Respiratory outcomes of late preterm infants of mothers with early and late onset preeclampsia

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Received: 21 January 2019 / Revised: 2 July 2019 / Accepted: 1 August 2019 / Published online: 24 September 2019
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Abstract
Objective To study the effect of early and late onset preeclampsia (EOPE, LOPE, respectively) on outcomes of late preterm infants.
Study design Cohort study of late preterm infants admitted to a tertiary care NICU from January 2014–July 2015. Outcomes of late preterm infants of EOPE mothers were compared with the next late preterm infant of a LOPE mother and the next two late preterm infants of normotensive non-PE mothers. Primary outcome comprised use of continuous positive airway pressure, mechanical ventilation and/or surfactant in the 24 h after birth.
Results Compared to normotensives (n = 131), adjusted odds ratio (AORs) of the primary outcome was higher in the EOPE (n = 64) and LOPE (n = 65) groups but reached statistical significance only in the EOPE group, AORs 12.9, 95% CI 3.5–37 and 2.7, 95% CI 0.95–8.1, respectively.
Conclusions Compared to late preterm infants of normotensive and LOPE mothers, infants of mothers with EOPE have significantly higher respiratory morbidity.

Introduction
Late preterm infants, defined as births between 34+0 and 36+6 weeks gestation, constitute the largest proportion of preterm births, being 85% in Canada [1–3]. There is significant morbidity associated with late preterm birth with respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTNB) the commonest [4, 5]. Compared with term infants, late preterm infants are nine times more likely to be placed on continuous positive airway pressure (CPAP), five times more likely to be placed on mechanical ventilation and forty two times more likely to need surfactant replacement [6]. The cost associated with the care of late preterm infants is substantial, corresponding to more than 208 million dollars annually in Canada [7].

Initial studies on morbidity in late preterm births compared outcomes to term births without taking into account underlying maternal medical conditions that may lead to preterm birth. This is now being questioned with the realization that in addition to prematurity per se, maternal conditions also contribute to morbidity in late preterm infants [8, 9]. One such condition is preeclampsia.

Preeclampsia is a pregnancy specific disorder characterized by hypertension and proteinuria manifesting at or after twenty weeks of gestation and is a major cause of maternal and neonatal mortality and morbidity worldwide [10]. Although placental dysfunction is a hallmark of preeclampsia, the disorder is heterogeneous [10]. Based on gestational age at onset of disease, preeclampsia is classified as early, occurring before 34 weeks gestation and late occurring at or after 34 weeks of gestation [10, 11]. Both have similarities and distinct features. Placental changes are more marked in early onset preeclampsia while maternal factors such as increased body mass index (BMI) and metabolic syndrome play a greater role in late onset disease [12]. Early onset preeclampsia is also associated with a greater adverse impact on maternal and fetal health [13]. Although early onset disease manifests before 34 weeks gestation, a third of women deliver at or after 34 weeks gestation [12, 14]. Surprisingly, reports of the effects...
preeclampsia on outcomes of late preterm infants have not
differentiated between early and late onset preeclampsia,
despite significant differences between the two. The objective
of our study was to investigate the effects of early and late
onset preeclampsia on the outcomes of late preterm infants,
with the primary objective being respiratory outcomes.

Methods

The Neonatal Intensive Care Unit (NICU) in Calgary main-
tains a prospectively collected electronic database of all infants
admitted to the NICU. Late preterm infants born between 34+0
and 36+6 gestation to a mother with early onset preeclampsia
between January 2014 and July 2015 were included in the
study. Their outcomes were compared with the next late
preterm infant born to a mother with late onset preeclampsia
and the next two late preterm infants born to normotensive
mothers. A prestructured data form was completed for all
infants. In case of missing data, the infant’s medical record
charts were reviewed. The Conjoint Health Research Ethics
Board of the University of Calgary approved the study.

The primary outcome comprised the use of CPAP or
mechanical ventilation and/or surfactant use in the first 24 h
after birth. We chose this primary outcome for several
reasons. Amongst all the morbidities faced by late preterm
infants, respiratory morbidity is the most common. The two
most common diagnosis for respiratory distress in late
preterm period, RDS and TTNB, can sometimes be difficult
to distinguish based on clinical manifestations and chest
X-ray [15]. Importantly, similar definition of respiratory
morbidity has been used in other large studies [4, 5]. Sec-
ondary outcomes included (i) RDS-diagnosed based on
signs of respiratory distress, a typical chest X-ray and/or
need for surfactant [16]. (ii) TTNB-diagnosed on a chest
X-ray showing good volume with increased vascularity and
the presence of a transverse fissure [17]. (iii) Use of sup-
plemental oxygen by nasal cannula. (iv) Small for gesta-
tional age (SGA)-defined as birthweight below the 10th
centile using the Fenton growth charts [18]. (v) Length of
hospital stay in days. (vi) Hypoglycemia defined as blood
glucose levels <2.6 mmol/L (Canadian Pediatric Society
Position Statement, available at www.cps.ca). (vii) Number
of infants in each group needing phototherapy.

