OBSTETRICS

Using ultrasound and angiogenic markers from a 19- to 23-week assessment to inform the subsequent diagnosis of preeclampsia

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BACKGROUND: A definition of preeclampsia that incorporates the assessment of maternal, fetal, and uteroplacental status would optimize the identification of pregnancies at risk of complications at term gestational age. This definition would include "carrying forward" angiogenic test results from 35 to 36 weeks of gestation to term gestational age. Would this approach still be useful if testing is performed earlier or at a routine midgestation scan and the result is used to inform the diagnosis of preeclampsia that developed thereafter?

OBJECTIVE: This study aimed to evaluate whether fetoplacental assessment at a 19- to 23-week scan could be "carried forward" to contribute to the classification of preeclampsia and improve the detection of women and fetuses at risk of adverse outcomes associated with hypertension.

STUDY DESIGN: In this prospective cohort study of singleton pregnancies at 2 maternity hospitals in England (October 2011 to March 2020), women attending a routine hospital visit at 19 to 23 weeks of gestation underwent an assessment that included history, ultrasonographic estimated fetal weight, Doppler measurements of the pulsatility index in uterine arteries, and serum placental growth factor. Preeclampsia was defined according to various definitions: (1) traditional, based on new-onset proteinuria at ≥20 weeks of gestation; (2) 2013 American College of Obstetricians and Gynecologists; (3) 2018 International Society for the Study of Hypertension in Pregnancy maternal factor; (4) 2018 International Society for the Study of Hypertension in Pregnancy maternal-fetal factor (death or growth restriction), based on ultrasound scans at the 19 0/7 to 23 6/7 week of gestation (an estimated fetal weight of <3rd percentile or estimated fetal weight between the 3rd and 10th percentiles with a uterine artery pulsatility index of >95th percentile); and (5) 2021 International Society for the Study of Hypertension in Pregnancy maternal-fetal factor plus placental growth factor (with abnormal placental growth factor defined as an estimated fetal weight of <5th percentile for gestational age). The detection rates for outcomes of interest (ie, severe maternal hypertension, major maternal morbidity, perinatal mortality or major neonatal morbidity, neonatal intensive care unit admission ≥48 hours, and birthweight of <3rd percentile) ascertained by health record review were compared using the chi-square test. A *P* value of <.05 was considered statistically significant.

RESULTS: Among 40,241 singleton pregnancies, preeclampsia incidence varied by definition, from lows of 2.6% (traditional) and 3.0% (American College of Obstetricians and Gynecologists) to a high of 3.8% (International Society for the Study of Hypertension in Pregnancy maternal-fetal factor plus placental growth factor). The International Society for the Study of Hypertension in Pregnancy maternal-fetal factor plus placental growth factor definition (vs the traditional) best identified women who developed adverse outcomes: severe hypertension (detection rate: 70.6% vs 52.8%; *P*<.001), major maternal morbidity (detection rate: 100% vs 87.5%; *P*=.027), perinatal mortality or major morbidity (detection rate: 84.6% vs 69.5%; *P*=.004), neonatal intensive care unit admission ≥48 hours (detection rate: 76.6% vs 63.2%;, *P*=.0002), and birthweight of <3rd percentile (detection rate: 81.3% vs 61.9%; *P*<.0001]. The detection rates improved, going from the American College of Obstetricians and Gynecologists definition to the International Society for the Study of Hypertension in Pregnancy maternal-fetal factor plus placental growth factor definition, for severe hypertension (11.4%; *P*=.003), perinatal mortality or major morbidity (10.6%; *P*=.03), neonatal intensive care unit admission ≥48 hours (8.6%; *P*=.01), and birthweight of <3rd percentile (16.2%; *P*<.001). However, going from the International Society for the Study of Hypertension in Pregnancy maternal-fetal factor definition to the International Society for the Study of Hypertension in Pregnancy maternal-fetal factor plus placental growth factor definition, the detection of fetuses with a birthweight of <3rd percentile improved by 7.0% (*P*=.01), but no other improvement was seen for severe hypertension (1.7%; *P*=.33), major maternal morbidity (0%), perinatal mortality or major morbidity (4.0%; *P*=.20), and neonatal intensive care unit admission ≥48 hours (3.2%; *P*=.17).

CONCLUSION: The criteria for uteroplacental dysfunction (including placental growth factor) from the 19- to 23-week assessment can be used in the assessment of women who are later suspected of having PE, to best identify pregnancies at risk of adverse outcomes.

Key words: definition, outcomes, placental growth factor, preeclampsia, preterm, term, ultrasound

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Introduction

Preeclampsia (PE) is the hypertensive disorder of pregnancy associated with the greatest risk of pregnancy complications. Its identification is an antenatal care priority that is the basis of blood pressure measurement at each antenatal visit.

To date, there is international consensus that PE should be defined "broadly," incorporating not only proteinuria but also other relevant end-organ manifestation.[1] This approach reflects the systemic nature of the disease and its multifaceted syndrome[2] and aims to optimize the identification of mothers and fetuses at risk of complications. Most national and international pregnancy hypertension guidelines now include relevant maternal symptoms,

AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate whether ultrasound and angiogenic marker results at a 19- to 23-week ultrasound scan can be used later in pregnancy when a diagnosis of preeclampsia (PE) is suspected, to improve the detection of women and fetuses at risk of adverse outcomes.

Key findings

A definition of PE that included maternal end-organ and uteroplacental dysfunctions—abnormalities in placental perfusion or function—best identified women and fetuses at increased risk of adverse outcomes, at preterm and term gestational ages. This definition was particularly true when the findings from routine second-trimester ultrasonographic assessment and placental growth factor (PlGF) were used to inform a diagnosis of PE when hypertension subsequently developed.

What does this add to what is known?

