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Population screening for gestational hypertensive disorders using maternal, fetal and placental characteristics: A population-based prospective cohort study

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Abstract

Objective: To determine screening performance of maternal, fetal and placental characteristics for selecting pregnancies at risk of gestational hypertension and preeclampsia in a low-risk multi-ethnic population.

Method: In a prospective population-based cohort among 7124 pregnant women, we collected maternal characteristics including body mass index, ethnicity, parity, smoking and blood pressure in early-pregnancy. Fetal characteristics included second and third trimester estimated fetal weight and sex determined by ultrasound. Placental characteristics included first and second trimester placental growth factor concentrations and second and third trimester uterine artery resistance indices.

Results: Maternal characteristics provided the best screening result for gestational hypertension (area-under-the-curve [AUC] 0.79 [95% Confidence interval {CI} 0.76-0.81]) with 40% sensitivity at 90% specificity. For preeclampsia, the maternal characteristics model led to a screening performance of AUC 0.74 (95% CI 0.70-0.78) with 33% sensitivity at 90% specificity. Addition of second and third trimester placental ultrasound characteristics only improved screening performance for preeclampsia (AUC 0.78 [95% CI 0.75-0.82], with 48% sensitivity at 90% specificity).

Conclusion: Routinely measured maternal characteristics, known at the start of pregnancy, can be used in screening for pregnancies at risk of gestational hypertension or preeclampsia within a low-risk multi-ethnic population. Addition of combined second and third trimester placental ultrasound characteristics only improved screening for preeclampsia.

1 | INTRODUCTION

Gestational hypertensive disorders (GHD) are common complications affecting 5% to 10% of pregnancies and are major risk-factors for maternal and fetal mortality and morbidity.[1-4] Up to 50% of women with gestational hypertension will be diagnosed with preeclampsia.[5] Screening for women at risk of GHD may provide an opportunity for intensified monitoring, leading to earlier diagnosis and possible interventions before severe disease develops.

Several maternal, fetal and placental characteristics are associated with the risks of GHD.[5-9] First trimester screening models for GHD have been developed, using different screening parameters.[10] "Simple" first trimester screening models mainly consist of maternal characteristics such as age, body mass index (BMI), parity, and medical or obstetric history.[11] More advanced first trimester screening models, which next to maternal characteristics often consist of biophysical and biochemical parameters, such as uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and biomarkers, report higher area-under-the-receiver-operating-characteristic (ROC) curves.[6,12] Performances of these advanced parameters vary among studies, which may be partly explained by differences in population characteristics. Many studies have focused on Caucasian women and specifically selected high-risk women, including multiparous women with previous pregnancy complications, nulliparous women or women with a high BMI. Restrictions to specific populations limit translation to clinical practice, and replication of obtained screening performance remains challenging.

We first assessed the potential of routinely measured maternal characteristics known in early-pregnancy, for screening of gestational hypertension and preeclampsia within a multi-ethnic population-based prospective cohort study among 7124 low-risk pregnancies. Next, we further explored whether the addition of detailed fetal biometry measurements, placental Doppler vascular resistance indices and placental biomarkers, obtained throughout pregnancy, further improved screening of gestational hypertension and preeclampsia.

What is already known on this topic?

- Several maternal, fetal and placental characteristics are associated with the risks of gestational hypertension and preeclampsia.
- Screening of the general population for gestational hypertensive disorders in clinical practice remains highly challenging.

What does this study add?

- Maternal characteristics known at the start of pregnancy can be used for screening for gestational hypertensive disorders.
- Addition of combined second and third trimester placental ultrasound screening results only improved screening performance for preeclampsia, in addition to simple maternal characteristics.

2 | METHODS

2.1 | Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early-pregnancy onwards in Rotterdam, the Netherlands.[13] The study was approved by the local Medical Ethical Committee (MEC 198.782/2001/31). Written consent was obtained from participating women. Pregnant women were enrolled between 2001 and 2006. Response rate at birth was 61%. In total, 8879 women were enrolled during pregnancy. We excluded non-singleton live-births, women with pre-existing hypertension and women without information on GHD, leading to 7124 pregnant women (Figure S1).

2.2 | Maternal, fetal and placental characteristics used for screening

2.2.1 | Maternal characteristics in early-pregnancy

We selected maternal characteristics, known in early-pregnancy, associated with GHD.[14] Maternal age was assessed at enrolment and categorized: <25.0 years, 25.0 to 34.9 years and ≥35.0 years.[15] Maternal height and weight were measured without shoes and heavy clothing at enrolment. BMI was calculated and categorized: normal weight (BMI < 25 kg/m^2), overweight (BMI 25.0-30.0 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2).[16] Information about ethnicity (categorized as previously described), parity (nulliparous or multiparous) and smoking status (non-smoking, early-pregnancy-only and continued smoking) was obtained at enrolment by questionnaire.[14,15,17,18] Blood pressure was measured at a median 13.8 (IQR 12.4-16.1) weeks gestation using Omron-907 automated digital oscillometer sphygmomanometer (OMRON Healthcare Europe, Hoofddorp, the Netherlands). The mean value of two blood pressure readings over a 60-second interval was documented.[19,20] As blood pressure is part of the diagnosis of GHD, only blood pressure measured <20th weeks gestation was used.

