Original Article

Caesarean section and neonatal survival and neurodevelopmental impairments in preterm singleton neonates

Abhay Lodha MBBS MD DM MSc^{1,2,3,4,5}, Krystyna Ediger MD^{1,2,3}, Dianne Creighton PhD^{2,3},
Selphée Tang BSc², Arijit Lodha BSc (S)⁶, Stephen Wood MD^{1,2,4,7,8}

¹Cumming School of Medicine, University of Calgary, Calgary, Alberta; ²Alberta Health Services, Calgary, Alberta;

³Department of Pediatrics, Foothills Medical Center, Calgary, Alberta; ⁴Department of Community Health Sciences, University of Calgary, Calgary, Alberta; ⁵Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta; ⁶Faculty of Kinesiology, University of Calgary, Calgary, Alberta; ⁷Department of Obstetrics & Gynaecology, Foothills Medical Center, Calgary, University of Calgary, Calgary, Alberta; ⁸O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta

Correspondence: Abhay Lodha, Department of Pediatrics, Foothills Medical Center, Rm C211, 1403-29th St NW Calgary, Alberta, T2N 2T9. Telephone 403-944-8163, fax 403-944-4892, e-mail aklodha@ucalgary.ca

Abstract

Introduction: Evidence is lacking regarding the benefit of caesarean section (CS) for long-term neurodevelopmental outcomes in singleton preterm neonates. Therefore, uncertainty remains regarding obstetrical best practice in the delivery of premature neonates.

Objective: Our objective was to determine the association between the mode of delivery and neurodevelopmental outcomes in preterm singleton neonates who were delivered by vaginal route (VR), CS with labour (CS-L), or CS without labour (CS-NL).

Methods: Singleton neonates of less than 29 weeks' gestation born January 1995 through December 2010 and admitted to our NICU and then assessed at neonatal follow-up clinic were studied. The primary outcome was neurodevelopmental impairment (NDI) defined as cerebral palsy, cognitive delay, major or minor visual impairment, or hearing impairment or deafness at 36 months' corrected age.

Results: In this retrospective cohort study of 1,452 neonates, 1,000 were eligible for the study and 881 (88.1%) were available for follow-up. There was no significant difference in mortality between VR group, CS-L group, and CS-NL group. At 3 years, there was no significant difference between the three groups in terms of NDI. The odds of composite outcome of mortality or NDI for neonates born via CS-NL versus VR, and CS-L versus VR were 0.90 (95% confidence interval [CI]: 0.59 to 1.37) and 1.08 (95% CI: 0.72 to 1.61), respectively. Propensity score-based matched-pair analyses did not show a significant association between the composite outcome and CS with or without labour.

Conclusions: CS was not associated with increased survival or decreased risk of NDI in premature singleton neonates born at less than 29 weeks' gestation.

Keywords: *caesarean section; developmental disabilities; developmental outcomes; follow-up studies; infant; preterm birth*

Advancements in fetal monitoring, obstetric practices, and neonatal care have prevented maternal and neonatal morbidity and mortality (1). However, the optimal mode of delivery for preterm neonates remains a source of debate among health care

providers (2–4). Unnecessary caesarean sections (CS) remain a global concern (5) and it has been established that CS deliveries are not without risk for mothers (6,7) and neonates (8). Studies examining the effects of mode of delivery on outcomes

in premature neonates yield inconsistent findings (8–11). As a result, the potential benefit of early gestation CS deliveries remains unclear (2,7).

Herbst et al. reported that CS delivery yields lower mortality, especially in preterm breech delivery (12). As well, Barber et al. found that infants delivered by vaginal route (VR) had higher mortality rates than those delivered by CS (26.7% versus 10%) (13). In contrast, other studies have reported that survival rates are significantly higher in infants born vaginally (78%) than CS (43%) (13). It has been reported that CS compared with VR deliveries reduce the risk of morbidities such as intraventricular hemorrhage (IVH) (8) and periventricular leukomalacia (PVL) (8,9,14,15), thereby possibly improving eventual neurodevelopmental (ND) outcomes.

