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Adverse Maternal and Neonatal Outcomes in Indicated Compared with Spontaneous Preterm Birth in Healthy Nulliparas; a secondary analysis of a randomized trial

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Abstract

Objective—To compare the risks of adverse maternal and neonatal outcomes associated with spontaneous (SPTB) vs. indicated (IPTB) preterm birth.

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Methods—A secondary analysis of a multicenter trial of vitamin C and E supplementation in healthy low-risk nulliparous women. Outcomes were compared between women with SPTB (due to spontaneous membrane rupture or labor) and those with IPTB (due to medical or obstetric complications). A primary maternal composite outcome included: death, pulmonary edema, blood transfusion, adult respiratory distress syndrome, cerebrovascular accident, acute tubular necrosis, disseminated intravascular coagulopathy or liver rupture. A neonatal composite outcome included: neonatal death, RDS, grades 3 or 4 IVH, sepsis, NEC, or retinopathy of prematurity.

Results—Of 9867 women, 10.4% (N=1038) were PTBs; 32.7% (n=340) IPTBs and 67.3% (n=698) SPTBs. Compared with SPTB, the composite maternal outcome was more frequent in IPTB – 4.4% vs. 0.9% (adjusted OR 4.0 95% CI 1.4–11.8) as were blood transfusion and prolonged hospital stay (3.2 and 3.7 times respectively). The frequency of composite neonatal outcome was higher in IPTBs (aOR 1.8; 1.1–3.0), as were RDS (1.7 times), SGA<5th percentile (7.9 times) and NICU admission (1.8 times).

Conclusion—Adverse maternal and neonatal outcomes were significantly more likely with IPTB than with SPTB.

Keywords

Spontaneous preterm birth; indicated preterm birth; preeclampsia; pregnancy outcomes

Introduction

Preterm birth (PTB) is a major cause of neonatal and infant morbidity and mortality as well as long-term neurodevelopmental disability.^{1–3} Concern about PTB is the leading indication for antenatal hospitalization; considered together with postnatal care costs, PTB is associated with enormous health care costs.^{1–2} In the United States, PTB accounts for 12% or more of live births; approximately 65–75% occur spontaneously (SPTB) as a result of preterm labor or preterm premature membrane rupture. The remaining 25–35% of these PTBs are indicated (IPTBs) due to medical or obstetric complications such as preeclampsia, abruption and fetal demise.^{3–4} Given this disparity in proportion, SPTBs may be accorded a higher public health priority. However, the burden of adverse maternal and perinatal outcomes may indeed be expected to be higher in IPTBs. However, few studies have directly compared the frequency of adverse outcomes associated with the two major PTB types to better understand their public health burden. Single studies suggested an approximate 2-fold increase in respiratory distress syndrome in early PTBs and neonatal deaths in late PTBs in those with IPTBs as compared with SPTBs (7–8). Therefore, the objective of this study was to quantify and compare the risks of adverse maternal and perinatal outcomes associated with IPTB vs. SPTB among healthy nulliparous women enrolled in a preeclampsia prevention trial.

Methods

This retrospective cohort study is a secondary analysis of the NICHD Maternal-Fetal Medicine Units Network multicenter randomized trial of vitamin C and E supplementation or placebo to prevent preeclampsia. The trial enrolled low-risk nulliparous women with

singleton gestations between 9 0/7 and 16 6/7 weeks from 2003 to 2008 at 16 participating centers.⁵ Gestational age (GA) for all patients was determined by a previously described algorithm using the date of the last menstrual period (if reliable) and the results of the earliest ultrasound examination.⁶ Detailed exclusion criteria for the trial including preexisting hypertension or proteinuria, pregestational diabetes, and fetal anomalies are described in the primary manuscript. Women were randomized to either 1000 mg of vitamin C + 400 IU of vitamin E daily or matching placebo. Data were collected by certified research personnel at the clinical centers and uploaded to a database that was managed by an independent data coordinating center. The study was approved by the institutional review board at each clinical site and the data coordinating center. All participants provided written informed consent before enrollment. Of note, vitamin supplementation did not influence the primary outcome (severe pregnancy-associated hypertension alone or severe or mild hypertension with elevated liver-enzyme levels, thrombocytopenia, elevated serum creatinine levels, eclamptic seizure, medically indicated preterm birth, fetal-growth restriction, or perinatal death) or preeclampsia.⁵