2.2.2 | Fetal characteristics

Ultrasound examinations were carried out in two dedicated research centres in first (median 13.2 [IQR 12.2-14.7] weeks), second (median 20.5 [IQR 19.9-21.3] weeks) and third trimester (median 30.3 [IQR 29.8-30.9]weeks). We established gestational age from the first ultrasound examination.[15] Estimated fetal weight (EFW) was calculated

according to Hadlock et al.[21] Gestational age-adjusted standard-deviation-scores (SDS) for EFW was based on reference growth charts from the whole study population, and represent the equivalent of z-scores.[15] We defined screen-positive as EFW < 10th percentile in second or third trimester.

2.2.3 | Placental characteristics

Uterine artery resistance index (UtA-RI) was derived from flow velocity waveforms in second and third trimester.[22-25] We defined screen-positive UtA-RI as UtA-RI SDS value in the highest decile. Placental growth factor (PlGF) was measured in first and second trimester maternal venous blood samples at a median of 13.2 (IQR 12.2-14.9) and 20.3 (IQR 19.9-21.07), respectively.[26,27] Gestational-age-adjusted multiples of the medians (MoM) were calculated.[26,27] Screen-positive was defined as first or second trimester PlGF MoM in the lowest decile.

2.3 | Gestational hypertensive disorders

Information about GHD was obtained from medical records.[28] Occurrence of hypertension and related complications were cross-validated using hospital registries, and defined using criteria of the International Society for the Study of Hypertension in Pregnancy.[28,29] Gestational hypertension (n = 273, 3.8%) was defined as de-novo hypertension (blood pressure ≥ 140/90 mmHg), appearing >20 weeks gestational age. Preeclampsia (n = 149, 2.1%) was defined as de-novo hypertension (blood pressure ≥ 140/90 mmHg) after 20 weeks gestation with concurrent proteinuria. As secondary outcome, we defined early-onset preeclampsia (n = 14, 0.2%) as preeclampsia with a delivery <34 weeks gestational age based on our available data.[30] Any GHD was defined as either gestational hypertension or preeclampsia.

2.4 | Statistical analyses

Because our study is focused on screening for GHD in a low-risk population, we aimed to use maternal, fetal and placental characteristics which are obtained routinely or are simple and relatively cost-effective to obtain where possible, to enable simple translation of findings to clinical practice. Therefore, we first constructed a baseline model, consisting of maternal characteristics known in early-pregnancy and associated with GHD, including maternal age, BMI, ethnicity, parity and smoking to assess the screening potential of a simple maternal characteristics model. To evaluate the additional effect of first trimester blood pressure, we added first trimester MAP, per 10 mmHg, to the baseline model. Second, as fetal ultrasounds are routinely available in second trimester and often in third trimester, we added fetal parameters to the model: fetal sex and second trimester and/or third trimester EFW screening result. Next, we added placental parameters, which are not routinely available during pregnancy in low-risk populations: second and/or third trimester UtA-RI screening result and first and/or second trimester screening result of PlGF. We assessed the variance explained for each logistic regression model. We obtained predicted values from these regression models and assessed model performance via ROC curves and calculation of area-under-the-curve (AUC), along with the sensitivity at different false-positive-rates (1-specificity). Positive predictive values (PPV) and negative predictive values (NPV) and positive likelihood ratios (PLR) and negative likelihood ratios (NLR) at a 10% false-positive-rate (90% specificity) were calculated from the models. To compare model performance of different models, we assessed whether the change in effect size of obtained AUCs from the different models was clinically relevant and statistically significant. Based on previous studies focused on screening for similar adverse outcomes, we considered an approximate 4% to 5% change in AUC as clinically relevant, as this change is likely associated with a detectable increase in sensitivity.[11,31,32] When model comparison fulfilled this criterion, we tested whether this change was statistically significant using the test of DeLong et al.[33] When addition of a characteristic clinically and statistically significantly improved screening performance of the model, this characteristic was included and used as a new baseline model for further analyses. Screening models were developed for gestational hypertension and any preeclampsia separately. As secondary outcome, we explored the screening performance of these characteristics for early-onset preeclampsia separately. We performed two sensitivity analyses to assess the robustness of our findings: (a) we assessed model performance when we used "any gestational hypertensive disorder" as outcome; (b) we explored if we obtained similar screening models if we added screening characteristics to the baseline model, in order of their occurrence during pregnancy, instead of based on clinical availability within a low risk population. Missing values were dealt with by adding a missing category for each maternal and fetal characteristic to the models, which resembles clinical practice. Analyses were performed using Statistical Package of Social Sciences version 24.0 for Windows (IBM Corp., Armonk, New York).

3 | RESULTS

3.1 | Population characteristics

Table 1 shows population characteristics according to presence of gestational hypertension or preeclampsia. Table S1 shows population characteristics according to presence of early-onset preeclampsia and any GHD.

3.2 | Screening for gestational hypertension using maternal, fetal and placental characteristics

Maternal early-pregnancy characteristics had a moderate screening performance for gestational hypertension (AUC0.73 [95% Confidence interval {CI} 0.70-0.76]) (Figure 1). Model performance improved

TABLE 1 Characteristics of mothers and their children (n = 7124)

