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ORIGINAL ARTICLE

The association between pre-eclampsia and neonatal complications in relation to gestational age

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Abstract

Aim: There has been limited research about the associations between pre-eclampsia and neonatal complications in relation to gestational age. This register-based study aimed to address that gap in our knowledge.

Methods: We used Swedish Medical Birth Register to carry out a population-based study on primiparas with singleton pregnancies from 1999 to 2017. Descriptive statistics and logistic regressions were used to study the associations between pre-eclampsia and neonatal complications in different gestational ages. The data is presented as adjusted odds ratios (aORs) with 95% CI.

Results: The study comprised 805 591 primiparas: 2.9% had mild to moderate pre-eclampsia and 1.4% had severe pre-eclampsia. Neonates born to women with pre-eclampsia had increased risks of several complications compared to those born to mothers without pre-eclampsia. After adjustment for confounding variables, the risk of being small for gestational age (aOR 5.3, CI: 5.1–5.5) and needing resuscitation (aOR 2.6, CI: 2.4–2.7) were increased. The risk of a low Apgar score and convulsions/hypoxic ischemic encephalopathy was increased at 32–41 weeks of gestation. Moreover, the overall risk of sepsis (aOR 1.9. CI: 1.8–2.1) and perinatal death (aOR 1.2, CI: 1.1–1.5) was also increased.

Conclusion: Compared with infants of mothers without pre-eclampsia, those exposed to pre-eclampsia had higher risks of all the studied neonatal complications.

KEYWORDS
hypertension, neonatal complications, perinatal mortality, pre-eclampsia, prematurity

1 | INTRODUCTION

Pre-eclampsia is a multifactorial and multisystem disorder that occurs in 3%–8% of all pregnancies. The disorder is a major cause of maternal and foetal morbidity.[1,2] Pre-eclampsia is traditionally defined by increased blood pressure and proteinuria during pregnancy. The diagnose is based on blood pressure of ≥140 systolic or ≥90 mmHg diastolic, measured on two separate occasions, combined with proteinuria ≥0.3 g for 24 h or 1+ or more on dipstick on at least one subsequent occasion.[1] The diagnostic criteria for

Abbreviations: BMI, body mass index; HIE, hypoxic ischaemic encephalopathy; ICD-10, International Classification of Disease, tenth revision; SGA, small for gestational age.

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pre-eclampsia was changed in 2014 by the International Society for the Study of Hypertension in Pregnancy. It now includes hypertension after 20 weeks of gestation combined with various factors. These are either proteinuria of >30 mg/mmol or >300 mg/day or 1 g/L equals '2+' on dipstick, or other maternal organ dysfunction, namely renal insufficiency, liver involvement, neurological complications, haematological complications or uteroplacental dysfunction with foetal growth restriction.[2] There is also a clinical distinction between early-onset pre-eclampsia before 34 weeks of gestation and late-onset pre-eclampsia from 34 weeks of gestation. Early-onset pre-eclampsia is often more severe than late-onset pre-eclampsia, and poses a risk of both short-term and long-term morbidity and mortality for both the mother and infant.[3,4]

A main pathologic feature of early-onset pre-eclampsia, is abnormal development of the placenta. This includes impaired remodelling of the spiral arteries, which causes placental ischaemia, damage to the placental villi and oxidative stress, which leads to foetal growth restriction. For the mother, this leads to abnormal protein levels in the blood, causing vascular endothelial injury, hypertension and multi-organ injuries.[1] The aetiology of pre-eclampsia is not totally elucidated, but one major contributor has been identified. That is immunological mismatching between maternal and paternal antigens, leading to immune system interactions in the trophoblast cells and decidua.[1]