Our study data has provided further evidence for the use of a PE definition that includes maternal end-organ dysfunction (including but not restricted to proteinuria) and uteroplacental dysfunction, at any point from 20 weeks of gestation. Importantly, the data showed that 19- to 23-week results of fetoplacental ultrasound and PlGF testing can be subsequently used by clinicians to evaluate pregnant women with hypertension suspected for PE.

signs, and abnormal laboratory test results in their PE definitions. However, although the International Society for the Study of Hypertension in Pregnancy (ISSHP) endorses the inclusion of uteroplacental dysfunction—abnormalities in placental perfusion or function—in the definition of PE, the inclusion in other guidelines is variable. Interestingly, 1 guideline includes abnormal fetal heart rate or oligohydramnios; few guidelines include placental abruption, abnormal umbilical artery Doppler, or fetal death; and approximately 75% of guidelines include fetal growth restriction (FGR) in their PE definitions.[1] In their 2021 guidance, the ISSHP has included angiogenic imbalance as a manifestation of uteroplacental dysfunction.[3] Although 3 other guidelines recommend angiogenic marker testing either to "rule out"[4,5] or "rule in" PE[6] when suspected, abnormalities in these markers are not part of their formal PE definitions. Of note, the American College of Obstetricians and Gynecologists (ACOG) pregnancy hypertension guidance includes none of these uteroplacental manifestations, although they are acknowledged to be associated with PE.[7]

Previously, we have shown that a definition of PE that incorporates uteroplacental assessment optimizes the identification of women and fetuses at risk of complications at term gestational age.[8] However, these findings were based on an evaluation, including angiogenic marker testing, at a 35- to 36-week fetal assessment that is not routine. Of note, up to one-third of PE occurred preterm and before 35 to 36 weeks of gestation. As both ultrasound and angiogenic markers are specialized tests, we evaluated whether their performance at a routine 19- to 23-week assessment could be "carried forward" to be used as diagnostic criteria for PE if hypertension subsequently developed, to optimize the identification of women and fetuses at risk of adverse outcomes associated with hypertension. We hypothesized that ultrasonographic and angiogenic marker results from 19 to 23 weeks of gestation when "carried forward" would increase the detection rate of subsequent preterm or term PE and better identify women and fetuses at risk of adverse outcomes.

Methods

Study design and participants

The study data were derived from a prospective screening study for adverse obstetrical outcomes in women attending routine pregnancy care at 19 0/7 to 23 6/7 weeks of gestation at King's College Hospital and Medway Maritime Hospital in the United Kingdom between October 2011 and March 2020. The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee.

In brief, at the routine hospital visit at 19 0/7 to 23 6/7 weeks of gestation, women underwent (1) recording of maternal demographic characteristics and medical history, (2) an ultrasound examination for fetal anatomy and growth, (3) measurement of the mean of the left and right uterine artery pulsatility indices (PIs) using transvaginal or transabdominal color Doppler ultrasound,[9,10] and (4) measurement of the mean arterial pressure using validated automated devices and a standardized protocol.[11] The fetal head circumference, abdominal circumference, and femur length were measured, and the estimated fetal weight (EFW) was calculated using the Hadlock formula,[12] identified as the most accurate model by systematic review.[13] Serum placental growth factor (PlGF) was measured by BRAHMS Kryptor compact PLUS (Thermo Fisher Scientific, Hennigsdorf, Germany), DELFIA Xpress system (PerkinElmer Life and Analytical Sciences, Waltham, MA), or Cobas e411 (Roche Diagnostics, Penzberg, Germany). Gestational age was determined by the measurement of the fetal crown-rump length at 11 to 13 weeks of gestation or the fetal head circumference at 19 to 24 weeks of gestation.[14,15]

Data related to pregnancy outcomes were abstracted from electronic hospital maternity records or those of the women's general medical practitioners. The obstetrical records of all women with chronic hypertension or pregnancy-associated hypertension were examined to determine the diagnosis of PE or gestational hypertension (GH).

The diagnosis of GH was based on the finding of new-onset hypertension developing after 20 weeks of gestation in previously normotensive women.[16] The diagnosis of chronic hypertension was based on a prepregnancy history of such hypertension at <20 weeks of gestation. Hypertension was defined as a systolic blood pressure (BP) of ≥140 mm Hg or diastolic BP of ≥90 mm Hg, on at least 2 occasions, at least 4 hours apart.

The inclusion criteria for this analysis were singleton pregnancies delivering a nonmalformed live birth or stillbirth at ≥24 0/7 weeks of gestation. We excluded pregnancies with aneuploidy or major fetal abnormalities.

Diagnosis of preeclampsia

Here, 5 different definitions of PE were considered (Supplemental Table). The traditional definition of PE was based on new-onset proteinuria (ie, ≥300 mg per 24 hours, protein-to-creatinine ratio of ≥30 mg/mmol, or ≥2+ on urinary dipstick testing).[16]

The broader definitions of PE, from both the ACOG and ISSHP definitions,[16,17] were based on evidence of maternal end-organ dysfunction (ACOG and ISSHP definitions) or uteroplacental dysfunction (ISSHP definition only). Neither broad definition requires the presence of proteinuria. In defining maternal end-organ dysfunction, we included only quantitative measures of renal, hepatic, or hematologic dysfunction, reliably documented in clinical care notes. The ACOG definition of PE was based on the development of at least 1 of the following: new-onset proteinuria, serum creatinine of >97 μmol/L (in the absence of underlying renal disease), serum transaminases more than twice the upper limit of normal (.e, ≥65 IU/L for our laboratory), platelet count of <100,000/μL, headache or visual symptoms, or pulmonary edema.[17] The ISSHP definition of PE was examined according to its maternal (ISSHP-M) and uteroplacental (ISSHP-MF) components. The ISSHP-M definition was based on at least 1 of the following: new-onset proteinuria, serum creatinine of ≥90 μmol/L (in the absence of underlying renal disease), serum transaminases of >40 IU/L, platelet count of <150,000/μL, or neurologic complications (ie, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata); the criteria of altered mental status and clonus were not available. The ISSHP-MF definition included all criteria of ISSHP-M, with the addition of fetal death or FGR; FGR was defined according to ultrasound findings at 19 0/7 to 23 6/7 weeks of gestation, defined as an EFW of <3rd percentile or an EFW between the 3rd and 10th percentiles together with the uterine artery PI multiple of the median (MoM) of >95th percentile. The ISSHP-MF+PlGF definition included all criteria of the ISSHP-MF definition, with the addition of low serum PlGF MoM of <5th percentile at 19 to 23 weeks of gestation.