Whether or not a mother goes into active labour before delivery may also play a role in both short- and long-term neonatal outcomes. It has been hypothesized that stress due to active labour (16) and vaginal delivery (9) may contribute. Compression of the compliant premature skull may lead to elevation of venous pressure during labour (17), increasing risk for these morbidities (18). It has been reported that CS delivery in mothers in labour is a risk factor for the development of cerebral palsy (19).

A recent Cochrane review concluded that evidence is insufficient to evaluate policies of planned CS for preterm neonates, based on a lack of randomized trials and difficulties with recruitment (20).

There is some literature examining outcomes of premature infants at 18 to 24 months corrected age (CA) based on the mode of delivery (17,21). However, we know from previous studies that ND assessments at 18 to 24 months CA are not strong predictors of outcomes later in childhood (22–26), necessitating research into longer-term ND outcomes. In the absence of information on ND outcomes later in childhood, obstetrical decision making regarding mode of delivery options as well as parental counselling regarding long-term ND outcomes is challenging and incomplete (18).

This study aimed to determine the association of mode of delivery and ND outcome or mortality at 36 months CA in very preterm singleton neonates who were delivered by VR versus CS with labour (CS-L) versus CS without labour (CS-NL). Recognizing existing information and controversy, we hypothesized that CS with or without labour may have beneficial impact on the long-term ND or mortality outcomes in premature singleton neonates at 36 months CA.

MATERIAL AND METHODS

Design and study participants

This retrospective cohort study included all premature neonates born January 1, 1995 through December 31, 2010 at less than 29 weeks' gestational age (GA) who were admitted to the

regional tertiary neonatal intensive care unit (NICU) in southern Alberta and who were subsequently followed prospectively at the Neonatal Follow-up Clinic (NFC). Excluded were neonates from a multiple pregnancy, neonates with major congenital malformations or chromosomal disorders, and neonates born at less than 23 weeks GA, as the latter group generally are not offered CS.

Data collection

Maternal, perinatal, and neonatal data were collected from patients' charts and entered into a computerized database by trained data abstractors. All surviving neonates (<29 weeks GA) were prospectively followed with longitudinal multidisciplinary examinations at 4, 8, and 18 months and 3 years CA at a regional NFC. This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary.

Outcomes

The primary outcome for this study was a composite of mortality or neurodevelopmental impairment (NDI) at 3 years CA. Secondary outcomes included severe NDI and individual components of the primary outcome.

Definitions

CS without labour

CS with no initiation of labour (not spontaneous and not induced).

NDI

The presence by 3 years of CA any of the following: cognitive score ≥ 1 standard deviation (SD) below the mean, mild or moderate–severe CP, visual impairment or blindness, or hearing impairment or deafness (27). Cognitive score was assessed using Wechsler Preschool and Primary Scale of Intelligence, 3rd or 4th edition (WPPSI-III or WPPSI-IV).

Severe NDI

The presence by 3 years of CA of any of: cognitive score > 2 SD below the mean, moderate–severe CP, blindness, or deafness (27).

Cerebral palsy (CP)

Diagnosed by the neonatologist/developmental paediatrician based on a detailed neurological examination (28). A permanent disability consisting of a marked deficiency in muscle control and posture characterized by abnormal reflexes and muscle tone. Minor CP has the characteristic deficits in muscle tone and reflexes without impairments on activities of daily living. Moderate–severe CP requires daily assistance or the use of specialized appliances (28).

Blindness

Corrected visual acuity of <20/200 in the better eye.

Visual impairment

Corrected visual acuity between 20/60 and 20/200 in the better eye, significant myopia or hypermetropia, or unilateral blindness (27).

Deafness

Bilateral sensorineural loss requiring cochlear implants or amplification.

Hearing impairment

Unilateral sensorineural hearing loss requiring amplification unilaterally or bilateral sensorineural hearing loss not necessitating amplification or cochlear implants (27).

