
Systolic	122 (13)	164 (18)	<0.001
Diastolic	75 (10)	104 (10)	<0.001
Fetal			
No of infants	3329†	186	
Mean (SD) birth weight (g)	3408 (581)	3033 (809)	<0.001
Mean (SD) gestation at delivery (weeks)	39.5 (2.7)	37.9 (2.8)	<0.001
SGA (<10th customised centile)‡	332 (10)	44 (24)	<0.001
Preterm birth:			
<37 weeks	214 (6)	47 (25)	<0.001
<34 weeks	76 (2)	19 (10)	<0.001
Admission to neonatal unit	349 (11)	57 (31)	<0.001
Perinatal death	18 (0.5)	1 (0.5)	1.0

SGA=small for gestational age.

*P values are comparisons between groups with χ^2 or Student's *t* test.

†Excludes miscarriages and abortions.

‡For 3327 women in "no pre-eclampsia" group as customised centiles unavailable when fetus died in utero before 20 weeks' gestation.

from the 20±1 week dataset, in most cases because of missing data from the Doppler ultrasound (n=157) (fig 1).

In total 186 (5%) women developed pre-eclampsia; in eight the diagnosis was postpartum and 47 (1%) delivered preterm. Table 1 shows background characteristics and table 2 shows outcomes of pregnancy in women who did and did not develop pre-eclampsia. Women who developed pre-eclampsia were younger, had a lower socioeconomic index, and at 15 weeks' gestation were more likely to be obese and have higher blood pressure. Pre-eclampsia developed at a mean of 36.9 (SD 3.3) weeks' gestation, with a median protein:creatinine ratio of 88 mg/mmol (range 30-2445 mg/mmol) and 24 hour urinary protein excretion of 0.78 g (range 0.30-9.9 g). The diagnosis of pre-eclampsia was based on hypertension in combination with multisystem complications in 24 of the 186 women (13%), four of whom had "+" proteinuria. Forty two per cent of the women had at least one multisystem complication: 8% (n=14) had a diagnosis of HELLP (haemolysis, elevated liver enzymes, and low platelets) or ELLP (elevated liver enzymes and low platelets), 5% (n=9) developed impaired renal function, and one woman had eclampsia. A quarter of the babies were born preterm and 24% were small for gestational age.

Prediction of pre-eclampsia with clinical risk factors and uterine artery Doppler

Table 3 shows the clinical risk factors independently associated with pre-eclampsia on multivariable analysis (see tables B1 and B2 in appendix 2 on bmj.com for unadjusted odds ratios). Addition of ultrasound scan variables to the 15 week clinical data resulted in age and the number of cigarettes a day being removed from the model and inclusion of duration of sexual

relationship of six months or less and uterine artery Doppler waveform indices. Based on clinical risk factors, the mean AUC from the ten 10-fold cross validations was 0.71 (SE 0.002) (fig 2). The AUC for the proposed model based on the observations used to create the model was 0.76, indicating a bias in the C statistic of about 5%. The addition of 20 week uterine artery Doppler indices did not improve performance based on the study population (internally validated AUC 0.71 (SE 0.003)). Figure 3 shows that the model has a reasonable level of calibration, but there is an indication that, at the higher probabilities for pre-eclampsia, it might underestimate cases.

Table 4 summarises the screening characteristics of the models at a false positive rate of 5%, 10%, and 25% based on the women from whom the model was created and from the internal validation where the values reported are the means of those derived from each of the cross validation analyses.

To estimate a woman's probability of pre-eclampsia, a risk score can be calculated based on the formulas in the footnote of table 3. The predicted probability of pre-eclampsia can then be calculated from $1/(1+e^{-\text{riskscore}})$.³¹ For example, for a 28 year old nulliparous woman whose birth weight was 2400 g, with a mean arterial pressure of 96 mm Hg, BMI 30, a family history of pre-eclampsia, and no protective factors, her probability of pre-eclampsia is 39%. Her risk of pre-eclampsia decreases as each risk factor is removed in stepwise fashion; if her mean arterial pressure is 80 mm Hg her probability of pre-eclampsia would be 18%, if her BMI was 24 her probability would be 14%, if she had no family history of pre-eclampsia her probability would be 8%, and if her birth weight had been 3500 g her probability would be 5%. If she had protective factors, such as a previous early miscarriage with her partner, her risk would be reduced to 2%.

