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# Causes and short-term outcomes of preterm infants

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**SUMMARY**

**Introduction/Objective** Preterm birth (PB) is the most important reason of neonatal mortality, and the second most common direct cause of death for children under the age of five years.
The aim of this study was to analyze the clinical features and outcomes of preterm infants.

**Methods** The clinical data of 307 preterm infants delivered in the Qingdao University hospital from January 1, 2012 to December 31, 2012 were retrospectively analyzed.

**Results** The incidence of PB was 6.52%. There were 143 cases of preterm prelabour rupture of membranes (PPROM) (46.58%), 66 cases of spontaneous PB (21.5%), and 98 cases of therapeutic PB (31.92%). Deliveries with gestational weeks (GW) < 32 were mainly vaginal (60.72%), but deliveries with GW ≥ 32 exhibited higher C-section rate (60.99%) than the vaginal delivery rate ($p < 0.05$). The birth weight was 2,340.46 ± 606.26 g, and the Z-score at birth was -0.15 ± 1.08. The Z-score in the group with GW within 28 to $31^{+6}$ weeks was less than that in the group with GW within 32 to $33^{+6}$ and with GW ≥ 34 ($p < 0.05$). The average hospital stay of preterm infants was 15.17 ± 12.35 days, and the most common complication in these preterm infants was respiratory distress syndrome with 13.92%.

**Conclusion** PB could cause a variety of serious complications in infants. The main causes of PB, such ac PPROM, should be actively prevented and treated; meanwhile, preterm infants should also be actively treated so as to improve their outcomes.

**Keywords:** infant; pregnancy outcomes; preterm birth; Z score

## INTRODUCTION

Preterm birth (PB) refers to the delivery with less than 37 gestational weeks, and it is estimated that there are more than 41,000 cases of preterm delivery daily in the world [1]. PB is the most important reason of neonatal mortality, and the second direct reason of death for children under the age of five years. Average global incidence of PB is estimated to be 11.1%, and there are differences in incidence of PB among different countries and regions – in Africa, for instance, it could be up to 15%, but in some European countries it might be as low as 5–6%. In recent years, with the large-scale application of assisted reproductive technologies and the increase in the number of mothers of advanced age, the incidence of PB is also rising [2, 3].

Preterm infants can experience serious complications, such as respiratory distress syndrome (RDS), sepsis, patent ductus arteriosus, cerebral palsy, and cognitive defects [4, 5]. Approximately 3.1 million neonatal deaths occur worldwide each year, 35% of which are due to prematurity-related complications [6]. Global statistics showed that more than 60% of PB occurred in South Asia and Africa, while incidences of PB differ largely in Asia, which was the lowest in East Asia, with about 7.2%, followed by that in West Asia, with about 10.1%, and the rate was the highest in Southeast Asia, with about 13.6% [7]. There has been no incidence of PB report at the national level for China, and the estimated incidence of PB is below the global level. Furthermore, China has large geographic span, so regional incidences of PB also differ; for example, in Jiangsu Province, the incidence was reported as 2.6–2.9% [8, 9]. This study retrospectively analyzed the clinical data collected from two tertiary referral hospitals, aiming to explore the conditions of PB, remedy levels, and outcomes of preterm infants in this region, thus hoping to provide evidence for the diagnosis and treatment of PB.

The aim of this study was to analyze the cause, clinical features, and outcomes of preterm infants.

## METHODS

### Data sources

Three hundred and seven puerperae were enrolled, hospitalized in the Yantai Affiliated Hospital of Binzhou Medical University and the Yuhuangding Affiliated Hospital of Qingdao University from January 1, 2012 to December 31, 2012 and pretermly delivered with gestational age of $28–36^{+6}$ weeks. This study was conducted in accordance with the declaration of Helsinki and with approval from

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the ethics committees of Binzhou Medical University and Qingdao University. Written informed consent was obtained from all participants.

