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Prenatal Vitamin C and E Supplementation in Smokers is Associated with Reduced Placental Abruption and Preterm Birth: A Secondary Analysis

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Abstract

OBJECTIVE—Smoking and Preeclampsia (PE) are associated with increases in preterm birth, placental abruption and low birth weight. We evaluated the relationship between prenatal vitamin C/E supplementation and perinatal outcomes by maternal self-reported smoking status focusing on outcomes known to be impacted by maternal smoking.

DESIGN/POPULATION—A secondary analysis of a multi-center trial of vitamin C/E supplementation starting at 9–16 weeks in low-risk nulliparous women with singleton gestations.

METHODS—We examined the effect of C/E by smoking status at randomization using the Breslow-Day test for interaction.

MAIN OUTCOME MEASURES—The trial's primary outcomes were PE and a composite outcome of pregnancy-associated hypertension (PAH) with serious adverse outcomes. Perinatal outcomes included preterm birth and abruption.

RESULTS—There were no differences in baseline characteristics within subgroups (smokers vs. non-smokers) by vitamin supplementation status. The effect of prenatal vitamin C/E on the risk of PE (p=0.66) or PAH composite outcome (p=0.86) did not differ by smoking status. Vitamin C/E was protective for placental abruption in smokers [RR of 0.09 (95% CI 0.00, 0.87)], but not in non-smokers [RR 0.92 (0.52, 1.62)] (p= 0.01), and for preterm birth in smokers [RR 0.76 (0.58, 0.99)] but not in non-smokers [RR 1.03 (0.90, 1.17)] (p= 0.046).

CONCLUSION—In this cohort of women, smoking was not associated with a reduction in PE or the composite outcome of PAH.. Vitamin C/E supplementation appears to be associated with a reduction in placental abruption and preterm birth among smokers.

Tweetable abstract—Vitamin C/E associated with a reduction in placental abruption and preterm birth among smokers.

Keywords

Smoking; Placental abruption; Preterm birth

Introduction

Multiple studies have identified maternal tobacco use as one of the strongest modifiable risk factors for intrauterine growth restriction (IUGR). Smoking is also implicated in other adverse pregnancy outcomes such as preterm birth, placental abruption, and stillbirth.[1–3] Further, there is a dose response to cigarette smoke and pregnancy complications. [4] The mechanisms leading to growth restriction and adverse outcomes following in-utero tobacco exposure are also poorly understood. One proposed mechanism is that nicotine may have direct effects on the uterine and umbilical vessels, causing vasoconstriction and subsequent compromise of utero-placental circulation and chronic fetal hypoxia.[5]

Preeclampsia (PE) is associated with adverse pregnancy outcomes similar to those found among pregnancies complicated by maternal tobacco use. Numerous studies have shown that smoking decreases the risk of PE by up to 32%.[6] Combustion products of cigarette smoke have also been implicated in smoking related adverse pregnancy outcomes and the

reduced risk of PE among smokers. [7] Some investigators have hypothesized that both smoking and PE are associated with alterations in hypoxia responsive pathways and circulating angiogenic factors.[8, 9] Among women with PE who smoke, there is an increase in the risk of adverse pregnancy outcomes compared to preeclamptic women who do not smoke.[10] These studies showed that smoking decreases the risk of PE, but smokers with PE have a 2–6 fold increased risk of adverse pregnancy outcomes when compared to non-smoking women with PE. [8] This paradoxical association is not completely understood.

Smoking is associated with reduced dietary intake as well as decreased consumption of vitamin C. [11] In humans and animals low birth weight has been associated with diets low in vitamin C even after controlling for smoking status. [12, 13] Like smokers, women with PE have lower circulating levels of vitamin C, heightened inflammation, and evidence of oxidative damage; these observations have prompted numerous multicenter trials of combined vitamin C and E prophylaxis during pregnancy. [13]

Therefore, although the risk of PE overall is not influenced by Vitamin C/E supplementation,[14, 15] we hypothesized that the effects of antioxidant supplementation with vitamin C and E may differ by smoking status, leading to sub-group specific reductions in the adverse maternal, fetal, or neonatal outcomes related to pregnancy-associated hypertension (PAH) and tobacco use.

