OBSTETRICS

Impact of new definitions of preeclampsia at term on identification of adverse maternal and perinatal outcomes

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BACKGROUND: Any definition of preeclampsia should identify women and babies at greatest risk of adverse outcomes.

OBJECTIVE: This study aimed to investigate the ability of the American College of Obstetricians and Gynecologists and International Society for the Study of Hypertension in Pregnancy definitions of preeclampsia at term gestational age (≥37 0/7 weeks) to identify adverse maternal and perinatal outcomes.

STUDY DESIGN: In this prospective cohort study at 2 maternity hospitals in England, women attending a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation underwent assessment that included history; ultrasonographic estimated fetal weight; Doppler measurements of the pulsatility index in the uterine, umbilical, and fetal middle cerebral arteries; and serum placental growth factor—to—soluble fms-like tyrosine kinase-1 ratio. Obstetrical records were examined for all women with chronic hypertension and those who developed new-onset hypertension, with preeclampsia (de novo or superimposed on chronic hypertension) defined in 5 ways: traditional, based on new-onset proteinuria; American College of Obstetricians and Gynecologists 2013 definition; International Society for the Study of Hypertension in Pregnancy maternal factors definition; International Society for the Study of Hypertension in Pregnancy maternal factors plus fetal death or fetal growth restriction definition, defined according to the 35 0/7 to 36 6/7 weeks' gestation scan as either estimated fetal weight <3rd percentile or estimated fetal weight at the 3rd to 10th percentile with any of uterine artery pulsatility index >95th percentile, umbilical artery pulsatility index >95th percentile, or middle cerebral artery pulsatility index <5th percentile; and International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance definition, defined as placental growth factor <5th percentile or soluble fms-like tyrosine kinase-1—to—serum placental growth factor >95th percentile. Detection rates for outcomes of interest (ie, severe maternal hypertension, major maternal morbidity, perinatal mortality or major neonatal morbidity, neonatal unit admission ≥48 hours, and birthweight <10th percentile) were compared using the chi-square test, and $P<.05$ was considered significant.

RESULTS: Among 15,248 singleton pregnancies, the identification of women with preeclampsia varied by definition: traditional, 15 of 281 (1.8%; 248); American College of Obstetricians and Gynecologists, 15 of 326 (2.1%; 248); International Society for the Study of Hypertension in Pregnancy maternal factors, 15 of 400 (2.6%; 248); International Society for the Study of Hypertension in Pregnancy maternal-fetal factors, 15 of 434 (2.8%; 248); and International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance, 15 of 500 (3.3%; 248). Compared with the traditional definition of preeclampsia, the International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance best identified the adverse outcomes: severe hypertension (40.6% [traditional] vs 66.9% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance, $P<.0001$], 59.2% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors, $P=.004$], 56.2% [International Society for the Study of Hypertension in Pregnancy maternal factors, $P=.013$], 46.1% [American College of Obstetricians and Gynecologists, $P=.449$]); $P<.0001$); composite maternal severe adverse event (72.2% [traditional] vs 100% for all others; $P=.046$); composite of perinatal mortality and morbidity (46.9% [traditional] vs 71.1% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance, $P=.002$], 62.2% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors, $P=.06$], 59.8% [International Society for the Study of Hypertension in Pregnancy maternal factors, $P=.117$], 49.4% [American College of Obstetricians and Gynecologists, $P=.875$]); neonatal unit admission for ≥48 hours (51.4% [traditional] vs 73.4% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance, $P=.001$], 64.5% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors, $P=.070$], 60.7% [International Society for the Study of Hypertension in Pregnancy maternal factors, $P=.213$], 53.3% [American College of Obstetricians and Gynecologists, $P=.890$]); birthweight <10th percentile (40.5% [traditional] vs 78.7% [International Society for the Study of Hypertension in Pregnancy maternal-fetal factors plus angiogenic imbalance, $P<.0001$], 70.1% [International Society for the Study of Hypertension in Pregnancy maternal-fetal, $P<.0001$], 51.3% [International Society for the Study of Hypertension in Pregnancy maternal factors, $P=.064$], 46.3% [American College of Obstetricians and Gynecologists, $P=.349$]).

CONCLUSION: Our findings present an evidence base for the broad definition of preeclampsia. Our data suggest that compared with a traditional definition, a broad definition of preeclampsia can better identify women and babies at risk of adverse outcomes. Compared with the American College of Obstetricians and Gynecologists definition, the more inclusive International Society for the Study of Hypertension in Pregnancy definition of maternal end-organ dysfunction seems to be more sensitive. The addition of uteroplacental dysfunction to the broad definition optimizes the identification of women and babies at risk, particularly when angiogenic factors are included.

