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Impact of fetal growth on pregnancy outcomes in women with severe preeclampsia

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Abstract

Objective—To estimate whether pregnancy outcomes in women with severe preeclampsia (sPE) with small for gestational age (SGA) fetuses differ from those with sPE without SGA or isolated SGA.

Study Design—We conducted a retrospective cohort study of consecutive non-anomalous, livebirths in a single tertiary care institution from 2004–2008. We compared pregnancy outcomes in women who had sPE with SGA (birthweight<10th percentile), and sPE without SGA to those with isolated SGA as reference. The primary outcome was a neonatal composite score including low 5-minute APGAR, NICU admission and neonatal death. Secondary outcomes were components of the composite as well as placental abruption and cesarean delivery. Analysis was repeated with SGA defined as birthweight<5th percentile. Multivariable logistic regression was used to adjust for confounders.

Results—1,905 women met inclusion criteria: 156 sPE with SGA, 746 sPE without SGA, 1,003 isolated SGA. The risk of the neonatal composite score was higher for sPE with SGA (adjusted odds ratio [aOR] 2.29; 95% confidence interval [CI] 1.39–3.79) and sPE without SGA (aOR 3.66; 95% CI 2.71–4.93) compared to isolated SGA. The risk of abruption and cesarean were similarly increased in women with sPE with SGA and sPE without SGA compared to those with isolated SGA.

Conclusion—Similar to women with sPE without SGA fetus, women who have sPE with SGA are at a higher risk for several adverse maternal and neonatal outcomes compared to isolated SGA. These findings suggest that women with preeclampsia and SGA should be managed as sPE rather than as isolated SGA.

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Keywords

small for gestational age; maternal outcomes; neonatal outcomes; preeclampsia; severe preeclampsia; fetal growth restriction

INTRODUCTION

Severe preeclampsia (sPE) is an important contributor to increased morbidity and mortality in pregnancy, but the diagnostic criteria that defines sPE is less clear. Management for patients with sPE can vastly differ from those with non-severe disease features, making clear diagnostic criteria vital to optimal patient care. The American Congress of Obstetrics and Gynecology (ACOG) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) recently published expanded definitions of preeclampsia that include non-proteinuric hypertension (Table 1).(1, 2) The two guidelines differ in whether to designate a subset of patients with “severe” disease features and whether to include intrauterine growth restriction (IUGR) as a diagnostic criterion. ACOG abandoned the terminology “severe preeclampsia” in favor of a distinction for severe disease, but does not include IUGR, while ISSHP broadly defines preeclampsia without subdivisions and includes IUGR among the diagnostic criteria. sPE and IUGR are both independently associated with an increased risk of neonatal morbidity and mortality(3, 4), but there is a paucity of literature regarding whether the risks are additive.

We sought to estimate whether perinatal outcomes in women who had preeclampsia with IUGR differ from those with sPE by other diagnostic criteria using patients with isolated IUGR as the reference group.

MATERIALS AND METHODS

This was a retrospective cohort study of all consecutive women who were admitted to the Barnes Jewish Hospital Labor and Delivery unit, a tertiary referral center from 2004–2008. Institutional review board approval was obtained from Washington University School of Medicine. Women were eligible if they had a live birth during the study period. Exclusion criteria included pregnancies with fetal anomalies and multiple gestations. Trained obstetrics research assistants extracted information on maternal demographics, medical history, antepartum course, labor and delivery records and neonatal outcomes from the medical record. Since IUGR is based on estimated fetal weight that may be inaccurate, we used birthweight as the measure of fetal growth. Birthweight less than the 10th% on the Alexander growth standard was considered small for gestational age (SGA). (5)

Patients in the following groups within the cohort were identified: sPE with SGA, sPE without SGA, or Isolated SGA. Since sPE without SGA and sPE with SGA were both considered variants of sPE by the diagnostic criteria used during the study period, both groups received the same clinical management at our institution. Mild preeclampsia was defined by new onset hypertension with systolic blood pressure ≥140 mm Hg or diastolic ≥90 mm Hg on two occasions at least 6 hours apart and proteinuria (>300 mg in 24 hours or 1+ on a urine dip when a 24 hour urine was not available) after 20 weeks of pregnancy based

