




## RESEARCH ARTICLE

## Maternal medicine

# Preterm and term pre-eclampsia: Relative burdens of maternal and perinatal complications

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## Abstract

**Objective:** To determine the relative burdens of maternal and perinatal complications for preterm and term pre-eclampsia.

**Design:** Prospective observational cohort study.

**Setting:** Two English maternity units.

**Population:** Unselected women with singleton pregnancies who developed pre-eclampsia (International Society for the Study of Hypertension in Pregnancy definition).

**Methods:** Outcomes were ascertained by health record review and compared between pregnancies with preterm (versus term) pre-eclampsia.

**Main outcome measures:** Severe maternal hypertension, maternal mortality or major maternal morbidity, perinatal mortality or major neonatal morbidity, neonatal unit (NNU) admission  $\geq 48$  hours, and birthweight  $< 3$ rd percentile.

**Results:** Among 40 241 singleton pregnancies, 298 (0.7%, 95% confidence interval [CI] 0.66–0.83) and 1194 (3.0%, 95% CI 2.8–3.1) developed preterm and term pre-eclampsia, respectively. Women with preterm (versus term) pre-eclampsia more commonly experienced adverse maternal or perinatal events: severe hypertension 18.5% (95% CI 14.5–23.3) versus 13.6% (95% CI 11.7–15.6); maternal mortality/major morbidity 7.4% (95% CI 4.9–10.9) versus 2.2% (95% CI 1.5–3.2); perinatal mortality/major neonatal morbidity 29.5% (95% CI 24.6–34.9) versus 2.2% (95% CI 1.5–3.2); and birthweight  $< 3$ rd percentile 54.4% (95% CI 48.7–59.9) versus 14.2% (95% CI 12.4–16.3). However, in absolute terms, most maternal complications occurred in women with term pre-eclampsia, as did a large proportion of perinatal complications: severe hypertension 74.7% (95% CI 68.5–80.0); maternal mortality/major morbidity 54.2% (95% CI 40.3–67.4); perinatal mortality/major neonatal morbidity 22.8% (95% CI 16.1–31.3); NNU admission  $\geq 48$  hours 38.1% (95% CI 32.4–44.1); and birthweight  $< 3$ rd percentile 51.2% (95% CI 45.8–56.5).

**Conclusions:** Although adverse event risks are greater with preterm (versus term) pre-eclampsia, term disease is associated with at least equivalent total numbers of maternal, and a significant proportion of perinatal, adverse events. Increased efforts should be made to decrease the incidence of term pre-eclampsia.

## KEY WORDS

adverse maternal outcomes, adverse perinatal outcomes, pre-eclampsia, preterm, term

 This article includes Author Insights, a video abstract presented by Laura A. Magee available at: <https://vimeo.com/790715868>

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## 1 | INTRODUCTION

Pre-eclampsia remains a leading cause of maternal mortality and severe morbidity and is associated with increased perinatal risks.<sup>1</sup> For individual women, earlier onset of pre-eclampsia is an independent predictor of adverse maternal<sup>2-5</sup> and perinatal<sup>6,7</sup> events in both less- and more-developed countries. Therefore, there has been a focus on identifying women at increased risk of early-onset pre-eclampsia, with aspirin proving effective at improving pregnancy outcomes in women identified.<sup>8-10</sup>

The incidence of pre-eclampsia increases with gestational age.<sup>1</sup> In Canada, the population-level incidences of all of the following are higher in women with term (versus preterm) pre-eclampsia: 'severe pre-eclampsia'; haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome; and eclampsia.<sup>2</sup> However, it is unclear what the population-level implications of preterm and term pre-eclampsia are for a broader definition of maternal and perinatal morbidity and mortality, based on the core maternal and perinatal outcomes for reporting studies of pre-eclampsia.<sup>11</sup>

To clarify both clinical burden and research priorities, our objective was to determine the relative contributions of preterm and term pre-eclampsia to the burden of associated adverse maternal and perinatal events.