Prophylactic acetylsalicylic acid can reduce the risk of pre-eclampsia but there are no curative treatments apart for delivering the foetus and placenta.[5] That is why, obstetricians must weigh the risks to both the mother and foetus when making decisions. The maternal risks are cardiovascular complications and potential progression with haemolysis elevated liver enzymes and low platelets (HELLP) syndrome and abruptio placentae. The foetal risks are preterm birth at <37 weeks of gestation, intrauterine growth restriction and intrauterine death.[1] The current management approach is to induce labour if pre-eclampsia is diagnosed at ≥37 weeks of gestation. Not inducing labour at this stage can have potential adverse outcomes for the mothers and these needs to be weighed up against the small benefits for the foetus. If pre-eclampsia is diagnosed before 34 weeks of gestation, this is often managed with close monitoring and expedited birth if there are signs of maternal organ dysfunction or foetal compromise.[6] If women are diagnosed with pre-eclampsia between 34 and 37 weeks of gestation, the timing of birth should be based on comparing the maternal and foetal risks, and involving the mother in the decision-making.[1,7,8]

It is not clear whether the neonatal outcomes of infants born to mothers with pre-eclampsia are determined by prematurity, pre-eclampsia complications or other key factors. Therefore, the aim of this study was to investigate neonatal complications in singleton neonates born to women with pre-eclampsia at various gestational ages. The data was compared with controls, matched by gestational age and born to women without pre-eclampsia.

Key notes

- This register-based study of 805 591 primiparas examined the associations between pre-eclampsia and complications in singleton neonates born at different gestational ages.
- A number of risks were higher in neonates born to mothers with pre-eclampsia: being small for gestational age, needing resuscitation, sepsis and hypoxic ischaemic encephalopathy/convulsions and a low Apgar score.
- The risk of perinatal death was increased in the whole group exposed to pre-eclampsia but not in respective gestational age-groups.

2 | METHODS

We conducted a nationwide cohort study on neonates born to mothers with and without pre-eclampsia, in Sweden between from 1999 to 2017. The study was based on data from the Swedish Medical Birth Register, which included more than 98% of all births in Sweden during this period. The register included information on maternal characteristics, complications during pregnancy, childbirth and the neonatal period.

2.1 | Study population

The study population was 805 591 primiparas who gave birth to singleton infants in 1999–2017. Only primiparas were included because the risk of pre-eclampsia predominantly occurs in primiparous women. Further, multiparas were excluded to make the study population more homogenous and reduce the risk of residual confounding. We excluded multiple pregnancies, *gestational hypertension without significant proteinuria, according to the* International Classification of Diseases, Tenth revision *(ICD-10), code O13* and infants with congenital malformations. The internal dropouts consisted of 374 births with missing variables in the registry, accounting for <0.01% of the births.

2.2 | Exposure

Pre-eclampsia was defined according to the ICD-10 codes O14-O15, in line with national Swedish guidelines during the study period. The clinical definition of mild/moderate pre-eclampsia was: blood pressure ≥140 systolic or ≥90 mmHg diastolic, measured on two separate occasions, combined with proteinuria of ≥0.3 g per 24 h or 1+ or more on dipstick, on at least one subsequent occasion. Severe pre-eclampsia was defined as at least one of following findings: blood pressure ≥160/110,

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proteinuria >5 g per 24 h (criteria until 2014), new cerebral symptoms, oliguria, haemolysis elevated liver enzymes and low platelets (HELLP) syndrome or epigastric pain. Pre-eclampsia was categorised as: mild/moderate pre-eclampsia (ICD-10: code O14.0), severe pre-eclampsia (ICD-10 codes O14.1, O14.2 and O15) and no pre-eclampsia in the descriptive analyses. Pre-eclampsia was divided into pre-eclampsia or not pre-eclampsia in the regression analyses.

2.3 | Co-variates

The following co-variates were considered as possible confounders: maternal body mass index (BMI), smoking in early pregnancy, height, age, maternal diabetes, maternal kidney disease and maternal systemic lupus erythematosus. The choice of co-variates was based on previous reports of associations[9–13] and are categorised in Table 1.

The maternal co-variates included maternal age which was categorised as ≤19, 20–29, 30–34, ≥35 years). Maternal height was categorised as ≤162 cm, 163–171 cm, ≥172 cm); BMI was divided into underweight (≤18.4), normal weight (18.5–24.9), overweight (25.0–29.9), obese (≥30) and missing. Smoking was categorised as yes, no or missing. Women with pre-gestational diabetes were identified by a check box, as well as by the ICD-10 codes O24.0 and O24.3. Those with systemic lupus erythematosus were identified by a check box and by ICD-10 codes M32.1, M32.8 and M32.9. Women with kidney disease were identified by a check box.