Maternal characteristics	No gestational hypertensive disorders n = 6702	Preeclampsia n = 149	*P*-value[a]	Gestational hypertension n = 273	*P*-value[b]
Age (years)					
< 25, no. (%)	1364(20.4)	30(20.1)	0.07	47(17.2)	0.60
25–35, no. (%)	4364(65.1)	102(68.5)		188(68.9)	
> 35, no. (%)	974(14.5)	17(11.4)		38(13.9)	
Height, mean (SD) (cm)	167.3(7.3)	165.9(7.2)	0.03	168.8(6.9)	<0.01
Weight, mean (SD) (kg)	68.3(12.5)	72(16.1)	<0.01	78.4(17.8)	<0.01
Body mass index, mean (SD) (kg/m^2)					
Normal, no. (%)	4298(64.1)	70(47.0)	<0.01	115(42.1)	<0.01
Overweight, no. (%)	1661(24.8)	47(31.5)		77(28.2)	
Obese, no. (%)	698(10.4)	30(20.1)		79(28.9)	
Education, no. higher education (%)	2720(40.6)	41(27.5)	0.05	108(39.5)	0.19
Race / ethnicity					
Dutch or European, no. (%)	3232(58.2)	75(53.6)	0.18	198(73.6)	<0.01
Surinamese, no. (%)	561(8.8)	19(13.6)		23(8.6)	
Turkish, no. (%)	575(9.0)	11(7.9)		11(4.1)	
Moroccan, no. (%)	431(6.7)	5(3.6)		8(3.0)	
Cape Verdean or Dutch Antilles, no. (%)	469(7.3)	17(12.2)		12(4.5)	
Parity, no. nulliparous (%)	3667(55.2)	117(79.1)	<0.01	208(76.2)	<0.01
Smoking, no. (%)					
None, no. (%)	4265(72.1)	97(74.0)	0.09	173(70.0)	0.67
Early-pregnancy only, no. (%)	531(9.0)	17(13.0)		26(10.5)	
Continued, no. (%)	1121(18.9)	17(13.0)		48(19.4)	
Mean systolic blood pressure, median (IQR), mmHg	114(107-122)	120 (112-128)	<0.01	124(116-132)	<0.01
Mean diastolic blood pressure, median (IQR), mmHg	67(61-73)	73(66-80)	<0.01	75(70-83)	<0.01
Mean arterial pressure, median (IQR), mmHg	82.7(77.0-88.7)	88.3(81.4-95.3)	<0.01	91.3(85-98.5)	<0.01
Estimated fetal weight, mean (SD) (g)					
Second trimester, mean (SD), SDS	−0.15(0.96)	−0.20(0.87)	0.52	0.00(1.08)	0.03
Second trimester, mean (SD), (g)	371(86)	376(90)		383(92)	
Third trimester, mean (SD), SDS	0.00(0.98)	−0.19(1.17)	<0.01	0.15(1.18)	0.08
Third trimester, mean (SD), (g)	1612(255)	1550(249)		1639(255)	
Placental growth factor					
First trimester, median (IQR) MOM	1.01(0.76-1.35)	0.80(0.59-1.13)	<0.01	0.92(0.68-1.15)	0.07
First trimester, median (IQR), ng/ml	43.5(29.2-73.0)	35.5(23.2-57.58)		35.2(26.4-60.0)	
Second trimester, median (IQR), MOM	1.00(0.73-1.39)	0.71(0.50-1.11)	<0.01	0.86(0.65-1.17)	<0.01
Second trimester, median (IQR), ng/ml	199.3(145.4-286.9)	145.8(93.9-213.4)		174.0(131.6-244.1)	
Uterine artery resistance index					
Second trimester, mean (SD), SDS	−0.01(0.99)	0.53(1.27)	<0.01	0.02(1.10)	0.76
Second trimester, mean (SD)	0.54(0.09)	0.59(0.11)		0.54(0.10)	
Third trimester, mean (SD), SDS	−0.01(0.99)	0.75(1.43)	<0.01	−0.14(1.00)	0.14
Third trimester, mean (SD)	0.48(0.08)	0.54(0.11)		0.47(0.08)	

Abbreviation: IQR: inter quartile range.

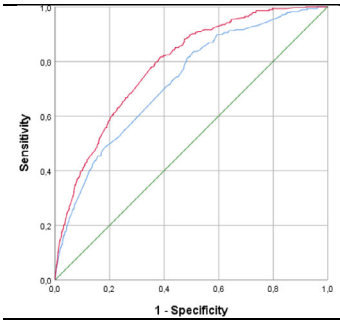
Note: Values are observed data and represent means (SD), medians (IQR) or number of subjects (valid %). Differences in subject characteristics between participants with and without gestational hypertensive disorders were evaluated using one-way ANOVA tests for continuous variables and chi-square tests for categorical variables.

[a]*P*-value for comparison of population characteristics among women without gestational hypertensive disorders and with pre-eclampsia.

[b]*P*-value for comparison of population characteristics among women without gestational hypertensive disorders and with gestational hypertension.

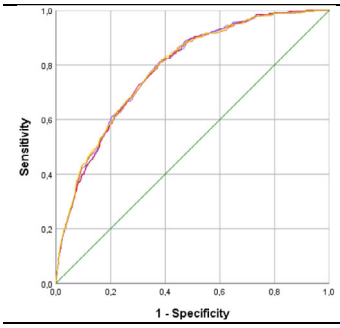
significantly when blood pressure was added (AUC 0.79 [95% CI 0.76-0.81], *P*-value for model comparison to maternal characteristics model: 0.003). Using this model led to 40% sensitivity at 90% specificity with PPV of 0.14, NPV of 0.97, PLR of 4, and NLR of 0.67. Table S2 shows effect estimates for the maternal characteristics in this model for the risk of gestational hypertension. The maternal

