

# Impact of new definitions of pre-eclampsia on incidence and performance of first-trimester screening

N. KHAN<sup>1</sup>, W. ANDRADE<sup>1</sup>, H. DE CASTRO<sup>1</sup>, A. WRIGHT<sup>2</sup>, D. WRIGHT<sup>2</sup> and K. H. NICOLAIDES<sup>1</sup>

<sup>1</sup>Fetal Medicine Research Institute, King's College Hospital, London, UK; <sup>2</sup>Institute of Health Research, University of Exeter, Exeter, UK

**KEYWORDS:** first trimester; pre-eclampsia; screening; small-for-gestational age

## CONTRIBUTION

*What are the novel findings of this work?*

The traditional definition of pre-eclampsia (PE), based on the development of hypertension and proteinuria, has been revised to include cases without proteinuria but with evidence of renal, hepatic or hematological dysfunction. The new definitions of PE resulted in, first, an increase in pregnancies classified as having PE but the additional cases had milder disease, and, second, a non-significant decrease in the performance of first-trimester screening for PE.

*What are the clinical implications of this work?*

The new definitions of PE will inevitably be adopted by professional organizations and will be incorporated into routine clinical practice. In terms of first-trimester assessment of risk for development of PE, the new definitions of PE would have a minimal impact on the performance of screening.

## ABSTRACT

**Objective** The traditional definition of pre-eclampsia (PE) is based on the development of hypertension and proteinuria. This has been revised recently to include cases without proteinuria but with evidence of renal, hepatic or hematological dysfunction. The aim of this study was to examine the impact of new definitions of PE on, first, the incidence and severity of the disease and, second, the performance of the competing-risks model for first-trimester assessment of risk for PE.

**Methods** This was a retrospective study of 66 964 singleton pregnancies that were classified as having PE, gestational hypertension (GH) or no PE or GH, according to the traditional criteria of the International

Society for the Study of Hypertension in Pregnancy (ISSHP-old), which defines PE as the presence of both hypertension and proteinuria. We reviewed the records of pregnancies with GH, and those cases with high creatinine or liver enzymes or low platelet count were reclassified as having PE, according to the new criteria of ISSHP (ISSHP-new) and the new criteria of the American College of Obstetricians and Gynecologists (ACOG). The groups of PE according to the traditional and new criteria were compared for, first, gestational age at delivery, birth-weight percentile and incidence of a small-for-gestational-age (SGA) neonate with birth weight < 10<sup>th</sup> percentile and perinatal death, and, second, the predictive performance for preterm PE of the competing-risks model based on the combination of maternal risk factors, uterine artery pulsatility index, mean arterial pressure and serum placental growth factor at 11–13 weeks' gestation (triple test).

**Results** According to ISSHP-old, 1870 (2.8%) cases had PE, 2182 (3.3%) had GH and 62 912 (94.0%) had no PE or GH. The incidence of PE according to ACOG was 3.0% (2029/66 964) and ISSHP-new was 3.4% (2301/66 964). Median gestational age at delivery in the extra cases of PE according to ACOG (difference, 1.3 weeks; 95% CI, 0.71–1.71 weeks) and in the extra cases of PE according to ISSHP-new (difference, 1.5 weeks; 95% CI, 1.29–1.71 weeks) was higher than in cases with PE according to ISSHP-old (38.4 weeks). The incidence of a SGA neonate in the extra cases of PE according to ACOG (relative risk, 0.57; 95% CI, 0.42–0.79) and in the extra cases of PE according to ISSHP-new (relative risk, 0.52; 95% CI, 0.42–0.65) was lower than in the cases of PE according to ISSHP-old (33.64%). In first-trimester screening for preterm PE by the triple test, the detection rate, at a 10% false-positive rate, was 75.9% (95% CI, 70.8–80.6%) for ISSHP-old,

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

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74.3% (95% CI, 69.2–79.0%) for ACOG and 74.0% (95% CI, 68.9–78.6%) for ISSHP-new.