The primary exposure variable was preterm birth (<37 weeks of gestation): IPTB vs. SPTB. For perspective, we also present the incidence outcomes in term births but the statistical comparisons are between preterm birth subtypes. SPTB was defined as a birth <37 weeks of gestation primarily due to spontaneous preterm membrane rupture or labor regardless of mode of delivery; all other births <37 weeks of gestation not due to SPTB were defined as IPTBs. Thus IPTBs were births by induction of labor or pre-labor cesarean due to medical or obstetric complications such as hypertensive disorders, abruption, placenta previa, non-reassuring fetal status, suspected severe intrauterine growth restriction or oligohydramnios. In additional analyses, we compared IPTBs due to preeclampsia (the most common indication) to SPTBs.

The primary maternal outcome was a pre-defined composite of death, pulmonary edema, blood transfusion, adult respiratory distress syndrome (ARDS), cerebrovascular accident (CVA), acute tubular necrosis (ATN), disseminated intravascular coagulopathy (DIC), or liver rupture. These maternal outcomes were defined based on a clinician diagnosis documented in the patient's medical record. This composite is based on outcomes that can occur in the same direction and were specified in the primary protocol. We also examined other secondary maternal outcomes including endometritis (which can occur in an opposite direction to those in the composite) and prolonged maternal hospitalization (>3 days after vaginal delivery or >4 days after cesarean), as a proxy for serious maternal morbidities. The primary neonatal outcome was a composite of outcomes associated with preterm birth: neonatal death prior to hospital discharge following birth, respiratory distress syndrome (RDS), grades 3 or 4 IVH, sepsis, necrotizing enterocolitis (NEC), or retinopathy of prematurity (ROP). We excluded preterm births due to pregnancy terminations from assessment of neonatal outcomes as well as all stillbirths (because of concerns about the occurrence of the outcome prior to determination of the birth type). RDS was defined as a clinical diagnosis of RDS Type I and oxygen therapy ($\text{FiO}_2 \geq 0.40$) for greater than or equal to 24 hours or death before 24 hours of age of a neonate that received a clinical diagnosis of RDS Type I and oxygen therapy ($\text{FiO}_2 \geq 0.40$). This specifically excluded any diagnosis of transient tachypnea of the newborn. Sepsis was defined as either suspected (suspicious

clinical findings of infection on physical examination, but negative blood, CSF, or urine cultures and non-confirmatory x-rays) or proven (positive cultures of blood, CSF, or urine (catheterized or suprapubic), with or without suspicious clinical findings of infection on physical examination, or in the absence of positive cultures, clinical evidence of cardiovascular collapse or an unequivocal x-ray confirming infection in an infant believed to be clinically septic). NEC was defined as a confirmed clinical diagnosis of unequivocal presence of intramural air on abdominal x-ray; perforation seen on abdominal x-ray, clinical evidence as suggested by erythema and induration of the abdominal wall, or intra-abdominal abscess formation; or stricture formation following an episode of suspected NEC. IVH grade III or IV was based on a medically documented diagnosis with the most severe radiographic finding prior to discharge indicating ventricular dilation (grade III) or a parenchymal extension (grade IV). ROP was based on an ophthalmological exam showing ROP. Secondary perinatal outcomes examined included small for gestational age (SGA) <5th percentile (i.e. birth weight less than the 5th percentile for gestational age by Alexander population normograms) and any NICU admission.

For data analysis, chi-square and Wilcoxon two-sample tests were used as appropriate to compare baseline and demographic characteristics by IPTB vs. SPTB groups. Chi square tests or Fisher exact tests, where applicable, were also used to compare the incidence of composite and individual maternal and neonatal outcomes by category of preterm birth. Unadjusted and adjusted odds ratios (95% CIs) were then computed to quantify the association of maternal and neonatal outcomes by birth type and to directly compare IPTBs with SPTBs (as referent). The adjusted results were derived from multivariable logistic regression models adjusting for population characteristics including maternal age, race, BMI, type of provider (obstetrician vs. others such as family practitioner or midwife, nurse practitioner or physician assistant), payor, smoking status, mode of delivery (vaginal vs. cesarean delivery), prenatal vitamin use, and trial treatment assignment. Models comparing PTB types included birth gestational age (completed weeks). All models for neonatal but not maternal outcomes adjusted additionally for baby gender. Covariates were selected because they had significant associations with either the birth type or the maternal/perinatal composite. We conducted supplementary analyses adjusting for center. For all outcomes, a nominal p value less than 0.05 was considered to indicate a statistical significance, without adjusting for multiple comparisons. Analysis was performed using SAS software (Cary, NC).

