Cesarean section does not affect neonatal outcomes of pregnancies complicated with preterm premature rupture of membranes

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Abstract

Background: Preterm premature rupture of membranes (PPROM) is associated with high neonatal morbidity and mortality. However, the influences of cesarean section (CS) on neonatal outcomes in preterm pregnancies complicated with PPROM are not well elucidated. The aim of this study was to investigate the influence of delivery modes on neonatal outcomes among pregnant women with PPROM.

Methods: A retrospective cross-sectional study was conducted in 39 public hospitals in 14 cities in the mainland of China from January 1st, 2011 to December 31st, 2011. A total of 2756 singleton pregnancies complicated with PPROM were included. Adverse neonatal outcomes including early neonatal death, birth asphyxia, respiratory distress syndrome (RDS), pneumonia, infection, birth trauma, and 5-min/10-min Apgar scores were obtained from the hospital records. Binary variables and ordinal variables were respectively calculated by binary logistic regressions and ordinal regression. Numerical variables were compared by multiple linear regressions.

Results: In total, 2756 newborns were involved in the analysis. Among them, 1166 newborns (42.31%) were delivered by CS and 1590 newborns belonged to vaginal delivery (VD) group. The CS proportion of PPROM obviously increased with the increase of gestational age ($\chi^2 = 5.014$, $P = 0.025$). Compared with CS group, VD was associated with a higher risk of total newborns mortality (odds ratio [OR], 2.38; 95% confidence interval [CI], 1.102–5.118; $P = 0.027$), and a lower level of pneumonia (OR, 0.32; 95% CI, 0.126–0.811; $P = 0.016$). However, after multivariable adjustment and stratification for gestational age, only pneumonia was significantly related with CS in 28 to 34 weeks group (OR, 0.34; 95% CI, 0.120–0.940; $P = 0.038$). There were no differences regarding to other adverse outcomes in the two groups, including neonatal mortality, birth asphyxia, Apgar scores, RDS, pneumonia, and sepsis.

Conclusions: The proportion of CS of pregnant women with PPROM was very high in China. The mode of delivery does not affect neonatal outcomes of pregnancies complicated with PPROM.

Keywords: Preterm premature rupture of membranes; Cesarean section; Vaginal delivery; Perinatal outcomes

Introduction

Preterm premature rupture of membranes (PPROM) complicates approximately 2% to 3% of all pregnancies in the United States and other countries.[1-3] PPROM is associated with up to 30% to 40% preterm birth, which could result in increased neonatal morbidity and mortality, specifically caused by respiratory distress syndrome (RDS), and infections.[4-7] The treatment of antibiotics (amoxicillin, ampicillin, etc) for infection of the lower genital tract after PPROM supports a prolonged pregnancy to allow maturation of vital organs of the fetus.[8] However, prolonging pregnancy does not always work due to the onset of labor and maternal as well as fetal complications. Therefore, even without serious pregnancy complications, PPROM is associated with a higher proportion of adverse neonatal outcomes compared with preterm deliveries after spontaneous preterm labor.[9]

Even though the management of PPROM is conservatively preformed, it is generally accepted that the pregnancy should be prolonged for fetal maturation to improve neonatal outcomes.[1-3] In cases of PPROM, the fetuses are considered adequately mature when pregnancy time is more than 34 weeks, while the modes of delivery are selected based upon obstetrical indications. Previous studies have revealed the potential risks of PPROM, the relationship between PPROM and adverse neonatal outcomes, the proper delivery time and the management before delivery.[10-13] However, the influences of delivery modes (vaginal delivery [VD] or cesarean section [CS]) on

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neonatal outcomes in preterm pregnancies complicated by PPROM are not well disclosed. Despite the fact that CS is thought to be the prior choice for extremely preterm infants,[14,15] no consensus has been reached for the optimum mode of delivery in those with low birth weight and preterm birth.[14-18] In this study, we aimed to investigate the association between mode of delivery and neonatal outcomes and present our experience on optimal delivery mode from 2756 cases with PPROM in 39 centers in the mainland of China.

Methods

Ethical approval

This study was approved by the Medical Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Beijing, China. Informed consent was obtained from each participant for their clinical records.