**Conclusions** The new definitions of PE resulted in, first, an increase in pregnancies classified as having PE but the additional cases had milder disease, and, second, a non-significant decrease in the performance of first-trimester screening for PE. © 2019 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

## INTRODUCTION

The traditional definition of pre-eclampsia (PE), according to the International Society for the Study of Hypertension in Pregnancy (ISSHP), is new onset of hypertension (blood pressure  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic) at  $\geq 20$  weeks' gestation and proteinuria ( $\geq 300$  mg/24 h or protein-to-creatinine ratio  $> 30$  mg/mmol or  $\geq 2+$  on dipstick testing)<sup>1</sup>. This has been revised recently by the ISSHP<sup>2</sup> and the American College of Obstetricians and Gynecologists (ACOG)<sup>3</sup> to include cases without proteinuria but with evidence of renal, hepatic or hematological dysfunction.

In previous studies investigating the value of screening for PE by a combination of maternal demographic characteristics and medical history with biomarkers in the first, second and third trimesters in singleton and twin pregnancies, the outcome measure was PE as defined originally by the ISSHP<sup>1,4–22</sup>. In the first trimester, screening has been achieved successfully by a combination of maternal demographic characteristics and medical history, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and serum placental growth factor (PlGF) through application of the competing-risks approach<sup>4–8</sup>. In women identified by this approach as being at high risk of preterm PE, with delivery at  $< 37$  weeks' gestation, administration of aspirin (150 mg/day) from 11–14 weeks until 36 weeks reduces the incidence of early PE by about 90% and that of preterm PE by  $> 60\%$ <sup>23</sup>.

The objective of this study was to examine the impact of the new definitions of PE on, first, the incidence and severity of the disease, and, second, the performance of the competing-risks model for first-trimester assessment of risk for PE.

## METHODS

### Study population

This was a retrospective study of 66 964 singleton pregnancies that delivered at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between January 2011 and June 2018. All women had a routine examination at 11 + 0 to 13 + 6 weeks' gestation, which included recording of maternal characteristics and medical history<sup>4</sup>, and ultrasound examination for assessment of gestational age from fetal crown–rump length<sup>24</sup> and diagnosis of fetal abnormalities. In the

last 48 671 pregnancies, we also assessed the risk for subsequent PE through measurements of left and right UtA-PI by transabdominal color Doppler ultrasound for calculation of the mean PI<sup>25</sup>, MAP by validated automated devices and standardized protocol<sup>26</sup> and serum concentration of PlGF (DELFLIA Xpress system, PerkinElmer Life and Analytical Sciences, Waltham, USA or BRAHMS KRYPTOR analyzer, Thermo Fisher Scientific, Hennigsdorf, Germany). The women gave written informed consent to participate in studies for prediction of pregnancy complications, which were approved by the relevant research ethics committee in each participating hospital.

Data on serum creatinine, transaminases, platelet count, 24-h urine protein and protein-to-creatinine ratio were obtained from the computerized laboratory records of the two participating hospitals, and data on dipstick protein testing and pregnancy outcome were obtained from the computerized maternity records which were available throughout the period of 2011 to 2018.

The inclusion criteria for this study were singleton pregnancy undergoing first-trimester assessment and subsequent delivery in our hospitals of a morphologically normal liveborn or stillborn neonate at  $> 24$  weeks' gestation. We excluded pregnancies with aneuploidy and major fetal abnormality and those ending in termination, miscarriage or fetal death before 24 weeks.

### Diagnosis of pre-eclampsia

Pregnancies were classified as having PE or gestational hypertension (GH) according to the traditional criteria of the ISSHP (ISSHP-old), which defines PE as the presence of both hypertension and proteinuria<sup>1</sup>. We reviewed the records of cases with GH, and those with high creatinine or liver enzymes or low platelet count were reclassified as having PE according to the new criteria of ISSHP (ISSHP-new)<sup>2</sup> and the criteria of ACOG<sup>3</sup>. The criteria for PE in the absence of proteinuria according to ISSHP-new include serum creatinine  $\geq 90$   $\mu\text{mol/L}$ , alkaline or aspartate transaminase  $> 40$  IU/L and platelet count  $< 150\,000/\mu\text{L}$ , neurological complications (including altered mental status, blindness, stroke, clonus, severe headaches and persistent visual scotomata) and uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis or stillbirth)<sup>2</sup>. We did not provide the criteria for diagnosis of fetal growth restriction and acknowledge that there is controversy as to whether this should be included in the diagnostic criteria for PE in the absence of proteinuria or abnormal creatinine, transaminases or platelet count<sup>2</sup>. For the purpose of this study, we did not include neurological complications and uteroplacental dysfunction for diagnosis of PE according to ISSHP-new. The criteria for PE in the absence of proteinuria according to ACOG include serum creatinine  $> 97$   $\mu\text{mol/L}$ , transaminases more than twice the upper limit of normal ( $\geq 65$  IU/L for our laboratory) and platelet count  $< 100\,000/\mu\text{L}$ , pulmonary edema or new-onset headache unresponsive to acetaminophen

and not accounted for by alternative diagnoses or visual disturbances<sup>3</sup>. For the purpose of this study, we included only quantitative measures of renal, hepatic or hematological dysfunction for diagnosis of PE according to ACOG<sup>3</sup>.