Impact of definition of pre-eclampsia

To evaluate the impact of 24 women receiving a diagnosis of pre-eclampsia based on the presence of gestational hypertension combined with multisystem complications, the model was reconstructed defining

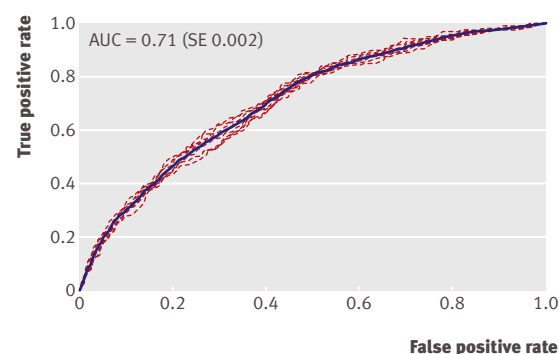


Fig 2 Receiver operating characteristics curves based on independent predicted values from ten 10-fold cross validation runs of model of clinical risk factors at 15 weeks

Table 3 | Clinical risk factors at 15 weeks and ultrasound scan variables at 20 weeks included in logistic regression model for pre-eclampsia

	Clinical risk factors at 15 weeks*			Plus ultrasound scan at 20 weeks†		
	No pre-eclampsia (n=3343)	Pre-eclampsia (n=186)	Adjusted OR (95%CI)	No pre-eclampsia (n=3167)	Pre-eclampsia (n=180)	Adjusted OR (95%CI)
Risk factors‡						
Decrease of 5 years in age	28.2 (5.8)	27 (5.8)	1.2 (1.1 to 1.4)	—	—	—
Increase of 5 mm Hg in MAP§	78 (8)	84 (8)	1.4 (1.3 to 1.5)	78 (8)	84 (8)	1.4 (1.2 to 1.5)
Increase of 5 in BMI	25.4 (5.1)	28.2 (6.7)	1.3 (1.1 to 1.4)	25.4 (5.1)	28.3 (6.8)	1.3 (1.1 to 1.5)
Family history of pre-eclampsia	309 (9%)	35 (19%)	2.0 (1.3 to 3.0)	299 (9%)	35 (19%)	1.9 (1.3 to 2.9)
Family history of coronary heart disease¶	384 (12%)	35 (19%)	1.9 (1.2 to 2.8)	359 (11%)	35 (19%)	1.8 (1.2 to 2.8)
Decrease of 500 g in woman's birth weight**	3293 (552)	3177 (540)	1.2 (1.1 to 1.4)	3292 (551)	3177 (547)	1.2 (1.1 to 1.4)
Vaginal bleeding ≥5 days	125 (4%)	13 (7%)	2.0 (1.1 to 3.8)	116 (4%)	12 (7%)	1.9 (1.0 to 3.7)
≤ 6 months in sexual relationship††	—	—	—	256 (8%)	26 (14%)	1.7 (1.04 to 2.6)
Bilateral notches	—	—	—	327 (10%)	33 (18%)	1.7 (1.1 to 2.6)
Increase of 0.1 in mean uterine artery RI	—	—	—	0.56 (0.10)	0.60 (0.12)	1.2 (1.04 to 1.5)
Protective factors						
One miscarriage ≤10 weeks, same partner	301 (9%)	8 (4%)	0.45 (0.22 to 0.93)	284 (9%)	8 (4%)	0.44 (0.21 to 0.92)
≥12 months to conceive	384 (12%)	12 (7%)	0.40 (0.22 to 0.75)	357 (11%)	12 (7%)	0.41 (0.22 to 0.76)
High fruit intake (≥3/day)	1347 (40%)	52 (28%)	0.69 (0.49 to 0.98)	1266 (40%)	48 (27%)	0.65 (0.45 to 0.92)
Alcohol consumption 1st trimester	1705 (51%)	69 (37%)	0.60 (0.44 to 0.83)	1616 (51%)	65 (36%)	0.57 (0.41 to 0.79)
Increase of 5 cigarettes/day	0.8 (3.0)	0.6 (2.4)	0.73 (0.53 to 1.0)	—	—	—

