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Early-onset preeclampsia is associated with perinatal mortality and severe neonatal morbidity

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ABSTRACT

Objective: To evaluate neonatal outcomes of pregnancies complicated by early-onset pre-eclampsia (PE) and compare these outcomes to those of gestational age matched neonates born to mothers whose pregnancy was not complicated by early-onset PE.

Methods: We analyzed the outcome in 97 neonates born to mothers with early-onset PE (24–32 weeks amenorrhea at diagnosis) and compared it to that of 680 gestational age-matched neonates born between 25–36 weeks due to other etiologies and admitted to the Neonatal Intensive Care Unit (NICU) of a tertiary referral hospital in the Netherlands. We used Chi-square test, Wilcoxon test, and logistic regression analyses.

Results: Neonates born to PE mothers had a higher perinatal mortality (13% vs. 7%, $p = 0.03$) and infant mortality (16% vs. 9%, $p = 0.03$), a 20% lower birth weight (1150 vs. 1430 g, $p < 0.001$), were more often SGA (22% vs. 9%, $p < 0.001$) and had more neonatal complications as compared to neonates born to mothers without PE.

Conclusions: Overall adverse perinatal outcome is significantly worse in neonates born to mothers with early-onset PE. The effect of early-onset PE on perinatal mortality seems partially due to SGA. Whether these differences are due to uteroplacental factors or intrinsic neonatal factors remains to be elucidated.

Introduction

In the Netherlands, yearly about 12,000 women (6–7%) deliver before 37 weeks gestation, of which 1500 deliver before 32 weeks gestation. Preterm delivery is an important cause of perinatal mortality and morbidity [1], mainly due to neurological sequelae. The percentage of medically induced preterm deliveries is rising at a steeper rate than spontaneous preterm deliveries. Pregnancies that are complicated by hypertensive disorders, contribute to this rise. About 16% of pregnancies in the Netherlands are complicated by pregnancy induced hypertension (PIH) and 2% by pre-eclampsia (PE) [1]. PE is characterized by hypertension with proteinuria. Pregnancies complicated by PE contribute to maternal and perinatal mortality and morbidity [2,3]. All reported studies recommended intensive fetal surveillance for early detection of fetal compromise. Delivery of the fetus and placenta remain to date the only causal treatment. There is a broad agreement to terminate pregnancy when maternal or fetal conditions are altered or once 34 weeks of gestation are reached [4]. But early-onset PE poses a management dilemma. Delivery may benefit the mother, but may harm a premature fetus. Expectant management in women with early-onset PE before 34 weeks' gestation may reduce neonatal complications and stay in a Neonatal Intensive Care Unit (NICU), [4,5] but could aggravate the maternal condition [3,4].

It is uncertain whether neonatal outcome in PE mothers is determined by prematurity itself, by PE complications or other main factors. Gestational hypertension occurring early in pregnancy is associated with a higher rate of small for gestational age (SGA) infants and lower gestational age at delivery when compared to late gestational hypertension in previous studies [6]. SGA is often caused by uteroplacental insufficiency, which is associated with PIH. In addition, pregnancies complicated by early-onset PE are associated with the highest rate of SGA neonates comparing to PIH, suggesting the influence of the pathophysiology of

early-onset PE on fetal outcome in hypertensive diseases [7]. Maternal lifestyle [8], congenital malformations and chronic maternal (kidney) disease [9] are also etiologic factors of SGA. Less is known of the impact of early-onset PE on perinatal mortality. Previous studies have shown differences in the prevalence of perinatal mortality most likely as a result of methodological etiology or power [10,11].

Therefore, the aim of this study was to address neonatal outcome in women with early-onset PE and compare these outcomes to those of gestational age matched premature neonates born to women not affected by early-onset PE.

Materials and methods

All medical records of singleton pregnancies with early-onset PE (gestational age 24–32 weeks at diagnosis for the current study) admitted to the Obstetric High Care (OHC) unit of the Radboud University Medical Center Nijmegen (Netherlands) between January 2008 and December 2011 were studied. We excluded pregnancies complicated by congenital anomalies that have a significant impact on survival and neonatal complications.

The definitions of hypertension and proteinuria used were those described in Dutch guidelines and the guideline of the Royal College of Obstetricians and Gynecologists produced by the National Collaborating Center for Women's and Children's Health (NCC-WCH) on behalf of the National Institute of Health and Care Excellence (NICE) [12]. Briefly, PE is defined as a combination of blood pressure $\geq$140/90 mmHg and proteinuria $\geq$0.3 g total protein within a 24-h urine collection, or ratio of protein to creatinine $\geq$0.03 g/mmol.