Gestational age was categorised into six groups to establish whether there was a diverse distribution of complications at different gestational ages in the descriptive analysis. These were 22–27, 28–31, 32–36, 37–38, 39–41 and ≥42 gestational weeks. In order to conduct the risk analysis, gestational age was divided into wider groups in the regression models: early pre-eclampsia (22–31 weeks

TABLE 1 Characteristics of the study population.

	No PE, *N* = 771 806	Mild/moderate PE, *N* = 22 898	Severe PE, *N* = 11 247
***N* = 805 591**	***n* (%)**	***n* (%)**	***n* (%)**
Age (years)			
≤19	24 402 (3.2)	661 (2.9)	324 (2.9)
20–29	440 799 (57.2)	12 761 (55.8)	5797 (51.6)
30–34	220 590 (28.6)	6273 (27.4)	3361 (29.9)
≥35	85 315 (11.1)	3191 (13.9)	1757 (15.6)
Height (cm)			
≤162	192 637 (26.4)	6045 (27.8)	3231 (31.0)
163–171	376 187 (51.6)	11 169 (51.3)	5280 (50.6)
≥172	160 452 (22.0)	4544 (20.9)	1920 (18.4)
Body mass index (BMI)			
Under weight	21 219 (2.7)	302 (1.3)	211 (1.9)
Normal	457 359 (59.3)	9743 (42.5)	5389 (47.9)
Overweight	156 523 (20.3)	6060 (26.5)	2645 (23.5)
Obesity	64 231 (8.3)	4750 (20.7)	1772 (15.8)
Missing data	72 474 (9.4)	2043 (8.9)	1230 (10.9)
Gestational age			
22–27	2207 (0.3)	65 (0.3)	380 (3.4)
28–31	3288 (0.4)	188 (0.8)	1098 (9.8)
32–36	33 939 (4.4)	1790 (7.8)	3631 (32.3)
37–38	124 965 (16.2)	5997 (26.2)	2930 (26.1)
39–41	536 657 (69.6)	13 629 (59.5)	3048 (27.1)
≥42	70 401 (9.1)	1220 (5.3)	144 (1.3)
Diabetes	3116 (0.4)	482 (2.1)	299 (2.7)
Kidney disease	3400 (0.4)	179 (0.8)	96 (0.9)
Pre-gestational hypertension	2322 (0.3)	268 (1.2)	260 (2.3)
Systemic lupus erythematosus (SLE)	795 (0.1)	36 (0.2)	22 (0.2)
Smoking	52 720 (6.8)	1323 (5.8)	487 (4.3)
Missing data	42 445 (5.5)	1190 (5.2)	837 (7.4)

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of gestation), moderately early (32–36 weeks), term (37–41 weeks) and post-term (≥42 weeks).

The neonatal outcomes included being small for gestational age (SGA) which was defined as ≤2 standard deviations,[14] and a low Apgar score of less than seven at 5 min. We also included convulsions and/or hypoxic ischaemic encephalopathy HIE (ICD-10 code P90), neonatal sepsis (ICD-10 code P36) and the need for resuscitation. Perinatal death included both antepartum deaths, intrapartum deaths and neonatal deaths up to day 27.

2.4 | Statistical methods

Descriptive statistics and logistic regressions were used to study the associations between pre-eclampsia and different neonatal complications. Crude and adjusted models were used. The co-variates adjusted for were: the infant's year of birth, the mother's age, height, BMI and diabetes, kidney disease, maternal systemic lupus erythematosus and smoking. Significance was defined as $p = 0.05$ and 95% confidence intervals (CI) were used. All the analyses were performed with SPSS, version 28 (IBM Corp, New York, NY, USA).

2.5 | Ethics

The study was approved by The Swedish Ethical Review Authority in March 2020 decision number 2020-00113.