Definitions

Preeclampsia definition was based on Society of Obstetrics
and Gynecology Canada recommendations and was defined
as systolic blood pressure ≥ 140 mmHg or a diastolic level of
(Korotkoff 5) ≥ 90 mmHg on two or more occasions at least
15 min apart after 20 weeks gestation in a woman with
previously normal blood pressure. Proteinuria was defined
as ≥0.3 g protein in a 24 h urine sample. When a 24 h
urinary sample was not feasible, or ≥30 mg/mmol urinary
creatinine in a spot urine sample or ≥1 + on a urinary
dipstick test-strip was used as criteria for proteinuria [19].
Early onset preeclampsia was onset of symptoms at
<34 weeks gestation and late onset preeclampsia onset of
symptoms ≥34 weeks gestation. Histological chor-
ioamnionitis was defined as infiltration of polymorpho-
nuclear leukocytes in the fetal membranes and chorionic
plate, and funisitis as the presence of these cells in the
umbilical cord blood vessel walls and Wharton’s jelly [20].
Antenatal steroids were considered a course if more than
twelve hours had elapsed after the first dose [21]. Diabetes
included both gestational and pregestational forms of the
disease. Gestational age was based on a first trimester
ultrasound and date of embryo transfer in cases of in vitro
fertilization. Surfactant was administered when oxygen
requirements were persistently >30%. Exclusion criteria
included infants born with any congenital malformations or
chromosomal anomalies, infants of mothers with chronic
hypertension (onset before 20 weeks of gestation), maternal
renal, cardiovascular, endocrine or autoimmune disease,
substance abuse, and TORCH infections. Women who did
not have a first trimester ultrasound were also excluded.

Statistics

As the distribution of the relevant variables was not normal,
we chose conservative nonparametric analysis for continuous
variables, using the Kruskal–Wallis test. Categorical vari-
bles were compared using the χ² or Fisher’s exact test as
appropriate. Bonferroni correction was used post hoc for
multiple comparisons. To identify risk factors for develop-
ment of the primary outcome, multivariable ordered logistic
regression with backward elimination approach was per-
formed. Any risk factors that demonstrated associations,
whether statistically significant or judged to be clinically
significant, with both preeclampsia and the primary outcome
but were not intermediate variables, were included in the
modeling process as possible confounders [22]. The least
significant variables were then removed until all remaining
variables were significant at P value of 0.2. The P value of
0.2 was set conservatively as an entry for variables to pro-
cceed to the next step in the analysis [23]. The adjusted odds
ratio (OR) and their 95% confidence interval (CI) are
reported. A P < 0.05 was considered significant. Data were
analyzed using STATA v. 13 (College Station, Texas, USA).

Results

During the study period, there were 1760 admissions
to the NICU. Amongst the 67 women with early onset
preeclampsia, four women with chronic hypertension and two with a history of substance abuse were excluded. There were three sets of twins in the group resulting in 64 infants eligible for the study. Of the 68 women with late onset preeclampsia, two women with substance abuse and one with chronic hypertension were excluded. There were no twins in the group resulting in 65 infants eligible for the study. One hundred and thirty three normotensive women who delivered late preterm infants between 34 and 36 weeks gestation were included as controls. On chart review, four of these women had a history of substance abuse, two had chronic hypertension and one each had systemic lupus erythematosus and antiphospholipid syndrome. They were excluded from the study. There were six sets of twins in the group resulting in 131 infants eligible for the study (Fig. 1).

