Original Article

Effect of preeclampsia and premature rupture of membrane on neonatal birth weight and length by gestational age: A retrospective study in China

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Background: Preeclampsia (PE) and premature rupture of membrane (PROM) are considered significant risk factors for lower neonatal birth weight and birth length. However, very limited studies have reported the impact of PE and PROM on neonatal birth weight and birth length by gestational week. Therefore, we aimed to determine the effect of PE and PROM on neonatal birth weight and length by gestational age. **Materials and Methods:** A total of 9707 singleton neonates were selected for this study. All the data were collected and documented in the obstetric register by the trained nurses in the Gynecology and Obstetrics Department. **Results:** The neonatal mean birth weights and birth lengths were statistically significantly ($P < 0.05$) lowered among preeclamptic mothers compared to mothers without PE throughout the gestational age. Statistically significantly ($P < 0.05$) lowered mean birth weights and birth lengths were found among neonates born to mothers with PROM than among neonates born to mothers without PROM by all gestational weeks except for 32 weeks and 36 weeks. Moreover, in a multiple linear regression model, PE and PROM were significantly negatively associated with neonatal birth weights and birth lengths by almost all gestational weeks ($\beta < 0$, $P < 0.05$). **Conclusion:** We concluded that after adjustment for covariates and confounding factors, PE and PROM had a significantly negative association with neonatal birth weights and birth lengths by all gestational weeks.

Key words: Birth length, birth weight, gestational age, preeclampsia, premature rupture of membrane

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INTRODUCTION

Preeclampsia (PE) is one of the most common pregnancy complications leading to maternal and infant mortality and morbidity worldwide. It is considered the second most common significant cause of an abnormal pregnancy outcome.[1] PE is most commonly observed after the 20th week of gestation, with an elevated blood pressure (140/90 mmHg) and proteinuria (albumin >300 mg in 24 h).[2] The prevalence of PE has been reported as 2%–8% of all pregnancies in various countries of the world, even among different ethnic groups living in the same country.[3] The significant risk factors of PE include the previous history of hypertension, autoimmune system, renal disease, high blood glucose level, maternal weight, the age of the pregnant women, ethnicity, and family history.[4]

Premature rupture of membranes (PROMs) is the rupture of the membrane an hour before the onset of uterine contractions, regardless of gestational age.

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According to gestational age, PROM can be divided into two categories: after the 37^{th} week of gestation defined as term PROMs and before the 37^{th} week of pregnancy referred to preterm PROMs (pPROMs). PROM is one of the common obstetric complications but to estimate its accurate incidence is quite difficult due to the wide variations reported in the current literature. Recent data suggest that it complicates approximately 3%–10% of all pregnancies.[5] PROM is a potential risk factor for both maternal and infant mortality and morbidity. Neonatal complications associated with PROM include prematurity, trauma, fetal distress, intraventricular hemorrhage, respiratory distress syndrome, and intrauterine infection. These complications ultimately result in poor fetal growth during pregnancy.[6]

Fetal growth is one of the significant markers for neonatal well-being. Neonatal birth size is generally evaluated by measuring neonatal birth weight, length, and head circumference immediately after birth. Either neonatal birth weight or length at birth depicts the expression of fetal utero growth because of maternal-fetal and placental factors.[7] Neonatal birth weight and length are significant indicators of neonatal morbidity and survival during later life.[8] Neonatal birth weight and length are influenced by obstetrical complications, in particular PE and PROM. Therefore, the identification of factors that influence neonatal birth weight and length is of special interest to perinatologists, gynecologists, and public health researchers.[9]

To study the impact of PE and PROM on neonatal birth weight and length, it is very important to compare the fetal growth of neonates born to preeclamptic and PROM mothers with that of neonates born to mothers without these complications at the same gestational ages. In China, most of the previous studies have conducted to find the effect of early onset and late onset of PE, term PROM, and preterm PPROM on maternal and neonatal outcomes. However, to our knowledge, no previous study has been conducted to determine the impact of PE and PROM on neonatal birth weights and lengths by gestational weeks. Using the current data, we conducted a study to determine the effect of PE and PROM on fetal growth by gestational age.

MATERIALS AND METHODS

Study population

A hospital-based retrospective study was conducted in the Wuhan University Renmin Hospital, Department of Obstetrics and Gynecology, Hubei, China. during 2013–2017. The data were collected and documented in the obstetric register by trained nurses during individual examination in the Gynecology and Obstetrics Department. The study protocol was approved by the Ethical Review Board of Renmin Hospital in accordance with the Declaration of Helsinki. This documented information was only used for research purpose.

