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Competing-risks model for pre-eclampsia and adverse pregnancy outcomes

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KEYWORDS: Cesarean section; competing-risks model; gestational hypertension; neonatal death; neonatal unit admission; pre-eclampsia; small-for-gestational age; stillbirth

CONTRIBUTION

What are the novel findings of this work?
Women at 35–37 weeks' gestation that are identified by the competing-risks model to be at high risk of pre-eclampsia are also at increased risk of developing gestational hypertension, Cesarean section, stillbirth, delivering a small-for-gestational-age neonate and having a neonate requiring admission to the neonatal unit for ≥ 48 h.

What are the clinical implications of this work?
Women identified by third-trimester screening as being at high risk for pre-eclampsia should be made aware of the increased risk of other adverse pregnancy outcomes. The extent to which pre-eclampsia and other adverse outcomes can be reduced by planned early delivery remains to be determined.

ABSTRACT

Objective *The competing-risks model for assessment of risk for pre-eclampsia (PE) at 35–37 weeks' gestation identifies the majority of women who are at high risk of subsequent delivery with PE. We aimed to examine the incidence and relative risk of adverse pregnancy outcomes in patient groups stratified according to the estimated risk of delivery with PE.*

Methods *This was a prospective non-interventional, observational study in women with a singleton pregnancy attending for a routine hospital visit at 35 + 0 to 36 + 6 weeks' gestation. The risk of delivery with PE for each patient in the study population was estimated using the competing-risks model, combining the prior distribution of gestational age at delivery with PE and the likelihood from multiples of the median values of mean arterial pressure, placental growth factor and soluble fms-like tyrosine kinase-1. The patients were assigned to one of the following five risk categories: Group A, ≥ 1 in 2; Group B, 1 in 5 to 1 in 3; Group C, 1 in 20 to 1 in 6; Group D, 1 in 50 to 1 in 21; and Group E, < 1 in 50. The outcome measures were delivery with PE, gestational hypertension (GH), small-for-gestational age (SGA) at birth, delivery by Cesarean section, stillbirth, neonatal death, perinatal death and admission to the neonatal unit (NNU) for at least 48 h. In each risk category, the proportion of women with each adverse outcome was determined and relative risks (RR) were calculated as compared with the lowest-risk Group E.*

Results *In the study population of 29 035 women, 1.6%, 2.7%, 8.2%, 9.8% and 77.8% were categorized into Groups A, B, C, D and E, respectively. Compared with women in Group E, women in the higher-risk groups were more likely to have an adverse outcome. The RR of delivery with PE in Group A compared with Group E was 65.5 (95% CI, 54.1–79.1) and the respective values were 11.9 (95% CI, 9.1–15.5) for GH, 1.8 (95% CI, 1.5–2.1) for delivery by emergency Cesarean section, 1.5 (95% CI, 1.2–1.8) for delivery by elective Cesarean section, 8.9 (95% CI, 7.4–10.8) for SGA with birth weight < 3rd percentile, 4.8 (95% CI, 4.3–5.4) for SGA with birth weight < 10th percentile, 5.3 (95% CI, 1.4–20.5) for stillbirth and 3.4 (95% CI, 2.8–4.2) for NNU admission for ≥ 48 h. The RR for these pregnancy complications in higher-risk groups (*vs *Group E) was particularly high for cases with delivery within 2 weeks after assessment. In terms of SGA, both for birth weight < 10th and < 3rd*

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percentiles, the trend in all cases was stronger than that observed when the analysis was confined to normotensive pregnancies. The rates of neonatal death were too small to allow meaningful comparisons between risk groups.

Conclusion *Pregnant women identified by the competing-risks model to be at high risk of PE are also at increased risk of GH, Cesarean section, stillbirth, SGA and NNU admission for ≥ 48 h. © 2022 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Preterm pre-eclampsia (PE) with delivery at < 37 weeks' gestation can be predicted and prevented by screening at 11–13 weeks' gestation and treating high-risk women with aspirin[1–6]. However, in the case of term PE, which is three times more common than preterm PE, first-trimester screening predicts only 40% of cases, at a 10% false-positive rate (FPR)[2], and administration of aspirin has no significant effect on the incidence of the disease[5,6].