Outcome measures

The maternal and perinatal outcomes of interest were as follows: severe maternal hypertension,[18] a composite of maternal death or major morbidity, a composite of perinatal death or major neonatal morbidity, neonatal intensive care unit (NICU) admission ≥48 hours, and birthweight (BW) of <3rd percentile.

Severe maternal hypertension was defined as systolic BP ≥160 mm Hg and/or diastolic BP ≥110 mm Hg. Major maternal morbidity was defined as one or more of the following: eclampsia, blindness, stroke, myocardial ischemia, pulmonary edema, elevated liver enzymes, hepatic hematoma, low platelet count, or acute kidney injury; these were based on the core maternal outcome set in PE, except for outcomes that were not available (ie, liver rupture, postpartum hemorrhage, ICU admission, and intubation and ventilation other than for childbirth), exclusion of placental abruption (which was defined clinically and underreported), and addition of myocardial ischemia (based on the Delphi-derived Preeclampsia Integrated Estimate of Risk score[19,20]).

Perinatal death was defined as stillbirth or neonatal death prior to hospital discharge. Major neonatal morbidity was defined as one or more of the following, as indicated in the BadgerNet Neonatal discharge summary: ventilation (ie, need for continuous positive airway pressure or nasal continuous positive airway pressure or intubation), respiratory distress syndrome (ie, the need for surfactant and ventilation), brain injury (ie, hypoxic-ischemic encephalopathy, intraventricular hemorrhage grade ≥2, or periventricular leukomalacia), sepsis (based on positive blood cultures), anemia treated with blood transfusion, or necrotizing enterocolitis requiring surgical intervention. The BW percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight charts.[21] Perinatal outcomes covered the core perinatal outcome set in PE, except for neonatal seizures.

Statistical analysis

Descriptive analysis was undertaken for (1) baseline data of assessment at 19 0/7 to 23 6/7 weeks of gestation and subsequent pregnancy outcomes for the study population overall, (2) the contribution of the components contributing to a diagnosis of PE among relevant women, and (3) pregnancy outcomes according to different definitions of PE (and the related impact on GH). Continuous variables were summarized by median and interquartile range, and categorical variables were summarized by number (percentage). The chi-squared test was used to compare the detection rate for adverse maternal and perinatal outcomes for each of the broad definitions of PE, relative to the traditional one; this was undertaken for PE overall and preterm (delivery at <37 weeks of gestation) and term PE. A P value of <.05 was considered statistically significant.

Results

Study participants

There were 40,241 pregnancies evaluated at visits at 19 0/7 to 23 6/7 weeks of gestation and included in this analysis.

Table 1 shows that, on average, women were in their early 30s and overweight, with 25% of women considered obese. Most women were White, with a substantial minority of Black race. Few women (<10%) were cigarette smokers. Medical history was

TABLE 1
Baseline characteristics and outcomes of the screening population

Characteristic	N=40,241 pregnancies
Maternal demographics	
Age (y)	31.9 (27.9–35.5)
Body mass index (kg/m^2)	26.2 (23.5–30.0)
≥30	10,103 (25.1)
Racial origin	
White	31,195 (77.5)
Black	5226 (13.0)
South Asian	1923 (4.8)
East Asian	784 (1.9)
Mixed	1113 (2.8)
Cigarette smoker	3016 (7.5)
Medical history	
Chronic hypertension	425 (1.1)
On antihypertensive medication	354 (83.3)
SLE or antiphospholipid antibody syndrome	85 (0.2)
Diabetes mellitus (type 1 or 2)	354 (0.9)
Obstetrical history	
Nulliparous	18,954 (47.1)
Parous without previous PE	20,300 (50.4)
Parous with previous PE	987 (2.5)
Family history	
Mother had PE	1451 (3.6)
This pregnancy	
Interpregnancy interval (y)	2.7 (1.7–4.7)
Conception	
Natural	38,433 (95.5)
Assisted by use of ovulation drugs	295 (0.7)
In vitro fertilization	1513 (3.8)
On aspirin for PE prevention	1339 (3.3)
Gestational age at screening (wk)	21.6 (21.1–22.0)
Screening markers for PE at 19 0/7 to 23 6/7 wk	
Mean arterial pressure (mm Hg)	85.7 (80.8–90.7)
Uterine artery PI MoM	1.0 (0.8–1.2)
Uterine artery PI MoM>95th percentile	2022 (5.0)
PlGF MoM	1.0 (0.7–1.4)
PlGF MoM<5th percentile	2112 (5.2)
Pregnancy outcomes	
Gestational age at birth (wk)	39.9 (39.0–40.7)
Preterm birth	2319 (5.8)

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usually unremarkable, with few women reporting chronic hypertension (most of whom were treated with antihypertensive therapy), pregestational diabetes mellitus, or rheumatic disease. Just over half of women were parous, with 2.5% of parous women having had previous PE. Few women reported that their mothers had suffered from PE. Almost all conceptions were natural, following an interpregnancy interval of just under 3 years, when relevant. Few women were on aspirin for PE prevention, the prescription of which was guided entirely by routine clinical care.

