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ORIGINAL ARTICLE

# Pregnancies complicated by both preeclampsia and growth restriction between 34 and 37 weeks' gestation are associated with adverse perinatal outcomes*

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**Abstract**

*Objective*: To determine whether adverse outcomes were more common in late preterm pregnancies complicated by preeclampsia and growth restriction compared to those affected by preeclampsia alone.

*Methods*: This was a retrospective cohort study of 8927 singleton pregnancies with preeclampsia. Pregnancies with small for gestational age (SGA) neonates (birth weight <10th percentile) were compared to those appropriate for gestational age (AGA) neonates. Maternal outcomes included cesarean delivery (CD) rate, CD for fetal heart rate (FHR) abnormalities, abruption, postpartum hemorrhage (PPH), maternal transfusion, acute renal failure, and peripartum cardiomyopathy. Neonatal outcomes studied included respiratory distress syndrome (RDS), jaundice, hypoglycemia, seizure, asphyxia, neonatal death, and intrauterine fetal demise (IUFD).

*Results*: Women with preeclampsia and SGA infants were more likely to experience abruption (5.3% versus 3.0%, $p < 0.001$), higher CD rate (66.5% versus 55.0%, $p < 0.001$), and higher likelihood of a CD for FHR abnormalities (21.7% versus 10.0%, $p < 0.001$). SGA infants were more likely to experience adverse neonatal outcomes including RDS (10.1% versus 4.9%, $p < 0.001$), jaundice (59.8% versus 39.2%, $p < 0.001$), hypoglycemia (8.9% versus 3.9%, $p < 0.001$), asphyxia (0.6% versus 0.2%, $p = 0.015$), and IUFD (1.5% versus 0.3%, $p < 0.001$).

*Conclusions*: Preeclamptic women and their neonates were more likely to experience adverse perinatal outcomes when SGA pregnancies were compared to those with AGA neonates.

**Keywords**

Preeclampsia, growth restriction, late preterm, expectant management

**History**

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## Introduction

Hypertension complicating pregnancy is common and is associated with significantly increased risks of maternal and neonatal morbidity and mortality [1]. Preeclampsia is thought to result from placental hypoxia in association with endothelial dysfunction [2]. Intrauterine growth restriction (IUGR) and preeclampsia may arise from similar pathophysiological mechanisms, namely abnormal placentation. IUGR may precede, or arise subsequent to, a diagnosis of preeclampsia [3]. The risk of developing growth restriction is approximately 4-fold higher in women with preeclampsia compared to controls [4,5]. Additionally, about 15% of pregnancies initially complicated by only IUGR were subsequently observed to develop preeclampsia [3,6].

Conflicting data exists regarding the impact of fetal growth restriction on maternal and neonatal outcomes in pregnancies complicated by hypertension. Several retrospective studies have demonstrated that adverse perinatal outcomes, including stillbirth and neonatal death, may be associated with IUGR in the setting of preeclampsia [6–10]. However, the majority of these studies limited their analysis to those pregnancies delivered before 34 weeks' gestation. Other studies have investigated the role of fetal growth restriction on maternal disease in the setting of preeclampsia, and its influence remains unclear [3,6,9,10].

In November 2013, the American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy recommended that intrauterine growth restriction should no longer be used to differentiate preeclampsia with severe features from that without. However, most clinicians remain hypervigilant when managing preeclamptic women with IUGR, especially between 34 and 37 weeks, given the perceived concern and tradeoffs between increased maternal and neonatal morbidity and mortality.

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In light of this recommendation, our aim was to determine whether an association exists between adverse perinatal outcomes in pregnancies complicated by preeclampsia and fetal growth restriction in the late preterm period (between 34 0/7 and 36 6/7 weeks' gestation). Our primary objective was to elucidate whether adverse maternal and neonatal outcomes were more common in pregnancies complicated by preeclampsia and growth restriction compared to those that were affected only by preeclampsia. Our secondary objective was to determine if there is a particular week during this late preterm period during which adverse perinatal outcomes become more likely.