Effective screening for term PE is provided by the competing-risks model at 35 + 0 to 36 + 6 weeks' gestation[4] using a combination of maternal risk factors and measurements of mean arterial pressure (MAP), serum placental growth factor (PlGF) and serum soluble fms-like tyrosine kinase-1 (sFlt-1). The detection rate of the model is about 80%, at a FPR of 10%[7,8]. A prospective multicenter study involving 29 677 pregnancies has validated the results of the original algorithm[7] and demonstrated good agreement between the predicted risk and observed incidence of PE[8]. However, we have not examined the extent to which screening for PE can identify patients at high risk of other pregnancy complications, such as gestational hypertension (GH), small-for-gestational-age (SGA) neonate, delivery by Cesarean section, perinatal death and admission to the neonatal unit (NNU).

The objective of this non-interventional screening study at 35 + 0 to 36 + 6 weeks' gestation was to examine the incidence and relative risk of adverse pregnancy outcomes in a population of 29 035 women with singleton pregnancy, stratified according to their estimated risk of delivery with PE.

METHODS

Study design and participants

This was a prospective observational cohort study of women who attended for 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 2021. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks' gestation or fetal head circumference at 19–24 weeks' gestation[9,10].

The visit included recording of maternal demographic characteristics and medical history, measurement of maternal weight, height and MAP[11], ultrasound examination for fetal anatomy and biometry and measurement of maternal serum PlGF and sFlt-1 in pg/mL by an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). Participants completed a questionnaire, which was then reviewed by a doctor together with the woman. Patient characteristics included maternal age, race (white, black, South Asian, East Asian or mixed), method of conception (natural or assisted via *in-vitro* fertilization or ovulation induction), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), family history of PE (woman's mother affected) and obstetric history, which included parity (parous or nulliparous, if no previous pregnancy at ≥ 24 weeks' gestation) and, for parous women, previous pregnancy with PE and interpregnancy interval.

The inclusion criteria for this study were singleton pregnancy delivering a non-malformed liveborn or stillborn fetus at ≥ 24 + 0 weeks' gestation. Pregnancies with aneuploidy or major fetal abnormality were excluded. Women gave written informed consent to take part in the study, which was approved by the NHS research ethics committee.

Risk strata

The competing-risks model, combining the prior distribution of gestational age at delivery with PE and the likelihood from multiples of the median (MoM) values of MAP, PlGF and sFlt-1[7], was used to estimate the risk of delivery with PE for each patient in the study population. The patients were then assigned to one of five risk categories: Group A, ≥ 1 in 2; Group B, 1 in 5 to 1 in 3; Group C, 1 in 20 to 1 in 6; Group D, 1 in 50 to 1 in 21; and Group E, < 1 in 50.

Outcome measures

Outcome measures were PE, GH, SGA, elective and emergency Cesarean section, stillbirth, neonatal death and NNU admission for ≥ 48 h. Data related to pregnancy outcome were collected from hospital maternity records or from general medical practitioners of the women. The obstetric records of all women with pre-existing hypertension, GH or PE were reviewed to determine if the condition was GH or PE, as defined by the International Society for the study of Hypertension in Pregnancy[12]. GH was defined as new-onset hypertension (systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg, on at least two occasions, 4 h apart and developing at ≥ 20 weeks' gestation in previously normotensive women), in the absence of end organ dysfunction. The criteria for diagnosis of PE were new-onset or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h or protein-to-creatinine ratio ≥ 30 mg/mmol or ≥ 2 + on dipstick testing), renal insufficiency (with serum creatinine ≥ 90 µmol/L in the absence

of underlying renal disease), hepatic dysfunction with blood concentration of transaminases > 40 IU/L, thrombocytopenia (platelet count < 150 000/μL), neurological complications (altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata) or uteroplacental dysfunction (such as fetal growth restriction or stillbirth)[12]. Fetal growth restriction was diagnosed if estimated fetal weight was < 3rd percentile or if it was between the 3rd and 10th percentiles with uterine artery pulsatility index or umbilical artery pulsatility index > 95th percentile or middle cerebral artery pulsatility index < 5th percentile. The Fetal Medicine Foundation fetal and neonatal population weight charts were used to determine birth-weight percentile[13].