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on the 2002 ACOG diagnostic criteria (Table 1). sPE was diagnosed if the patient had one or more of the following criteria in addition to mild preeclampsia: systolic blood pressure ≥160 mm Hg or diastolic ≥110 mm Hg on two occasions at least 6 hours apart, proteinuria (>5 g in 24 hours or 3+ or greater protein on two random urine samples collected at least 4 hours apart when a 24 hour urine was not available), oliguria of less than 500 mL in 24 hours, renal impairment with creatinine ≥1, cerebral or visual disturbances, pulmonary edema, epigastric or right upper-quadrant pain, impaired liver function (aspartate aminotransferase > 1.5 normal), low platelets (<120,000), or IUGR. All women with sPE at our institution received magnesium while on labor and delivery during the time of the study. Gestational age was estimated by last menstrual period (LMP) and first or second trimester ultrasound. (6)

sPE with SGA and sPE without SGA were compared to isolated SGA as the reference group. The primary outcome was a neonatal composite score including low 5-minute APGAR (<7), NICU admission (greater than 12 hours) and neonatal death. Secondary outcomes were the individual components of the composite as well as adverse obstetric and maternal outcomes of placental abruption and cesarean delivery. A secondary analysis defining severe SGA as birthweight < 5th% was performed.

Data analysis was performed with descriptive and bivariate statistics. Analysis of variance (ANOVA) was used for continuous variables and Chi-square or Fisher exact test for categorical variables. Normality of distribution was tested with the Kolmogorov-Smirnov test. Backwards step-wise multi-variable logistic regression models for outcomes of interest were developed to estimate the impact of sPE with SGA or without SGA, after adjusting for potential confounders including African-American race, AMA, chronic hypertension, diabetes, smoking, and obesity. Relevant covariates for inclusion in the initial multivariable statistical models were selected based on biological plausibility and results of the stratified analyses. Fit for the final models were tested with the Hosmer-Lemeshow goodness-of-fit test.

To explore whether gestational age at delivery explained the increased risk of the composite neonatal morbidity, we used time-to-event analysis to account for gestational age at delivery. The Cox proportional hazard model was fitted to estimate hazard ratios (HRs), adjusting for potentially confounding factors, including AMA, BMI, African-American race, chronic hypertension, diabetes, smoking, illicit drug use and nulliparity. The proportional hazards assumption was tested graphically and using the Schoenfeld's global test. We included all subjects meeting inclusion criteria; no a priori sample size estimation was performed. Analysis was performed with STATA software (version 11, College Station, TX).

RESULTS

Of 10,457 eligible births in our institution over the study period, 1905 patients with a diagnosis of SGA and/or preeclampsia were included in the cohort (Figure 1). Of these, 156 had sPE with SGA, 746 had sPE without SGA and 1003 had isolated SGA. Women with isolated SGA tended to have the lowest rates of chronic disease while women with sPE without SGA had the highest rates of chronic hypertension (12.5%) and diabetes (5.6%) as

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well as the highest BMI of the three groups (Table 2). With regard to substance abuse, women with isolated SGA were more likely to smoke ($p<0.001$) or use illicit drugs ($p<0.001$) than women with sPE with or without SGA and had the lowest BMI ($p<0.001$).

The primary outcome (composite neonatal morbidity score including low 5 minute APGAR, NICU admission or neonatal death) was higher in both sPE with SGA (aOR 2.29; 95% CI 1.39–3.79) and sPE without SGA (aOR 3.66; 95% CI 2.71–4.93) compared to isolated SGA (Table 3). Similarly, the risk of placental abruption was higher in women who had sPE with SGA (adjusted odds ratio [aOR] 3.26; 95% confidence interval [CI] 1.13–9.43) and sPE without SGA (aOR 4.00; 95% CI 2.06–7.79) compared to isolated SGA. sPE with or without SGA conferred more than a two-fold greater risk of low 5-minute APGAR score compared to isolated SGA, but there was not a statistically significant difference in neonatal death rates between groups. Women who had sPE with SGA or sPE without SGA were nearly two times as likely to have a cesarean delivery compared to women with SGA in isolation.

We used a time-to-event analysis to account for the effect of gestational age at delivery on the neonatal composite morbidity. After adjusting for confounders in a Cox proportional hazard model, the risk for the composite neonatal morbidity was still significantly higher for both sPE without SGA (HR 4.20;95% CI 3.18–5.55) and sPE with SGA (HR 2.22; 95% CI 1.35–3.65), compared to isolated SGA.

