Original Article

Effect of Mode of Delivery on Neonatal Outcomes of Appropriately Grown Preterm Infants

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Objective: To determine the impact of mode of delivery on neonatal outcomes in appropriately grown very to moderately preterm infants.

Materials and Methods: A retrospective cohort study was performed on 190 singleton pregnant women who gave birth to an appropriately grown infant at 28^{+0} to 33^{+6} weeks of gestation in our institution between 2011 and 2014. The study group (n = 95) comprised women who had undergone cesarean delivery. The control group (n = 95) included those who had vaginal delivery. Both groups were matched 1: 1 by gestational age at delivery. Neonatal outcomes were compared between the two groups. Multiple logistic regression analysis was used to determine the risk of neonatal complications.

Results: Complete data of all 190 women were obtained. According to univariable analysis, cesarean delivery increased the risk of 5-minute Apgar score <7 by threefold (95% confidence interval 1.12 to 8.06) compared to vaginal delivery. The risk remained significant after controlling for confounding factors (adjusted odds ratio = 4.33; 95% confidence interval 1.16 to 16.13). There were no significant differences between both groups in terms of respiratory distress, sepsis, intraventricular hemorrhage, seizure and neonatal death.

Conclusion: In appropriately grown infants who were born at 28^{+0} to 33^{+6} weeks of gestation, cesarean delivery did not improve neonatal outcomes compared to vaginal delivery. On the other hand, it increased the risk of 5-minute Apgar score <7.

Keywords: Modes of delivery, Neonatal complications, Preterm infant

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With an estimated 15 million global preterm births per year[1], preterm delivery is considered a major obstetric problem worldwide. The incidence rates of preterm birth vary across countries ranging from 5 to 18% of babies born, and have steadily increased in the past several years[1]. The reasons for this upward trend are because of the rise in assisted reproductive technologies and non-medically indicated labor induction and cesarean delivery as well as the trend towards delayed childbearing among reproductive-aged women[2]. Preterm neonates are at high risk of mortality and morbidity, which result in prolonged hospitalization and financial burden[3]. Although the majority (75%) of preterm cases are late preterm (34^{+0} to 36^{+6} weeks of gestation) infants[4], very to moderately preterm (28^{+0} to 33^{+6} weeks of gestation) babies are preterm subgroups who make up a large proportion of admissions and bed-days in neonatal intensive care units.

Several factors have been linked to premature neonatal complications, such as gestational age, neonatal birth weight, maternal co-morbid diseases, and mode of delivery[5]. Among these causes, mode of delivery, specifically cesarean delivery, is a factor that is partly influenced by personal reasons e.g. doctors' convenience, preference of patients, etc. aside from the safety reason[6,7]. Recent data indicate that the rate of cesarean sections in preterm births has been rising along with the rate in term births[2]. Neonatal outcomes of cesarean delivery in preterm births have been reported[8-17]. However, the results varied from decreased[8-11], unchanged[12,13], or increased[14-17] mortality and morbidity risks. In addition, these studies were conducted among various population groups. As results from several studies suggested that there were racial/ethnic disparities in mortality and morbidity among preterm infants[18-20], data obtained from White or Black populations might not be suitable to be applied to Asian people. We therefore conducted this study with the aim of determining the impact of mode of delivery on neonatal outcomes in appropriately grown very to moderately preterm infants of Thai ethnicity.

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Materials and Methods

Study population

This retrospective cohort study was conducted after approval from the Vajira Institutional Review Board

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(COA No. 26/2557). The medical records of pregnant women who had given birth to singleton infants at gestational age between 28^{+0} and 33^{+6} weeks in Faculty of Medicine Vajira Hospital between July 2011 and December 2014 were collected. Inclusion criteria were cephalic presentation and appropriately grown infant which was determined based on the preterm infant growth chart adapted by earlier reports[21,22]. All included cases must have received at least one dose (6 mg intramuscular administration) of dexamethasone to promote fetal lung maturity. Pregnant women who had HIV infection, major congenital fetal anomaly, intrapartum complications including chorioamnionitis, fetal distress (classified by the NICHD classification), and those who had undergone operative vaginal delivery were excluded. Data were extracted to identify the mode of delivery, categorized as vaginal delivery or cesarean section. Matching was done 1: 1, based on the same gestational age, between a woman who had undergone a cesarean section (the cesarean group), and a woman who had had vaginal delivery (the vaginal group) at, or as close to, the same time. The sample size was calculated using respiratory distress syndrome as the primary outcome measure, based on the findings of 39.2% and 25.6% respiratory distress syndrome rates in women with cesarean section and vaginal delivery, respectively from the study of Werner et al[14]. The sample size was then calculated using 10% type I error and 20% type II error, with an added 10% to the number calculated in the event that any case was excluded. This resulted in totals of 95 cesarean sections and 95 vaginal delivery cases needed.