### Statistical analysis

Data were summarized according to outcome (no PE or GH, GH or PE according to ISSHP-old, PE according to ACOG and PE according to ISSHP-new) as median and interquartile range (IQR) for continuous variables and as number and percentage for categorical variables.

We compared median gestational age at delivery, median birth-weight percentile<sup>27</sup>, incidence of a small-for-gestational-age (SGA) neonate with birth weight <10<sup>th</sup> percentile and incidence of perinatal death in cases classified according to ISSHP-old as having PE, GH and no PE or GH, with those in the extra cases of PE according to ACOG and in the extra cases of PE according to ISSHP-new. Differences in median gestational age at delivery and birth-weight percentile were calculated between pregnancies with PE according to ISSHP-old and each other group; 95% CI for these differences were calculated via bootstrapping. Relative risks of SGA and perinatal death were calculated between pregnancies with PE according to ISSHP-old and each other group; 95% CI for the relative risks were produced.

In the subset of 48 671 pregnancies with measurements of MAP, UtA-PI and PlGF, patient-specific risks of delivery with PE at < 34, < 37 and < 41 + 3 weeks' gestation were calculated using the competing-risks model to combine the prior distribution of the gestational age at delivery with PE, obtained from maternal factors, with multiples of the median (MoM) values of MAP, UtA-PI and PlGF<sup>5,28–30</sup>. The performance of screening for early PE, preterm PE and all PE by maternal factors alone and by the triple test was assessed. The area under the receiver–operating characteristics curve and detection rate, at a 10% false-positive rate, for each of the three definitions of PE (ISSHP-old, ACOG and ISSHP-new) was examined.

The statistical software package R, along with the library PropCIs, was used for data analyses<sup>31,32</sup>.

## RESULTS

The maternal and pregnancy characteristics of the study population of 66 964 pregnancies are summarized in Table 1. According to ISSHP-old, 1870 (2.8%) cases had PE, 2182 (3.3%) had GH and 62 912 (94.0%) had no PE or GH. The incidence of PE according to ACOG was 3.0% (2029/66 964) and ISSHP-new was 3.4% (2301/66 964). In the extra cases that were classified as having PE according to the new definitions, compared to those with PE according to ISSHP-old, body mass index was lower and there were higher incidences of no PE in a previous pregnancy, high serum creatinine, high transaminases and low platelet count (Table 1).

Pregnancy outcome in the cases of PE and GH according to ISSHP-old and in the extra cases of PE according to ACOG and ISSHP-new is summarized in Table 2 and illustrated in Figure 1. In PE according to ACOG or ISSHP-new (excluding PE according to ISSHP-old), compared with PE according to ISSHP-old, there was higher median gestational age at delivery and median birth-weight percentile and a lower incidence of a SGA neonate with birth weight <10<sup>th</sup> percentile, but there was no significant difference in the incidence of perinatal death.

In 48 671 pregnancies, MAP, UtA-PI and PlGF were measured and these included 1171 with PE according to ISSHP-old, 1272 with PE according to ACOG, 1457 with PE according to ISSHP-new, and 1472 with GH and 46 028 without PE or GH according to ISSHP-old. The demographic characteristics of pregnancies according to the three definitions of PE were similar and in all three UtA-PI and MAP were higher and PlGF was lower than in normal pregnancies (Table 3). The detection rates of all PE, preterm PE and early PE, at a 10% false-positive rate, and areas under the receiver–operating characteristics curve in screening by maternal risk factors and combination of maternal risk factors, MAP, UtA-PI and PlGF (triple test) at 11–13 weeks' gestation, for each of the three definitions of PE, are shown in Table 4. There was a non-significant decrease in the performance of screening when PE was defined according to the criteria of ACOG<sup>3</sup> or ISSHP-new<sup>2</sup>, compared to ISSHP-old<sup>1</sup>.