Statistical analysis

Data were expressed as median and interquartile range (IQR) for continuous variables and *n* (%) for categorical variables across the five risk groups. In each group, the proportion of women with adverse outcome was determined and the relative risk with 95% CI was calculated relative to the lowest-risk group (Group E). The statistical software package R was used for data analysis (R Foundation for Statistical Computing, Vienna, Austria)[14].

RESULTS

Study participants

The maternal and pregnancy characteristics of the study population of 29 035 women are summarized in Table 1. The proportions of women stratified according to estimated risk for delivery with PE into Groups A, B, C, D and E were 1.6%, 2.7%, 8.2%, 9.8% and 77.8%, respectively. In the higher-risk (*vs* lower-risk) groups, women tended to be older and heavier, and there were higher proportions

Table 1 Maternal and pregnancy characteristics of study population according to estimated risk of delivery with pre-eclampsia (PE)

Characteristic	*Group A Risk ≥ 1 in 2* (n = *471*)	*Group B Risk 1 in 5 to 1 in 3* (n = *783*)	*Group C Risk 1 in 20 to 1 in 6* (n = *2370*)	*Group D Risk 1 in 50 to 1 in 21* (n = *2832*)	*Group E Risk < 1 in 50* (n = *22 579*)
Age (years)	33.0 (28.4–37.0)	32.6 (28.5–36.4)	32.3 (28.2–36.3)	32.3 (28.4–36.1)	32.5 (28.7–35.9)
Weight (kg)	83.7 (73.0–99.0)	82.0 (72.5–96.0)	81.1 (72.0–94.0)	81.0 (72.0–93.0)	78.5 (70.7–88.9)
Height (cm)	163 (159–168)	164 (160–168)	164 (160–169)	165 (160–169)	166 (161–170)
Body mass index (kg/m^2)	31.4 (27.6–36.2)	30.9 (26.9–36.0)	30.1 (27.0–34.5)	30.1 (26.9–34.1)	28.5 (25.9–32.1)
GA at examination (weeks)	36.0 (35.6–36.3)	36.0 (35.6–36.3)	36.0 (35.7–36.3)	36.0 (35.6–36.3)	36.0 (35.6–36.3)
Race					
White	307 (65.2)	566 (72.3)	1745 (73.6)	2071 (73.1)	18 477 (81.8)
Black	104 (22.1)	138 (17.6)	361 (15.2)	473 (16.7)	2000 (8.9)
South Asian	43 (9.1)	48 (6.1)	148 (6.2)	155 (5.5)	991 (4.4)
East Asian	10 (2.1)	13 (1.7)	48 (2.0)	50 (1.8)	475 (2.1)
Mixed	7 (1.5)	18 (2.3)	68 (2.9)	83 (2.9)	636 (2.8)
Chronic hypertension	36 (7.6)	36 (4.6)	62 (2.6)	48 (1.7)	69 (0.3)
DM Type I	7 (1.5)	18 (2.3)	19 (0.8)	16 (0.6)	20 (0.1)
DM Type II	21 (4.5)	11 (1.4)	41 (1.7)	31 (1.1)	88 (0.4)
SLE/APS	1 (0.2)	7 (0.9)	15 (0.6)	11 (0.4)	40 (0.2)
Smoker	29 (6.2)	55 (7.0)	134 (5.7)	166 (5.9)	1166 (5.2)
Family history of PE	57 (12.1)	60 (7.7)	181 (7.6)	170 (6.0)	696 (3.1)
Method of conception					
Spontaneous	419 (89.0)	713 (91.1)	2182 (92.1)	2617 (92.4)	21 701 (96.1)
IVF	46 (9.8)	65 (8.3)	171 (7.2)	199 (7.0)	750 (3.3)
Ovulation drugs	6 (1.3)	5 (0.6)	17 (0.7)	16 (0.6)	128 (0.6)
Parity					
Nulliparous	279 (59.2)	494 (63.1)	1391 (58.7)	1643 (58.0)	9960 (44.1)
Parous, no previous PE	149 (31.6)	237 (30.3)	875 (36.9)	1080 (38.1)	12 273 (54.4)
Parous, previous PE	43 (9.1)	52 (6.6)	104 (4.4)	109 (3.8)	346 (1.5)
Interpregnancy interval (years)	4.5 (2.4–7.3)	3.6 (2.2–5.9)	3.5 (2.0–6.0)	3.2 (1.9–5.9)	2.5 (1.5–4.1)
GA at delivery (weeks)	38.1 (37.3–39.1)	39.0 (37.9–39.7)	39.3 (38.6–40.3)	39.4 (38.9–40.3)	39.7 (39.0–41.1)
Delivery					
Iatrogenic	316 (67.1)	361 (46.1)	883 (37.3)	985 (34.8)	7570 (33.5)
Spontaneous	155 (32.9)	422 (53.9)	1487 (62.7)	1847 (65.2)	15 009 (66.5)
Biomarker					
MAP MoM	1.145 (1.098–1.204)	1.090 (1.049–1.130)	1.063 (1.017–1.106)	1.039 (0.995–1.081)	0.991 (0.943–1.039)
PlGF MoM	0.221 (0.152–0.329)	0.295 (0.203–0.443)	0.383 (0.259–0.578)	0.533 (0.353–0.813)	1.221 (0.735–2.033)
sFlt-1 MoM	3.774 (2.905–4.784)	2.796 (2.204–3.546)	2.010 (1.573–2.552)	1.504 (1.222–1.860)	0.862 (0.654–1.137)