Methods

We performed a secondary analysis of the NICHD Maternal-Fetal Medicine Units Network multicenter randomized, double–masked trial of low risk nulliparas assigned to daily vitamin C and E supplementation or matching placebo to prevent PAH.[14] The trial was conducted from July 2003 through February 2008 and included 16 participating centers. Eligibility criteria included singleton gestation between 9 weeks 0 days and 16 weeks and 6 days at time of randomization.[16] Gestational age was determined before randomization by a previously described algorithm using the date of the last menstrual period (if reliable) and the results of the earliest ultrasound examination. Women were excluded for preexisting hypertension or proteinuria, intake of more than 150 mg of vitamin C or more than 75 IU of vitamin E daily, pregestational diabetes, treatment with antiplatelet drugs, serious medical complication, known fetal anomaly or aneuploidy, or illicit drug or alcohol abuse. Eligible women were randomly assigned to receive either a combination of 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E (RRR-alpha-tocopherol acetate) or matching placebo (mineral oil) with stratification by clinical center[17]. All data were collected by certified research personnel at the clinical centers and uploaded to a database that was managed by an independent data coordination center. The diagnosis of the key study outcomes were confirmed by central review by at least three reviewers of de-identified medical charts of all women with PAH, PE, and the composite outcome. The institutional review board at each clinical site and the data coordination center approved the study. All participants provided written informed consent before enrollment.

For this secondary analysis of women randomized to vitamin or placebo supplementation, we examined outcomes by smoking status. Smoking status was self-reported as never

smoked, quit smoking before the start of pregnancy, quit smoking after start of pregnancy, or currently smoking. Those women who reported any smoking during pregnancy (quit smoking after the start of pregnancy or currently smoking) were classified in the smoking group. The average number of cigarettes/day was recorded for the patients in the currently smoking group.

The main outcomes of interest were maternal or fetal outcomes potentially influenced by maternal smoking status. The maternal outcomes included PE (overall, severe and early onset), the trial composite of adverse outcomes associated with PAH, gestational hypertension, placental abruption, and preterm premature rupture of membranes (PPROM). The composite outcome was defined as severe hypertension OR mild hypertension with elevated liver enzymes, elevated serum creatinine, thrombocytopenia, eclampsia, small for gestational age (<3rd centile), medically indicated preterm birth or perinatal death. Mild PE was defined as mild PAH (≥140/90 mmHg on two occasions 2–240 hours apart) with documentation of proteinuria within 72 hours before or after an elevated blood-pressure measurement. Proteinuria was defined as total protein excretion of 300 mg or more in a 24-hour urine sample or 2+ or higher on dipstick testing, or a protein –to-creatinine ratio of 0.35 or more if a 24-hour urine sample was not available. Severe PE was defined as PE with either severe PAH (≥160/110 on two occasions 2240 hours apart, or a single occurrence treated with antihypertensive medications) or protein excretion of 5 g or more in a 24-hour urine sample or as mild pregnancy–associated hypertension with oliguria (<500 ml in a 24-hour urine sample), pulmonary edema (confirmed by radiography), or thrombocytopenia (platelet count of <100,000 per cubic millimeter). PE included mild and severe preeclampsia, HELLP and eclampsia. Early PE was defined as onset of diagnosis prior to 34 weeks gestation. PPROM was defined as spontaneous rupture of membranes and one of the following: membrane rupture 60 minutes or more before the onset of labor, labor induced for pre-labor ruptured membranes, or no labor and onset of rupture 60 minutes or more before delivery.

Neonatal outcomes included: preterm birth (categorized as delivery either prior to 37 weeks' gestation or prior to 32 weeks' gestation), small for gestational age (SGA; birthweight <3rd centile or <10th centile), and a composite perinatal morbidity (including RDS, sepsis, retinopathy of prematurity, intraventricular hemorrhage, or necrotizing enterocolitis).

Categorical variables were compared using the chi-square test and continuous variables using the Wilcoxon rank-sum test. The incidence, relative risk, and 95% confidence interval relating the outcomes of interest to Vitamin C and E supplementation status within each subgroup (smokers and nonsmokers) were computed. Exact confidence intervals were computed as appropriate. For each outcome, the Breslow-Day test for homogeneity was used to estimate if there was a difference in treatment effect (Vitamin C/E supplementation vs. placebo) between smokers and non-smokers. For all outcomes, a nominal p value less than 0.05 was considered to indicate statistical significance. Analysis was performed using SAS software (Cary, NC).

