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*Original Article*

# Spectrum of clinical disease in a series of 65 hospitalized premature twin infants from south China

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**Abstract:** Objective: To investigate the neonatal disease spectrum of hospitalized premature twin infants and help guide intensive medical care. Methods: Sixty-five twin babies admitted to a tertiary care hospital in south China, for premature birth between March and November 2022, were studied. Comparisons of neonatal disease were carried out between different gestational ages, and IVF-ET or not. Results: The incidence of intrauterine infection, anemia, and electrolyte imbalance in IVF-ET newborn infants was higher than that in natural conception infants ($P < 0.05$). Neonatal jaundice (100%) was commonest in very premature twin infants, followed by neonatal respiratory distress syndrome (NRDS) (90%), patent foramen ovale (90%) and electrolyte imbalance (90%). Neonatal jaundice (100%) was most common in moderate premature twin infants, followed by NRDS (87.5%) and patent foramen ovale (81.25%). Patent foramen ovale (74.36%) was most common in late premature twin infants, followed by neonatal jaundice (64.1%) and neonatal hypoglycemia (35.9%). Conclusion: Medical staff should strengthen the observation and care of neonatal jaundice, NRDS and patent foramen ovale during perioperative management of twin premature infants. Due to significant differences in the disease spectrum of twin premature infants at different stages, appropriate health care should be taken to decrease illnesses based on specific clinical circumstances. Monitoring for intrauterine infection, anemia, and electrolyte imbalance should be paid attention to in IVF-ET premature twin infants' during nursing. Twins from very premature infants had higher incidence of anemia and electrolyte imbalance, and needed more care in comparison to moderate and late premature infants. Twins from very premature infants had higher incidence of intrauterine infection, and needed more care in comparison to late premature infants. Twins being very and moderately premature as infants had higher incidence of NRDS, and needed more care in comparison to late premature infants. Twins as extremely premature infants had higher incidence of acid-base imbalances, and needed more care in comparison to premature infants. Monitoring for neonatal hypoglycemia should be paid attention to for late premature infants.

**Keywords:** Spectrum, preterm infants, twin, neonatal period

## Introduction

Preterm labor is being born before 37 weeks of pregnancy [1]. In 2019, the World Health Organization published the global average incidence of premature infants was 10.6%. The incidence rate of premature infants increases annually, and this rate increase gradually arouses social concern. About 1.5 million preterm babies are born in China every year, more than a tenth of all premature births globally [2]. More than 75% of newborn deaths are directly related to preterm birth, with the characteristics of high mortality rate and many sequelae in clinical practice [3].

The classification of premature infants can be based on standards such as birth weight and gestational age. The frequently used clinical classification methods in China are: extremely premature infants < 28 weeks, very premature infants 28-32 weeks, moderate premature infants 32-34 weeks, and late premature infants 34-37 weeks.

With the increase of social and life pressures, use of assisted reproductive technology increases the incidence of multiple pregnancies. Twins are the most common type of multiple pregnancy. Twin pregnancy accounts for 2 to 4% of total births [4]. Due to the excessive dila-

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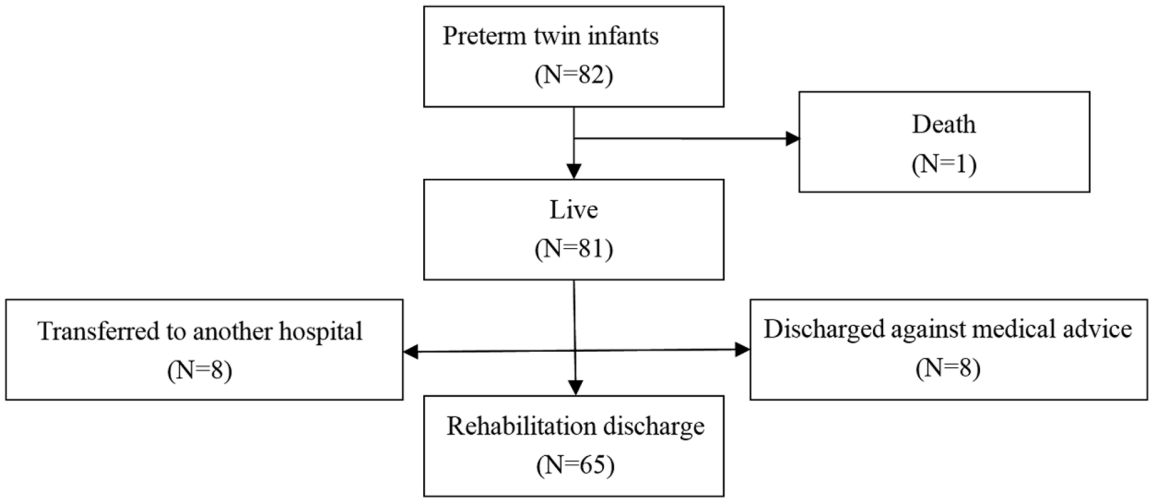