## 2 | METHODS

### 2.1 | Study design and participants

The study data were derived from a previous prospective screening study for adverse obstetric outcomes in an unselected cohort of women attending routine pregnancy care, at 19<sup>+0</sup> to 23<sup>+6</sup> weeks' gestation, at King's College and Medway Maritime Hospitals, UK, between October 2011 and March 2020.<sup>12</sup> All women gave written informed consent to participate in the study, which was conducted according to the guidelines of the Declaration of Helsinki, and approved by the NHS Research Ethics Committee (REC reference: 02-03-033 on 11 March 2003). There was no patient involvement in the study.

In that study,<sup>12</sup> we assessed the risk of development of pre-eclampsia (PE) from a combination of maternal characteristics and medical history, together with the measurements of mean arterial pressure, uterine artery pulsatility index and serum placental growth factor. The results from this assessment were not given to the patients or health-care providers. Gestational age was determined by measurement of the fetal crown-rump length at 11-13 weeks' gestation, or the fetal head circumference at 19<sup>+0</sup> to 23<sup>+6</sup> weeks' gestation.<sup>13,14</sup>

Inclusion criteria for this analysis were: singleton pregnancies and delivery of a non-malformed liveborn or stillborn at  $\geq 24$  weeks. We excluded pregnancies with major fetal abnormalities, termination or fetal death before 24 weeks.

Data related to pregnancy outcomes were abstracted from electronic hospital maternity records or those of the women's general practitioners. The maternity records of all women with chronic hypertension or gestational hypertension were examined to determine the diagnosis of pre-eclampsia. Pre-eclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy, as the presence at  $\geq 20$  weeks' gestation, of: maternal hypertension (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg); and either significant proteinuria (urinary protein: creatinine ratio  $\geq 30$  mg/mmol or 24 h proteinuria  $\geq 300$  mg), other maternal end-organ dysfunction or evidence of uteroplacental dysfunction.<sup>15</sup> In this context, uteroplacental dysfunction was defined as either intrauterine fetal death or birthweight  $< 3$ rd percentile for gestational age.

### 2.2 | Outcome measures

The maternal and perinatal outcomes of interest were as follows: severe maternal hypertension,<sup>16</sup> a composite of maternal death or major morbidity, a composite of perinatal death or major neonatal morbidity, neonatal unit (NNU) admission  $\geq 48$  hours, and birthweight  $< 3$ rd percentile for gestational age.<sup>17</sup>

Severe maternal hypertension was defined as systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 110$  mmHg. Major maternal morbidity was defined as one or more of the following: eclampsia, myocardial ischaemia, pulmonary oedema, hepatic haematoma or HELLP syndrome. These were based on the core maternal outcome set in pre-eclampsia, except for outcomes that were not available (i.e. liver rupture, postpartum haemorrhage, admission for critical care, and intubation and ventilation other than for childbirth), exclusion of placental abruption (which was defined clinically and under-reported) and the addition of myocardial ischaemia (based on the Delphi-derived Pre-eclampsia Integrated Estimate of Risk score).<sup>5,11</sup>

Perinatal death was defined as stillbirth or neonatal death prior to hospital discharge. Major neonatal morbidity was defined as one or more of the following, as indicated in the BadgerNet Neonatal discharge summary: ventilation (i.e. need for continuous positive airway pressure or nasal continuous positive airway pressure or intubation), respiratory distress syndrome (i.e. the need for surfactant and ventilation), brain injury (i.e. hypoxic-ischaemic encephalopathy, intraventricular haemorrhage grade  $\geq 2$ , or periventricular leucomalacia), sepsis (based on positive blood cultures), anaemia treated with blood transfusion or necrotising enterocolitis requiring surgical intervention. The birthweight percentile for gestational age was determined using the Fetal Medicine Foundation fetal and neonatal weight charts.<sup>17</sup> Perinatal outcomes covered the core perinatal outcome set for pre-eclampsia, other than neonatal seizures.<sup>11</sup>

Other outcomes included mode of delivery.

