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Maternal Outcomes Associated With Lower-Range Stage 1 Hypertension

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Abstract

Objective: To evaluate maternal and neonatal outcomes in healthy, nulliparous women classified with stage 1 hypertension under the revised American College of Cardiology (ACC) and American Heart Association Guidelines (AHA) and to evaluate the effects of low-dose aspirin on maternal and neonatal outcomes in this population.

Methods: We conducted a secondary analysis of data from a multicenter randomized, double blind, placebo-controlled trial of low-dose aspirin for prevention of preeclampsia in nulliparous, low-risk women recruited between 13 and 25 weeks of gestation. Of the 3,134 nulliparous women enrolled in the original study, 2,947 women with singleton pregnancies and without missing data were included in this analysis. Blood pressure was measured at enrollment between 13 and 25 weeks of gestation and outcomes were adjudicated from the medical record.

Results: One hundred sixty-four participants were identified with lower range stage 1 hypertension (5.6%), systolic blood pressure 130–135 mmHg and/or diastolic blood pressure 80–85mmHg, by the new ACC–AHA guidelines. Within the placebo group (n=1482), women with stage 1 hypertension had a significantly increased incidence of preeclampsia compared to normotensive women, 15.3% (15/98) versus 5.4% (75/1384), RR 2.66; 95%CI 1.56–4.54, p<0.001. Moreover, stage 1 hypertension women had increased incidence of gestational diabetes (GDM) (6.1% vs. 2.5%, p=0.03) and more indicated preterm deliveries (4.2% vs. 1.1%, p=0.01). Comparing stage 1 hypertensive women and normotensive women receiving low-dose aspirin during pregnancy (n=1465), no differences in rates of preeclampsia (7.6% vs. 4.4% respectively, p=0.2), GDM, or indicated preterm deliveries were observed. Rates of placenta abruption, SGA, and spontaneous preterm birth did not differ significantly between groups.

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Conclusions: Application of the new ACC–AHA guidelines in a pregnant population identifies a cohort of women who are at increased risk of preeclampsia, gestational diabetes and preterm birth.

Precis

Application of the new American College of Cardiology and American Heart Association Guidelines in pregnancy identifies a cohort of women at increased risk of preeclampsia.

Introduction

The American Heart Association (AHA) and the American College of Cardiology (ACC) Task Force on Clinical Practice Guidelines recently revised the recommendations for diagnosis of chronic hypertension in adults[1]. Citing the strength of evidence that incremental increases in blood pressure increase the risk of cardiovascular disease (CVD), clinical complications, and death, the parameters for the diagnosis of stage 1 hypertension were revised from a systolic blood pressure of 140 mmHg to 130 mmHg and a diastolic blood pressure of 90 mmHg to 80 mmHg. Although the clinical practice guideline extensively outlined the effect of graded blood pressure increases in non-pregnant adults, discussions of pregnancy implications are limited to a brief section on prevention of severe hypertension and the teratogenicity of various anti-hypertensive agents.

Women entering pregnancy with pre-existing hypertension have increased pregnancy-related morbidity, including an increased risk of preeclampsia, preterm delivery, a small for gestational age (SGA) infant, placental abruption, and stillbirth[2,3]. As such, women with chronic hypertension in pregnancy are managed with additional maternal and fetal monitoring as well as prophylaxis with low-dose aspirin[4]. Multiple randomized trials and meta-analyses have shown that treatment with low-dose aspirin during pregnancies complicated by chronic hypertension reduces these risks, particularly the risks of preeclampsia and indicated preterm delivery without apparent harm[2,5–8]. However, studies of universal low-dose aspirin treatment in low-risk, normotensive women have not as clearly shown these benefits[9–11].

We considered that maternal and neonatal outcomes in otherwise healthy women entering pregnancy with newly identified stage 1 hypertension by the revised guidelines (systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg) may be worse compared to normotensive women, and that low-dose aspirin may mitigate these adverse maternal and neonatal outcomes in affected women.

Materials and Methods

This is a secondary analysis of data collected in a randomized, double-blinded, placebo controlled trial of low-dose aspirin for prevention of preeclampsia in nulliparous, low-risk women[9]. The study was conducted at seven centers in the United States within the Maternal Fetal Medicine Unit Network of the National Institute of Child Health and Human Development (NICHD) between 1989 and 1992. The original study design, population, and findings have been previously reported[9], and the data are publicly available through the

NICHD Data and Specimen Hub (DASH). Studies were approved and monitored by each institution's respective Institutional Review Board, and subjects provided written informed consent prior to study participation.