Neonatal outcomes as defined in the Canadian Neonatal Network Abstractor's Manual

(29,30): IVH was defined in accordance with Papile's classification (31). Patent ductus arteriosus was diagnosed based on clinical findings with or without echocardiography (29). Bronchopulmonary dysplasia (BPD) was defined as respiratory support at 36 weeks' postmenstrual age (32). Late-onset sepsis (LOS) was defined based on blood or cerebrospinal fluid culture collected after 3 days of age in a symptomatic neonate (29). Retinopathy of prematurity (ROP) was defined according to the international classification of ROP (33). Necrotizing enterocolitis was defined based on Bell's criteria (34). Small for gestational age (SGA) was defined as birth weight below the 10th percentile for GA based on Fenton growth curves (35,36).

Statistical analysis

Maternal and neonatal characteristics were described and compared across groups using Pearson Chi-square or Fisher's exact test for categorical variables and, as they were not normally-distributed, the Kruskal-Wallis test for continuous variables. To determine whether mode of delivery was a significant predictor of the primary outcome of mortality or any NDI after controlling for perinatal and neonatal factors, a logistic regression model was fit; CS groups were separated into CS-NL and CS-L due to potential inherent differences between those deliveries that did not involve any labour and those that did (such as infection risk, maternal indications, or emergency deliveries).

Covariates were chosen based on clinical importance and included antenatal steroid use, GA, sex, inborn, breech presentation, SGA, and chorioamnionitis. Due to baseline differences between the groups, post-hoc analyses using propensity scores (PS) were conducted. Propensity scores were calculated separately for each paired group (CS-NL versus VR and CS-L versus VR) using a logistic regression model with mode of delivery as

the response variable and categorical GA, antenatal steroid use, SGA, inborn, multigravida, breech presentation, maternal antibiotic use, maternal antihypertensive use, sex, and clinical chorioamnionitis as predictor variables. Cases (CS-NL or CS-L) were matched to controls (VR) using a caliper width of 0.2 SD of the logit of the propensity score. One-to-one matching was done using the SAS GMATCH macro. Balance between groups in the matched samples was assessed using standardized differences of the covariates used in the propensity score estimation. Odds ratios and 95% confidence intervals (CIs) for each of the matched samples were calculated by fitting a generalized estimating equation using the logit link function and an unstructured correlation matrix. All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA) with significance level 0.05.

RESULTS

There were 1,452 neonates born at less than 29 weeks during the study period with 1,000 children eligible for this study (Figure 1). Excluding the 119 children lost to follow up at 3 years CA, a total 881 (88.1%) were included in the analysis. These children were divided into three groups: delivery by VR (n=471), CS-NL (n=191), or CS-L (n=219).

Maternal and infant characteristics of the study cohort are presented in Table 1. Neonates delivered by CS-NL were more likely to have a higher GA and to be extremely low birth weight than those delivered by VR or CS-L ($P<0.001$). Neonates delivered via CS-NL were more likely born to mothers requiring antihypertensive medication and less likely to have had clinical chorioamnionitis, rupture of membranes ≥ 24 hours, and maternal antibiotics. Neonates in the CS-L group were more likely to have breech presentation.

When comparing participants to those lost to follow up, the group that was lost to follow up had higher GA at birth, higher birth weight and lower rates of common morbidities of prematurity (Table 2).

NDI and mortality at 3 years CA are summarized in Table 3. Mode of delivery was not found to be significantly associated with any of the outcomes. Of neonates with breech presentation, the proportion without the composite outcome of mortality or NDI was higher in both CS groups than VR group (VR 32% versus CS-NL 62% versus CS-L 62%, $P<0.001$).