MAP=mean arterial pressure, BMI=body mass index, RI=uterine resistance index.

*Risk score for pre-eclampsia from logistic regression model based on clinical risk factors is calculated as $-6.8855-0.0393 \times \text{age}+0.0659 \times \text{MAP}+0.0483 \times \text{BMI}+0.6861 \times \text{family history of pre-eclampsia}+0.6232 \times \text{family history of coronary heart disease}-0.3881 \times \text{participant's birth weight (kg)}+0.7129 \times \text{vaginal bleeding} \geq 5 \text{ days}-0.8033 \times \text{one miscarriage} \leq 10 \text{ weeks, same partner}-0.9070 \times \geq 12 \text{ months to conceive}-0.3733 \times \text{high fruit intake at 15 weeks}-0.508 \times \text{alcohol consumption in first trimester}-0.063 \times \text{No of cigarettes/day at 15 weeks}$.

†Risk score for pre-eclampsia from logistic regression model based on clinical risk factors and ultrasound scan data calculated as $-9.1113+0.0634 \times \text{MAP}+0.0485 \times \text{BMI}+0.6539 \times \text{family history of pre-eclampsia}+0.6093 \times \text{family history of coronary heart disease}-0.3787 \times \text{participant's birth weight (kg)}+0.6493 \times \text{vaginal bleeding} \geq 5 \text{ days}+0.5008 \times \text{months in sexual relationship} \leq 6 \text{ months}+0.5084 \times \text{bilateral notches}+2.0802 \times \text{mean uterine artery RI}-0.8248 \times \text{one miscarriage} \leq 10 \text{ weeks, same partner}-0.8983 \times \geq 12 \text{ months to conceive}-0.4389 \times \text{high fruit intake at 15 weeks}-0.5573 \times \text{alcohol consumption in first trimester}$.

‡Variable name (unit change for adjusted odds ratio (OR)).

§MAP calculated from second blood pressure measurement at 14-16 weeks.

¶Participant's father had coronary heart disease.

**Because of missing data numbers for woman's birth weight were 3145, 174, 2993, and 168, respectively.

††≤6 months in sexual relationship with father of baby before conceiving.

the cases as pre-eclamptic women with proteinuria (n=162). Most risk factors and protective factors remained with similar odds ratios, except that age, high intake of fruit, and cigarettes were excluded and a sexual relationship of six months or less (odds ratio 1.7, 95% confidence interval 1.05 to 2.7), hyperemesis at 15 weeks (2.0, 1.1 to 3.7), and maternal height (0.87, 0.76 to 1.0) per 5 cm increase) were included.

Reproducibility of prediction model

To investigate the stability and potential reproducibility of the model (using all candidate predictors) we constructed 10 "best models" that included 10 variables. The risk factors (mean arterial blood pressure, BMI, family history of pre-eclampsia, family history of coronary heart disease (woman's father), participant's birth weight) and protective factors (≥12 months to conceive, alcohol used in the first trimester) occurred in all "10 best models." Of the other variables in our model (table 3), six occurred in three to seven of the best models, while cigarettes a day was not selected by the stepwise model fitting procedure.

Risk estimates with specific combinations of clinical risk factors

Table 5 shows the proportion of women with specific combinations of key clinical risk factors and abnormal

result on uterine artery Doppler who developed pre-eclampsia. We have shown systolic blood pressure rather than mean arterial blood pressure as that requires calculation and, unless incorporated into an algorithm, is not easily applied in a routine clinic setting.