Briefly, nulliparous women with a singleton pregnancy between 13 and 25 weeks of gestation were recruited. Exclusion criteria included a diagnosis of chronic hypertension (>135/85 mmHg), renal disease, diabetes, and proteinuria on a dipstick urine analysis. Eligible women were assigned to a single-blind compliance test and were considered compliant if they ingested at least half of 10 placebo tablets during a 10-day run-in period. Women passing the run-in phase were randomly assigned to receive either 60mg aspirin or placebo (lactose) daily from the time of randomization until delivery.

Maternal blood pressure was measured by study staff using a mercury sphygmomanometer with patients seated comfortably in a quiet location following a 10 minute rest as previously described[12]. Multiple cuff sizes were available to ensure use of the appropriate size based on the patient's arm circumference. Maternal and neonatal outcome data were collected on women and their newborns via medical record extraction. For this analysis, data were analyzed with subjects classified according to blood pressure measurement at enrollment (≤25 weeks of gestation). Women with a systolic blood pressure 130–139mmHg or diastolic blood pressure of 80–89mmHg were newly identified with stage 1 hypertension under the recent ACC–AHA guidelines[1] and compared to women with blood pressure below 130mmHg systolic and 80mmHg diastolic. Of important note, due to eligibility criterion excluding women with chronic hypertension (>135/85 mmHg) at enrollment, the enrollment blood pressure range within the stage 1 hypertension group was limited to lower-range stage 1 hypertension, i.e. 130–135 and/or 80–85mmHg. We also performed an additionally sensitivity analysis restricting our sample to women who were enrolled prior to 20 weeks of gestation (n=1661). Our primary outcome was preeclampsia, the diagnosis of which was adjudicated by the blinded (to treatment allocation) principal investigator of each study site. Secondary outcomes included small for gestational age infant, placental abruption, indicated or spontaneous preterm delivery (PTD), and neonatal intensive care unit (NICU) admission. Preeclampsia was defined using guidelines in place at the time as hypertension (≥140 mmHg systolic or 90 mmHg diastolic onset after 20 weeks of gestation) plus proteinuria (either ≥300mg per 24 hours or 2+ or more by dipstick on two or more occasions)[9]. Severe preeclampsia was defined as severe hypertension (≥160/110mmHg) and proteinuria; urinary protein excretion ≥5 grams per day with any degree of hypertension; hypertension complicated by pulmonary edema or thrombocytopenia (≤100,000); hemolysis, elevated liver function tests and a low platelet count (HELLP syndrome). Small for gestational age was defined as a birth weight below the 10th percentile[13]. Indicated preterm delivery was defined as delivery performed for maternal or fetal indications prior to 37 weeks of gestation. Spontaneous preterm delivery denotes delivery prior to 37 weeks after spontaneous preterm labor or premature rupture of membranes. The diagnosis of placental abruption was by clinical findings of vaginal bleeding and uterine tenderness. NICU admission was collected from the infant medical record.

Statistical analysis was conducted using STATA software, version 14 (StataCorp, College Station, TX). Continuous variables were compared using student t-tests and Wilcoxon-Mann

Whitney tests as appropriate. Categorical variables were analyzed using Chi-square or Fisher's exact where appropriate. Multivariable analysis included log binomial regression to evaluate the independent association between enrollment systolic and diastolic blood pressure (as a discrete variable: hypertensive versus normal) and preeclampsia in women treated with aspirin and placebo. Adjustment covariates were chosen *a priori* based on previous literature and included age, body mass index (BMI), race, and smoking. Results were presented as adjusted risk ratios with corresponding 95% confidence intervals, and a p-value <0.05 was considered statistically significant. No adjustments were made for multiple comparisons as *a priori*, preeclampsia was our primary endpoint.