In a logistic regression model (Table 3), after adjusting for sex, inborn, clinical chorioamnionitis, antenatal corticosteroids, GA, SGA, and breech presentation, the adjusted odds ratio (aOR) for mortality or NDI for children born via CS-NL versus VR was 0.90 (95% CI: 0.59 to 1.37), the aOR of mortality or NDI for children born via CS-L versus VR was 1.08 (95% CI: 0.72 to 1.61), and the aOR of mortality or NDI for children born via CS-L versus CS-NL was 1.20 (95% CI: 0.76 to 1.90). Post-hoc analyses using propensity score-matched samples did not show

Figure 1. Flow diagram of the study cohort

significant differences for the CS-L and CS-NL groups compared to VR group. Further, to explore any potential change in outcomes over the study time period resulting from changes in NICU practice, we analyzed data based on various epochs (1995 to 2000 versus 2001 to 2005 versus 2006 to 2010). With epoch included in the model, the adjusted odds of composite outcome of NDI or mortality comparing CS-NL versus VR, CS-L versus VR and CS-L versus CS-NL were 0.97 (95% CI 0.63 to 1.48) and 1.17 (0.78 to 1.76) and 1.21 (95% CI: 0.76 to 1.93), respectively. Propensity score-matched models also did not show any difference in the adjusted odds of the composite outcome of NDI or mortality between CS-NL versus VR (1.05 [95% CI: 0.57 to 1.92]) and CS-L versus VR (0.78 [95% CI: 0.45 to 1.36]) groups when epoch was included.

DISCUSSION

In this single-centre, population-based cohort study of preterm neonates, birth via CS with or without labour was not associated with reduced odds of composite outcomes of NDI or mortality at 3 years CA. Post-hoc propensity score-based analyses

also confirmed this finding. Our study results are based on follow-up to 3 years CA, which are more predictive of longer-term ND outcomes compared with other studies that have reported outcomes at 18 to 24 months CA (37,38).

Our study results further confirmed the findings of smaller follow-up studies of premature infants born by CS (37,38). Haque et al. reported that preterm neonates weighing less than 1,250 g born by CS (n=110) versus VR (n=103) did not show either reduced mortality or neuro-disability at 2 years of age (39). A study by Obican et al. found no difference in Bayley II scores between modes of delivery in periviable neonates (23 to 25 weeks' GA [vaginal delivery=91, caesarean delivery=67]) (37).

We did not find any association in the mortality rates between CS with or without labour versus vaginal delivery. Batton et al. recently reported a significant rise in the CS rate in the USA from 1999 to 2005 for neonates born at less than 28 weeks GA, but noted no associated improvement in the infant mortality rate (40). In contrast, Malloy et al. found that preterm neonates born ≤ 25 weeks' gestation by CS showed a reduced mortality rate independent of maternal risk factors for CS (41).

Table 1. Characteristics of mothers and neonates included in the study and their outcomes[†]