## DISCUSSION

### Main findings

This study has demonstrated that replacement of the traditional definition of the ISSHP for PE, which requires the development of both hypertension and proteinuria<sup>1</sup>, with new definitions that include cases without proteinuria but with evidence of renal, hepatic or hematological dysfunction<sup>2,3</sup>, results in, first, an increase in the incidence of PE by about 21% (from 2.8% to 3.4%) in the case of the new criteria of the ISSHP<sup>2</sup> and 7% (from 2.8% to 3.0%) in the case of the criteria of ACOG<sup>3</sup>, second, gestational age at delivery, birth-weight percentile and incidence of a SGA neonate in the additional cases of PE were similar to those in cases with GH and less severe than those in cases with PE as defined by the previous criteria of the ISSHP<sup>1</sup>, third, the incidence of perinatal death was low and there were no significant differences between the groups of PE, and, fourth, the performance of first-trimester screening for PE by maternal factors or a combination of maternal factors, MAP, UtA-PI and PlGF, was similar when the condition was defined by ISSHP-old<sup>1</sup>, ISSHP-new<sup>2</sup> or ACOG<sup>3</sup>, but there was a non-significant trend for lower detection rate, at a 10% false-positive rate, for PE according to ISSHP-new or ACOG compared with PE according to ISSHP-old.

**Table 1** Maternal and pregnancy characteristics of study population of 66 964 singleton pregnancies, according to diagnosis

Variable	Diagnosis according to ISSHP-old			Extra cases of PE according to new criteria*	
	PE (n = 1870)	No PE or GH (n = 62 912)	GH (n = 2182)	ACOG (n = 159)	ISSHP-new (n = 431)
Maternal age (years)	31.0 (26.3–35.0)	31.3 (27.0–34.9)	32.0 (27.7–35.7)	33.3 (29.9–36.2)	32.9 (29.2–36.1)
Body mass index (kg/m <sup>2</sup> )	28.1 (24.3–33.4)	24.6 (22.0–28.5)	27.7 (24.1–32.4)	26.6 (23.4–31.9)	26.4 (23.6–30.8)
Gestational age (weeks)	12.7 (12.3–13.1)	12.8 (12.4–13.2)	12.7 (12.3–13.1)	12.7 (12.2–13.1)	12.7 (12.3–13.1)
Racial origin					
White	1150 (61.50)	46 403 (73.76)	1517 (69.52)	110 (69.18)	287 (66.59)
Black	570 (30.48)	10 298 (16.37)	476 (21.81)	38 (23.90)	112 (25.99)
South Asian	92 (4.92)	2960 (4.70)	89 (4.08)	3 (1.89)	13 (3.02)
East Asian	22 (1.18)	1409 (2.24)	31 (1.42)	1 (0.63)	5 (1.16)
Mixed	36 (1.93)	1842 (2.93)	69 (3.16)	7 (4.40)	14 (3.25)
Chronic hypertension	196 (10.48)	666 (1.06)	0 (0)	0 (0)	0 (0)
Diabetes mellitus	47 (2.51)	698 (1.11)	32 (1.47)	1 (0.63)	4 (0.93)
SLE/APS	5 (0.27)	157 (0.25)	5 (0.23)	1 (0.63)	1 (0.23)
Smoker	105 (5.61)	5047 (8.02)	109 (5.00)	7 (4.40)	13 (3.02)
Family history of PE	134 (7.17)	2299 (3.65)	118 (5.41)	5 (3.14)	22 (5.10)
Method of conception					
Natural	1765 (94.39)	60 589 (96.31)	2099 (96.20)	149 (93.71)	411 (95.36)
In-vitro fertilization	89 (4.76)	1807 (2.87)	69 (3.16)	10 (6.29)	18 (4.18)
Use of ovulation drugs	16 (0.86)	516 (0.82)	14 (0.64)	0 (0)	2 (0.46)
Parity					
Nulliparous	1176 (62.89)	28 868 (45.89)	1310 (60.04)	104 (65.41)	259 (60.09)
Parous with no previous PE	471 (25.19)	32 922 (52.33)	690 (31.62)	47 (29.56)	138 (32.02)
Parous with previous PE	223 (11.93)	1122 (1.78)	182 (8.34)	8 (5.03)	34 (7.89)
Interpregnancy interval (years)	3.6 (2.1–6.5)	2.9 (1.9–4.8)	3.4 (2.2–5.8)	3.5 (2.6–5.7)	3.5 (2.2–6.1)
Serum creatinine					
≥ 90 µmol/L	90 (4.8)	—	—	35 (22.0)	58 (13.5)
> 97 µmol/L	62 (3.3)	—	—	33 (20.8)	33 (7.7)
Serum transaminases					
> 40 IU/L	260 (14.0)	—	—	121 (76.1)	218 (50.6)
≥ 65 IU/L	122 (6.6)	—	—	112 (70.4)	112 (26.0)
Platelet count					
< 150 000/µL	260 (14.0)	—	—	43 (27.0)	213 (49.4)
< 100 000/µL	55 (3.0)	—	—	26 (16.4)	26 (6.0)