### Study methods and diagnostic criteria

A retrospective analysis was performed, and PB records that met the criteria were inspected, including general information of pregnant women, pregnancy complications, delivery mode, gestational age at delivery, preterm outcomes (including both neonates and parturient women), as well as the therapy and the course. Meanwhile, the Z-score of neonatal birth weight was also recorded, which depends on the birth weight, Z-score = (birth weight of the infant - mean birth weight with the same number of gestational weeks [GW]) / standard deviation of the birth weight with the same number of GW. The evaluation criteria referred to the standards of neonatal physical development with different number of GW in 15 Chinese cities, and the normal range was usually considered to be within ± 2.

PB was defined as delivery within 28–$36^{+6}$ GW. Classification (three categories according to the reasons) is as follows: spontaneous PB, preterm prelabour rupture of the membrane (PPROM), and iatrogenic PB.

### Statistical methods

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis; the qualitative data were analyzed by the $\chi^2$ test, and the quantitative data were analyzed by the Student's t-test, with $p < 0.05$ considered to be statistically significant.

## RESULTS

The average age of women with PB was 30.09 ± 4.45 years, and the mean number of pregnancies was 2 ± 1.29, including 257 primipara (83.71%) and 50 multipara (16.29%), as shown in Table 1.

**Table 1.** Comparison of pregnancies and deliveries with different number of gestation weeks (GW)

| Parameter | Group 1 28–$31^{+6}$ weeks (n = 25) | Group 2 32–$33^{+6}$ weeks (n = 58) | Group 3 34–$36^{+6}$ weeks (n = 224) |
|---|---|---|---|
| Age (years) | 30.52 ± 5.88 | 30.50 ± 4.57 | 29.91 ± 4.25 |
| GW on admission | 29.67 ± 1.54 | 32.44 ± 1.19 | 35.17 ± 1.39 |
| Pre-pregnancy BMI | 23.45 ± 3.31 | 22.98 ± 3.78 | 22.69 ± 3.72 |
| Time for tocolysis (days) | 5.48 ± 10.08 | 4.88 ± 7.53 | 3.81 ± 7.50 |
| Delivery mode | | | |
| Cephalic vaginal delivery | 14 (56%) | 19 (32.76%) | 86 (38.39%) |
| C-section | 9 (36%) | 38 (65.52%) | 134 (59.82%) |
| Breech vaginal delivery | 2 (8%) | 1 (1.72%) | 4 (1.79%) |
| Number of newborns | 31 | 67 | 269 |

BMI – body mass index;
Comparison between GW 28–$31^{+6}$ and GW 34–$36^{+6}$ showed a significant difference, $p < 0.05$;
Comparison between GW 28–$31^{+6}$ and GW 32–$33^{+6}$ showed a significant difference, $p < 0.05$;
Comparison between GW 32–$33^{+6}$ and GW 34–$36^{+6}$ showed a significant difference, $p < 0.05$

### Causes of PB

The age of pregnant women with iatrogenic PB was 31.26 ± 4.98 years, higher than that of the PPROM group ($p < 0.05$), but not different than that of spontaneous PB ($p > 0.05$). The vaginal delivery rates of spontaneous PB and the PPROM were higher than the iatrogenic PB ($p < 0.05$), as shown in Table 2.

The average gestational age on admission of the 307 cases with PB was 34.13 ± 2.31 weeks, the hospitalization time for tocolysis was 4.13 ± 7.69 days, and the gestational age at delivery was 34.7 ± 2.02 weeks, in which gestational age on admission of the iatrogenic PB was less than that of PPROM ($p < 0.05$). There was no significant difference in the gestational age at delivery among the three groups ($p > 0.05$). The duration for tocolysis of the spontaneous PB was less than the iatrogenic PB but longer than that of PPROM ($p < 0.05$) (Table 3).

### Outcomes of preterm infants

The 307 cases with PB delivered a total of 367 neonates, including 56 cases of twin pregnancy (both live birth), three cases of twin pregnancy while one fetus died in utero, and two cases of triplet pregnancy (both live birth). Eight neonates had congenital malformations, including three cases of hypospadias, one of anal atresia, one of congenital esophageal stenosis, one of complete endocardial cushion defect, one of congenital choanal atresia, and one of omphalocele (treated surgically). Among the 367 newborns, neonatal asphyxia occurred in 32, including 11 cases of severe asphyxia, and six newborns died within 30 minutes

