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

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CONDENSATION

A broad definition of preeclampsia that includes maternal end-organ involvement and objective assessment of uteroplacental dysfunction improves the detection of adverse maternal and perinatal risks.

SHORT VERSION OF TITLE:

Preeclampsia definitions and their relationship with outcomes

AJOG AT A GLANCE

Why was this study conducted?

To investigate the ability of different definitions of preeclampsia at term gestational age (≥37+0 weeks), to identify adverse maternal and perinatal outcomes.

Key findings

Compared with the traditional definition of preeclampsia, a broad definition significantly improved the detection of adverse outcomes for mothers and babies, due to addition of less abnormal platelet, creatinine, and liver enzyme results, but particularly associated with addition of uteroplacental dysfunction based on 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 preeclampsia that includes uteroplacental dysfunction at term.

ABSTRACT

Objective: To investigate the ability of the American College of Obstetricians and Gynecologists (ACOG) and International Society for the Study of Hypertension in Pregnancy (ISSHP) definitions of preeclampsia at term gestational age (≥37+0 weeks), to identify adverse maternal and perinatal outcomes.

Study design: In this prospective cohort study at two maternity hospitals in England, women attending a routine hospital visit at 35^{+0}-36^{+6} weeks underwent assessment that included: history, ultrasonographic estimated fetal weight (EFW), Doppler measurements of pulsatility index (PI) in the uterine (UtA), umbilical (UA) and fetal middle cerebral artery (MCA), and serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt):PlGF ratio. Obstetric 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 five ways: traditional, based on new-onset proteinuria; ACOG 2013; ISSHP maternal factors (ISSHP-M); ISSHP-M plus fetal death or fetal growth restriction ('ISSHP-MF'), defined according to the 35-36^{+6} week scan as either estimated fetal weight (EFW) <3^{rd} percentile or 3^{rd}-10^{th} percentile with any of UtA-PI >95^{th} percentile, UA-PI >95^{th} percentile, or MCA-PI <5^{th} percentile; and ISSHP-MF plus angiogenic imbalance ('ISSHP-MF-AI'), as PlGF <5^{th} percentile or sFlt:PlGF >95^{th} percentile. Detection rates for outcomes of interest (i.e., severe maternal hypertension, major maternal morbidity, perinatal mortality or major neonatal morbidity, neonatal unit admission ≥48 hours, and birthweight <10th percentile) were compared by chi-square, and $p<0.05$ was considered significant.

Results: Among 15,248 singleton pregnancies, the identification of women with preeclampsia varied by definition: traditional 1.8% (281/15,248); ACOG 2.1% (326/15,248); ISSHP-M 2.6% (400/15,248); ISSHP-MF 2.8% (434/15,248); and ISSHP-MF-AI 3.3% (500/15,248). Compared with the traditional definition of preeclampsia, the ISSHP-MF+AI best identified adverse outcomes: severe hypertension (40.6% [traditional] vs. 66.9% [ISSHP-MF+AI, p<0.0001], 59.2% [ISSHP-MF, p=0.004], 56.2% [ISSHP-M, p=0.013], 46.1% [ACOG, p=0.449]); p<0.0001); composite maternal severe adverse event (72.2% [traditional] vs. 100% for all others, p=0.046); composite of perinatal mortality and morbidity (46.9% [traditional] vs. 71.1% [ISSHP-MF+AI, p-0.002], 62.2% [ISSHP-MF, p=0.06], 59.8% [ISSHP-M, p=0.117], 49.4% [ACOG, p=0.875]); neonatal unit admission for ≥48 hours (51.4% [traditional] vs. 73.4% [ISSHP-MF+AI, p=0.001], 64.5% [ISSHP-MF, p=0.070], 60.7% [ISSHP-M, p=0.213], 53.3% [ACOG, p=0.890]); birthweight <10th percentile (40.5% [traditional] vs. 78.7% [ISSHP-MF+AI, p<0.0001], 70.1% [ISSHP-MF, p<0.0001], 51.3% [ISSHP-M, p=0.064], 46.3% [ACOG, p=0.349]).

Conclusions: 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. The more inclusive ISSHP definition of maternal end-organ dysfunction, compared with ACOG, appears to be most sensitive. Addition of uteroplacental dysfunction to the broad definition optimizes identification of women and babies at risk, particularly when angiogenic factors are included.

