

No relationship between mode of delivery and neonatal mortality and neurodevelopment in very low birth weight infants aged two years

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Background: To compare neonatal mortality and neurodevelopmental outcomes at two years of age in very low birth weight infants (≤ 1500 g) born by cesarean with those by vaginal delivery.

Methods: In this retrospective, case-control study, we evaluated neonatal mortality, medical conditions and neurodevelopmental outcomes at two years of corrected age in 710 very low birth weight (VLBW) infants born between January 2005 and December 2010. Of the 710 infants, 351 were born by the cesarean and 359/710 by vaginal route.

Results: There were no significant differences in neonatal mortality between the cesarean delivery group and vaginal delivery group [56/351 (15.9%) vs. 71/359 (19.8%), $P=0.20$]. VLBW infants delivered by the cesarean procedure had a higher incidence of respiratory distress syndrome than those born by the vaginal route [221/351 (63.0%) vs. 178/359 (49.6%), $P<0.001$]. There were no differences in other neonatal morbidities, including intraventricular hemorrhage [126/351 (35.9%) vs. 134/359 (37.3%), $P=0.69$], bronchopulmonary dysplasia [39/351 (11%) vs. 31/359 (8.6%), $P=0.38$] and necrotising enterocolitis [40/351 (11.4%) vs. 32/359 (8.9%), $P=0.32$] between the two groups. The incidence of poor neurodevelopment after cesarean delivery was similar to that after vaginal delivery [105/351 (29.9) vs. 104/359 (29.0%), $P=0.78$].

Conclusions: In neither neurodevelopment nor neonatal mortality did cesarean birth offered significant

advantages to VLBW infants. Moreover, the operation might be associated with an increased risk of respiratory distress syndrome for VLBW infants. The mode of delivery of VLBW infants should be largely based on obstetric indications and maternal considerations rather than perceived better outcomes for the neonate.

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Key words: cesarean delivery; neonatal mortality; neurodevelopment outcomes; vaginal delivery; very low birth weight

Introduction

In recent years, cesarean delivery rates have been increasing across all gestational ages.^[1] In 2010, cesarean delivery rates among infants at 32 weeks of gestation or less were reported to be almost 50% among primigravid women in China. Despite increasing cesarean delivery rates, the mortality for very low birth weight (VLBW) infants (≤ 1500 g) has remained relatively stable with 244.3 deaths per 1000 live births in 2000 and 244.5 deaths per 1000 live births in 2004.^[1,2] Whether cesarean delivery offers any survival advantage for very preterm (<32 weeks of gestation) or VLBW infants has been a matter of debate for several years.^[3-8] Lee et al^[8] reported a survival advantage among VLBW infants delivered by the cesarean procedure, independent of a number of maternal medical, labor complications and demographic risk factors in a US national survey. Later the same authors also suggested that prematurity alone was not a valid indication for cesarean birth.^[7] The question arises whether this information is relevant to clinical practice in developing countries. This retrospective study was undertaken to evaluate the impact of different modes of delivery on neonatal mortality and other short-term outcomes and neurodevelopment outcomes of VLBW infants at the corrected age (CA) of two years.

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Methods

Population

From January 2005 to December 2009, all preterm infants weighing 1500 g or less born at the Women's Hospital of Zhejiang University School of Medicine were enrolled in this study of neonatal outcomes. The ethics committee of the Women's Hospital approved the study.

Indications for cesarean delivery

Indications for cesarean delivery were absolute (e.g., central placental previa, obvious cephalopelvic disproportion) or relative [e.g., delay in labor, poor obstetric history, such as preeclampsia, intrauterine growth retardation (IUGR) in previous pregnancy, etc]. All decisions involved both the mother and her obstetrician.

Assessment of neurodevelopment outcomes

Follow-up examinations were performed for all infants at two years of corrected age in our outpatient clinic by an independent pediatrician, who was a specialist in neurodevelopmental evaluation. Neurodevelopmental status was evaluated with Bayley Scale II for cognitive, social, speech and gross and fine motor skills (mean 100 points at 2 years CA, range 85-115 points). A result of less than 70 points indicates severe impairment.^[9] Cerebral palsy (CP) was diagnosed and assessed in keeping with the European consensus paper.^[10] Auditory evoked potentials and visual acuity checks were done at Children's Hospital, Zhejiang University School of Medicine. In the study, poor neurodevelopmental outcome was defined as one or more of the following criteria including CP, Bayley mental development index score of less than 70, bilateral blindness, bilateral hearing loss or hearing aid requirement, at the CA of two years.