Data are given as median (interquartile range) or *n* (%). \*Excluding cases of pre-eclampsia (PE) according to ISSHP-old. ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid syndrome; GH, gestational hypertension; ISSHP-old/new, old/new criteria of International Society for the Study of Hypertension in Pregnancy; SLE, systemic lupus erythematosus.

### Comparison with results of previous studies

A study from Australia compared pregnancy outcome in 958 women with PE according to ISSHP-old, 357 with non-proteinuric PE, classified as hypertension with renal, hepatic or hematological dysfunction, and 1192 with GH<sup>33</sup>. Proteinuric PE, compared to non-proteinuric PE, was associated with a higher incidence of severe hypertension (39% *vs* 30%), preterm birth (39% *vs* 30%) and perinatal death (2.5% *vs* 0.6%); the respective rates in GH were 9%, 11% and 0.7% and the authors concluded that non-proteinuric PE has a poorer outcome for women and their fetus than does GH but is a more benign condition than is proteinuric PE<sup>33</sup>.

Kallela *et al.* evaluated the impact of new definitions of PE on the incidence of the disease using the data of the Finnish Pre-eclampsia Consortium (FINNPEC) case-control cohort, which was recruited to study the genetic background of PE and fetal growth<sup>34</sup>. The cohort included 1379 women with PE according to the old ISSHP criteria, 272 with GH or chronic hypertension without

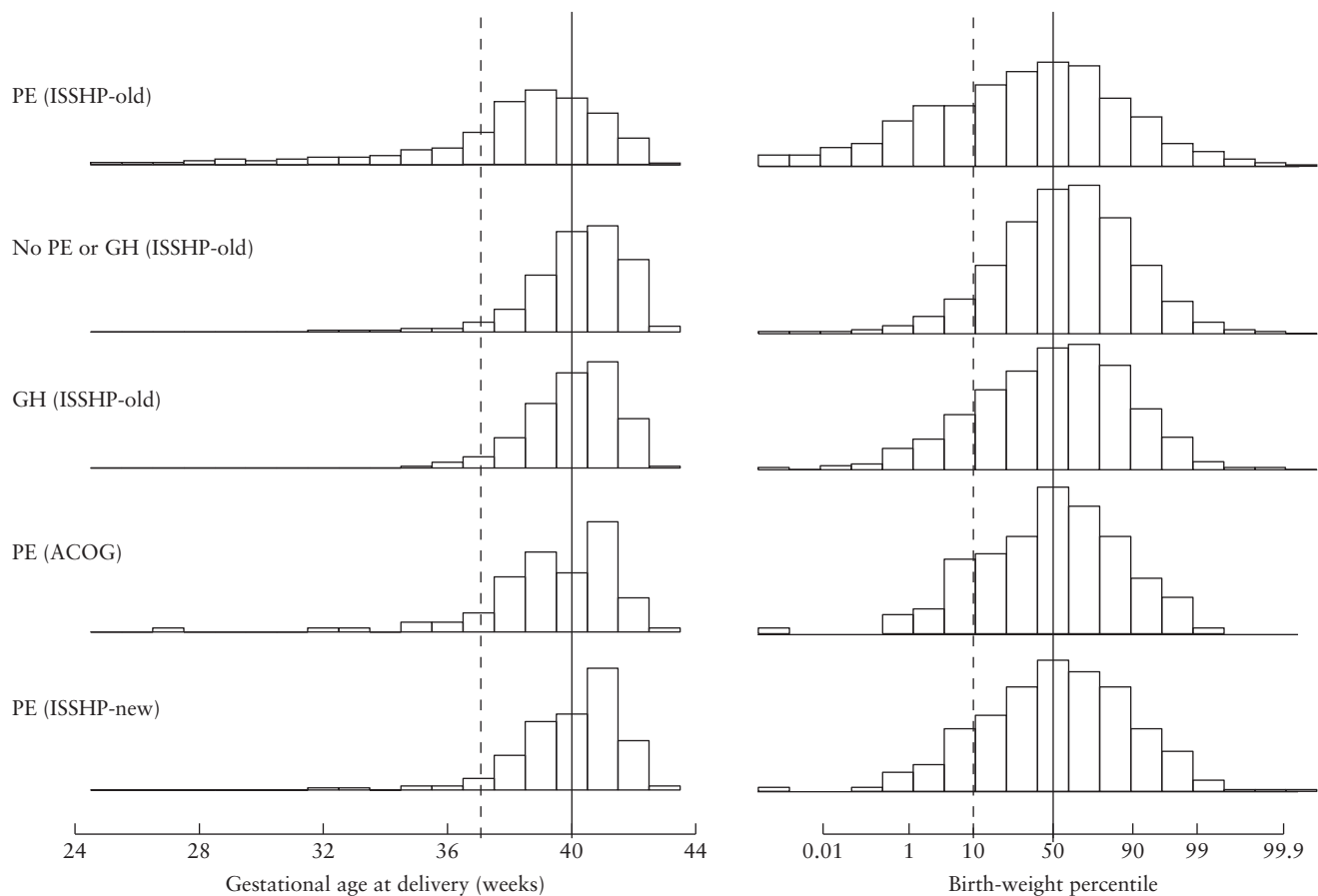
proteinuria (defined as ≥ 2+ on dipstick testing) and 864 without hypertensive disorders. When the new criteria of the ISSHP were applied to the 272 women with GH or chronic hypertension, 76 (27.9%) were reclassified as PE. The case-control nature of the study does not allow conclusions to be drawn concerning the impact of the new definitions of PE on the incidence of the disease. However, their finding that with ISSHP-new a high proportion of cases that would have been considered previously to have GH are reclassified as PE is consistent with our results.