Results

Of the 10,154 women randomized to the trial, 9,969 had outcome data available for analysis (4,993 were assigned to receive vitamins, and 4,976 were assigned to receive placebo). Of the 9,969 women, 1,551 (16%) self-reported current tobacco use during the pregnancy (n=571) or having quit after the start of pregnancy (n=980), and 8,418 (84%) reported never having smoked or quitting before the start of pregnancy. Of the currently smoking population, 49% (n=280) reported smoking 0–4 cigs/day and 51% (n=291) reported ≥ 5 cigs/day. Of the selfreported tobacco users, 51% (n=788) received vitamin C and E supplementation and 49% (n=763) received placebo. Of the women without tobacco use, 50% (n=4,205) received vitamin supplementation, and 50% (n=4,213) received placebo.

Table 1 shows patient characteristics for the subgroups of smokers and non-smokers, by vitamin C/E vs. placebo. Overall, there were no differences in baseline characteristics including maternal age, race/ethnicity, BMI and previous pregnancy between treatment groups within smoking categories. Mean gestational age at entry was approximately 13 weeks.

The effect of vitamin C/E supplementation on selected maternal outcomes stratified by smoking status are presented in Table 2. The effect of vitamin supplementation on PE (p=0.66) and the composite outcome of PAH (p=0.86) did not differ by smoking status; vitamin supplementation did not reduce these outcomes in either group. Similar findings were observed for pregnancy associated hypertension, PPROM, severe PE and early onset PE (Table 2). However, vitamin C/E supplementation was associated with a significantly lower risk of placental abruption in smokers RR of 0.09 (95% CI 0.00, 0.87) but not in non-smokers (RR 0.92; 95% CI (0.52, 1.62), with the p-value for interaction <0.01.

Results for selected neonatal outcomes are presented in Table 3. There was no significant difference in vitamin effect by smoking status for SGA<3rd% (p=0.28), NICU admissions (p=0.13), neonatal morbidity (p=0.44) and neonatal composite outcome (p=0.54). However, the risk for preterm birth <37 weeks was significantly reduced among smokers receiving vitamin supplementation (RR 0.76; 95% CI 0.58, 0.99) but not in non-smokers (RR 1.03; 95% CI 0.90, 1.17), with p-value for interaction < 0.05. The incidence of preterm birth (<37 weeks) among smokers in the placebo group was 13.9%. The incidence was reduced to 10.5% in smokers receiving vitamin C/E, which was comparable to non- smokers (10.0% in placebo group and 10.2% in vitamins group).

In additional analyses, we performed subgroup analyses using the number of cigarettes smoked per day (0, 1–4, 5–9 and ≥ 10) and none of the tests for interaction were significant. This may be due to the very small number (n=138) of women that smoked ten or more cigarettes per day. Lastly, we examined the effect of self-reported smoking on pregnancy outcomes regardless of vitamin supplementation. Smoking was associated with increases in most adverse outcomes (Table 4). Rates of PE and placental abruption did not differ significantly by smoking status.

Discussion

Main findings

Vitamin C/E supplementation in this low-risk nulliparous cohort of women had no effect on the primary outcomes of PE, severe PE, or the PAH composite outcome by smoking status. However, we did observe a reduction in placental abruption and preterm birth <37 weeks among smokers assigned to daily vitamin C/E compared with placebo in this secondary analysis. The incidence of preterm birth among smokers was reduced to levels seen among the non-smokers in the cohort (13.9% to 10.5%) with vitamin supplementation however, this was not associated with reduction in neonatal composite outcome or neonatal morbidity. Previous studies have linked vitamin C deficiency to the occurrence of spontaneous preterm birth.[18–20] This may be compounded by maternal tobacco use. There is also evidence indicating that vitamin C/E supplementation in pregnancy may ameliorate deleterious placental effects.[21, 22] Gallo and colleagues proposed that the adverse effects of prenatal smoking on the placenta may be counteracted by antioxidant therapy such as vitamin C and E, two essential nutrients that can scavenge free radicals. In an in vitro model, they were able to demonstrate that vitamin C and E in combination had protective placental properties and can prevent the decrease of glutathione(antioxidant molecule) and increase the secretion of malondialdehyde (oxidative stress molecule); both induced by nicotine.[23]