Table 1 shows the maternal and neonatal demographic variables between the three groups. There was no difference in the maternal age, diabetes, twins, chorioamnionitis, smoking, number of male infants and Apgar scores <7 at 5 min between the three groups. Compared to the normotensive group, the number of primigravida mothers was

**Table 1** Maternal and neonatal demographics

|                  | Normotensive | Early onset preeclampsia | Late onset preeclampsia | P-value |
|------------------|--------------|--------------------------|-------------------------|---------|
| Maternal age (years) | 31 (28–35)   | 32 (27–38)               | 34 (30–35)              | 0.15    |
| Primigravida n (%)     | 54 (41)      | 31 (48)                  | 35 (53)                 | 0.19    |
| Gestation (weeks)      | 35 (35–35)   | 34 (34–35)               | 35 (35–36)              | 0.00ac  |
| Birthweight (g)        | 2450 (2216–2450) | 2036 (1698–2515)    | 2290 (210–2675)         | 0.00c   |
| Diabetes n (%)         | 24 (18)      | 10 (16)                  | 11 (17)                 | 0.89    |
| Antenatal steroids n (%) | 14 (11)    | 34 (53)                  | 4 (6)                   | 0.00abc |
| Twins n (%)            | 8 (6)        | 3 (5)                    | 0                       | 0.13    |
| Chorioamnionitis n (%)     | 14 (11)     | 4 (6)                    | 4 (6)                   | 0.43    |
| C-section n (%)        | 47 (36)      | 44 (69)                  | 26 (40)                 | 0.00ac  |
| Smoking n (%)          | 12 (9)       | 2 (3)                    | 4 (6)                   | 0.28    |
| Male n (%)             | 84 (64)      | 35 (55)                  | 43 (66)                 | 0.33    |
| Apgar <7 at 1 min n (%) | 16 (12)     | 28 (43)                  | 9 (14)                  | 0.00ac  |
| Apgar <7 at 5 min n (%) | 4 (3)       | 6 (9)                    | 3 (5)                   | 0.16    |

*a*Early onset preeclampsia vs. normotensive

*b*Late onset preeclampsia vs. normotensive

*c*Early onset preeclampsia vs. late onset preeclampsia
higher in the two preeclamptic groups but the difference did not reach statistical significance. Compared with the other two groups, gestational age was significantly lower in the early onset preeclampsia group. Birthweight was significantly lower and SGA rates significantly higher in the two preeclampsia groups compared with the normotensive group ($P<0.00$). Antenatal steroid use, C-section rates, and Apgar scores $<7$ at 1 min were significantly higher in the early onset preeclampsia group.

Table 2A shows the univariate analysis of the primary outcome and its components in the three groups. All infants who received surfactant were also placed on mechanical ventilation. The composite outcome as well as the individual components were significantly higher in the early onset preeclampsia group ($P = 0.02$ for surfactant and $<0.00$ for the other variables).

Table 2B shows the results of multivariable ordered logistic regression as the odds ratio (ORs) of the primary outcome in early and late onset preeclampsia with the normotensive group as the reference group. The final model included gestation, mode of delivery, sex, antenatal steroids, and small for gestational age. The odds of the primary outcome—CPAP use, mechanical ventilation and/or surfactant use—was greater in the two preeclampsia group with the early onset preeclampsia group having the higher odds. However, the higher odds in the late onset group did not reach statistical significance (OR 12.95% CI 3.8–37, $P = <0.00$ for early onset preeclampsia and OR 2.7 95% CI 0.94–8.1, $P = 0.06$).

Table 3 shows the secondary outcomes between the three groups. Compared to the normotensive group, TTNB, nasal cannula oxygen, hypoglycemia, SGA infants and use of phototherapy, duration of hospital stay was higher in the two preeclampsia groups. RDS was significantly higher in the early onset group.

During the study period, there were no deaths in any of the groups. Although infants were placed on anti-biotics for suspected sepsis, none of the infants had a positive blood or cerebrospinal fluid culture.

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**Table 2A** Primary outcome—univariate analysis

|                  | Normotensive N = 131 | Early onset preeclampsia N = 64 | Late onset preeclampsia N = 65 | P-value |
|------------------|----------------------|---------------------------------|-------------------------------|---------|
| Surfactant n (%) | 1 (0.8)              | 5 (8)                           | 2 (3)                         | 0.02$^{a, c}$ |
| CPAP n (%)       | 10 (7)               | 26 (41)                         | 7 (11)                        | 0.00$^{a, c}$ |
| MV n (%)         | 1 (0.8)              | 11 (17)                         | 4 (6)                         | 0.00$^{a, c}$ |
| Composite$^d$ n (%) | 11 (8)           | 37 (58)                         | 11 (26)                       | 0.00$^{a, c}$ |

$^a$Early onset preeclampsia vs. normotensive

$^b$Late onset preeclampsia vs. normotensive

$^c$Early onset preeclampsia vs. late onset preeclampsia

$^d$Mechanical ventilation (MV) and/or continuous positive airway pressure (CPAP) and/or surfactant use