Results

Among the 9968 eligible women with outcome information, 1038 (10.4%) had a PTB; 340 (3.4% of all births or 32.7% of PTBs) were indicated and 698 (7.0% of all births or 67.3% of PTBs) were spontaneous. The primary identifiable reasons leading to IPTBs in decreasing frequency were hypertensive disease including preeclampsia (52.1%), fetal death (8.5% - all excluded from analyses of neonatal outcomes), suspected IUGR (4.7%), oligohydramnios (4.1%), abnormal antepartum testing or tracing (2.9%), abruption (2.1%), placenta previa (1.2%) and intraamniotic infection or chorioamnionitis (1.2%). Multiple other indications including gestational diabetes and elective terminations accounted for 12.9% (not included in neonatal composite), while no specific indication was abstracted in 10.3%.

The characteristics of the study population presented by term births and preterm birth categories are shown in Table 1. Mean GA (SD) for IPTB and SPTB were 32.5 (6.0) and 31.0 (7.3) weeks, respectively (p-value =0.16). The mean GA for term births was 39.7 (1.2) weeks. Mean BMI on entry and risk of cesarean delivery were significantly higher among IPTBs; other characteristics including racial/ethnic distribution, payor status, smoking status, prenatal vitamin intake, maternal age, type of provider, randomization to vitamin C and E vs. placebo and infant gender did not differ by preterm birth type.

The unadjusted incidence rates of maternal outcomes by birth type are presented in Table 2; IPTB and SPTB types are compared. The composite outcome was more frequent in IPTBs than SPTBs. There was no maternal death in either group but other components of the primary outcome, specifically pulmonary edema, blood transfusion and (albeit non-significantly) other rare outcomes, followed a similar pattern. Blood transfusion was the main driver of the observed results. The incidence of endometritis did not differ significantly by preterm birth type, whereas long maternal hospital stay was more frequent following IPTB than SPTB. Maternal outcomes of SPTBs were more similar to outcomes of term births than IPTBs.

The unadjusted incidence rates of neonatal outcomes by birth type (IPTB compared to SPTB only) are also presented in Table 2. The incidence of the primary neonatal outcome and of RDS (the most frequent component), were not significantly different by PTB type. Less frequent components of the composite including neonatal death, IVH, NEC, sepsis and ROP appeared to be higher in SPTBs than IPTBs but only unadjusted findings for neonatal death and ROP were significant. Both secondary perinatal outcomes – SGA < 5th percentile and NICU admission were significantly more frequent in IPTBs. The frequencies of adverse neonatal outcomes in term births were lower than in IPTBs or SPTBs except SGA < 5th percentile which was higher than in SPTBs.

Unadjusted and adjusted results focusing on the direct relationship between preterm birth types and maternal/perinatal outcomes are presented in Table 3. After multivariable adjustments including gestational age, IPTBs as compared with SPTBs were associated with a significant increase in the primary composite maternal outcome (4-fold) as well as blood transfusion (3.2-fold) and long hospital stay (3.7-fold). Endometritis (adjusted OR=0.4) was less frequent among IPTBs but the finding was not statistically significant. For neonatal outcomes, IPTBs were associated with increases in the primary composite (1.8-fold), RDS (1.7-fold), SGA<5th percentile (7.9-fold) and NICU admission (1.8-fold). Outcomes for neonatal death, IVH, sepsis, NEC and ROP were too rare to fit the multivariable logistic regression model; therefore, odds ratios were not computed.