**Table 2.** Short-term outcome of neonates in different GW groups

| Parameter | Group 1 28–$31^{+6}$ weeks (n = 25) | Group 2 32–$33^{+6}$ weeks (n = 58) | Group 3 34–$36^{+6}$ weeks (n = 224) |
|---|---|---|---|
| Birth weight (g) | 1,483.23 ± 418.47 | 1,963.88 ± 418.72 | 2,562.42 ± 488.31 |
| Z-score of birth weight | -0.54 ± 0.89 | -0.28 ± 0.93 | -0.08 ± 1.12 |
| Number of the newborns | 31 | 67 | 269 |
| 1-minute Apgar | | | |
| ≤ 3 points | 7 (22.58%) | 3 (4.48%) | 1 (0.37%) |
| ≤ 7 points | 3 (9.68%) | 8 (11.94%) | 10 (3.72%) |
| Number of newborns transferred to NICU | 25 (80.65%) | 64 (95.52%) | 99 (36.80%) |
| Pediatric hospitalization (days) | 26.86 ± 22.07 | 16.57 ± 9.29 | 10.67 ± 6.29 |
| Ventilator use | 19 (61.29%) | 20 (29.85%) | 18 (6.69%) |

NICU – neonatal intensive care unit;
Comparison between GW 28–$31^{+6}$ and GW 34–$36^{+6}$ showed a significant difference, $p < 0.05$;
Comparison between GW 28–$31^{+6}$ and GW 32–$33^{+6}$ showed a significant difference, $p < 0.05$;
Comparison between GW 32–$33^{+6}$ and GW 34–$36^{+6}$ showed a significant difference, $p < 0.05$

after birth; a total of 188 neonates were referred to a neonatal intensive care unit (NICU).

### Birth weight and Z-score of birth weight for PB neonates

The birth weight of PB neonates was 2,340.46 ± 606.26 g; the birth weight of single-pregnancy neonates was 2,432.77 ± 602.23 g, and that of twin-pregnancy neonates was 2,148.55 ± 565.10, showing no significant difference between these two groups ($p > 0.05$). The average Z-score of the birth weight of PB neonates was -0.15 ± 1.08). The birth weights gradually increased with gestational weeks, and there were significant differences among PB with 28–$31^{+6}$ weeks, 32–$33^{+6}$ weeks, and 34–$36^{+6}$ weeks ($p < 0.05$); Z-score of PB with 28–$31^{+6}$ weeks was lower than that of neonates with 32–$33^{+6}$ weeks and with 34–$36^{+6}$ weeks ($p < 0.05$), but Z-score of neonates between 32–$33^{+6}$ weeks and 34–$36^{+6}$ weeks showed no significant difference ($p > 0.05$) (Table 2). The birth weights and Z-scores of spontaneous PB and PPROM were higher than those of the iatrogenic PB group ($p < 0.05$). The birth weight of the neonates without glucocorticoids administration was higher than of those with glucocorticoids administration ($p < 0.05$), but the Z-scores among those with glucocorticoids administered in less than one course, one course, and none showed no significant difference ($p > 0.05$), as shown in Table 4.

### Hospitalized treatment of preterm neonates

Among the 188 neonates with PB referred to NICU, three died of ineffective rescue, and the average hospital stay was 15.17 ± 12.35 days. There was no significant difference in hospital stay among the spontaneous PB, PPROM, and iatrogenic PB groups, but the hospital stay of neonates with delivery less than 32 weeks was longer than that of neonates with 32–$36^{+6}$ weeks ($p < 0.05$), as shown in Table 3 and Table 4.

Ventilator was applied in 57 PB neonates, accounting for 30.32% of those transferred to NICU; the duration of ventilator usage was 5.09 ± 6.91 days. Pulmonary surfactant was administrated in 19 preterm neonates once, and another three infants received pulmonary surfactant twice.

There were 60 cases diagnosed with other diseases: 27 cases of RDS (13.92%), six cases of hypoxic-ischemic encephalopathy (3.09%), two cases of intracranial hemorrhage (1.03%), one case of gastrointestinal bleeding (0.52%), one case of necrotizing enterocolitis (0.52%), two cases of gastroesophageal reflux (1.03%), seven cases of congenital heart disease (3.61%), three cases of shock (1.55%), one case of persistent pulmonary hypertension (0.52%), five cases of disseminated intravascular coagulation (2.58%), two cases of anemia (1.03%), and one case of retinal dysplasia (0.52%).