## 2.3 | Statistical analysis

Descriptive analysis was undertaken for (i) baseline data from the assessment at 19<sup>+0</sup> to 23<sup>+6</sup> weeks' gestation, and subsequent pregnancy outcomes for the study population overall; and (ii) pregnancy outcomes according to occurrence of preterm or term pre-eclampsia. Continuous variables were summarised by median (interquartile range [IQR]), and categorical variables by numbers (percentage [95% confidence interval, CI]). There was no adjustment of outcome rates for confounders, as we were interested in examining the burden of disease relative only to gestational age at birth with pre-eclampsia. No power calculation was undertaken. Analyses were undertaken using the statistical software package SPSS, and the VassarStats computational website ([www.vassarstats.net](http://www.vassarstats.net)).

## 3 | RESULTS

### 3.1 | Study participants

During the study period, 41 002 women with singleton pregnancies consented to participate in the study; however, we excluded 761 (1.9%) pregnancies because of major fetal abnormalities, pregnancy termination or fetal death before 24 weeks ( $n = 428$ ) or loss to follow-up ( $n = 333$ ). Therefore, the study population consisted of 40 241 pregnancies with complete outcome data.

Table 1 shows that, on average, women in the study were in their early 30s, with 25% of women considered obese according to mid-trimester body mass index. Most women were white, with a substantial minority of women of black race. Few

**TABLE 1** Baseline characteristics of the screened population

Characteristic	All pregnancies ( $n = 40\,241$ )	Preterm PE ( $n = 298$ )	Term PE ( $n = 1194$ )
GA at assessment (weeks)	21.6 (21.1–22.0)	21.6 (21.1–22.0)	21.6 (21.1–22.0)
Maternal demographics			
Age at screening (years)	31.9 (27.9–35.5)	32.0 (27.7–35.8)	32.2 (27.6–36.6)
BMI at screening (kg/m <sup>2</sup> )	26.2 (23.5–30.0)	29.0 (25.8–33.7)	28.2 (25.1–33.1)
≥30 kg/m <sup>2</sup>	10 103 (25.1 [24.7–25.5])	129 (43.3 [37.8–49.0])	471 (39.4 [36.7–42.2])
Race <sup>a</sup>			
White	31 195 (77.5 [77.1–77.9])	173 (58.1; 52.4–63.5)	839 (70.3; 67.6–72.8)
Black	5226 (13.0 [12.7–13.3])	97 (32.6; 27.5–38.1)	252 (21.1; 18.9–23.5)
South Asian	1923 (4.8 [4.6–5.0])	24 (8.1; 5.5–11.7)	46 (3.9; 2.9–5.1)
East Asian	784 (1.9 [1.8–2.1])	1 (0.3; 0.1–1.9)	21 (1.8; 1.2–2.7)
Mixed/Other	1113 (2.8 [2.6–2.9])	3 (1.0; 0.3–2.9)	36 (3.0; 2.2–4.1)
Cigarette smoker	3016 (7.5 [7.2–7.8])	12 (4.0; 2.3–6.9)	66 (5.5; 4.4–7.0)
Medical history			
Chronic hypertension	425 (1.1 [1.0–1.2])	42 (14.1; 10.6–18.5)	114 (9.5; 8.0–11.3)
On antihypertensive(s)	354 (0.9 [0.8–1.0])	39 (13.1; 9.7–17.4)	103 (8.6; 7.2–10.4)
SLE or APAS	85 (0.2 [0.2–0.3])	1 (0.3; 0.1–1.9)	3 (0.3; 0.1–0.7)
DM (type 1 or 2)	354 (0.9 [0.8–1.0])	18 (6.0; 3.9–9.3)	18 (1.5; 1.0–2.4)
Obstetric history			
Nulliparous	18 954 (47.1 [46.6–47.6])	189 (63.4; 57.8–68.7)	773 (64.7; 62.0–67.4)
Parous without prior PE	20 300 (50.4 [50.0–50.9])	65 (21.8; 17.5–26.8)	323 (27.1; 24.6–29.6)
Parous with prior PE	987 (2.5 [2.3–2.6])	44 (14.8; 11.2–19.2)	98 (8.2; 6.8–9.9)
Family history			
Patient's mother had PE	1451 (3.6 [3.4–3.8])	33 (11.1; 8.0–15.1)	78 (6.5; 5.3–8.1)
Index pregnancy			
Inter-pregnancy years	2.5 (1.7–4.7)	3.5 (2.2–5.5)	3.6 (2.2–6.2)
Conception			
Natural	38 433 (95.5 [95.3–95.7])	272 (91.3; 87.5–94.0)	1110 (93.0; 91.4–94.3)
Assisted by ovulation drugs	295 (0.7 [0.7–0.8])	4 (1.3; 0.5–3.4)	11 (0.9; 0.5–1.6)
In vitro fertilisation	1513 (3.8 [3.6–4.0])	22 (7.4; 4.9–10.9)	73 (6.1; 4.9–7.6)
Receiving aspirin for PE prevention	1339 (3.3 [3.2–3.5])	39 (13.1; 9.7–17.4)	100 (8.4; 6.9–10.1)