The 19- to 23-week assessment occurred at a median of 21.6 weeks; at which point, approximately 5% of women had abnormal uterine artery Doppler readings or abnormal PlGF (Table 1).

Birth occurred at a median of approximately 40 weeks, following induction for approximately 20% of women and by cesarean delivery for almost 30% of women (Table 1). Perinatal mortality was mainly because of stillbirth, and neonatal morbidity was because of respiratory problems, for which just under 7% of neonates overall required prolonged NICU admission. Just under 5% of neonates were born with a BW of <3rd percentile.

Preeclampsia definitions

Table 2 presents the elements of the PE definitions, for women with new-onset hypertension (n=2188) or chronic hypertension (n=425). Most commonly, women with hypertension satisfied the maternal diagnostic criteria for PE based on proteinuria, particularly among women with new-onset hypertension (44.7%). Less often, abnormal routine laboratory tests defined PE in women with hypertension, particularly related to low platelet count of $<150\times10^9$/L (10.6% of women) or elevated liver enzymes (11.4% of women). Almost 10% of women with new-onset hypertension had uteroplacental dysfunction based on low PlGF at 19 0/7 to 23 6/7 weeks of gestation, with about half that rate (approximately 5%) among women with chronic hypertension. More women satisfied the more liberal ISSHP (vs more

TABLE 1
Baseline characteristics and outcomes of the screening population *(continued)*

Characteristic	N=40,241 pregnancies
Induction of labor	8244 (20.5)
Vaginal delivery	29,020 (72.1)
Spontaneous vaginal delivery	23,128 (57.4)
Cesarean delivery	11,221 (27.9)
Perinatal mortality or major morbidity[a]	983 (2.4)
Stillbirth	113 (0.3)
Neonatal death	18 (0.04)
Ventilation	810 (2.0)
RDS	275 (0.7)
Brain injury	48 (0.1)
Sepsis	97 (0.2)
Anemia	114 (0.3)
NEC	9 (0.02)
Neonatal intensive care unit admission≥48 h	2662 (6.6)
BW<3rd percentile[b]	1923 (4.8)

Data are presented as number (percentage) or median (interquartile range).

BW, birthweight; *MoM*, multiple of the median; *NEC*, necrotizing enterocolitis; *PE*, preeclampsia; *PI*, pulsatility index; *RDS*, respiratory distress syndrome; *PlGF*, placental growth factor; *SLE*, systemic lupus erythematosus.

[a] Major neonatal morbidity was defined as one or more of the following: ventilation, RDS, brain injury, sepsis, anemia, or NIC; [b] The BW percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight charts.[22]

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conservative ACOG) criteria for thrombocytopenia (231 [10.6%] vs 38 [1.7%], respectively) and elevated liver enzymes (249 [11.4%] vs 141 [6.4%], respectively). Few women met the criteria for PE based on gestational or chronic hypertension with headache (77 [3.5%]) or visual symptoms (5 [1.2%]).

Performance of each preeclampsia definition

Table 3 summarizes the incidence of GH and PE, according to each PE definition, and the associated incidence of adverse pregnancy outcomes.

First, the incidence of PE was the lowest with the traditional definition (2.6%) and rose progressively to reach its highest value with the ISSHP-MF+PlGF definition (3.8%) (Table 3). Most of the increases in PE were attributable to fewer women being diagnosed with GH, although some of the increase resulted from women with chronic hypertension being diagnosed with PE superimposed on chronic hypertension, thereby increasing the column total.

Second, each PE definition was associated with a similar incidence of adverse maternal and perinatal outcomes (ie, true positives) that reflected a high-risk population (Table 3). For all definitions, the incidence of severe hypertension was approximately 14% to 15%, and the incidence of major maternal morbidity was approximately 3% to 4%, most commonly because of hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), followed in frequency by eclampsia. Just over half of women with PE were induced with a similar proportion delivered by cesarean delivery, whereas just under half of women with GH were induced and approximately 40% delivered by cesarean delivery. Perinatal death or major morbidity occurred in approximately 3% of pregnancies with GH and approximately 8% with PE. Major neonatal morbidity was most commonly respiratory in nature (ie, need for ventilation or a diagnosis of respiratory distress syndrome). NICU admission ≥48 hours occurred in just under 10% of pregnancies with GH and more than 15% of those with PE. Neonates with a BW of <3rd percentile occurred in no more than 10% of pregnancies with GH and close to 20% of pregnancies with PE.

Table 4 shows that the detection rate (sensitivity) of PE definitions for adverse outcomes rose progressively from the traditional PE definition to ACOG, ISSHP-M, ISSHP-MF, and ISSHP-MF+PlGF; these results are presented graphically in the Figure. The exception was major maternal morbidity for which detection rates were high across PE definitions (87.5% to 100%), but the increase in detection rate was seen going from the traditional PE definition (87.5%) to the ACOG PE definition (97.9%). Otherwise, the detection rates for adverse outcomes rose from 52.8% to 69.5% with the traditional PE definition to 70.6% to 84.6% with the ISSHP-MF+PlGF definition. The gains in the detection of adverse maternal and perinatal outcomes were achieved with similar true-positive rates (ie, similar rates associated with adverse outcomes) (Table 3). The enhanced detection for adverse outcomes was the greatest with the ISSHP-MF+PlGF (vs traditional) definition for severe maternal hypertension (17.8%), major maternal morbidity (12.5%), perinatal mortality or major morbidity (15.1%), NICU admission ≥48 hours (13.4%), and BW of <3rd percentile (19.4%). Moreover, there were incremental gains in the detection, going from the ACOG definition to the ISSHP-MF+PlGF definition, for severe hypertension (11.4%; P=.003), perinatal mortality or major morbidity (10.6%; P=.03), NICU admission ≥48 hours (8.6%; P=.01), and BW of <3rd percentile (16.2%; P<.001). However, going from the ISSHP-MF definition to the ISSHP-MF+PlGF definition, the detection of fetuses with a BW of <3rd percentile improved (by 7.0%; P=.01), but no significant improvement was seen for other