Key words: angiogenic markers, definition, outcomes, preeclampsia, ultrasound

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EDITORS' CHOICE

Introduction

Preeclampsia (PE) complicates 2% to 4% of pregnancies worldwide,[1,2] with most occurring at term gestational age (≥37 0/7 weeks). The traditional definition of PE is based on the development of hypertension and proteinuria.

PE is distinguished from other hypertensive disorders of pregnancy, namely, chronic and gestational hypertension, based on its greater risk of adverse maternal and perinatal

AJOG at a Glance

Why was this study conducted?

This study aimed to investigate the ability of different definitions of preeclampsia (PE) at term gestational age (≥37 0/7 weeks) to identify adverse maternal and perinatal outcomes.

Key findings

Compared with the traditional definition of PE, a broad definition significantly improved the detection of adverse outcomes for mothers and babies, owing to the addition of less abnormal platelet, creatinine, and liver enzyme results but particularly associated with the addition of uteroplacental dysfunction based on an objective assessment of fetal growth restriction and angiogenic markers.

What does this add to what is known?

These data contribute to the evidence base for use of a broad definition of PE that includes uteroplacental dysfunction at term.

outcomes. However, it is well recognized that many women with chronic or gestational hypertension still suffer from complications typically associated with PE. For example, many women with gestational hypertension suffer end-organ complications, such as pulmonary edema,[3] and those with severe hypertension more frequently experience adverse outcomes (compared with women with traditionally defined PE), such as placental abruption, preterm delivery, perinatal death, small-for-gestational-age (SGA) infants, and neonatal respiratory distress syndrome (RDS).[4,5] Among women with chronic hypertension, the traditional definition of superimposed PE accounts for fewer than 50% of preterm births and a minority of SGA infants and high-level neonatal care admissions.[6–10]

To better reflect the risk of adverse pregnancy complications among women with a hypertensive disorder of pregnancy, the definition of PE has been revised to include cases without proteinuria but with evidence of other maternal end-organ or uteroplacental dysfunction. This "broad" definition has now been adopted by most national and international clinical practice guidelines, notably the American College of Obstetrics and Gynecology (ACOG),[11,12] the International Society for the Study of Hypertension in Pregnancy (ISSHP),[13] and, most recently, the National Institute for Health and Care Excellence (NICE), United Kingdom, that adopted the ISSHP definition.[14] However, controversy remains, concerning how maternal end-organ dysfunction should be defined, whether uteroplacental dysfunction should be included in the diagnostic criteria for PE, and, if so, how should uteroplacental dysfunction be defined.

Any definition of PE should optimally identify women and babies at increased risk of adverse outcomes. The objective of this study was to investigate the ability of different definitions of PE at term gestational age to identify adverse maternal and perinatal outcomes. We compared the traditional definition of PE (established clinical standard), ACOG definition (maternal criteria only), and ISSHP definition (maternal and/or uteroplacental criteria), considering the definitions of uteroplacental dysfunction that incorporated fetal growth restriction (FGR) and the measurements of angiogenic markers.

Methods

Study design and participants

This was a prospective cohort study of women who attended a routine hospital visit at 35 0/7 to 36 6/7 weeks' gestation at King's College Hospital, London, and Medway Maritime Hospital, Gillingham, United Kingdom, between October 2016 and September 2018. The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee.

This 35 0/7 to 36 6/7 weeks' gestation visit included the following: recording of maternal demographics and medical history; ultrasound examination for fetal anatomy and estimated fetal weight (EFW) from measurements of fetal head circumference, abdominal circumference, and femur length[15,16] and Doppler measurements of the pulsatility index (PI) in the uterine artery (UtA), umbilical artery (UA), and fetal middle cerebral artery (MCA); and measurement of maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age was determined by the measurement of fetal crown-rump length at 11 to 13 weeks' gestation or the fetal head circumference at 19 to 24 weeks' gestation.[17,18]

The inclusion criteria for this analysis were singleton pregnancies that delivered a nonmalformed live-born or stillborn baby. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Diagnosis of preeclampsia

Data related to pregnancy outcome were collected from the hospital maternity records or those of their general medical practitioners. The obstetrical records of all women with chronic hypertension and those with new-onset, pregnancy-associated hypertension were examined to determine the diagnosis of gestational hypertension or PE.

Gestational hypertension was defined as new-onset hypertension (ie, systolic blood pressure [BP] of ≥140 mm Hg or diastolic BP of ≥90 mm Hg, on at least 2 occasions, 4 hours apart) that developed after 20 weeks' gestation, in a previously normotensive woman.[19]

In this study, 5 definitions of PE were considered (Supplemental Table), based on the finding of an additional feature (ie, a maternal end-organ dysfunction, with or without uteroplacental dysfunction, depending on the definition) among women with chronic hypertension or in association with new-onset hypertension among other women (as defined above).