Population

From January 1st, 2011 to December 31st, 2011, a cross-sectional study was conducted by the Chinese Obstetric Pregnancy and Delivery Collaborated Group in 39 public hospitals from 14 cities in the mainland of China, including central area (Hubei, Shanxi), eastern area (Beijing, Hebei, Shanghai, Jiangsu, Shandong, Guangdong), northeastern area (Jilin, Liaoning), western area (Sichuan, Inner Mongolia, Shaanxi, and Xinjiang). The specific hospitals were listed in Supplemental File 1, http://links.lww.com/CM9/A149. The exclusion criteria were as follows: pregnancies younger than 14 years or older than 60 years, without PPROM, multifetal pregnancies and gestational age of PPROM before 24 weeks.

Demographics and clinical data (maternal medical history, pregnancy comorbidities, and complications) were collected from records of perinatal health care. Data of PPROM, mode of delivery and newborn outcome were collected directly from hospital charts.

Definition and measurements

Premature rupture of membranes (PROM) was defined as rupture of the membranes of the amniotic sac and chorion more than 1 h before the onset of labor and diagnosed based upon the symptoms, physical examination, pH evaluation or measurement of insulin-like growth factor binding protein-1. PPROM was defined when PROM happened before 37 weeks of pregnancy.[19] Standard operating protocols for preterm delivery that included the prenatal steroid treatment with betamethasone were performed. According to records, all pregnancies have been divided into CS and VD groups.

Gestational age of the fetus was calculated by referring to the date of last menstrual period (LMP) and had been confirmed by first-trimester ultrasonography. If LMP was unknown or if the mother's menstrual period was irregular, gestational age was determined according to fetal size measured by B-ultrasound at early pregnancy. Thereafter, pregnant women with PPROM were divided into three sub-groups: 24 to <28 weeks, 28 to <34 weeks, and 34 to <37 weeks based on the gestational weeks.[20]

Study endpoints

Based on the largest available register study by Thongren-Jerneck and Herbst,[21,22] the 5 and 10-min Apgar scores usually implicated clinical prognosis, whereas the low Apgar score at 1 min often reflected a temporary depression. We used 5-min Apgar scores of <7 and 10-min Apgar scores as predictors for neonatal outcome.[22]

Adverse neonatal outcomes included early neonatal death (neonatal death in 7 days), birth asphyxia, RDS, pneumonia, infection, and birth trauma. Birth asphyxia was evaluated by Apgar score at 1 min: Apgar score ≤ 3 at 1 min were defined as severe birth asphyxia and $4 \leq$ Apgar score ≤ 7 at 1 min was defined as mild birth asphyxia, according to the Chinese expert consensus about diagnosis of neonatal asphyxia.[23]

Statistical analysis

Continuous variables such as birth weight were expressed as mean ± standard deviation and compared by Student's t test with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The skewed distributed variables were summarized by median and interquartile range such as Apgar scores, and were compared by the Wilcoxon rank-sum test. Categorical variables were summarized by absolute frequencies and percentages, which were analyzed by the Chi-square test (area distribution, gender, etc). The adjusted odds ratios (ORs, 95% confidence intervals [CIs]) of binary variables were calculated by binary logistic regressions. Ordinal regression was applied to compare the birth asphyxia degrees of newborns. Numerical variables were compared by multiple linear regressions. A $P < 0.05$ was considered as significant difference.

Results

Basic information

The study design was shown in Figure 1. In total, 2756 pregnant women with PPROM were involved in this study. Among them, 1166 (42.31%) delivered by CS and 1590 (57.70%) delivered vaginally. Total newborn mortality was 2.54% (70/2756), and severe birth asphyxia was 3.23% (89/2756). The rate of Apgar scores <7 at 5 min was 3.70% (102/2756) and the average Apgar score was 9.6 ± 1.3 at 10 min. The rates of RDS, pneumonia, sepsis, and birth trauma were 2.21% (61/2756), 1.12% (31/2756), 1.02% (28/2756), and 0.03% (1/2756), respectively. There was an obviously positive correlation between the proportion of CS and the gestational age. The proportions of different delivery modes at different gestational ages (from 24 to 36 weeks) were displayed in Table 1.