3 | RESULTS

There were 805 591 primiparous women in this study and 22 898 (2.9%) were diagnosed with mild to moderate pre-eclampsia and 11 247 (1.4%) with severe pre-eclampsia. Of the women diagnosed with pre-eclampsia, 3.7% developed pre-eclampsia at term, 0.9% had moderately early pre-eclampsia and 0.2% developed early pre-eclampsia. A quarter of the women had a BMI above normal (≥25.0) in early pregnancy: 17.7% had overweight (BMI 25.0–29.9) 4.8% had obesity class I (BMI 30.0–34.9) and 1.7% had obesity class II–III (BMI ≥35.0) (Table 1).

Table 1 shows the characteristics of the study population. The rates of pre-eclampsia at different gestational ages increased with increasing maternal age and BMI. Increased maternal height was associated with decreased rates of pre-eclampsia. Smokers had lower rates of pre-eclampsia, but those that did were more likely to have early rather than late pre-eclampsia. Women with pre-gestational and gestational diabetes, chronic renal disease, pre-gestational hypertension and systemic lupus erythematosus had increased rates of pre-eclampsia.

The rate of pre-eclampsia according to maternal co-variates is described in Table 1. The proportion of women with pre-eclampsia increased by age and 15.6% of the women who developed severe pre-eclampsia were 35 years of age or older. Women with overweight or obesity were more likely to be diagnosed with pre-eclampsia than normal weight women. There was an increased proportion of pre-eclampsia among pregnant women with any kind of kidney disease (Table 1).

The rate of neonatal complications associated with mild and moderate pre-eclampsia and severe pre-eclampsia according to gestational age is seen in Table 2.

Compared with infants of mothers without PE, those with PE had higher rates of SGA in all gestational weeks. From 32 weeks of gestation, there was an association with a lower Apgar score in the pre-eclampsia group compared to the group without pre-eclampsia. Furthermore, the need for resuscitation at full term in those with severe pre-eclampsia was double that of the group without pre-eclampsia. The proportion of perinatal death was higher in the whole pre-eclampsia group 0.7% compared with infants not exposed to pre-eclampsia 0.5%.

The risks of neonatal complications are shown with crude odds ratios and after adjustments for the infant's year of birth and the maternal co-variates of age, height, BMI, diabetes, kidney disease, systemic lupus erythematosus and smoking (Table 3).

An increased risk of SGA was seen in all weeks of gestation among infants exposed to pre-eclampsia as well as for the whole group (aOR 5.26, 95% CI: 5.07–5.46). Compared with non-exposed infants, those of mothers with pre-eclampsia had an increased risk of a low Apgar score (aOR 2.05, 95% CI: 1.94–2.16), but in respective gestational age, the risk was only significantly increased between gestational weeks 32 and 41. Pre-eclampsia was also associated with a significantly increased risk of convulsions and/or HIE among infants born in 37–41 weeks of gestation (aOR 1.80, 95% CI: 1.51–2.15). There was an overall increased risk of newborn infants suffering from sepsis if the woman had pre-eclampsia in all weeks of gestation (aOR 1.93, 95% CI: 1.77–2.09) except weeks 32–36 and post-term, compared to women without pre-eclampsia. An increased risk of resuscitation (aOR 2.56, 95% CI: 2.43–2.69) following birth was seen among infants born at all weeks of gestation if the mother had pre-eclampsia. There was a general increased risk of perinatal death (aOR 1.21, 95% CI: 1.05–1.49) among the infants of mothers with pre-eclampsia, although the risk was lower in each gestational age-group.

4 | DISCUSSION

This population-based study found that pre-eclampsia was associated with a low Apgar score, need for resuscitation, sepsis, convulsions and/or HIE, SGA and perinatal mortality. The neonatal complications were more common if pre-eclampsia was severe, as reported by other studies.[15,16]

The long-term consequences for newborn infants following pre-eclampsia may include hypertension, increased risks of cardiovascular diseases, cognitive impairment and hormonal changes, as reported elsewhere.[3,17–20] A well-known risk factor in early-onset pre-eclampsia is abnormal development of the placenta, leading to

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TABLE 2 Neonatal complications in relation to pre-eclampsia (PE) and gestational age, *n* (%).