**Table 2B** Primary outcome—multivariable analysis

|                  | Early onset N = 64 | Late onset N = 65 |
|------------------|--------------------|-------------------|
|                  | OR (95% CI)        | P-value            |
| Composite$^a$    | 13 (3.5–37)        | 0.00               |

$^a$Mechanical ventilation and/or continuous positive airway pressure (CPAP) and/or surfactant use

**Discussion**

Our results show that late preterm infants of mothers with preeclampsia have worse respiratory outcomes compared to late preterm infants of normotensive mothers. The outcome is significantly worse in infants of mothers with early onset preeclampsia and persisted after controlling for potential confounders. We also demonstrate that late preterm infants of mothers with preeclampsia also have significantly more non-respiratory morbidity. This is the first study to differentiate between outcomes of late preterm infants of early and late onset preeclampsia.

Studies on the outcomes of late preterm infants of preeclamptic mothers show divergent results with worse outcomes and no difference when compared to late preterm infants of normotensive mothers [9, 24–26]. These conflicting results are, we believe, due to investigators not differentiating between late preterm infants of early and late onset preeclampsia. Gouyon et al., using a large cohort from France, reported higher risk of severe respiratory morbidity, in late preterm infants of mothers with hypertensive disorder of pregnancy [9]. As in our study, severe respiratory morbidity was defined as the need for mechanical ventilation and/or CPAP. Habli et al., in a secondary analysis of
the Calcium for Preeclampsia Prevention trial, investigated neonatal outcomes of infants born at 35–37 weeks of gestation to hypertensive and normotensive women [24]. Respiratory morbidity, defined by the need for oxygen, CPAP or mechanical ventilation was higher at each gestational age in infants of hypertensive mothers but reached statistical significance only at 37 weeks. Lagenveld et al. compared outcomes of late preterm infants of mothers with preeclampsia, gestational hypertension and normotensive pregnancies in a large cohort from the Netherlands [25]. They found higher rates of hypoglycemia and SGA in the preeclampsia group, results similar to our study. The odds of RDS were lower in the preeclampsia group with no difference in TTNB and need for oxygen. However, the study did not have data on antenatal corticosteroid use, systolic blood pressure was not used in the definition of preeclampsia and 30% of the cohort was excluded because of missing data. Masoura et al. reported increased rates of hypoglycemia and RDS and lower Apgar scores in late preterm infants of preeclamptic mothers [26]. In a study from Australia, of infants 30–36 weeks gestation, ventilator support was required significantly more in infants of mothers with preeclampsia [27]. As in other studies, no distinction was made between early and late onset preeclampsia.

Our results demonstrate increased TTNB in late preterm infants of both early and late onset preeclampsia and increased RDS in early onset preeclampsia. In addition, the use of surfactant CPAP and mechanical ventilation was higher in late preterm infants of mothers with preeclampsia, with higher rates in infants of mothers with early onset preeclampsia. As primary CPAP is associated with better respiratory outcomes compared with elective intubation, nine of the fifteen infants placed on mechanical ventilation were initially tried on CPAP but had to be intubated because of worsening respiratory status and increasing oxygen requirements [28]. Of these nine patients, six were from the early onset, two from the late onset and one from the normotensive group. Increased respiratory morbidity in preterm infants of mothers with preeclampsia can potentially be explained by the antiangiogenic state in preeclampsia. Several studies have demonstrated higher levels of antiangiogenic factors, soluble vascular endothelial growth factor receptor-1 (sFlt-1) and soluble Endoglin and lower levels of angiogenic factors, vascular endothelial growth factor (VEGF), and placental growth factor in preeclampsia [10, 29–32]. VEGF plays a key role in lung vascular development, which promotes alveolar growth, and also enhances surfactant protein production [33, 34]. In animal models, VEGF prevents RDS and higher levels of sFlt1 and lower levels of VEGF are described in more severe RDS [35–37]. Importantly, this antiangiogenic state is much more pronounced in early onset preeclampsia with levels of sFlt much higher and levels of VEGF much lower in early onset preeclampsia as compared with late onset preeclampsia [38, 39]. In addition, in early onset preeclampsia the fetus is exposed to the hostile intrauterine antiangiogenic environment for a longer period. These factors may be responsible for the worse respiratory outcomes in late preterm infants of mothers with early onset preeclampsia as compared with infants of mothers with late onset preeclampsia and normotensive mothers. A negative correlation between sFlt1 levels and birthweight is reported in preeclampsia, with higher sFlt1 levels associated with lower birthweight [38, 40]. In our cohort, the lower birthweight in infants of preeclamptic mothers, more marked in the early onset group, can conceivably be attributed to this negative correlation.