Perinatal outcome was defined as a composite of mortality and variables of neonatal morbidity. Mortality was divided into perinatal mortality, occurring within the first 28 days of life, and infant mortality, occurring within the first year of life. We defined perinatal complications as infant respiratory distress syndrome (IRDS), use of surfactant therapy, clinical sepsis with positive blood culture, stage I, II or III necrotizing enterocolitis [13] (NEC), grades III or IV intraventricular hemorrhage [14] (IVH) and grades II, III or IV periventricular leukomalacy [15] (PVL) diagnosed by utrasonographic examination. Stage I–V retinopathy of prematurity (ROP) was defined as abnormal vasoproliferation and tortuosity, retinal ridge, scarring and retinal detachment. Pneumothorax was diagnosed by radiographic findings. Furthermore, we registered Apgar scores after 1 and 5 minutes and the neonatal birth weight. We defined SGA as a birth weight below the 10th percentile of the new Dutch reference curves for birth weight by gestational age corrected for parity and gender [16].

Statistical methods

To determine the effect of early-onset PE on the endpoints described earlier, we made a comparison between neonates born to PE mothers and to non-PE mothers, which we defined as controls (non-PE neonates). Patients admitted for suspected fetal distress or placental abruption were excluded. We used the Radboud University Medical Center NICU-registration between January 2008 and December 2011 to collect the data from the control group that consisted of gestational age-matched neonates at delivery.

Differences between groups were evaluated with the Chi-square test for dichotomous and with the Wilcoxon test for continuous variables. Odds ratios and adjusted odds ratios were calculated using logistic regression analysis. Statistical analysis was performed using SPSS 22.0 statistical software (IBM Corp., Armonk, NY), a p values of <0.05 was considered significant.

This study did not need approval of our ethical committee because it was a retrospective collection of data in women who received standard management at the hospital.

Results

Maternal characteristics

We registered 109 patients with early-onset PE of which 78% were nulliparous. Mean gestational age at diagnosis was 29 ± 2 weeks. Mean maternal age was 30 ± 5 years (17–41 years) and the ethnic origin of 81% of this study group was Dutch. There were no maternal deaths reported. According to the hospital guidelines, temporizing treatment was given to PE mothers consisting of antepartum corticosteroids (81% of cases) to accelerate fetal lung maturation in addition to antihypertensive treatment. The median of days gained by temporizing management was 6 days (range 1–52 days). All mothers delivered after 25 weeks amenorrhea.

Neonatal characteristics

A total of 109 neonates were born to early-onset PE mothers and were admitted to the NICU department. Three neonates were excluded from statistical analysis because of missing data. There was one case of fetal death. A further eight neonates were excluded because of severe congenital anomalies, as microcephaly (1), gastrointestinal atresia (1), diaphragmatic

Table 1. Perinatal outcome.

	PE neonates N = 97	Non-PE neonates N = 680	p values
Gestational age at delivery (weeks)	30 [25–36]	30 [25–36]	0.89
Male gender	41 (43)	344 (51)	0.18
Female gender	56 (57)	336 (49)	0.18
1 min Apgars score	7 [1–10]	7 [0–10]	0.30
5 min Apgars score	9 [0–10]	8 [0–10]	*0.015*
Birth weight (grams)	1150 [400–2710]	1430 [480–4147]	*0.001*
SGA (<p10)	21 (22)	58 (9)	*0.001*
Cesarean section	64 (66)	226 (34)	*0.001*
Perinatal mortality	13 (13)	48 (7)	*0.03*
Infant mortality	15 (16)	58 (9)	*0.03*

Data are number of patients (%) or median [range].
p values of <0.05 was considered significant and indicated in italic font.

hernia (1), chromosomal anomalies (1), lung hypoplasia (1), tuberous sclerosis (1), congenital hypothyroidism (1) and colpocephaly (1). The perinatal outcome of the remaining 97 neonates was analyzed (Table 1).

The control group consisted of 739 gestational age-matched neonates born with other etiologies that were admitted to the NICU during the same study period. Fifty-nine neonates were excluded from analysis because of severe congenital anomalies. Most prevalent anomalies were gastrointestinal atresia (10), microcephaly (5), diaphragmatic hernia (3), chromosomal anomalies (5), renal diseases (8) and lung hypoplasia (3). Perinatal outcome of the remaining 680 neonates was analyzed (Table 1).

Perinatal outcome

While the median gestational age at delivery was similar, the birth weight of early-onset PE neonates was significantly lower as compared to non-PE neonates (1150 g vs. 1430 g, $p < 0.001$). PE neonates were more often SGA at birth as compared to non-PE neonates (22% vs. 9%, $p < 0.001$). Perinatal mortality (13% vs. 7%, $p = 0.03$) and infant mortality (16% vs. 9%, $p = 0.03$) of PE neonates were significantly higher as compared to controls. Using logistic regression analysis, the odds ratio for perinatal mortality was 2.038 (95% CI: 1.06–3.92) when comparing the PE group with the controls cases, and odds ratio for infant mortality was 1.962 (95% CI: 1.06–3.62). Fifteen neonates died in the PE group, of which thirteen in the first 28 days after delivery.