Models based on maternal characteristics



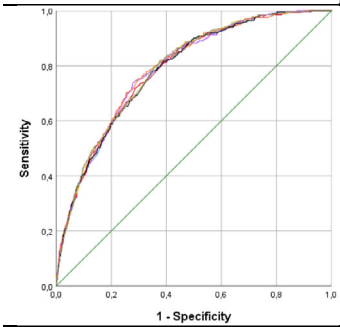
Models†	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Maternal characteristics: (Blue line)	0.73 (0.70-0.76)			
Blood pressure: (Red line)	0.79 (0.76-0.81)	69%	58%	40%

Models based on maternal and fetal characteristics



Models‡	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Baseline: (Blue line)	0.79 (0.76-0.81)	69%	58%	40%
Fetal sex: (Red line)	0.79 (0.76-0.81)			
2nd trimester EFW: (Purple line)	0.79 (0.76-0.81)			
3rd trimester EFW: (Orange line)	0.79 (0.76-0.81)			
2nd and 3rd trimester EFW: (Yellow line)	0.79 (0.76-0.81)			

Models based on maternal and placental characteristics



Models§	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Baseline: (Blue line)	0.79 (0.76-0.81)	69%	58%	40%
2nd trimester UtA-RI: (Red line)	0.79 (0.76-0.81)			
3rd trimester UtA-RI: (Purple line)	0.79 (0.77-0.82)			
2nd and 3rd trimester UtA-RI: (Orange line)	0.79 (0.77-0.82)			
1st trimester PlGF: (Yellow line)	0.79 (0.77-0.82)			
2nd trimester PlGF: (Black line)	0.79 (0.76-0.81)			
1st and 2nd trimester PlGF: (Gray line)	0.79 (0.77-0.82)			

AUC: area under the curve; CI: confidence interval; EFW: Estimated fetal weight; PlGF: Placental Growth Factor; UtA-RI: Uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity.

† Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking;
Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mm Hg.

‡ Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mm Hg;
Fetal sex model: Baseline model + fetal sex;
2nd trimester EFW model: Baseline model and 2nd trimester estimated fetal weight <10th percentile;
3rd trimester EFW model: Baseline model and 3rd trimester estimated fetal weight <10th percentile;
2nd and 3rd trimester EFW model: Baseline model, 2nd and 3rd trimester estimated fetal weight <10th percentile.

§ Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mm Hg;
2nd trimester UtA-RI model: Baseline model, 2nd trimester uterine artery resistance index >90th percentile;
3rd trimester UtA-RI model: Baseline model, 3rd trimester uterine artery resistance index >90th percentile;
2nd and 3rd trimester UtA-RI model: Baseline model, 2nd and 3rd trimester uterine artery resistance index >90th percentile.
1st trimester PlGF model: Baseline model, 1st trimester placental growth factor < 10th percentile;
2nd trimester PlGF model: Baseline model, 2nd trimester placental growth factor < 10th percentile;
1st and 2nd trimester PlGF model: Baseline model, 1st and 2nd trimester placental growth factor < 10th percentile.

FIGURE 1 Legend on next page.

characteristics model (with blood pressure in early-pregnancy) was used as baseline model for further analyses. Addition of fetal or placental screening results to the maternal characteristics model did not improve screening performance. When adding screening characteristics in chronological order to the screening model for gestational hypertension, the best model did not change (Figure S2).

3.3 | Screening for preeclampsia using maternal, fetal and placental characteristics

Maternal characteristics model had a moderate screening performance (AUC 0.70 [95% CI 0.66-0.74]) for preeclampsia (Figure 2). Addition of blood pressure to the model led to a higher AUC (0.74 [95% CI 70-0.79]), but the difference was not statistically significant. Using this model, we obtained a sensitivity of 33% at 90% specificity. Table S2 shows the effect estimates for the included maternal characteristics in this model for the risk of preeclampsia. Addition of fetal characteristics did not improve screening for preeclampsia in comparison to the maternal characteristics model including early-pregnancy blood pressure. Addition of both second and third trimester UtA-RI led to a clinically improved screening performance (AUC 0.78 [95% CI 0.75 to 0.82]), sensitivity 48% at 90% specificity, PPV of 0.09, NPV of 0.99, PLR of 4.8, NLR of 0.58, *P*-value for comparison with maternal characteristics model including early-pregnancy blood pressure < 0.01, Figure 2]. Subsequent addition of first or second trimester PlGF did not further improve model performance. Figure S2 shows that when adding screening characteristics in chronological order to the screening model for any preeclampsia, the addition of second trimester PlGF clinically and significantly improved the maternal characteristics with blood pressure model. Subsequent further addition of second and third trimester UtA-RI improved model performance (AUC 0.80 [95% CI 0.77 to 0.84]). This obtained model did not perform better in screening for preeclampsia than the obtained model based on clinical availability including maternal characteristics, blood pressure and second and third trimester UtA-RI only (*P*-value for comparison >0.05).

Maternal characteristics with blood pressure achieved a good performance for the secondary outcome early-onset preeclampsia (AUC 0.86 [95% CI 0.78-0.94] with a sensitivity 57% at 90% specificity), which was better than screening for preeclampsia at any gestational age (Figure 3). Addition of third trimester EFW screening result, but not other fetal or placental characteristics, clinically significantly improved model performance (AUC 0.95 [95% CI 0.91-0.99], sensitivity 86% at 90% specificity, *P*-value for comparison to the maternal characteristics model including early-pregnancy blood pressure: 0.039). When adding screening characteristics in chronological order to the screening model for early-onset preeclampsia, the best model did not change (Figure S3).

When we assessed screening for any GHD, we observed a moderate model performance for maternal characteristics including blood pressure (AUC 0.77 [95% CI 0.74-0.79], Figure S4). Addition of fetal or placental characteristics did not improve screening. When adding screening characteristics in chronological order to the screening model for any GHD, the best model did not change (Figure S3).