The proportions of CS in different areas were significantly different ($P < 0.001$; Table 2). The proportion of CS in northeastern area (49.1%, 291/593) was significantly higher than that in central area (35.3%, 53/150; $P < 0.05$)

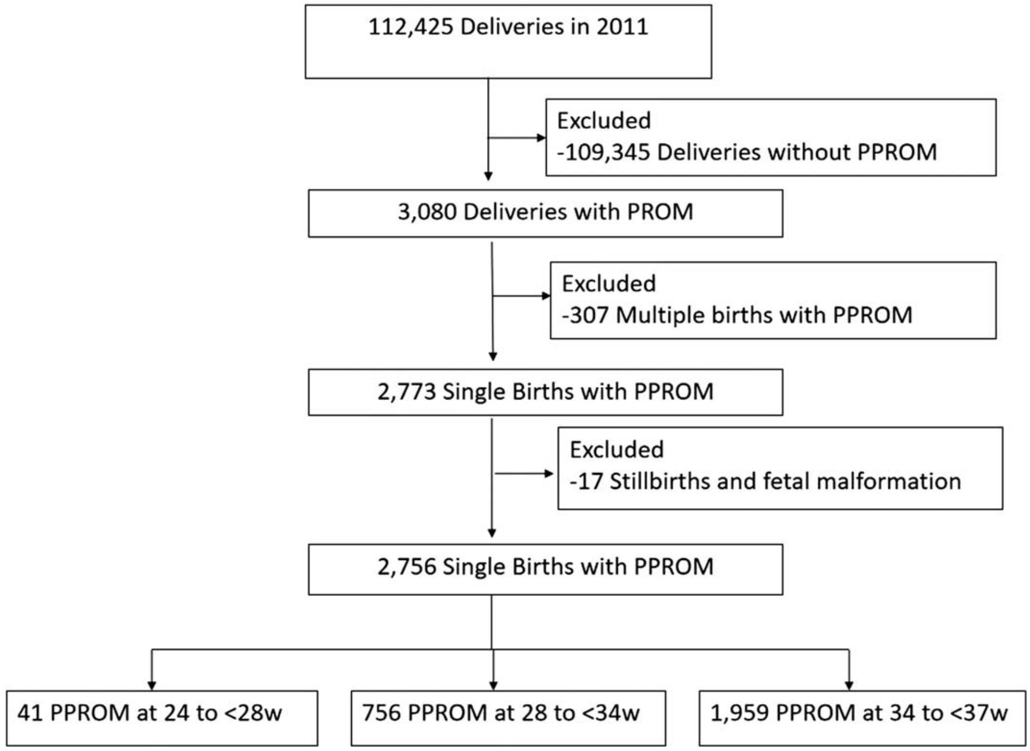

Figure 1: Study flowchart. PPROM: Preterm premature rupture of membranes; PROM: Premature rupture of membranes.

Table 1: Status of PPROM with different delivery mode based on gestational ages.

Groups	Total	Cesarean delivery	Vaginal delivery	χ^2	P^*
24 to <28 weeks	41	7 (17.1)	34 (82.9)	5.014	0.025
28 to <34 weeks	756	312 (41.3)	444 (58.7)		
34 to <37 weeks	1959	847 (43.2)	1112 (56.8)		

Data were shown as *n*, or *n* (%). *Linear-by-linear association. Data were analyzed by Chi-square test. PPROM: Preterm premature rupture of membranes.

Table 2: Status of PPROM with different delivery mode based on areas of the mainland of China.

Groups	Total	Central area	Eastern area	Northeastern area	Western area	χ^2	P
Cesarean delivery	1166 (42.3)	53 (35.3)	563 (41.1)	291 (49.1)*	259 (40.3)	16.016	0.001
Vaginal delivery	1590 (57.7)	97 (64.7)	807 (58.9)	302 (50.9)	384 (59.7)		

Data were shown as *n* (%). *Indicated $P < 0.05$ compared with Central area. PPROM: Preterm premature rupture of membranes.

[Table 2]. As shown in Figure 2, 32.8% (383/1166) of the CS were conducted under maternal requests, which accounted for 13.9% (383/2756) of all births with PPROM in the mainland of China.

Newborns in CS group had longer gestational age and higher proportions of fetal distress compared with those babies in VD group [Table 3].

Adverse neonatal outcomes

A higher incidence of newborn mortality, Apgar score <7 at 5 min and lower 10-min Apgar score were found in VD group ($P < 0.05$) [Table 4].