Gestational age, *n* (%)	No PE	Mild/Moderate PE	Severe PE	No PE	Mild/Moderate PE	Severe PE	No PE	Mild/Moderate PE	Severe PE
	Small for gestational age, *N* = 25 539			**Apgar <7 at 5 min, *N* = 13 258**			**Convulsions and/or HIE 2676**		
22–27	341 (15.5)	54 (83.1)	274 (72.1)	1041(54.0)	33 (54.1)	129 (36.9)	56 (2.5)	2 (3.1)	3 (0.8)
28–31	618 (18.8)	136 (72.3)	644 (58.7)	549 (18.7)	25 (13.7)	152 (14.6)	70 (2.1)	3 (1.6)	12 (1.1)
32–36	1800 (5.3)	477 (26.6)	942 (25.9)	1088 (3.3)	83 (4.7)	238 (6.7)	157 (0.5)	16 (0.9)	19 (0.5)
37–38	3684 (2.9)	598 (10.0)	271 (9.2)	1239 (1.0)	140 (2.2)	87 (3.0)	264 (0.2)	38 (0.6)	17 (0.6)
39–41	12 846 (2.4)	674 (4.9)	198 (6.5)	6438 (1.2)	291 (2.1)	100 (3.3)	1537 (0.3)	73 (0.5)	23 (0.8)
>41	1928 (2.7)	46 (3.8)	8 (5.6)	1590 (2.3)	28 (2.3)	7 (4.9)	380 (0.5)	6 (0.5)	0 (0.0)
	Neonatal sepsis, *N* = 7880			**Resuscitation, *N* = 18 125**			**Perinatal death, *N* = 3876**		
22–27	599 (27.1)	22 (33.8)	134 (35.3)	689 (31.2)	21 (32.3)	130 (34.2)	717 (32.5)	15 (23.1)	65 (17.1)
28–31	301 (9.2)	26 (13.8)	149 (13.6)	552 (16.8)	42 (22.3)	253 (23.0)	459 (14.0)	7 (3.7)	47 (4.3)
32–36	536 (1.6)	20 (1.1)	50 (1.4)	1239 (3.7)	112 (6.3)	382 (10.5)	686 (2.0)	25 (1.4)	35 (1.0)
37–38	628 (0.5)	57 (1.0)	24 (0.8)	1845 (1.5)	193 (3.2)	157 (5.4)	469 (0.4)	12 (0.2)	6 (0.2)
39–41	4175 (0.8)	177 (1.3)	38 (1.2)	9702 (1.8)	451 (3.3)	136 (4.5)	1104 (0.2)	29 (0.2)	7 (0.2)
>41	917 (1.3)	22 (1.8)	4 (2.8)	2157 (3.1)	48 (3.9)	16 (11.1)	191 (0.3)	2 (0.2)	0 (0.0)

intrauterine growth restriction. We observed increased risk of being born SGA among newborn infants exposed to pre-eclampsia born at all gestational ages, with the most pronounced effects among those born before 32 weeks. This echoed the findings of other studies.[1] From 32 weeks of gestation, there was a larger proportion of newborn infants with Apgar scores of less than seven at 5 min in the group exposed, than those who were not exposed to pre-eclampsia[21] Furthermore, there was a correlation between increased levels of proteinuria/severity of pre-eclampsia and low Apgar scores, possibly due to impaired placental function.[22]

This study showed an increased risk of convulsions and/or HIE among newborn infants who were born from 32 to 41 weeks of gestation and exposed to pre-eclampsia than those who were not exposed. The aetiology of convulsions is multifactorial and HIE has been reported to be the most common cause among full-term infants.[23] In addition, convulsions are associated with low birth weight, prematurity and sepsis, which also are associated with pre-eclampsia.[23,24] Pre-eclampsia has previously been identified as an independent risk factor for neonatal sepsis and is seen among 0.7%–25% of these newborn infants.[9] This may be explained by maternal dysregulation of the immune function, with inflammatory cytokines disrupting the placenta and altering the foetal, and thereafter the neonatal, susceptibility to infections. This have been measured by higher rates of neonatal leukopenia and tromocytopenia.[9] Our study found an increased risk of sepsis in the pre-eclampsia group compared to the group without, below 32 weeks of gestation and from 37 to 41 weeks.