Specialist referral framework for nulliparous women

To better understand potential clinical implications, we developed a framework for specialist referral in a population (n=1000) based on observations in our study population (fig 4). In the first stage, women

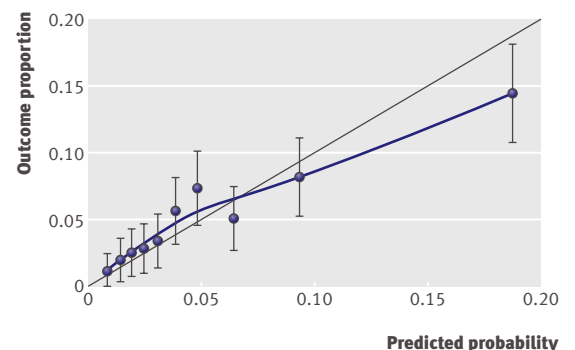


Fig 3 | Observed rate of pre-eclampsia compared with predicted probabilities of pre-eclampsia based on clinical risk factors model

Table 4 | Prediction of pre-eclampsia from algorithms based on clinical risk factors at 14–16 weeks' gestation in cohort and independent predicted values from ten 10-fold cross validation runs. Values are shown with 95% confidence intervals

No (%) with abnormal test result	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
Training cohort*						
218 (6)	27 (22 to 34)	95 (94 to 96)	24 (22 to 25)	96 (95 to 97)	5.5 (4.2 to 7.2)	0.76 (0.70 to 0.84)
403 (11)	37 (30 to 44)	90 (89 to 91)	17 (16 to 18)	96 (96 to 97)	3.6 (2.9 to 4.5)	0.71 (0.63 to 0.79)
949 (27)	61 (54 to 68)	75 (74 to 76)	12 (11 to 13)	97 (97 to 98)	2.5 (2.2 to 2.8)	0.52 (0.43 to 0.62)
Ten 10-fold cross validation†						
205 (6)	20 (18 to 22)	95 (95 to 95)	18 (16 to 20)	96 (95 to 96)	3.9 (3.5 to 4.4)	0.85 (0.83 to 0.87)
392 (11)	30 (28 to 33)	90 (89 to 91)	14 (13 to 16)	96 (96 to 96)	3.0 (2.8 to 3.3)	0.78 (0.75 to 0.80)
935 (27)	53 (48 to 58)	75 (74 to 76)	10 (10 to 12)	97 (96 to 97)	2.1 (1.9 to 2.3)	0.63 (0.56 to 0.70)

*Based on clinical risk factor algorithm from table 2 using cut-offs at 5%, 10%, and 25% false positive rates

†Average test characteristics across 10 different cross validation repeats.

were referred to a specialist if their post-test probability of pre-eclampsia generated by the model was at least 15%. Among those not referred, women with a systolic blood pressure >120 mm Hg, a BMI \geq 30, or a family history of pre-eclampsia underwent a uterine Doppler ultrasound with their fetal anatomy scan at 20 weeks, and those with an abnormal uterine artery resistance index also had a specialist referral. Of the women referred for a specialist opinion, 21% developed pre-eclampsia and 8% developed preterm pre-eclampsia. The relative risk for developing pre-eclampsia and preterm pre-eclampsia in the specialist referred group compared with standard care group was 5.5 and 12.2, respectively.

Overall, application of this framework for specialist referral would result in 34% of women with pre-eclampsia (63 of 186) and 53% of those who develop preterm pre-eclampsia (25 of 47) being referred. If the referral criteria did not include uterine Doppler, fewer cases of preterm pre-eclampsia (16 of 47, 34%) would be detected. These results also show that negative prediction based on clinical risk assessment, with or without Doppler ultrasonography, is too inaccurate to allow a reduction in antenatal care.