INTRODUCTION

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

Preeclampsia is distinguished from the other hypertensive disorders of pregnancy, namely chronic and gestational hypertension, based on its greater risk of adverse maternal and perinatal outcomes. However, it is well-recognized that many women with chronic or gestational hypertension still suffer from complications typically associated with preeclampsia. For example, many women with gestational hypertension suffer end-organ complications like pulmonary edema,[3] and those with severe hypertension more frequently experience adverse outcomes (compared with women with traditionally-defined preeclampsia), such as placental abruption, preterm delivery, perinatal death, small-for-gestational age (SGA) infants, and neonatal respiratory distress syndrome.[4,5] Among women with chronic hypertension, the traditional definition of superimposed preeclampsia 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 preeclampsia 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 the majority of national and international clinical practice guidelines, notably the

American College of Obstetrics and Gynecology (ACOG)[11,12] and the International Society for the Study of Hypertension in Pregnancy (ISSHP),[13] and most recently, the National Institute of Health and Care Excellence (NICE), UK, that adopted the ISSHP definition.[14] However, controversy remains, with regards to how maternal end-organ dysfunction should be defined, whether uteroplacental dysfunction be included in the diagnostic criteria for preeclampsia, and if so, how uteroplacental dysfunction should 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 preeclampsia at term gestational age, to identify adverse maternal and perinatal outcomes. We compared with the traditional definition of preeclampsia (established clinical standard), ACOG (maternal criteria only) and ISSHP (maternal and/or uteroplacental criteria) definitions, considering definitions of uteroplacental dysfunction that incorporated fetal growth restriction and the measurements of angiogenic markers.

METHODS

Study design and participants

This was a prospective cohort study in women who attended a routine hospital visit at 35^{+0} to 36^{+6} weeks' gestation at King's College Hospital, London and Medway Maritime Hospital, Gillingham, UK, between October 2016 and September 2018. The

151 women gave written informed consent to participate in the study, which was
152 approved by the NHS Research Ethics Committee.
153
154 This 35^{+0} to 36^{+6} visit included: recording of maternal demographics and medical
155 history; ultrasound examination for fetal anatomy and estimated fetal weight (EFW)
156 from measurements of fetal head circumference, abdominal circumference and
157 femur length,[15,16] and Doppler measurements of pulsatility index (PI) in the uterine
158 artery (UtA), umbilical artery (UA) and fetal middle cerebral artery (MCA); and
159 measurement of maternal serum placental growth factor (PlGF) and soluble fms-like
160 tyrosine kinase-1 (sFlt) by an automated biochemical analyzer (BRAHMS KRYPTOR
161 compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). Gestational age
162 was determined by the measurement of fetal crown-rump length at 11-13 weeks'
163 gestation or the fetal head circumference at 19-24 weeks.[17,18]
164
165 The inclusion criteria for this analysis were singleton pregnancies that delivered a
166 non-malformed liveborn or stillborn. We excluded pregnancies with aneuploidies and
167 major fetal abnormalities.
168
169 **Diagnosis of preeclampsia**
170
171 Data related to pregnancy outcome were collected from the hospital maternity
172 records or those of their general medical practitioners. The obstetric records of all
173 women with chronic hypertension and those with new-onset, pregnancy associated
174 hypertension were examined to determine the diagnosis of gestational hypertension
175 or preeclampsia.

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

Five different definitions of preeclampsia were considered (Supplementary Table 1), based on the finding of an additional feature (i.e., a maternal end-organ dysfunction, without 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 hematological dysfunction, according to ACOG and ISSHP criteria.[12,19]

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

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

The ISSHP definition of preeclampsia was examined according to its maternal (ISSHP-M) and uteroplacental components (ISSHP-MF). The ISSHP-M definition was based on at least one of the following: new-onset proteinuria, renal insufficiency (serum creatinine ⩾90 µmol/L) in the absence of underlying renal disease, hepatic involvement with serum transaminases >40 IU/L, thrombocytopenia (i.e., platelet count <150,000/µL), or neurological complications (i.e., altered mental status, blindness, stroke, clonus, severe headaches and persistent visual scotomata); the criteria of 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 fetal growth restriction (FGR); FGR was defined according to the findings of the 35-36^{+6} week scan, as either EFW <3^{rd} percentile, or EFW at the 3^{rd} to 10^{th} percentile in the presence of any one of: UtA-PI >95^{th} percentile, UA-PI >95^{th} percentile, or MCA-PI <5^{th} percentile. The ISSHP-MF-AI definition included all criteria as above for ISSHP-MF, with the addition of angiogenic imbalance, defined as serum PlGF <5^{th} percentile or sFlt-1 / PlGF ratio >95^{th} percentile.

