Related factors of preterm birth in monochorionic twins after single intrauterine death: a case-control study

Jingyi Liu[1], Cai xia Liu[2], Na Shin[3], Na Li[1], Sishi Liu[1], and Quan Na[1]

[1]Shengjing Hospital of China Medical University
[2]ShengJing Hospital affiliated to China Medical University
[3]Johns Hopkins University School of Medicine

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Abstract

Objectives: To analyze preterm birth related factors for single intrauterine death in monochorionic twins. Design: Retrospective case-control study. Setting: A single medical centre in Shenyang, China, 2012-2018. Sample: preterm delivery with intrauterine fetal death in monochorionic twins (cases, n = 35) were compared with a group of full term birth (controls, n = 4). Methods: Related factors were compared in the two groups and logistic regression was used to adjust for confounding. Main outcome measures: Odds ratio (OR) and 95% confidence interval (CI) for the related factors of preterm birth Results: This study included 39 monochorionic twins following single intrauterine death. The significant risk factor associated with preterm birth is the gestational age of single intrauterine death (OR=1.317, 95% CI: 1.027-1.689). The timing of prolong gestational age shorten with the increasing gestational age of single intrauterine death. We found that in all monochorionic twins cases and spontaneous preterm birth cases, increases in the gestational age at single intrauterine death was associated with shorter prolongation of gestational age in the surviving twin. Conclusions: The gestational age of single intrauterine death was a risk factor of preterm delivery. Increases in the gestational age at single intrauterine death led to a shorter prolongation in gestation of the surviving twin. Funding: This study was funded by Prenatal diagnosis, intrauterine intervention and prognosis evaluation of complicated twins (No. 2018YFC1002902) Tweetable abstract: The gestational age of intrauterine fetal death was a risk factor of preterm delivery. Keywords Gestational age; Prolongation of gestational age; Twin pregnancy;

Introduction

Single intrauterine death (sIUD) in twin pregnancy has become a relatively frequent complication of twin pregnancy. The overall incidence of sIUD is estimated to be up to 2.6-6.2% of all twin pregnancies. [1-5] The surviving twin has many complications, such as brain damage, preterm birth, and survivor intrauterine death. [1, 6, 7]Out of these complications, preterm birth (PTB) is a problem that can not be ignored due to its lasting adverse impact on the surviving twin. For instance, brain damage and multiple organ immaturity caused by PTB aggravate the bad prognosis in the surviving twin. [6] Because of peculiar chorionic problem in twins and vascular communication in monochorionic (MC) twins, some previous systematic reviews reported that the rate of PTB was higher in MC twins than in dichorionic (DC) twin pregnancy.[2, 7, 8] However, studies about PTB related to sIUD in MC twins are limited. Therefore, the purpose of this study was to analyze PTB-related factors for sIUD in MC twins.

Methods

This was a retrospective cohort study of all MC twins undergoing sIUD at 14-40 weeks from 2012 through 2018 at Shengjing Hospital of China Medical University. Inclusion criteria included delivery between January 2012 and April 2018 with complete information, including pregnancy outcomes. The gestational age of birth was assigned based on the first day of a woman's last menstrual period. If this dating was not consistent with

dating based on the earliest ultrasound (±7 days in the first trimester or ±10 days in the second trimester), the gestational age was reassigned. [9] The gestational age of sIUD was estimated according to the size of the dead fetus measured via ultrasound and previous ultrasound. Chorionicity was determined by ultrasound evaluation according to the presence of the lambda or T signs and confirmed after birth.[10] If the patient did not undergo chorionic identification ultrasound during pregnancy, the placenta was examined after delivery to determine the chorionicity.[11] sIUD was defined as spontaneous death and spontaneous death after fetoscopic laser occlusion after 14 weeks of gestation. Exclusion criteria included sIUD by radio frequency ablation and miscarriage occurring before 26 weeks and double fetal loss.

Information on each case was recorded to include the following: age (year), the gestational age of sIUD, parity, the gestational age at birth, history of fetoscopic laser occlusion, pregnancy method(including natural pregnancy and assisted reproductive conception), fetal complication, maternal complication, premature rupture of membranes, abnormality in amniotic fluid, and spontaneous labor or not.

According to the gestational age of birth, the cases were divided into PTB group (¡37 weeks) and full term birth group (¿37 weeks). We also divided these cases into four groups according to the gestational age of sIUD (14-19weeks, 20-24weeks, 25-30weeks, 31-36weeks) and compared the four groups using the chi-square test for trends.

Statistical analyses were performed with SPSS software (Version 17.0, SPSS). Chi-square analysis was performed to test the significance of the findings. Logistic regression analysis was conducted to determine risk factors for preterm delivery. $P < 0.05$ was considered statistically significant.