DISCUSSION

In this large prospective international cohort of “healthy” nulliparous women an algorithm for pre-eclampsia, which included clinical risk factors at 15 weeks' gestation, had moderate predictive performance. The algorithm included well recognised risk factors (blood pressure, BMI, and a family history of pre-eclampsia) along with less established factors, such as prolonged vaginal bleeding, maternal low birth weight, and the woman's father having coronary artery disease. The algorithm had moderate predictive performance—the area under the receiver operating characteristics curve (AUC) was 0.76—and detected 37% and 61% of women who developed pre-eclampsia with a false positive rate of 10% and 25%, respectively. Addition of information from ultrasonography did not significantly improve performance of the algorithm, with an AUC of 0.77. We would expect poorer screening performance of the algorithm in other nulliparous populations, as evident by the AUC of 0.71 on internal

validation. Given the prospective design, cohort size, comprehensive range of candidate predictors, high quality data, and completeness of follow-up, this is likely to be indicative of the best performance achievable using clinical and ultrasonography data to predict pre-eclampsia in a “healthy” nulliparous population. To considerably improve prediction performance will require either the development of specific clinical risk algorithms for disease subtypes, such as preterm and term pre-eclampsia, or the addition of biomarkers, or both.

The concept of a personalised clinical risk estimate for disease, to which biomarkers can be added, is established in several areas of medicine. The algorithm to predict pre-eclampsia reported here provides a first step towards a personalised risk score for pre-eclampsia among nulliparous women. It is inevitable the model will be overfitted to our population and external validation of the algorithm in other nulliparous populations is essential. We plan to evaluate its performance in the next 3000 women recruited into SCOPE, nearly all of whom will be recruited in different centres than the initial 3500 women. Validation should also be performed in other study populations of nulliparous women.

Strengths and weaknesses

A major strength of this study is its large multicentre prospective design with excellent follow-up. As the focus of the SCOPE study is development of tests to predict pregnancy outcome with potential to translate into clinical care, we recruited a clearly defined population of nulliparous women, enabling identification of similar populations for external validation. This is critical for generalisability of a risk assessment algorithm; the population in which the algorithm is developed needs to be identifiable if a screening test is to be used in clinical care.³²

We obtained high quality data for all known risk factors for pre-eclampsia from questionnaires administered at interviews, along with detailed standard operating procedures. Use of a real time database, with automated checking procedures, reduced data entry errors and transcription errors. For a dataset of this size, the rate of missing data was minimal. The

Table 5 | Probability of pre-eclampsia in presence of combinations of clinical risk factors at 15 weeks* and uterine artery Doppler at 20 weeks†

No of women	Systolic BP >120 mm Hg	BMI ≥30	FH PE†	FH coronary artery disease	Maternal birth weight <2500 g	Vaginal bleeding ≥5 days	Abnormal mean uterine artery RI	Proportion PE % (95% CI)	Proportion preterm PE % (95% CI)
310	•	—	—	—	—	—	—	14 (10 to 18)	5 (3 to 8)
579	—	•	—	—	—	—	—	10 (8 to 13)	2 (1 to 4)
344	—	—	•	—	—	—	—	10 (7 to 14)	3 (2 to 6)
419	—	—	—	•	—	—	—	8 (6 to 11)	3 (2 to 5)
224	—	—	—	—	•	—	—	9 (6 to 13)	3 (2 to 6)
138	—	—	—	—	—	•	—	9 (6 to 16)	1 (0.4 to 5)
131	•	•	—	—	—	—	—	16 (11 to 23)	4 (2 to 9)
46	•	—	•	—	—	—	—	20 (11 to 33)	7 (2 to 18)
52	•	—	—	•	—	—	—	15 (8 to 28)	8 (3 to 18)
21	•	—	—	—	•	—	—	33 (17 to 55)	24 (11 to 45)
15	•	—	—	—	—	•	—	27 (11 to 52)	13 (4 to 38)
73	—	•	•	—	—	—	—	18 (11 to 28)	7 (3 to 15)
77	—	•	—	•	—	—	—	14 (8 to 24)	4 (1 to 11)
41	—	•	—	—	•	—	—	17 (9 to 31)	5 (1 to 16)
24	—	•	—	—	—	•	—	8 (2 to 26)	—
12	—	—	•	—	—	•	—	42 (19 to 68)	—
24	—	—	—	•	•	—	—	17 (7 to 36)	8 (2 to 26)
326	—	—	—	—	—	—	•	10 (7 to 14)	6 (4 to 9)
29	•	—	—	—	—	—	•	24 (12 to 42)	14 (6 to 31)
65	—	•	—	—	—	—	•	17 (10 to 28)	11 (5 to 21)
44	—	—	•	—	—	—	•	16 (8 to 29)	16 (8 to 29)
32	—	—	—	•	—	—	•	13 (5 to 28)	6 (2 to 20)
25	—	—	—	—	—	•	•	8 (2 to 25)	—
33	—	—	—	—	•	—	•	9 (3 to 24)	9 (3 to 24)

