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Prediction of Preeclampsia and Delivery of Small for Gestational Age Babies Based on a Combination of Clinical Risk Factors in High-Risk Women

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Objective. To develop clinical risk tools for preeclampsia and small for gestational age (SGA) in high-risk women. *Methods*. Individual risk scores based on clinical risk factors were calculated using logistic regression and validated in 1687 women with obesity in first pregnancy, chronic hypertension, or previous preeclampsia. *Results*. The risk of preeclampsia varied from 7% in obese primiparae without hypertension to 30% when previous preeclampsia and chronic hypertension occurred together. A prediction model incorporating these risk factors had a sensitivity of 48 and 89% for preeclampsia delivered <34 weeks' gestation. *Conclusion*. Multiple clinical risk factors increase the risk of preeclampsia and SGA.

Keywords Preeclampsia, SGA, Prediction, Risk factors.

INTRODUCTION

Preeclampsia and fetal growth restriction remain important causes of morbidity and mortality. An accurate method of antenatal screening for these conditions would be of great value in targeting antenatal care and interventions effectively (1). A number of clinical characteristics and preexisting diseases are recognized as increasing the risk of pregnant women developing preeclampsia. These include obesity, chronic hypertension, and previous preeclampsia (2–5). Antenatal screening for these and other clinical risk factors for

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preeclampsia has been proposed in the UK National Institute for Clinical Excellence guidelines, with specialist care recommended for women identified at increased risk (1). The presence of comorbidities undoubtedly modifies a woman's risk of preeclampsia and small for gestational age (SGA) babies, but no method has yet been developed which permits accurate quantification of risk when these conditions coexist (1).

In clinical practice, the probability of developing either preeclampsia or SGA among "high-risk" women approximates 20–30% (6,7). The incidence of preeclampsia reported in obese women (0.9–13.5%) (8–10), those with chronic hypertension (10–45%) (4,10–13), and previous preeclampsia (7.5–47%) (10,14–16) varies depending on the construct of the cohort studied. Within each condition, it would be clinically useful to identify women at lower probability and a smaller subset at very high probability of developing preeclampsia and SGA. For instance, in chronic hypertension, preeclampsia occurs in over 40% of women with severe hypertension in early pregnancy compared with 10–24% in those women with milder chronic hypertension (4,11,12).

The principal goal of prediction is to identify women in whom interventions can be indicated to prevent preeclampsia, and also in order to stratify or tailor antenatal care. Relevant interventions include low-dose aspirin, which in a meta-analysis of over 37,000 women has been shown to reduce the risk of preeclampsia, SGA, and perinatal deaths by 17, 10, and 14%, respectively (17). A meta-analysis of individual patient data from randomized low-dose aspirin trials recently reported a 10% relative risk reduction in preeclampsia with aspirin (18). Given the size of treatment effect, the probability of developing preeclampsia is an important factor in determining whether to treat or not (17,18). Risk estimates for women with chronic hypertension and previous preeclampsia can range from a low probability where intervention is probably inappropriate, to high risk where aspirin is clearly indicated. Risk assessment modeling would be useful if it improved upon the current methods and identify those women at higher risk who require intervention.

The Vitamins in Preeclampsia (VIP) trial established a large cohort of women at high risk of preeclampsia, with detailed obstetric information and pregnancy outcomes on over 2400 women (10). In this study, we have used the VIP data set to evaluate combinations of clinical risk factors, to enable identification of those women with a clinically significant risk of preeclampsia and/or SGA in whom treatment may be indicated, and to discriminate these women from those at lower risk.

Our aims were to (1) determine the risk of preeclampsia and SGA in women affected by chronic hypertension, previous preeclampsia, and obesity in first pregnancy or combinations thereof; (2) evaluate the efficacy of combining other clinical risk factors with these well-recognized "at-risk" conditions to provide improved risk assessment; and (3) produce a practical method of estimating the risk of adverse outcomes in high-risk women using commonly available clinical data only.