Results

Of the 3134 nulliparous women enrolled in the original study, 2947 with singleton pregnancies and complete data were included in this analysis (Table 1). Eighty-nine women (3%) were excluded due to missing BMI data, otherwise no other outcome or covariate data were missing. Most of the study population (94.4% or n=2783) was normotensive prior to 25 weeks of gestation, and 164 (5.6%) women were newly identified with stage 1 hypertension according to the current ACC–AHA guidelines. Both groups had similar gestational age at delivery and infant birth weights. The normotensive group tended to be slightly younger, thinner and were more likely to be white or Hispanic compared to women with stage 1 hypertension (Table 1). Women with newly classified stage 1 hypertension randomized to receive placebo or aspirin were also similar at enrollment (Table 2).

In the group of women randomized to receive placebo (n=1482), the incidence of preeclampsia was significantly increased in women with newly identified stage 1 hypertension compared to normotensive women, 15.3% versus 5.4%, risk ratio (RR) 2.66; 95% confidence interval (CI) 1.56–4.54), p<0.001 (Table 3). This appeared to be a result of an increase in cases of both mild and severe preeclampsia diagnoses. The prevalence of mild preeclampsia tripled, from 2.9% in normotensive women to 9.2% in stage 1 hypertensive women (p=0.001). Cases of severe preeclampsia more than doubled, shown by a prevalence of 2.5% in normotensive women versus 6.1% in stage 1 hypertensive women, p=0.04. (Table 3). Stage 1 hypertensive women randomized to placebo had more indicated preterm deliveries (4.2% vs. 1.1% respectively, p=0.01) and an increased incidence of gestational diabetes (6.1% vs. 2.5%, p=0.03). Rates of placental abruption, SGA infants, NICU admission, and spontaneous preterm delivery were not different between groups. Similarly, systolic blood pressures 120–129 mmHg or diastolic blood pressures 70–79 mmHg were associated with an increased risk of preeclampsia, with a preeclampsia incidence of 7.6% compared to 4.1% among women with lower blood pressures (RR 1.83; 95%CI 1.35–2.49). In a sensitivity analysis, we included only women with an enrollment blood pressure measured <20 weeks of gestation with similar findings (Appendix 1, available online at http://links.lww.com/xxx). Additionally, given the change in the diagnostic criteria for preeclampsia deemphasizing the importance of proteinuria, we repeated our analysis including both preeclampsia and gestational hypertension and also found an increased risk for gestational hypertension and preeclampsia when entering pregnancy with newly classified stage 1 hypertension RR 1.87 (95%CI 1.36–2.57).

Participants with stage 1 hypertension randomized to receive aspirin did not display the same increase in preeclampsia prevalence seen in the stage 1 hypertensive women receiving placebo. When treated with aspirin, there was no statistically significant difference in the rate of preeclampsia in stage 1 hypertensive women compared to normotensive women (7.6% versus 4.4%, p=0.2) (Table 3). The increases in indicated preterm delivery and gestational diabetes observed in stage 1 hypertensive women taking placebo were also reduced in hypertensive women taking aspirin (Table 3). As in the placebo group, rates of placental abruption, SGA infants, spontaneous PTD, and NICU admission were not statistically different between groups randomized to receive aspirin.

In comparison with normotensive women receiving placebo, stage 1 hypertension was associated with an increased risk of preeclampsia (risk ratio (RR) 2.06; 95% CI, 1.14–3.73) after adjusting for age, race, and pre-pregnancy BMI (Table 4). Classification of stage 1 hypertension by either systolic or diastolic blood pressure were both observed to be associated with this increased risk of preeclampsia (data not shown). Compared to normotensive women receiving placebo, prophylaxis with low-dose aspirin in women with stage 1 hypertension was not associated with the same increased risk of preeclampsia, (RR 1.01; 95% CI 0.43–2.36). Prophylaxis with low-dose aspirin had no significant effect on women entering pregnancy as normotensive (RR 0.80; 95% CI 0.57–1.11). When evaluating risk between stage 1 hypertensive women randomized to aspirin prophylaxis, contrasted to stage 1 hypertensive women receiving placebo, the risk of both mild and severe preeclampsia was not significantly reduced with aspirin (RR 0.66; 95% CI 0.21–2.06) and (RR 0.25; 95%CI 0.03–2.02), respectively (Table 5).