Data collection

Maternal demographic data including age, ethnicity, gestational age at delivery, history of prolonged ruptured membranes (ruptured membranes more than 18 hours before delivery), and medical disease (diabetes and hypertension), as well as neonatal complications diagnosed by an attending pediatrician, were collected and compared between the two groups. Neonatal outcomes of interest included respiratory distress, neonatal sepsis, 5-minute Apgar score <7, intraventricular hemorrhage, seizure, and neonatal death.

Statistical analysis

Data were analyzed using SPSS version 22.0 (IBM corporation, Armonk, NY, USA). Continuous data are presented as mean with standard deviation. Pearson's Chi-square test was used to compare categorical variables. Multiple logistic regression analysis with an adjustment for confounding factors was used to determine the impact of mode of delivery on the risk of neonatal complications. The *p*-value <0.05 was considered significant for all tests.

Results

During the study period, 8,269 women gave birth in our institution. Of these, 992 (11.9%) had preterm deliveries: 258 (26%) of which had very preterm or moderately preterm births. Among these, 68 cases were excluded due to the following reasons: no dexamethasone administration (n = 31), non-vertex presentation (n = 11), twin pregnancy (n = 4), congenital fetal anomaly (n = 3), maternal HIV infection (n = 7), and intrapartum complications (n = 12) including chorioamnionitis (n = 4) and fetal distress (n = 8). Because the number of cesarean section cases was less than that of vaginal delivery cases, the authors firstly selected a woman who underwent cesarean section, followed by a matched subject with vaginal delivery. Finally, datasets of 95 women in each group were obtained.

Maternal and neonatal characteristic features are shown in Table 1. There were no significant differences between cesarean section and vaginal delivery groups in terms of maternal age, gestational age at delivery, ethnicity, maternal diabetes (gestational diabetes or overt diabetes), a history of prolonged rupture of membranes, neonatal weight and gender. Women who underwent cesarean delivery were more likely to have hypertensive disorders (gestational hypertension, preeclampsia, or chronic hypertension) than the vaginal delivery group (33.7% vs. 9.5%; $p<0.01$).

Neonatal complications of women in cesarean section and vaginal delivery groups are presented in Table 2. The authors found that both groups had comparable neonatal outcomes except low 5-minute Apgar score, which was significantly higher in the cesarean section group (OR 3.00, 95% confidence interval (CI) 1.12 to 8.06). Sepsis was also more commonly observed in the cesarean section group, but with only marginal significance. When a multivariable analysis

Table 1. Maternal and neonatal characteristics of the study population (n = 190)

Characteristic	Vaginal route (n = 95)	Cesarean route (n = 95)	*p*-value
Maternal age (years)	25.3 (8.1)	28.8 (6.8)	0.26
Gestational age (weeks)			1.00
28^{+0} to 31^{+6}	31 (32.6)	31 (32.6)	
32^{+0} to 33^{+6}	64 (67.4)	64 (67.4)	
Ethnicity			0.76
Thai	90 (94.7)	89 (93.7)	
Non-Thai	5 (5.3)	6 (6.3)	
Diabetes			0.55
Yes	5 (5.3)	7 (7.4)	
No	90 (94.7)	88 (92.6)	
Hypertension			<0.01
Yes	9 (9.5)	32 (33.7)	
No	86 (90.5)	63 (66.3)	
Prolonged ruptured of membrane			0.34
Yes	30 (31.6)	24 (25.3)	
No	65 (68.4)	71 (74.7)	
Neonatal weight (grams)	1,816 (419.7)	1,751 (409.5)	0.29
Neonatal gender			0.39
Male	55 (57.9)	48 (50.5)	
Female	40 (42.1)	46 (48.4)	

Data are presented as mean (standard deviation) or n (%)

with an adjustment for variables in Table 1 was performed, cesarean section remained a significant factor for low 5-minute Apgar score (OR 4.33, 95% CI 1.16 to 16.13). The multivariable analysis also indicated that gestational age of 28^{+0} to 31^{+6} weeks was an independent factor for low 5-minute Apgar score (OR 13.35, 95% CI 4.10 to 43.44), whereas other remaining variables in Table 1 were not identified as significant factors.