METHODS

About 2404 women with clinical risk factors for developing preeclampsia were recruited from 25 UK hospitals and 1 in the Netherlands between August 2003

and June 2005 as part of the VIP trial (10). The eligibility criteria were gestational age 14^{+0}–21^{+6} weeks' gestation with one or more of eight risk factors, chronic hypertension, primigravidae with a body mass index (BMI) of 30 kg/m^2 or more, previous history in the immediately preceding pregnancy of preeclampsia requiring delivery before 37 weeks gestation or any prior eclampsia or HELLP syndrome, type 1 or type 2 diabetes, multiple pregnancy, antiphospholipid syndrome, chronic renal disease, and abnormal uterine artery Doppler studies. Gestation was based on last menstrual period and ultrasound scan, with the last menstrual period date being used only when it was within 7 days of the scan result before 12 weeks gestation and within 10 days of a scan after 12 weeks gestation. MREC approval was granted through the South East Multi Ethics Research Committee (number 00/01/027) and site-specific approval was acquired in each participating center. All participants gave written consent. Overall, 52% of eligible women approached (2404/4614) agreed to be part of the study. Women were randomized to receive either 1000 mg vitamin C and 400 IU natural source vitamin E (RRR α-tocopherol) or matching placebo tablets, and pregnancy outcome recorded. Vitamin supplementation did not modify the risk of preeclampsia or SGA overall, or in women who met the entry criteria of obesity, chronic hypertension, or previous preeclampsia (10). Women in both treatment arms were therefore included in this study.

Disease Endpoints

Four endpoints were defined: preeclampsia, preeclampsia with early onset, SGA, and severe adverse perinatal outcome. Preeclampsia was defined as gestational hypertension with proteinuria according to the International Society for the Study of Hypertension in Pregnancy (19). For women with preexisting hypertension and/or proteinuria, each case of superimposed preeclampsia was reviewed by the trial management team and the diagnosis confirmed by two senior clinicians acting independently. Early-onset preeclampsia was defined as preeclampsia resulting in delivery before 34 weeks gestation. SGA was defined as birthweight below the 10th centile, adjusting for gestational age, gender, maternal ethnicity, and BMI (within normal limits) by customized birthweight centile calculator, using version 6.1 of the bulk centile calculator (20). Severe adverse perinatal outcome was chosen to include infants with a birthweight <1st customized centile or those with birthweight <10th customized centile complicated by either delivery before 34 weeks or a perinatal death.

Data Set

Among the 2404 women, we excluded 17 women who had missing outcome data for either preeclampsia or SGA, 379 with multiple pregnancies, and 31 with an abnormal uterine artery Doppler as their only entry criterion, as this involved ultrasonography which is not a screening test based on clinical risk factors. A further 290 women with type 1 or 2 diabetes, chronic renal disease, or antiphospholipid syndrome were excluded as information about other established risk factors for preeclampsia in these conditions was not collected on all women. The resulting set of 1687 women had at least one of the following

criteria: a booking BMI >30 kg/m^2 in a first pregnancy, chronic hypertension or previous preeclampsia in the last pregnancy, or HELLP and/or eclampsia in any previous pregnancy.

These data were randomly divided in the ratio 2:1 into training (n = 1121) and validation (n = 566) subsets (21). The resulting data sets were inspected to ensure a reasonable balance of risk factors and outcomes between the two sets. All outcome data were removed from the validation set. The models were therefore developed on a training set where the outcomes were known and the findings tested on a validation set with unknown outcomes. Only after the models had been developed and the predictions made they were tested against the true outcomes in the validation set.

Clinical Explanatory Variables

The data set was reduced to 13 key predictive variables. To achieve this, variables were removed if they were redundant (e.g., height and weight replaced by BMI), not clinical risk factors (gestation recruited into VIP) or laboratory tests that were not available on all subjects. Following preliminary multivariable analyses in the training data set, several variables that were not significantly associated with the disease endpoints were also eliminated. These included randomization to vitamin C and E, parity, previous fetal loss, marital and employment status, educational qualifications, dipstick proteinuria, and low-dose aspirin or heparin/dalteparin usage during pregnancy.

The 13 explanatory variables used, all determined once only at trial entry (14^{+0}–21^{+6} weeks gestation), were chronic hypertension, previous preeclampsia, time of delivery with preeclampsia, maternal and paternal ethnicity, maternal age, SBP and DBP, BMI, smoking status, current antihypertensive therapy, and use of folate and multivitamin preparations. Chronic hypertension was defined as diastolic blood pressure ≥90 mmHg before 20 weeks or taking antihypertensive therapy prior to pregnancy or at recruitment. Preeclampsia in the last pregnancy and any previous HELLP or eclampsia were combined. Gestation of previous preeclampsia was categorized as <34 weeks, ≥34 weeks, and not applicable (no previous preeclampsia or nulliparous). Three categories of maternal and paternal ethnicity were used: African or Afro-Caribbean, Indian or Pakistani or Bangladeshi, and Caucasian/other. Women taking folate only in multivitamins were included as taking folate supplements.