Data are given as median (interquartile range) or *n* (%). APS, antiphospholipid syndrome; DM, diabetes mellitus; GA, gestational age; IVF, *in-vitro* fertilization; MAP, mean arterial pressure; MoM, multiples of the median; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; SLE, systemic lupus erythematosus.

of black or South Asian women, those with history of chronic hypertension or diabetes mellitus, those who conceived by assisted reproductive technology, those with family history of PE, nulliparous women and those with previous history of PE. Women in higher-risk groups also had longer interpregnancy interval, higher MAP and sFlt-1, and lower PlGF.

Relative risk for pregnancy complications in different risk groups

Compared with women in Group E, women in higher-risk Groups A–D were significantly more likely to deliver with PE, develop GH, deliver (for any indication) within the next 2 weeks, deliver by emergency Cesarean section, have a SGA neonate or have a neonate admitted to the NNU for ≥ 48 h (Table 2, Figure 1). Women in higher-risk groups (*vs* Group E) were also more likely to develop the composite adverse perinatal outcome. The association between higher risk for PE and increasing RR for other pregnancy complications was more marked in cases with delivery within 2 weeks after assessment. In the case of SGA, both for birth weight < 10th and < 3rd percentiles, the observed association in all cases was stronger than that observed when the analysis was confined to normotensive pregnancies. The rates of neonatal death ($n = 4$ overall) were too small to allow meaningful comparisons between groups.

Table 2 Incidence and relative risk (RR) of adverse pregnancy outcomes according to estimated risk of delivery with pre-eclampsia (PE)