TABLE 2
The elements of the preeclampsia definitions for women with new-onset hypertension and those with a history of chronic hypertension

Characteristic	New-onset hypertension (n=2188)	Chronic hypertension (n=425)
Proteinuria[a]	979 (44.7)	81 (19.1)
Maternal symptoms[b]		
Headache	77 (3.5)	5 (1.2)
Visual symptoms	42 (1.9)	2 (0.5)
Maternal signs[c]		
Eclampsia	13 (0.6)	0 (0)
Myocardial ischemia	0 (0)	0 (0)
Pulmonary edema	4 (0.2)	0 (0)
Abnormal maternal laboratory tests[d]		
Platelet count<150×10^9/L	231 (10.6)	41 (9.6)
Platelet count<100×10^9/L	38 (1.7)	2 (0.5)
Serum creatinine≥90 μmol/L	79 (3.6)	28 (6.6)
Serum creatinine>97 μmol/L	51 (2.3)	19 (4.5)
AST or ALT of >40 IU/L	249 (11.4)	45 (10.6)
AST or ALT of ≥65 IU/L	141 (6.4)	17 (4.0)
Uteroplacental dysfunction		
Intrauterine fetal death	10 (0.5)	3 (0.7)
EFW<3rd percentile	58 (2.7)	16 (3.8)
EFW between the 3rd and 10th percentiles with uterine artery PI MoM>95th percentile	32 (1.5)	3 (0.7)
PlGF MoM <5th percentile	201 (9.2)	22 (5.2)

ACOG, American College of Obstetricians and Gynecologists; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *EFW*, estimated fetal weight; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *MoM*, multiple of the median; *PE*, preeclampsia; *PI*, pulsatility index; *PlGF*, placental growth factor.

[a] Proteinuria was defined as ≥2+ by urinary dipstick testing, ≥30 mg/mmol or 0.3 mg/dL by protein-to-creatinine ratio, or ≥0.3 g/d by 24-hour urine collection; [b] Headache was defined by the ACOG as new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, whereas the ISSHP defined headache as "severe;" visual symptoms were not defined by the ACOG but were defined by the ISSHP as persistent visual scotomata; [c] There was no information available on altered mental status or clonus. There was no case of blindness; [d] There was no information available on disseminated intravascular coagulation or hemolysis.

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maternal or perinatal outcomes: severe hypertension (1.7%; *P*=.33), major maternal morbidity (0%), perinatal mortality or major morbidity (4.0%; *P*=.20), and NICU admission ≥48 hours (3.2%; *P*=.17).

Discussion

Principal findings

In a cohort of more than 40,000 women assessed at 19 to 23 weeks of gestation, the incidence of subsequent PE was the lowest with the use of the traditional PE definition (2.6%) and rose progressively to reach its highest value with the ISSHP-MF+PlGF definition (3.8%). Most of the increases in PE were attributable to fewer women diagnosed with GH rather than an increase in superimposed PE. However, each of the traditional and broad ACOG and ISSHP definitions was associated with an incidence of adverse maternal and perinatal outcomes that reflected a high-risk population. The 2021 ISSHP definition best identified women and fetuses at increased risk of adverse outcomes, when the results of a 19-to 23-week ultrasonographic assessment and PlGF were used later to inform a diagnosis of the hypertensive disorder that subsequently developed.

Comparison with published literature

Angiogenic markers have been evaluated for the prediction, diagnosis, and prognosis of PE. The prediction of PE is informed by angiogenic markers as part of multivariable modeling at 11 to 13 weeks of gestation to identify approximately 75% of preterm PE and at 35 to 36 weeks of gestation to identify approximately 70% of term PE.[23] At ≥20 weeks of gestation, when women present with hypertension or symptoms suggestive of PE, a systematic review has shown that angiogenic markers show promise for the identification of women who develop adverse maternal or perinatal outcomes (33 studies, which included 9426 women), although there was substantial between-study heterogeneity.[22] The use of angiogenic markers to guide care reduced time to diagnosis of PE (by 2 days, on average)[24,25] and adverse maternal outcomes (5%−4%),[24] although, in other trials, hospital admission and gestational age at birth were not reduced,[25] and benefits did not extend to women with suspected PE primarily related to FGR.[26] Additional data suggest that these markers may identify women at increased risk of peripartum severe maternal morbidity (including postnatal hypertension)[27] and may be cost-saving in the United Kingdom.[5] Similar findings are emerging from less-resourced settings.[28]

In 2021, the ISSHP included angiogenic imbalance as an example of uteroplacental dysfunction in their PE definition.[3] Our findings have added to this work. We provided further support for the inclusion of the fetal criteria in the ISSHP definition of PE.[16] Importantly, we have shown that angiogenic marker results measured at 19 to 23 weeks of gestation as part of a routine assessment can be used at a later time point to aid in the differentiation of PE

TABLE 3
Adverse pregnancy outcomes according to the definitions of gestational hypertension and preeclampsia