Methods of Analysis

Clinical data are summarized as mean (SD) or number (percentages) and comparisons made using Student's t-test and χ^2-tests as appropriate. A p-value <0.05 was considered significant.

Overall approach to model development

Predictive models for the four endpoints defined above (preeclampsia, preeclampsia with early delivery, SGA, severe adverse perinatal outcome) were developed in the training data set and then evaluated in the validation data set, with the investigators blinded to pregnancy outcome at the validation stage. Overall performance on the training set was used to determine the

critical values to define a test-positive or test-negative woman for each endpoint. The performance of each model was determined by comparing disease predictions to actual pregnancy outcome for each woman and calculating the screening test characteristics in the validation set. To maintain blinding, this was carried out by an investigator (KKP) who played no other part in the development of the predictive tools.

Construction of predictive models

Three statistical approaches were taken in the construction of the predictive models. These were logistic regression [forward stepwise selection in combination with the Akaike Information Criterion (22), rather than statistical significance, to select variables for inclusion in the model], classification and regression trees (CART) (23), and Evolving Connectionist Systems (24).

The probabilities of early-onset preeclampsia and severe adverse perinatal outcome were calculated using the conditional probability formula as follows: where Pr(early-onset | preeclampsia) is the conditional probability of early-onset preeclampsia in women who developed preeclampsia (estimated by logistic regression on a subset of the data), and Pr(severe adverse perinatal outcome | SGA) is defined likewise (25):

$$\Pr(\text{early-onset preeclampsia}) = \Pr(\text{preeclampsia}) \times \Pr(\text{early-onset} \mid \text{preeclampsia})$$

$$\Pr(\text{severe adverse perinatal outcome}) = \Pr(\text{SGA}) \times \Pr(\text{severe adverse perinatal outcome} \mid \text{SGA})$$

For each approach, the training data were used to construct predictive models for the four endpoints. These models were then used to produce probabilities of being disease positive for each woman.

Model assessment and determination of critical values

The performance of each model was assessed in the training data across the full range of possible decision thresholds: 0.01, 0.02, 0.03, . . ., 0.99. The analysis was performed 10 times in the training data for each disease (10-fold cross-validation). In each of the 10 iterations, 90% of the training data were used to build a logistic regression model, which was then used to predict the probability of being disease positive for the remaining 10% of women. Five performance criteria were calculated at each proposed threshold: overall classification rate, sensitivity, specificity, positive predictive value, and negative predictive value.

Using the results of the training data, cut-points were selected for each endpoint. For each endpoint, the cut-point was determined by reviewing the performance criteria described above and considering the clinical implications of false-positive and false-negative tests within a framework of population screening (26). Specifically, we considered the number of women identified at risk and treated, the number who developed disease but were not detected, the number treated that were false positives and the overall number of women to benefit for each woman harmed through screening. The decision thresholds selected for the four endpoints were used for all further prediction model development.

Choice of statistical method

The performance of each statistical method (logistic regression, CART, and Evolving Connectionist Systems) was calculated in the training data set using the decision thresholds. A set of predictive models was generated for each disease. The statistical methods were then applied in a blinded fashion to the validation data set. For each woman in the validation set, the predictive models were used to calculate a risk score for each disease, as well as "disease Yes or No," using the cut-point determined in the training data.

RESULTS

Maternal characteristics investigated as clinical risk factors and the main outcomes in the training and validation sets are shown in Table 1. The distribution of risk factors was similar in the training and validation sets, except for a chance imbalance in randomized treatment with antioxidants 545 (49%) in the training set and 307 (54%) in the validation set, $p = 0.03$. As this variable was not associated with any disease endpoint, it was not included in the final set of explanatory variables. Overall, 16% developed preeclampsia, 3% early-onset preeclampsia, and 23% of babies were SGA, with 9% having a severe adverse perinatal outcome.

The relationship between chronic hypertension, previous preeclampsia, and obesity in first pregnancy is shown in Figure 1 for all 1687 women. Obesity in first pregnancy was the only trial entry criterion for 588 primiparous women, but an additional 450 women (143 primiparae, 307 multiparae) in the cohort also had a BMI of 30 kg/m^2 or greater. Forty-nine percent of the women with chronic hypertension and 31% of women with a past history of preeclampsia were obese.

Table 2 summarizes the incidence of preeclampsia and delivery of SGA babies in pregnancies affected by chronic hypertension, previous preeclampsia, or obesity, alone or in combination. The risk of early preeclampsia was lowest in obese primiparae without hypertension, and highest when previous preeclampsia and chronic hypertension occur together. Other outcomes showed less variation, but with the same general pattern.