		Estimated risk of delivery with PE								
		Group A ≥ *1 in 2* (n = *471*)		*Group B* *1 in 5 to 1 in 3* (n = *783*)		*Group C* *1 in 20 to 1 in 6* (n = *2370*)		*Group D* *1 in 50 to 1 in 21* (n = *2832*)		*Group E* < *1 in 50* (n = *22 579*)
Outcome	*Total* (n *(%)*)	n *(%)*	*RR (95% CI)*	n *(%)*	*RR (95% CI)*	n *(%)*	*RR (95% CI)*	n *(%)*	*RR (95% CI)*	n *(%)*
PE	844 (2.9)	205 (43.5)	65.5 (54.1–79.1)	154 (19.7)	29.6 (23.9–36.6)	219 (9.2)	13.9 (11.4–17.0)	116 (4.1)	6.2 (4.9–7.8)	150 (0.7)
Delivery < 2 weeks	168 (0.6)	86 (18.3)	294.5 (169.7–510.5)	34 (4.3)	70.0 (38.1–128.7)	20 (0.8)	13.6 (7.0–26.6)	14 (0.5)	8.0 (3.9–16.4)	14 (0.1)
Gestational hypertension	675 (2.3)	60 (12.7)	11.9 (9.1–15.5)	91 (11.6)	10.8 (8.6–13.6)	177 (7.5)	7.0 (5.8–8.4)	105 (3.7)	3.5 (2.8–4.3)	242 (1.1)
Delivery < 2 weeks	57 (0.2)	12 (2.5)	82.2 (33.5–201.4)	15 (1.9)	61.8 (25.9–147)	20 (0.8)	27.2 (11.8–62.7)	3 (0.1)	3.4 (1.0–12.1)	7 (0.03)
Any delivery < 2 weeks	2247 (7.7)	170 (36.1)	6.5 (5.7–7.4)	193 (24.6)	4.4 (3.9–5.1)	355 (15)	2.7 (2.4–3.0)	278 (9.8)	1.8 (1.6–2)	1251 (5.5)
Emergency CS	4379 (15.1)	115 (24.4)	1.8 (1.5–2.1)	175 (22.3)	1.6 (1.4–1.9)	468 (19.7)	1.5 (1.3–1.6)	560 (19.8)	1.5 (1.3–1.6)	3061 (13.6)
Elective CS	3725 (12.8)	90 (19.1)	1.5 (1.2–1.8)	106 (13.5)	1.1 (0.9–1.3)	283 (11.9)	0.9 (0.8–1.0)	338 (11.9)	0.9 (0.8–1.0)	2908 (12.9)
Stillbirth	28 (0.1)	2 (0.4)	5.3 (1.4–20.5)	2 (0.3)	3.2 (0.8–12.4)	5 (0.2)	2.6 (1.0–6.9)	1 (0.04)	0.4 (0.1–2.6)	18 (0.1)
Neonatal death	4 (0.01)	0 (0)	0 (0–61.2)	0 (0)	0 (0–36.8)	0 (0)	0 (0–12.2)	1 (0.04)	2.7 (0.4–18.5)	3 (0.01)
SGA < 3rd percentile	1025 (3.5)	100 (21.2)	8.9 (7.4–10.8)	88 (11.2)	4.7 (3.8–5.8)	178 (7.5)	3.2 (2.7–3.7)	123 (4.3)	1.8 (1.5–2.2)	536 (2.4)
Delivery < 2 weeks	242 (0.8)	57 (12.1)	30.7 (22.3–42.1)	29 (3.7)	9.4 (6.2–14.1)	47 (2.0)	5.0 (3.5–7.1)	20 (0.7)	1.8 (1.1–2.9)	89 (0.4)
Normotensive	884 (3.0)	40 (8.5)	3.7 (2.7–4.9)	59 (7.5)	3.2 (2.5–4.2)	148 (6.2)	2.7 (2.2–3.2)	112 (4.0)	1.7 (1.4–2.1)	525 (2.3)
Delivery < 2 weeks	188 (0.6)	23 (4.9)	13.0 (8.3–20.2)	22 (2.8)	7.5 (4.7–11.8)	41 (1.7)	4.6 (3.2–6.6)	17 (0.6)	1.6 (1.0–2.7)	85 (0.4)
SGA < 10th percentile	2911 (10.0)	179 (38.0)	4.8 (4.3–5.4)	171 (21.8)	2.8 (2.4–3.2)	412 (17.4)	2.2 (2.0–2.4)	373 (13.2)	1.7 (1.5–1.9)	1776 (7.9)
Delivery < 2 weeks	468 (1.6)	82 (17.4)	17.9 (14.1–22.6)	46 (5.9)	6.0 (4.4–8.2)	76 (3.2)	3.3 (2.5–4.3)	44 (1.6)	1.6 (1.2–2.2)	220 (1.0)
Normotensive	2606 (9.0)	66 (14.0)	1.8 (1.4–2.3)	120 (15.3)	2.0 (1.7–2.4)	338 (14.3)	1.9 (1.7–2.1)	346 (12.2)	1.6 (1.4–1.8)	1736 (7.7)
Delivery < 2 weeks	379 (1.3)	31 (6.6)	7.0 (4.9–10.1)	33 (4.2)	4.5 (3.1–6.4)	66 (2.8)	3.0 (2.3–3.9)	38 (1.3)	1.4 (1.0–2.0)	211 (0.9)
NNU admission ≥ 48 h	1831 (6.3)	86 (18.3)	3.4 (2.8–4.2)	93 (11.9)	2.2 (1.8–2.7)	242 (10.2)	1.9 (1.7–2.2)	211 (7.5)	1.4 (1.2–1.6)	1199 (5.3)
Delivery < 2 weeks	410 (1.4)	48 (10.2)	11.3 (8.4–15.2)	37 (4.7)	5.3 (3.7–7.4)	76 (3.2)	3.6 (2.8–4.6)	46 (1.6)	1.8 (1.3–2.5)	203 (0.9)
Composite*	8656 (29.8)	375 (79.6)	3.2 (3.1–3.4)	470 (60.0)	2.4 (2.3–2.6)	1144 (48.3)	2.0 (1.9–2.0)	1092 (38.6)	1.6 (1.5–1.6)	5575 (24.7)
Delivery < 2 weeks	1099 (3.8)	146 (31.0)	13.6 (11.5–15.9)	116 (14.8)	6.5 (5.4–7.8)	189 (8.0)	3.5 (3.0–4.1)	132 (4.7)	2.0 (1.7–2.5)	516 (2.3)