The authors also divided all neonates into two subgroups: very preterm (28^{+0} to 31^{+6} weeks) and moderately preterm (32^{+0} to 33^{+6}) infants (Table 3). Upon further univariable analysis of the very preterm subgroup, risks of neonatal complications were not significantly different between the two modes of delivery. On the other hand, the authors observed a significant increase in risks of neonatal sepsis and low 5-minute Apgar score in the cesarean section group compared to the vaginal delivery group among women who gave birth to a moderately preterm infant. After controlling for potential confounding factors by using a multivariable analysis, cesarean section was identified as a significant factor for neonatal sepsis in a moderately preterm subgroup: an adjusted odds ratio was 2.47 (95% CI 1.05 to 5.78).

Discussion

Over the past decade, preterm birth has become a significant public health problem in many countries, including Thailand. Although the prevalence of very to moderately preterm births is less than that of late preterm deliveries, these two preterm subgroups account for a large proportion of admissions and bed-days in neonatal intensive care units. During the study period, the prevalence of very to moderately preterm births in our population was 3.1%. This was consistent with the prevalence of 3.1% reported by Hantanong et al who also conducted a study on Thai population[23] but slightly higher than the 2.8% rate observed in the US[4]. Nevertheless, the incidence in our institution was much lower than the 10% rate observed in Bangladesh[24]. The difference among our and other studies might be because the clinical characteristics and backgrounds of subjects in each study are dissimilar. In the studies reported from Bangladesh and the US, all pregnant women were included for analysis while our study comprised only singleton pregnant women.

Our results demonstrated that mode of delivery had an impact on 5-minute Apgar score among very preterm and moderately preterm infants. This was in agreement with the results of Reddy et al[15] who studied 4,352 singleton

Table 2. Neonatal outcomes of women who underwent cesarean delivery or vaginal delivery at 28^{+0} to 33^{+6} weeks of gestation

	Vaginal route	Cesarean route (n = 95)	Crude Odds ratio (n = 95)	*p*-value
Respiratory distress syndrome	22 (23.2)	27 (28.4)	1.32 (0.69 to 2.53)	0.51
Sepsis	32 (33.7)	45 (47.4)	1.77 (0.99 to 3.18)	0.06
Intraventricular hemorrhage	3 (3.2)	1 (1.1)	0.33 (0.03 to 3.19)	0.31
5-minute Apgar score <7	6 (6.3)	16 (16.8)	3.00 (1.12 to 8.06)	0.02
Seizure	1 (1.1)	0 (0)	-	0.32
Death	0 (0)	1 (1.1)	-	0.32

Data are presented as n (%) or odds ratio (95% confidence interval)

Table 3. Neonatal Outcomes of women who underwent cesarean delivery or vaginal delivery by gestational age of delivery

	28^{+0} to 31^{+6} weeks			32^{+0} to 33^{+6} weeks		
	Vaginal route (n = 31)	Cesarean route (n = 31)	Crude odds ratio	Vaginal route (n = 64)	Cesarean route (n = 64)	Crude odds ratio
Respiratory distress syndrome	17 (27.4)	17 (27.4)	1.00 (0.37 to 2.72)	5 (7.8)	10 (15.6)	2.19 (0.70 to 6.80)
Sepsis	19 (30.6)	19 (30.6)	1.00 (0.36 to 2.78)	13 (20.3)	26 (40.6)	2.68 (1.22 to 5.89)
Intraventricular Hemorrhage	3 (4.8)	0 (0)	-	0 (0)	1 (1.6)	-
5-minute Apgar score <7	6 (9.7)	11 (17.7)	2.29 (0.72 to 7.28)	0 (0)	5 (7.8)	-
Seizure	1 (1.6)	0 (0)	-	0 (0)	0 (0)	-
Death	0 (0)	0 (0)	-	0 (0)	1 (1.6)	-