Multiple logistic regression models were fitted for each outcome in the training set as described. Based on these data from the training set, together with interpretation of the results in accordance with the impact on screening a population (26), the following probability cut-points were selected; for preeclampsia 20%, early-onset preeclampsia 7%, SGA 25%, and for severe adverse perinatal outcome 10%. These cut-points reflects a clinical judgment on the relative importance of missing a case (a false negative) compared to a misclassifying a normal pregnancy as a case (a false positive). Specifically, a false negative was regarded as 4.0 times as important as a false positive for preeclampsia, 13.3 times for early-onset preeclampsia, 3.0 times for SGA, and 9.0 times for severe adverse perinatal outcome.

Once each model had been developed and its performance determined in the training set, it was then applied in a blinded fashion to the previously unused validation set. The three statistical methods: logistic regression, CART and Evolving Connectionist Systems, achieved similar performance in

Table 1: Characteristics at booking and outcome among training and validation groups.

Maternal characteristics	Training *n* = 1121	Validation *n* = 566	*p*-Value
Entry criteria			
Obesity in first pregnancy	490 (44%)	241 (43%)	0.658
Chronic hypertension	490 (44%)	251 (44%)	0.804
Previous preeclampsia in most recent pregnancy/HELLP/eclampsia	343 (31%)	161 (28%)	0.362
Age	30.8 (5.8)	30.3 (5.9)	0.062
Ethnicity of mother			0.094
White or other	972 (87%)	471 (83%)	
African or Afro-Caribbean	112 (10%)	66 (12%)	
Indian, Bangladeshi, or Pakistani	37 (3%)	29 (5%)	
Ethnicity of father			0.093
White or other	977 (87%)	474 (84%)	
African or Afro-Caribbean	103 (9%)	60 (11%)	
Indian, Bangladeshi, or Pakistani	41 (4%)	32 (6%)	
Smoking			0.256
Never	669 (60%)	317 (56%)	
Before pregnancy	215 (19%)	132 (23%)	
During pregnancy	98 (9%)	49 (9%)	
Current smoker	139 (12%)	68 (12%)	
Medication at booking visit			
Folate	478 (43%)	234 (42%)	0.610
Multivitamins	276 (25%)	135 (24%)	0.728
Antihypertensive therapy	189 (17%)	104 (18%)	0.438
Randomized to antioxidants	545 (49%)	307 (54%)	0.027
Time of delivery for preeclampsia in last pregnancy			0.451
<34 weeks	151 (13%)	86 (15%)	
≥34 weeks	233 (21%)	106 (19%)	
SBP (mmHg)	124 (15)	124 (15)	0.902
DBP (mmHg)	76 (11)	75 (11)	0.234
Body mass index (kg/m^2)	31.7 (6.9)	31.72 (6.72)	0.847
Outcomes			
Preeclampsia	190 (17%)	79 (14%)	0.196
Preeclampsia requiring early delivery (<34 weeks)	34 (3%)	21 (4%)	0.460
SGA	255 (23%)	140 (25%)	0.363
Severe adverse perinatal outcome*	104 (9%)	50 (9%)	0.765

*Defined as birthweight <1st customized centile or birthweight <10th customized centile complicated by either delivery before 34 weeks or a perinatal death.

the training data for all endpoints, with logistic regression having a slight advantage. Only results from the logistic regression are therefore shown.

Results for prediction of preeclampsia and early-onset preeclampsia are given in Tables 3 and 4. In the validation set, the pre-test probability of preeclampsia was 14%. Women were categorized using the clinical risk model; those with a negative test had a 9% post-test probability of disease and those with a positive test had a 24% chance of developing preeclampsia. Similarly,

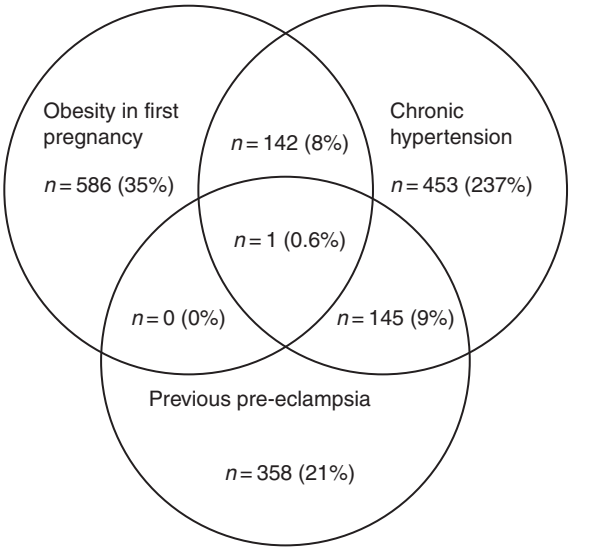

Figure 1: Venn diagram of the main clinical risk groups in the cohort.

there was a 3.7% overall probability of developing early-onset preeclampsia. If the test was positive, this became a 1 in 7 chance of delivery before 34 weeks because of preeclampsia and if negative, an estimated 1 in 50 women would develop early-onset preeclampsia. For both endpoints, sensitivity was close to 50%.

