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Original Article

Clinical analysis of 122 Chinese cases of twin pregnancy complicated with preterm birth and outcomes of preterm infants

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Abstract: This study aims to analyze the clinical features of twin pregnancy complicated with preterm birth and outcomes of preterm infants in China. A retrospective study was conducted on 122 hospitalized cases of twin pregnancy complicating preterm birth with gestational weeks from 26 weeks to 36 weeks^{+6} out of 10868 pregnancies from January 1st, 2012 to December 31st, 2013 in Yantai affiliated hospital of Binzhou medical university and Yuhuangding hospital. The information of general data and causes of preterm birth and outcomes of preterm infants were summarized. There were 122 cases of twin pregnancy with preterm birth, which accounted for 21.37% of preterm birth and 46.04% of twin pregnancy. The gestational weight gain, the prenatal usage rate of glucocorticoids, the rate of Cesarean section and the incidence of spontaneous preterm labor in twin group were higher than in singleton group ($P<0.05$). The birth weight and the mean Z scores of birth weight of preterm infants in twin group were lower than in singleton group ($P<0.05$), but the ventilator-usage period in twin group was longer than in singleton group ($P<0.05$). The rate of respiratory distress syndrome (RDS), pneumonitis, sepsis, hypoglycemia and anemia of preterm infants in twin group were higher than in singleton group ($P<0.05$). Preterm birth is the severe complication for twin pregnancy. Because twin-pregnancy could cause serious harm to preterm infants, high attention should be paid to prevent and treat the preterm birth of twin pregnancies.

Keywords: Twin pregnancies, preterm birth, pregnancy outcomes, infant

Introduction

Preterm birth refers to the delivery before 37 completed weeks, and it is estimated that there are more than 41,000 preterm birth cases per day worldwidely [1]. Preterm birth is the most important reason of neonatal death and the second direct cause of death in children under 5 years old. The average worldwide incidence of preterm birth is estimated as 11.1%; different races and regions show differences in the incidence of preterm birth, for example, it could be up to 15% in Africa while in some European countries, it might be as low as 5% to 6%. In recent years, with the large-scale implementation of adjunctive reproductive technology and the increase of puerpera with advanced age, the incidence of preterm birth has also been risen [2, 3].

Twin-pregnancy is the leading cause of preterm birth, and the worldwide incidence of twin pregnancies also shows an upward trend [4]. In USA, the incidence of twin pregnancies rose by 76% from 1980 to 2009 [5], and in England, the incidence of twin pregnancies was increased from 9.6/1000 (in 1980) to 16.1/1000 (in 2009), among which the recent five-year incidence rate was increased by 20%. In approximately 54% of twin pregnancies, delivery would occur before 37 weeks, and approximately 9% occurred before 32 weeks [6, 7]. Since twin pregnancies could be accompanied with some severe complications, the preterm infants of twin pregnancies might occur a variety of serious complications, such as respiratory distress syndrome (RDS), sepsis, patent ductus arteriosus, cerebral palsy, or cognitive defects [8, 9].

WHO estimates that there are about 287,000 cases of maternal death and 3,000,000 cases of neonatal death each year, among which 99% occurs in developing countries. The statistics targeting the 23 middle- and low-income countries worldwidely showed that the incidence of twin pregnancies was 1.2%, and the mean time on delivery of twin pregnancies was 36.8 weeks, accounting for 35.2% of preterm birth [10]. China is a developing country, and there is no report about the incidence of preterm birth from the national level; it was estimated that the preterm birth rate was lower than the global level, such as Jiangsu Province (2.6%~2.9%) [5, 11]. In addition to the ethnic difference, it's also because that the lower limit of preterm birth defined in China is 28 weeks, and the delivery less than 28 weeks of pregnancy is not included into the scope of preterm birth, so there is certain difference in the preterm profiles between China and other countries. Currently, reports about the preterm birth of twin pregnancies from mainland of China are still rare. This study analyzed the clinical characteristics of preterm birth and the outcomes of preterm infants with twin pregnancy in the northeast China, aiming to provide evidence for the diagnosis and treatment of preterm birth of twin pregnancies in China.