Results from analyses comparing IPTBs due to preeclampsia only and SPTBs revealed an increase in the maternal composite (AOR 6.3; 1.6–24.4), blood transfusion (5.9; 1.5–23.3) and long hospital stay (5.4; 2.3–12.7) associated with these IPTBs. Similarly, an increase was observed for SGA <5th (7.4; 3.5–15.8) and NICU admission (1.8; 1.2–2.7) but not for the primary neonatal composite (1.2; 0.7–2.3) or RDS (1.4; 0.8–2.3). In the additional adjusted analyses, chorioamnionitis (not included in the key analyses because of the uncertainty of the temporal relationship vis-à-vis study groups) occurred in 6.9% of IPTBs

vs. 9.9% of SPTBs (aOR 0.7; 0.4–1.1). Furthermore, in multivariable adjusted analyses comparing either preterm birth sub-type to term births, IPTB (adjusted OR 2.0; 95% CI 1.1–3.5) but not SPTB (aOR 0.6; 0.3–1.4) was associated with the maternal composite outcome. As expected both IPTB (aOR 15; 10–21) and SPTB (aOR 21; 16–28) were strongly associated with the neonatal composite outcome compared with term births. Additional analyses adjusting by center did not materially change the findings and was limited by the high number of centers included.

Discussion

Main findings

Our results suggest that the public health burden of adverse outcomes from preterm birth differs by preterm birth sub-type. IPTBs as compared with SPTBs were independently associated with a 3 to 4-fold higher incidence of adverse maternal outcomes including the primary composite outcome, need for blood transfusion and prolonged hospitalization. IPTBs were further associated with a 1.7 to 7.9-fold adjusted increase in adverse neonatal outcomes including the primary composite outcome and NICU admission (each increased by 1.8-fold). Higher prevalence of prolonged maternal hospitalization and NICU admission suggest higher costs and use of resources with IPTB. The strength of association of IPTB with specific outcomes became stronger after multivariable adjustments for the gestational age at delivery, as well as the more than 2-fold increased frequency of cesarean delivery and higher maternal BMI of IPTBs. Furthermore, the most frequent reason for IPTBs was pregnancy-associated hypertension. When restricted to IPTBs due to this indication alone, results are similar, except the neonatal composite and RDS are no longer increased compared with SPTBs. It is also noteworthy that the crude risk of neonatal death is higher with spontaneous preterm birth.

Strengths and Limitations

The strengths of our study include the use of a well-characterized, well-dated relatively large closed cohort. Several findings are consistent with previous reports and lend support to the validity of our results. These findings include the proportion of preterm births that were indicated (32.7%) and the higher mean gestational age of IPTBs compared with SPTBs.^{3–4,7,9} We acknowledge a number of study limitations. We were not able to conduct adjusted analyses for some of the individual rare severe maternal and perinatal outcomes. Examination of multiple outcomes could have contributed to associations by chance, although it is noteworthy that we had pre-specified primary composite outcomes. Also, since we studied only nulliparous women with singleton pregnancies, the applicability of our findings to multiparous women is limited although we would expect similar results. We could not reliably assess stillbirths as an outcome since we could not tease out stillbirths that were secondary to unidentified indications for preterm delivery. This limits causal interpretations relating preterm birth type and outcomes that include fetal death. Another limitation is the potential overlap between IPTBs and SPTBs – for example a patient with PPROM who subsequently develops preeclampsia may be classified as a SPTB. However, we believe such instances are exceedingly rare and unlikely to materially change our findings. The use of composite outcomes gives equal weighting to all components in

composite; however, we also show results for the individual components for full disclosure. The pre-defined maternal composite did not include infections but they are examined as secondary outcomes. We acknowledge that not all materially important outcomes are included in the primary maternal composite; others are reflected by secondary outcomes. Finally, we recognize the IPTB group is comprised of heterogeneous indications and findings may not be uniformly applicable to all indications. Of note, our cohort included only healthy nulliparous women at baseline – those with preexisting conditions such as diabetes and hypertension were excluded. Gestational diabetes was one indication for preterm birth - if poorly controlled or present in association with other subjective findings (e.g. reduced fetal movement), it can reasonably be an indication for preterm delivery. We included terminations only in the assessment of maternal morbidity and excluded them for neonatal outcomes. It is possible that the 10% of IPTBs without clear indications occurred due to provider appraisal of subjective circumstances but did not necessarily note down indications for preterm delivery, or the research team abstracting at the time could not clearly identify the indication. Of note, patients with IPTBs and SPTBs were similar in baseline characteristics at enrollment except BMI (adjusted for in our analyses) before developing intervening factors associated with preterm birth such as preeclampsia, SGA, or gestational diabetes.