Characteristics	VR group n=471	CS-NL group n=191	CS-L group n=219	P-value*
Maternal Characteristics				
Maternal age at delivery, > 40 years, n (%)	8 (2)	3 (2)	5 (2)	0.794
Multi gravida, n (%)	291/450 (65)	129/188 (69)	163/218 (75)	0.031
Maternal education > high school, n (%)	206/369 (56)	87/163 (53)	111/188 (59)	0.559
Median Blisshen score [†] (IQR)	41 (32–57)	39 (32–53)	42 (33–56)	0.446
Maternal race aboriginal/First Nations, n (%)	31/399 (8)	10/166 (6)	9/180 (5)	0.432
Maternal smoking during pregnancy, n (%)	141/449 (31)	45 (24)	57/218 (26)	0.093
Maternal use of street drugs during pregnancy, n (%)	30/447 (7)	10/190 (5)	10/216 (5)	0.521
Antenatal steroids, n (%)				0.008
None	98/454 (22)	22/188 (12)	29/215 (13)	
Partial <2 doses	153/454 (34)	62/188 (33)	74/215 (34)	
Complete ≥2 doses	203/454 (45)	104/188 (55)	112/215 (52)	
Maternal antihypertensives, n (%)	11/453 (2)	86/187 (46)	17/214 (8)	<0.001
Maternal antibiotics, n (%)	333/454 (73)	82/188 (44)	144/212 (68)	<0.001
Clinical chorioamnionitis, n (%)	162/434 (37)	37/187 (20)	61/208 (29)	<0.001
Rupture of membranes ≥24 hours, n (%)	159/458 (35)	36/188 (19)	71/212 (33)	<0.001
Breech presentation at delivery, n (%)	85/466 (18)	76/187 (41)	136/216 (63)	<0.001
Neonatal Characteristics				
Gestational age, weeks, n (%)				<0.001
23–26 weeks	300 (64)	79 (41)	119 (54)	
27–28 weeks	171 (36)	112 (59)	100 (46)	
Median gestational age, weeks, (IQR)	26 (24–27)	27 (26–28)	26 (25–27)	<0.001
Birth weight, g, n (%)				<0.001
≤750 g	163 (35)	88 (46)	55 (25)	
751–1,000 g	172 (37)	67 (35)	95 (43)	
1,001–1,250 g	107 (23)	34 (18)	64 (29)	
>1,250 g	29 (6)	2 (1)	5 (2)	
Median birth weight, g, (IQR)	860 (710–1040)	760 (640–940)	910 (750–1,040)	<0.001
Male, n (%)	269 (57)	101 (53)	126 (58)	0.557
Inborn, n (%)	384 (82)	176 (92)	188 (86)	0.002
Small for gestational age <10th percentile, n (%)	11 (2)	51 (27)	10 (5)	<0.001
5-minute APGAR score, n (%)				0.975
0–3	30/462 (6)	11/189 (6)	12/219 (5)	
4–6	148/462 (32)	59/189 (31)	73/219 (33)	
7–10	284/462 (61)	119/189 (63)	134/219 (61)	
Median cord pH [†] , (IQR)	7.32 (7.24–7.36)	7.27 (7.21–7.31)	7.30 (7.23–7.34)	<0.001
Cord pH <7.20, n (%)	58/396 (15)	36/167 (22)	35/184 (19)	0.108
Postnatal steroids (Dexamethasone), n (%)	116 (25)	47 (25)	42 (19)	0.255
Neonatal outcomes				
PDA, n (%)	294/469 (63)	111 (58)	120 (55)	0.127
RDS, n (%)	403/470 (86)	166 (87)	186 (85)	0.848
Confirmed LOS, n (%)	122/463 (26)	38 (20)	52/218 (24)	0.213
IVH grade ≥ 3, n (%)	67/469 (14)	19 (10)	26/218 (12)	0.290
PVL, n (%)	24/263 (5)	2 (1)	11/218 (5)	0.046

Table 1. Continued

Characteristics	VR group n=471	CS-NL group n=191	CS-L group n=219	P-value*
ROP stage $\geq$ III $\pm$ plus disease $\pm$ laser, n (%)	89/316 (28)	27/143 (19)	41/153 (27)	0.101
BPD (respiratory support at 36 weeks GA), n (%)	227/426 (53)	121/180 (67)	121/201 (60)	0.005
Necrotizing enterocolitis, n (%)	69 (15)	17 (9)	35 (16)	0.081

BPD Bronchopulmonary dysplasia; CS Caesarean section; IQR Interquartile range; IVH Intraventricular haemorrhage; L Labour; LOS Late-onset sepsis; NL No labour; PDA Patent ductus arteriosus; PVL Periventricular leukomalacia; RDS Respiratory distress syndrome; ROP Retinopathy of prematurity.

*Kruskal–Wallis test for continuous variables; Pearson χ^2 or Fisher's exact test for categorical variables.

†Excludes missing values.

‡Denominators may be different for each characteristic if the data is missing or unknown.