	Traditional		ACOG		ISSHP-M		ISSHP-MF		ISSHP-MF+PIGF	
Outcome	GH	PE	GH	PE	GH	PE	GH	PE	GH	PE
n (%)	1209 (3.0)	1060 (2.6)	1095 (2.7)	1197 (3.0)	951 (2.4)	1393 (3.5)	920 (2.3)	1434 (3.6)	847 (2.1)	1521 (3.8)
Superimposed on chronic hypertension	—	81 (7.6)	—	104 (8.7)	—	156 (11.2)	—	166 (11.6)	—	180 (11.8)
Maternal										
Severe hypertension	146 (12.1)	163 (15.4)	126 (11.5)	183 (15.3)	99 (10.4)	210 (15.1)	96 (10.4)	213 (14.9)	91 (10.7)	218 (14.3)
Major morbidity	6 (0.5)	42 (4.0)	1 (0.09)	47 (3.9)	0 (0)	48 (3.4)	0 (0)	48 (3.3)	0 (0)	48 (3.2)
Death	0 (0)	1 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
Eclampsia	0 (0)	13 (1.2)	0 (0)	13 (1.1)	0 (0)	13 (0.9)	0 (0)	13 (0.9)	0 (0)	13 (0.9)
Myocardial ischemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary edema	1 (0.1)	3 (0.3)	0 (0)	4 (0.3)	0 (0)	4 (0.3)	0 (0)	4 (0.3)	0 (0)	4 (0.3)
Hepatic hematoma	0 (0)	2 (0.2)	0 (0)	2 (0.2)	0 (0)	2 (0.1)	0 (0)	2 (0.1)	0 (0)	2 (0.1)
HELLP syndrome	5 (0.4)	28 (2.6)	1 (0.1)	32 (2.7)	0 (0)	33 (2.4)	0 (0)	33 (2.3)	0 (0)	33 (2.2)
Labor and delivery										
Induction of labor	568 (47.0)	598 (56.4)	512 (46.8)	662 (55.3)	441 (46.4)	751 (53.9)	426 (46.3)	772 (53.8)	394 (46.5)	808 (53.1)
Vaginal delivery	728 (60.2)	525 (49.5)	671 (61.3)	594 (49.6)	582 (61.2)	712 (51.1)	565 (61.4)	736 (51.3)	526 (62.1)	779 (51.2)
Spontaneous vaginal delivery	361 (29.9)	160 (15.1)	335 (30.6)	191 (16.0)	293 (30.8)	248 (17.8)	286 (31.1)	257 (17.9)	269 (31.8)	277 (18.2)
Cesarean delivery	481 (39.8)	535 (50.5)	424 (38.7)	603 (50.4)	369 (38.8)	681 (48.9)	355 (38.6)	698 (48.7)	321 (37.9)	742 (48.8)
Perinatal										
Perinatal mortality or major neonatal morbidity	40 (3.3)	91 (8.6)	34 (3.1)	97 (8.1)	28 (2.9)	106 (7.6)	26 (2.8)	108 (7.5)	21 (2.5)	115 (7.6)
Stillbirth	4 (0.3)	8 (0.8)	3 (0.3)	9 (0.8)	0 (0)	13 (0.9)	0 (0)	13 (0.9)	0 (0)	13 (0.9)
Neonatal death	0 (0)	2 (0.2)	0 (0)	2 (0.2)	0 (0)	3 (0.2)	0 (0)	3 (0.2)	0 (0)	3 (0.2)
Ventilation	33 (2.7)	79 (7.5)	28 (2.6)	84 (7)	25 (2.6)	89 (6.4)	23 (2.5)	91 (6.3)	19 (2.2)	97 (6.4)
RDS	10 (0.8)	41 (3.9)	8 (0.7)	43 (3.6)	8 (0.8)	45 (3.2)	6 (0.7)	47 (3.3)	4 (0.5)	51 (3.4)
Brain injury	3 (0.2)	8 (0.8)	2 (0.2)	9 (0.8)	2 (0.2)	9 (0.6)	2 (0.2)	9 (0.6)	2 (0.2)	9 (0.6)
Sepsis	4 (0.3)	10 (0.9)	3 (0.3)	11 (0.9)	3 (0.3)	11 (0.8)	3 (0.3)	11 (0.8)	3 (0.4)	12 (0.8)
Anemia	6 (0.5)	12 (1.1)	6 (0.5)	12 (1.0)	6 (0.6)	12 (0.9)	6 (0.7)	12 (0.8)	4 (0.5)	15 (1.0)
NEC	0 (0)	2 (0.2)	0 (0)	2 (0.2)	0 (0)	2 (0.1)	0 (0)	2 (0.1)	0 (0)	2 (0.1)
Neonatal intensive care unit admission≥48 h	119 (9.8)	204 (19.2)	105 (9.6)	223 (18.6)	94 (9.9)	238 (17.1)	89 (9.7)	245 (17.1)	79 (9.3)	258 (17.0)
Birthweight<3rd percentile	121 (10.0)	197 (18.6)	113 (10.3)	211 (17.6)	99 (10.4)	233 (16.7)	87 (9.5)	251 (17.5)	64 (7.6)	278 (18.3)

ACOG, American College of Obstetricians and Gynecologists; *GH*, gestational hypertension; *HELLP syndrome*, hemolysis, elevated liver enzymes, and low platelet count; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *ISSHP-M*, ISSHP maternal factor, *ISSHP-MF*, ISSHP maternal-fetal factor; *ISSHP-MF+PIGF*, ISSHP maternal-fetal definition plus placental growth factor; *NEC*, necrotizing enterocolitis; *PE*, preeclampsia; *RDS*, respiratory distress syndrome.