Perinatal mortality was further evaluated by SGA subgroup analysis (Figure 1). In PE pregnancies, perinatal mortality was 29% in infants born SGA compared to 9% of infants born non SGA ($p = 0.02$). In non-PE infants, perinatal mortality was also higher in the SGA group (19% vs. 6%, $p < 0.001$). Using logistic regression analysis the adjusted effect of PE correcting for SGA revealed an odds ratio of 1.640 (95% CI: 0.831–3.235)
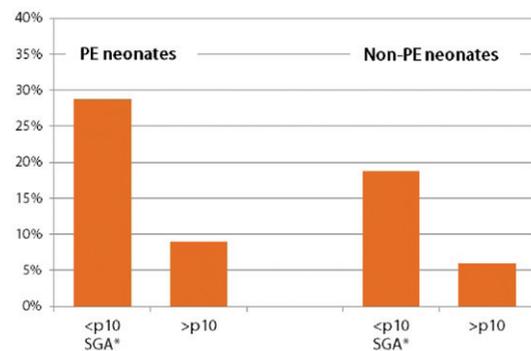
* SGA is significantly correlated with a higher perinatal mortality in PE-pregnancies (29% vs. 9%, p=0,02) and non-PE pregnancies (19% vs. 6%, p<0,001); adjusted odds-ratio: 1.64 (CI 0.831–3.255).

Figure 1. Perinatal mortality rate among PE vs. non-PE neonates according to SGA subgroup analysis.

for perinatal mortality, indicating that the difference of 0.4 in OR is due to SGA. A comparison of these analyses suggests that the effect of PE on perinatal mortality is partially due to SGA. In the control group, SGA infants also showed a higher perinatal mortality.

Perinatal mortality was also analyzed according to sex. In both PE- and non-PE pregnancies, gender had no significant influence on the perinatal mortality rate (male 7% vs. female 17%, $p = 0.17$ in PE pregnancies and male 8% vs. female 7%, $p = 0.60$, in non-PE pregnancies).

Furthermore, the incidence of some neonatal complications was increased in PE neonates. In particular, IRDS (62% vs. 50%, $p = 0.045$) and sepsis (43% vs. 30%, $p < 0.01$) occurred more often in PE neonates than in non-PE neonates. No differences between groups were found for pneumothorax, PVL, IVH or ROP (Table 2).

Discussion

This study shows that neonatal outcome in pregnancies complicated by early-onset PE differs from that of age-matched NICU neonates born to mothers not affected by PE. Early-onset PE neonates are more often

Table 2. Neonatal complications.

	PE neonates N = 97	Non-PE neonates N = 680	p values
IRDS[a]	56 (62)	342 (50)	*0.045*
Surfactant treatment[a]	45 (50)	226 (33)	*0.002*
Pneumothorax[a]	3 (3)	17 (3)	0.67
Sepsis[a]	41 (43)	204 (30)	*0.01*
Intracranial hemorrhage[a]			0.77
grade I	13 (14)	103 (15)	
grade II	1 (1)	13 (2)	
grade III–IV	0 (0)	0 (0)	
Periventricular leukomalacia[a]			0.50
grade I	11 (12)	96 (14)	
grade II–IV	0 (0)	0 (0)	
Retinopathy[a]			0.66
grade I	5 (6)	26 (4)	
grade II	0 (0)	2 (0.3)	
grade III–V	0 (0)	0 (0)	
Necrotizing enterocolitis[a]			0.92
stage I–III	9 (9)	61 (9)	

Data are number of patients (%).
[a]Some patients match more than one complication.
Some data (N = 7) are missing.

SGA at birth, and perinatal and infant mortality and morbidity are increased. These results demonstrate the adverse effects of early-onset PE on the overall perinatal outcome and demonstrate the impact of early-onset PE as a proxy for perinatal survival.