In the predictive model for preeclampsia, the explanatory variables associated with an increased risk were history of early-onset preeclampsia; Indian, Bangladeshi, or Pakistani ethnicity; systolic blood pressure; and chronic hypertension (Table 3). A reduced risk of preeclampsia was associated with folate supplementation and ethnicity other than Indian, Bangladeshi, Pakistani, African, or Afro-Caribbean.

Similar explanatory variables were associated with early-onset preeclampsia. The principal predictor was previous preeclampsia with delivery before 34 weeks: 11.0%, compared to 2.0%, risk ratio 5.49 [3.29, 9.15]. Indian, Bangladeshi, or Pakistani ethnicity; systolic blood pressure; and antihypertensive medication at recruitment were also associated with an increased risk of early-onset preeclampsia. No history of preeclampsia and ethnicity other than Indian, Bangladeshi, Pakistani, African, or Afro-Caribbean were associated with a reduced risk of early-onset preeclampsia. Folate supplementation was not included in the algorithm.

The performance of clinical algorithms to predict SGA or severe adverse perinatal outcome was less impressive (Tables 5 and 6). Explanatory variables associated with an increased risk of SGA were history of preeclampsia, Indian, Bangladeshi, or Pakistani ethnicity, systolic blood pressure, and antihypertensive medication at recruitment. For severe adverse perinatal outcome, early-onset preeclampsia; Indian, Bangladeshi, or Pakistani ethnicity; systolic blood pressure; and smoking at recruitment were associated with an increased risk, and a reduced risk was associated with folate use. The exact prediction formulae are given below Tables 3 and 5.

Table 2: Incidence of main outcomes in nulliparous and multiparous women with a single risk factor or combinations of risk factors (training and validation groups combined).

Risk group	*N*	Preeclampsia (%)	Early preeclampsia (%)	SGA (%)	Severe adverse perinatal outcome* (%)
Nulliparous women					
One risk factor					
BMI > 30	588	7	0.5	20	6
Chronic hypertension	132	19	6	27	10
Two risk factors					
Chronic hypertension and BMI > 30	142	23	4	18	10
Multiparous women					
One risk factor					
Chronic hypertension	164	15	1.2	23	7
Previous preeclampsia	265	21	4	29	10
Two risk factors					
Chronic hypertension and BMI > 30	157	21	2.5	20	9
Previous preeclampsia and BMI > 30	89	16	4	29	15
Chronic hypertension and previous preeclampsia	81	30	12	32	20
Three risk factors					
Chronic hypertension, previous preeclampsia, and BMI > 30	62	23	10	27	13
All women†	1680	16	3	23	9

*SGA with one or more of delivery <34 weeks, birthweight <1st centile or perinatal death.
†Seven primaparous women with pregnancy loss before 24 weeks because of preeclampsia are not shown.

DISCUSSION

Although it is widely recognized that obesity, chronic hypertension, and previous preeclampsia often occur together and that comorbidities may alter the risk for preeclampsia, this is the first large study of high-risk pregnancy women to provide information about the absolute risks of preeclampsia and customized SGA in the presence of different combinations of these conditions. The obesity epidemic has created a pressing need for better risk stratification information for obese women that could be applied daily in antenatal clinics in many countries (9,27).

A similar increase in the risk of preeclampsia in women with chronic hypertension and a history of previous preeclampsia (32%) compared with chronic hypertension alone (23%), OR 1.6 [1.1, 2.3] was reported in a cohort from a randomized trial conducted in the United States (12). Most other relevant studies have been retrospective epidemiological studies using hospital or government databases and have reported adjusted odds ratios, not absolute risk levels (2,8,13,28). In the recent Preeclampsia Community Guideline,

Table 3: Observed incidence of preeclampsia and early-onset preeclampsia (<34 weeks gestation), according to risk of disease, as predicted from clinical risk algorithms.