*Composite outcome includes PE, gestational hypertension, small-for-gestational age at birth (SGA), stillbirth, emergency Cesarean section (CS), neonatal death and neonatal unit (NNU) admission ≥ 48 h.

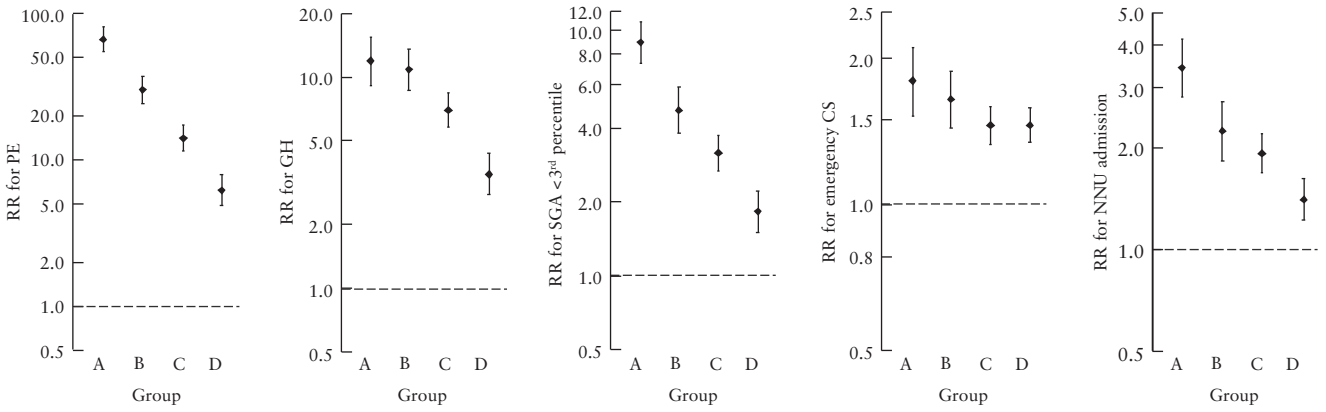

Figure 1 Relative risk (RR), with 95% CI, for adverse pregnancy outcomes in women with high risk for pre-eclampsia (PE) compared with group whose risk was < 1 in 50. Group A, risk ≥ 1 in 2; Group B, risk 1 in 5 to 1 in 3; Group C, risk 1 in 20 to 1 in 6; Group D, risk 1 in 50 to 1 in 21. CS, Cesarean section; GH, gestational hypertension; NNU, neonatal unit; SGA, small-for-gestational age at birth.