## Materials and methods

We conducted a retrospective cohort study of 8927 singleton pregnancies between 34 0/7 and 36 6/7 weeks gestation with preeclampsia who delivered in California between 2005 and 2008. Birth certificates and/or infant death certificates were linked to hospital discharge diagnoses using International Classification of Diseases–9 (ICD-9) codes. Institutional review board approval was obtained from the University of California, from Oregon Health & Science University, and from the State of California. Given that the linked data set did not contain patient identifying data, the study was exempted from informed consent.

Maternal outcomes collected included cesarean delivery (CD) rate, CD rate for fetal heart rate (FHR) abnormalities, placental abruption, postpartum hemorrhage (PPH), maternal transfusion, acute renal failure, pulmonary edema, and peripartum cardiomyopathy. Neonatal outcomes studied included respiratory distress syndrome (RDS), jaundice, hypoglycemia, neonatal seizure, asphyxia, neonatal death, and intrauterine fetal demise (IUFD). ICD-9 code-based diagnoses were used to identify patients with preeclampsia. Small for gestational age (SGA) was defined as birth weight below the 10th percentile for gestational age. Pregnancies complicated by preeclampsia with and without severe features were included. Pregnancies that were complicated by a large for gestational age neonate were excluded.

Baseline patient characteristics were collected and the association between growth restriction and perinatal outcomes of interest in women with preeclampsia was analyzed. The data were then stratified by gestational age at delivery (34 0/7–34 6/7 weeks, 35 0/7–35 6/7 weeks and 36 0/7–36 6/7 weeks).

Categorical variables were compared using the chi-square test. Multivariable analyses were utilized to control for such potential confounders as age, race, parity, education, insurance status, prenatal visits, and medical comorbidities. Statistical significance was designated at a $p$ value $= 0.05$ or a 95% confidence interval that did not include unity. Statistical analysis was performed using STATA v12.0 (StataCorp, College Station, TX) statistical software.

## Results

The cohort consisted of 8927 women who had preeclampsia and delivered between 34 0/7 weeks and 36 6/7weeks gestation during the study period. Of these, 1553 women delivered SGA infants (17.4%) and 7394 were appropriate for gestational age (AGA) at delivery. Baseline characteristics are similar between SGA versus AGA groups (Table 1). Those with SGA infants were more likely to have inadequate prenatal care (<5 visits), but less likely to have pre-gestational or gestational diabetes.

Adverse maternal outcomes were more common in the SGA group compared to the AGA group, including placental abruption (5.3% versus 3.0%, $p < 0.001$), higher CD rate (66.5% versus 55.0%, $p < 0.001$), and higher rate of CD for FHT abnormalities (21.7% versus 10.0%, $p < 0.001$, Table 2). The SGA neonates were more likely to experience adverse neonatal outcomes including RDS (10.1% versus 4.9%, $p < 0.001$), neonatal jaundice (59.8% versus 39.2%, $p < 0.001$), hypoglycemia (8.9% versus 3.9%, $p < 0.001$), asphyxia (0.6% versus 0.2%, $p = 0.015$), and IUFD (1.5% versus 0.3%, $p < 0.001$) compared to AGA neonates (Table 3). These adverse maternal and neonatal outcomes remained more likely in the SGA group compared to the AGA group, even when controlling for potential confounders (Tables 4 and 5).