A study from Japan examined 308 women diagnosed with hypertensive disorders of pregnancy at a tertiary center and divided them, according to the new criteria of the ISSHP (including neurological complications and uteroplacental dysfunction), into three groups: PE with proteinuria (*n* = 218), PE without proteinuria (*n* = 45) and GH (*n* = 45); in 69% (31/45) of cases of PE without proteinuria, there was uteroplacental dysfunction<sup>35</sup>. Applying the ISSHP-new criteria increased the number of pregnant women diagnosed as having PE by 15%;

**Table 2** Pregnancy outcome in 66 964 singleton pregnancies, according to diagnosis

Outcome	Diagnosis according to ISSHP-old			Extra cases of PE according to new criteria*	
	PE	No PE or GH	GH	ACOG	ISSHP-new
GA at birth (weeks)					
Median	38.43	40.00	39.80	39.71	39.93
Difference	Reference	1.57 (1.52–1.71)	1.37 (1.29–1.57)	1.29 (0.71–1.71)	1.50 (1.29–1.71)
Birth-weight percentile					
Median	28.42	49.25	43.10	42.28	43.39
Difference	Reference	20.83 (18.22–24.38)	14.68 (11.18–19.26)	13.86 (3.94–25.27)	14.97 (9.70–22.00)
SGA neonate					
%	33.64	11.58	20.26	19.50	17.63
Relative risk	Reference	0.34 (0.32–0.37)	0.60 (0.54–0.67)	0.57 (0.42–0.79)	0.52 (0.42–0.65)
Perinatal death					
%	1.34	0.39	0.41	1.26	0.46
Relative risk	Reference	0.29 (0.20–0.44)	0.31 (0.15–0.65)	0.94 (0.25–3.51)	0.34 (0.09–1.31)

Values in parentheses are 95% CI. \*Excluding cases of pre-eclampsia (PE) according to ISSHP-old. ACOG, American College of Obstetricians and Gynecologists; GA, gestational age; GH, gestational hypertension; ISSHP-old/new, old/new criteria of International Society for the Study of Hypertension in Pregnancy; SGA, small-for-gestational age.