We conducted a secondary analysis of the three categories limited to severe SGA (sSGA) less than the 5^{th} % with the following groups: sPE with sSGA, sPE without sSGA, and isolated sSGA. There were 67 who had sPE with sSGA, 835 with sPE without sSGA and 448 women with isolated sSGA. The neonatal composite was still significantly higher for women who had sPE without SGA (aOR 3.50; 95% CI 2.49–4.91), but the difference was not statistically significant in women who had sPE with SGA (aOR 1.83; 95% CI 0.94–3.53). There was no difference in low minute APGAR score between groups, but the same significant associations in our primary analysis, with regard to NICU admission, placental abruption and cesarean delivery, were seen (data not shown).

DISCUSSION

We found that women who had sPE with and without SGA are at similarly increased risk for adverse neonatal, obstetric, and maternal outcomes compared to those with isolated SGA. The similarity in maternal and neonatal outcomes of women who had sPE with SGA and without SGA suggests it is more appropriate to manage these women as sPE than preeclampsia with isolated IUGR. The 2014 ACOG Hypertensive task force guidelines recommend delivery in a woman with preeclampsia at 34 weeks if the fetus has SGA<5%.

There is debate regarding the role of abnormal implantation of the placenta and aberrant trophoblast invasion as a common pathway to both preeclampsia and SGA. This is illustrated in a case-control study by Srinivas et al. of 430 cases with preeclampsia (161 mild and 269 severe) and 568 controls without preeclampsia delivering at term at the University of Pennsylvania Hospital from 2005–2007.(7) A unique feature of the study was that SGA was

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not part of the diagnostic criteria for preeclampsia and the prevalence of SGA was calculated among cases and controls. Patients with preeclampsia were more likely to have SGA than controls. Furthermore, among patients without chronic hypertension, cases were more likely to have SGA while there were no differences in rates of SGA between cases and controls in patients with chronic hypertension. The authors concluded that preeclampsia is independently associated with SGA, and that SGA may evolve through a different pathway in women with superimposed preeclampsia.

A large secondary analysis of the World Health Organization Antenatal Care Trial by Villar et al. compared perinatal outcomes in the following subgroups: preeclampsia and SGA, gestational hypertension and SGA, and unexplained SGA as the reference group.(8) Women with preeclampsia and SGA had the highest risk of NICU stay≥7 days and neonatal death after adjusting for study site and socioeconomic status, but this difference disappeared after adjusting for birthweight and gestational age. This suggests that the excess risk associated with preeclampsia and SGA may be accounted for by these variables. Two other studies of sPE suggested that gestational age less than 30 weeks was the strongest predictor of perinatal outcome.(9, 10)

Our study offers several strengths over the previous literature on this subject. We utilized a robust and validated database with very little missing information. Furthermore, our findings are consistent with the prior literature with regard to the characteristics of our study population, which lends credibility to our results and suggests greater generalizability. In addition, because gestational age at delivery is in the causal pathway of our primary outcome, we used time-to-event analysis to account for the effect of gestational age on the association between sPE with SGA and the composite neonatal morbidity. Finally, we used a stringent definition of sPE, in which patients meeting laboratory criteria also needed to receive magnesium while on labor and delivery, which was the standard practice for managing sPE at our institution during the study period.

There are also limitations that should be considered when interpreting our results. The study sample was taken from a cohort of women with livebirths. Therefore, we were unable to account for fetal demise and comment on the distribution of stillbirth among our 3 study groups and potential implications this may have on management decisions. We also did not have data on important perinatal complications, including respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage and necrotizing enterocolitis. However, neonates with these morbidities were most likely reflected in the outcome of NICU admission. Although magnesium assured strict diagnostic criteria for sPE, it may also be a confounding variable if it was associated with the neonatal outcome measures. We used SGA, rather than IUGR, to define suboptimal fetal growth. This has the advantage of eliminating the error inherit in estimated fetal weights. In addition, this is consistent with the methodology of prior studies cited above. Finally, while we used appropriate statistical methods to adjust for confounding, there is the possibility for residual confounding by unmeasured factors.

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CONCLUSION

Our results show that women diagnosed as having sPE with SGA have worse outcomes than those with SGA alone and closely mirror the outcomes of sPE without SGA. Whereas the Task Force guidelines removed IUGR from the diagnostic criteria for preeclampsia with severe features because IUGR is “managed similarly in pregnant women with and without preeclampsia,”(1) our findings suggest that women with preeclampsia and SGA should be managed as sPE rather than as isolated SGA.