**Figure 1.** Flowchart for inclusions in the study.

tion and increased cavity pressure of the uterus caused by twins, this stimulates contractions and leads to a high frequency of painless contractions. The cervix gradually stretches, the texture becomes soft, shortens, and the even cervix expands, resulting in premature birth. Twin pregnancy accounts for 20.0% of all preterm deliveries in America [3]. These pregnancies not only lead to an increase in neonatal incidence rate and mortality, but also increases the risk of maternal complications, resulting in an increase in medical costs.

It's known that there are significant differences in the incidence of complications of premature infants. There are many studies [5-10] on common complications of premature birth both domestically and internationally, which are about respiratory complications, circulatory system disease, anemia, neonatal jaundice and infection. However, twin pregnancies are often excluded from most of these studies. Additionally, premature infants' complications in several studies [11, 12] were not totally consistent because of regional and demographic variations. Consequently, carrying out pertinent research in certain demographics and places has greater practical guiding value. The aim of this study was to collect clinical data and analyze the disease spectrum of different stages in this region, which helped to clarify the effectiveness of various treatments and provide scientific basis for further improving the treatment and management of premature twins. This could also provide a research basis on assessment or screening for common neonatal complications, which may also reduce the risk of premature infant re-admission, helping them grow up healthy. It would also reduce the nursing cost and economic burden, saving social resources ultimately.

## Methods

### *Design*

This was a descriptive, cross-sectional study. The infants' diagnoses were acquired after discharged from the hospital.

### *Subjects*

The premature twin babies were hospitalized in Dongguan Maternal and Child Health Care Hospital, Guangdong Province, China. They were recruited by purposive sampling, the inclusion criteria were as follows: twins born before 37 weeks of pregnancy, informed consent from the mother and voluntary participation in the study. Exclusion criteria were as follows: death, discharged against medical advice, transferred to another hospital (**Figure 1**).

### *Research instrument*

Conditions for preterm infants included birth weight, gender, and complications. Anemia, Intrauterine infection, Acid-base imbalance, Neonatal pneumonia, Neonatal Coagulation disorders, Neonatal jaundice, Patent foramen ovale,

Neonatal hypoglycemia, Patent ductus arteriosus, NRDS, Electrolyte Imbalance, Ventricular septal defect, and Intraventricular hemorrhage were included in the complications.

*Data collection and analysis*

Data were collected from March to November 2022. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 26.0 software). The measurement data were expressed by mean and standard deviation, and the count data were expressed by the frequency and component ratio. The $\chi^2$ test and Fisher's exact test were used to compare the groups. The *p* value of < 0.05 was considered significant.

This study was approved by the Medical Ethics Committee of Dongguan Maternal and Child Health Care Hospital (2022-1).

## Results

*Demographic data*

Sixty-five babies were born in 36 cases of twin pregnancy. There were 24 first time mothers, accounting for 66.67%, and 12 pluripara, accounting for 33.33% of the enrolled cases. Mothers had a mean age of 30.58 years (SD=5.94, range =19-48 years). Nine of the mothers gave birth to 16 premature twin babies using assisted reproductive technology, accounting for 25%. Forty-nine of premature twin infants were conceived by natural conception by 27 of the mothers, accounting for 75% of cases. Sixty-two (95.38%) babies were born by cesarean delivery, and 3 (4.62%) babies were born by vaginal delivery. Mothers of the 3 natural birth twin pregnancies gave birth vaginally to one child first, and then had the other twin by caesarean.