We included only quantitative measures of renal, hepatic, or hematologic dysfunction, according to the ACOG and ISSHP criteria.[12,19]

The traditional definition of PE was based on new-onset proteinuria (ie, ≥300 mg/24 h or protein-to-creatinine ratio of ≥30 mg/mmol or ≥2+ on dipstick testing).[20]

The ACOG definition of PE was based on the development of at least 1 of the following: new-onset proteinuria, renal insufficiency (ie, serum creatinine of >97 μmol/L) in the absence of underlying renal disease, hepatic involvement with serum transaminases more than twice the upper limit of normal (ie, ≥65 IU/L for our laboratory), thrombocytopenia (ie, platelet count of <100,000/μL), neurologic complications (ie, headache or visual symptoms), or pulmonary edema.[12]

The ISSHP definition of PE was examined according to its maternal (ISSHP maternal factors [ISSHP-M]) and uteroplacental components (ISSHP maternal-fetal factors [ISSHP-MF]). The ISSHP-M definition was based on at least 1 of the following: new-onset proteinuria, renal insufficiency (serum creatinine of ≥90 μmol/L) in the absence of underlying renal disease, hepatic involvement with serum transaminases of >40 IU/L, thrombocytopenia (ie, platelet count of <150,000/μL), or neurologic complications (ie, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); the criteria for altered mental status and clonus were not available. The ISSHP-MF definition included all criteria as above for ISSHP-M, with the addition of fetal death or FGR; FGR was defined according to the findings of the 35 0/7 to 36 6/7 weeks' gestation scan, as either EFW <3rd percentile or EFW at the 3rd to 10th percentile in the presence of either of the following: UtA-PI >95th percentile, UA-PI >95th percentile, or MCA PI <5th percentile. The ISSHP-MF-AI definition included all criteria as above for ISSHP-MF, with the addition of angiogenic imbalance, defined as serum PlGF <5th percentile or sFlt-1—to—PlGF ratio >95th percentile.

TABLE 1
Baseline characteristics and outcomes of the screening population

Characteristic	Pregnancies (N=15,248)
Maternal demographics	
Age (y)	32.2 (28.3—35.8)
BMI (kg/m^2)	29.0 (26.1—32.7)
BMI>30 kg/m^2	6447.0 (42.2)
Weight (kg)	79.0 (71.0—89.9)
Height (cm)	165.0 (161.0—170.0)
Racial origin	
White	12,125 (79.5)
Black	1688 (11.1)
South Asian	680 (4.5)
East Asian	316 (2.1)
Mixed	439 (2.9)
Cigarette smoker	963 (6.3)
Family history	
Mother had PE	569 (3.7)
Medical history	
Chronic hypertension	147 (1.0)
On antihypertensive medication	119 (81.0)
Systemic lupus erythematosus or antiphospholipid antibody syndrome	36 (0.2)
Diabetes mellitus (type 1 or 2)	148 (1.0)
Obstetrical history	
Nulliparous	7122 (46.7)
Parous without previous PE	7857 (51.5)
Parous with previous PE	269 (1.8)
Interpregnancy interval (y)	2.8 (1.8—4.7)
This pregnancy	
Conception	
Natural	14,584 (95.6)
Assisted by use of ovulation drugs	87 (0.6)
In vitro fertilization	577 (3.8)
Gestational age at screening (wk)	36.1 (35.9—36.4)
Gestational diabetes mellitus[a]	636 (4.2)
Screening markers for PE at 35 0/7 to 36 6/7 wk	
Mean arterial pressure (mm Hg)	88.1 (83.2—93.2)
Systolic BP (mm Hg)	118.5 (111.8—125.0)
Systolic BP≥140 mm Hg	221 (1.4)

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Outcome measures

The outcomes of interest were major maternal and perinatal outcomes: severe maternal hypertension, a composite of maternal death or major morbidity, a composite of perinatal