**Figure 1** Distribution of gestational age at delivery and birth-weight percentile in pregnancies with pre-eclampsia (PE), those with no PE or gestational hypertension (GH) and those with GH, according to old criteria of International Society for the Study of Hypertension in Pregnancy (ISSHP-old), and in extra cases of PE according to new criteria of American College of Obstetricians and Gynecologists (ACOG) and ISSHP (ISSHP-new).

the cases with and without proteinuria had a similar incidence of maternal complications, composite neonatal complications, gestational age at delivery and birth weight and these outcomes were worse than in the group with GH. The main difference from our study is the inclusion

of fetal growth restriction in the definition of ISSHP-new, which would have inevitably increased adverse maternal and neonatal outcomes; in PE, the incidence of a SGA neonate is inversely related to gestational age at delivery<sup>36</sup>.

**Table 3** Characteristics of study population of 48 671 singleton pregnancies with available data on uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP) and serum placental growth factor (PIGF), according to diagnosis

Variable	Diagnosis according to ISSHP-old*		Diagnosis of PE according to new criteria	
	No PE or GH (n = 46 028)	PE (n = 1171)	ACOG (n = 1272)	ISSHP-new (n = 1457)
Maternal age (year)	31.4 (27.1–35.0)	31.3 (26.7–35.1)	31.4 (26.9–35.2)	31.7 (27.1–35.2)
Body mass index (kg/m <sup>2</sup> )	24.6 (22.0–28.4)	28.2 (24.1–33.6)	28.1 (24.0–33.4)	27.8 (23.9–33.0)
Gestational age (weeks)	38.9 (36.3–41.5)	38.9 (36.3–41.5)	38.9 (36.3–41.5)	38.9 (36.3–41.5)
Racial origin				
White	33 381 (72.52)	710 (60.63)	784 (61.64)	900 (61.77)
Black	8044 (17.48)	368 (31.43)	390 (30.66)	444 (30.47)
South Asian	2182 (4.74)	55 (4.70)	56 (4.40)	64 (4.39)
East Asian	1072 (2.33)	15 (1.28)	16 (1.26)	18 (1.24)
Mixed	1349 (2.93)	23 (1.96)	26 (2.04)	31 (2.13)
Medical history				
Chronic hypertension	502 (1.09)	146 (12.47)	146 (11.48)	146 (10.02)
Diabetes mellitus Type 1	172 (0.37)	15 (1.28)	15 (1.18)	15 (1.03)
Diabetes mellitus Type 2	306 (0.66)	21 (1.79)	21 (1.65)	21 (1.44)
SLE/APS	114 (0.25)	4 (0.34)	5 (0.39)	5 (0.34)
Smoker	3716 (8.07)	59 (5.04)	65 (5.11)	69 (4.74)
Family history of PE	1687 (3.67)	83 (7.09)	87 (6.84)	99 (6.79)
Method of conception				
Natural	44 368 (96.39)	1111 (94.88)	1204 (94.65)	1385 (95.06)
In-vitro fertilization	1275 (2.77)	52 (4.44)	60 (4.72)	63 (4.32)
Use of ovulation drugs	385 (0.84)	8 (0.68)	8 (0.63)	9 (0.62)
Parity				
Nulliparous	21 216 (46.09)	697 (59.52)	763 (59.98)	862 (59.16)
Parous with no previous PE	23 907 (51.94)	318 (27.16)	347 (27.28)	412 (28.28)
Parous with previous PE	905 (1.97)	156 (13.32)	162 (12.74)	183 (12.56)
Interpregnancy interval (years)	3.0 (1.9–4.9)	3.7 (2.1–6.5)	3.7 (2.1–6.4)	3.7 (2.1–6.5)
UtA-PI MoM	1.000 [0.998–1.002]	1.123 [1.104–1.143]	1.113 [1.094–1.131]	1.100 [1.084–1.118]
MAP MoM	1.000 [0.999–1.001]	1.046 [1.042–1.051]	1.046 [1.042–1.050]	1.047 [1.043–1.051]
PIGF MoM	1.000 [0.996–1.004]	0.785 [0.765–0.807]	0.796 [0.776–0.816]	0.810 [0.791–0.829]

Data are given as median (interquartile range), *n* (%) or mean [95% CI]. \*1472 pregnancies were diagnosed with gestational hypertension (GH) according to ISSHP-old. ACOG, American College of Obstetricians and Gynecologists; APS, antiphospholipid syndrome; ISSHP-old/new, old/new criteria of International Society for the Study of Hypertension in Pregnancy; MoM, multiples of the median; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