There were 5 deliveries at 28 to 32 gestational weeks, accounting for 13.89%, and 8 deliveries at 32 to 34 gestational weeks, accounting for 22.22%, and 23 deliveries at 34 to 37 gestational weeks, accounting for 63.89% of the women. The twin babies included 42 boys and 23 girls, and the male/female ratio was 1.826. The mean birth weight of twin babies was 2012.6 g (SD=439.2, range =1040~2880 g). Forty-six (70.77%) premature twin infant's birth weight was mainly between 1500 and 2500 g.

*Complications*

*In vitro fertilization and embryo transfer (IVF-ET) newborn neonatal complications:* There was a statistically significant difference in gestational age between the IVF-ET group and the natural conception group ($P < 0.05$). The natural conception preemie was mainly late premature infants (31/63.27%), followed by moderate premature infants (14/28.57%), and very preterm infants (4/8.16%) was the least. The IVF-ET preemie was mainly late premature infants (8/50%), followed by very premature infants (6/37.5%), and moderate premature infants (2/12.5%) was the least. No significant difference was observed in gender and birth weight between the IVF-ET group and the natural conception group.

The proportion of intrauterine infection, anemia, and electrolyte imbalance in IVF-ET newborn infants was higher than that in natural conception infants, and the differences were statistically significant in $\chi^2$ test, which were available in **Table 1**.

No significant difference was observed in the other 10 complications between the IVF-ET group and the natural conception group.

*Spectrum of preterm twin infants' neonatal complications:* The most common diseases of preterm twin infants are neonatal jaundice and patent foramen ovale, the incidence rate is 78.46% (51), followed by 53.85% of NRDS (35).

*Comparison of the incidence rates of various diseases in premature twin infants:* The incidence of common diseases varying among premature twins of different gestational ages was slightly different. In addition to the above three, the top three most common diseases also included neonatal hypoglycemia and electrolyte imbalance.

There were statistically significant differences in the incidence of anemia among premature twins of different gestational ages. Very premature twins had the highest incidence, followed by moderate premature twins, and late premature twins had the lowest.

NRDS of very and moderate premature twins were significantly higher than late premature twins. The electrolyte imbalance of very premature twins was significantly higher than in mod-

**Table 1.** Effects of different pregnancy patterns on complications of preterm twin infants n (%)

| Complications | IVF-ET (n=16) | Natural conception (n=49) | F | P* |
|---|---|---|---|---|
| Intrauterine infection | 8 (50) | 5 (10.20) | 11.939 | 0.001 |
| Anemia | 8 (50) | 7 (14.29) | 8.667 | 0.003 |
| Electrolyte Imbalance | 8 (50) | 11 (22.45) | 4.426 | 0.035 |

Note. P < 0.05. *chi-squared test.

**Table 2.** Spectrum of clinical disease at different gestational ages in preterm twin infants n (%)

| Gestational age of preemie | 28 to 32 wks (n=10) | 32 to 34 wks (n=16) | 34 to 37 wks (n=39) | $\chi^2$ | P* |
|---|---|---|---|---|---|
| Intrauterine infection | 7 (70)[a] | 4 (25)[a,b] | 2 (5.13)[b] | 18.480 | 0.000 |
| Anemia | 8 (80)[a] | 5 (31.25)[b] | 2 (5.13)[c] | 23.555 | 0.000 |
| Neonatal pneumonia | 2 (20) | 1 (6.25) | 7 (17.95) | 1.403 | 0.615 |
| Neonatal coagulation disorders | 6 (60) | 5 (31.25) | 12 (30.77) | 3.007 | 0.250 |
| Patent foramen ovale | 9 (90) | 13 (81.25) | 29 (74.36) | 0.998 | 0.699 |
| Neonatal hypoglycemia | 2 (20) | 7 (43.75) | 14 (35.9) | 1.462 | 0.474 |
| Patent ductus arteriosus | 6 (60) | 6 (37.5) | 9 (23.08) | 5.076 | 0.078 |
| NRDS | 9 (90)[a] | 14 (87.5)[a] | 12 (30.77)[b] | 21.287 | 0.000 |
| Electrolyte imbalance | 9 (90)[a] | 6 (37.5)[b] | 4 (10.26)[b] | 23.795 | 0.000 |
| Ventricular septal defect | 2 (20) | 2 (12.5) | 1 (2.56) | 4.388 | 0.063 |
| Intraventricular hemorrhage | 2 (20) | 1 (6.25) | 5 (12.82) | 1.211 | 0.580 |

Note. P < 0.05. Each superscript letter (a, b, c) indicates a subset of a group category whose column proportions do not differ significantly from each other at the .05 level; *Partitioning Chi-Square.

erate and late premature twins. The intrauterine infection of very premature twins was significantly higher than late premature twins. Incidence of other common diseases were available in **Table 2**.