Considering that gestational age clearly influences neonatal outcomes, stratified analysis across the different gestational age was applied to investigate the relationship between mode of delivery and neonatal outcomes. In the sub-group of 24 to <28 weeks, the rate of newborns sepsis was lower in VD group ($P = 0.047$). There were no significant differences of newborn mortality, severe birth asphyxia, Apgar score <7 at 5 min, RDS, pneumonia, sepsis, and birth trauma between the two groups ($P > 0.05$) [Table 4].

In the sub-group of 28 to <34 weeks, newborn mortality showed higher level in VD group compared to CS group ($\chi^2 = 4.128$, $P = 0.042$). In contrast, there was a lower pneumonia rate in VD group (*vs*. CS, $\chi^2 = 3.941$,

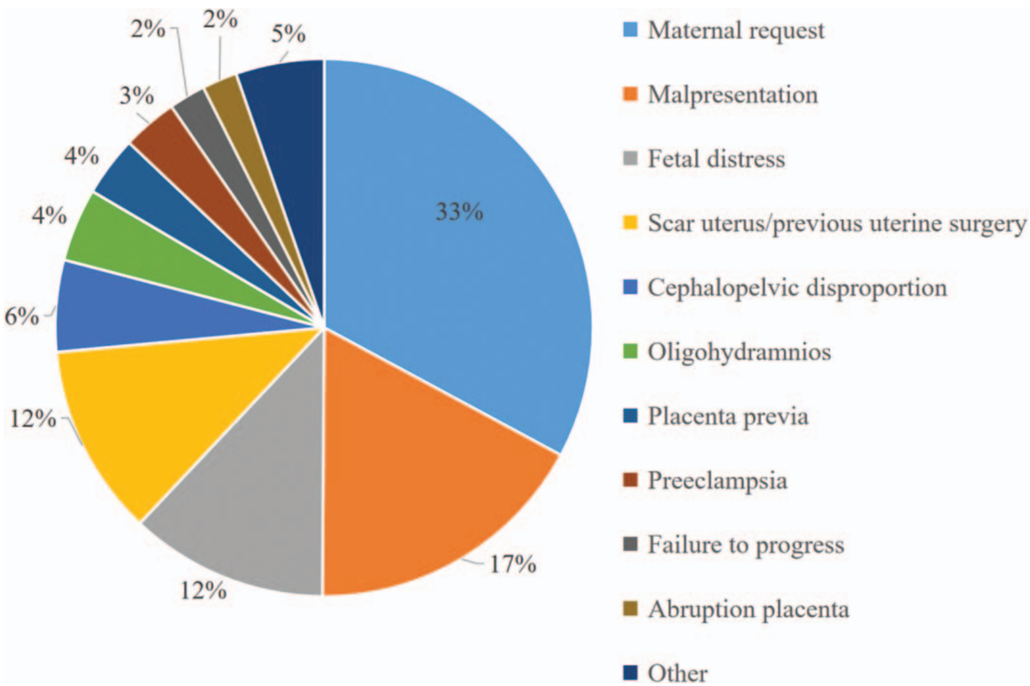

Figure 2: Reasons for cesarean section in the 1166 cases.

Table 3: Baseline characteristics of the newborns.

Clinical parameters	Cesarean delivery	Vaginal delivery	χ^2/t	*P*
Male fetal gender, *n* (%)	684 (58.7)	926 (58.2)	0.050	0.824
Birth weight (g), mean ± SD	2416.8 ± 585.4	2388.9 ± 598.1	1.167	0.243*
Antenatal corticosteroids, *n* (%)	460 (39.5)	590 (37.2)	1.548	0.213
Fetal distress, *n* (%)	91 (7.8)	57 (3.6)	23.569	<0.001
Fetal growth restriction, *n* (%)	27 (2.3)	29 (1.8)	0.817	0.366
Initial antibiotics therapy, *n* (%)	733 (63.3)	1033 (65.1)	0.981	0.322
Gestational age (weeks), mean ± SD	34.2 ± 2.0	34.0 ± 2.4	2.981	0.003*

* Student's *t* test. SD: Standard deviation.

$P = 0.047$). The outcomes of severe birth asphyxia, Apgar scores of <7 at 5 min, Apgar scores at 10 min, RDS, and sepsis were indistinguishable between the two groups ($P > 0.05$) [Table 4].