Table 2. Demographic characteristics of neonates included in the study compared to neonates lost to follow up

Characteristics	Included n=881	Lost to follow-up n=119	P-value*
Median gestational age, weeks, IQR	26 (25–27)	27 (26–28)	<0.001
Median birth weight, g, IQR	850 (710–1,020)	965 (790–1,110)	<0.001
Male, n (%)	496 (56)	68 (57)	0.862
Inborn, n (%)	752 (85)	102 (86)	0.918
Mode of delivery, n (%)			
Vaginal	471 (53)	63 (53)	0.435
CS without labour	191 (22)	21 (18)	
CS with labour	219 (25)	35 (29)	
Confirmed sepsis, n (%)	212/872 (24)	13/117 (11)	0.001
IVH Grade $\geq$ 3, n (%)	112/878 (13)	1 (1)	<0.001
ROP stage $\geq$ III $\pm$ plus disease $\pm$ laser treated, n (%)	180/783 (23)	12/99 (12)	0.014
BPD (oxygen at 36 weeks GA), n (%)	469/806 (58)	57/101 (56)	0.737
NEC, n (%)	121 (14)	4 (3)	0.001

BPD Bronchopulmonary dysplasia; CS Caesarean section; IQR Interquartile range; IVH Intraventricular hemorrhage; L Labour; NL No labour; NEC Necrotizing enterocolitis; ROP Retinopathy of prematurity.

*Mann–Whitney U test for continuous variables; Pearson χ^2 or Fisher's exact test for categorical variables.

In the past, it was speculated that the stress of labour during vaginal birth was higher than that of CS leading to elevations in venous pressure during labour and causing IVH, PVL and resulting poor ND outcomes. However, Wadhawan et al. reported that CS delivery with labour did not lead to any increase in adverse neonatal outcomes and NDI at 18 to 22 months (17). This finding was confirmed with other reports in the literature (9,38,42–44).

When evaluating the long-term ND outcomes of neonates delivered via CS, we did not find any impact of labour prior to CS delivery. This finding was consistent with other studies where the ND outcomes at 18 to 22 months CA in neonates born less than 28 weeks GA and/or with birth weight less than 1,000 g were evaluated (16,41). Our study suggests that labour

does not increase the incidence of mortality or NDI in premature neonates.

Regarding breech presentation, we found that neonates delivered by CS had a lower risk of composite outcome of mortality or NDI compared with those delivered vaginally. Previous studies that have shown vaginal birth for preterm neonates in breech presentation is possibly associated with a higher risk of adverse neonatal outcomes, including mortality, BPD, ROP, and IVH compared with caesarean birth (10,45,46).

The retrospective nature of the study possibly introduces bias. Our sample size was limited to the time period for which data were available, with 881 children followed to age 3. As far as we can tell, this is the first large study of mode of delivery in preterm infants with follow-up to age 3 years when standardized