**Table 3.** Comparison of pregnancy and delivery with different preterm birth reasons

| Parameter | SPB (n = 66) | PPROM (n = 143) | TPB (n = 98) |
|---|---|---|---|
| Age (years) | 30.01 ± 4.27 | 29.32 ± 3.99 | 31.26 ± 4.98 |
| GW on admission | 34.04 ± 2.87 | 34.55 ± 2.08 | 33.58 ± 2.09 |
| Pre-pregnancy BMI | 21.52 ± 3.38 | 22.92 ± 3.75 | 23.71 ± 3.62 |
| GW at delivery | 34.66 ± 2.58 | 34.84 ± 1.86 | 34.53 ± 1.80 |
| Time for tocolysis (days) | 4.46 ± 8.54 | 2.01 ± 4.40 | 7.05 ± 9.71 |
| Delivery mode | | | |
| Cephalic vaginal delivery | 32 (48.48%) | 85 (59.03%) | 3 (3.06%) |
| C-section | 32 (48.48%) | 54 (37.50%) | 95 (96.94%) |
| Breech vaginal delivery | 2 (3.04%) | 5 (3.47%) | 0 |

SPB – spontaneous preterm birth; PPROM – prelabour rupture of membranes; TPB – therapeutic preterm birth; GW – gestation weeks
Comparison between the SPB group and the PPROM group showed a significant difference, $p < 0.05$;
Comparison between the TPB group and the PPROM group showed a significant difference, $p < 0.05$;
Comparison between the SPB group and the TPB group showed a significant difference, $p < 0.05$

## DISCUSSION

### Incidence of PB

In recent years, the incidence of PB has been increased mainly due to the popularity of assisted reproductive technologies and the increase in the number of mothers of advanced age [8]; however, incidences of PB reported all over the world, including Asia, are not consistent. For example, 7% in the UK, 13% in India, and more than 15% in Indonesia, Pakistan, etc. [1]. China has a large geographical span; therefore, variation of its PB incidence is also large. An investigation targeting 14 Chinese provinces and cities reported the incidence of PB as 7.04% [10].

**Table 4.** Short-term outcome of neonates for different preterm birth reasons

| Parameter | No hormone treatment (n = 157) | Less than one course of hormone treatment (n = 69) | One course of hormone treatment (n = 81) |
|---|---|---|---|
| Birth weight (g) | 2,504.92 ± 594.96 | 2,185.69 ± 607.74 | 2,146.85 ± 538.43 |
| Z-score of birth weight | -0.24 ± 1.07 | -0.19 ± 1.06 | -0.12 ± 1.11 |
| Number of the newborns | 193 | 78 | 96 |
| 1-minute Apgar | | | |
| ≤ 3 points | 4 (2.07%) | 4 (5.13%) | 3 (3.13%) |
| ≤ 7 points | 11 (7.01%) | 4 (5.13%) | 4 (4.17%) |
| Number of newborns transferred to NICU | 64 (33.16%) | 52 (66.67%) | 72 (75%) |
| Pediatric hospitalization (days) | 16.03 ± 15.24 | 15.81 ± 12.22 | 13.50 ± 8.52 |
| Ventilator use | 24 (12.44%) | 16 (20.51%) | 17 (17.71%) |

Comparison between the non-hormone group and the < 1-course hormone group showed a significant difference, $p < 0.05$;
Comparison between the non-hormone group and the 1-course hormone group showed a significant difference, $p < 0.05$;
Comparison between the < 1-course hormone group and the 1-course hormone group showed a significant difference, $p < 0.05$

Furthermore, it showed that the incidence of PB was the highest in southwest regions of China (10.3%), but lowest in central regions (2.3%), and 6% in eastern coastal areas [11]. Another report from Jiangsu province showed that its incidence was low, about 2.6–2.9% [12]. Because the lower limit of gestational age defined for PB in China is 28 weeks, those delivered before 28 weeks are not included in the scope of PB, so there are certain differences between Chinese and international information on PB. The two hospitals included in this study were both tertiary hospitals in Yantai district, as well as the upper-level referral hospitals, and the incidence of PB was reported as 6.58%, similar to the national level.