deliveries at 24^{+0} to 31^{+6} weeks of gestation and found that vaginal delivery was associated with lower rates of perinatal asphyxia. However, their results demonstrated higher rates of intraventricular hemorrhage in neonates born by vaginal delivery compared to cesarean section, which was inconsistent with our finding. Nevertheless, the number of infants who had intraventricular hemorrhage in our study was only four. This would certainly had no adequate power to prove that vaginal delivery was associated with such a complication. Moreover, the ranges of gestational ages of infants in the study of Reddy et al[15] and the present study were different (24^{+0} to 31^{+6} weeks in the study of Reddy et al vs. 28^{+0} to 33^{+6} weeks in the present study). As gestational age at delivery has an inverse relationship with the risk of intraventricular hemorrhage[25], the dissimilar characteristics of subjects between the two studies would have affected the prevalence rates of intraventricular hemorrhage in both studies. Apart from the study of Reddy et al, another study conducted by Werner et al[16] in 20,231 preterm neonates at 24^{+0} to 34^{+0} weeks of gestation also reported that cesarean delivery increased risks of respiratory distress and 5-minute Apgar score <7 compared to vaginal delivery. Although the range of gestational ages in the study of Werner et al[16] was broader than that in the present study, their findings were compatible with our results.

The mechanism by which cesarean section affects neonatal respiratory distress and low 5-minute Apgar score is still unknown. It has been hypothesized that the etiologic cause is likely due to the disruption of the process of transitioning of the lung epithelial sodium channel caused by delivery without prior labor[26]. To verify this hypothesis, the authors further explored our data, but found that rates of neonatal respiratory distress and low 5-minute Apgar score in women who had undergone intrapartum cesarean section (cesarean with labor) were higher than those in women who had undergone pre-labor cesarean section. One explanation for the conflicting results between our findings and such a hypothesis is likely due to a small number of pre-labor cesarean sections in the present study. Furthermore, although the authors excluded patients with intrapartum chorio-amnionitis and fetal distress which might lead to adverse neonatal outcomes, other intrapartum conditions which could also affect low 5-minute Apgar score, e.g. magnesium sulfate administration[27], pethidine use[28], prolonged labor[29,30], presence of meconium[30,31] etc could not be controlled. In this regard, any definite conclusion regarding our findings could not be made until further studies with larger pre-labor and intrapartum cesarean samples along with more rigid inclusion criteria are performed.

This is the first study to explore the impact of delivery mode on neonatal outcomes among Thai pregnant women who gave birth to a very preterm or moderately preterm infant. The strength of the present study was that we minimized a confounding factor of adverse neonatal outcomes by matching each woman in the cesarean section group to a woman in the vaginal delivery group by gestational age at delivery. Another potential strength was that all women in the present study had a certain last menstrual period along with a mid-trimester ultrasound confirmation, so their gestational ages were reliable. Finally, the authors selected only women who received dexamethasone therapy and those with appropriately grown infants in order to diminish a variety of clinical characteristics of the study population which could affect birth outcomes.

Nevertheless, there were some limitations in the present study. As this was a retrospective study, some data could be imprecise or unavailable; for example, a diagnosis of neonatal complication, or some laboratory tests). In addition, the sample size of our population was not large enough to determine the impact of mode of delivery on uncommon adverse neonatal complications, such as intraventricular hemorrhage and neonatal death. Lastly, our study was conducted in a low-risk group of appropriately grown infants who were born between 28^{+0} and 33^{+6} weeks of gestation, so it could not be applied to high risk groups, such as intrauterine growth restriction or fetal distress.

Conclusion

In conclusion, our results demonstrated that among appropriately grown infants who were born at 28^{+0} to 33^{+6} weeks of gestation, cesarean delivery did not improve neonatal outcomes compared to vaginal delivery. On the other hand, it increased the risk of low 5-minute Apgar score.

What is already known on this topic?

Preterm delivery is a major obstetric problem worldwide. The majority of preterm cases are late preterm (34^{+0} to 36^{+6} weeks of gestation) infants. Preterm neonates are at high risk of mortality and morbidity, leading to prolonged hospitalization and financial burden of family and healthcare sector.

What this study adds?

Vaginal delivery should be the preferred mode of delivery in appropriately grown infants who were born at 28^{+0} to 33^{+6} weeks of gestation. This was because cesarean delivery did not improve neonatal outcomes but increased the risk of low 5-minute Apgar score compared to vaginal delivery.

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Potential conflicts of interest

The authors declare no conflict of interest.

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