Table 3. Logistic regression model and neurodevelopmental outcomes*

Outcome	VR group N=471	CS group N=410	CS-NL group N=191	CS-L group N=219	Adjusted OR (95% CI) ^a CS vs. VR	Adjusted OR (95% CI) ^b CS-NL vs. VR	Adjusted OR (95% CI) ^b CS-L vs. VR	Adjusted OR (95% CI) ^b CS-L vs. CS-NL	Propensity score-matched OR (95% CI) ^c (87 pairs in each group)	Propensity score-matched OR (95% CI) ^c (121 pairs in each group)
Primary Outcome	232 (49)	170 (41)	77 (40)	93 (42)	0.99 (0.70–1.39)	0.90 (0.59–1.37)	1.08 (0.72–1.61)	1.20 (0.76–1.90)	0.83 (0.48–1.45)	0.82 (0.48–1.39)
Mortality or NDI, n (%)										
Mortality, n (%)	90 (19)	57 (14)	25 (13)	32 (15)	0.82 (0.51–1.32)	0.76 (0.40–1.43)	0.86 (0.50–1.47)	1.13 (0.57–2.23)	0.74 (0.33–1.63)	0.81 (0.44–1.50)
NDI, n (%)	143/382 (37)	114/354 (32)	52/166 (31)	62/188 (33)	1.04 (0.71–1.54)	0.94 (0.59–1.52)	1.14 (0.72–1.79)	1.21 (0.72–2.02)	0.90 (0.48–1.68)	0.88 (0.49–1.60)
Severe NDI, n (%)	47/382 (12)	47/354 (13)	23/166 (14)	24/188 (13)	1.46 (0.86–2.49)	1.46 (0.76–2.82)	1.46 (0.79–2.71)	1.00 (0.50–2.00)	0.93 (0.40–2.17)	0.95 (0.44–2.01)
Cerebral palsy, n (%)	45/383 (12)	33/356 (9)	12/166 (7)	21/190 (11)	1.16 (0.65–2.09)	1.12 (0.53–2.36)	1.20 (0.61–2.35)	1.07 (0.48–2.36)	1.06 (0.40–2.81)	0.96 (0.38–2.44)
Blindness or visual impairment, n (%)	28/384 (7)	24/355 (7)	13/166 (8)	11/189 (6)	0.97 (0.46–2.05)	0.97 (0.38–2.49)	0.97 (0.41–2.31)	1.00 (0.36–2.73)	1.23 (0.44–3.43)	1.08 (0.38–3.05)
Deafness or hearing impairment, n (%)	16/383 (4)	16/356 (4)	6/167 (4)	10/189 (5)	1.21 (0.51–2.86)	0.85 (0.27–2.70)	1.53 (0.59–3.99)	1.80 (0.56–5.82)	0.69 (0.15–3.19)	1.38 (0.43–4.42)
Cognitive impairments, n (%)	101/368 (27)	75/346 (22)	34/162 (21)	41/184 (22)	0.99 (0.64–1.52)	0.87 (0.50–1.49)	1.10 (0.67–1.82)	1.27 (0.71–2.29)	0.76 (0.38–1.53)	0.79 (0.42–1.50)

CI Confidence interval; CS Caesarean section; L Labour; NL No labour; N Number in group; NDI Neurodevelopmental impairment; n Number in category; OR Odds ratio.

^aAdjusted for gestational age, sex, inborn, chorioamnionitis, antenatal steroids, small for gestational age, breech (these factors are predelivery).^bAdjusted for gestational age, sex, inborn, chorioamnionitis, antenatal steroids, small for gestational age, breech.^cPropensity score estimated from gestational age, antenatal steroid use, small for gestational age, inborn, multigravida, breech presentation, maternal antibiotic use, maternal antihypertensive use, male, and chorioamnionitis.

*Denominators may be different for each outcome if the outcome is missing, unknown, or unable to be assessed.

intellectual assessment can be performed. We do not have information about the stage or duration of labour or indications for CS. The fact that our perinatal centres have no standard obstetrical guidelines for mode of delivery decisions based on GA may introduce some provider bias in decision making and limit generalizability of findings. In addition, the propensity score matching was only able to match approximately 50% of individuals in each of the CS-L and CS-NL groups to the VR reference group. There may be unobserved factors that affect the propensity for CS. It is reassuring, however, that the conclusions did not change based on analysis of the matched samples that compare those with similar observed baseline characteristics. We did not have complete information of *Gross Motor Function Classification System* (GMFCS) (47) based severity of CP on all neonates included in the study period.

We also have a risk of attrition bias due to loss-to-follow-up. However, the distribution of mode of delivery for those lost-to-follow-up was similar to those included in the analysis, suggesting that loss-to-follow-up occurred completely at random between groups.

The World Health Organization (WHO) recommends that CS should be performed only when there is an obstetric indication (48). Our results support the recommendation to avoid unnecessary CS solely in the anticipation of beneficial effects on the long-term ND outcomes of premature neonates. We found that, except in the case of breech deliveries of premature neonates, delivery of singleton preterm neonates less than 29 weeks' GA by CS was not associated with reduced odds of composite outcomes of NDI or mortality or severe NDI at 3 years CA. Until we have evidence from randomized control trials, we would not recommend CS as a mode of delivery for preterm neonates based on potential ND outcomes and instead suggest these decisions should be based on obstetric and fetal indications and facilitated through joint discussion amongst obstetricians, parents and neonatologists.

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