Inclusion and exclusion criteria

A total of 9707 primipara and multipara pregnant women with singleton gestation were selected for the study. Live singleton neonates with all gestational weeks were included. We excluded 492 with missing data on maternal age, neonatal sex, birth weight, birth length, and gestational age.[10] Mothers with gestational hypertension, twin neonates, and died neonates were also excluded from the analysis of data, as shown in Figure 1.

Definition of exposure and neonatal birth outcomes

PE is defined as an elevated blood pressure (140/90 mmHg) with proteinuria (albumin >300 mg in 24 h) after the 20^{th} week of gestation. PROM referred to the rupture of the membrane an hour before the onset of uterine contractions, regardless of gestational age. Neonatal birth outcomes were recorded immediately after neonatal birth including birth weight in grams using electronic infant scale and birth length in centimeter using a standard measuring board for the neonate. Apgar score was determined by evaluating the newborn baby on five simple criteria on a scale from 0 to 2 and then summing up the five values obtained. Apgar score was recorded at 1 min and at 5 min after birth. Apgar score was divided into three categories: (i) low (0–3), (ii) marginal (4–6), and (iii) normal (≥7).

Definition of confounding factors and covariates

Confounding factors were selected based on previous literature and the plausible association with both exposure and neonatal birth outcomes. The confounding factors included in this analysis were maternal age, prepregnancy body weight (≤45 kg and ≥91 kg), parity, and neonatal gender. Moreover, gestational diabetes mellitus, diabetes, oligohydramnios, and nuchal cord were selected as covariates.

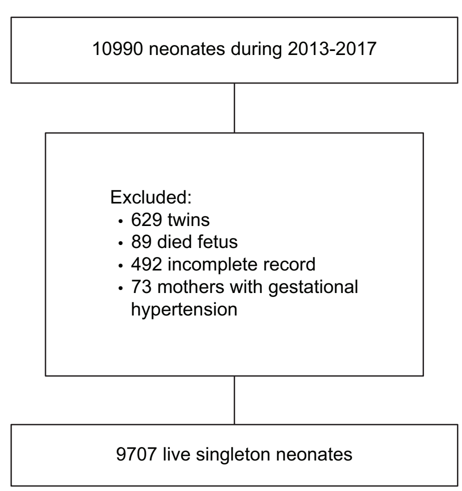

Figure 1: Flowchart of study population

Statistical analysis

In this study, birth weights and birth lengths were considered as the outcome variables. Other variables such as exposure variables (PE and PROM), confounding factors, and covariates were taken as predictor variables. Descriptive statistics such as frequencies and percentages were calculated for categorical variables and mean ± standard deviation for the quantitative variables. The independent sample *t*-test was performed to compare mean birth weights and mean birth lengths by gestational weeks between pregnant women with PE or PROM and normal pregnant women. To adjust for covariates and confounding factors, a multiple linear regression model was applied using birth weights and birth lengths as the outcome variables and PE (PE = 1 and normal = 0), PROM (PROM = 1 and normal = 0), and other variables such as confounding factors, and covariates were taken as predictor variables. P value (two-tailed < 0.05) was taken as statistical significant. The data were analyzed using the Statistical Package for the Social Sciences for Window version 22 (IBM Corporation, Chicago, IL, USA).

RESULTS

The study population consisted of n = 9707 women. The mean maternal age was 29.8 ± 4.5 (years) and the mean gestational age was 37.7 ± 2.5 (weeks). The incidences of PE and PROM were 3.9% and 10.5%, respectively. The mean neonatal birth weight and the mean birth length were recorded 3111.6 ± 642.6 (g) and 48.6 ± 2.9 (cm), respectively. About 97% of neonates were found with normal (≥7), 2.2% with marginal (4–6), and 0.8% with a low Apgar score [Tables 1 and 2].