## Causes of PB

Many reports considered PPROM to be a common type of PB, and more than 40% of PB were caused by PPROM; PPROM accounted for 2–4% of singleton pregnancies and 7–20% of twin pregnancies [4, 13]. There is still some controversy about the optimal gestational age of delivery for PPROM, and the American Congress of Obstetricians and Gynecologists once recommended it to be more than $34^{+6}$ weeks [14]. In this study, PPROM was the most common type, accounting for 46.58 % of PB and 3.06% of total deliveries; the gestational age at delivery was 34.84 ± 1.86 weeks, where delivery time of more than $34^{+6}$ weeks accounted for 68.75%; the tocolysis time was significantly shorter than in the spontaneous PB and iatrogenic PB groups. Therefore, PPROM should be actively prevented before 37 GW, and attempts should be made to postpone the delivery to after $34^{+6}$ GW.

In recent years, an important reason leading to the increased incidence of PB is the increase of iatrogenic PB, and it was reported to account for 35–40% of all PB cases in other countries [5]. In this study, the incidence of iatrogenic PB accounted for 31.61%, similar to the reports abroad. The increasing of iatrogenic PB is related with the improvements of medical care level, which makes many pregnancy conditions that were not suitable for pregnancy in the past maintain after 28 GW. In this study, the pregnant women in the iatrogenic PB group were older, had less GW on admission and longer tocolysis time, which all indicated that patients' own diseases had significant impacts on PB.

The reasons of iatrogenic PB could be further divided into three categories. One is caused by maternal diseases, such as intrauterine infection, chorioamnionitis, preeclampsia, or other maternal system disorders; the second is caused by fetal diseases, such as fetal distress or fetal growth restriction; the third is caused by placental diseases, such as placenta previa, or placental abruption [9]. This study showed that the most important reason of iatrogenic PB was pregnancy-induced hypertension (57.14%), similar to studies in Australia and Beijing [15]. The second reason in this study was the prenatal placental factors, such as placenta previa and placental abruption, accounting for 28.57%, which was associated with the increased gravidity and parity, especially in patients with a history of Cesarean section [16]. Therefore, the study suggests that the maternal management of late pregnancy in our region should be focused on the prevention and treatment of the occurrence and progression of pregnancy-induced hypertension.

## Analysis of birth weight of preterm infants

Birth weight of preterm infants is closely related to their mortality. In 2010, the mortality rate of live infants in the USA was 6.14‰, in which PB accounted for 35.2%; the mortality of neonates with birth weight less than 1,500 g was 100-fold greater than that of neonates with birth weight greater than 2,500 g [17]. This study introduced the Z-score of birth weight, and the results showed that the Z-score of preterm infants with $28–31^{+6}$ GW was lower than in those with more than 32 GW, while those with $32–33^{+6}$ GW and more than 34 GW showed no significant difference, indicating that gestational age less than 32 GW had a greater impact on fetal body weight in this region, higher than the national average, so nutritional support treatments should be strengthened to increase the fetal body weight in utero.

The study also showed that the birth weight of non-glucocorticoid administration group was higher than the other two groups with glucocorticoid therapy, but there was no significant difference in the Z-score among these groups. It might be so because the gestational age on admission of the non-glucocorticoid group was higher than the other two groups with glucocorticoid therapy, so after eliminating the influence of gestational age, no more difference could be displayed among the treatment groups, indicating that glucocorticoid therapy within one course would not affect fetal birth weight.

## Short-term outcomes of preterm infants

Due to immature organ development, complications in preterm infants are numerous [18]. In developed countries, the survival rate of preterm infants with 24 GW was about 50%, and of those with 28 GW it was 90%; however, in developing countries, the survival rate of infants with 28 GW was less than 10%, which could increase to more than 50% only after gestational age reached 34 GW. In 2011, Chinese large-sample data analysis showed the average mortality of preterm infants to be 3.3% [11]. In this study, it was 0.82%, lower than the national average.