DISCUSSION

Main findings

The main findings of this large prospective study of women with a singleton pregnancy who were screened at 35 + 0 to 36 + 6 weeks for PE risk, demonstrate that, in groups with high risk for PE, there is also increased risk for other pregnancy complications. These complications include GH, delivery by elective or emergency Cesarean section, stillbirth, SGA at birth and admission to the NNU for ≥ 48 h. The trend of increasing RR for these pregnancy complications in the high-risk groups, compared to those with risk < 1 in 50, was more marked in cases with delivery within 2 weeks after assessment.

In 1.6% of our population, the estimated risk for delivery with PE was ≥ 1 in 2 and the incidence of delivery with PE was 44%. In addition, 13% developed GH, 38% delivered a SGA neonate with birth weight < 10th percentile, 44% delivered by Cesarean section and, in 18% of cases, the neonate stayed in the NNU for ≥ 48 h. In contrast, in the group with an estimated risk for delivery with PE < 1 in 50, which constituted about 78% of the population, 0.7% delivered with PE, 1% had GH, 8% had neonatal SGA < 10th percentile, 26% delivered by Cesarean section and, in 5% of cases, the neonate stayed in the NNU for ≥ 48 h. The RR of delivery with PE in the group with risk ≥ 1 in 2, compared to those with risk < 1 in 50, was 66 and the RR for delivery with PE within 2 weeks after assessment was 295.

Interpretation of results and implications for clinical practice

The performance of screening for term PE in the first, second and early third trimesters of pregnancy is poor, so it is necessary to delay screening for this pregnancy complication until 35–37 weeks' gestation[2,15–17]. Additional benefits of routine ultrasound examination of pregnancies at 35–37 weeks include diagnosis of fetal defects that become apparent only in the third trimester, diagnosis of breech and transverse presentation and detection of large-for-gestational-age and SGA fetuses[18–23]. While screening for PE risk at 35–37 weeks can identify a high proportion of women destined to develop term PE, treating all women in this high-risk group with pravastatin was ineffective in preventing term PE[24].

Although not quantified previously, it is perhaps unsurprising that the 35–37 weeks' competing-risks model for PE identifies risk for a broader range of pregnancy complications. Our competing-risks model for PE (at multiple gestational ages)[4] shares many predictors with our models for SGA[25,26] and stillbirth[27], based on shared underlying placental pathophysiology[28]. The association of PE risk with both Cesarean section and NNU admission likely reflects diminishing placental reserve near or at term; term NNU admission most commonly results from perinatal asphyxia[29].

An alternative strategy for reducing the risk of PE and other adverse outcomes assessed in our study would be to undertake screening for PE at 35–37 weeks, stratify the population into five risk categories, as was done in the present study, and plan early birth according to the risk group, from 37 + 0 weeks for Group A, 38 + 0 weeks for Group B, 39 + 0 for Group C, 40 + 0 for Group D and 41 + 0 for Group E. The extent to which such a strategy would achieve its objectives is the subject of a planned clinical trial.

Strengths and limitations

The main strengths of our study are, first, prospective examination of a large population of women with a singleton pregnancy attending for routine pregnancy care at 35–37 weeks' gestation and, second, establishment of the appropriate infrastructure for collection of data on several adverse pregnancy outcomes.

The main limitation of the study is that the data were restricted to women with a singleton pregnancy near term. Therefore, our findings that PE risk is associated with the risk of other pregnancy complications may not necessarily

apply to women with a multiple pregnancy or those at earlier gestational ages.

Conclusions

Women identified by late third-trimester screening as being at high risk of PE are also at increased risk of other adverse pregnancy outcomes. The extent to which both PE and other adverse outcomes can be reduced by planned early term delivery remains to be determined.