Material and methods

Data sources

A total of 122 cases of twin pregnancies (26 to 36^{+6} weeks of gestation) delivered in the department of obstetrics, affiliated Yantai Yuhuangding Hospital of Qingdao University and the affiliated Yantai Hospital of Binzhou Medical College, from January 1, 2012, to December 31, 2013, were selected as the study subjects (twin group), and the preterm birth cases with singleton pregnancy over the same period was set as the control group (singleton group). The above two hospitals were both the referral centers for women with preterm birth, in which the total delivery cases during the same period were 10,868, and a total of 571 cases was preterm birth. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Yuhuangding hospital. Written informed consent was obtained from all preterm cases.

Data collection

The retrospective analysis method was adopted. The preterm profiles that met the criteria were inspected; meanwhile, the hospital stay conditions of the mothers and preterm infants were recorded. Maternal clinical characteristics and the outcomes of preterm infants included: general information of pregnant women, pregnancy complications, hospital delivery method, gestational week on delivery, and preterm outcomes, etc. According to the chorionic nature judged by early pregnancy ultrasound, intrapartum chorionic inspection, and histopathological examination of postpartum placentas and fetal membranes, twin pregnancies were further divided into the dichorionic diamnionic twin pregnancies (DCDA) and monochorionic diamnionic twin pregnancies (MCDA). The cases of triplet pregnancies or one fetal death in utero of twin pregnancies were excluded.

Diagnostic criteria

Preterm birth: the upper limit of preterm birth referred to the delivery with less than 37 weeks, and the lower limit of preterm birth was set as 26 weeks. Preterm birth was divided into three categories according to the reasons: spontaneous preterm labor (SPL), preterm prelabour rupture of the membrane (PPROM), and iatrogenic preterm labor (IPL).

The Z score of birth weight

Calculation formula: Z score = (birth weight of the newborn - average birth weight of this gestational age)/standard deviation of the birth weight of this gestational age. The average birth weight and standard deviation of birth weight with different gestational ages referred to the physical development criteria of the newborns with different gestational ages in 15 Chinese cities. There was no sex difference for the criteria.

Twin-pregnancy complications

Inconsistent growth: diagnostic criterion, birth weight difference of the twin pregnancies ≥25%, birth weight difference = (bigger fetal body weight - smaller fetal body weight)/large fetal body weight × 100%. Selective intrauterine growth restriction (selective IUGR, sIUGR): the smaller fetal body weight was below the

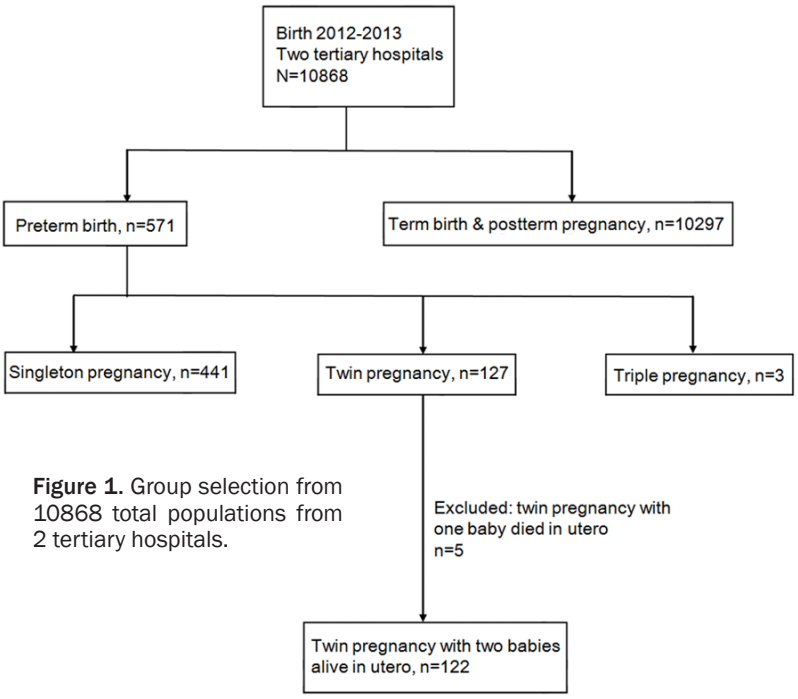

Figure 1. Group selection from 10868 total populations from 2 tertiary hospitals.

10th percentile value of the fetuses with the same gestational age regardless of the twin growth inconsistencies.