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

Severe maternal hypertension was defined as systolic BP ≥160 mmHg and / or

diastolic BP ≥110 mmHg. Major maternal morbidity was defined as one 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 preeclampsia, with the exception of liver rupture, postpartum hemorrhage, intensive care unit admission, and intubation and ventilation (not for childbirth) which were not available, placental abruption that was defined clinically and underreported, and the addition of myocardial ischemia based on the Delphi-derived PIERS (Pre-eclampsia Integrated Estimate of RiSk) score.[21,22]

Neonatal death was considered up to 28 days after birth. Major neonatal morbidity was defined as one or more of the following, as indicated in the BadgerNet Neonatal discharge summary: ventilation (i.e., need for continuous positive airway pressure or nasal continuous positive airway pressure or intubation), respiratory distress syndrome (RDS, the need for surfactant and ventilation), brain injury (i.e., 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 charts.[23] Perinatal outcomes covered the core perinatal outcome set in preeclampsia, with the exception of neonatal seizures.

Statistical analysis

Data were summarized descriptively for the total population and for different definitions of preeclampsia, with the associated impact on gestational hypertension

also presented. Median and interquartile range (IQR) 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 preeclampsia relative to the traditional one, were performed by the chi-square test.

RESULTS

Study participants

Table 1 summarizes the maternal and pregnancy characteristics of the study population, as well as details of the screening marker results and pregnancy outcomes. On average, women were in their early 30s, and overweight. The vast majority were White. Few were cigarette smokers. Very few reported that their mothers had suffered from preeclampsia. Medical history was usually unremarkable, with few women reporting chronic hypertension (most of which was treated with antihypertensive therapy), gestational diabetes mellitus (GDM), or rheumatic disease. Most conceptions were natural, and just over half of women were parous, with few of them (3.4%, 269/7857) reporting a previous pregnancy complicated by preeclampsia. 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:PlGF ratio. Birth occurred at a median of 40.0 weeks, for ≈20% of women following induction and for ≈25% overall by cesarean.

Preeclampsia definitions

Table 2 presents the elements of the preeclampsia definitions, for women with new-onset (N=741) or chronic hypertension (N-147). Most commonly, women satisfied maternal diagnostic criteria for preeclampsia based on abnormal routine laboratory tests (i.e., 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 35-36^{+6} weeks.

Performance of each classification

Table 3 summarizes the number of women with gestational hypertension and preeclampsia, according to each preeclampsia definition, and the associated occurrence of adverse maternal and perinatal outcomes. Preeclampsia 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 preeclampsia superimposed on chronic hypertension, particularly with the move to the ISSHP definitions. Each definition of preeclampsia 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 about 5%, most commonly due to HELLP syndrome, followed by eclampsia. At least two-thirds of women with preeclampsia were induced and 40% delivered by cesarean, while just over half of women with gestational hypertension were induced and about one-third delivered by cesarean. Perinatal death or major morbidity occurred in ≈9% of pregnancies with gestational

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

Table 4 shows that the detection rate (sensitivity) of preeclampsia 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 centile), and ISSHP-MF-AI definitions (for all outcomes). The higher detection rates were achieved with similar true positive rates, as presented in Table 3.

COMMENT

Principal findings

In a large cohort of women assessed at 36-37 weeks' gestation, the proportion of women with preeclampsia defined traditionally by new-onset hypertension and proteinuria was almost half 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 preeclampsia, and corresponding lower prevalence of gestational hypertension and chronic hypertension, using a broad, rather than traditional, definition of preeclampsia.[24-27] Our data confirm that these observations hold true when focused on preeclampsia at term, when the largest proportion of cases occur.

Prior studies of the relationship between preeclampsia definitions and outcomes have questioned the value of a broad (vs. traditional) definition of preeclampsia 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 baseline rates,[24,27] similar to our findings, suggesting that 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 fetal growth restriction were recently demonstrated[27]; while the role of headache and visual symptoms was not, 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 preeclampsia.