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from GH or superimposed PE from chronic hypertension. This was similar to our previous work at 35 to 36 weeks of gestation; in that article, the detection rates for adverse pregnancy outcomes with the ISSHP definitions were similar to our findings here. However, as the traditional definition performed less well at 35 to 36 weeks of gestation than at 19

TABLE 4
Detection rate of adverse pregnancy outcomes according to different definitions of preeclampsia

Detection rate	Traditional	Ref	ACOG	*P* value	ISSHP-M	*P* value	ISSHP-MF	*P* value	ISSHP-MF+PlGF	*P* value
Severe maternal hypertension	52.8 (163/309)	—	59.2 183/309)	.124	68.0 210/309)	.0002	68.9 213/309)	<.0001	70.6 (218/309)	<.0001
Major maternal morbidity	87.5 (42/48)	—	97.9 (47/48)	.111	100 (48/48)	.027	100 (48/48)	.027	100 (48/48)	.027
Perinatal mortality or major morbidity[a,b]	69.5 (91/131)	—	74.0 (97/131)	.493	79.1 106/134)	.091	80.6 108/134)	.046	84.6 (115/136)	.004
Neonatal intensive care unit admission≥48 h[b]	63.2 (204/323)	—	68.0 223/328)	.216	71.7 238/332)	.024	73.4 245/334)	.006	76.6 (258/337)	.0002
BW<3rd percentile[b,c]	61.9 (197/318)	—	65.1 (211/324)	.413	70.2 (233/332)	.031	74.3 (251/338)	.0008	81.3 (278/342)	<.0001

Data are presented as percentage (number/total number). The *P* value represents the comparison of the detection rate with the traditional definition of preeclampsia, with cells highlighted in yellow representing statistically significant effects on the basis of $P<.05$.

ACOG, American College of Obstetricians and Gynecologists; *BW*, birthweight; *HELLP* syndrome, hemolysis, elevated liver enzymes, and low platelet count; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *ISSHP-M*, ISSHP maternal factor; *ISSHP-MF*, ISSHP maternal-fetal factor; *ISSHP-MF+PlGF*, ISSHP maternal-fetal factor plus placental growth factor; *PE*, preeclampsia; *Ref*, reference interval.

[a] Major neonatal morbidity was defined as one or more of the following: ventilation, respiratory distress syndrome, brain injury, sepsis, anemia, or necrotizing enterocolitis; [b] The denominator increases slightly from traditional to ISSHP-MF+PlGF definitions because additional women with PE superimposed on chronic hypertension meet inclusion criteria; [c] The BW percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight charts.[22]

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to 23 weeks of gestation, the incremental performance of the ISSHP definitions was greater at 35 to 36 (vs 19−23) weeks of gestation.

Clinical implications

To best identify women and fetuses at risk of adverse outcomes when diagnosing PE, particularly for those with less clinical experience, the ISSHP definition of PE that includes maternal and fetal components outperforms the ACOG definition that focuses only on maternal components. Although having a PlGF value from 19 to 23 weeks of gestation to further inform the uteroplacental dysfunction component of the 2021 ISSHP PE definition is optimal, "carrying forward" this PlGF adds only a small incremental value to the other components of the PE definition that are available through routine clinical, laboratory, and ultrasonographic assessment. As such, if PlGF were available, as in centers performing routine second-trimester risk stratification for PE,[29] the PlGF result should be used to inform classification of pregnancy hypertension into GH or PE or chronic hypertension or superimposed PE; otherwise, the additional cost of performing PlGF routinely with the 19- to 23-week scan would not be warranted, even if offered at low cost.

Research implications

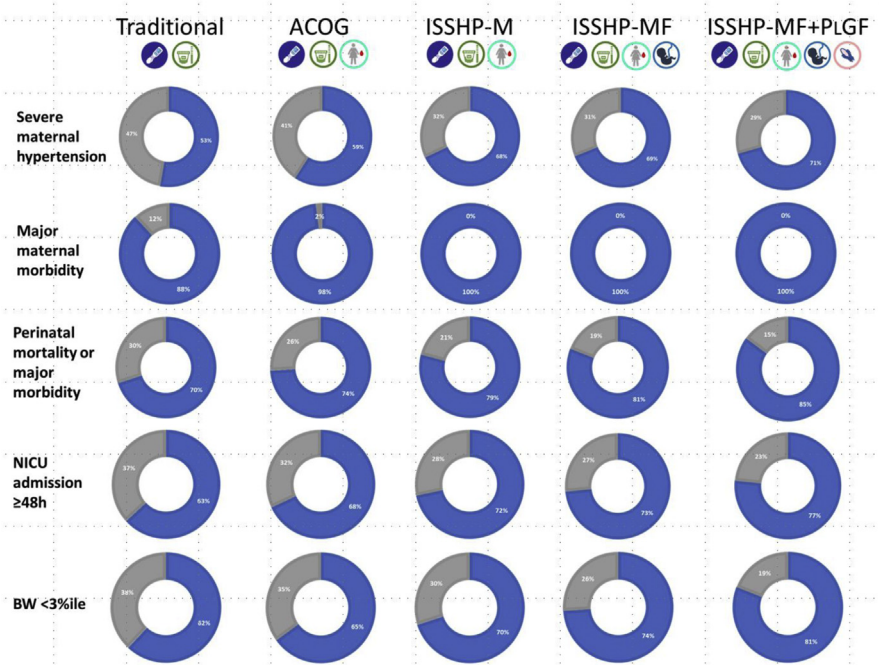
Our findings should be replicated in a study population with uteroplacental dysfunction assessment (ultrasound and angiogenic markers) at fixed time points (ie, 19−23 and 35−36 weeks of gestation, if relevant) and again if and when pregnancy hypertension subsequently develops, to establish the stability of gestational age-corrected PlGF results over time and the need to repeat them if performed previously, to optimize the identification of women and fetuses at increased risk of adverse outcomes. Trials should evaluate whether timed term birth based on a definition of PE that includes uteroplacental dysfunction is associated with potentially greater benefits, as demonstrated for PE based on the traditional definition.[30]

Strengths and limitations

The strengths of our study included the very large sample size, unselected nature of women presenting for their 19- to 23-week routine ultrasonographic assessment, and prospective, comprehensive documentation of baseline characteristics, PE diagnostic criteria, and outcomes at preterm and term gestational ages when PE developed. We investigated the ACOG and ISSHP PE definitions based on the maternal and uteroplacental criteria and included Doppler findings with EFW to define FGR (instead of an EFW of <10th percentile or an antenatal diagnosis of "intrauterine growth restriction"), intrauterine fetal death, and angiogenic imbalance (as determined by low PlGF). Importantly, the women studied were recruited from October 2011 to March 2020 in the United Kingdom, where only a traditional definition of PE was accepted until June 2019[31] and angiogenic markers were advised only for women with suspected PE at <35 0/7 weeks of gestation as part of "time-of-disease" assessment from May 2016.[5]