Definition of some medical conditions

The diagnosis of respiratory distress syndrome (RDS) was based on the occurrence of classic signs of respiratory distress such as the need for oxygen supplementation, tachypnea, intercostal muscle retraction, grunting, and the exclusion of other causes of respiratory failure. The diagnosis was also confirmed radiologically by reduced lung volumes, a reticulogranular pattern of lung consolidation, and air bronchograms.^[11] Bronchopulmonary dysplasia (BPD) was defined as oxygen requirement at 36 weeks of postconceptional age.^[12] Necrotizing enterocolitis (NEC) was clinically and radiographically diagnosed using modified Bell's criteria.^[13,14] Intraventricular hemorrhage (IVH) was graded according to Papile.^[15]

Retinopathy of prematurity (ROP) was graded according to the International Classification of ROP.^[16]

Statistical analysis

The data were expressed as proportion, mean±standard deviation or median (range). Proportions were compared by the chi-square test. Continuous variables were compared by Student's *t* test or the Mann-Whitney *U* test according to their distribution. To identify the factors associated with the mortality and neurodevelopment at the CA of two years, a logistic regression model was developed. The classical factors, such as GA, birth weight, antenatal steroids, gender, Apgar score at 1 and 5 minutes, small for gestational age (SGA), multiple births and mode of delivery were included in the model. A *P* value <0.05 was considered as statistically significant. Data analysis was carried out using the SPSS software, version 19.0 for Windows (SPSS, Inc, Chicago, IL, USA).

Results

In the total of 42 375 infants born at the period of study, 807 infants had a birth weight of 1500 g or less. Of the 807 infants, 25 died in the delivery room or soon after birth because of obvious abnormality or extreme gestational age, and 72 were excluded because they were transported to other hospitals or because of other reasons such as surgical conditions or incomplete data. Finally, 710 neonates were included in the study, including 359 infants delivered by the vaginal route, and 351 infants by the cesarean procedure.

Demographic data

The incidence of maternal complications was similar between the two groups. The number of multiple births delivered by cesarean was 1.5 times higher than that by vaginal delivery (92 vs. 60). There were 368 male and 342 female infants in this study. Their gestational age ranged from 25 to 35 weeks and body weight ranged from 550 g to 1500 g. No differences were found in clinical characteristics and morbidities between the two groups except that VLBW infants who were delivered by the cesarean procedure had a higher incidence of RDS (Table 1).

Neurodevelopment outcomes at the CA of two years

The incidence of poor neurodevelopment at the CA of two years was not different between the two groups [104/359 (29.0%) vs. 105/351 (29.9%), *P*=0.78]. The rate of loss of follow-up was similar between the two groups [30/359 (8.4%) vs. 32/351 (9.1%), *P*=0.72] (Table 2). The results of logistic regression analysis for

Table 1. Characteristics of mothers, perinatal, and neonatal morbidity data summarized according to different delivery modes

Variables	Vaginal delivery n=359	Cesarean delivery n=351	P value
Maternal characteristics			
Maternal age, mean (SD), y	29.3 (5.3)	29.6 (4.8)	0.78
Diabetes, n (%)	17 (4.7)	15 (4.3)	0.86
Hypertension, n (%)	140 (39.0)	121 (34.5)	0.21
PROM, n (%)	98 (27.3)	97 (27.6)	0.93
ICP, n (%)	21 (5.8)	32 (9.1)	0.09
Multiple births, n (%)	60 (16.7)	92 (26.2)	0.002
Full course of antenatal steroids course, n (%)	201 (56.0)	188 (53.6)	0.54
Perinatal data			
Gestation age, mean (SD), wk	29.7 (1.1)	29.8 (1.2)	0.25
26-27 wk, n (%)	43 (12.0)	44 (12.5)	0.82
28-29 wk, n (%)	192 (53.5)	175 (49.9)	0.23
30-31 wk, n (%)	90 (25.1)	97 (28.0)	0.44
≥32 wk, n (%)	34 (9.5)	35 (10.0)	0.82
Birth weight (SD)	1247 (168.0)	1263 (190.2)	0.23
500-749 g, n (%)	6 (1.7)	6 (1.7)	0.98
750-999 g, n (%)	33 (9.2)	30 (8.5)	0.72
1000-1249 g, n (%)	194 (54.0)	188 (53.6)	0.90
1250-1500 g, n (%)	126 (35.1)	127 (36.2)	0.76
Male/female (%)	186/173 (1.08)	182/169 (1.08)	0.99
SGA, n (%)	37 (10.3)	41 (11.7)	0.56
Neonatal morbidity			
RDS, n (%)	178 (49.6)	221 (63.0)	<0.001
Surfactant, n (%)	145 (40.4)	189 (53.8)	<0.001
Mechanical ventilation, n (%)	89 (24.8)	117 (33.3)	0.01
BPD, n (%)	31 (8.6)	39 (11.1)	0.38
Grade 1-2 IVH, n (%)	121 (33.7)	115 (32.8)	0.81
Grade 3-4 IVH, n (%)	13 (3.6)	11 (3.1)	0.84
ROP, n (%)	14 (3.9)	12 (3.4)	0.73
NEC, n (%)	32 (8.9)	40 (11.4)	0.32