Most clinical practice guidelines (12/15) identified by systematic review recommend a broad definition of preeclampsia, based on new-onset hypertension and manifestations including, but not limited to, new-onset proteinuria.[28] There is widespread agreement for inclusion of proteinuria (N=12/12 guidelines), maternal symptoms of headache or visual disturbances (N=12/12), and abnormal routine laboratory testing of low platelet count (N=11/12), raised serum creatinine (N=11/12), or elevated liver enzymes (N=12/12), but there is no agreement on how these should be defined. Our data suggest that the definitions proposed by ISSHP (rather than ACOG) may better identify women at risk, such as those who go on to develop severe hypertension; ISSHP includes women with organ dysfunctions other than pulmonary edema (e.g., eclampsia, stroke), and less severe perturbations of platelets (<150 vs. <100 $x10^9$/L), serum creatinine (≥1mg/dL vs. >1.1mg/dL), or liver enzymes (AST or ALT >40IU/L rather than ≥twice normal) (Supplementary Table 1). Also, guidelines do not widely endorse inclusion of uteroplacental dysfunction in the broad definition of preeclampsia, based on any of the following criteria: intrauterine fetal death (N=4/12 guidelines), FGR (N=9/12), abnormal umbilical artery Doppler (N=3/12), angiogenic imbalance (N=3/12), abruption (N=2/12), oligohydramnios (N=1/12), or abnormal fetal cardiotocography (N=1/12). Only angiogenic imbalance is defined, as a low PlGF or elevated sFlt-1 / PlGF ratio, but two guidelines recommend their use as a 'rule-out' test for preeclampsia when normal (but not part of the definition when abnormal positive),[29,30] and one as a 'rule-in' test, even in the absence of other manifestations of preeclampsia.[31]

Clinical implications

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, over and above the risks associated with gestational hypertension. The more inclusive ISSHP definition of maternal end-organ dysfunction, compared with ACOG, appears to be most sensitive. Addition of uteroplacental dysfunction to the broad definition optimizes 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 preeclampsia, that includes uteroplacental dysfunction (including angiogenic imbalance, if available) is associated with similar benefits as demonstrated for preeclampsia based on a 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, preeclampsia criteria, and outcomes. We investigated ACOG and ISSHP preeclampsia definitions based on maternal and uteroplacental

400 criteria, and expanded the prior definition studied[24] by adding three criteria: Doppler
401 findings to EFW to define FGR (instead of EFW <10th percentile or an antenatal
402 diagnosis of “intrauterine growth restriction”), intrauterine fetal death, and angiogenic
403 imbalance. Importantly, the women studied were managed in the UK where only a
404 traditional definition of preeclampsia was accepted[33] and angiogenic markers were
405 advised only for women with suspected preeclampsia at <35^{+0} weeks[34].
406
407 A limitation of our data is that all women enrolled had singleton pregnancies, so our
408 results do not necessarily apply to multiples. We studied a cohort of women who had
409 reached near-term gestational age; while our results may not apply to women
410 preterm, they are consistent with studies that have included such women, and the
411 majority of preeclampsia occurs at term. We were unable to include all maternal
412 criteria advocated by ISSHP; no information was available on the clinical criteria of
413 altered mental status or clonus, or the laboratory findings of disseminated
414 intravascular coagulation or hemolysis. We used the 35-36^{+6} week uteroplacental
415 assessment to diagnose subsequent new-onset hypertension as gestational
416 hypertension or preeclampsia; while this makes full use of information collected
417 where the 36-week scan is routine, it would have been ideal to have repeat
418 ultrasonographic assessment of EFW and Dopplers, or angiogenic balance.
419 However, we feel that our carry-forward of observations was likely to underestimate
420 the prevalence of abnormalities at the time that hypertension developed, and thus,
421 under-estimate the strength of the uteroplacental assessment-outcome relationship.
422
423 **Conclusions**
424

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. The more inclusive ISSHP definition of maternal end-organ dysfunction, compared with ACOG, appears to be most sensitive. Addition of uteroplacental dysfunction to the broad definition optimizes identification of women and babies at risk, particularly when angiogenic factors are included.

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567 **Table 1**: Baseline characteristics and outcomes of the screening population.

