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Mode of delivery and neonatal respiratory morbidity among HIV-exposed newborns in Latin America and the Caribbean: NISDI Perinatal–LILAC Studies

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Conflict of interest

The authors have no conflicts of interest.

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Abstract

Objective—To evaluate respiratory morbidity (RM) in HIV-exposed newborns according to mode of delivery.

Methods—The NISDI Perinatal/LILAC prospective cohort studies enrolled HIV-infected pregnant women and their newborns in Latin America and the Caribbean. Associations between RM and delivery mode or other characteristics were evaluated.

Results—Between September 2002 and December 2009, 1630 women were enrolled, and 1443 mother–infant pairs met the inclusion criteria. There were 561 vaginal (VD), 269 cesarean before labor and membrane rupture (SCS) for preventing mother-to-child transmission (SCS–PMTCT), 248 other SCS, and 365 cesarean after labor and/or ruptured membranes (NSCS) deliveries. In total, 108 (7.5%) newborns had RM: 49 had respiratory distress syndrome (RDS), 39 had transient tachypnea (TTN), and 28 had other events (7 newborns had >1 RM event). Delivery mode was associated with RDS ($P<0.001$) and TTN ($P<0.001$). The proportion with RDS and TTN was lowest for VD (1.6% and 0.5%, respectively), highest for NSCS (4.9% and 4.7%), and intermediate for SCS–PMTCT (3.0% and 2.6%). Newborns with RDS or TTN were hospitalized longer (median +1 day) than those without. A minority required ventilatory support (RDS, 24.5%–28.6%; TTN, 2.6–15.4%).

Conclusions—SCS–PMTCT is relatively safe for newborns of HIV-infected women.

Keywords

Cesarean delivery; HIV; Newborn; Respiratory distress syndrome

1. Introduction

Cesarean delivery before labor and before ruptured membranes (SCS) is efficacious in preventing mother-to-child transmission (MTCT) of human HIV as compared with other modes of delivery [1]. On the basis of the results of a randomized clinical trial [1] and an individual patient data meta-analysis [2], the US Public Health Service [3] and the American College of Obstetricians and Gynecologists [4] has recommended that SCS should be considered for some subgroups of HIV-infected pregnant women: namely, those with a plasma HIV RNA concentration (viral load) of more than 1000 copies/mL, irrespective of antiretroviral (ARV) regimen; and those with an unknown viral load.

The American College of Obstetricians and Gynecologists recommends that, to prevent MTCT of HIV, SCS should be performed at 38 weeks of gestation, owing to the potential risk of labor and rupture of membranes before 39 weeks of gestation (the recommended timing of operative delivery in women not infected with HIV) [5]. Guidelines for preventing MTCT in Latin American countries such as Argentina and Brazil have been updated to include these recommendations [6,7]. Since the release of these guidelines, the rate of cesarean delivery has increased markedly among HIV-infected women in several countries: in Brazil, Argentina, the United States, and Sweden, it has reached 50%, 55%, 58%, and 80%, respectively [8–11].

However, studies of women not infected with HIV have shown an increased risk of neonatal respiratory morbidity among newborns delivered by cesarean as compared with those born by vaginal delivery (VD) [12,13], with the risk decreasing with increasing gestational age [14]. The aim of the present analysis was to test the hypothesis that mode of delivery is associated with neonatal respiratory morbidity, where VD has the lowest risk, non-SCS

delivery (NSCS) and SCS for indications other than preventing MTCT (SCS–other) have the highest risk, and SCS for prevention of MTCT (SCS–PMTCT) has intermediate risk.