The population was categorized into gestational weeks from ≤32 weeks to ≥41 weeks to determine the effect of PE and PROM on neonatal birth weights and lengths by gestational weeks. Referring to the gestational weeks from ≤32 weeks to ≥41 weeks, differences in mean birth weights and birth lengths ranged from −353.7 g to −838 g to −2 cm to −4.4 cm, respectively, between PE and normal groups. The mean birth weights and birth lengths were statistically significantly lowered among preeclamptic mothers than among mothers without PE throughout gestational age. Moreover, for mothers delivering at 37 weeks, the lower mean birth weight and birth length difference was found between PE and normal groups. However, for mothers delivering before and after 37 weeks, the mean birth weights and birth lengths generally decrease among preeclamptic mothers than among mothers without PE [Table 3]. In a multiple linear regression model, after adjustment for covariates and confounding variables, PE was significantly negatively associated with neonatal birth weights and birth lengths by all gestational weeks (β <0, P < 0.05) [Table 4].

The differences in mean birth weights between PROM and normal groups ranged from −59.5 g to −499.4 g, while the mean birth length differences ranged from − 0.2 cm to −2.5 cm. For mothers delivering at ≤37 weeks, the statistically significant fluctuated reduction of mean birth weights and birth lengths was found among neonates born to mothers with PROM than among neonates born to mothers without PROM, but the mean birth weight and birth length differences at 32 weeks and 36 weeks were not statistically significant (P > 0.05). However, in neonates born after 37 weeks, the mean birth weights and lengths were statistically significantly reduced with the advancement of gestational age [Table 5]. In a multiple linear regression model, after adjustment for covariates and confounding variables, PROM was significantly negatively associated with neonatal birth weights and birth lengths by all gestational weeks, except for 36 weeks (β <0, P < 0.05) [Table 6].

Table 1: Distribution of maternal age and pregnancy complications by gestational age (*n*=9707)

Maternal age and pregnancy complications	Maternal age (years), mean±SD	PE, *n* (%)	PROM, *n* (%)	GDM, *n* (%)	Diabetes, *n* (%)	Oligohydramnios, *n* (%)	Nuchal cord, *n* (%)	C-section, *n* (%)
Gestational age (weeks)								
≤32 (*n*=251)	29.8±5	20 (8)	59 (23.5)	12 (4.8)	2 (0.8)	4 (1.6)	5 (2)	124 (49)
33 (*n*=191)	30±5	15 (8)	46 (24)	3 (1.6)	2 (1)	3 (1.6)	9 (4.7)	112 (58)
34 (*n*=334)	29.8±5	40 (12)	69 (20.6)	12 (3.6)	2 (0.6)	8 (2.4)	9 (2.7)	215 (64)
35 (*n*=345)	29.7±4	31 (9)	60 (17.3)	17 (5)	1 (0.3)	13 (3.8)	12 (3.5)	238 (69)
36 (*n*=457)	30±4.7	35 (7.6)	63 (13.7)	25 (5.5)	4 (0.9)	10 (2.2)	15 (3.3)	325 (71)
37 (*n*=895)	30±4.6	43 (4.8)	102 (11)	62 (7)	5 (0.6)	36 (4)	46 (5)	608 (70)
38 (*n*=2018)	31±4.7	76 (3.7)	174 (8.6)	122 (6)	10 (0.5)	80 (4)	101 (5)	1348 (67)
39 (*n*=2554)	30±4.4	60 (2.3)	212 (8.3)	142 (5.6)	10 (0.4)	69 (2.7)	152 (6)	1553 (61)
40 (*n*=1878)	29±4.1	43 (2.3)	162 (8.6)	67 (3.6)	10 (0.5)	59 (3.1)	138 (7.3)	949 (50)
≥49 (*n*=784)	29±3.9	17 (2)	71 (9)	13 (1.6)	3 (0.3)	26 (3.3)	40 (5.1)	439 (56)

Percentage was calculated for each gestational weeks. SD=Standard deviation; PE=Preeclampsia; PROM=Premature rupture of membrane; GDM=Gestational diabetes mellitus

Table 2: Distribution of neonatal traits by gestational age (*n*=9707)