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

Characteristic	Pregnancies (N=15,248)
Diastolic BP (mm Hg)	73.0 (68.3–78.0)
Diastolic BP≥90 mm Hg	256 (1.7)
Uterine artery PI	0.7 (0.6–0.8)
Uterine artery PI >95th percentile	1068 (6.8)
Umbilical artery PI	0.91 (0.8–1.01)
Umbilical artery PI >95th percentile	435 (2.9)
Middle cerebral artery PI	1.75 (1.54–1.92)
Middle cerebral artery PI >95th percentile	521 (3.4)
PlGF (pg/mL)	251.0 (132.6–467.6)
PlGF <5th percentile	762 (5.0)
sFlt-1–to–PlGF ratio	8.3 (3.6–21.5)
sFlt-1–to–PlGF ratio >95th percentile	762 (5.0)
sFlt-1–to–PlGF ratio >95th percentile or PlGF <5th percentile	1008 (6.6)
Pregnancy outcomes	
Gestational age at birth (wk)	40.0 (39.1–40.9)
Induction of labor	3253 (21.3)
Vaginal delivery	11,187 (73.4)
Spontaneous vaginal delivery	8849 (58.0)
Cesarean delivery	4062 (26.6)
Perinatal mortality or major morbidity[b]	697 (4.6)
Intrauterine fetal death	33 (0.2)
Neonatal death	1 (0.006)
Ventilation	147 (1.0)
RDS	230 (1.5)
Brain injury	32 (0.2)
Sepsis	518 (3.4)
Anemia	12 (0.1)
NEC	1 (0.006)
Neonatal unit admission ≥48 h	1086 (7.1)
Birthweight <10th percentile[c]	1585 (10.4)

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

BMI, body mass index; *BP*, blood pressure; *NEC*, necrotizing enterocolitis requiring surgery; *PE*, preeclampsia; *PI*, pulsatility index; *PlGF*, placental growth factor; *RDS*, respiratory distress syndrome requiring surfactant; *sFlt-1*, soluble fms-like tyrosine kinase-1.

Adapted from Nicolaides et al.[23]

[a] Gestational diabetes was defined as hyperglycemia diagnosed in pregnancy; [b] Major neonatal morbidity was defined as 1 or more of the following: ventilation, RDS, brain injury, sepsis, anemia, or NEC; [c] The birthweight percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight medical records.

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death or major morbidity (ie, intrauterine fetal death, neonatal death to hospital discharge, or neonatal morbidity), neonatal unit admission for ≥48 hours, and birthweight <10th percentile.

Severe maternal hypertension was defined as systolic BP of ≥160 mm Hg or diastolic BP of ≥110 mm Hg. Major maternal morbidity was defined as 1 or more of eclampsia, blindness, stroke, myocardial ischemia, pulmonary edema, elevated liver enzymes, hepatic hematoma, low platelets, or acute kidney injury; morbidity was based on the core maternal outcome set in PE, with the exception of liver rupture, postpartum hemorrhage, intensive care unit admission, and intubation and ventilation (not for childbirth) that were not available, placental abruption that was defined clinically and underreported, and the addition of myocardial ischemia based on the Delphi-derived preeclampsia integrated estimate of risk score.[21,22]

Neonatal death was considered up to 28 days after birth. Major neonatal morbidity was defined as 1 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), RDS (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 birthweight percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight medical records.[23] Perinatal outcomes covered the core perinatal outcome set in PE, with the exception of neonatal seizures.

Statistical analysis

Data were summarized descriptively for the total population and for different definitions of PE, with the associated impact on gestational hypertension also presented. Median and interquartile range was used for continuous variables and number (percentage) for categorical variables. Comparisons of the occurrence of adverse maternal and perinatal outcomes according to definitions of PE relative to the traditional one were performed using the chi-square test.

Results

Study participants

Table 1 summarizes the maternal and pregnancy characteristics of the study population and details of the screening marker results and pregnancy outcomes. On average, women were in their early 30s and overweight. Most of the women were white. Few women were cigarette smokers. Very few women reported that their mothers had PE. Medical history was usually unremarkable, with few women reporting chronic hypertension (most of which was treated with antihypertensive therapy), gestational diabetes mellitus, or rheumatic disease. Most conceptions were natural, and just over half of the women were parous, with few of them (269 of 8126 [3.3%]) reporting a previous pregnancy complicated by PE. The assessment occurred at a median of 36 weeks at which point <2% of women had elevated BP, and <10% had abnormal readings of UtA, UA, or MCA PI or abnormal PlGF or sFlt-1—to—PlGF ratio. Birth occurred at a median of 40.0 weeks, for ≈20% of women following induction and for ≈25% overall by cesarean delivery.

Preeclampsia definitions

Table 2 presents the elements of the PE definitions for women with new-onset (n=741) or chronic hypertension (n=147). Most commonly, women satisfied maternal diagnostic criteria for PE based on abnormal routine laboratory tests (ie, low platelet count or elevated liver enzymes) or proteinuria specifically among women with chronic hypertension. Most women satisfied uteroplacental diagnostic criteria based on abnormal angiogenic markers at 35 0/7 to 36 6/7 weeks' gestation.