Note: Values presented as  $n$  (% [95% confidence interval]) or median (interquartile range).

Abbreviations: APAS, antiphospholipid antibody syndrome; BMI, body mass index; DM, diabetes mellitus; GA, gestational age; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

<sup>a</sup>Self-declared race.

women (<10%) were cigarette smokers. Medical history was usually unremarkable, with few women reporting chronic hypertension (most of whom were treated with antihypertensive therapy), pre-gestational diabetes mellitus or autoimmune disease. Just over half of women were parous, with 2.5% of them having had prior pre-eclampsia. Few women reported that their mothers had suffered from pre-eclampsia. Almost all conceptions were natural, following an interpregnancy interval of just under 3 years, when relevant. Few women were receiving aspirin for pre-eclampsia prevention, the prescription of which was guided entirely by routine clinical care. Women who developed preterm (versus term) pre-eclampsia more often: were of black or South Asian race; had a history of chronic hypertension treated with antihypertensives or pre-gestational diabetes; if parous, had a history of prior pre-eclampsia; were receiving aspirin for pre-eclampsia prevention; and had a family history of pre-eclampsia in their mother.

### 3.2 | Maternal complications, labour and delivery, and perinatal outcomes

Pre-eclampsia complicated the course of 1492 (3.7% [95% CI 3.7–3.9]) of pregnancies, of which 298 (20.0% [95% CI 18.0–22.1]) and 1194 (80% [95% CI 77.9–82.0]) were preterm and term, respectively. Women with preterm and term pre-eclampsia delivered at a median of 35.0 (IQR 32.9–36.3) weeks and 39.3 (IQR 38.3–40.4) weeks, respectively.

Women whose pregnancies were complicated by preterm (versus term) pre-eclampsia were at greater individual risk for adverse maternal events, caesarean delivery, perinatal loss, major neonatal morbidity and delivery of an infant with birthweight <3rd percentile, and they were less likely to deliver following an induction or vaginally (Table 2).