Due to the small sample size, it was not appropriate to conduct multiple sample rate comparisons for acid-base imbalances. We divided the sample into two groups: extremely premature infants (28 to 32 wks) and premature infants (32 to 37 wks), and the difference in the incidence of acid-base imbalance was statistically significant (P=0.004). The incidence (4/10) in extremely premature infants was higher than that (2/55) of premature infants.

Owing to the small sample size, it was not suitable to conduct multiple sample rate comparisons for neonatal jaundice either. Although the incidence (10/10) of jaundice in extremely premature infants was higher than that (41/55) of premature infants, the difference was not statistically significant (P=0.1779).

## Discussion

With the increase of twin pregnancies, it is crucial to have a correct understanding of twin pregnancies, improve the level of diagnosis and treatment, and ensure the safety of both mother and child. The fundamental cause of various diseases that occur in premature infants is still preterm birth. Insufficient gestational age and being underweight leads to incomplete development of various organs and systems in the fetus, as well as poor health or weakened immune capacity, making them more prone to complications in the digestive system and other aspects.

Basically, consistent with the survey of premature infants conducted by Kanghua Hospital in the same region [5], the gestational age of premature twin infants is mainly concentrated between 34-37 weeks, which is also consistent with the research of Ballabh [13]. The most common disease of preterm twin infants is neonatal jaundice, NRDS and patent foramen ovale. The findings of this study are basically consistent with other findings [5, 6]. There was a difference in disease spectrum when grouped according to gestational age.

*Neonatal jaundice*

The incidence rate of neonatal jaundice in premature infants is 78.46% (51/65), conform to

another study [14], and this was higher than in another research report [15]. Neonatal jaundice is most common [10, 16] in premature twins, consistent with Rui Hua's research [6]. Neonatal jaundice is caused by abnormal bilirubin metabolism, due to the immature development of the liver and various systems in premature infants. Breastfeeding plays a crucial role in improving the clinical efficacy of premature infants [17]. Paying attention to keeping the child warm and breastfeeding them as soon as possible to avoid worsening jaundice due to factors such as hypothermia, hypoglycemia, and acidosis, is important.

*NRDS*

Human lung development typically completes tubulation within 26 weeks of pregnancy, followed by gradual improvement of alveolar development in 4-6 weeks. Twin pregnancies can significantly restrict fetal growth and development, leading to incomplete lung development and lower activity of pulmonary surfactants, thereby increasing the incidence of NRDS. The incidence of NRDS in this study is 53.85% (35/65), which ix higher than that in Li Si-Hui's study [11]. The incidence of NRDS decreases with increasing gestational age, and the incidence of neonatal pneumonia in very and moderate premature infants is higher than that in late preterm infants ($P < 0.05$). Due to severe insufficient secretion of pulmonary surfactant, very and moderate premature infants experience more severe alveolar collapse and progressive atelectasis compared to late-stage premature infants.

*Fluid, electrolyte and acid-base disorders*

Due to the relatively high volume of body fluids, low oral milk intake, and immature development of various systems, premature infants have weak regulatory ability for water and electrolyte balance, making them prone to disturbances in water and electrolyte balance after birth. The younger the gestational age, the more likely it is for electrolyte disorders to occur. The incidence of electrolyte disorders is 29.23% (19/65), which consistent with that in Beibei's study [7] (22.69%).