PROM: premature rupture of membrane; ICP: intrahepatic cholestasis of pregnancy; SGA: small for gestation age; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; IVH: intraventricular hemorrhage.

Table 2. Outcomes of VLBW infants at the corrected age of two years

Variables	Vaginal delivery n=359	Cesarean delivery n=351	P value
Death, n (%)	71 (19.8)	56 (15.9)	0.18
Loss of following up, n (%)	30 (8.4)	32 (9.1)	0.72
Hearing loss or hearing aid, n (%)	11 (3.1)	13 (3.7)	0.64
Blind, n (%)	0 (0)	0 (0)	1.0
Cerebral palsy, n (%)	25 (7.0)	23 (6.5)	0.83
Bayley MDI 2 years, <70, n (%)	68 (18.9)	73 (20.8)	0.54
Poor neurodevelopment, n (%)	104 (29.0)	105 (29.9)	0.78
Combined poor results, n (%)	175 (48.8)	161 (45.9)	0.45

Poor neurodevelopment: including hearing loss or hearing aid, blind, cerebral palsy and Bayley MDI 2 years<70; Combined poor results: including death and poor neurodevelopmental outcome. MDI: mental development index; VLBW: very low birth weight.

variables affecting the neurodevelopment in the study population are shown in Table 3. Among the variables, delivery mode, Apgar score at 1 minute, male gender, multiple births and treatment with antenatal steroids

Table 3. Factor potentially affecting the neurodevelopment outcomes at the corrected age of two years

Variables	Odds ratio (95% CI)	P value
Gestational age	0.811 (0.359-0.930)	0.033
Birth weight	0.825 (0.301-0.961)	0.041
Male gender	1.371 (0.512-2.711)	0.563
Cesarean section	1.019 (0.580-4.203)	0.612
Antenatal steroid	0.873 (0.518-1.492)	0.374
Small for gestational age	2.301 (1.034-6.935)	0.046
Apgar score at 1 min	0.980 (0.379-4.271)	0.701
Apgar score at 5 min	0.793 (0.187-0.967)	0.043

Hosmer-Lemeshow goodness-of-fit=0.46. CI: confidence interval.

Table 4. Factors potentially affecting the mortality at the corrected age of two years

Variables	Odds ratio (95% CI)	P value
Gestational age	0.758 (0.619-0.929)	0.013
Birth weight	0.794 (0.583-0.881)	0.022
Male gender	1.053 (0.793-1.534)	0.495
Cesarean section	0.901 (0.698-1.210)	0.375
Antenatal steroid	0.806 (0.531-1.017)	0.091
Small for gestational age	1.523 (0.675-3.385)	0.553
Apgar score at 1 min	0.901 (0.439-2.271)	0.398
Apgar score at 5 min	0.862 (0.514-0.981)	0.039

Hosmer-Lemeshow goodness-of-fit=0.57. CI: confidence interval.

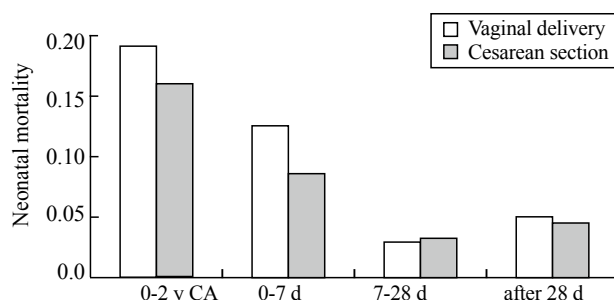


Fig. Neonatal mortality in the vaginal delivery group and cesarean delivery group. CA: corrected age.

were not statistically significant, whereas the logistic regression analysis confirmed that gestational age, birth weight, Apgar score at 5 minutes and SGA were significantly associated with poor neurodevelopment at the CA of two years.