A limitation of our data was the enrollment only of women with singleton pregnancies; as such, our findings did not necessarily apply to multiple pregnancy. Because of the lack of availability in routinely collected data,

FIGURE
Detection rates for maternal and perinatal outcomes of interest



The figure presents the detection rates (represented in *blue*; a full ring in *blue* represents 100%) for maternal and perinatal outcomes of interest, according to various definitions of preeclampsia: (1) traditional, based on new-onset proteinuria at ≥20 weeks of gestation; (2) 2013 ACOG; (3) 2018 ISSHP-M; (4) 2018 ISSHP-MF (death or growth restriction) (ISSHP-MF), based on ultrasound scans at 19 0/7 to 23 6/7 weeks of gestation (an EFW of <3rd percentile or an EFW between the 3rd and 10th percentiles with a uterine artery pulsatility index of >95th percentile); and (5) 2021 ISSHP-MF+PlGF (with abnormal PlGF defined as an EFW of <5th percentile for gestational age).

ACOG, American College of Obstetricians and Gynecologists; *BW*, birthweight; *EFW*, estimated fetal weight; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *ISSHP-M*, ISSHP maternal factor; *ISSHP-MF*, ISSHP maternal-fetal factor; *ISSHP-MF+PlGF*, ISSHP maternal-fetal factor plus PlGF; *NICU*, neonatal intensive care unit; *PlGF*, placental growth factor.

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we were unable to include some maternal criteria in the ISSHP definition of PE (ie, altered mental status, clonus, disseminated intravascular coagulation, or hemolysis), although none of these are independently associated with adverse maternal outcomes.[20] From a 19- to 23-week ultrasound scan visit at a routine time point for evaluation in maternity care, we used uteroplacental assessment, including PlGF, to inform the classification of subsequent new-onset hypertension as GH or PE (de novo or superimposed on chronic hypertension); this made full use of information that was available at the time that women presented with new-onset hypertension, although it may have been better to have additional "time-of-disease" (repeat) ultrasonographic assessment of EFW and Dopplers and angiogenic markers. However, as 25% of PlGF results may become more abnormal as gestational age progresses,[32] we feel that our carry forward of observations likely underestimated the prevalence of angiogenic imbalance when hypertension developed.

Conclusions

Our findings supported using the results of previously assessed uteroplacental dysfunction at 19 to 23 weeks of gestation, to optimize the diagnosis of PE in pregnant women with hypertension and the identification of those with PE at the greatest risk of adverse maternal and perinatal outcomes. This approach would be particularly useful where specialized fetal assessment is not readily available, at all times, and in the many places that women with pregnancy hypertension present. ■

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SUPPLEMENTAL TABLE

Definitions of de novo preeclampsia, based on new-onset hypertension with 1 or more other features

Variable	Traditional	ACOG	ISSHP		
			ISSHP-M	ISSHP-MF	ISSHP-MF+PIGF
Proteinuria[a]	●	●	●	●	●
Maternal symptoms					
Headache[b]		●	●	●	●
Visual symptoms[c]		●	●	●	●
Maternal signs					
Eclampsia	-	-	●	●	●
Altered mental status	-	-	●	●	●
Blindness	-	-	●	●	●
Stroke	-	-	●	●	●
Clonus	-	-	●	●	●
Pulmonary edema	-	●	●	●	●
Maternal routine laboratory tests					
Platelet count$<150\times10^9$/L	-	-	●	●	●
Platelet count$<100\times10^9$/L	-	●	●	●	●
DIC	-	-	●	●	●
Hemolysis	-	-	●	●	●
Serum creatinine of $\geq$90 μmol/L or $\geq$1 mg/dL	-	-	●	●	●
Serum creatinine>1.1 mg/dL	-	●	●	●	●
Serum creatinine doubling in the absence of other renal disease	-	●	-	-	-
AST or ALT greater than or equal to twice normal ($\geq$65 IU/L)	-	●	●	●	●
AST or ALT of >40 IU/L	-	-	●	●	●
Uteroplacental dysfunction					
Intrauterine fetal death	-	-	-	●	●
FGR at screening[d]	-	-	-	●	●
Abnormal PIGF at screening[e]	-	-	-	-	●

ACOG, American College of Obstetricians and Gynecologists; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *DIC*, disseminated intravascular coagulation; *EFW*, estimated fetal weight; *FGR*, fetal growth restriction; *ISSHP*, International Society for the Study of Hypertension in Pregnancy; *ISSHP-M*, ISSHP maternal factor; *ISSHP-MF*, ISSHP maternal-fetal factor; *ISSHP-MF+PIGF*, ISSHP maternal-fetal factor plus placental growth factor; *PE*, preeclampsia; *PI*, pulsatility index; *PIGF*, placental growth factor.

[a] Proteinuria was defined as $\geq$2+ by urinary dipstick testing, $\geq$ 30 mg/mmol or 0.3 mg/dL by protein-to-creatinine ratio, or $\geq$0.3 g/d by 24-hour urine collection; [b] Headache was defined by the ACOG as new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, whereas ISSHP defined headache as "severe;"; [c] Visual symptoms were not defined by the ACOG but were defined by the ISSHP as persistent visual scotomata; [d] FGR was not defined by the ISSHP but was taken here to be defined as an EFW of <3rd percentile or an EFW between the 3rd and 9th percentiles with abnormal Dopplers, defined as a uterine artery PI MoM of >95th percentile; [e] Abnormal PIGF was defined as an MoM of <5th percentile for gestational age.

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