Discussion

In this study, application of the current ACC–AHA guidelines in a pregnant population shows higher rates of maternal complications in women entering pregnancy with newly classified stage 1 hypertension compared to women who are normotensive. In our cohort, these women have preeclampsia rates in-between women with stage 2 chronic hypertension (BP≥140/90) and women with normotension, with 15.3% of stage 1 chronic hypertensive women developing preeclampsia, compared to 5.4% of normotensive women and 25% of women with stage 2 chronic hypertension[14].

This study is limited by our use of blood pressure measurements during pregnancy for reclassification of chronic hypertension diagnoses. While pre-pregnancy blood pressures would be ideal for diagnosis, prior studies have shown that women do not consistently seek primary care outside of pregnancy. In the United States, pre-conception care engagement rates are between 18–45% in reproductive-age women, thus early pregnancy blood pressures may be all that is available for the obstetrician[15]. Further, patients were recruited into the study up to 25 weeks gestational age, and therefore the enrollment blood pressure could have been collected past the 20 weeks of gestation milestone established by the US Preventive Task Force for diagnosis of chronic hypertension in pregnancy. To address this limitation, we confirmed our findings in a sensitivity analysis restricting our cohort to women <20 weeks of gestation.

The scientific rigor of the standardized measurement of blood pressure by study staff is a strength of these data along with the large study size considering the challenges and burden of conducting a clinical trial in thousands of pregnant participants. However, there are limitations to this secondary analysis that should also be considered. The original study's eligibility criteria excluded women with an enrollment blood pressure >135/85mmHg, thereby halving the range of mmHg available in these data for newly identifying mothers with stage 1 hypertension (130–135/80–85 mmHg). However, this narrowed eligibility criteria likely renders our results to be more conservative, and we would anticipate an even more robust effect in a population with blood pressures spanning the full diagnostic range (130–139/80–89mmHg). Moreover, we observed intake systolic blood pressure between 120–129 mmHg was also associated with an increased risk of preeclampsia, with a smaller magnitude of risk compared to stage 1 hypertension. These findings suggest preliminarily that when considering preeclampsia risk based on early pregnancy blood pressure, perhaps blood pressure could be considered as a continuous variable rather than categorical. It is also important to note the small sample of women within this clinical trial with blood pressures that met the new ACC–AHA criteria for stage 1 hypertension (n= 164).

Also important to consider is that the enrollment blood pressures as collected by the original study is a single reading, and the ACC–AHA guidelines recommend use of blood pressure averages of ≥2 readings obtained on ≥2 occasions. Finally, this secondary analysis is performed on a cohort recruited between 1989 and 1992. Unquestionably, the demographics of this group differ from a contemporaneous cohort with advancing maternal age and increasing rates of obesity. The diagnostic criteria for preeclampsia should also be considered as they have since changed, limiting our ability to broadly apply our findings to current clinical practice[2]. When we repeat our analysis utilizing the updated diagnostic criteria for preeclampsia, our findings are unchanged.

As the adoption of the new ACC-AHA guidelines becomes more widespread, there will be an increasing number of reproductive age women who will fall into the category of stage 1 hypertension. Our study provides evidence that stage 1 hypertension is associated with an increased risk of adverse pregnancy outcomes and raises the possibility that aspirin prophylaxis may be beneficial in this group.

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Appendix 1.: Maternal and Neonatal Outcomes in Normotensive and Stage 1 Hypertensive Women Classified With Enrollment Blood Pressure Measured <20 Weeks of Gestation and Randomized to Receive Placebo or Low-Dose Aspirin (N=1661)

	PLACEBO			ASPIRIN		
	Normotension N=766	Stage 1 Hypertension N=54	P value	Normotension N=803	Stage 1 Hypertension N=38	P value
Preeclampsia	47 (6.1)	9 (16.7)	0.003	40 (5.0)	2 (5.3)	0.9
Mild Preeclampsia	25 (3.3)	6 (11.1)	0.003	23 (2.9)	2 (5.3)	0.4
Severe Preeclampsia	22 (2.9)	3 (5.6)	0.3	17 (2.1)	0	0.4
Gestational diabetes	19 (2.5)	4 (7.4)	0.04	26 (3.4)	1 (2.6)	0.8
Placental abruption	1 (0.1)	0	0.8	6 (0.8)	0	0.6
Small for gestational age	41 (5.4)	7 (13.0)	0.02	40 (5.0)	3 (7.9)	0.4
Indicated PTD	9 (1.2)	1 (1.9)	0.7	17 (2.1)	0	0.4
Spontaneous PTD	61 (8.0)	2 (3.8)	0.3	60 (7.5)	3 (8.1)	0.9
NICU admission	77 (10.1)	5 (9.3)	0.9	62 (7.7)	5 (13.2)	0.2

Data presented as n (%); PTD= preterm delivery, NICU= neonatal intensive care unit.