2. Materials and methods

The International Site Development Initiative (NISDI) Perinatal Study (2002–2007) and subsequent Longitudinal Study in Latin American Countries (LILAC) (2008–2012) are prospective cohort studies of HIV-infected women and HIV-exposed, uninfected infants conducted at sites in Latin America and the Caribbean [15]. The primary objectives of these protocols were to describe the characteristics of enrolled women and infants, including utilization of interventions to prevent MTCT of HIV, use of antiretrovirals (ARVs), and rates of MTCT of HIV; and to characterize adverse events according to use of and exposure to ARVs and mode of delivery. Women were enrolled during pregnancy and followed through delivery and postpartum. In both studies, maternal and infant study visits are conducted at hospital discharge after birth, at 6–12 weeks, and at 6 months after birth. LILAC participants are followed every 6 months thereafter, with planned follow-up for at least 3 years after birth. Study visits include a medical history, a physical examination, and collection of laboratory samples. The protocol was approved by the ethical review board at each clinical site, as well as by institutional review boards at the sponsoring institution (NICHD) and at the data management center (Westat). All participants provided written informed consent for participation in the study.

The study population for the present analysis comprised newborns born to women enrolled in the NISDI Perinatal and LILAC studies from September 27, 2002, to December 31, 2009, who had not had a previous pregnancy included in the study and who delivered a singleton live newborn after 20 weeks of gestation with known mode of delivery and without cardiac or pulmonary congenital anomalies. The exposure of interest was the mode of delivery (VD, SCS–PMTCT, SCS–other, or NSCS). The outcome of interest was the occurrence of any neonate respiratory morbidity within the first 28 days of life.

Diagnoses of respiratory distress syndrome (RDS), pulmonary hemorrhage, and persistent pulmonary hypertension of the newborn were assigned at the discretion of the treating physician. The following diagnoses were made in accordance with documents associated with the NISDI protocol. Transient tachypnea of the newborn (TTN) was defined as a noninfectious acute respiratory disease in the newborn, where signs of respiratory distress become evident shortly after birth and usually resolve by age 72 hours. Meconium aspiration syndrome was defined as aspiration of meconium mixed with amniotic fluid in utero or during delivery, causing a partial or complete blockage of the airways associated with poor gas exchange in the lungs and chemical pneumonitis.

Cases of pneumonia were categorized as “presumed” if clinical findings and a chest X-ray were temporally consistent and microbiologic testing was negative or not performed, or “suspected” if there were clinical findings but a chest X-ray was not done or not available and microbiologic testing was negative or not performed. A diagnosis of aspiration pneumonia was assigned if clinical findings and a chest X-ray were consistent with pneumonia and associated with aspiration of oral or gastrointestinal contents. Pneumothorax was defined as a collection of air or gas in the pleural cavity. For a newborn diagnosed with RDS or TTN within 28 days of birth, the study site was queried to obtain additional information regarding the clinical severity of the case in terms of receipt of supplemental oxygen, admission to a neonatal intensive care unit, and respiratory support.

Bivariate associations between mode of delivery or respiratory morbidities and categorical study variables were evaluated via Fisher–Freeman–Halton tests. Missing data were

excluded from analyses. The Kruskal–Wallis test was used to evaluate median gestational age by mode of delivery and median duration of hospital stay by respiratory morbidities. $P<0.05$ was considered to be statistically significant. All P values were two-sided. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

Between September 27, 2002, and December 31, 2009, there were 1630 enrollments in the NISDI Perinatal and LILAC studies, of which 1548 represented women with their first pregnancy on study. Among these, the pregnancy outcome was known in 1537 women, of whom 1512 delivered singleton neonates. Of these 1512 neonates, 1478 were born live, and 1477 had a known gestational age of more than 20 weeks. Of these, 1471 had complete mode of delivery data and 1443 did not have cardiopulmonary congenital anomalies. As a result, the study population comprised 1443 newborns and their mothers.

The characteristics of the study population—overall and according to mode of delivery—are shown in Table 1. Most women (31.1%) delivered by cesarean: 269 (18.6%) by SCS–PMTCT; 248 (17.2%) by SCS–other; and 365 (25.3%) by NSCS. By contrast, 561 women (38.9%) delivered vaginally. There were significant differences according to mode of delivery for the maternal characteristics of country, age, education, reason for using ARVs during pregnancy, most complex ARV regimen used for 28 days or more during pregnancy, parity, and CD4 (count and percentage) and plasma viral load at both enrollment and hospital discharge; and for the newborn characteristics of preterm and low birth weight.