With one exception, maternal outcomes did not differ when stratified by gestational week at delivery. Notably, women who delivered at 35 weeks of gestation were more likely to experience placental abruption in the SGA group compared to the AGA group (6.5% versus 3.2%, $p < 0.001$). In contrast, similar rates of placental abruption were noted between SGA versus AGA groups at 34 and 36 weeks' gestation. Other maternal outcomes did not differ between

Table 1. Baseline maternal characteristics by birth weight.

| | SGA ($N = 1533$) | AGA ($N = 7394$) | $p$ values |
|---|---|---|---|
| Race | | | <0.001 |
| White | 21.1% | 23.3% | |
| Black | 8.5% | 8.5% | |
| Hispanic | 56.1% | 57.1% | |
| Asian | 12.8% | 9.0% | |
| Maternal age > 35 years | 22.6% | 22.2% | 0.74 |
| Maternal age < 20 years | 11.7% | 11.9% | 0.85 |
| Nulliparity | 58.4% | 55.6% | 0.04 |
| Chronic hypertension | 13.0% | 14.2% | 0.22 |
| Pregestational diabetes | 2.1% | 3.7% | 0.002 |
| Gestational diabetes | 9.5% | 13.6% | <0.001 |
| Some college education | 45.6% | 44.0% | 0.25 |
| Public insurance | 50.4% | 49.15% | 0.37 |
| Less than 5 prenatal care visits | 7.3% | 5.17% | 0.001 |

Table 2. Maternal outcomes by birth weight for all deliveries (Weeks 34–37).

| Maternal outcomes | | | |
|---|---|---|---|
| | SGA ($N = 1533$) | AGA ($N = 7394$) | $p$ values |
| Placental abruption | 5.3% | 3.0% | <0.001 |
| Postpartum hemorrhage | 4.5% | 5.8% | 0.035 |
| Cesarean delivery | 66.5% | 55.0% | <0.001 |
| Cesarean delivery for fetal heart tracing abnormalities | 21.7% | 10.0% | <0.001 |
| Blood transfusion | 2.8% | 2.7% | 0.787 |
| Pulmonary edema | 0.06% | 0.01% | 0.226 |
| Acute renal failure | 0.5% | 0.4% | 0.620 |
| Peripartum cardiomyopathy | 0% | 0.2% | 0.074 |

Table 3. Neonatal outcomes by birth weight for all deliveries (Weeks 34–37).

| Neonatal outcomes | SGA ($N = 1533$) | AGA ($N = 7394$) | $p$ values |
|---|---|---|---|
| Respiratory distress syndrome | 10.1% | 4.9% | <0.001 |
| Neonatal jaundice | 59.8% | 39.2% | <0.001 |
| Hypoglycemia | 8.9% | 3.89% | <0.001 |
| Neonatal seizure | 0.12% | 0.13% | 0.939 |
| Asphyxia | 0.6% | 0.2% | 0.015 |
| Neonatal death | 0.3% | 0.1% | 0.094 |
| Intrauterine fetal demise | 1.5% | 0.3% | <0.001 |

Table 4. Maternal outcomes by SGA, controlled for potential confounders.

| Maternal outcomes | SGA |
|---|---|
| Abruption | 1.79 (1.37–2.33) |
| Postpartum hemorrhage | 0.78 (0.60–1.01) |
| Cesarean delivery | 1.73 (1.54–1.95) |
| Cesarean delivery for abnormal fetal heart tracing | 2.57 (2.22–2.97) |
| Blood transfusion | 1.06 (0.75–1.45) |
| Platelet transfusion | 1.15 (0.66–2.01) |
| Acute renal failure | 1.13 (0.49–2.59) |

Data are given as adjusted odds ratio (95% confidence interval).
Multivariable logistic regression was used controlling for potential confounders as age, race, parity, education, insurance status, prenatal visits, and medical comorbidities.

Table 5. Neonatal outcomes by SGA, controlled for potential confounders.

| Neonatal outcomes | SGA |
|---|---|
| Respiratory distress syndrome | 2.34 (1.91–2.87) |
| Jaundice | 2.39 (2.13–2.68) |
| Hypoglycemia | 2.45 (1.97–3.04) |
| Neonatal seizure | 0.93 (0.20–4.30) |
| Asphyxia | 2.65 (1.16–6.05) |
| Intrauterine fetal demise | 11.05 (3.87–31.55) |
| Neonatal demise | 2.23 (0.43–11.64) |

Data are given as adjusted odds ratio (95% confidence interval).
Multivariable logistic regression was used controlling for potential confounders as age, race, parity, education, insurance status, prenatal visits, and medical comorbidities.