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=741)	Chronic hypertension (n=147)
Proteinuria[a]	270 (3.6)	11 (7.5)
Maternal symptoms[b]		
Headache	21 (2.8)	0
Visual symptoms	20 (2.7)	0
Maternal signs[c]		
Eclampsia	4 (0.5)	0
Myocardial ischemia	1 (0.1)	0
Pulmonary edema	2 (0.3)	0
Abnormal maternal laboratory tests[d]		
Platelet count<150×10^9/L	78 (10.3)	7 (4.8)
Platelet count<100×10^9/L	12 (1.7)	1 (0.7)
Serum creatinine≥90 μmol/L	23 (3.1)	2 (1.4)
Serum creatinine>97 μmol/L	22 (3.0)	1 (0.7)
AST or ALT>40 IU/L	96 (13.0)	9 (6.1)
AST or ALT≥65 IU/L	54 (7.3)	0
Uteroplacental dysfunction		
Intrauterine fetal death	2 (0.3)	0
EFW <3rd percentile	32 (4.3)	4 (2.7)
EFW at the 3rd to 10th percentile with abnormal Dopplers[e]	10 (1.3)	3 (2.0)
Abnormal angiogenic markers at screening[f]	214 (28.9)	15 (10.2)

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, *PI*, pulsatility index; *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[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 medications 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] No information was available on altered mental status or clonus. There were no cases of blindness; [d] No information was available on disseminated intravascular coagulation or hemolysis; [e] Abnormal Dopplers were defined as any of the following: uterine artery PI >95th percentile, umbilical artery PI >95th percentile, or middle cerebral artery PI <5th percentile; [f] Abnormal angiogenic markers were defined as PlGF <5th percentile or sFlt-1—to—PlGF ratio >95th percentile.

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Performance of each classification

Table 3 summarizes the number of women with gestational hypertension and PE, according to each PE definition and the associated occurrence of adverse maternal and perinatal outcomes. PE was least common with the traditional definition (1.8%) and become progressively more common, reaching its highest value with the ISSHP-MF-AI definition (3.3%). Most of the increase was attributable to fewer women being diagnosed with gestational hypertension, although some women were classified as having PE superimposed on chronic hypertension, particularly with the move to the ISSHP definitions. Each definition of PE was associated with a similar prevalence of adverse maternal and perinatal outcomes that reflected a high-risk population. For all definitions, severe hypertension occurred in just under 20% of women, and major maternal morbidity was approximately 5%, most commonly because of hemolysis, elevated liver enzyme levels, and low platelet count, followed by eclampsia. At least two-thirds of women with PE were induced and 40% delivered by cesarean delivery, whereas just over half of women with gestational hypertension were induced and about one-third delivered by cesarean delivery. Perinatal death or major morbidity occurred in ≈9% of pregnancies with