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Table 1.

Maternal characteristics at study enrollment by hypertensive group

Characteristic	Normotension	Stage 1 Hypertension*	P value
n	2783	164	NA
Age	20.4 ± 4.5	21.9 ± 5.5	<0.001
Pre-pregnancy Body Mass Index (kg/m^2)	23.5 ± 4.7	27.7± 6.8	<0.001
Predominant Race Non-Hispanic White African American Hispanic Other	480 (17.3) 1,391 (50.0) 888 (31.9) 24 (0.1)	41 (25.0) 92 (56.1) 31 (18.9) 0	0.001
Smoker at start of pregnancy	586 (21.1)	39 (23.8)	0.4
Gestational age at delivery (weeks)	38.8 ± 2.9	38.7± 3.6	0.5
Birth weight (grams)	3214 ± 581	3214 ± 679	0.7
Systolic blood pressure (mmHg) **	105 ± 10	124± 9	<0.001
Diastolic blood pressure (mmHg) **	60 ± 8	76± 7	<0.001

* Stage 1 hypertension= systolic blood pressure 130-135 mmHg or diastolic 80-85 mmHg;

** Measured at enrollment (13-25 weeks of pregnancy)

Data are presented as mean ± standard deviation or n (%)

Table 2.

Maternal characteristics as study enrollment by randomization group in stage 1 hypertensive women

	Placebo	Aspirin	P value
n	98	66	NA
Age	22.4 ± 5.9	21.3 ± 4.8	0.3
Pre-pregnancy BMI	28.0 ± 7.4	27.3 ± 5.9	0.9
Race White,non-Hispanic African American Hispanic	26 (26.5) 52 (53.1) 20 (20.4)	15 (22.7) 40 (60.6) 11 (16.7)	0.6
Smoker at start of pregnancy	24 (24.5)	15 (22.7)	0.8
Gestational age at delivery (weeks)	38.6 ± 3.3	38.7 ± 4.1	0.1
Birth weight (grams)	3197 ± 674	3240 ± 691	0.4
Systolic blood pressure (mmHg) **	125 ± 8	122 ± 10	0.07
Diastolic blood pressure (mmHg) **	75 ± 7	77 ± 7	0.2

* Stage 1 hypertension= systolic blood pressure 130-135 mmHg or diastolic 80-85 mmHg;

** Measured at enrollment (13-25 weeks of pregnancy); BMI= body mass index

Data are presented as mean ± standard deviation or n (%)

Table 3.

Maternal and neonatal outcomes in normotensive and stage 1 hypertensive women randomized to receive placebo or low-dose aspirin

	PLACEBO			ASPIRIN		
Outcome	**Normo-tension N=1384**	**Stage 1 Hyper-tension N=98**	**RR (95% CI)**	**Normo-tension N=1399**	**Stage 1 Hyper-tension N=66**	**RR (95% CI)**
Preeclampsia	75 (5.4)	15 (15.3)	2.66 (1.56-4.54)	61 (4.4)	5 (7.6)	1.74 (0.72-4.18)
Mild Preeclampsia	40 (2.9)	9 (9.2)	3.21 (1.61-6.42)	33 (2.4)	4 (6.1)	2.57 (0.94-7.04)
Severe Preeclampsia	35 (2.5)	6 (6.1)	2.04 (0.82-5.09)	28 (2.00)	1 (1.5)	0.76 (0.10-5.48)
Gestational diabetes	34 (2.5)	6 (6.1)	2.51 (1.08-5.84)	50 (3.6)	2 (3.0)	0.84 (0.21-3.40)
Placental abruption	2 (0.2)	0	NA	11 (0.8)	0	NA
Small for gestational age	77 (5.6)	10 (10.2)	1.67 (0.86-3.22)	65 (4.7)	5 (7.6)	1.63 (0.68-3.91)
Indicated PTD	15 (1.1)	4 (4.2)	3.83 (1.30-11.31)	27 (1.9)	0	NA
Spontaneous PTD	109 (7.9)	4 (4.2)	0.53 (0.20-1.41)	107 (7.7)	5 (7.7)	1.02 (0.43-2.42)
NICU admission	120 (8.7)	12 (12.2)	1.31 (0.73-2.34)	111 (7.9)	8 (12.1)	1.53 (0.78-3.00)

Data presented as n (%) and risk ratios (95% confidence interval); PTD= preterm delivery, NICU= neonatal intensive care unit; RR= risk ratio; CI= confidence interval

Table 4.