Characteristic	N=15,248 pregnancies
Maternal demographics	
Age (years)	32.2 (28.3-35.8)
BMI (kg/m^2)	29.0 (26.1-32.7)
BMI >30 kg/m^2	6,447 (42.2)
Weight (Kg)	79.0 (71.0-89.9)
Height (cm)	165 (161-170)
Racial origin	
White	12,125 (79.5)
Black	1,688 (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 / Antiphospholipid antibody syndrome	36 (0.2)
Diabetes mellitus (type 1 or 2)	148 (1.0)
Obstetrical history	
Nulliparous	7,122 (46.7)
Parous without previous PE	7,857 (51.5)
Parous with previous PE	269 (1.8)
Inter-pregnancy interval (years)	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 (weeks)	36.1 (35.9-36.4)
Gestational diabetes mellitus ł	636 (4.2)
Screening markers for PE at 35-36^{+6} weeks	
Mean arterial pressure (mmHg)	88.1 (83.2-93.2)
Systolic BP (mmHg)	118.5 (111.8-125.0)
Systolic BP ≥140 mmHg	221 (1.4)
Diastolic BP (mmHg)	73.0 (68.3-78.0)
Diastolic BP ≥90 mmHg	256 (1.7)
Uterine artery PI	0.7 (0.6-0.8)
Uterine artery PI >95th percentile	1,068 (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 / PlGF ratio	8.3 (3.6-21.5)
sFlt-1 / PlGF ratio >95th percentile	762 (5.0)
sFlt-1 / PlGF ratio >95th percentile or PLGF <5th percentile	1,008 (6.6)

Pregnancy outcomes	
Gestational age at birth (wk)	40.0 (39.1-40.9)
Induction of labour	3,253 (21.3)
Vaginal delivery	11,187 (73.4)
Spontaneous vaginal delivery	8,849 (58.0)
Caesarean delivery	4,062 (26.6)
Perinatal mortality / major morbidity*	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 hr	1,086 (7.1)
Birthweight <10th percentile ǂ	1,585 (10.4)

Data presented as N (%) or median (Interquartile range).

BMI = body mass index, BP = blood pressure, NEC = Necrotising 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

* Major neonatal morbidity was defined as one or more of the following: ventilation, RDS, brain injury, sepsis, anemia, or NEC.

† Gestational diabetes was defined as hyperglycemia diagnosed in pregnancy.

ǂ The birthweight percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight charts.[23]

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*	270 (3.6)	11 (7.5)
Maternal symptoms ł		
Headache	21 (2.8)	0
Visual symptoms	20 (2.7)	0
Maternal signs ǂ		
Eclampsia	4 (0.5)	0
Myocardial ischemia	1 (0.1)	0
Pulmonary oedema	2 (0.3)	0
Abnormal maternal laboratory tests §		
Platelet count <150x10^9/L	78 (10.3)	7 (4.8)
Platelet count <100x10^9/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 3rd -10th percentile with abnormal Dopplers ǁ	10 (1.3)	3 (2.0)
Abnormal angiogenic markers at screening ¶	214 (28.9)	15 (10.2)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EFW = estimated fetal weight, IQR = interquartile range, PI = pulsatility index, PlGF = placental growth factor, sFlt-1 = soluble fms-like tyrosine kinase-1

* Proteinuria was defined as ≥2+ by urinary dipstick testing, ≥30mg/mmol or 0.3mg/dL by protein:creatinine ratio, or ≥0.3g/d by 24-hour urine collection.

ł Headache was defined by ACOG as new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, whereas ISSHP defined headache as "severe"; Visual symptoms were not defined by ACOG, but were defined by ISSHP as persistent visual scotomata.

ǂ No information was available on altered mental status or clonus. There were no cases of blindness.

§ No information was available on disseminated intravascular coagulation or haemolysis.

ǁ 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.

¶ Abnormal angiogenic markers were defined as PlGF<5th percentile or sFlt-1 / PlGF ratio >95th.

Preeclampsia definitions and their relationship with outcomes

Table 3: Adverse pregnancy outcomes according to definitions of gestational hypertension and preeclampsia.