Similar to our study, a recent systematic review and meta-analysis of nine trials, which included the MFMU Network trial of Vitamin C/E supplementation for the prevention of PE, confirmed no benefit of C/E supplementation on the outcome PE, regardless of maternal risk, while some studies have highlighted adverse maternal effects. In the five trials that included the outcome of placental abruption, all found a decreased risk of 37% among women who received supplementation. [15] Smoking was not considered in this review, and most studies focused on high risk women. With regard to preterm birth, Hauth et al. have already reported reduced preterm births among women receiving daily vitamin supplementation prior to 32 weeks of gestation in this cohort which was attributed to a reduction in preterm PROM.[20] While smoking was controlled for in this study, the potential interaction with smoking was not addressed. However, smoking is associated with an increased rate of preterm birth prior to 32 weeks of gestation.[24]

We found that self-reported smoking was associated with increased incidences of the maternal composite outcome, neonatal composite outcome, preterm birth, low birth weight and small for gestational age which is consistent with previous studies[1–3]. Surprisingly, in this cohort, smoking was not associated with a decreased rate of preeclampsia. Although these findings, specifically the lack of risk reduction for preeclampsia among smokers is contradictory to previous reported literature.[7, 8, 24] It is possible that the large proportion (~50%) of women identified as smokers in this study who smoked less than 5 cigarettes per day contributed to this result by reducing the dose of cigarette smoke in our smoking group.[4] Secondly, our study consisted of a large proportion of African American and Hispanic women, who were not equally distributed between smokers and non-smokers, which could potentially influence the interpretation of our outcomes data.[25] More recent literature suggests that tobacco use during pregnancy and its risk of PE is dependent on timing of

exposure, specifically that smoking habits in the middle or late rather than in the beginning of pregnancy that seem to affect the risk of PE.[7] Our study is limited by the knowledge of smoking habits only at recruitment, or early in the pregnancy, among this cohort. As in our study, other investigators have shown that although smoking decreases the risk of PE, women who smoke during their pregnancy and develop PE have an increased risk of adverse pregnancy outcomes, i.e. preterm birth (OR 5.77), abruption (OR 6.16), and stillbirth (OR 3.39) when compared with nonsmoking preeclamptics.[8]

Strengths/Limitations

This study is not without limitations. Although the findings for abruption and preterm birth were statistically different by smoking status, the possibility that they were the result of Type I (alpha) error is a plausible explanation. We conducted multiple comparisons for our analysis and the likelihood of two positive chance findings especially given the test for interaction was significant for only two outcomes must be taken into consideration as a limitation of our study Alternatively, in patients who smoke, only in the outcomes that were significantly influenced by smoking in the cohort would vitamin C/E supplementation have potential effectiveness. Another limitation is the small number of cases of abruption, as a slight change in the numbers may materially change our results, and a definitive association between vitamin intake and reduction in adverse outcomes therefore cannot be made.

Interpretation

However, we did note a higher rate of placental abruption in the smokers who received placebo (1.5%) when compared to the smokers receiving vitamin C/E (0.1%) and the non-smoking group (0.6%) which is consistent with previously reported adverse outcomes among smokers. Another potential limitation is the reliance on self-reported tobacco use in our cohort. However, self admission to tobacco use has been well validated based on prior publications demonstrating high concordance with serum and urine cotinine levels.[26–29] We would anticipate that error in self reported smoking would trend toward under-reporting which would introduce error into the large non-smoking control group for our study. We acknowledge that analysis of blood samples would enhance our findings and future projects.

Conclusion

In summary, our findings suggest the possibility that maternal supplementation with vitamin C and E among smokers may reduce the risk of placental abruption and preterm birth <37 weeks. We do not believe a trial of supplementation restricted only to pregnant women who smoke is indicated at this time because there have been several trials of vitamin C/E supplementation for PE prevention.[14, 30–36] Additional systematic reviews and even individual patient data meta-analysis combining the data and patients from these randomized trials with consideration of smoking status may further assess the robustness of and validate our findings. Such studies should specifically examine abruption and preterm birth. Although smoking cessation remains the most important intervention to prevent these outcomes in smokers, [2–3,8] unfortunately this is not achieved in a considerable proportion of pregnant patients. Therefore, the potential role of vitamin C/E supplementation as an adjunctive intervention in this at-risk group to prevent adverse outcomes deserves further investigation.