4 | DISCUSSION

4.1 | Main findings

Maternal characteristics including age, BMI, ethnicity, parity, smoking and blood pressure known in early-pregnancy have a moderate screening performance for pregnancies at risk of gestational hypertension and preeclampsia in a low risk multi-ethnic population. Addition of combined second and third trimester placental ultrasound screening results only improved screening performance for preeclampsia, in addition to simple maternal characteristics.

4.2 | Interpretation of main findings

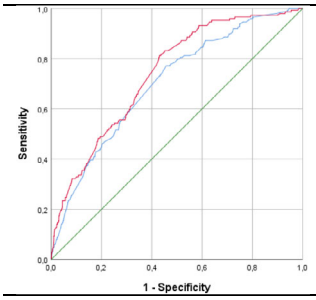
GHD are a major cause of maternal, fetal and neonatal morbidity and mortality.[2,3,5,7] It is well known that maternal, fetal and placental characteristics are associated with GHD, but the strength of associations of different factors varies across studies and populations.[11,34,35] Based on these associations, screening models for GHD can be developed using groups of screening parameters, which may aid earlier

FIGURE 1 Screening performance for gestational hypertension based on maternal, fetal and placental characteristics. AUC, area under the curve; CI, confidence interval; EFW, estimated fetal weight; PlGF, placental growth factor; UtA-RI, uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity. †Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking; Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mmHg. ‡Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mmHg; Fetal sex model: Baseline model + fetal sex; second trimester EFW model: Baseline model and second trimester estimated fetal weight <10th percentile; third trimester EFW model: Baseline model and third trimester estimated fetal weight <10th percentile; second and third trimester EFW model: Baseline model, second and third trimester estimated fetal weight <10th percentile. §Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mmHg; second trimester UtA-RI model: Baseline model, second trimester uterine artery resistance index >90th percentile; third trimester UtA-RI model: Baseline model, third trimester uterine artery resistance index >90th percentile; second and third trimester UtA-RI model: Baseline model, second and third trimester uterine artery resistance index >90th percentile. First trimester PlGF model: Baseline model, first trimester placental growth factor <10th percentile; second trimester PlGF model: Baseline model, second trimester placental growth factor <10th percentile; first and second trimester PlGF model: Baseline model, first and second trimester placental growth factor <10th percentile [Colour figure can be viewed at wileyonlinelibrary.com]

identification of women at risk of GHD. However, screening of the general population of pregnant women for GHD in clinical practice remains highly challenging.

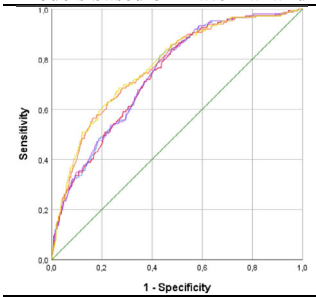
Previous studies have focused on using maternal characteristics for the prediction of preeclampsia, whereas fewer studies have focused on prediction of gestational hypertension.[11,34,36-38] A previous

Models based on maternal characteristics



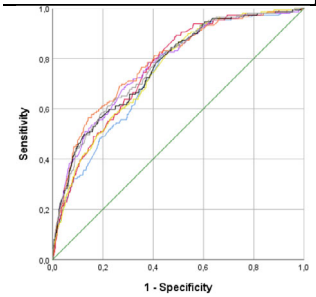
Models†	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Maternal characteristics: (Blue line)	0.70 (0.66-0.74)	55%	45%	28%
Blood pressure: (Red line)	0.74 (0.70-0.78)	58%	49%	33%

Models based on maternal and fetal characteristics



Models‡	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Baseline: (Blue line)	0.74 (0.70-0.78)	58%	49%	33%
Fetal sex: (Red line)	0.74 (0.70-0.76)			
2nd trimester EFW: (Purple)	0.74 (0.70-0.78)			
3rd trimester EFW: (Orange line)	0.77 (0.73-0.81)			
2nd and 3rd trimester EFW: (Yellow line)	0.77 (0.74-0.81)			

Models based on maternal and placental characteristics



Models§	AUC (95% CI)	Sensitivity at specificity 70%	80%	90%
Baseline: (Blue line)	0.74 (0.70-0.78)	58%	49%	33%
2nd trimester UtA-RI: (Red line)	0.76 (0.73-0.80)			
3rd trimester UtA-RI: (Purple line)	0.77 (0.74-0.81)			
2nd and 3rd trimester UtA-RI: (Orange line)	0.78 (0.75-0.82)	71%	61%	48%
2nd and 3rd trimester UtA-RI and 1st trimester PlGF: (Yellow line)	0.79 (0.75-0.83			
2nd and 3rd trimester UtA-RI and 2nd trimester PlGF: (Black line)	0.80 (0.77-0.84)			
2nd and 3rd trimester UtA-RI and 1st and 2nd trimester PlGF: (Gray line)	0.80 (0.77-0.84)			

AUC: area under the curve; CI: confidence interval; EFW: Estimated fetal weight; PlGF: Placental Growth Factor; UtA-RI: Uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity.

†Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking;
Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mm Hg.

‡ Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mm Hg;
Fetal sex model: Baseline model + fetal sex;
2nd trimester EFW model: Baseline model and 2nd trimester estimated fetal weight <10th percentile;
3rd trimester EFW model: Baseline model and 3rd trimester estimated fetal weight <10th percentile;
2nd and 3rd trimester EFW model: Baseline model, 2nd and 3rd trimester estimated fetal weight <10th percentile.

§ Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mm Hg;
2nd trimester UtA-RI model: Baseline model, 2nd trimester uterine artery resistance index >90th percentile;
3rd trimester UtA-RI model: Baseline model, 3rd trimester uterine artery resistance index >90th percentile;
2nd and 3rd trimester UtA-RI model: Baseline model, 2nd and 3rd trimester uterine artery resistance index >90th percentile.
2nd and 3rd trimester UtA-RI model and 1st trimester PlGF model: 2nd and 3rd trimester UtA-RI model, 1st trimester placental growth factor < 10th percentile;
2nd and 3rd trimester UtA-RI model and 2nd trimester PlGF model: 2nd and 3rd trimester UtA-RI model , 2nd trimester placental growth factor < 10th percentile;
2nd and 3rd trimester UtA-RI model and 1st and 2nd trimester PlGF model: 2nd and 3rd trimester UtA-RI model, 1st and 2nd trimester placental growth factor < 10th percentile.

FIGURE 2 Legend on next page.

systematic review among 29 studies, reporting on 70 models for prediction of preeclampsia using routinely collected maternal characteristics, showed that screening performance for preeclampsia at any gestational age ranges from moderate (AUC 0.67 [95% CI 0.59-0.76]) to good (AUC 0.81 [95% CI 0.80-0.82]).[11] The study with the highest screening performance was conducted among 6015 mainly Caucasian (74%) women and developed a screening model for preeclampsia at any gestational age using maternal characteristics including ethnic origin, BMI, previous preeclampsia and family history of preeclampsia.[37] A review among 92 studies, examining 25 356 688 pregnancies, assessed risk of preeclampsia among women with and without individual clinical risk-factors determined <16 weeks gestation, to select risk-factors for future development of prediction models.[36] The authors noted that for selection of pregnancies at risk of preeclampsia on a population level, the use of common risk-factors may be more useful than the use of rare but strongly associated risk-factors. These rare but strong risk-factors could be more useful on an individual level.[36] Fewer studies developed models for prediction of gestational hypertension using only maternal characteristics.[37,38] The previously mentioned study among 6015 women showed moderate screening performance for gestational hypertension (AUC 0.69 [95% CI 0.68-0.70]), using a model consisting of maternal characteristics including ethnic origin, BMI, previous preeclampsia and family history of preeclampsia.[37]

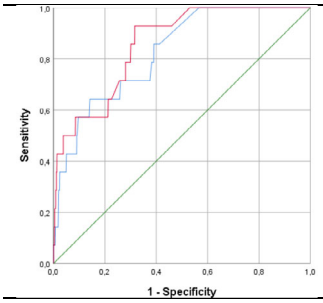
We observed that routinely measured maternal characteristics in early-pregnancy can be used in screening for risk of both gestational hypertension and preeclampsia with sensitivity ranging from 33% to 40% at 90% specificity. Screening performance improved to 57% at 90% specificity, when we only focused on early-onset preeclampsia. Screening performance of our screening model based on maternal characteristics is quite comparable to previously developed models.[11] The strength of our maternal characteristics model is that, in contrast with most models which use previous preeclampsia, pre-existing conditions or family history, we only used maternal characteristics routinely collected in clinical care, and as such are available early in pregnancy. These characteristics can be used in low-resource settings and are applicable for both nulliparous and parous women. Furthermore, in contrast to studies using tertiary or infertility care populations, we fitted our maternal characteristics model on a low-risk multi-ethnic population, which is more representative of the general obstetric population. We used a similar model for prediction of gestational hypertension and preeclampsia, which may be easier to use in clinical practice. Taken together, the current study shows that one model consisting of routinely measured maternal characteristics including blood pressure in early-pregnancy may be used to detect pregnancies at risk of gestational hypertension and preeclampsia in a low-risk multi-ethnic population and leads to a moderate screening performance. This screening performance seems comparable to screening models using more specific and rare maternal characteristics, which may only be applicable in specific populations.

The value of fetal and placental characteristics in addition to maternal characteristics for screening for GHD is debated. EFW has been associated with GHD, and newborns born from pregnancies complicated by preeclampsia have a 5% to 23% lower birthweight compared newborns born after uncomplicated pregnancies.[39-41] To our knowledge, EFW has not been studied as predictor for gestational hypertension or preeclampsia.[39] In our study, addition of second or third trimester EFW to maternal characteristics did not lead to better screening performance for gestational hypertension and preeclampsia. For early-onset preeclampsia, sensitivity did improve to 86% at 90% specificity. This positive effect on screening performance may be explained by reversed causation as fetal ultrasound was performed around 30 weeks gestation. Although increased UtA impedance and low PlGF have been described as predictors for GHD, evidence on added value of these parameters is conflicting.[11,12,42,43] A prospective screening study for gestational hypertension and preeclampsia in a low-risk multi-ethnic population among 8366 women created first trimester models consisting of maternal history, blood pressure, PAPP-A, and UtA-PI, and reported that there was a small contribution of placental measurements. Model performance was better for screening for preeclampsia than for gestational hypertension.[12] A recent study among 4212 nulliparous singleton pregnancies reported that in addition to maternal characteristics, blood pressure, 20-week UtA-PI, PAPP-A and PlGF did not improve screening performance for early-onset preeclampsia.[43] In our low-risk multi-ethnic population, single addition of more advanced fetal and placental screening parameters did not improve screening for gestational hypertension and