In the sub-group of 34 to <37 weeks, there were no significant differences of newborn mortality, severe birth asphyxia, Apgar scores of <7 at 5 min, Apgar scores at 10 min, RDS, pneumonia, infection, and birth trauma between the two groups ($P > 0.05$) [Table 4].

Because there were significant differences in neonatal baseline characteristics between the CS and VD groups, multivariate analysis including binary logistic regressions, ordinal regression, and multiple linear regression were performed to verify whether there were similar outcomes in CS and VD groups. 20 newborns gave up resuscitation and therapy in vaginal birth during 24 to <28 weeks and it could affect the research outcomes. Therefore, multivariate analysis of the effects of delivery modes on neonatal outcomes was not performed.

After controlling of multiple covariates including fetal distress and gestational weeks, adverse neonatal outcomes were summarized [Table 5]. Compared with CS group, VD group was associated with an increased risk of total newborn mortality (OR, 2.38; 95% CI, 1.102–5.118; $P = 0.027$), but a decreased risk of pneumonia (OR, 0.32; 95% CI, 0.126–0.811; $P = 0.016$) [Table 5]. However, when stratified by gestational age, CS did not show advantage in newborns mortality and risk of pneumonia, except in 28 to 34-week group (OR, 0.34; 95% CI, 0.120–0.940; $P = 0.038$). Compared with VD group, CS group did not show decreased risks of birth asphyxia (1-min Apgar score), Apgar scores <7 at 5 min, Apgar scores at 10 min, RDS, and sepsis ($P > 0.05$) [Table 6].

Discussion

Our study revealed that the proportion of CS with PPROM increased with the prolonged gestational week in the mainland of China. Critically, CS did not improve outcomes of newborns when gestational age was stratified from the data analysis.

Previously, the data from 1991 to 2006 of United States reported that the proportion of CS was obviously higher in

Table 4: Neonatal outcomes of different delivery modes.

Clinical parameters	Cesarean delivery	Vaginal delivery	χ^2/ t/Z	P
Total				
Newborns mortality	12 (1.0)	58 (3.6)	18.635	<0.001
Apgar scores (1-min)			2.176	0.337
8–10	1058 (90.7)	1432 (90.1)		
4–7	77 (6.6)	100 (6.3)		
0–3	31 (2.7)	58 (3.6)		
Apgar scores (5-min) (<7)	28 (2.4)	74 (4.7)	9.597	0.002
Apgar scores (10-min)	9.7 ± 1.0	9.6 ± 1.5	1.987	0.047†
RDS	29 (2.8)	32 (2.2)	0.700	0.403
Pneumonia	18 (1.5)	13 (0.8)	3.189	0.074
Sepsis	13 (1.1)	15 (0.9)	0.197	0.657
Birth trauma	0	1 (0.1)		1.000*
24 to <28 weeks				
Newborns mortality	3 (42.9)	26 (76.5)		0.165*
Apgar scores (1-min)				0.780*
8–10	5 (71.4)	18 (52.9)		
4–7	0	2 (5.9)		
0–3	2 (28.6)	14 (41.2)		
Apgar scores (5-min) (<7)	3 (42.9)	24 (72.7)		0.187*
Apgar scores (10-min)	9 (0, 9.5)	0 (0, 8.5)	−1.068	0.371‡
RDS	4 (57.1)	8 (23.5)		0.165*
Pneumonia	3 (42.9)	6 (17.6)		0.165*
Sepsis	4 (57.1)	6 (17.6)		0.047*
Birth trauma	0	0		n/a
28 to <34 weeks				
Newborns mortality	8 (2.6)	25 (5.6)	4.128	0.042
Apgar scores (1-min)			0.236	0.888
8–10	252 (80.8)	353 (79.5)		
4–7	40 (12.8)	59 (13.3)		
0–3	20 (6.4)	32 (7.2)		
Apgar scores (5-min) (<7)	18 (5.8)	38 (8.6)	2.079	0.149
Apgar scores (10-min)	9.3 ± 1.5	9.2 ± 2.2	0.917	0.360†
RDS	18 (5.8)	18 (4.1)	1.189	0.276
Pneumonia	11 (3.5)	6 (1.4)	3.941	0.047
Sepsis	6 (1.9)	7 (1.6)	0.130	0.718
Birth trauma	0	0		n/a
34 to <37 weeks				
Newborns mortality	1 (0.1)	7 (0.6)		0.149*
Apgar scores (1-min)			0.956	0.620
8–10	801 (94.6)	1061 (95.4)		
4–7	37 (4.4)	39 (3.5)		
0–3	9 (1.1)	12 (1.1)		
Apgar scores (5-min) (<7)	7 (0.8)	12 (1.1)	0.320	0.572
Apgar scores (10-min)	9.9 ± 0.6	9.8 ± 0.8	0.777	0.437†
RDS	7 (0.8)	6 (0.5)	0.600	0.438
Pneumonia	4 (0.5)	1 (0.1)		0.173*
Sepsis	3 (0.4)	2 (0.2)		0.658*
Birth trauma	0	1 (0.1)		1.000*