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

Outcome	Traditional		ACOG		ISSHP-M		ISSHP-MF		ISSHP-MF-AI	
	GH n=471 (3.1)	PE n=281 (1.8)	GH n=427 (2.8)	PE n=326 (2.1)	GH n=367 (2.4)	PE n=400 (2.6)	GH n=338 (2.2)	PE n=434 (2.8)	GH n=279 (1.8)	PE n=500 (3.3)
Superimposed on CH	—	11 (3.9)	—	12 (3.7)	—	26 (6.5)	—	31 (7.1)	—	38 (7.6)
Maternal										
Severe hypertension	76 (16.1)	52 (18.5)	69 (16.2)	59 (18.1)	57 (15.5)	73 (18.3)	53 (15.6)	77 (17.7)	43 (15.4)	87 (17.4)
Major morbidity	5 (1.1)	13 (4.6)	0	18 (5.5)	0	18 (4.5)	0	18 (4.1)	0	18 (3.6)
Death	0	1 (0.4)	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Eclampsia	0	4 (1.4)	0	4 (1.2)	0	4 (1.0)	0	4 (0.9)	0	4 (0.8)
Myocardial ischemia	0	1 (0.4)	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Pulmonary edema	0	2 (0.7)	0	2 (0.6)	0	2 (0.5)	0	2 (0.5)	0	2 (0.4)
HELLP syndrome	5 (1.1)	7 (2.5)	0	12 (3.7)	0	12 (3.0)	0	12 (2.8)	0	12 (2.4)
Hepatic hematoma	0	1 (0.4)	0	1 (0.3)	0	1 (0.3)	0	1 (0.2)	0	1 (0.2)
Labor and delivery										
Induction of labor	252 (53.5)	205 (73.0)	229 (53.6)	228 (69.9)	199 (54.2)	262 (65.5)	180 (53.3)	284 (65.4)	147 (52.7)	319 (63.8)
Vaginal delivery	312 (66.2)	160 (56.9)	283 (66.3)	189 (58.0)	238 (64.9)	240 (60.0)	220 (65.0)	260 (59.9)	187 (67.0)	294 (58.8)
Spontaneous vaginal delivery	136 (28.9)	38 (13.5)	121 (28.3)	53 (16.3)	99 (27.0)	79 (19.8)	97 (28.7)	81 (18.7)	84 (30.1)	94 (18.8)
Cesarean delivery	159 (33.8)	121 (43.1)	144 (33.7)	137 (42.0)	129 (35.1)	160 (40.0)	119 (35.2)	173 (39.9)	92 (33.0)	206 (41.2)
Perinatal										
Perinatal mortality or major neonatal morbidity	43 (9.1)	38 (13.5)	41 (9.6)	40 (12.3)	33 (9.0)	49 (12.3)	31 (9.2)	51 (11.8)	24 (8.6)	59 (11.8)
Intrauterine fetal death	1 (0.2)	1 (0.4)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.3)	0	2 (0.5)	0	2 (0.4)
Neonatal death	0	0	0	0	0	0	0	0	0	0
Ventilation	6 (1.3)	11 (3.9)	5 (1.2)	12 (3.7)	4 (1.1)	13 (3.3)	4 (1.2)	13 (3.0)	3 (1.1)	14 (2.8)
RDS	12 (2.5)	10 (3.6)	12 (2.8)	10 (3.1)	10 (2.7)	12 (3.0)	10 (2.9)	12 (2.8)	7 (2.5)	16 (3.2)
Brain injury	2 (0.4)	4 (1.4)	2 (0.5)	4 (1.2)	2 (0.5)	4 (1.0)	2 (0.6)	4 (0.9)	1 (0.4)	5 (1.0)
Sepsis	33 (7.0)	29 (10.3)	32 (7.5)	30 (9.2)	25 (6.8)	38 (9.5)	24 (7.1)	39 (9.0)	19 (6.8)	45 (9.0)
Anemia	1 (0.2)	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	0	1 (0.2)
NEC	1 (0.2)	0	1 (0.2)	0	1 (0.3)	0	1 (0.3)	0	1 (0.4)	0

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(continued)

TABLE 3
Adverse pregnancy outcomes according to the definitions of gestational hypertension and PE *(continued)*

Outcome	Traditional		ACOG		ISSHP-M		ISSHP-MF		ISSHP-MF-AI	
	GH n=471 (3.1)	PE n=281 (1.8)	GH n=427 (2.8)	PE n=326 (2.1)	GH n=367 (2.4)	PE n=400 (2.6)	GH n=338 (2.2)	PE n=434 (2.8)	GH n=279 (1.8)	PE n=500 (3.3)
Neonatal unit admission ≥48 h	51 (10.8)	54 (19.2)	49 (11.5)	56 (17.2)	42 (11.4)	65 (16.3)	38 (11.2)	69 (15.9)	29 (10.4)	80 (16.0)
Birthweight <10th percentile	88 (18.7)	60 (21.4)	80 (18.7)	69 (21.2)	73 (19.9)	77 (19.3)	46 (13.6)	108 (24.9)	33 (11.8)	122 (24.4)

Data are presented as number (percentage).

ACOG, American College of Obstetricians and Gynecologists; *CH*, chronic hypertension; *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 definition; *ISSHP-MF*, ISSHP maternal-fetal definition; *ISSHP-MF-AI*, ISSHP maternal-fetal plus angiogenic imbalance definition; *NEC*, necrotizing enterocolitis requiring surgery; *PE*, preeclampsia; *RDS*, respiratory distress syndrome requiring surfactant.

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gestational hypertension and ≈11% with PE. Major neonatal morbidity was most commonly due to sepsis and RDS. Neonatal unit admission for ≥48 hours occurred in just over 10% of pregnancies with gestational hypertension and more than 15% of those with PE. Babies with a birthweight <10th percentile occurred in <20% (and as low as 12%) of pregnancies with gestational hypertension and more than 20% with PE.

Table 4 shows that the detection rate (sensitivity) of PE definitions for adverse outcomes was higher with all broad definitions, with statistical significance reached for ACOG (for major maternal morbidity), ISSHP-M (for severe hypertension and major maternal morbidity), ISSHP-MF (for severe hypertension, major maternal morbidity, and birthweight <10th percentile), and ISSHP-MF-AI definitions (for all outcomes). The higher detection rates were achieved with similar true positive rates (Table 3).