	Observed risk of preeclampsia		Observed risk of early-onset preeclampsia	
Predicted probability of disease estimated by algorithm*,† (%)	**Training set**	**Validation set**	**Training set**	**Validation set**
0–10	6% (21/351)	7% (14/187)	3% (17/1045)	3% (14/526)
10–20	17% (73/436)	11% (23/202)	19% (10/54)	8% (2/25)
20–30	25% (47/190)	17% (15/89)	27% (4/15)	30% (3/10)
30–40	30% (27/89)	31% (6/52)	0% (0/4)	25% (1/4)
40–50	38% (14/37)	18% (4/22)	100% (3/3)	100% (1/1)
50–60	75% (3/4)	60% (6/10)	– (0/0)	– (0/0)
60–70	– (0/0)	25% (1/4)	– (0/0)	50% (1/2)
70–100	– (0/0)	– (0/0)	– (0/0)	– (0/0)

The probability of disease can be calculated from log odds using the inverse logit function:
Pr(disease) = $e^{(\log\ odds)}/(1 + e^{(\log\ odds)})$, where e is the base of the natural log = 2.718281828. For early-onset preeclampsia, the product of the two probabilities is used.
CHT, chronic hypertension, determined by current or previous antihypertensive therapy of DBP >90 mmHg; HELLP, hemolysis, elevated liver enzymes, and low platelet count.
*Individual log odds for preeclampsia calculated as: –1.2422 + 0.4061 (if CHT) + 0.5071 (if DBP > 70) –0.3846 (if DBP > 90) + 0.8890 (if SBP > 120) + 0.7040 (if previous preeclampsia) – 0.4043 (if on folates) + 0.8311 (if mother is Indian, Bangladeshi, Pakistani, African, or Afro-Caribbean). All adjustments that apply are used.
†Individual conditional log odds for early-onset preeclampsia calculated as: –2.693 + 1.735 (if SBP > 140) + 1.004 (if on antihypertensive therapy) –0.9790 (if previous preeclampsia in most recent pregnancy | HELLP | eclampsia) + 2.121 (if previous preeclampsia with delivery before 34 weeks) + 1.285 (if mother is Indian, Bangladeshi, Pakistani, African, or Afro-Caribbean). All adjustments that apply are used.

insufficient data precluded calculation of absolute risks of preeclampsia in the presence of comorbidities (1).

We report an increased risk of customized SGA associated with obesity, as described previously (29). The risk of severe adverse perinatal outcome, with important morbidity for the infant, was surprisingly high. Of the women who delivered an SGA infant, there was a severe adverse perinatal outcome (defined as a birthweight <1% or resulting in delivery before 34 weeks or a perinatal death) in a third of women with either obesity, chronic hypertension, or a history of preeclampsia alone; the proportion of severe adverse perinatal outcome increased to close to half of the SGA infants when more than one clinical risk factor were present. In the predictive models, the ethnic group comprising Indian, Bangladeshi, or Pakistani women was associated with an increased risk of preeclampsia and SGA, despite adjustment for maternal size and ethnicity in the customized centiles. This suggests that these ethnic groups may have other independent risk factors for SGA.

The risk prediction algorithms for preeclampsia, SGA, and severe adverse perinatal outcome performed at a modest level, improving risk classification a little, but not sufficiently for implementation as a screening tool. The increase

Table 4: Prediction of preeclampsia and early-onset preeclampsia (before 34 weeks gestation), as predicted from clinical risk algorithms, based on observations made at 14–21 weeks gestation.

	Preeclampsia		Early-onset preeclampsia	
	Training set	**Validation set**	**Training set**	**Validation set**
Prevalence	17%	14%	3.0%	3.7%
Positive test results	30%	31%	10%	12%
Sensitivity	51%	53%	59%	48%
Specificity	74%	72%	92%	89%
Positive predictive value	29%	24%	18%	15%
Negative predictive value	88%	90%	98.6%	97.8%
Positive likelihood ratio	1.98	1.92	6.95	4.49
Area under ROC curve	0.70	0.66	0.85	0.81

A positive test is taken as probability >20% for preeclampsia, and >7% for early-onset preeclampsia.

Table 5: Observed incidence of small for gestational age (SGA, birthweight less than 10th adjusted birthweight centile) and severe adverse perinatal outcome (SGA with delivery <34 weeks gestation, birthweight <1st centile or perinatal death) according to risk of disease, as predicted from clinical risk algorithms, based on observations made before 22 weeks gestation.