FIGURE 2 Screening performance for preeclampsia based on maternal, fetal and placental characteristics. CI, confidence interval; EFW, estimated fetal weight; PlGF, placental growth factor; UC, area under the curve; UtA-RI, uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity. †Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking; Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mmHg.‡Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mmHg; Fetal sex model: Baseline model + fetal sex; second trimester EFW model: Baseline model and second trimester estimated fetal weight <10th percentile; third trimester EFW model: Baseline model and third trimester estimated fetal weight <10th percentile; second and third trimester EFW model: Baseline model, second and third trimester estimated fetal weight <10th percentile.§Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mmHg; second trimester UtA-RI model: Baseline model, second trimester uterine artery resistance index >90th percentile; third trimester UtA-RI model: Baseline model, third trimester uterine artery resistance index >90th percentile; second and third trimester UtA-RI model: Baseline model, second and third trimester uterine artery resistance index >90th percentile. Second and third trimester UtA-RI model and first trimester PlGF model: second and third trimester UtA-RI model, first trimester placental growth factor < 10th percentile; second and third trimester UtA-RI model and second trimester PlGF model: second and third trimester UtA-RI model, second trimester placental growth factor <10th percentile; second and third trimester UtA-RI model and first and second trimester PlGF model: second and third trimester UtA-RI model, first and second trimester placental growth factor < 10th percentile [Colour figure can be viewed at wileyonlinelibrary.com]

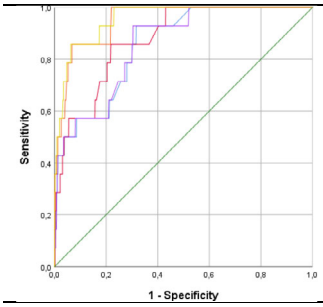
preeclampsia. Only when both second and third trimester UtA-Doppler screening results were added simultaneously, screening performance improved for preeclampsia only. The presence of screening benefit of repeated UtA-RI results for preeclampsia but not for gestational hypertension is likely due to a larger role of the placenta in the pathophysiology of preeclampsia.[4] Because our study was specifically focused on screening for GHD in low-risk pregnant populations, we used routinely measured or easily available characteristics as much as possible to enable translation of our findings to clinical practice and low-resource settings. We, therefore, added screening characteristics to the screening model based on clinical availability. However, earlier screening for GHD allows potential earlier interventions. We further explored whether addition of placental and fetal screening characteristics in a chronological order led to different screening models.

Models based on maternal characteristics



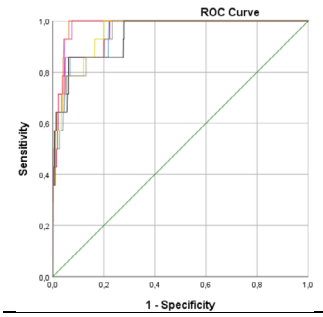
Models†	AUC (95% CI)	Sensitivity at specificity		
		70%	80%	90%
Maternal characteristics: (Blue line)	0.83 (0.73-0.92)			
Blood pressure: (Red line)	0.86 (0.78-0.94)	79%	57%	57%

Models based on maternal and fetal characteristics



Models‡	AUC (95% CI)	Sensitivity at specificity		
		70%	80%	90%
Baseline: (Blue line)	0.86 (0.78-0.94)			
Fetal sex: (Red line)	0.88 (0.80-0.95)			
2nd trimester EFW: (Green line)	0.86 (0.76-0.94)			
3rd trimester EFW: (Orange line)	0.95 (0.91-0.99)	100%	86%	86%
2nd and 3rd trimester EFW: (Yellow line)	0.96 (0.92-0.99)			

Models based on maternal characteristics, fetal and placental characteristics



Models§	AUC (95% CI)	Sensitivity at specificity		
		70%	80%	90%
Baseline: (Blue line)	0.95 (0.91-0.99)	100%	86%	86%
2nd trimester UtA-RI: (Red line)	0.96 (0.92-0.99)			
3rd trimester UtA-RI: (Green line)	0.98 (0.97-0.99)			
2nd and 3rd trimester UtA-RI: (Orange line)	0.98 (0.97-0.99)			
1st trimester PlGF: (Red line)	0.95 (0.92-0.99)			
2nd trimester PlGF: (Green line)	0.95 (0.90-0.99)			
1st and 2nd trimester PlGF: (Orange line)	0.95 (0.91-0.99)			

AUC: area under the curve; CI: confidence interval; EFW: Estimated fetal weight; PlGF: Placental Growth Factor; UtA-RI: Uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity.

† Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking;
Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mm Hg.

‡ Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mm Hg;
Fetal sex model: Baseline model + fetal sex;
2nd trimester EFW model: Baseline model and 2nd trimester estimated fetal weight <10th percentile;
3rd trimester EFW model: Baseline model and 3rd trimester estimated fetal weight <10th percentile;
2nd and 3rd trimester EFW model: Baseline model, 2nd and 3rd trimester estimated fetal weight <10th percentile.

§ Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mm Hg, and 3rd trimester EFW;
2nd trimester UtA-RI model: Baseline model, 2nd trimester uterine artery resistance index >90th percentile;
3rd trimester UtA-RI model: Baseline model, 3rd trimester uterine artery resistance index >90th percentile;
2nd and 3rd trimester UtA-RI model: Baseline model, 2nd and 3rd trimester uterine artery resistance index >90th percentile.
1st trimester PlGF model: Baseline model, 1st trimester placental growth factor < 10th percentile;
2nd trimester PlGF model: Baseline model, 2nd trimester placental growth factor < 10th percentile;
1st and 2nd trimester PlGF model: Baseline model, 1st and 2nd trimester placental growth factor < 10th percentile.