Most women were aged 20–29 years (54.8%), and VD was most common among this age group (43.1%). More women aged 29 years or older delivered by NSCS (29.3%) or SCS–other (19.8%) than women in younger age groups. Most women had completed 7–12 years of education (62.7%). Overall, the proportion of women with VD was highest among women with 0–6 years of education (46.2%; $P=0.0039$).

Overall, slightly more women used ARVs during pregnancy for prophylaxis (50.6%) than for treatment (49.4%), and those using ARVs for prophylaxis had a higher proportion of VD (43.9%). Women with the highest CD4 counts at enrollment and/or hospital discharge had the highest percentages of VD. Most women had a plasma viral load of less than 1000 copies/mL at enrollment (63.8%) and at hospital discharge (84.1%). Among women with a viral load of either 1000–10 000 copies/mL or 10 000 copies/mL or more at enrollment, a higher proportion delivered by NSCS and by SCS–PMTCT as compared with women with a viral load of less than 1000 copies/mL. However, many women with either 1000–10 000 copies/mL or 10 000 copies/mL or more at enrollment had VD (30.5% and 32.6%, respectively). These same patterns in mode of delivery by viral load group were observed at hospital discharge.

Overall, 9.7% of births were preterm and a higher proportion of neonates born preterm were delivered by NSCS and by SCS–other (41.4% and 25.7%, respectively; $P<0.0001$). Overall, the median gestational age of neonates was 39 weeks. Those who delivered vaginally and by SCS–PMTCT had the highest median gestational age (39 weeks). Overall, as compared with VD, the median gestational age was lower for SCS–other (38 weeks) and NSCS (38 weeks) deliveries ($P<0.0001$; data not shown). Overall, 10.0% of neonates were born with low birth weight, and a higher proportion of low birth weight neonates were delivered by NSCS or SCS–other (38.9% and 25.7%, respectively; $P<0.0001$).

Overall, 108 (7.5%) newborns had 116 respiratory morbidity diagnoses during the first 28 days of life (Table 2). The most common morbidities were RDS (45.4%) and TTN (36.1%).

Other respiratory morbidities occurred much less frequently; therefore, all subsequent analyses were restricted to RDS or TTN.

The distributions of TTN and RDS according to mode of delivery are shown in Table 3. Overall, both RDS and TTN were associated with the mode of delivery (P=0.0052 and P<0.0001, respectively). Newborns delivered vaginally had the lowest rate of RDS (1.6%), followed by those delivered by SCS–PMTCT (3.0%; odds ratio (OR), 1.88; 95% confidence interval (CI), 0.72–4.93). SCS–other and NSCS deliveries had the highest rates of RDS (4.9–5.6%; as compared with VD: OR, 3.67 and 3.18; 95% CI, 1.57–8.60 and 1.41–7.16). Similarly, newborns delivered vaginally had the lowest rate of TTN (0.5%), followed by those delivered by SCS–PMTCT (2.6%; OR, 4.97; 95% CI, 1.27–19.37). SCS–other and NSCS deliveries had the highest rates of TTN (4.7–4.8%; as compared with VD: OR, 9.46 and 9.09; 95% CI, 2.64– 33.82 and 2.64–31.23).

Other characteristics of the study population with significant associations with RDS or TTN are also shown in Table 3. RDS was associated with maternal country of residence, tobacco use during pregnancy, preterm birth, and low birth weight. TTN was associated with preterm birth and low birth weight.