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REFERENCES

1. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing-risks model in screening for preeclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 103.e1–12.
2. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, Akolekar R, Konstantinidou L, Tsavdaridou M, Galeva S, Ajdacka U, Molina FS, Persico N, Jani JC, Plasencia W, Greco E, Papaioannou G, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 186–195.
3. Wright D, Tan MY, O'Gorman N, Poon LC, Syngelaki A, Wright A, Nicolaides KH. Predictive performance of the competing risk model in screening for preeclampsia. *Am J Obstet Gynecol* 2019; **220**: 199.e1–13.
4. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. *Am J Obstet Gynecol* 2020; **223**: 12–23.e7.
5. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017; **377**: 613–622.
6. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2018; **218**: 287–293.e1.
7. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016; **48**: 72–79.
8. Döbert M, Wright A, Varouxaki AN, Mu AC, Syngelaki A, Rehal A, Delgado JL, Akolekar R, Muscettola G, Janga D, Singh M, Martin-Alonso R, Dütemeyer V, De Alvarado M, Atanasova V, Wright D, Nicolaides KH. STATIN trial: predictive performance of competing-risks model in screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2022; **59**: 69–75.
9. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. *Br J Obstet Gynaecol* 1975; **82**: 702–710.
10. Snijders RJ, Nicolaides KH. Fetal biometry at 14–40 weeks' gestation. *Ultrasound Obstet Gynecol* 1994; **4**: 34–48.
11. Poon LC, Zymeri NA, Zamprakou A, Syngelaki A, Nicolaides KH. Protocol for measurement of mean arterial pressure at 11–13 weeks' gestation. *Fetal Diagn Ther* 2012; **31**: 42–48.
12. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens* 2018; **13**: 291–310.
13. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. *Ultrasound Obstet Gynecol* 2018; **52**: 44–51.
14. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.
15. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing-risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. *Am J Obstet Gynecol* 2016; **214**: 619.e1–17.
16. Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for preeclampsia by maternal factors and biomarkers at 30–34 weeks' gestation. *Am J Obstet Gynecol* 2016; **215**: 87.e1–17.
17. Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 501–506.
18. Ficara A, Syngelaki A, Hammami A, Akolekar R, Nicolaides KH. Value of routine ultrasound examination at 35–37 weeks' gestation in diagnosis of fetal abnormalities. *Ultrasound Obstet Gynecol* 2020; **55**: 75–80.
19. De Castro H, Ciobanu A, Formuso C, Akolekar R, Nicolaides KH. Value of routine ultrasound examination at 35–37 weeks' gestation in diagnosis of non-cephalic presentation. *Ultrasound Obstet Gynecol* 2020; **55**: 248–256.
20. Khan N, Ciobanu A, Karampitsakos T, Akolekar R, Nicolaides KH. Prediction of large-for-gestational-age neonate by routine third-trimester ultrasound. *Ultrasound Obstet Gynecol* 2019; **54**: 326–333.
21. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet* 2015; **386**: 2089–2097.
22. Ciobanu A, Khan N, Syngelaki A, Akolekar R, Nicolaides KH. Routine ultrasound at 32 *vs* 36 weeks' gestation: prediction of small-for-gestational-age neonates. *Ultrasound Obstet Gynecol* 2019; **53**: 761–768.
23. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 *vs* 32 weeks' gestation: a randomized trial (ROUTE). *Ultrasound Obstet Gynecol* 2015; **46**: 391–397.
24. Döbert M, Varouxaki AN, Mu AC, Syngelaki A, Ciobanu A, Akolekar R, De Paco Matallana C, Cicero S, Greco E, Singh M, Janga D, Del Mar Gil M, Jani JC, Bartha JL, Maclagan K, Wright D, Nicolaides KH. Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia. *Circulation* 2021; **144**: 670–679.
25. Papastefanou I, Wright D, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonate from maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2020; **56**: 196–205.
26. Papastefanou I, Nowacka U, Buerger O, Akolekar R, Wright D, Nicolaides KH. Evaluation of the RCOG guideline for the prediction of neonates that are small-for-gestational age and comparison with the competing-risks model. *BJOG* 2021; **128**: 2110–2115.
27. Nicolaides KH, Papastefanou I, Syngelaki A, Ashoor G, Akolekar R. Predictive performance for placental dysfunction related stillbirth of the competing-risks model for small-for-gestational-age fetuses. *BJOG* 2022; **29**: 1530–1537.
28. Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. *N Engl J Med* 2022; **386**: 1817–1832.
29. Clapp MA, James KE, Bates SV, Kaimal AJ. Unexpected term NICU admissions: a marker of obstetrical care quality? *Am J Obstet Gynecol* 2019; **220**: 395.e1–12.