BP=blood pressure; FH=family history; PE=pre-eclampsia; RI=resistance index.

*In 3529 women; 5% developed pre-eclampsia and 1% developed preterm pre-eclampsia.

†In 3347 women; abnormal result=uterine artery RI >0.695 or bilateral notches.

intensive two stage data monitoring adds confidence in data integrity. Potential measurement errors, such as in self reported family history,³³ could have occurred, but as the goal was to develop a prototype algorithm ultimately for clinical use, this limitation was accepted. Principal investigators reviewed outcome data for cases, ensuring accurate diagnosis. One of the challenges when predicting rare events in prospective cohorts, such as SCOPE, is the relatively low numbers of cases compared with studies based on huge epidemiological databases. While the latter might have a substantially greater number of events, their interpretation is restrained by less accurate diagnosis.

There is no consensus as to the best method for selection of variables.³¹ Given the rich dataset of potential predictors for pre-eclampsia, we used a pruning step based on significance testing and then selected a subset of candidate variables on a priori knowledge. This could have introduced variable selection bias, but it is reassuring that the clinical risk factors and their strength of association with pre-eclampsia are consistent with the literature. While we could undertake only internal validation at this stage, external validation is planned.

Comparisons with other studies

Previous studies investigating risk factors for pre-eclampsia have used birth registries or hospital

databases,^{6,34} randomised trials with negative results (that is, no treatment effect shown),^{35,36} and, in a few studies, prospective cohorts (usually general obstetric populations) designed to investigate outcomes of pregnancy.^{9,12,13,37} Consistent with other contemporary studies, the women who developed pre-eclampsia were younger, more obese, and more likely to have lower socioeconomic status.³⁷⁻³⁹

Many of the risk factors included in the algorithm presented here are associated with a similar degree of risk to that previously reported, giving confidence regarding the potential applicability of the algorithm to other populations. Higher blood pressure within the normal range, a higher BMI, and a family history of pre-eclampsia had similar predictive characteristics to those observed in other studies.^{8,39-41} In our algorithm, blood pressure was the most important risk factor driving the estimated probability of pre-eclampsia.⁹ Mean arterial pressure, rather than systolic or diastolic blood pressure, was selected by stepwise logistic regression and included in the model.⁸ If it was implemented into clinical practice, the clinician would derive the mean arterial pressure from systolic and diastolic blood pressure entered into the algorithm. A history of coronary artery disease in the woman's father was associated with a 1.9-fold increase in the risk of pre-eclampsia, consistent with a previous report and the association between pre-eclampsia and subsequent

ischaemic heart disease.^{42,43} Confirming the results of a case-control study,⁴⁴ a lower maternal birth weight was associated with an increased risk of pre-eclampsia, with an even greater risk when low maternal birth weight coexisted with other key risk factors. Prolonged vaginal bleeding in early pregnancy was associated with a twofold increase in risk of pre-eclampsia. As reported by others, most of these bleeds were mild in severity, suggesting that a discrete bleeding pattern could be associated with later pre-eclampsia.⁴⁵