The median duration of hospitalization was slightly longer among those with RDS or with TTN (both 3.0 days; quartile 1 to quartile 3 [Q1–Q3], 2–5 days) than among those without (both 2.0 days; both Q1–Q3, 2–3 days) (both P<0.002) (data not shown). Among those with RDS, 87.8% received supplemental oxygen (n=43; 42 with known duration: median duration, 1 day), 65.3% were admitted to a neonatal intensive care unit (n=32; median duration, 7 days), 24.5% were intubated and placed on mechanical ventilation (n=12; median duration, 3 days), and 28.6% received continuous positive airway pressure support (n=14; median duration, 1 day). Among those with TTN, 82.1% received supplemental oxygen (n=32; median duration, <1 day), 48.7% were admitted to a neonatal intensive care unit (n=19; median duration, 4 days), 2.6% were intubated and placed on mechanical ventilation (n=1; duration, 12 days), and 15.4% received continuous positive airway pressure support (n=6; median duration, 1.5 days).

4. Discussion

In the present large cohort of HIV-infected women and their newborns in Latin America and the Caribbean, most mothers (87%) were at an early stage of clinical HIV disease, and most (84%) had a plasma viral load of less than 1000 copies/mL at the time of delivery. Almost all (99.4%) women used ARVs during pregnancy. Most women delivered by cesarean (61.1%), including SCS–PMTCT (18.6%). Of note, a relatively high proportion of women with plasma viral loads of more than 1000 copies/mL delivered vaginally, even though it has been recommended for several years that women with a viral load of more than 1000 copies/mL should be counseled regarding the potential benefit of SCS–PMTCT. As expected, women who delivered by SCS–PMTCT tended to have higher plasma viral loads and lower CD4 values, and were more likely to have received no ARVs for more than 28 days or only 1 NRTI.

Importantly, the median gestational age of newborns delivered by SCS–PMTCT was the same as that of newborns delivered vaginally (39 weeks), whereas it was 38 weeks for those born by other types of cesarean delivery. Less than 10% of newborns had any type of neonatal respiratory morbidity, most commonly RDS and TTN. Newborns delivered vaginally had the lowest rates of RDS and TTN (1.6% and 0.5%, respectively), those delivered by SCS–PMTCT presented intermediate rates (3.0% and 2.6%, respectively), and those delivered by other types of cesarean presented the highest rates (4.9%–5.6% and

4.7%–4.8%, respectively). Preterm birth and low birth weight were associated with both RDS and TTN. Newborns with RDS or TTN tended to be hospitalized for a median of 1 day longer than those without such morbidities, and a minority required ventilatory support (RDS, 24.5%–28.6%; TTN, 2.6%–15.4%).

Cesarean delivery has been associated with neonatal respiratory morbidity—especially RDS [13,14,16]—in a general obstetrical population and in 1 study of HIV-infected women in North America [17]. It has been proposed that the hormonal and physiologic changes associated with labor, necessary for lung maturation in neonates, do not occur among newborns delivered by SCS [18]. Gestational age at the time of delivery also is an important factor related to neonatal respiratory morbidity [19].

The strengths of the present analysis include the use of prospectively collected data from a large population of HIV-infected women and their newborns. Importantly, classification of the mode of delivery discriminated among SCS deliveries according to indication: those with PMTCT as the indication were analyzed separately from SCS deliveries with other indications. As a result, the risk of neonatal respiratory morbidity according to an intervention known to be efficacious for PMTCT (SCS–PMTCT) could be more accurately estimated. In addition, not only was the overall risk of RDS and TTN assessed, but the clinical severity of cases of RDS and TTN was characterized. This is essential in contrasting the potential benefit of SCS– PMTCT (preventing transmission of an ultimately fatal viral infection) with its potential harm (iatrogenic prematurity, with an increased risk of respiratory morbidity, especially RDS, with a wide spectrum of clinical severity).

A limitation of the study is that, unlike TTN, RDS was not specifically defined *a priori* for clinicians caring for the HIV-exposed newborns, but was a diagnosis assigned at the discretion of the treating physician. However, RDS is a well-known clinical entity for all pediatricians caring for newborns, and misclassification, if it did occur, would probably entail over-diagnosis. We would not expect a differential misclassification in the diagnosis according to mode of delivery. Another limitation is that the sample size was insufficient to explore possible confounders of the associations between mode of delivery and respiratory morbidity—most importantly preterm birth, which is strongly associated with mode of delivery and both RDS and TTN. Because the study was an observational study, the clinical management of each participant in the cohort was directed by his or her own physician—for example, there were no standardized criteria for administration of supplemental oxygen or admission to an intensive care unit.