Statistical methods

SPSS13.0 software was used for the statistical analysis. The data were expressed as the mean and standard deviation. One-way analysis of variance (ANOVA) was used to determine the statistically significant differences between different groups. Chi-square test was performed for analysis on proportions as represented by percentages. A multiple logistic regression analysis was preformed adjusting for parity, age, preeclampsia, gestational diabetes, asss-ited reproductive techniques (ART) and other significant baseline population characteristics. Differences were defined as statistically significant at the leverl of $P<0.05$. Two-tailed P values less than 0.05 were considered statistically significant.

Results

General information of the preterm birth cases

A total of 10,868 deliveries were implemented in the above two hospitals from January 1, 2012, to December 31, 2013, among who 268 cases were of multiple pregnancies, accounting for 2.47%. 571 cases were delivered within $26\sim36^{+6}$ weeks, accounting for 5.25%, including three cases of thriple pregnancies and five cases of one fetal death in utero of twin pregnancies. A total of 122 cases had the preterm infants both alive, accounting for 21.37% of the preterm birth cases and 46.04% of twin pregnancies. A total of 441 cases were preterm single pregnancy, accounting for 77.23% of of the preterm birth cases (**Figure 1**). The average age of the pregnant women of the 122 twin-pregnancy cases was (30.11±4.01) years, and the mean pregnancy time was (1.80±0.99) times, including 112 cases of primipara (91.80%) and 10 cases of multipara (8.20%). DCDA had 68 cases (55.74%), and MCDA had 54 cases (44.6%). Parity, age, BMI, preeclampsia and ART had no effect on the occurrence of twin pregnancy with preterm birth. Statistically significant risk factor for twin pregnancy with preterm birth was gestational diabetes (OR 0.07, 95% CI 0.02 to 0.42).

Maternal height and body mass index (BMI)

The height and weight on admission and pre-pregnancy BMI of the patients in twin pregnancy showed no significant difference with those in singleton pregnancy ($P>0.05$). The weight gain during twin pregnancy was (19.15±6.60) kg, higher than singleton pregnancy ($P<0.05$) (**Table 1**). 10 cases in twin pregnancy showed the pre-pregnancy BMI<18.5 (8.20%), 81 cases were within 18.5~24.9 of (66.39%), 27 cases were within 25 to 29.9 (22.13%), and four cases were ≥30 (3.28%).

The gestational weeks on delivery and situations during hospital stay

The average gestational weeks on admission of twin pregnancy were earlier than singleton pregnancy ($P<0.05$); the hospitalization time for tocolysis of twin pregnancy was (6.63±10.61) days, longer than that of singleton pregnancy (3.53±6.69) days ($P<0.05$); but there was no

Table 1. General information of the preterm birth cases ($\bar{x}\pm s$)

Item	TP	SP	t	*P*
Age (years)	30.11±4.01	30.08±4.56	-0.05	0.96
Height (m)	1.63±0.05	1.62±0.05	-0.76	0.45
Body weight on admission (kg)	77.91±9.55	76.68±12.21	-0.69	0.49
Weight gain during pregnancy (kg)	19.15±6.60	16.01±5.88	-3.58	0.00
Pre-pregnancy BMI	22.33±3.21	22.96±3.82	1.11	0.27
BMI on delivery	29.55±3.33	29.19±4.32	-0.57	0.57
Gestational age on admission (weeks)	33.59±2.86	34.26±2.14	2.04	0.04
Gestational age on delivery (weeks)	34.53±2.54	34.74±1.88	0.75	0.45
Birth weight of preterm infants (g)	2084.93±595.83	2436.02±604.45	2.70	0.007
Z score of birth weight of preterm infants	-0.59±0.95	0.06±1.06	3.43	0.001

significant difference for the delivery time between twin pregnancy and singleton pregnancy (P>0.05) (**Table 1**). 24 cases in twin pregnancy were vaginal delivery (19.67%), and 98 cases were delivered by cesarean section (80.33%). 60 cases (49.18%) in twin pregnancy were not administrated dexamethasone before delivery; 20 cases (16.39%) were administrated dexamethasone for less than 1 course; 42 cases (34.43%) were administrated one-course of hormone treatment; no case received multiple courses of hormone therapy.

Reasons of preterm birth

Among the 122 twin-pregnancy cases, 49 cases were received with assisted reproductive technologies (40.16%). The reasons resulting in the preterm birth of twin pregnancies included: 44 cases of PPROM (36.06%), 42 cases of SPL (34.43%), and 36 cases of IPL (29.51%).