SGA and AGA groups if delivery occurred at 34 weeks, 35 weeks or 36 weeks' gestation (Table 6).

Though the overall risk of adverse neonatal outcomes decreased with increasing gestational age, several adverse outcomes became increasingly more common in SGA infants compared to AGA infants during each subsequent week of the late preterm period (Table 7). Jaundice and hypoglycemia were more common in SGA infants than AGA infants at 34 weeks (jaundice with 70.2% versus 58%, $p < 0.001$; hypoglycemia 8.3% versus 5.4%, $p < 0.001$). At 35 weeks, RDS and IUFD were increased in SGA infants as compared AGA infants (RDS 9.1% versus 4.4%, $p < 0.001$; IUFD 1.3% versus 0.3%, $p < 0.001$). At 36 weeks, this findings persisted for RDS and IUFD; additionally asphyxia became more common in the SGA infants (0.5% versus 0.1%, $p = 0.01$).

## Discussion

We found that adverse perinatal outcomes were more common in pregnancies complicated by preeclampsia in the setting of fetal growth restriction as compared to those complicated by preeclampsia alone with appropriate grown neonates in the late preterm period, between 34 and 37 weeks' gestation. This remains true even when controlling for potential confounders. When we evaluated whether there was a particular week of delivery during which adverse events appeared more common, we found that, with the exception of placental abruption, which was more common particularly at 35 weeks of gestation, rates of adverse outcomes persisted across gestational age strata. And, though the overall risk of adverse neonatal outcomes decreased with gestational age, several adverse outcomes were increasingly more common in SGA infants compared to AGA infants during each subsequent week of the late preterm period.

Previously, studies have investigated the association between growth restriction and maternal and neonatal outcomes. Three retrospective studies, involving fewer than 240 patients each, demonstrated an association between preeclampsia and adverse neonatal outcomes, including stillbirth and neonatal mortality [7–9]. In contrast, two other retrospective studies, involving 155 and 306 women respectively, failed to confirm this association between IUGR and adverse neonatal outcomes [6,10]. Interestingly, four of the five studies limited their inclusion criteria to those pregnancies delivered before 34 weeks' gestation [7–10].

More conflicting evidence also exists for maternal outcomes in the setting of growth restriction complicating preeclampsia. Mitani et al. investigated pregnancies complicated by preeclampsia with and without growth restriction delivered before 37 weeks. IUGR was significantly associated with severe maternal disease, defined as severe hypertension, severe proteinuria, and other critical maternal conditions [6]. On the contrary, other authors have found no association between the severity of the maternal condition and the presence of fetal growth restriction. However, again three of these four authors included only pregnancies delivered before 34 weeks [3,9,10].

Though quite large in sample size, our study is not without limitations. As a retrospective study of primarily administrative data, there may be issues of misclassification. Thus, there may be patients with preeclampsia that were missing from our cohort, particularly those with more mild disease. It is unclear whether this would contribute to a higher or lower rate of complications among our cohort. Our analysis is also limited to those variables for which data was collected. We unfortunately had no data on rates of maternal stroke or mortality though, despite the size of our cohort, would still have been underpowered even had they been available [11,12]. Additionally, we dichotomized our neonates into SGA and AGA using birth weight. This information is not fully available antepartum at which time we must use the estimated fetal weight to determine whether the fetus is thought clinically to be SGA. Because the estimated fetal weight would lead to misclassification of both SGA and AGA neonates, the actual prospective effect of a suspected SGA diagnosis may be less than we have found here. Finally, we