Comment

Principal findings

In a large cohort of women assessed at 35 to 36 weeks' gestation, the proportion of women with PE defined traditionally by new-onset hypertension and proteinuria was almost half of that when the definition included not only new-onset proteinuria but also other maternal end-organ involvement or uteroplacental dysfunction. The higher prevalence was associated with improved identification of women at increased risk of adverse maternal and perinatal outcomes with similar true positive rates.

Comparison with published literature

Consistent with our findings, a number of studies have documented a higher prevalence of PE and corresponding lower prevalence of gestational hypertension and chronic hypertension, using a broad, rather than traditional, definition of PE.[24–27] Our data confirm that these observations hold true when focused on PE at term, when the largest proportion of cases occurs.

Previous studies of the relationship between PE definitions and outcomes have questioned the value of a broad (vs traditional) definition of PE based on concerns that a low-risk population is being identified by the broad definition, at least at gestational ages preterm.[24,25,27] However, adverse maternal and neonatal outcome rates have been well above the baseline rates,[24,27] similar to our findings, suggesting that the use of a broad definition with uteroplacental function, as defined by EFW, Dopplers, and angiogenic imbalance, is clinically useful. In addition, the independent value of routine maternal laboratory test results and FGR were recently demonstrated[27]; although the role of headache and visual symptoms was not demonstrated, these have been shown to have prognostic value in the absence of laboratory testing, such as in the self-monitored setting in high-income countries or in low-resource settings where most women and babies die of PE.

Most clinical practice guidelines (12 of 15) identified by systematic review recommend a broad definition of PE, based on new-onset hypertension and manifestations including, but not limited to, new-onset proteinuria.[28] There is widespread agreement for the inclusion of proteinuria (12 of 12 guidelines), maternal symptoms of headache or visual disturbances (12 of 12), and abnormal routine laboratory testing of low platelet count (11 of 12), raised serum creatinine (11 of 12), or elevated liver enzymes (12 of 12), but there is no agreement on how these should be defined. Our data suggest that the definitions proposed by the ISSHP (rather than the ACOG) may better identify women at risk, such as those who go on to develop severe hypertension; the ISSHP includes women with organ dysfunctions other than pulmonary edema (eg, eclampsia, stroke) and less severe perturbations of platelets ($<150\times10^9$/L vs $<100\times10^9$/L), serum creatinine (≥1 mg/dL vs >1.1 mg/dL), or liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] of >40 IU/L rather than ≥twice normal) (Supplemental Table). In addition, guidelines do not widely endorse the inclusion of uteroplacental dysfunction in the broad definition of PE, based

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

Outcome	Traditional (n=281)	Reference	ACOG (n=326)	*P* value	ISSHP-M (n=338)	*P* value	ISSHP-MF (n=434)	*P* value	ISSHP-MF-AI (n=500)	*P* value
Detection rate, % (n/N)										
Severe maternal hypertension	40.6 (52/128)	—	46.1 (59/128)	.449	56.2 (73/130)	.013	59.2 (77/130)	.004	66.9 (87/130)	<.0001
Major maternal morbidity	72.2 (13/18)	—	100 (18/18)	.046	100 (18/18)	.046	100 (18/18)	.046	100 (18/18)	.046
Perinatal mortality and major morbidity	46.9 (38/81)	—	49.4 (40/81)	.875	59.8 (49/82)	.117	62.2 (51/82)	.060	71.1 (59/83)	.002
Neonatal unit admission ≥48 h	51.4 (54/105)	—	53.3 (56/105)	.890	60.7 (65/107)	.213	64.5 (69/107)	.070	73.4 (80/109)	.001
Birthweight <10th percentile	40.5 (60/148)	—	46.3 (69/149)	.349	51.3 (77/150)	.064	70.1 (108/154)	<.0001	78.7 (122/155)	<.0001

The *P* value represents the comparison of the detection rate with the traditional definition of preeclampsia.
ACOG, American College of Obstetricians and Gynecologists; *ISSHP-M*, ISSHP maternal definition; *ISSHP-MF*, ISSHP maternal-fetal definition; *ISSHP-MF-AI*, ISSHP maternal-fetal plus angiogenic imbalance definition.
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on any of the following criteria: intrauterine fetal death (4 of 12 guidelines), FGR (9 of 12), abnormal UA Doppler (3 of 12), angiogenic imbalance (3 of 12), abruption (2 of 12), oligohydramnios (1 of 12), or abnormal fetal cardiotocography (1 of 12). Only angiogenic imbalance is defined as a low PlGF or elevated sFlt-1—to—PlGF ratio, but 2 guidelines recommend their use as a "rule-out" test for PE when normal (but not part of the definition when abnormal)[29,30] and 1 guideline as a "rule-in" test, even in the absence of other manifestations of PE.[31]

Clinical implications

Our findings present an evidence base for the broad definition of PE. Our data suggest that compared with a traditional definition, a broad definition of PE can better identify women and babies at risk of adverse outcomes, over and above the risks associated with gestational hypertension. Compared with the ACOG definition, the more inclusive ISSHP definition of maternal end-organ dysfunction seems to be more sensitive. The addition of the uteroplacental dysfunction to the broad definition optimizes the identification of women and babies at risk, particularly when angiogenic factors are included.