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Appendix

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Table 1

Patient Characteristics by Smoking Status and Vitamin C/E Supplementation*

Subject Characteristics		Smoker Placebo (n = 763)	Smoker Vitamins (n = 788)	p-Value	Non- Smokers Placebo (n = 4213)	Non- Smoker Vitamins (n = 4205)	p- Value
Age – years		22.2±4.6	22.4±4.6	0.31	23.8±5.3	23.7±5.3	0.43
Gestational age at randomization – week		13.1±2.2	13.1±2.2	0.54	13.5±2.1	13.4±2.1	0.69
Race or ethnic group – n (% within treatment group)	Caucasian	382 (50.1%)	428 (54.3%)	0.29	1698 (40.3%)	1678 (39.9%)	0.59
	African American	292 (38.3%)	265 (33.6%)		981 (23.3%)	980 (23.3%)	
	Hispanic	82 (10.7%)	88 (11.2%)		1442 (34.2%)	1471 (35.0%)	
	Other	7 (0.9%)	7 (0.9%)		92 (2.2%)	76 (1.8%)	
Pre-pregnancy body mass index – kg/m^2		26.6±7.1	26.2±6.7	0.57	25.2±5.7	25.2±5.9	0.55
Total years of schooling		12.3±2.0	12.3±2.0	0.88	12.9±2.8	12.9±2.8	0.80
Use of prenatal vitamins or multivitamins prior to randomization – n (%)		656 (86.0%)	687 (87.2%)	0.49	3182 (75.5%)	3166 (75.3%)	0.80
Previous pregnancy – n (%)		260 (34.1%)	234 (29.7%)	0.06	889 (21.1%)	904 (21.5%)	0.66
Family history of preeclampsia – n (%)		113 (14.8%)	89 (11.3%)	0.04	546 (13.0%)	549 (13.1%)	0.90
Blood pressure at entry (9–16 weeks) – mmHg	Systolic	110±10	111±10	0.11	109±10	109±10	0.82
	Diastolic	65±8	65±8	0.22	65±8	66±8	0.19
Drinking alcohol during pregnancy		170 (22.3%)	165 (20.9%)	0.52	397 (9.4%)	383 (9.1%)	0.62

*Plus-minus values are mean ± standard deviation

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Table 2

Effect of Vitamin C/E Supplementation on Maternal Outcomes by Smoking Status

Outcome	Smoker Placebo (n = 763)	Smoker Vitamins (n = 788)	Non-Smokers Placebo (n = 4213)	Non-Smoker Vitamins (n = 4205)	Smokers	Non-Smokers	B-D Test*
					Relative Risk (95% CI)	Relative Risk (95% CI)	p- Value
Preeclampsia	52/763 (6.8%)	62/788 (7.9%)	280/4213 (6.6%)	296/4205 (7.0%)	1.15 (0.81,1.65)	1.06 (0.90,1.24)	0.66
Primary Composite Outcome†	58/763 (7.6%)	62/788 (7.9%)	227/4213 (5.4%)	243/4205 (5.8%)	1.04 (0.73,1.46)	1.07 (0.90,1.28)	0.86
Pregnancy Associated Hypertension	236/763 (30.9%)	278/786 (35.4%)	1086/4209 (25.8%)	1179/4203 (28.1%)	1.14 (0.99,1.32)	1.09 (1.01,1.17)	0.47
Placental Abruption	11/748 (1.5%)	1/782 (0.1%)	25/4190 (0.6%)	23/4175 (0.6%)	0.09 (0.00,0.87) **	0.92 (0.52,1.62)	**0.010**
PPROM	24/744 (3.2%)	20/774 (2.6%)	105/4179 (2.5%)	104/4160 (2.5%)	0.80 (0.45,1.44)	1.00 (0.76,1.30)	0.51
Severe Preeclampsia	28/763 (3.7%)	27/788 (3.4%)	113/4213 (2.7%)	119/4205 (2.8%)	0.93 (0.56,1.57)	1.06 (0.82,1.36)	0.68
Pre-eclampsia Early Onset±	12/763 (1.6%)	8/788 (1.0%)	31/4213 (0.7%)	30/4205 (0.7%)	0.65 (0.27,1.57)	0.97 (0.59,1.60)	0.43

*Breslow-Day Test for Homogeneity comparing smokers to non-smokers

†Severe hypertension OR mild hypertension with elevated liver enzymes, elevated serum creatinine, thrombocytopenia, eclampsia, SGA (<3rd%), medically indicated preterm birth or perinatal death.