Our previous analysis of postpartum morbidity among HIV-infected women according to mode of delivery [10] provides support for both a recent review [20] and current guidelines suggesting that the risk of postpartum morbidity with SCS is outweighed by the potential benefit [3]. Similarly, the present analysis of data from more than 1400 mother–infant pairs supports the safety of SCS for PMTCT of HIV in terms of neonatal respiratory morbidity. In addition, it is consistent with another study assessing respiratory morbidity among North American newborns of HIV-infected women [17], but it expands on those results (by more carefully defining the mode of delivery categories to include cesarean delivery before labor and before ruptured membranes for PMTCT).

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Table 1

Characteristics of the study population: overall and according to mode of delivery [a,b]

Variable [c]	Overall (n=1443)	Vaginal (n=561)	SCS-PMTCT (n=269)	SCS-other (n=248)	NSCS (n=365)	*P* value [d]
Maternal variables						
Country of residence						
Argentina	349 (24.2)	132 (37.8)	52 (14.9)	44 (12.6)	121 (34.7)	<0.0001
Bahamas	41 (2.8)	28 (68.3)	0 (0.0)	7 (17.1)	6 (14.6)	
Brazil	906 (62.8)	369 (40.7)	134 (14.8)	195 (21.5)	208 (23.0)	
Jamaica	35 (2.4)	28 (80.0)	3 (8.6)	1 (2.9)	3 (8.6)	
Mexico	42 (2.9)	2 (4.8)	24 (57.1)	0 (0.0)	16 (38.1)	
Peru	70 (4.9)	2 (2.9)	56 (80.0)	1 (1.4)	11 (15.7)	
Age, years						
<20	86 (6.0)	29 (33.7)	23 (26.7)	12 (14.0)	22 (25.6)	0.0014
20–29	791 (54.8)	341 (43.1)	149 (18.8)	124 (15.7)	177 (22.4)	
>29	566 (39.2)	191 (33.7)	97 (17.1)	112 (19.8)	166 (29.3)	
Education, years						
0–6	461 (31.9)	213 (46.2)	84 (18.2)	64 (13.9)	100 (21.7)	0.0039
7–12	905 (62.7)	324 (35.8)	169 (18.7)	171 (18.9)	241 (26.6)	
≥13	77 (5.3)	24 (31.2)	16 (20.8)	13 (16.9)	24 (31.2)	
Most complex ARV regimen used for ≥28 days during third trimester						
No ARV for ≥28 days	70 (4.9)	14 (20.0)	27 (38.6)	5 (7.1)	24 (34.3)	<0.0001
1 NRTI	56 (3.9)	23 (41.1)	15 (26.8)	5 (8.9)	13 (23.2)	
2 NRTIs	77 (5.3)	32 (41.6)	14 (18.2)	8 (10.4)	23 (29.9)	
2 NRTIs + 1 NNRTI	393 (27.2)	155 (39.4)	69 (17.6)	66 (16.8)	103 (26.2)	
2 NRTIs + 1 PI	810 (56.1)	330 (40.7)	134 (16.5)	158 (19.5)	188 (23.2)	
Other	37 (2.6)	7 (18.9)	10 (27.0)	6 (16.2)	14 (37.8)	
Reason for use of ARVs during pregnancy						
Prophylaxis	706 (50.6)	310 (43.9)	138 (19.5)	106 (15.0)	152 (21.5)	0.0004
Treatment	689 (49.4)	236 (34.3)	122 (17.7)	133 (19.3)	198 (28.7)	
Data missing	48	15	9	9	15	
Number of prior live births						