Outcomes of preterm infants

The 122 women delivered a total of 244 preterm infants, among who 46 cases of male/male fetus, 34 cases of female/female fetus, and 42 cases of male/female fetus. Two cases had birth defects, including one case of hypospadias and one case of omphalocele (followed by surgical treatment). The 1 and 5-minute Apgar scores of the preterm twin pregnancies were (9.21±1.71) and (9.50±1.36), respectively; 30 cases with neonatal asphyxia (12.30%), including six cases of severe asphyxia (2.46%). Two preterm infants died within half an hour of birth, and 126 infants were transferred into the department of pediatrics (51.64%). The 1-minute and 5-minute Apgar scores of the preterm singleton pregnancy were (9.53±1.40) and (9.56±1.13), respectively, and there was no significant difference when compared with twin pregnancy (P>0.05).

Z score of birth weight of preterm infants

The birth weight of twin pregnancy was lower than that of singleton pregnancy (P<0.05). Due to lacking the average birth weight and standard deviation of nationwide newborns less than 28 weeks, the Z score of the preterm infants with ≥28 weeks in twin pregnancy was calculated (-0.59±0.95), which was also lower than that in singleton pregnancy (P<0.05); further analysis showed that the birth weight and Z score of twin pregnancies with 35~35^{+6} weeks and 36~36^{+6} weeks were lower than those in singleton pregnancy (P<0.05) (**Table 2**).

A total of 18 cases in twin pregnancy exhibited inconsistent growth (14.75%), including 4 cases of DCDA, and 14 cases of MCDA. Similarly, due to lacking the 10th percentile value of the newborns delivered before 28 weeks, the 116 twin pregnancies delivered after 28 weeks were performed the statistics, and the results showed 44 cases of sIUGR (37.93%), including 30 cases of MCDA and 14 cases of DCDA.

Hospital stay conditions of preterm infants

Among the 126 cases of twin pregnancies that were transferred into the department of pediatrics, four died after their guardian gave up therapy. Among the successfully rescued 122 twin pregnancies, the longest hospital stay period was 58 days, and the average hospital stay period was (15.54±12.41) days; the average hospital stay period of the singleton pregnancy

Table 2. GW distribution, birth weight, and PS usage of 122 twin-pregnancy cases

Group	28 to 28^{+6} gestational weeks at delivery			29 to 29^{+6} gestational weeks at delivery			30 to 30^{+6} gestational weeks at delivery		
	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)
Twin pregancy	4	1042.50±164.59	-1.14±0.54	4	1330.00±42.43	-0.44±0.13	4	1316.67±160.73	-0.99±0.40
Singleton pregnancy	5	1086.67±120.55	-1.00±0.39	9	1349.00±249.76	-0.38±0.75	9	1748.00±704.11	0.08±1.76
t		0.38	0.38		0.10	0.10		1.01	1.01
P		0.720	0.720		0.920	0.920		0.350	0.350
Group	31 to 31^{+6} gestational weeks at delivery			32 to 32^{+6} gestational weeks at delivery			33 to 33^{+6} gestational weeks at delivery		
	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)
Twin pregancy	8	1825.00±104.08	-0.23±0.20	12	1641.67±273.67	-0.75±0.62	22	2040.00±376.05	-0.21±0.87
Singleton pregnancy	12	1646.43±297.50	-0.58±0.58	25	1841.79±436.05	-0.29±0.99	62	2045.00±417.47	-0.20±0.96
t		-1.14	-1.14		1.03	1.03		0.04	0.04
P		0.280	0.280		0.320	0.320		0.970	0.970
Group	34 to 34^{+6} gestational weeks at delivery			35 to 35^{+6} gestational weeks at delivery			36 to 36^{+6} gestational weeks at delivery		
	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)	n	Birth weight ($\bar{x}\pm s$)	Z score of birth weight ($\bar{x}\pm s$)
Twin pregancy	18	2043.57±235.35	-0.71±0.52	76	2292.63±491.59	-0.65±1.19	84	2477.67±361.89	-0.57±0.90
Singleton pregnancy	71	2344.50±400.89	-0.04±0.89	103	2589.83±503.53	0.07±1.22	145	2865.24±408.08	0.39±1.02
t		1.92	1.92		2.90	2.90		5.24	5.24
P		0.060	0.060		0.005	0.005		0.000	0.000

that were transferred into the department of pediatrics was (14.78±12.67) days, and the above two groups showed no significant difference (P>0.05).