Interpretation in light of other evidence

Since indicated births typically occur in the context of ongoing or impending risk of adverse outcome to mother and/or fetus, our findings are not surprising. However, few prior studies have examined and quantified the potential differential impact in terms of actual maternal and neonatal outcomes by preterm birth type. IPTB as compared with SPTB was associated with a 2.3-fold increased risk of RDS in one US study of 257 preterm births at 24–32 weeks of gestation a finding consistent with ours.⁷ A larger study based on U.S vital statistics data also showed a 2-fold adjusted increase in neonatal death at 34–36 weeks of gestation with IPTB compared with SPTB due to preterm labor.⁸ No differences in neonatal morbidity were observed in one study of neonates weighing <1000g at birth.¹⁷ Because neonatal death was rare in our study population we could not conduct valid adjusted analyses to examine its true relationship with preterm birth types. The higher frequency of infections with SPTB may contribute to the higher frequency of neonatal deaths. The potential reduction in endometritis (as well as chorioamnionitis) observed in our cohort among IPTBs as compared with SPTBs (albeit non-significant) is consistent with both the findings of a lower risk of chorioamnionitis in a prior study⁷ and the well-established association of SPTBs with infection.³ Studies focusing solely on preeclampsia as the indication for PTB reported increased risks of SGA, respiratory distress syndrome and intensive care unit admission but a decrease in neonatal mortality as compared with SPTBs.^{15–16}

Conclusion

In nulliparas, we observed, as expected, that adverse maternal and some neonatal outcomes are disproportionately more common with IPTB than with SPTB. Even more noteworthy, we quantified this relationship. These findings are useful considering several reports from the US and other settings of a consistent ongoing increase in indicated preterm births.^{10–13}

Therefore, although IPTBs make up only approximately a third of all preterm births, their contribution to the adverse health outcomes, use of resources and potential economic burden associated with preterm birth may be disproportionately higher than expected. Furthermore, women at increased risk for IPTB including those with chronic hypertension, pregestational diabetes and serious medical disorders were excluded from the primary study population. This suggests that the proportion of IPTBs may be higher in the nulliparous population. Thus, from a public health perspective, interventions to prevent the underlying causes of IPTBs such as preeclampsia, in order to reduce the risk of IPTBs and hence reduce the associated burden of adverse outcomes may deserve as much attention as directed towards SPTBs. Because the temporal increase in IPTBs has been associated with a reduction in perinatal deaths¹², further investigation is needed to better define the burden of perinatal deaths associated with IPTB. While a PTB should be undertaken when faced with an appropriate indication, a key public health goal is to prevent the incidence of IPTBs and their indications such as preeclampsia. In addition to the need for preventive interventions for indicated preterm births, further research is needed to further clarify the attributable risks of adverse maternal and perinatal outcomes due to spontaneous preterm births and indicated preterm births particularly due to preeclampsia. In sum, our findings suggest that the repercussions and costs of IPTB may be more severe than SPTBs; therefore, more effort and resources should be devoted to studying and preventing the the underlying causes for IPTB.

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Table 1

Characteristics of pregnant women by birth type

Outcome	IPTB (n=340)	SPTB (n=698)	Term (n=8930)	P-value*
Maternal age (mean±sd)	23.1±5.1	23.4±5.7	23.5±5.2	0.809
Race/ethnicity (%)				0.255
Caucasian	128 (37.6)	258 (37.0)	3799 (42.5)	
African American	133 (39.1)	255 (36.5)	2130 (23.8)	
Hispanic	78 (22.9)	174 (24.9)	2831 (31.7)	
Other	1 (0.3)	11 (1.6)	170 (1.9)	
BMI on entry (mean±sd)	28.4±7.4	26.5±6.6	26.2±6.0	<0.001
Obstetrician as provider (%)	187 (55.0)	407 (58.3)	5117 (57.3)	0.312
Private payor (%)	118 (34.7)	222 (31.8)	3273 (36.6)	0.350
Smoker (%)	61 (17.9)	128 (18.3)	1362 (15.2)	0.876
Cesarean delivery (%)**	148/323 (45.8)	124/652 (19.0)	2221/8923 (24.9)	<0.001
Prenatal vitamin intake (%)	276 (81.2)	565 (80.9)	6849 (76.7)	0.929
Vitamin C/E group (%)	156 (45.9)	356 (51.0)	4480 (50.2)	0.122
Female infant (%)**	147/305 (48.2)	271/601 (45.1)	4299/8928 (48.1)	0.376