Neonatal traits	Neonatal gender		Apgar score, *n* (%)			Mean±SD	
	Male, *n* (%)	Female, *n* (%)	0-3	4-6	≥7	Mean birth weight (g)	Mean birth length (cm)
Gestational age (weeks)							
≤32 (*n*=251)	118 (47)	133 (53)	11 (4)	23 (9)	217 (87)	2462±909	45.4±4.6
33 (*n*=191)	109 (57)	82 (43)	6 (3)	7 (4)	178 (93)	2569±771	46.3±3.7
34 (*n*=334)	193 (58)	141 (42)	3 (1)	13 (4)	318 (95)	2620±683	46.5±3.7
35 (*n*=345)	192 (56)	153 (44)	3 (0.7)	8 (2.3)	334 (97)	2720±644	47.1±3.4
36 (*n*=457)	243 (53)	214 (47)	4 (0.7)	6 (1.3)	447 (98)	2918±537	48±2.4
37 (*n*=895)	514 (57)	381 (43)	7 (1)	33 (4)	855 (95)	3063±520	48.7±2.3
38 (*n*=2018)	1103 (54)	915 (46)	11 (0.6)	48 (2.4)	1959 (97)	3200±530	49±2.2
39 (*n*=2554)	1353 (53)	1201 (47)	11 (0.5)	40 (1.5)	2503 (98)	3260±534	49±2.3
40 (*n*=1878)	995 (53)	883 (47)	5 (0.1)	17 (0.9)	1856 (99)	3280±558	49.4±2.4
≥41 (*n*=784)	416 (53)	368 (47)	0	24 (3)	760 (97)	3310±573	49.4±2.3

Percentage and mean±SD were calculated for each gestational week. SD=Standard deviation

Table 3: Preeclampsia and neonatal birth weight and length by gestational weeks

Gestational age (weeks)	Birth weight±SD				Birth length±SD			
	PE	Normal	MD (g)	*P*	PE	Normal	MD (cm)	*P*
≤32	1691±633	2529±900	−838	0.0001	41.6±4.4	45.7±4.4	−4.1	0.0001
33	2014±646	2616.4±764	−602.4	0.003	43.6±4.2	46.5±3.6	−2.8	0.004
34	1930.5±472	2703.8±657	−773.3	0.0001	42.5±3.7	47±3.8	−4.4	0.0001
35	2339.1±559	2763.6±639	−424.5	0.0001	44.8±3.2	47.2±3.3	−2.4	0.0001
36	2422.9±515	2949.3±523	−526.4	0.0001	45.8±3.4	48.1±2.3	−2.2	0.0001
37	2726.4±556	3080.2±513	−353.7	0.0001	46.7±3	48.8±2.2	−2	0.0001
38	2762.2±791	3215.8±511	−453.5	0.0001	46.9±3.6	49.1±2.1	−2.1	0.0001
39	2590±904	3274.4±513	−684.6	0.0001	46±4.6	49.3±2.2	−3.3	0.0001
40	2753.9±821	3292.6±545	−538.6	0.0001	46.9±4	49.5±2.3	−2.5	0.0001
≥41	2531.2±957	3325.6±554	−794.4	0.0001	45.1±4.5	49.5±2.2	−4.3	0.0001

Independent sample *t*-test was used to calculate *P* value. SD=Standard deviation; PE=Preeclampsia; MD=Mean difference

Table 4: Multiple linear regression of preeclampsia with neonatal birth weight and length by gestational weeks

Gestational age (weeks)	Birth weight			Birth length		
	B†	95% CI	*P*	*B*†	95% CI	*P*
≤32	−820.1	−1211.5-−428.6	0.0001	−3.9	−5.9-−1.9	0.0001
33	−959.8	−1321-−598.5	0.0001	−4.2	−6.1-−2.4	0.0001
34	−908.4	−1117.4-−699.4	0.0001	−4.9	−6.1-−3.7	0.0001
35	−540.8	−737.5-−344.1	0.0001	−2.9	−4.0-−1.7	0.0001
36	−525.7	−726.4-−325	0.0001	−2.1	−3.0-−1.1	0.0001
37	−371.8	−523.9-−219.7	0.0001	−2.0	−2.7-−1.3	0.0001
38	−498.4	−613.3-−383.5	0.0001	−2.3	−2.8-−1.8	0.0001
39	−685.8	−815.6-−556.0	0.0001	−3.3	−3.9-−2.8	0.0001
40	−558.6	−717.5-−399.8	0.0001	−2.7	−3.4-−2.0	0.0001
≥41	−876.5	−1240.9-−512.0	0.0001	−4.7	−6.3-−3.2	0.0001

Multiple linear regression model was used to calculate *P* value. †Adjusted for maternal age, prepregnancy body weight (≤45 kg and≥91 kg), gestational diabetes mellitus, diabetes, oligohydramnios, nuchal cord, PROM, parity, and neonatal gender. CI=Confidence interval

DISCUSSION

In China, most of the previous studies have conducted to find the effect of early onset and late onset of PE, term PROM, and preterm PROM on maternal and neonatal outcomes. However, to our knowledge, no previous study has been conducted to determine the impact of PE and PROM on neonatal birth weights and lengths by gestational weeks.