A total of 46 preterm infants in twin pregnancy was received ventilator therapy, accounting for 18.85% and showing no significant difference with singleton pregnancy (14.45%) (P>0.05); the ventilator-usage period was (7.48±9.84) days, significantly longer than singleton pregnancy (3.74±3.16) days (P<0.05). A total of 24 preterm infants in twin pregnancy were administrated with pulmonary surfactant (PS).

Common complications in twin pregnancies were: 76 cases of neonatal infective pneumonia (31.15%), 32 cases of neonatal respiratory distress syndrome (RDS) (13.11%), 2 cases of heart failure (0.82%), one case of gastrointestinal bleeding (0.41%), one case of diffuse intravascular coagulation (0.41%), 6 cases of neonatal sepsis (2.46%), 24 cases of neonatal hypoglycemia (9.84%), 7 cases of neonatal hypocalcemia (2.87%), and 22 cases of anemia (9.02%).

Discussion

Preterm birth incidence of twin pregnancies

The definition of preterm birth in China refers to the delivery with at least 28 weeks while less than 37 weeks, but the worldwide limit of survival of preterm neonatal is 25 weeks and 750 g of birth weight [10]. In addition to preeclampsia and postpartum hemorrhage, twin pregnancy also has linked with the more common complication such as preterm birth than single pregnancy. The data of America showed that more than 50% of twin pregnancies and 90% of triple pregnancies had the delivery time less than 37 weeks. Therefore, preterm delivery is the main reason of high neonatal morbidity and mortality towards twin pregnancies. In the near 30 years, the global incidence of twin pregnancies is gradually increasing [7]. The main reasons for this are the application and promotion of ART and older age of pregnant women, etc [12, 13]. In most of the developed countries, the preterm birth incidence of twin pregnancies have all been increased [14, 15]. WHO reported from 24 developing countries, and showed that the preterm birth incidence of twin pregnancies was 35.2%, among which 6.1% with the infants less than 32 weeks; the preterm birth of twin pregnancies in developing countries is mainly related with the older maternal age, low education level, multiparity, and poor prenatal care, etc [10].

This study showed that the preterm birth incidence of twin pregnancies was higher than the level in developing countries reported by WHO; the incidence with preterm infants ≤32 weeks accounted for 6.04%, consistent with the levels of other developing countries. ART had no effect on preterm birth of twin pregnancy in China, but the gestational diabetes was independent risk factor for preterm birth of twin pregnancy, which indicated that the doctors worried about the fetal lung immaturity of twin and wished to postpone the delivery time after 37 weeks. In this study, the survival rate of the newborns delivered before 28 weeks was 66.67%, although lower than the European and American standards [16, 17], it should be considered in clinical work that Chinese medical technology has been continuously improved, so the referral hospitals have generally had the abilities to rescue extremely preterm infants. However, the key factor that currently restricted this region's successful rescue and survival rate of preterm infants was the expensive treatment cost, many families could not afford hospital fees, and they also worried about the long-term neurological sequelae, so they could not insist on the preterm infant rescue treatment.

Causes of preterm twin pregnancies

This study showed that the main reason of preterm twin pregnancies was PPROM, followed by SPL and IPL, and the difference among these three categories was not significant. The data in developed countries were different [8]. American studies reported that from 1999 to 2002, 58%~62% of preterm twin pregnancies belonged to IPL, 30%~32% belonged to SPL, while only about 8%~10% belonged to PPROM [18, 19]. Another study showed that from 1995 to 2005, the proportion of IPL was increased by about 60%, while those of PPROM and SPL were decreased by 5.3% and 22.2%, respectively [20]. In this study, the proportion of PPROM was significantly higher. The reason for higher IPL might be that in developed countries, the pregnant women were at higher age, which related to maternal factors such as gestational hypertension, placenta previa, placental abruption, pregnancy diabetes, or infections

as well as fetal factors such as sIUGR, or fetal distress. Pregnant women ≥35 years of age accounted for 25%~30% of twin pregnancies in developed countries; however, in this study, the average age of the pregnant women with twin pregnancies was (30.11±4.01) years old, only 19.67% was ≥35 years old, so it might be the reason that the proportion of IPL in this study was lower than that abroad. In addition, the application of fetoscopy has not been popular in these two hospitals, resulting in less active intervention.