The unusual result with an increased risk of perinatal death in the whole group, but not in respectively gestational age-group, could be explained by the differences in numbers of infants in the different gestational weeks, with the largest group among term infants. The risk of perinatal death in our cohort, namely antepartum, intrapartum and neonatal deaths, was lower among preterm newborn infants exposed to pre-eclampsia, than those who were not exposed. These inverted results have previously been reported.[10] The authors of that study discussed the fact that preterm births among mothers diagnosed with pre-eclampsia are iatrogenic and therefore have a different aetiology to spontaneous preterm births. Previous studies that have only focused on stillbirths have reported an increased risk if the mother had pre-eclampsia.[11]

In accordance with previous research, our study showed that the risk of developing pre-eclampsia rose with increases in maternal age and BMI, diabetes and if the mother had kidney disease and systemic lupus erythematosus. These co-variates which can affect neonatal outcomes, were adjusted for in the regression model. Another co-variate that we adjusted for was short maternal stature, which has previously been associated with both pre-eclampsia and coronary heart diseases.[13,25] A suggested explanation for this association is a low socioeconomic background, with poor nutrition, infections and poor foetal or early-life growth among the mothers.[25] We also found that pre-eclampsia was less common among smokers as seen in other studies. However, the mechanisms of this inverse association

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TABLE 3 Association between pre-eclampsia (PE) and neonatal complications in relation to gestational age presented as frequencies, crude and adjusted OR among women with and without PE.

Gestational age	No PE = *n* (%)	PE *n* (%)	OR (95% CI)	Adjusted OR (95% CI)[a]
SGA = 25 539				
All	21 217 (2.8)	4322 (12.7)	5.13 (4.95–5.31)	5.26 (5.07–5.46)
22–31	959 (17.15)	1108 (64.0)	8.41 (7.46–9.49)	8.19 (7.16–9.36)
32–36	1800 (5.3)	1419 (25.2)	6.33 (5.86–6.84)	7.04 (6.47–7.65)
37–41	16 530 (2.5)	1741 (6.8)	2.85 (2.71–3.00)	3.02 (2.86–3.18)
≥42	1928 (2.7)	54 (4.0)	1.46 (1.11–1.93)	1.56 (1.17–2.06)
Apgar < 7 at 5 min = 13 258				
All	11 945 (1.6)	1313 (3.9)	2.34 (2.22–2.46)	2.05 (1.94–2.16)
22–31	1590 (32.7)	339 (20.8)	0.50 (0.44–0.56)	0.47 (0.41–0.54)
32–36	1088 (3.3)	321 (6.0)	1.51 (1.35–1.69)	1.47 (1.31–1.65)
37–41	7677 (1.2)	618 (2.4)	1.87 (1.73–2.01)	1.66 (1.53–1.80)
≥42	1590 (2.3)	35 (2.6)	1.00 (0.72–1.39)	0.94 (0.67–1.31)
Convulsions and/or HIE = 2676				
All	2464 (0.3)	212 (0.6)	1.95 (1.69–2.25)	1.66 (1.43–1.93)
22–31	126 (2.3)	20 (1.2)	0.50 (0.31–0.80)	0.47 (0.27–0.83)
32–36	157 (0.5)	35 (0.6)	1.40 (0.97–2.02)	1.42 (0.97–2.09)
37–41	1801 (0.3)	151 (0.6)	2.17 (1.84–2.57)	1.80 (1.51–2.15)
≥42	380 (0.5)	6 (0.4)	0.81 (0.36–1.83)	0.66 (0.27–1.60)
Neonatal sepsis = 7880				
All	7157 (0.9)	723 (2.1)	2.31 (2.14–2.50)	1.93 (1.77–2.09)
22–31	901 (16.4)	331 (19.1)	1.21 (1.05–1.39)	1.19 (1.02–1.39)
32–36	536 (1.6)	70 (1.3)	0.82 (0.63–1.05)	0.74 (0.57–0.97)
37–41	4803 (0.7)	296 (1.2)	1.60 (1.42–1.80)	1.34 (1.18–1.51)
≥42	917 (1.3)	26 (1.9)	1.47 (0.99–2.18)	1.30 (0.87–1.95)
Resuscitation = 18 125				
All	16 184 (2.1)	1941 (5.7)	2.81 (2.68–2.93)	2.56 (2.43–2.69)
22–31	1241 (22.6)	446 (25.8)	1.19 (1.05–1.35)	1.23 (1.07–1.41)
32–36	1239 (3.7)	494 (9.1)	2.65 (2.37–3.95)	2.63 (2.35–2.95)
37–41	11 547 (1.7)	937 (3.7)	2.14 (2.00–2.29)	1.94 (1.81–2.09)
≥42	2157 (3.1)	64 (4.7)	1.56 (1.21–2.01)	1.60 (1.24–2.06)
Perinatal death = 3876				
All	3626 (0.5)	250 (0.7)	1.56 (1.37–1.77)	1.21 (1.05–1.49)
22–31	1176 (21.4)	134 (7.7)	0.31 (0.26–0.37)	0.26 (0.21–0.33)
32–36	686 (2.0)	60 (1.1)	0.54 (0.42–0.71)	0.51 (0.38–0.67)
37–41	1573 (0.2)	54 (0.2)	0.89 (0.68–1.16)	0.69 (0.52–0.93)
≥42	191 (0.3)	2 (0.1)	0.54 (0.13–2.18)	0.46 (0.11–1.88)