For the 1492 women whose pregnancies were complicated by pre-eclampsia, term pre-eclampsia contributed

**TABLE 2** Pregnancy outcomes among 1492 women with preterm and term pre-eclampsia

Outcome	<i>n</i>	Preterm pre-eclampsia ( <i>n</i> = 298, 0.7 [0.66–0.83])	Term pre-eclampsia ( <i>n</i> = 1194, 3.0 [2.8–3.1])	Contribution of term pre-eclampsia to adverse outcome
<b>Maternal</b>				
Severe hypertension	217	55 (18.5 [14.5–23.3])	162 (13.6 [11.7–15.6])	162/217 (74.7 [68.5–80.0])
Major morbidity	48	22 (7.4 [4.9–10.9])	26 (2.2 [1.5–3.2])	26/48 (54.2 [40.3–67.4])
Death	1	0	1	1/1
Eclampsia	13	7	6	6/13
Myocardial ischaemia	0	0	0	0
Pulmonary oedema	4	1	3	3/4
Hepatic haematoma	2	0	2	2/2
HELLP	33	17	16	16/33
<b>Labour and delivery</b>				
Gestation at delivery (weeks)		35.0 (32.9–36.3)	39.3 (38.3–40.4)	—
Induction of labour	802	89 (29.9 [25.0–35.3])	713 (59.7 [56.9–62.5])	713/802 (88.9 [86.5–90.9])
Vaginal delivery	758	79 (26.5 [21.8–31.8])	679 (56.9 [54.0–59.7])	679/758 (89.6 [87.2–91.6])
Spontaneous vaginal delivery	263	25 (8.4 [5.8–12.1])	238 (19.9 [17.8–22.3])	238/263 (90.5 [86.3–93.5])
Caesarean delivery	734	219 (73.5 [68.2–78.2])	515 (43.1 [40.4–46.0])	515/734 (70.2 [66.8–73.4])
<b>Perinatal</b>				
Perinatal mortality or major neonatal morbidity	114	88 (29.5 [24.6–34.9])	26 (2.2 [1.5–3.2])	26/114 (22.8 [16.1–31.3])
Stillbirth	13	10	3	3/13
Neonatal death	3	3	0	0/3
Ventilation	96	76	20	20/96
RDS	49	45	4	4/49
Brain injury	9	6	3	3/9
Sepsis	13	10	3	3/13
Anaemia	13	12	1	1/13
NEC	2	2	0	0/2
NNU admission for ≥48 h	260	161 (54.0 [48.4–59.6])	99 (8.3 [6.9–10.0])	99/260 (38.1 [32.4–44.1])
Birthweight <3rd percentile	332	162 (54.4 [48.7–59.9])	170 (14.2 [12.4–16.3])	170/332 (51.2 [45.8–56.5])

Note: Values presented as *n* (% [95% confidence interval]) or median (interquartile range). By definition, the gestational age at birth for women delivering with preterm pre-eclampsia is earlier than for women with term pre-eclampsia.

Abbreviations: HELLP, haemolysis, elevated liver enzymes, low platelets syndrome; NEC, necrotising enterocolitis; NNU, neonatal unit; RDS, respiratory distress syndrome.

equivalent numbers of adverse maternal events within the whole cohort, including the sole maternal death, 6/13 cases of eclampsia, 16/33 cases of HELLP syndrome and over two-thirds of the caesarean deliveries (Table 2). With respect to adverse perinatal events, term pre-eclampsia was associated with a significant minority of events, with the exception of birthweight <3rd percentile for gestational age (Table 2). However, the proportion of perinatal deaths or major morbidity was clinically important, including 3/13 stillbirths, 20/96 babies who required ventilation, 3/9 brain injuries and 99/260 of NNU admissions.

## 4 | DISCUSSION

### 4.1 | Main findings

In this racially diverse cohort of women with 40 241 unselected pregnancies in southern England, pre-eclampsia complicated 3.7% of pregnancies, and 80% of cases of pre-eclampsia arose at term. Although women who developed preterm (versus term) pre-eclampsia had more risk factors for the disease and experienced higher individual adverse event risks, the total numbers of adverse maternal events were at least equal between preterm and term disease, and a significant proportion of adverse perinatal events complicated the course of women with term pre-eclampsia.