FIGURE 3 Legend on next page.

However, this did not affect our findings. We hypothesize that differences between screening performances of parameters in different models may be due to the fact that maternal characteristics are strongly correlated to GHD, but also with fetal and placental parameters, possibly reducing screening potential of these more advanced fetal and placental measurements.[16,18,44] Thus, our results suggest that the additional screening benefit of fetal and placental parameters for screening for gestational hypertension and preeclampsia is limited. Only when both second and third trimester UtA-Doppler screening results were added simultaneously, screening performance improved for preeclampsia only. Use of fetal and placental measurements may have a larger contribution to screening for GHD among higher risk populations.

Our study adds to existing evidence that maternal characteristics, routinely measured in clinical practice, known early in any pregnancy, can be used in screening for risk of gestational hypertension and preeclampsia in low-risk multi-ethnic populations. It should be further explored if maternal characteristics and MAP collected before pregnancy yield similar screening results to enable early risk selection and modify risk-factors even before conception.[45,46] Before any screening model for GHD can be implemented in clinical practice, further research is necessary. To date, aggregated analysis of screening models was not possible due to large heterogeneity of studies. Future large studies should test promising models in diverse populations, utilizing maternal characteristics as much as possible, before adding more advanced fetal and placental measurements, as maternal characteristics are more easy and cost-effective to use in clinical practice and can also be implemented in low-resource settings, in which GHD leads to the poorest outcomes.[47] In these studies, benefits due to identification of true-positives vs harm caused by false-positives should be evaluated in contemporary low-risk populations. For current clinical practice, this study shows that maternal characteristics in early-pregnancy contain valuable information for assessment of risk of GHD, and should be considered in routine care.

4.3 | Strengths and limitations

We collected prospective data from early-pregnancy onwards in 7124 women with information regarding GHD. We defined diagnosis of preeclampsia according to the 2001 ISSHP criteria.[28,29] As no exact gestational age at diagnosis of GHD was available, misclassification of the onset of preeclampsia may have occurred. We considered it important to specifically assess screening performance of our models for early-onset preeclampsia, as this is often regarded as a different entity with a higher risk of adverse outcomes. Our findings of a better screening performance for early-onset preeclampsia are in line with previous studies.[11] However, as misclassification of gestational age at diagnosis of preeclampsia may have occurred, early-onset preeclampsia needs to be considered as secondary outcome and our models for screening for early-onset preeclampsia need to be interpreted with more caution and replicated among other study populations. Measurements of blood pressure, ultrasound examinations and blood samples collection were performed according to the study protocol and blinded with regard to pregnancy outcomes due to the prospective nature of the study.[48] Research findings were reported to healthcare providers, which may have led to intensified monitoring or interventions influencing the outcome and possibly effecting screening performance. Current guidelines recommend low-dose Aspirin-prophylaxis for women at higher risk of developing preeclampsia.[49] Use of prophylaxis likely influences occurrence of preeclampsia and could therefore influence obtained model performance of the screening models. However, as our study participants were pregnant between 2001 and 2006, low-dose aspirin prophylaxis was not yet part of obstetric guidelines. Thus, our screening models were not affected by low-dose aspirin-prophylaxis among women at higher risk of preeclampsia. The current population is not a clinical population, but a low-risk population, which may have influenced screening performance.

4.4 | Conclusion

Routinely measured maternal characteristics and blood pressure in early-pregnancy have a moderate screening performance for pregnancies at risk of gestational hypertension and preeclampsia in a contemporary multi-ethnic, low-risk population. Addition of combined second and third trimester placental ultrasound screening results only improved screening performance for preeclampsia, in addition to simple maternal characteristics.

FIGURE 3 Screening performance for secondary outcome early-onset preeclampsia based on maternal, fetal and placental characteristics. AUC, area under the curve; CI, confidence interval; EFW, estimated fetal weight; PlGF, placental growth factor; UtA-RI, uterine artery resistance index. Values are AUC (95% CI), Sensitivity at 70%, 80% and 90% specificity. †Maternal characteristics model: maternal age, BMI, ethnicity, parity and smoking; Blood pressure model: Maternal characteristics model and first trimester mean arterial pressure per 10 mmHg. ‡Baseline model: maternal age, BMI, ethnicity, parity and smoking, and first trimester MAP per 10 mmHg; Fetal sex model: Baseline model + fetal sex; second trimester EFW model: Baseline model and second trimester estimated fetal weight <10th percentile; third trimester EFW model: Baseline model and third trimester estimated fetal weight <10th percentile; second and third trimester EFW model: Baseline model, second and third trimester estimated fetal weight <10th percentile.§Baseline model: maternal age, BMI, ethnicity, parity, smoking, and first trimester MAP per 10 mmHg, and third trimester EFW; second trimester UtA-RI model: Baseline model, second trimester uterine artery resistance index >90th percentile; third trimester UtA-RI model: Baseline model, third trimester uterine artery resistance index >90th percentile; second and third trimester UtA-RI model: Baseline model, second and third trimester uterine artery resistance index >90th percentile. First trimester PlGF model: Baseline model, first trimester placental growth factor <10th percentile; second trimester PlGF model: Baseline model, second trimester placental growth factor <10th percentile; first and second trimester PlGF model: Baseline model, first and second trimester placental growth factor <10th percentile [Colour figure can be viewed at wileyonlinelibrary.com]

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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DATA AVAILABILITY STATEMENT

Data requests can be made to the secretariat of Generation R.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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