Preeclampsia and neonatal birth weight and birth length

Fetal growth is one of the significant markers for neonatal well-being. Intrauterine growth restriction (IUGR) is a pregnancy complication, defined as a pathological process of reduced fetal growth. PE is a hypertensive disorder with reduced uteroplacental blood perfusion and ischemia is a significant risk factor in the development of IUGR in nonanomalous neonates.[7] We observed that PE has a significant effect on fetal growth along all the gestational weeks

Table 5: Premature rupture of membrane and neonatal birth weight and length by gestational weeks

Gestational age (weeks)	Birth weight±SD				Birth length±SD			
	PROM	Normal	MD (g)	*P*	PROM	Normal	MD (cm)	*P*
≤32	2323±867	2499.4±919	−176.4	0.2	44.9±4.1	45.5±4.7	−0.5	0.4
33	2174.2±588	2673.7±781	−499.4	0.0001	44.2±3.2	46.8±3.7	−2.5	0.0001
34	2423.1±545	2666.3±703	−243.2	0.01	45.9±3.3	46.7±3.8	−0.7	0.1
35	2418.6±458	2775.3±658	−356.6	0.0001	45.7±2.8	47.2±3.5	−1.4	0.005
36	2865.7±415	2925.7±552	−59.5	0.4	47.7±2.0	48.0±2.5	−0.2	0.5
37	2959.7±541	3076.5±516	−116.8	0.03	48.5±2.6	48.7±2.2	−0.2	0.3
38	3000.9±597	3218.4±520	−217.5	0.0001	48.2±2.9	49.1±2.2	−0.9	0.0001
39	3148.2±570	3269.7±530	−121.4	0.002	48.9±2.6	49.3±2.3	−0.4	001
40	3047.4±689	3302.3±539	−254.8	0.0001	48.5±3.2	49.5±2.3	−0.9	0.0001
≥41	3007.0±728	3340.4±548	−333.4	0.001	48.5±3.0	49.5±2.3	−0.9	0.02

Independent sample *t*-test was used to calculate *P* value. SD=Standard deviation; PROM=Premature rupture of membrane; MD=Mean difference

Table 6: Multiple linear regression of premature rupture of membrane with neonatal birth weight and length by gestational weeks

Gestational age (weeks)	Birth weight			Birth length		
	B†	95% CI	*P*	*B*†	95% CI	*P*
≤32	−321.7	−575.0–−68.5	0.01	−1.1	−2.4-0.2	0.09
33	−502.1	−731.6–−272.6	0.0001	−2.4	−3.6–−1.3	0.0001
34	−313.8	−476.0–−151.6	0.0001	−1.1	−2.1–−0.2	0.01
35	−308.3	−472.7–−143.9	0.0001	−1.1	−2.0–−0.2	0.01
36	−89.7	−229-49.5	0.2	−0.3	−1.0-0.2	0.2
37	−135.7	−238.0–−33.4	0.009	−0.3	−0.8-0.07	0.1
38	−212.1	−288.7–−135.5	0.0001	−0.9	−1.3–−0.6	0.0001
39	−129.6	−199.2–−60.0	00001	−0.5	−0.8–−0.2	0.0001
40	−250.0	−333.6–−166.5	0.0001	−1.0	−1.3–−0.6	0.0001
≥0.0	−334.6	−510.6–−158.5	0.0001	−0.8	−1.6–−0.1	0.01

†Adjusted for maternal age, prepregnancy body weight (≤45 kg and≥591 kg), gestational diabetes mellitus, diabetes, oligohydramnios, nuchal cord, preeclampsia, parity, and neonatal gender; multiple linear regression model was used to calculate *P* value. CI=Confidence interval

regardless of term and preterm birth. Almost 63% of PE women delivered full-term neonates. These results are in contrast with the previous findings, in which they found that neonates born at term to preeclamptic mothers have similar mean birth weights to those of neonates born to mothers without PE. However, a statistically significantly lower mean birth weight was found among neonates born to preeclamptic mothers than among those neonates born to mothers with the normal group at preterm birth. Moreover, 61% of preeclamptic mothers gave birth at term; thus, most neonates born to preeclamptic mothers had normal birth weights for their gestational age.[11] A study conducted by Xiong *et al*.[7] found no statistically significant difference in mean birth weights between preeclamptic mothers (3213.1 g) and the normal group (3241.8 g) with (6.7%) preeclamptic mothers who delivered preterm neonates. In another study, where they found a significantly lower mean birth weight among neonates born to mothers with PE (2952.5 g) as compared with those born to mothers without PE (3380.5 g), the proportion of preterm births among preeclamptic mothers was high (27.5%).[12]