Neonatal growth

Neonatal outcome in pregnancies complicated by PE is mostly related to gestational age at delivery, [17,18] and gestational age is the strongest predictor of perinatal mortality and morbidity [19]. This study demonstrates that early-onset PE is a strong variable for perinatal outcome in premature neonates. Previous studies suggest that maternal hypertension and PE cause a reduced utero-placental perfusion and, consequently, impaired fetal growth [20,21]. The former could be explained by the lack of spiral artery remodeling that leads to high velocity pulsatile blood flow and syncytiotrophoblast damage. In established severe disease, acute atherosis leads to reduced utero-placental perfusion. The concomitant raised blood pressure, related to increased release of sFlt-1, could be interpreted as a fetal attempt to raise maternal blood pressure in order to increase perfusion pressure [22]. The present study shows that PE neonates born between 25 and 36 weeks' gestation have a 20% lower birth weight and a twofold higher rate of SGA (22% vs. 9%) than preterm infants born with similar gestational ages without maternal early-onset PE. These findings are in accordance with previous reports [7,10,21,23]. For example, Jelin et al. [10], in a cohort of 235 women affected by early onset PE, also found a threefold higher rate of SGA neonates as compared to non-PE women (18% vs. 6%). Whether this is related to the

time of onset of PE was studied in a Norwegian population by Rasmussen et al. [23]. They compared the effect of early- versus late-onset PE on birth weight and found an 11–23% reduced birth weight in early-onset PE neonates. This is in accordance with our study, where we report a 20% reduction.

Perinatal mortality

Regarding perinatal mortality rate, early-onset PE is associated with an almost twofold increase in perinatal death as compared to non-PE pregnancies in our study cohort. The increased perinatal mortality is congruent with the increased rate of SGA. SGA is correlated with a higher mortality rate and is an important predictor for perinatal survival [24]. In the present study cohort, early-onset PE pregnancies are associated with a higher mortality rate (29%) in infants born SGA compared to SGA infants in the non-PE group (19%). Regression analysis showed the effect of early-onset PE on perinatal mortality is mainly due to SGA. Besides, there could be common causes of SGA and mortality that we cannot make visual for bias correction. Explaining by the 'birth weight paradox' in Hernández-Diaz et al. [25], adjustment for birth weight is unwarranted when the analytical goal is to estimate overall effects of perinatal variables on infant mortality. Even for estimating direct effects of prenatal variables, adjustment for birth weight may be invalid when there is an unmeasured common cause of SGA and mortality.

Jelin et al. [10] described a 9% decrease in perinatal mortality in pregnancies complicated by PE as compared to the control group of other preterm deliveries (11% vs. 18%, p = 0.008) refuting previous studies that demonstrated no difference in perinatal survival [26]. One explanation for this decrease could be the relative high incidence of preterm premature rupture of membranes in the control group. Preterm premature rupture of membranes carries the highest neonatal morbidity of all etiologies of preterm labor [27]. Withagen et al. [11], who evaluated temporizing treatment in PE-pregnancies to assess its effect on neonatal outcome, found a 33% lower birth weight and higher rate of SGA neonates (52% vs. 3.2%) in PE pregnancies as compared to gestational age-matched non-PE control group. No significant difference was found in perinatal or infant mortality. The perinatal mortality rate in PE pregnancies in the present study population is higher (13% vs. 7%) compared to that of Withagen et al. and may be explained by the shorter mean temporization treatment (8 days vs. 14 days). In accordance with our study, Withagen et al. also observed a

better prognosis in infants born to mothers without early-onset PE.

Perinatal morbidity

In this study, infants born to mothers with early-onset PE were more likely to develop IRDS, with 62% of infants affected versus 50% in the control group, which is in accordance with others [10,28]. The postnatal course of early-onset PE neonates was more often complicated by sepsis (43% vs. 30%) compared to non-PE neonates. The increased risk of IRDS could at least be partially related to the higher frequency of cesarean delivery (66% vs. 35%, $p < 0.001$) in women with PE [29,30], despite the treatment of ante partum corticosteroids in 81% of cases. Witlin et al. [28] concluded in a cohort of 195 PE pregnancies that respiratory distress syndrome was inversely related to gestational age at delivery and directly related to cesarean delivery. Werner et al. [30] also reported increased odds of respiratory distress and sepsis in preterm neonates in cesarean compared with vaginal delivery.

Our study has some limitations, because it is a retrospective study. Therefore, our results should be interpreted with caution. However, the results show a worsened perinatal outcome in early-onset PE. In 2001, Withagen et al. [11] showed the benefit of temporizing treatment in neonatal outcome in PE pregnancies. As of 2016, despite all efforts, non-PE neonates still have a better outcome than infants born to mothers with early-onset PE. A previous attempt to address this issue in a randomized controlled trial was initiated in the Netherlands in which the risks of maternal complications by temporizing treatment in women with early-onset PE and the subsequent benefits for the neonate at 24 to 32 weeks' gestation were weighed [31]. Due to disappointing inclusion, the study did not meet inclusion targets and was canceled.

In summary, this study shows that neonatal outcome of infants born to mothers with early-onset PE is worse than that of infants born to mothers with other etiologies of preterm labor. Specifically, these infants were more often SGA and their mortality and neonatal complication rates were greater. This information can be used in the counseling of women with early-onset PE. Whether these differences are attributed to SGA alone or another yet unsolved pathophysiological mechanism remains unclear and warrant additional investigation.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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