Several factors were associated with a reduced risk of pre-eclampsia. A single early miscarriage with the same partner, eating a lot of fruit, and smoking were protective, again reassuringly consistent with previous reports.^{10,12,46} The protective influence of cigarette smoking in our cohort was less than previously reported, and cigarettes did not remain in the model when we added uterine artery Doppler indices.⁴⁶ Alcohol use in the first trimester was protective but requires confirmation in other cohorts.⁴⁷ Obese women are reported to drink less alcohol, possibly because food fulfils their addictive behaviour.^{48,49} Obesity is unlikely to be the only explanation, however, as the protective effect of alcohol is retained with BMI in the model, and there was no interaction between BMI and alcohol.

A recent series of publications reported algorithms to predict pre-eclampsia based on clinical risk factors in a general population comprising high risk women (previous pre-eclampsia and medical conditions), nulliparous women, and low risk women (multiparas with previous uncomplicated pregnancies).^{9,36,50} A model is fitted to the population in which it was developed, using the available candidate predictors.³⁰ A general antenatal population constructed of subgroups with different risk profiles is difficult to replicate and future “general populations” are likely to comprise a different case-mix. The importance of population differences is evident in the failure of one proposed algorithm to validate in a high risk population,⁵¹ raising questions as to more general applicability to other populations such as “healthy” nulliparous women. Poor performance on

validation might also occur because key predictors are missing from the model. When the list of candidate predictors includes strongly predictive factors, such as previous pre-eclampsia, renal disease, and chronic hypertension,^{16,34} these will take precedence, replacing other factors that might be more relevant to healthy nulliparous women. In contrast, in SCOPE, we investigated candidate predictors applicable to healthy nulliparous women.

Clinical relevance

The new information on the rate of pre-eclampsia in the presence of combinations of specific risk factors (table 5) could be used by clinicians to improve current guidelines for specialist referral in nulliparous women. When we applied the criteria proposed in the NICE guidelines to the SCOPE cohort, 16.5% of nulliparous women would be referred for a specialist opinion of whom 10% would develop pre-eclampsia.⁵² This included 31% of the 186 women who developed pre-eclampsia and 38% of the 47 of those who developed preterm pre-eclampsia. If we included only first pregnancy, as in the NICE guidelines,⁵² 12% would be referred and 23% and 28% cases of pre-eclampsia and preterm pre-eclampsia, respectively, would be detected. Our proposed framework for specialist referral based on the algorithm, along with uterine artery Doppler screening of a subpopulation, performed better than the NICE guidelines but requires validation. Among the referred women (9% of nulliparas), the rate of pre-eclampsia was 21%. Thirty four per cent of cases of pre-eclampsia and 53% of cases of preterm pre-eclampsia were identified. This framework has the potential to identify a subgroup of nulliparous women at high risk of pre-eclampsia who could benefit from low dose aspirin and more intensive antenatal surveillance. It does not, however, provide additional information for the rest, whose risk is similar to an unscreened nulliparous population. Hence a negative “test” result would not modify current clinical care. The algorithm requires external validation, followed by assessment of the impact of increased surveillance, the false positive and false negative results, and a health economics analysis. If externally validated, this algorithm could help to inform future NICE guidelines for specialist referral. It could be made accessible, including via the web, as a support for risk stratification of healthy nulliparous women in low resource settings. To improve overall accuracy and detection of cases, the clinical algorithm will require the addition of biomarkers.