Table 6. Maternal outcomes in SGA versus AGA infants stratified by delivery week.

| | 34 weeks | | | 35 weeks | | | 36 weeks | | |
|---|---|---|---|---|---|---|---|---|---|
| | SGA ($N=446$) | AGA ($N=1431$) | $p$ values | SGA ($N=527$) | AGA ($N=2330$) | $p$ values | SGA ($N=645$) | AGA ($N=3865$) | $p$ values |
| Abruption | 6.3% | 4.5% | 0.14 | 6.5% | 3.2% | <0.001 | 3.6% | 2.4% | 0.08 |
| Postpartum hemorrhage | 5.2% | 6.9% | 0.24 | 4.2% | 5.0% | 0.44 | 4.2% | 5.9% | 0.09 |
| Cesarean delivery (CD) | 76.2% | 63.2% | <0.001 | 64.7% | 56.4% | 0.001 | 61.2% | 51.1% | <0.001 |
| CD for FHR abnormalities | 22.7% | 13.0% | <0.001 | 23.9% | 11.1% | <0.001 | 19.2% | 8.3% | <0.001 |
| Blood transfusion | 3.1% | 3.4% | 0.82 | 3.4% | 2.3% | 0.15 | 2.0% | 2.6% | 0.37 |
| Acute renal failure | 0.4% | 0.3% | 0.36 | 0.2% | 0.5% | 0.37 | 0.6% | 0.4% | 0.40 |
| Peripartum cardiomyopathy | 0% | 0.5% | 0.14 | 0% | 0.17% | 0.34 | 0% | 0.1% | 0.41 |

Table 7. Neonatal outcomes in SGA versus AGA infants stratified by delivery week.

| | 34 weeks | | | 35 weeks | | | 36 weeks | | |
|---|---|---|---|---|---|---|---|---|---|
| | SGA ($N=446$) | AGA ($N=1431$) | $p$ values | SGA ($N=527$) | AGA ($N=2330$) | $p$ values | SGA ($N=645$) | AGA ($N=3865$) | $p$ values |
| RDS | 15.5% | 12.0% | 0.06 | 9.1% | 4.4% | <0.001 | 7.1% | 2.5% | <0.001 |
| Neonatal jaundice | 70.2% | 58% | <0.001 | 57.9% | 41.8% | <0.001 | 54.1% | 30.7% | <0.001 |
| Hypo-glycemia | 8.3% | 5.4% | 0.02 | 9.7% | 4.9% | <0.001 | 8.7% | 2.7% | <0.001 |
| Neonatal seizure | 0% | 0.3% | 0.26 | 0.4% | 0.1% | 0.10 | 0% | 0.1% | 0.41 |
| Asphyxia | 0.5% | 0.4% | 0.93 | 0.8% | 0.3% | 0.13 | 0.5% | 0.1% | 0.01 |
| Neonatal death | 0.2% | 0.1% | 0.69 | 0.4% | 0.1% | 0.10 | 0.2% | 0.1% | 0.53 |
| IUFD | 0.9% | 0.8% | 0.26 | 1.3% | 0.3% | 0.005 | 1.71% | 0.1% | <0.001 |

utilized SGA as a surrogate for IUGR given antepartum estimated fetal weight was not available. SGA infants are not always pathologically growth restricted therefore there may be a subgroup of our SGA pregnancies that would be even higher risk. Future studies should focus on better identification of those pregnancies at highest risk.

The treatment for preeclampsia is delivery. Expectant management is pursued solely for neonatal benefit. We would advocate that expectant management of otherwise mild preeclampsia with an SGA fetus should be undertaken with caution between 34 and 37 weeks' gestation and should certainly include close observation and frequent fetal testing. In particular, such pregnancies are at increased risk of obstetric and maternal complications of pregnancy, not just fetal or neonatal complications, so if expectant management is employed, very close observation should be employed.

## Declaration of interest

The authors report no conflict of interest.

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