Data were shown as *n* (%) or mean ± SD. Twenty newborns were given up to resuscitation and therapy in vaginal birth during 24 to <28 weeks. * Fisher exact test. † Student's *t* test. ‡ Wilcoxon rank-sum test. RDS: Respiratory distress syndrome; SD: Standard deviation; n/a: None.

early gestational age than that in late gestational age,[23] and a study including 17 European countries presented that the trend of CS proportion decreased with the increase of gestational weeks.[24,25] Racusin *et al*[25] reported that compared with a proportion of 33.2% CS in late preterm births, 53.8% of preterm infants were delivered by CS. A study on PPROM alone, also showed similar trend that the proportion of CS dropped from over 40% at 24 to 31 gestational weeks to 28.5% at 32 to 33 gestational weeks in PPROM infants.[26] The reason of the high proportion of CS at early gestational age was probably due to low birth weight. Moreover, neonates in early gestational age may lack the reserve ability to tolerate the contraction during the labor and the compression of the birth canal.

Table 5: Comparison of neonatal outcome between cesarean and vaginal delivery groups.

Clinical parameters	OR	95% CI	*P*
Newborns mortality (total)	2.38	1.102–5.118	0.027
28 to <34 weeks	1.84	0.801–4.241	0.150
34 to <37 weeks	6.70	0.800–56.115	0.079
Apgar score (1 min, total)	1.08	0.816–1.428	0.590
Apgar score (1 min)			
28 to <34 weeks	0.90	0.590–1.377	0.632
34 to <37 weeks	1.17	0.760–1.802	0.474
Apgar score (5 min, total)	1.40	0.841–2.343	0.195
28 to <34 weeks	1.28	0.702–2.338	0.419
34 to <37 weeks	1.75	0.659–4.625	0.262
RDS (total)	0.66	0.367–1.181	0.161
28 to <34 weeks	0.62	0.311–1.223	0.166
34 to <37 weeks	0.75	0.247–2.272	0.610
Pneumonia	0.32	0.126–0.811	0.016
28 to <34 weeks	0.34	0.120–0.940	0.038
34 to <37 weeks	0.30	0.032–2.900	0.304
Sepsis	0.69	0.267–1.772	0.438
28 to <34 weeks	0.69	0.228–2.101	0.516
34 to <37 weeks	0.62	0.101–3.848	0.611

Fetal distress and gestational age were adjusted. OR: Odds ratio; CI: Confidence interval; RDS: Respiratory distress syndrome.

Theoretically, CS can reduce the risk of intrapartum fetal trauma and asphyxia and allow timely delivery to insure neonatal intensive care.[27]

In our study, we assessed the effect of CS on neonatal outcomes in pregnant women with PPROM in China, because the proportion of CS in Chinese society was quite high.[28] Our research revealed an opposite result. In this present study, the CS proportion as low as 17.1% at extremely low gestational age (24–27 weeks) and increased to beyond 40% at late preterm births (34–36 weeks), which implicated that CS proportion increased with the increase of gestational weeks. The possible reason was that, the lowest boundary of preterm birth was considered to be 28 gestational weeks and preterm births before 28 gestational weeks were thought to abort in the mainland of China. The parents and their families would prefer to give up the treatment and may not be willing to delivery by CS. On the other hand, for those late preterm births, except necessary CS with indications, many women and their families requested for a quick delivery by CS to avoid the possible neonatal hypoxia, ensuring the neonatal safety and improving the prognosis of infants.[29-31]

In our study, the total CS proportion was 42.3% in PPROM and the proportion of CS under maternal requests reached up to 32.8% among all women taking CS. Another research on CS status in the mainland of China showed the overall proportion of CS was as high as 54.6%, of which 92.2% was primary CS and 7.8% was repeated CS.[28] Therefore, the high proportion of CS has become a social problem in the mainland of China.