This indicates that the observed overall effect on mean birth weights may depend on the relative proportion of term and preterm births among women with PE in the study. Similarly, Mayhew *et al*.[13] have studied that PE was significantly associated with lower mean birth weights. Furthermore, Evans *et al*.[14] found significantly lowered neonatal mean birth weights and birth lengths in preeclamptic mothers than those without PE, which are in line with our current results. The findings that neonates born to preeclamptic mothers have significantly lower mean birth weights and birth lengths than those born to without PE by all gestational week, follow the "ischemic model" which is a currently held belief that hypouteroplacental flow is the unique pathophysiologic process in PE.[15]

Premature rupture of membrane and neonatal birth weight and length

PROM is the rupture of the membrane an hour before the onset of uterine contractions, regardless of gestational age. It complicates approximately 3%–10% of all pregnancies. This complication is one of the significant causes of increased morbidity and mortality for both neonates and mothers. Neonatal complications caused by the PROM include intrauterine infection, fetal distress, and respiratory distress syndrome.[5] We found that the PROM had a significant impact on neonatal birth weights and birth lengths along almost all the gestational weeks. Gandhi *et al*.[6] and Feresu *et al*.[16] found that PROM was significantly associated with low birth weight. However, no such previous studies have been found to determine the effect of PROM on neonatal birth weights and lengths by gestational age.

It is believed that fetal membranes insulate fetus and amniotic fluid from microbial infections. One of the serious complications associated with PROM is intrauterine infection or chorioamnionitis.[17] The term intrauterine infection refers to different clinical or pathological conditions characterized by an infectious or inflammatory process that affects the chorioamniotic membranes, amniotic fluid, umbilical cord (funisitis), and eventually the fetus.[18] Intrauterine infection is one of the significant intrinsic causes of IUGR, since in intrauterine infection, the umbilical cord also gets infected which causes uteroplacental insufficiency which further reduces the transportation of nutrients and oxygen and ultimately results in poor fetal growth during pregnancy.[19] The findings that PROM has a significant adverse impact on neonatal birth weights and birth length by all gestational weeks, which indicate that it may be due to intrauterine infection of neonates, but unfortunately, we are missing the data regarding intrauterine infection in our study.

Prevalence of preeclampsia and premature rupture of membrane

The prevalence of PE in our study was 3.9%, which is lower than the previously reported studies with 6.83% in China[20] and 7.6% in Yemen.[21] However, this prevalence of PE was found to be higher than those reported in Canada[1] and in Sudan,[22] where a 1.7% and 3.5% prevalence of PE was noted, respectively. A large-scale study conducted by Hernández-Díaz *et al*.[23] reported a 3% prevalence of PE in pregnant women. The prevalence of PE varies greatly according to the population characteristics and size.

The findings of the present study show that the incidence of PROM was 10.5%, which is lower than the reported studies (20%) in mainland China[24] and Nigeria[25] but was much higher than that reported in developed countries.[26] A study conducted in East China demonstrated a 15.3% prevalence of PROM.[27] It has been suggested that the incidence of PROM is more common in China than in developed countries. Hence, it is most important to enhance antenatal health care in order to reduce the incidence of PROM, which can lead to fetal death and other neonatal complications.

We acknowledge that our study had certain limitations. The study was conducted in only one tertiary hospital, and therefore, the results cannot be generalized to the whole population. We had a low sample size of the population, which may affect the strength of our results. In future studies, to find the effect of PE and PROM on neonatal birth size by gestational age, it is highly recommended to take into consideration the mild and severe PE. Furthermore, a latency period of PROM and neonatal complications (intrauterine infection and fetal distress) during PROM must be taken.

CONCLUSION

Regardless of term and preterm births, PE and PROM were significantly negatively associated with neonatal birth weights and birth lengths by all gestational weeks.

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Conflicts of interest

There are no conflicts of interest.

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