Research implications

Our findings should be replicated in a population that includes both preterm pregnancies and uteroplacental dysfunction assessed at presentation with hypertension, with ultrasound, Dopplers, and, in particular, angiogenic factors. Cost consequences should be incorporated. Trials should evaluate whether timed term birth based on a broad definition of PE, which includes uteroplacental dysfunction (including angiogenic imbalance, if available) is associated with similar benefits as demonstrated for PE based on the traditional definition.[32]

Strength and limitations

Strengths of our study include the large sample size, unselected nature of women presenting for a 36-week assessment, and the prospective, detailed

documentation of baseline characteristics, PE criteria, and outcomes. We investigated the ACOG and ISSHP PE definitions based on the maternal and uteroplacental criteria and expanded the previous definition studied[24] by adding 3 criteria: Doppler findings to EFW to define FGR (instead of EFW <10th percentile or an antenatal diagnosis of "intrauterine growth restriction"), intrauterine fetal death, and angiogenic imbalance. Importantly, the women studied were managed in the United Kingdom where only a traditional definition of PE was accepted[33] and angiogenic markers were advised only for women with suspected PE at <35 0/7 weeks' gestation.[34]

A limitation of our data is that all women enrolled had singleton pregnancies, so our results do not necessarily apply to multiples. We studied a cohort of women who had reached near-term gestational age; although our results may not apply to preterm women, they are consistent with studies that have included such women, and most PE occurs at term. We were unable to include all maternal criteria advocated by the ISSHP; no information was available on the clinical criteria of altered mental status or clonus or the laboratory findings of disseminated intravascular coagulation or hemolysis. We used the 35 0/7 to 36 6/7 weeks' gestation uteroplacental assessment to diagnose subsequent new-onset hypertension as gestational hypertension or PE; although this makes full use of information collected where the 36-week scan is routine, it would have been ideal to have repeat ultrasonographic assessment of EFW and Dopplers or angiogenic balance. However, we feel that our carryforward of observations likely underestimated the prevalence of abnormalities when hypertension developed and thus underestimated the strength of the uteroplacental assessment-outcome relationship.

Conclusions

Our findings present an evidence base for the broad definition of PE. Our data suggest that compared with a traditional definition, a broad definition of PE can better identify women and babies at risk of adverse outcomes. Compared with the ACOG definition, the more inclusive ISSHP definition of maternal end-organ dysfunction seems to be more sensitive. The addition of uteroplacental dysfunction to the broad definition optimizes the identification of women and babies at risk, particularly when angiogenic factors are included. ■

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SUPPLEMENTAL TABLE

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

Outcome	Traditional	ACOG	ISSHP		
			ISSHP-M	ISSHP-MF	ISSHP-MF-AI
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$\geq$90 μmol/L or $\geq$1 mg/dL	-	-	●	●	●
Serum creatinine$>$1.1 mg/dL	-	●	●	●	●
Serum creatinine doubling in the absence of other renal diseases	-	●	-	-	-
AST or ALT $\geq$twice normal ($\geq$65 IU/L)	-	●	●	●	●
AST or ALT$>$40 IU/L	-	-	●	●	●
Uteroplacental dysfunction					
Intrauterine fetal death	-	-	-	●	●
FGR at screening[d]	-	-	-	●	●
Abnormal angiogenic markers at screening[e]	-	-	-	-	●

The solid dot means that the outcome was included in the definition. The dash means that it was not.

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 definition; *ISSHP-MF*, ISSHP maternal-fetal definition; *ISSHP-MF-AI*, ISSHP maternal-fetal plus angiogenic imbalance definition; *PI*, pulsatility index; *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[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 the 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 the EFW $<$3rd percentile or EFW at the 3rd to 9th percentile with abnormal Dopplers, defined as any of uterine artery PI $>$95th percentile, umbilical artery PI $>$95th percentile, or middle cerebral artery PI $<$5th percentile. This definition incorporates the abnormal umbilical artery Dopplers listed by the ISSHP as a separate criterion; [e] Angiogenic imbalance was defined as a PlGF $<$5th percentile or a sFlt-1—to—PlGF ratio $>$95th percentile for gestational age.

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