±Onset <34 weeks

**Exact estimate of 95% confidence interval

Table 3

Effect of Vitamin C/E Supplementation on Fetal Outcomes by Smoking Status

Outcome	Smoker Placebo (n =763)	Smoker Vitamins (n =788)	Non- Smokers Placebo (n =4213)	Non- Smoker Vitamins (n = 4205)	Smokers	Non-Smokers	B-D Test*
					Relative Risk (95% CI)	Relative Risk (95% CI)	p-Value
Preterm Birth (<32 wks)	49/763 (6.4%)	32/788 (4.1%)	124/4213 (2.9%)	117/4205 (2.8%)	**0.63 (0.41,0.98)**	0.95 (0.74,1.21)	0.11
Preterm Birth (<37 wks)	106/763 (13.9%)	83/788 (10.5%)	420/4213 (10.0%)	430/4205 (10.2%)	**0.76 (0.58,0.99)**	1.03 (0.90,1.17)	**0.046**
Small for Gest. Age (<3rd%)	22/734 (3.0%)	30/766 (3.9%)	110/4138 (2.7%)	103/4129 (2.5%)	1.31 (0.76,2.24)	0.94 (0.72,1.22)	0.28
Small for Gest. Age (<10th%)	88/734 (12.0%)	116/766 (15.1%)	438/4138 (10.6%)	446/4129 (10.8%)	1.26 (0.98,1.63)	1.02 (0.90,1.16)	0.14
NICU Admissions	94/761 (12.4%)	82/785 (10.4%)	463/4200 (11.0%)	495/4196 (11.8%)	0.85 (0.64,1.12)	1.07 (0.95,1.21)	0.13
Neonatal Morbidity	31/732 (4.2%)	29/764 (3.8%)	127/4129 (3.1%)	141/4120 (3.4%)	0.90 (0.55,1.47)	1.11 (0.88,1.41)	0.44
Neonatal Composite Outcomes	227/761 (29.8%)	230/782 (29.4%)	1043/4194 (24.9%)	1086/4190 (25.9%)	0.99 (0.85,1.15)	1.04 (0.97,1.12)	0.54

* Breslow-Day Test for Homogeneity comparing smokers to non-smokers

Table 4

Select Pregnancy Outcomes by Smoking Status

Subject Outcomes	Smokers (n = 1551)	Non-Smokers (n = 8418)	p- Value
Preeclampsia	114/1551 (7.4%)	576/8418 (6.8%)	0.47
Primary Composite Outcome*	120/1551 (7.7%)	470/8418 (5.6%)	0.001
Pregnancy Associated Hypertension	514/1549 (33.2%)	2265/8412 (26.9%)	<0.001
Preterm <37 weeks gestation	189/1551 (12.2%)	850/8418 (10.1%)	0.013
Preterm <32 weeks gestation	81/1551 (5.2%)	241/8414 (2.9%)	<0.001
Placental Abruption	12/1530 (0.78%)	48/8365 (0.57%)	0.33
SGA <3rd%	52/1500 (3.5%)	213/8267 (2.6%)	0.05
SGA<10th%	204/1500 (13.6%)	884/8267 (10.7%)	0.001
Neonatal Composite of Adverse Smoking Perinatal Outcomes†	457/1543 (29.6%)	2129/8348 (25.4%)	<0.001

*Severe hypertension OR mild hypertension with elevated liver enzymes, elevated serum creatinine, thrombocytopenia, eclampsia, SGA (<3rd%), medically indicated preterm birth or perinatal death

†RDS, sepsis, retinopathy of prematurity, intraventricular hemorrhage, or necrotizing enterocolitis