### 4.2 | Strengths and limitations

The strengths of our study include the large sample size, unselected and multiracial nature of women presenting for their 19- to 23-week routine anatomical ultrasound, and prospective, comprehensive documentation of baseline characteristics, pre-eclampsia diagnostic criteria, and maternal and perinatal outcomes at preterm and term gestational ages. In addition, the cohort was recruited in the UK from October 2011 to March 2020, during the majority of which time only a traditional definition of pre-eclampsia (hypertension and significant proteinuria) was accepted (until June 2019)<sup>18,19</sup> in maternity units that did not routinely use either the Pre-eclampsia Integrated Estimate of Risk Score (PIERS) or PRediction of complications in Early-onset Pre-eclampsia (PREP) outcome prediction models, which may have influenced the pre-eclampsia-adverse outcomes relation.<sup>3,5</sup>

A limitation of our data was that we enrolled only women with singleton pregnancies; therefore, our findings may not apply to women with multiple pregnancies who develop pre-eclampsia, for which they are at increased risk.<sup>20</sup> In addition, due to the limitations of routinely collected data, we were unable to include all components of both the Delphi-derived core outcome set for pre-eclampsia and PIERS combined adverse maternal outcome, as discussed above.<sup>5,11</sup> Finally, we did not have information to inform a health economics analysis, but it

has been estimated that treating pre-eclampsia costs the UK National Health Service an additional UK£9,000 per pregnancy, with major cost drivers including not only care of preterm infants but also surgical intervention and severe maternal morbidity.<sup>21,22</sup>

### 4.3 | Interpretation

Our results are consistent with, and expand, those from the Canadian dataset of 1 078 323 singleton births, which was limited to the outcomes of 'severe pre-eclampsia', HELLP syndrome and eclampsia identified by ICD-10-CA codes (O14.1, O14.2, and O15, respectively).<sup>2</sup> In that national cohort (excluding Quebec), they observed similarly increased adverse event risks per woman with preterm pre-eclampsia, but equivalent total numbers of events between preterm and term disease. These data reflect that with increasing gestational age, the maternal risks for individual women with pre-eclampsia decrease, but in both less- and more-developed countries, the number of women who develop pre-eclampsia increases.<sup>4,5,23</sup>

There has been substantial progress in identifying women at increased risk of developing pre-eclampsia at 11–13 weeks' gestation (10% test positive rate), and offering them 150 mg of aspirin at night; such a strategy is cost-effective and more than halves the burden of pre-eclampsia that arises preterm.<sup>8–10,24,25</sup> However, neither aspirin administered in this way, nor pravastatin administered from 35–36 weeks' gestation, reduces the burden of term pre-eclampsia and its attendant risks.<sup>9,26</sup>

In the absence of an effective and implemented prevention strategy for term pre-eclampsia, it remains important to identify those women at particular risk of pre-eclampsia at term. The 35- to 36-week competing risk model identifies 75% of women who subsequently develop pre-eclampsia.<sup>27</sup> At a minimum, such women could be advised to perform home blood pressure and symptom monitoring; ideally, they could be enrolled in trials of induction timed according to their individual risk level. Given the maternal and perinatal morbidity associated with term disease, this should be a research priority.

## 5 | CONCLUSION

Our findings emphasise the importance of term pre-eclampsia as a potentially dangerous condition for mothers and babies. At a minimum, these women must be diagnosed promptly and receive evidence-based care, including blood pressure control, and timely delivery. Future research should define timing of birth based on an individualised risk of term pre-eclampsia.

### AUTHOR CONTRIBUTIONS

All authors conceptualised and designed the study. PvD wrote the first draft of the paper. AS and RA were involved in the sample collection. All authors revised and contributed to the intellectual content of the paper.



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## CONFLICT OF INTERESTS

None declared. Completed disclosure of interest forms are available to view online as supporting information.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ETHICS APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the NHS Research Ethics Committee (REC reference: 02-03-033 on 11 March 2003).

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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