Neonatal mortality

There were no significant differences in neonatal mortality in three different periods between the vaginal delivery and cesarean delivery groups [44 (12.3%) vs. 30 (8.5%) on 0-7th day; 10 (2.8%) vs. 11 (3.1%) on 7-28th day and 17 (4.7%) vs. 15 (4.3%) after 28th day, $P=0.10$, 0.78 and 0.77, respectively]. However, a trend towards higher mortality rates during the first 7 days was found in the vaginal delivery group ($P=0.1$) (Fig.). The results of logistic regression analysis for variables affecting mortality at two years of CA in the study population are

shown in Table 4. Among the variables, delivery mode, Apgar score at 1 minute, multiple births, SGA and treatment with antenatal steroids were not statistically significant, whereas the logistic regression analysis confirmed that gestational age, birth weight, male gender, and Apgar score at 5 minutes were significantly associated with mortality at the CA of two years.

Discussion

To determine whether VLBW infants should be delivered by the vaginal or cesarean route, prospective, randomized controlled trials are not practicable because of difficulty in recruitment and implementation.^[17] One study^[18] reported that there is still no consensus on the indications of cesarean delivery for VLBW infants. A few retrospective studies were done, but no a consistent result was obtained.^[8,19-21] The sample size of our study was larger than that of other studies. Moreover, independent pediatricians responsible for neurodevelopmental evaluation in the entire period were also a distinctive positive feature of this study.

In our study, VLBW infants born by the cesarean procedure did not show reduced neonatal mortality or better neurodevelopment at the CA of two years. This result was consistent with that of a previous report,^[19] but contrary to others.^[8,20,21] The difference may be due to several factors: 1) Populations with different mean gestational age and mean body weight; 2) Antenatal factors including pregnancy complications, prenatal steroid use, and improved neonatal intensive care after birth; 3) Multiple births by the cesarean procedure.^[22-24] For the uncertainty, we did not separate multiple births from singletons in our study as other studies.^[25,26] reported that the neonatal mortality and the incidence of cerebral palsy were greater in infants delivered by the vaginal route, but this was not observed in our study. We postulate that different populations are still the main reason. As reported, infants with poor neurodevelopment at the CA of two years tend to have a birth weight of 750 g or less, and, are born at 26 weeks or less of gestation. However, VLBW neonates in our study were born at 28 to 32 weeks of gestation; extremely preterm infants who were born at 26 weeks or less of gestation only accounted for less than 5%. It was also an explanation for the relatively lower incidence of CP because the prevalence of CP expressed by gestational age was highest in children who were born before 28 weeks of gestation.^[27]

Another significant difference between our study and others is that our patients are primigravid at delivery owing to the national one-child family policy. Typical reproductive careers in eastern China include

one or two surgical terminations of pregnancy prior to a single delivery. That delivery is likely to be the cesarean procedure for a variety of different reasons including maternal request. The prior surgical procedures may be associated with significant rates of unrecognized adenomyosis that contributes to rates of preterm delivery and other obstetric complications. Other studies include primigravid and multigravid mothers who may alter the results significantly. It is important that our data are mostly compared between nulliparous groups rather than mixed parity populations in other studies.

In our study, VLBW infants delivered by the cesarean procedure had a higher morbidity of RDS. To identify the association between RDS and delivery mode, a logistic regression analysis was made. We found that cesarean delivery was an independent risk factor for RDS (OR=1.121, 95% CI=1.072-1.552), when corrected for gestation age, multiple births and gender. Similar to the previous study, we found that second twin was an independent risk factor for RDS (OR=1.270, 95% CI=1.0.93-2.419).^[23,24] We postulate that cesarean delivery and multiple births are the reasons for a higher incidence of RDS, and the better delivery mode for twins warrants further investigation.

There are some limitations in this study. First, this is a retrospective study from a single, tertiary centre, though there may be some advantages in consistency of practice and expertise. Second, we attempted to control for potential confounding factors including gestation, birth weight, gender, antenatal steroid use, postnatal use of surfactant, multiple births, maternal diseases, and prolonged rupture of membrane, etc, although we may have missed some other important factors. Third, we realized that doctors may unduly influence the mode of delivery in many cases. We were also aware of the exclusion of babies who were born in our unit but had to be transferred to other hospitals because of limited resources.

In our unit, cesarean delivery for VLBW infants did not offer any advantage to the infant, but increased the incidence of RDS. We believe that decisions about the appropriate mode of delivery for VLBW infants should be based on obstetric indications rather than neonatal considerations.

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Ethical approval: The Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine approved the

study.

Competing interest: None declared.

Contributors: Zhu JJ wrote the first draft of the paper. All authors contributed to the intellectual content and approved the final version. Wu MY is the guarantor.

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