Risk of adverse maternal and neonatal outcomes in normotensive and new stage 1 hypertensive women receiving placebo or low-dose aspirin

	PLACEBO		ASPIRIN	
Outcome	**Normo-tension N=1384**	**Stage 1 Hypertension N=98**	**Normotension N=1399**	**Stage 1 Hypertension N=66**
Preeclampsia	1.00 (ref)	RR 2.82 (1.69-4.73) aRR 2.06 (1.14-3.73)	RR 0.80 (0.58-1.12) aRR 0.80 (0.57-1.11)	RR 1.40 (0.58-3.34) aRR 1.01 (0.43-2.36)
Mild Preeclampsia	1.00 (ref)	RR 3.18 (1.59-6.36) aRR 2.17 (0.95-5.00)	RR 0.82 (0.52-1.29) aRR 0.81 (0.51-1.28)	RR 2.10 (0.77-5.69) aRR 1.44 (0.54-3.86)
Severe Preeclampsia	1.00 (ref)	RR 2.42 (1.04-5.62) aRR 1.81 (0.74-4.38)	RR 0.79 (0.48-1.29) aRR 0.78 (0.48-1.27)	RR 0.60 (0.08-4.31) aRR 0.46 (0.06-3.30)
Gestational diabetes	1.00 (ref)	RR 2.49 (1.07-5.78) aRR 0.84 (0.29-2.42)	RR 1.46 (0.95-2.24) aRR 1.50 (0.97-2.31)	RR 1.23 (0.30-5.02) aRR 0.73 (0.16-3.27)
Small for gestational age	1.00 (ref)	RR 1.83 (0.98-3.43) aRR 2.16 (1.12-4.16)	RR 0.84 (0.61-1.15) aRR 0.86 (0.62-1.19)	RR 1.36 (0.57-3.25) aRR 1.60 (0.68-3.78)
Indicated PTD	1.00 (ref)	RR 3.79 (1.28-11.20) aRR 3.98 (1.36-11.70)	RR 1.78 (0.95-3.33) aRR 1.75 (0.92-3.34)	NA
Spontaneous PTD	1.00 (ref)	RR 0.66 (0.27-1.57) aRR 0.78 (0.32-1.90)	RR 0.96 (0.74-1.24) aRR 0.95 (0.73-1.24)	RR 0.98 (0.41-2.32) aRR 1.08 (0.46-2.52)
NICU admission	1.00 (ref)	RR 1.41 (0.81-2.47) aRR 0.97 (0.53-1.78)	RR 0.92 (0.71-1.17) aRR 0.93 (0.73-1.19)	RR 1.40 (0.71-2.73) aRR 1.31 (0.64-2.69)

Data are risk ratios (95% confidence interval). aRR: risk ratios with adjustment for pre-pregnancy BMI, race, and maternal age; PTD= preterm delivery, NICU= neonatal intensive care unit

Table 5.

Risk of adverse maternal and neonatal outcomes in stage 1 hypertensive women randomized to aspirin compared to placebo

	PLACEBO N=96	ASPIRIN N=65
Preeclampsia	1.00 (ref)	0.49 (0.19-1.30)
Mild Preeclampsia	1.00 (ref)	0.66 (0.21-2.06)
Severe Preeclampsia	1.00 (ref)	0.25 (0.03-2.02)
Small for gestational age	1.00 (ref)	0.74 (0.26-2.08)
Spontaneous PTD	1.00 (ref)	1.49 (0.45-4.97)
NICU admission	1.00 (ref)	0.99 (0.43-2.30)

Data are risk ratios (95% confidence interval); PTD= preterm delivery, NICU= neonatal intensive care unit