**Table 4** Detection rate (DR), at 10% false-positive rate, and area under receiver–operating characteristics curve (AUC) for all pre-eclampsia (PE), preterm PE and early PE, in screening by maternal risk factors and combination of maternal risk factors, mean arterial pressure, uterine artery pulsatility index and placental growth factor (triple test) at 11–13 weeks' gestation, for three definitions of PE

Method of screening	Definition of PE					
	ISSHP-old		ACOG		ISSHP-new	
	DR (n/N (%; 95% CI))	AUC (95% CI)	DR (n/N (%; 95% CI))	AUC (95% CI)	DR (n/N (%; 95% CI))	AUC (95% CI)
Maternal factors						
All PE	459/1171 (39.2; 36.4–42.1)	0.762 (0.7486–0.7754)	487/1272 (38.3; 35.6–41.0)	0.7556 (0.7424–0.7688)	532/1457 (36.5; 34.0–39.0)	0.7441 (0.7316–0.7567)
PE < 37 weeks	137/316 (43.4; 37.8–49.0)	0.7811 (0.7567–0.8054)	142/327 (43.4; 38.0–49.0)	0.7803 (0.7563–0.8043)	146/334 (43.7; 38.3–49.2)	0.7791 (0.7551–0.8031)
PE < 34 weeks	57/129 (44.2; 35.5–53.2)	0.7881 (0.7512–0.8251)	57/131 (43.5; 34.9–52.4)	0.7852 (0.7485–0.8219)	59/134 (44.0; 35.5–52.9)	0.7869 (0.7507–0.823)
Triple test						
All PE	644/1171 (55.0; 52.1–57.9)	0.8205 (0.8079–0.8332)	667/1272 (52.4; 49.7–55.2)	0.8109 (0.7984–0.8233)	714/1457 (49.0; 46.4–51.6)	0.7982 (0.7863–0.8101)
PE < 37 weeks	240/316 (75.9; 70.8–80.6)	0.9132 (0.8989–0.9274)	243/327 (74.3; 69.2–79.0)	0.9067 (0.892–0.9215)	247/334 (74.0; 68.9–78.6)	0.9039 (0.8886–0.9192)
PE < 34 weeks	112/129 (86.8; 79.7–92.1)	0.9441 (0.9283–0.9599)	112/131 (85.5; 78.3–91.0)	0.9377 (0.9195–0.9559)	114/134 (85.1; 77.9–90.6)	0.9372 (0.9192–0.9552)

ACOG, American College of Obstetricians and Gynecologists; ISSHP-old/new, old/new criteria of International Society for the Study of Hypertension in Pregnancy.

## Implications for clinical practice

The new definitions of PE will inevitably be adopted by professional organizations and will be incorporated into routine clinical practice. We have shown that, in terms of first-trimester assessment of risk for development of early, preterm and all PE, the new definitions of PE would have a minimal impact on the performance of screening.

## Strengths and limitations

The main strengths of the study are, first, examination of a large unselected population with prospective recording of maternal demographic characteristics and medical history, and, second, first-trimester measurements of MAP, UtA-PI and PlGF and application of the competing-risks model for prediction of PE allowing assessment of the impact of the new definitions on prediction of PE.

The main limitations of the study relate to the retrospective assessment of renal, hepatic and hematological dysfunction based on information recorded in hospital computerized systems and exclusion of neurological complications from the new definitions of PE because these are often subjective and their recording would not have been consistent. Accurate assessment of such symptoms will be achieved only in prospective studies that incorporate these in the diagnosis of the disease. Another limitation is that, in the classification of cases according to ISSHP-new, we did not include the definition of fetal growth restriction, because this is controversial and not clearly defined; for example, is the condition based on ultrasonographic estimated fetal weight  $< 10^{\text{th}}$  or  $< 5^{\text{th}}$  or  $< 3^{\text{rd}}$  percentile and is it in addition necessary to have abnormal Doppler indices in the uterine arteries or umbilical arteries or fetal middle cerebral arteries, or is the diagnosis made retrospectively based on low birth weight? Another limitation of the study is that neonatal outcome was confined to gestational age at delivery, birth weight and perinatal death and that we did not provide information on maternal complications. As in the case of neurological symptoms, adequate examination of detailed maternal and neonatal complications requires prospective investigation of predefined outcome measures.

## Conclusions

The new definitions of PE result in, first, an increase in pregnancies classified as having PE but the additional cases have milder disease, and, second, a non-significant decrease in the performance of first-trimester screening for PE.

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