Due to physiological and anatomical characteristics, there is more or less hypoxia during the delivery of newborns. Newborns are prone to acid-base imbalance, which is more common in critically ill children. Maintaining a stable internal environment is crucial for premature infants to successfully overcome the critical period and meet the needs of growth and development. In addition to fluid imbalances, the infants' electrolytes, particularly sodium, potassium, calcium, phosphorus, and magnesium, should be closely monitored. Treatment should focus on the main symptoms of acid-base disorders, such as improving ventilation, supplementing blood volume, improving circulation, correcting acid, combating infections, increasing urine output, maintaining sufficient calorie intake, to maintain pH values within the normal range and avoid or reduce iatrogenic pathogenic factors.

*Anemia*

The most common cause of anemia is caused by homologous immunity of red blood cells [18]. The multiple physiological functions of premature infants have not yet fully developed. Due to insufficient erythropoietin and iron reserves, premature infants are more prone to anemia than full-term infants. Due to premature birth, fetal extramedullary hematopoiesis was prematurely stopped, and due to the weak hematopoietic function of the bone marrow, the baby cannot adapt to the rapid growth and development of the body after birth. This knowledge varies from one country to another. People living in low- and middle-income countries have more incidence, with 100% of Ecuadorian twins suffering from anemia [14].

With the decrease of gestational age, the incidence rate of anemia gradually increases. The incidence of anemia in the very premature infant group was significantly higher than that in the other two gestational age groups ($P < 0.05$).

Hemoglobin should therefore be tracked in order to increase the sensitivity of the early identification of anemia in clinical practice. Once diagnosed with anemia and appropriate iron and blood transfusion treatment is given, a stable internal environment can be preserved, promoting the normal growth and development of premature infants.

*Intrauterine infection*

The incidence rate in Minggao's retrospective study is about 48%, twice of this study (20%). It

may be related to the time (2017-2021) and location of the research (hospital in an economically underdeveloped area) [16]. Intrauterine infection is a major cause of fetal and neonatal infection. Lung infectious diseases are the most common form of infection. There are numerous factors that can induce intrauterine infection. Newborns with immature lung development have an inability of alveolar type II epithelial cells to secrete alveolar surface-active substances. The lack of carbonic anhydrase in red blood cells leads to insufficient carbon dioxide production, which in turn causes premature infants to develop NRDS, making it difficult for premature infants to inhale or expel secretions in the respiratory tract in a timely manner, ultimately leading to pulmonary infection.

*IVF-ET newborn*

The proportion of preterm twins in IVF-ET is consistent with Lianjuan's research [12, 19]. There is a significant difference in the time frame of 32 to 34 gestational age of preterm twin that exists between IVF-ET and the natural conception group. In other words, compared to the natural conception group, IVF-ET twins at 32 to 34 gestational weeks are more prone to premature birth. The birth rate of IVF-ET and cesarean section was higher than in previous statistical data [12], which may be related to the small sample size. The incidence rate of anemia in the IVF-ET group (50%) was basically consistent with Yu Jianhua's research (41%) [20]. It was found that intrauterine infection, anemia, and electrolyte imbalance were more likely to occur in IVF-ET premature twin infants. IVF is a related factor affecting anemia in premature infants [21]. IVF-ET premature twin infants are prone to water electrolyte imbalance, acidosis, and other conditions due to unstable metabolism in the body. Differences in conception methods and the potential role of low parental fertility may lead to differences in early respiratory development [22], which can lead to pulmonary (intrauterine) infections. In clinical diagnosis and treatment, attention should be given to monitoring relevant indicators to prevent the occurrence of adverse clinical outcomes.

*Limitations*

The sample size is small and may not represent the entire target population. The true effect cannot be detected, or the detected effect may not have actual significance, which reduces the reliability and persuasiveness of the study. This study is from a single medical institution with cross-sectional study, limited to the Dongguan Maternal and Child Health Care Hospital. It is necessary to further expand the sample size to improve and supplement future research conclusions.

## Conclusions

This study helped the medical team have a better understanding of the disease spectrum of premature twin infants. First of all, neonatology and obstetrics and gynecology medical staff should work together in order to prevent premature birth. Secondly, premature twins have different disease spectra at different gestational ages, and different disease prevention and treatment measures need to be developed for premature twins of different gestational ages to effectively reduce the occurrence of various diseases and improve prognosis. In future research, in order to better observe the development of the disease and formulate treatment plans, targeted evaluation of the differences in complications between twin premature birth and single premature birth will be considered.

## Disclosure of conflict of interest

None.

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