Respiratory complications are one type of the most common complications in preterm infants, as well as the main cause of death [19, 20]. RDS in preterm infants is caused by the deficiency of pulmonary surfactant [21]. The incidence of RDS among those with gestational age less than 28 GW accounted for up to 93% [18]. Among the survived preterm infants, approximately 40% would suffer bronchopulmonary dysplasia. When gestational age of preterm infants is increased by one week, or birth weight is increased by 100 g, the risk OR values of bronchopulmonary dysplasia would be 0.77 and 0.89, respectively; therefore, gestational age and birth weight are the key factors affecting the outcome of preterm infants. In this study, the most common complication was RDS, accounting for 13.92%.

Another serious complication in preterm infants is necrotizing enterocolitis, and it was reported abroad to be about 7–11% in preterm infants with birth weight < 1,500 g [22]. In this study, necrotizing enterocolitis occurred in one male preterm infant (delivered at $31^{+1}$ GW, PPROM, birth weight of 1,830 g, and hospital stay of 35 days), and was discharged when the body weight was increased to 1,920 g. In addition, attention should also be paid to nervous system complications in preterm infants, such as hypoxic-ischemic encephalopathy, intracranial hemorrhage, retinal development, etc. Perinatal infection and maternofetal inflammation caused by different viruses is strongly associated with PB, which represents an important mechanism for cerebral damage.

In short, the main causes of PB, such as PPROM, should be actively prevented and treated during the entire course of pregnancy; at the same time, health care during a pregnancy needs to be strengthened to actively prevent and treat iatrogenic PB, such as pregnancy-induced hypertensive disorders. Establishing effective intrauterine transportation system and actively managing respiratory complications could improve the outcome of PB infants. In this study, there were still some shortcomings; for example, the long-term outcome data of these preterm infants, such as neural development monitoring, were lacking. Therefore, if a perinatal information-sharing network among all the delivery units could be formed in the future, and if doctors in departments of obstetrics and pediatrics could systematically co-survey the outcomes of preterm infants, more accurate data of PB in this region, and even throughout China, would be provided, thus enabling better guidance for obstetricians towards the diagnosis and treatment of PB.

## CONCLUSION

The most common reason for PB is iatrogenic, especially maternal diseases. In this study, the birth weight of preterm neonates was less than normal, so Z-score was more adequate to define organ maturity; therapy with glucocorticoids within one course did not affect fetal birth weight. At the same time, since PB could cause a variety of serious complications in infants (such as PPROM), avoiding them based on pre-pregnancy physical examination, pregnancy monitoring, and proper treatment is of utmost importance; preterm infants should also be actively treated so as to improve their outcomes.

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# Узроци и непосредни исход код превремено рођене новорођенчади

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**САЖЕТАК**

**Увод/Циљ** Превремени порођај (ПП) главни је узрок смртности новорођенчади, а други непосредни узрок смрти до пете године живота детета.

Циљ овог рада је био да анализира клинички ток и исход код превремено рођене деце.

**Методе** Ретроспективно су анализирани подаци за 307 превремено рођене деце у болници Универзитета у Ћингдау, у периоду од 1. јануара 2012. до 31. децембра 2012.

**Резултати** Учесталост превременог рађања деце је 6,52%. Превремено пуцање водењака је био разлог у 46,58% ПП-а, спонтани ПП код 66 (21,5%), а терпијски ПП код 98 (31,92%) болесника. Природни порођај је чешћи (60,72%) код трудноћа са < 32 недеље, а чешћи царским резом (60,99%) код трудноћа са ≥ 32 недеље ($p < 0,05$). Порођајна тежина је била 2.340,46 ± 606,26 *g*, а 3-скор на рођењу -0,15 ± 1,08. 3-скор је био мањи у групи 28–$31^{+6}$ недеља него у групи 32–$33^{+6}$ и групи ≥ 34 недеље ($p < 0,05$). Просечна хоспитализација износила је 15,17 ± 12,35 дана, а најчешћа компликација је била респираторни дистрес синдром (13,92%).

**Закључак** Превремени порођај доводи до озбиљних компликација код новорођенчета. Главни разлози, као прерано пуцање водењака, морају се спречити и лечити, а сáмо новорођенче мора се интензивно лечити.

**Кључне речи**: одојче; исход трудноће; превремени порођај; 3-скор