Variable [c]	Overall (n=1443)	Vaginal (n=561)	SCS-PMTCT (n=269)	SCS-other (n=248)	NSCS (n=365)	*P* value [d]
0	311 (21.6)	104 (33.4)	66 (21.2)	43 (13.8)	98 (31.5)	
1	454 (31.5)	179 (39.4)	88 (19.4)	82 (18.1)	105 (23.1)	0.03
>1	678 (47.0)	278 (41.0)	115 (17.0)	123 (18.1)	162 (23.9)	
CD4 count at enrollment, cells/mm^3						
<200	188 (13.2)	54 (28.7)	43 (22.9)	40 (21.3)	51 (27.1)	
200–499	723 (50.9)	272 (37.6)	131 (18.1)	125 (17.3)	195 (27.0)	0.01
≥ 500	509 (35.8)	223 (43.8)	91 (17.9)	80 (15.7)	115 (22.6)	
Data missing	23	12	4	3	4	
CD4% at enrollment						
<14	99 (7.8)	29 (29.3)	20 (20.2)	20 (20.2)	30 (30.3)	
14–28	554 (43.8)	192 (34.7)	114 (20.6)	93 (16.8)	155 (28.0)	0.0028
≥29	612 (48.4)	278 (45.4)	111 (18.1)	81 (13.2)	142 (23.2)	
Data missing	178	62	24	54	38	
CD4 count at hospital discharge, cells/mm^3						
<200	133 (10.1)	40 (30.1)	30 (22.6)	21 (15.8)	42 (31.6)	
200–499	577 (43.6)	170 (29.5)	123 (21.3)	115 (19.9)	169 (29.3)	<0.0001
≥ 500	613 (46.3)	287 (46.8)	100 (16.3)	100 (16.3)	126 (20.6)	
Data missing	120	64	16	12	28	
CD4% at hospital discharge						
<14	70 (5.7)	23 (32.9)	13 (18.6)	15 (21.4)	19 (27.1)	
14–28	457 (37.5)	148 (32.4)	106 (23.2)	76 (16.6)	127 (27.8)	0.02
≥ 29	693 (56.8)	294 (42.4)	123 (17.7)	107 (15.4)	169 (24.4)	
Data missing	223	96	27	50	50	
Plasma viral load at enrollment (copies/mL)						
<1000	907 (63.8)	393 (43.3)	143 (15.8)	168 (18.5)	203 (22.4)	
1000–9999	275 (19.4)	84 (30.5)	65 (23.6)	38 (13.8)	88 (32.0)	<0.0001
≥10 000	239 (16.8)	78 (32.6)	55 (23.0)	38 (15.9)	68 (28.5)	
Data missing	22	6	6	4	6	
Plasma viral load at hospital discharge (copies/mL)						
<1000	1127 (84.1)	459 (40.7)	177 (15.7)	213 (18.9)	278 (24.7)	<0.0001
1000–9999	133 (9.9)	27 (20.3)	49 (36.8)	14 (10.5)	43 (32.3)	

Variable [c]	Overall (n=1443)	Vaginal (n=561)	SCS-PMTCT (n=269)	SCS-other (n=248)	NSCS (n=365)	*P* value [d]
≥10 000	80 (6.0)	22 (27.5)	31 (38.8)	8 (10.0)	19 (23.8)	
Data missing	103	53	12	13	25	
Infant variables						
Preterm birth (<37 completed weeks of gestation)						
Yes	140 (9.7)	35 (25.0)	11 (7.9)	36 (25.7)	58 (41.4)	<0.0001
No	1303 (90.3)	526 (40.4)	258 (19.8)	212 (16.3)	307 (23.6)	
Low birth weight (<2500 g)						
Yes	144 (10.0)	39 (27.1)	12 (8.3)	37 (25.7)	56 (38.9)	<0.0001
No	1299 (90.0)	522 (40.2)	257 (19.8)	211 (16.2)	309 (23.8)	

[a] Values are given as number (percentage) unless otherwise indicated.