Outcome	Traditional		ACOG		ISSHP-M		ISSHP-MF		ISSHP-MF+AI	
	GH	PE	GH	PE	GH	PE	GH	PE	GH	PE
	N=471 (3.1)	N=281 (1.8)	N=427 (2.8)	N=326 (2.1)	N=367 (2.4)	N=400 (2.6)	N=338 (2.2)	N=434 (2.8)	N=279 (1.8)	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	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)
LABOUR AND DELIVERY										
Induction of labour	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
Neonatal unit admission ≥48 hr	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 presented as N (%)

Preeclampsia definitions and their relationship with outcomes

CH = chronic hypertension; GH = gestational hypertension, ISSHP = International Society for the Study of Hypertension in Pregnancy, ISSHP-M = ISSHP maternal definition, ISSHP-MF = ISSHP maternal-fetal, ISSHP-MF+AI = ISSHP maternal-fetal plus angiogenic imbalance, PE = preeclampsia, RDS = respiratory distress syndrome requiring surfactant, NEC = necrotising enterocolitis requiring surgery.

Preeclampsia definitions and their relationship with outcomes

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

	Traditional (n=281)	Ref	**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)	0.449	56.2 (73/130)	0.013	59.2 (77/130)	0.004	66.9 (87/130)	<0.0001
Major maternal morbidity	72.2 (13/18)	-	100 (18/18)	0.046	100 (18/18)	0.046	100 (18/18)	0.046	100 (18/18)	0.046
Perinatal mortality and major morbidity	46.9 (38/81)	-	49.4 (40/81)	0.875	59.8 (49/82)	0.117	62.2 (51/82)	0.060	71.1 (59/83)	0.002
Neonatal unit admission ≥48 hr	51.4 (54/105)	-	53.3 (56/105)	0.890	60.7 (65/107)	0.213	64.5 (69/107)	0.070	73.4 (80/109)	0.001
Birthweight <10th percentile	40.5 (60/148)	-	46.3 (69/149)	0.349	51.3 (77/150)	0.064	70.1 (108/154)	<0.0001	78.7 (122/155)	<0.0001

The p value represents the comparison of the detection rate with the traditional definition of preeclampsia.

Supplementary Table 1: Definitions of *de novo* preeclampsia, based on new-onset hypertension with one/more other features

	Traditional	ACOG	ISSHP		
			SSHP-M	ISSHP-MF	ISSHP-MF+AI
Proteinuria*	●	●	●	●	●
Maternal symptoms					
Headache †		●	●	●	●
Visual symptoms ‡		●	●	●	●
Maternal signs					
Eclampsia	-	-	●	●	●
Altered mental status	-	-	●	●	●
Blindness	-	-	●	●	●
Stroke	-	-	●	●	●
Clonus	-	-	●	●	●
Pulmonary oedema	-	●	-	-	-
Maternal routine laboratory tests					
Platelet count <150x10^9/L	-	-	●	●	●
Platelet count <100x10^9/L	-	●	●	●	●
DIC	-	-	●	●	●
Haemolysis	-	-	●	●	●
Serum creatinine ≥90 µmol/L or ≥1 mg/dL	-	-	●	●	●
Serum creatinine >1.1 mg/dL	-	●	●	●	●
Serum creatinine doubling in absence of other renal disease	-	●	-	-	-
AST or ALT ≥twice normal (≥65 IU/L)	-	●	●	●	●
AST or ALT >40 IU/L	-	-	●	●	●
Uteroplacental dysfunction					
Intrauterine fetal death	-	-	-	●	●
FGR at screening §	-	-	-	●	●
Abnormal angiogenic markers at screening‖	-	-	-	-	●

ACOG = American College of Obstetricians and Gynecologists, ALT = alanine aminoransferase, 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, ISSHP-MF+AI = ISSHP maternal-fetal plus angiogenic imbalance, PI = pulsatility index, PlGF = placental growth factor, RUQ = right upper quadrant, sFlt-1 = soluble fms-like tyrosine kinase-1

* Proteinuria was defined as ≥2+ by urinary dipstick testing, ≥30mg/mmol or 0.3mg/dL by protein:creatinine ratio, or ≥0.3g/d by 24-hour urine collection.

† Headache was defined by ACOG as new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, whereas ISSHP defined headache as “severe”.

‡ Visual symptoms were not defined by ACOG, but were defined by ISSHP as persistent visual scotomata.

§ FGR was not defined by ISSHP, but was taken here to be EFW <3rd centile or EFW 3-9th centile with abnormal Dopplers, defined as any of uterine artery PI >95th centile, umbilical artery PI >95th centile, and/or middle cerebral artery PI <5th centile. This definition incorporates the abnormal umbilical artery Dopplers listed by ISSHP as a separate criterion.

‖ Angiogenic imbalance was defined as a PlGF <5th centile or a sFlt-1:PlGF ratio >95th centile for gestational age