### Table 3: Secondary outcomes

|                          | Normotensive N = 131 | Early onset preeclampsia N = 64 | Late onset preeclampsia N = 65 | P-value |
|--------------------------|---------------------|-------------------------------|-------------------------------|---------|
| RDS (n%)                 | 5 (4)               | 16 (25)                       | 4 (6)                         | 0.00\({}^a\)\(^c\) |
| TTNB                     | 19 (14.5)           | 26 (41)                       | 13 (20)                       | 0.00\(a\) |
| Nasal Cannula oxygen     | 2 (2)               | 6 (10)                        | 4 (6)                         | 0.03\(a\) |
| Duration of MV (days)\(d\) | 1                   | 2 (2–3)                       | 1.5 (1–2.75)                  | 0.14    |
| Hypoglycemic (n%)        | 18 (14)             | 18 (28)                       | 19 (28)                       | 0.01\(a\)\(^b\) |
| Small for gestational age (%) | 15 (11)           | 35 (54)                       | 24 (37)                       | 0.00\(a\)\(^b\) |
| Phototherapy (n%)        | 22 (17)             | 39 (61)                       | 22 (34)                       | 0.00\(a\)\(^c\) |
| Hospital stay (days)     | 7 (5–9)             | 13 (10–17)                    | 8 (4–12)                      | 0.00\(a\)\(^c\) |

*RDS* respiratory distress syndrome, *TTNB* transient tachypnea of the newborn, *MV* mechanical ventilation

\(a\)Early onset preeclampsia vs. normotensive

\(b\)Late onset preeclampsia vs. normotensive

\(c\)Early onset preeclampsia vs. late onset preeclampsia

\(d\)One infant in the normotensive group needed mechanical ventilation for 1 day
The composite outcome of CPAP and/or mechanical ventilation use in the normotensive group in our cohort was 8%, similar to the reports by Habli et al. and Gouyon where it was 9.5% and 8%, respectively [9, 24]. The rate of CPAP and/or mechanical ventilation use was higher in the preeclamptic group in our cohort compared to the study by Habli et al. (37 vs. 19%). However, their cohort included both preeclampsia and gestational hypertension which is a less severe disease associated with less respiratory morbidity, diluting the number of infants needing CPAP or mechanical ventilation.

Antenatal steroid use was 11% in our normotensive cohort and 20% (52/260) in the entire cohort. These mothers had received steroids for threatened preterm labor before 34 weeks gestation. Although no study has reported on the antenatal steroid use in late preterm infants of early and late onset preeclamptic mothers, Suga et al. and Gyamf-Bannerman et al. reported rates of 15.2% and 9.2%, respectively, in late preterm infants, not dissimilar to our cohort [41, 42]. The increased respiratory morbidity in infants of mothers with early onset preeclampsia in our cohort was despite the increased use of antenatal steroids.

In addition to being the first study to report on the outcomes of late preterm infants of mothers with early and late onset preeclampsia as distinct groups, there are other strengths to our study. We had a well-defined cohort from a recent era with little or no missing data and detailed demographic characteristics that affect outcomes, especially respiratory outcomes in late preterm infants. This included antenatal steroid use and chorioamnionitis, data that is missing from most studies. Importantly, our gestation was based on first trimester ultrasound or the date of embryo transfer in cases of IVF, largely limiting misclassification of gestation. In addition, health care in Canada is universal, negating the effect of socioeconomic status and differing antenatal and postnatal care on outcomes. However, there are limitations of our study. We did not investigate outcomes like intraventricular hemorrhage, bronchopulmonary dysplasia, or retinopathy of prematurity, which some studies have reported. These outcomes are, however, extremely uncommon in late preterm infants and an extremely large cohort would be needed to study them. Our population was also from single center making generalization of our results difficult. Although not the focus of the study, we did not measure any angiogenic or antiangiogenic factors in our population.

In summary we report, worse outcomes in late preterm infants of mothers with preeclampsia, which are considerably worse in infants of mothers with early onset preeclampsia as compared with late onset preeclampsia. There is uncertainty between planned immediate delivery or expectant management in women with preeclampsia between 34 and 36 weeks gestation [43]. Our data can be used to counsel mothers with preeclampsia in the late preterm period and help in identifying mothers who may benefit from delivery at facilities with higher levels of neonatal intensive care. Our results, however, need validation in a larger cohort.

Acknowledgements The authors are grateful to the Alberta Children’s Hospital Research Institute for providing the funding for the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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