Birth weight analysis of preterm twin pregnancies

It has been reported that the mortality of preterm twin pregnancies was closely associated with the birth weight, but the reports about the birth weight of preterm twin pregnancies were different. WHO data showed that the overall birth weight of twin pregnancies in 23 developing countries was lower than that of single pregnancy, but no birth weight of preterm twin pregnancies had been statistically analyzed [10]. Australian's 10-year data of twin pregnancies with less than 31 weeks indicated that no significant difference existed between twin pregnancy and singleton pregnancy [21]. American data showed that the birth weight of preterm twin pregnancies with 23~36^{+6} weeks was lower than that of single pregnancy with the same gestational age [22, 23]. The data of nine European countries in 2003 demonstrated there was no statistically significant difference between the twin and single pregnancies with 24~31^{+6} weeks [10]. Croatia's statistics showed that the birth weights of preterm twin pregnancies with 34~36^{+6} weeks were lower than those of single pregnancy with the same gestational age [24].

Our results were similar to those of other countries, the overall birth weight of preterm twin pregnancies was lower than that of single pregnancy. However, our study showed no difference in the birth weight between twin and single pregnancies with less than 35 weeks, and it might possibly be caused by small number of sampling, which could not fully reflect the overall level. In addition, neonatal birth weight would also be affected by ethnicity, chorionic feature, or maternal complications, which might also lead to the differences with the studies from different countries.

Because the birth weight would accordingly change with the gestational age, the birth weight alone could not eliminate the impacts of gestational age. Therefore, this study introduced the Z score of birth weight for properly evaluating whether the preterm infants had achieved the appropriate developmental level. This study referred to the physical development standards of newborns with different gestational ages in 15 Chines cities; because China still lacks the average birth weight and SD of newborns delivered before 28 weeks, this study could only calculate the Z score of birth weight of the preterm infants before 28 weeks. The results showed that the average birth-weight Z score of the overall preterm twin pregnancies was less than that of singleton pregnancy ($P<0.05$); there was no significant difference in the Z score among different gestational-age groups less than 35 weeks, which was consistent with the actual changes of the birth weight.

Outcomes of preterm infants

Preterm birth of twin pregnancies could cause high perinatal mortality and morbidity. One study reported that the neonatal mortality of twin pregnancies was 29.8/1000, and the neonatal mortality risk of twin pregnancies was five times than that of single pregnancy [25]. Statistics from WHO showed that the postpartum 7 days mortality rate of preterm twin pregnancies in developing countries was 3.1%, which related to the maternal factors such as mother-under-18-year-old, less than 10 years of education, less than 4 times of pregnancy examination, vaginal bleeding in second-trimester of pregnancy, and the fetal factors such as non-head presentation and low birth weight, etc [26, 27]. In this study, six cases of preterm twin pregnancies died (mortality rate 2.46%) lower than the average level in developing countries worldwide issued by WHO, and it might be caused by lacking the above maternal risk factors in this region.

Common complications in preterm twin pregnancies were respiratory complications, retinal immaturity, necrotic enterocolitis, cerebral palsy, and long-term neurocognitive deficit, etc [28, 29]. Our study reported the incidence of multiple complications in preterm infants, such as pneumonia, RDS, and neonatal sepsis, etc. Immature respiratory system was considered to be the main complication and the main

cause of premature death. However, due to the relatively short follow-up period of this study, the evaluation towards the neurological development and cognition in preterm infants were still lacking, which needed to be continuously followed up in future.

In short, twin pregnancy could cause serious adverse effects towards mothers and newborns, among which preterm birth is a major cause of neonatal mortality and morbidity; therefore, special attention should be paid for the prevention and treatment of preterm birth of twin pregnancies. Active actions should be prepared during the pregnancy period to prevent the leading reason of preterm birth, namely PPROM; meanwhile, prenatal care and effective intrauterine transportation system should also be strengthened and established, and such complications as RDS in preterm infants should be applied active treatment to improve the outcomes of preterm infants. In this study, there still were some shortcomings: the sample size needed to be expanded, and the long-term outcomes of these preterm infants should be continuously focused, especially on the nervous system development. In future, the cooperation between the department of obstetrics and pediatrics should be strengthened, and the outcomes of preterm twin pregnancies should be joint-observed in order to provide better large data for the treatment of preterm twin pregnancies and to guide the obstetric care of twin pregnancies.

Disclosure of conflict of interest

None.

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