[a]Adjusted for: year of birth, maternal age, maternal height, maternal BMI, maternal diabetes, maternal kidney disease maternal SLE and smoking.

are not completely understood and there are a large number of potential biological hypotheses. These include the suggestion that smoking reduces oxidative stress.[12] Some of these maternal risk-factors are difficult to prevent but high BMI and obesity can be addressed. Global obesity has increased considerably since 1975 and today about 15% of all women and nearly 20% of all children worldwide have obesity.[26] Future studies should focus on interventions to prevent maternal overweight and obesity, to prevent neonatal complications associated with pre-eclampsia.[27] Furthermore, the mothers of infants born SGA should be offered extended breastfeeding support, as both pre-eclampsia and SGA have been associated with cognitive and intellectual impairment. This may become less pronounced if the infant is exclusively breastfed.[14,18,28,29] Sepsis is also reduced by breastfeeding and there is growing evidence that suggest that breastfeeding might protect the infant from overweight and diabetes in adulthood.[28,30]

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4.1 | Strengths and limitations

The study had a number of strengths. It included all primiparous women in Sweden from 1999 to 2017, which provided a large study population and gave us the opportunity to study rare outcomes. We used high-quality registers that were based on medical birth records with standardised variables coded in the same way. They were collected independently from the birth data without involving the patients and this minimised various types of bias.

A limitation of the study was that the definition of pre-eclampsia changed during the study period. We addressed this by diagnosing the women using the criteria in place at the start of the study when we divided them into mild and moderate pre-eclampsia and severe pre-eclampsia sub groups. However, we merged the groups comparing women with and without pre-eclampsia diagnoses in the logistic regression analysis. Another limitation was that we had no information of the duration of pre-eclampsia or of the medical treatment that the women received. Furthermore, we lacked information on diagnoses other than diabetes, systemic lupus erythematosus and kidney diseases. In addition, we had no information on the mode of birth and were not able to separate the diagnoses of convulsions and HIE from each other.

5 | CONCLUSION

This population-based study provides a number of neonatal complications associated with maternal pre-eclampsia and gestational age. It also confirms the well-known association between pre-eclampsia and infants being born SGA. However, it also found that infants born to mothers with pre-eclampsia were more likely to need resuscitation at all gestational ages. Furthermore, pre-eclampsia was associated with a low Apgar score, convulsions and/or HIE at 32–41 weeks of gestation and sepsis at all gestational ages, except 32–36 weeks. There were differences between the different severities of pre-eclampsia. Interventions to prevent, and mitigate the effects of pre-eclampsia are warranted.

AUTHOR CONTRIBUTIONS

Hanna Ulfsdottir: Methodology; validation; visualization; writing – original draft. **Maria Grandahl:** Methodology; writing – review and editing. **Johanna Björk:** Writing – review and editing. **Sara Karlemark:** Writing – review and editing. **Cecilia Ekéus:** Conceptualization; data curation; formal analysis; methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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