There was no consensus concerning optimal mode of delivery in preterm birth. Malloy *et al*[32] reported that CS increased survival rate of the infants who were delivered between 22 and 25 weeks of gestation. Kallen *et al*[33] demonstrated a protective benefit of CS at extreme preterm birth and reported that the risk of death within 24 h after birth has decreased with CS. However, Bannister-Tyrrell *et al*[34] revealed an opposite view indicating that high CS was associated with higher severe neonatal morbidity at 26 to 31 gestational weeks, but this association was not found in the gestation 32 to 36 weeks group. Similarly, a systemic analysis including 116 women reported equal rates of neonatal mortality, birth asphyxia and Apgar score <7 at 5 min with respect to the delivery mode.[35] Racusin *et al*[25] also showed no improved outcomes after CS, when infants were stratified by the mode of delivery, both in the presence or absence of antenatal corticosteroid administration between 23^{+0} and 36^{+6} gestational weeks.

The uncomplicated PPROM increased the risk of composite adverse outcome, mortality, respiratory morbidity,[9] but there were few reports investigating the optimal mode of delivery in PPROM. Mousiolis *et al*[36] showed that there was a statistically significant benefit on survival in CS group compared with VD group in pregnancies of 30 gestational weeks.

In the mainland of China, the outcomes of infants who were delivered before 28 gestational weeks were assumed to be in a bad situation and high treatment costs increased the financial burden on their parents. Moreover, CS was supposed to be traumatic to women and exerted possible risks for next pregnancy, such as placenta implantation,[37] scarred uterus, and so on. VD was selected as the first choice for preterm infants before 28 gestational weeks. In our study, the reasons to receive CS before 28 gestational weeks were almost the maternal comorbidities that did not enable VD. Nearly half infants delivered by VD before 28 weeks were given up to resuscitation and continuing therapy. Therefore, we could not compare the advantage of CS and VD.

The results of middle and late preterm births from our study were similar with above studies. For those newborns who delivered from 28^{+0} to 36^{+7} gestational weeks, CS did not show convincing beneficial effect than VD to improve the newborns outcomes in PPROM, especially in the late PPROM. In addition, with the two children policy coming into force in the mainland of China, more women are willing to have a second child, but CS increases the risks of next pregnancy. The indications of CS should be evaluated carefully and the proportion of non-indicated CS should be decreased.

As a multicenter clinical epidemiological study, we assessed the largest number of deliveries from 39 hospitals in 14 provinces and regions in the mainland of China, and 2765 cases of single birth with PPROM were included in the study. The limitation of this study was that we only analyzed the effect of CS on short-term outcomes at birth but did not collect the data about long-term outcomes of these newborns. Therefore, further research is required to confirm whether CS shows more benefits to improve the long-term outcomes in PPROM. The proportion of CS has decreased significantly after the implementation of the second-child policy in China,[38] which is related to the

Table 6: Comparison of 10-min Apgar score between cesarean and vaginal delivery groups.

Clinical parameters	B	SE	*t*	95% CI	*P*
Apgar score (10 min, total)	−0.046	0.054	−0.851	−0.152–0.060	0.395
28 to <34 weeks	−0.011	0.176	−0.062	−0.356–0.334	0.951
34 to <37 weeks	−0.032	0.039	−0.826	−0.109–0.044	0.409

The adjusted odds ratios (ORs, 95% confidence intervals) of binary variables were calculated by binary logistic regressions. Fetal distress and gestational age were adjusted. SE: Standard error; CI: Confidence interval.

improvement of obstetric level and humanistic concept. We review the previous data in 2011, mainly to explore the impact of high CS rate on newborns, suggesting the importance of CS with indications, reducing the number of CS without indications.

In the mainland of China, the CS proportion of PPROM was very high and increased with the prolonged gestational weeks. CS did not show more benefits than VD to improve the outcome of the newborns.

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Conflicts of interest

None.

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