	Observed risk of SGA		Observed risk of severe adverse perinatal outcome	
Predicted probability of disease, estimated by algorithm*,† (%)	**Training set**	**Validation set**	**Training set**	**Validation set**
0–10	5% (2/37)	40% (8/20)	5% (35/694)	6% (21/333)
10–20	14% (55/383)	19% (36/188)	14% (47/348)	11% (19/180)
20–30	24% (29/454)	237% (46/203)	29% (17/58)	13% (5/39)
30–40	30% (52/171)	35% (37/107)	17% (3/17)	46% (5/11)
40–50	75% (12/16)	24% (9/37)	50% (2/4)	0% (0/3)
50–60	67% (2/3)	36% (4/11)	– (0/0)	– (0/0)
60–100	– (0/0)	– (0/0)	– (0/0)	– (0/0)

The probability of disease can be calculated from log odds using the inverse logit function: Pr(disease) = $e^{(\log\ odds)}/(1 + e^{(\log\ odds)})$, where e is the base of the natural log = 2.718281828. For severe adverse perinatal outcome, the product of the two probabilities is used.

BMI, body mass index (kg/m^2).

*Individual log odds of SGA calculated as: –2.0494 + 0.6705 (if SBP > 105) + 0.5382 (if SBP > 130) –0.3001 (if BMI ≥ 35) –0.4143648 (if on folates) + 0.4801764 (if mother smoked in pregnancy) + 0.7150611 (if previous preeclampsia) + 0.3676 (if mother is Black) + 1.141 (if mother is Asian). All adjustments that apply are used.

†Individual conditional log odds of severe adverse perinatal outcome calculated as: –1.897694 + 1.317 (if SBP > 105) + 0.4304 (if SBP > 130) –0.7186 (if age ≥ 25) + 0.7012 (if age ≥ 30) + 0.6124 (if on antihypertensives) + 0.8348 (if mother is Indian, Bangladeshi, Pakistani, African, or Afro-Caribbean). All adjustments that apply are used.

Table 6: Prediction of small for gestational age (SGA, birthweight less than 10th adjusted birthweight centile) and severe adverse perinatal outcome (SGA with delivery <34 weeks gestation, birthweight <1st centile or perinatal death), as predicted from clinical risk algorithms, based on observations made at 14–21 weeks gestation. A positive test is taken as probability >25% for SGA, and >10% for severe adverse perinatal outcome.

	SGA		Severe adverse perinatal outcome	
	Training set	**Validation set**	**Training set**	**Validation set**
Prevalence	23%	25%	9%	9%
Positive test	33%	39%	38%	41%
Sensitivity	51%	49%	66%	58%
Specificity	73%	65%	65%	60%
Positive predictive value	36%	32%	16%	12%
Negative predictive value	84%	80%	94%	94%
Positive likelihood ratio	1.87	1.40	1.88	1.47
Area under ROC curve	0.65	0.57	0.73	0.66

in pre-test prevalence of preeclampsia from 14% to a post-test probability of 24% is consistent with crossing an intervention threshold, but the sensitivity of 53%, precludes clinical application. The algorithm did allow identification of a subgroup of women where the risk of early-onset preeclampsia was 15%, in contrast to a pre-test prevalence of 3.7% (positive likelihood ratio, 4.49) and area under the receiver operator curve of 0.81.

Papageorghiou and coworkers reported results similar to those in our study from 17,480 "low-risk" women who completed a maternal history questionnaire and received uterine artery Doppler velocimetry (5,29). This "low-risk" population included hundreds of women with chronic hypertension, diabetes, renal disease, and previous preeclampsia, but the overall incidence of preeclampsia was 2% as outcomes for these at-risk women were diluted by those from the large numbers of healthy multiparous women in the cohort. In the same study, maternal factors alone gave an ROC area of 0.66 for detecting preeclampsia, increasing to 0.79 when the maternal history was combined with the results from uterine Doppler wave form analysis. Likelihood ratios associated with chronic hypertension, previous preeclampsia, and increased BMI were 12.5, 3.2, and 2.2, respectively, but the authors reported no association between any pair of variables, and absolute risk levels for these conditions were not provided. In a further study of 32,157 low-risk women by the same group, maternal characteristics (e.g., age, ethnicity) and uterine artery Doppler findings predicted preeclampsia with an AUC of 0.798 in a validation data set (30).

The absence of an association between aspirin prophylaxis and preeclampsia might seem at variance with the results of a recent meta-analysis of randomized controlled trials (17). However, in this study, aspirin was most commonly prescribed to women at higher risk, confounding any real benefit of treatment. We are confident that any possible effect of high-dose antioxidants on pregnancy outcome is modest, when compared to the differences associated with increments in the risk scores developed here, and that it is therefore reasonable to include women on both placebo and active treatment.