[b] There were no significant differences according to mode of delivery for the following variables (data not shown): number of people living in the household (*P*=0.18), gainful employment outside of the home (*P*=0.07), tobacco use during pregnancy (*P*=0.30), alcohol use during pregnancy (*P*=0.32), cocaine use during pregnancy (*P*=0.23), marijuana use during pregnancy (*P*=0.83), use of any antiretrovirals during pregnancy (*P*=0.19), number of prior stillbirths (*P*=0.51), CDC clinical disease stage at enrollment (*P*=0.11), CDC clinical disease stage at hospital discharge (*P*=0.20), and infant gender (*P*=0.38).

[c] Missing data were excluded from all *P* value calculations.

[d] *P* values are from Fisher exact test.

Table 2

Respiratory morbidity among neonates in the study population

Respiratory morbidity	**No. (%) (n=108)** [b]
Respiratory distress syndrome	49 (45.4)
Transient tachypnea of the newborn	39 (36.1)
Pneumonia [a]	10 (9.3)
Meconium aspiration	7 (6.5)
Persistent pulmonary hypertension of the newborn	6 (5.6)
Pneumothorax	2 (1.9)
Pulmonary hemorrhage	2 (1.9)
Aspiration pneumonia	1 (0.9)

[a] Suspected or presumed

[b] Seven neonates had multiple respiratory morbidities (6 neonates had 2 respiratory morbidities; 1 neonate had 3 respiratory morbidities).

Table 3

Mode of delivery and other characteristics of the mother–infant pairs according to neonatal respiratory distress syndrome and transient tachypnea of the newborn [a]

	Neonatal respiratory morbidity					
	Respiratory distress syndrome			Transient tachypnea of the newborn		
Variable [b]	**N (%)**	**OR (95%CI)**	***P* value** [c]	**n (%)**	**OR (95%CI)**	***P* value** [c]
Total	49 (3.4)			39 (2.7)		
Mode of delivery						
Vaginal (referent)	9 (1.6)	1.00	0.0052	3 (0.5)	1.00	<0.0001
SCS-PMTCT	8 (3.0)	1.88 (0.72–4.93)		7 (2.6)	4.97 (1.27–19.37)	
SCS-other	14 (5.6)	3.67 (1.57–8.60)		12 (4.8)	9.46 (2.64–33.82)	
NSCS	18 (4.9)	3.18 (1.41–7.16)		17 (4.7)	9.09 (2.64–31.23)	
Maternal characteristics						
Country of residence						
Argentina	17 (4.9)	2.06 (1.08–3.92)	<0.0001			
Bahamas	0 (0.0)					
Brazil (referent)	22 (2.4)	1.00				
Jamaica	0 (0.0)					
Mexico	9 (21.4)	10.96 (4.68–25.63)				
Peru	1 (1.4)	0.58 (0.08–4.39)				
Tobacco use during pregnancy						
Yes	20 (5.6)	2.23 (1.24–4.01)	0.0099			
No (referent)	28 (2.6)	1.00				
Missing data	1					
Infant characteristics						
Preterm birth (<37 completed weeks of gestation)						
Yes	21 (15.0)	1.00	<0.0001	16 (11.4)	1.00	<0.0001
No	28 (2.1)	0.12 (0.07–0.23)		23 (1.8)	0.14 (0.07–0.27)	
Low birth weight (<2500 g)						
Yes	15 (10.4)	4.33 (2.30–8.16)	<0.0001	15 (10.4)	6.18 (3.16–12.07)	<0.0001

	Neonatal respiratory morbidity					
	Respiratory distress syndrome			Transient tachypnea of the newborn		
Variable [b]	**N (%)**	**OR (95%CI)**	***P* value** [c]	**n (%)**	**OR (95%CI)**	***P* value** [c]
No	34 (2.6)	1.00		24 (1.8)	1.00	

[a] All of the variables included in Table 1 were assessed for associations with respiratory distress syndrome and with transient tachypnea of the newborn. Only the variables shown in this table had statistically significant associations with these infant outcomes.

[b] Missing data were excluded from all *P* value calculations.

[c] *P* values are from Fisher exact test.