Conclusions

We have identified the most important clinical risk factors for pre-eclampsia in healthy nulliparous women and provided new information on the level of risk associated with specific combinations of risk factors. The predictive performance of the algorithm is modest, but offers a considerable improvement on current practice in healthy nulliparous women. As all known risk factors were included in this large prospective

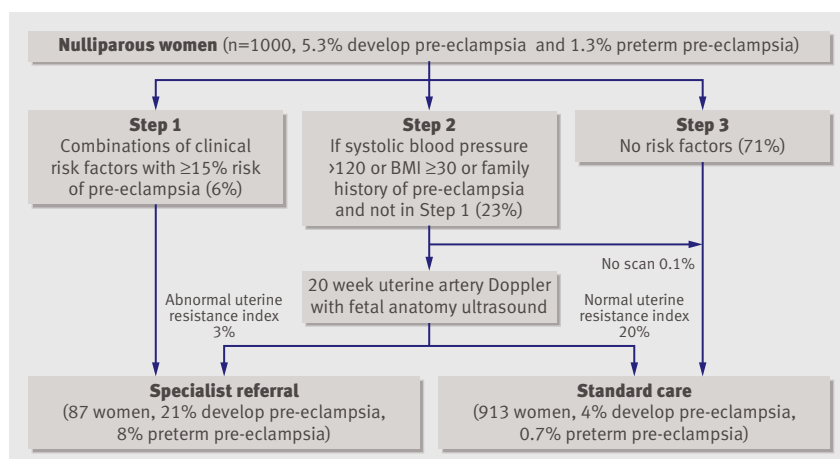


Fig 4 | Framework for specialist referral when estimated risk of pre-eclampsia is $\geq 15\%$ in model or presence of clinical risk factor with abnormal result on uterine artery Doppler scan

WHAT IS ALREADY KNOWN ON THIS TOPIC

There are many recognised clinical risk factors for pre-eclampsia, but the risk in nulliparous women associated with combinations of risk factors is largely unknown

No method exists to accurately risk stratify healthy nulliparous women

WHAT THIS STUDY ADDS

Use of data from a large international prospective cohort study provides new information on the level of risk of pre-eclampsia associated with specific combinations of clinical risk factors

The prototype algorithm based on clinical risk factors has modest ability to predict pre-eclampsia

If validated, the algorithm could provide a personalised estimation of clinical risk for pre-eclampsia in healthy nulliparous women to which biomarkers can be added

cohort, it shows the expected performance and limitations of using clinical phenotype to predict pre-eclampsia. The algorithm serves as a prototype that requires validation in other nulliparous populations. If validated, it might provide a personalised clinical risk profile for nulliparous women to which biomarkers could be added.

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Contributors: RAN was responsible for conception and design, analysis and interpretation of data, and drafting the article and revising it critically for important intellectual content. LMEMcC, GAD, LP, JJW, and PNB were responsible for conception and design and interpretation of data, and critical revision of paper for important intellectual content. EHYC, AWS, and MAB were responsible for statistical analyses and interpretation of data, and revising the article critically for important statistical content. RST was responsible for study design, coordination of clinical study, and revising the article critically for important intellectual content. LCK was responsible for conception and design, interpretation of data, drafting the article, and critical revision of paper for important intellectual content. All authors had full access to all of the data (including statistical reports and tables) in the study, can take responsibility for the integrity of the data and the accuracy of the data analysis, and approved the final version to be published. RAN is guarantor.

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; RAN and PNB have had consultancy relationships with Pronota in the previous three years; RAN has a consultancy relationship with Alere; LCK and PNB declare a US Provisional Patent Application in the name of University College Cork, Ireland (Louise Kenny and Philip Baker) "Detection of risk of pre-eclampsia" Application No USSN 61/288,465; RAN and MAB declares the following patent, which to date has not been licensed to a company: Blumenstein M, North RA, McMaster MT, Black MA, Kasabov NK, Cooper GJS. Biomarkers for prediction of pre-eclampsia and/or cardiovascular disease, PCT number WO/2009/108073. LP has a consultancy

relationship with Tate and Lyle Research Advisory Group and is chairing a working party with ILSI Europe; both are outside the area of the submitted work.

Ethical approval: This study was approved by local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London and Manchester O6/MRE01/98, and Cork ECM5 (10) 05/02/08), and all women provided written informed consent.

Data sharing: No additional data available.

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