* P-value for Chi-square or Wilcoxon two-sample test for differences between IPTBs and SPTBs only

** Denominators are different from column denominator because of missing information for the variable.

Table 2

Adverse maternal and perinatal outcomes by birth type

Outcomes	Incidence – n/N (%)			P-value*
	IPTB (n=340)	SPTB (n=698)	Term (n=8930)	
Maternal				
Maternal Composite	14/321 (4.4)	6/651 (0.9)	155/8903 (1.7)	<0.001
Maternal death	0 (0.0)	0 (0.0)	1 (0.0)	>.999
Pulmonary edema	3/321 (0.9)	0/651 (0.0)	10/8905 (0.1)	0.036
†Other rare outcome	2/323 (0.6)	0/652 (0.0)	4/8909 (0.04)	0.110
Blood transfusion	11/321 (3.4)	6/651 (0.9)	148/8908 (1.7)	0.005
Endometritis	6/321 (1.9)	14/651 (2.2)	187/8906 (2.1)	0.771
Long hospital stay**	28/323 (8.7)	12/651 (1.8)	129/8913 (1.4)	<0.001
Neonatal	(n=270) ‡	(n=571) ‡	(n=8845) ‡	
Neonatal composite	60/265 (22.6)	137/568 (24.1)	136/8815 (1.5)	0.640
Neonatal death	2/264 (0.8)	39/565 (6.9)	1/8815 (0.01)	< 0.001
RDS	56/268 (20.9)	101/568 (17.8)	121/8816 (1.4)	0.282
Grades 3/4 IVH	1/267 (0.4)	12/568 (2.1)	0/8817 (0.0)	0.072
NEC	5/268 (1.9)	16/568 (2.8)	2/8817 (0.02)	0.412
Neonatal sepsis	6/267 (2.3)	29/568 (5.1)	12/8817 (0.1)	0.055
ROP	5/268 (1.9)	29/568 (5.1)	0/8817 (0.0)	0.027
SGA < 5 th percentile	43/270 (15.9)	14/568 (2.5)	402/8835 (4.6)	< 0.001
NICU Admission	160/270 (59.3)	279/570 (48.9)	638/8820 (7.2)	0.005

* P-value for Chi-square or Fisher exact test for differences in outcome frequency between IPTB and SPTB types only.

** Maternal hospital stay >3 days after vaginal or >4 days after cesarean delivery

† Other rare maternal complications include ARDS, ATN, DIC and Liver rupture

‡ The sample size for neonatal outcomes is smaller because of the exclusion fetal deaths

Table 3

Maternal and perinatal outcomes in IPTB compared with SPTB (as referent)

Outcome				
Maternal	Unadjusted OR (95% CI)		Adjusted OR (95% CI)[†]	
Maternal Composite	4.9	(1.9–12.9)	4.0	(1.4–11.8)
Blood transfusion	3.8	(1.4–10.4)	3.2	(1.1–9.8)
Endometritis	0.9	(0.3–2.3)	0.4	(0.1–1.2)
Long hospital stay ^{**}	5.1	(2.5–10.1)	3.7	(1.8–7.7)
Perinatal				
Neonatal composite	0.9	(0.7–1.3)	1.8	(1.1–3.0)
RDS	1.2	(0.8–1.8)	1.7	(1.1–2.7)
SGA < 5 th percentile	7.5	(4.0–14.0)	7.9	(4.0–15.7)
NICU Admission	1.5	(1.1–2.0)	1.8	(1.3–2.5)

[†] Logistic regression to adjust for GA, maternal age, race, BMI, OB provider, private payor, smoking, peripartum infections (chorioamnionitis and cesarean delivery, prenatal vitamin intake, vitamin C/E group and baby gender (perinatal outcomes only). Results in bold indicate confidence interval does not cross 1.

^{**} Maternal hospital stay >3 days after vaginal or >4 days after cesarean delivery.