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Highlights

- The American Congress of Obstetricians and Gynecologists recently removed fetal growth restriction as a diagnostic criterion for preeclampsia with severe features (previously called “severe preeclampsia”)
- Women diagnosed as having severe preeclampsia with fetal growth restriction have worse outcomes than those with isolated fetal growth restriction and closely mirror the outcomes of severe preeclampsia without fetal growth restriction.
- Our findings suggest that women with preeclampsia and fetal growth restriction should be managed as severe preeclampsia

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CONDENSATION

Women with severe preeclampsia with and without a small for gestational age fetus are at higher risk for adverse pregnancy outcomes compared to women with an isolated small for gestational age fetus.

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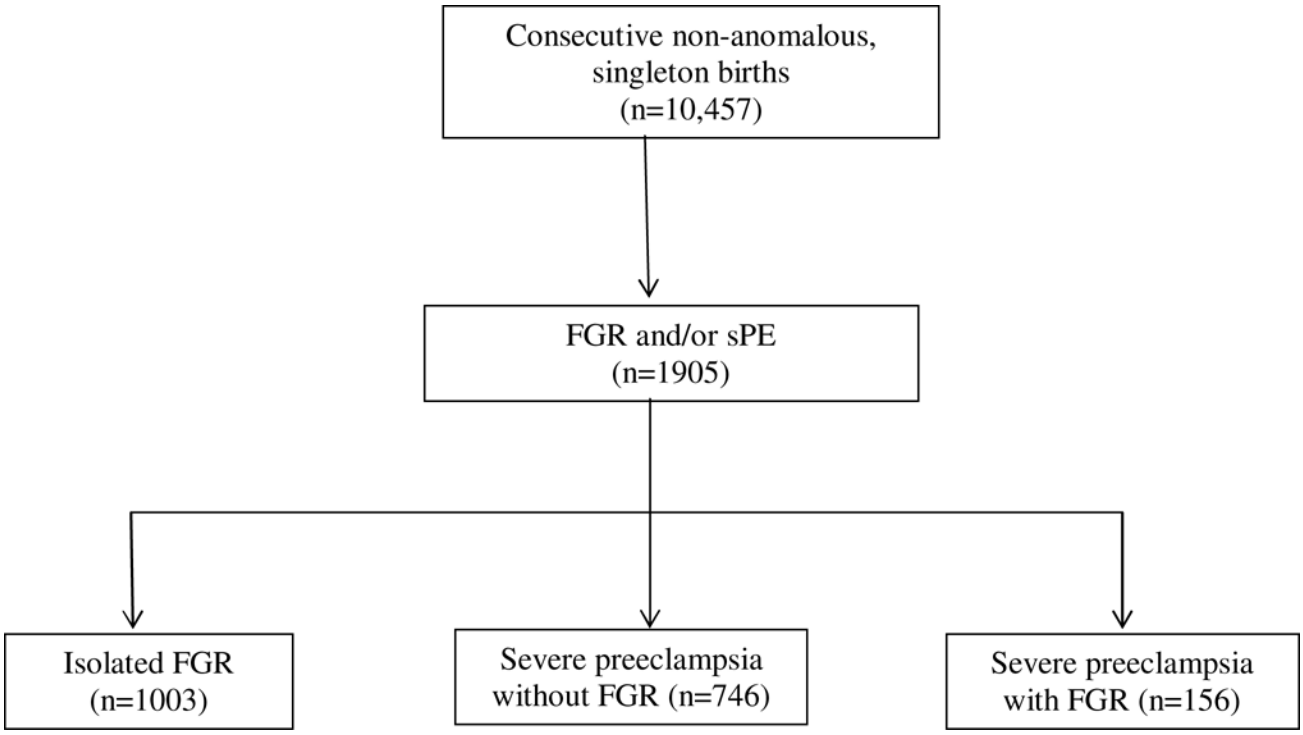