One of the strengths of the present study is the innovative statistical methodology, unusual among prediction studies for preeclampsia, and SGA. By dividing the data strictly into training and validations sets, we have demonstrated the test performance without risk of misrepresenting the results by overfitting. When determining the cut-off criterion for an abnormal test, the clinical implications of false-positive and false-negative test results were considered (26,31). The cut-off criterion determines the balance between detecting most women who will develop disease at the expense of incorrectly informing some women they are at risk (preserving sensitivity at the expense of specificity), versus failing to identify some women who will develop disease in order to reduce false positives (accepting lower sensitivity, to retain specificity). The relative importance of these alternatives is population dependent and influenced by the severity of the disease being predicted. For example, lower sensitivity may be acceptable if the disease outcome is "all disease," whereas high sensitivity is important for severe disease resulting in preterm birth or death. To better understand the implications of an abnormal screening test we undertook a harm–benefit analysis. The cut-off for an abnormal test was determined after reviewing the classification rate, sensitivity, specificity, positive and negative predictive values plotted against a series of cut-points, and then applied a series of cut-points to a theoretical population of high-risk pregnant women who would receive low-dose aspirin in response to a positive screening test (17,26). Such an exploration allows the investigator to better appreciate the clinical impact of the screening test under study, and this knowledge can then be factored into the decision where to set the cut-point to define an abnormal test.

A further strength of this study is that data were collected as part of a randomized trial, in which carefully collected diagnoses of clinical risk factors were used, with rigorous definitions of preeclampsia, including confirmation of the diagnosis by senior clinical staff acting independently. Previous reports have often relied on hospital event coding or discharge coding, both known to be fraught with inaccuracies (32). Although this gave us the confidence that the diagnoses were accurate, a potential limitation was that information was restricted to certain groups of women at high risk of preeclampsia. Other high-risk conditions—multiple pregnancy, diabetes, kidney disease, and antiphospholipid syndrome—are excluded as detailed information relevant to prediction of these conditions was not available.

It is a limitation of the study that our conclusions are limited to women with one or more of the risk factors: obesity in first pregnancy, chronic hypertension, or previous preeclampsia, but not any of multiple pregnancy, diabetes, kidney disease, or antiphospholipid syndrome. It must be noted that obesity was present as a comorbidity in 49 and 30% of the chronic hypertension and previous preeclampsia entry criteria groups, respectively. Fifty-two percent of the eligible women approached in the VIP study provided complete data.

In this study, there was no difference in the occurrence of preeclampsia by randomized treatment; the differences in neonatal outcomes between the groups were small by comparison with those according to the clinical risk factors used and not significant or close to significance in the multiple regression

models. Because of the importance of having an adequate sample size, it was decided to include them. Subsequent meta-analysis of a number of trials of antioxidants has shown no significant differences in SGA infants by randomized treatment (33).

In this study, information for the different combinations of previous preeclampsia, obesity and hypertension were sometimes available only for nulliparae and sometimes only for multiparae. However, our other publications suggest that parity is in itself not a major risk factor (29,34).

The goal of screening for preeclampsia or SGA in high-risk women is to reclassify accurately the risk status of women into those at higher risk in whom intensive surveillance and intervention are warranted and those at lower risk where reassurance and less-intensive surveillance is appropriate (7). Although there has been considerable research on individual biomarkers to predict preeclampsia, the role of combinations of clinical risk factors with biomarkers in high-risk women is little explored (7,35). August and coworkers developed a prediction model for preeclampsia using 110 women with chronic hypertension, using measurements of uric acid, low plasma renin activity, and systolic BP (35). The sensitivity and specificity were similar to those achieved here in a more varied high-risk population using clinical risk factors alone. There is therefore also the potential to improve the performance of the predictive algorithms in our high-risk cohort such as through the addition of blood biomarkers to the clinical risk factors and this warrants further study (36).

CONCLUSIONS

This large cohort of high-risk women enabled development of models to predict preeclampsia and SGA based on clinical risk factors. Obesity, chronic hypertension, and previous preeclampsia increase a woman's risk of preeclampsia and SGA, and the presence of comorbidities modifies the level of risk. Severe adverse perinatal outcome was surprisingly common in these women, possibly reflecting use of customized centiles. Combining clinical risk factors improved early identification of women at risk of developing early-onset preeclampsia. The addition of biomarkers to clinical risk factors is likely to lead to further improvements in risk classification of high-risk women.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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