Figure 1.
Flowchart of study population

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Table 1

Definitions of preeclampsia

	Blood Pressure Criteria	End Organ Criteria
Historic ACOG preeclampsia Defintion from Practice Bulletin 33-January, 2002(11)	• Blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic after 20 weeks of gestation in a woman with previously normal blood pressure **Severe Preeclampsia-one or more of the bolded items:** • **≥160 mm Hg systolic or ≥110 mm Hg diastolic on two occasions at least 6 hours apart while the patient is on bedrest**	• Proteinuria, defined as urinary excretion of 0.3 g protein or higher in a 24 hour urine specimen • **Proteinuria of 5 g or higher in a 24 hour urine specimen or 3+ or greater on two random urine samples collected at least 4 hours apart** • **Oliguria of less than 500 mL in 24 hours** • **Cerebral or visual disturbances** • **Pulmonary edema or cyanosis** • **Epigastric or right upper quadrant pain** • **Impaired liver function** • **Thrombocytopenia** • **Fetal growth restriction**
ACOG Hypertension in Pregnancy Task Force Preeclampsia Definition November, 2013(1)	• ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • **≥160 mm Hg systolic or ≥110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy**	Proteinuria • Greater than or equal to 300 mg per 24-hour urine collection • Protein/creatinine ratio≥0.3 • Dipstick reading of 1+ OR In the absence of proteinuria, new-onset hypertension with the new onset of any of the following: • **Thrombocytopenia** • **Renal insufficiency** • **Impaired liver function** • **Pulmonary edema** • **Cerebral or visual symptoms**
ISSHP Preeclampsia definition February, 2014(2)	Hypertension developing after 20 weeks gestation and the coexistence of one or more of the following new onset conditions:	**1** Proteinuria **2** Other maternal organ dysfunction ○ Renal insufficiency (Creatinine≥90 umol/L) ○ Liver involvement (elevated transaminases and/or severe right upper quadrant or epigastric pain) ○ Neurological complications ○ Hematological complications **3** Uteroplacental dysfunction **4** Fetal growth restriction

Bolded Items denote severe forms of disease

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Table 2

Baseline characteristics of women with preeclampsia and SGA compared to SGA alone

	Reference Isolated SGA n=1003	**Severe preeclampsia with SGA n=156**	**Severe preeclampsia without SGA n=746**	**P-value**
Maternal Age Median (IQR)	23 (20–28)	21 (19–26)	24 (20–29)	**0.037**
Gestational Age Median (IQR)	39.0 (37.4–39.9)	36.3 (34.2–38.4)	35.6 (31–38.4)	<**0.001**
Birthweight	2580 (2320–2750)	2142 (1663–2495)	2638 (1645–3200)	<**0.001**
BMI Mean (SD)	30.2 (7.0)	32.2 (8.1)	33.6 (9.0)	<**0.001**
African American	804 (80.2%)	126 (80.8%)	518 (69.4%)	<**0.001**
Chronic Hypertension	35 (3.5%)	13 (8.3%)	93 (12.5%)	<**0.001**
Diabetes	13 (1.3%)	2 (1.3%)	42 (5.6%)	<**0.001**
Smoking	295 (29.4%)	26 (16.7%)	146 (19.6%)	<**0.001**
Illicit drugs	187 (18.6%)	12 (7.7%)	84 (11.26%)	<**0.001**
Nulliparity	423 (42.2%)	98 (62.8%)	380 (50.9%)	<**0.001**

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Table 3

Perinatal outcomes in women with isolated SGA, severe preeclampsia with SGA and severe preeclampsia without SGA

	Reference Isolated SGA n=1003	Severe preeclampsia with SGA n=156		Severe preeclampsia without SGA n=746	
	n (%)	n (%)	Adjusted OR (95% CI)	n (%)	Adjusted OR (95% CI)
Primary Outcome					
Neonatal Composite	74 (7.4%)	20 (12.8%)	**2.29 (1.39–3.79)**	163 (21.9%)	**3.66 (2.71–4.93)**
Secondary Outcomes					
5-minute Apgar score <7	37 (3.7%)	13 (8.3%)	**2.30 (1.19–4.45)**	67 (9.0%)	**2.40 (1.58–3.65)**
NICU Admission	61 (6.1%)	15 (9.6%)	1.54 (0.85–2.79)	134 (18.0%)	**3.38 (2.45–4.67)**
Neonatal Death	11 (7.5%)	2 (2.6%)	0.27 (0.06–1.25)	29 (7.2%)	0.71 (0.35–1.42)
Abruption	13 (1.3%)	5 (3.2%)	**3.26 (1.13–9.43)**	32 (4.3%)	**4.00 (2.06–7.79)**
Cesarean	286 (28.5%)	65 (41.7%)	**1.80 (1.27–2.55)**	329 (44.1%)	**1.92 (1.57–2.35)**

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