Results

This study included 39 MC twins following sIUD. Among these cases, 89.7term birth. The incidence of spontaneous PTB was 66%. Furthermore, 87.2had spontaneous death after fetoscopic laser occlusion. The maternal ages were 20-41 years with the mean maternal age being 30.6 years. The mean gestational age of sIUD was 27.4 (17-35) weeks. The mean gestational age of birth was 32.8 (27-40) weeks. 23.1had maternal complications (4 cases of gestational hypertension, 5 cases of gestational diabetes mellitus). 38.4complications (10 cases of twin-twin transfusion syndrome, 5 cases of selective intrauterine growth restriction). 46.34conceived naturally. 5.12reproductive conception. 23.1fetal membranes. 17.9fluid (4 cases of hydramnios, 3 cases of hypamnion). 29 cases were spontaneous labor (including 26 preterm birth cases and 3 full term birth cases) and 10 cases underwent cesareean section due to obstetrical factors.

We compared the differences between the preterm birth group and the full term birth group (Table 1). We found that the gestational age of sIUD was a risk factor for preterm birth (p¡0.05). We conducted multifactor analysis for the above factors (Table 2). We also found that the gestational age of sIUD was a risk factor of preterm delivery (p¡0.05) with OR¿1, suggesting that higher gestational age of sIUD led to a higher risk of preterm birth.

To analyze the differences between the gestational age of sIUD and the gestational age of birth, we divided the cases into four groups according to the gestational age of sIUD (14-19 weeks, 20-24 weeks, 25-30 weeks, 31-36 weeks). We found that the 25-30 weeks at sIUD group had the youngest gestational age at birth (31.7 weeks) and 14-19 weeks at sIUD group had the oldest gestational age at birth (38.33 weeks) (Figure 1). Because the numbers representing the weeks in the third trimester are bigger than the numbers representing the weeks in first and second trimesters, we noticed that the numerical gestational age at birth will increase accordingly. Therefore, we used the timing of the surviving twin's prolonged gestational age after sIUD, rather than the surviving twin's absolute gestational age at birth, to analyze the trend in the four groups (Figure 2). We found that increases in the gestational age at sIUD was associated with shorter prolongation of gestational age in the surviving twin.

In the above cases, we found that some cases had iatrogenic PTB due to obstetric factors. Therefore, we wanted to exclude human intervention and re-analyze the relationship between the gestational age of sIUD and the gestational age of birth in cases of spontaneous PTB. In this study, there were 26 spontaneous

PTB cases. After re-analysis, we found that the gestational age of sIUD was still the main risk factor of preterm birth (p¡0.05). In addition, we found that OR¡1 in this association, meaning that older gestational age at sIUD was associated with younger gestational age at delivery (table 3). In order to further analyze the relationship between sIUD and spontaneous PTB,we divided spontaneous PTB cases into four groups according to the gestational age at sIUD (14-19 weeks, 20-24 weeks, 25-30 weeks, 31-36 weeks). We found 25-30 weeks at sIUD group had the youngest gestational age at birth for the surviving twin (31.29 weeks) and 14-19 weeks at sIUD group had the oldest gestational age at birth for the surviving twin (36 weeks) (Figure 3). Because the numbers representing the weeks in the third trimester are bigger than the numbers representing the weeks in first and second trimesters, we noticed that the numerical gestational week at birth will increase accordingly. Therefore, we calculated the amount of gestational weeks prolonged after sIUD to reach delivery, rather than the absolute gestational age at birth, to analyze the trend in the four groups (Figure 4). We found that in spontaneous PTB cases, increases in the gestational age at sIUD was associated with shorter prolongation of gestational age in the surviving twin. This trend was consistent in all MC twins cases and spontaneous PTB cases.

Discussion

For the first time, in our study, we found that the gestational age at sIUD is associated with PTB after sIUD in MC twins. We found that the 25-30 weeks at sIUD group had the youngest gestational age at birth and that the 14-19 weeks at sIUD group had the oldest gestational age at birth. Also, we found that the prolongation of gestational age in the surviving twin was shortened as the gestational age at sIUD increased.

Gestational age, whether for singletons or twins, is a key factor in determining the prognosis of surviving fetuses, since the risk of adverse consequences declines with increasing gestational age.[12] Therefore, we focused on the gestational age at sIUD and at birth to evaluate the prognosis of MC twins after sIUD. After analysis, we found that older gestational age at sIUD is associated with PTB in MC twins. When we further divided these cases into four groups according to their gestational age at sIUD, we found that the 25-30 weeks at sIUD group had the youngest gestational age at birth and the 14-19 weeks at sIUD group had the oldest gestational age at birth in all the cases. including spontaneous preterm birth cases. This indicates that MC twins undergoing sIUD at 14-19 weeks have the best prognosis out of these groups and that MC twins that undergo sIUD at 25-30 weeks have the worst prognosis.

In figure 1 and figure 3, we found that the first three groups (14-19 weeks, 20-24 weeks, and 25-30 weeks) showed a decreasing trend in their association with the prolongation of gestational age of the surviving twin. However, the fourth group (31-36 weeks) was not in line with this expected negative trend. This discrepancy was due to the fact that even if the fourth group cases immediately delivered after sIUD, the numerical gestational age at birth was larger than those of other groups. Therefore, we introduced the concept of the prolongation in gestational age after sIUD as the evaluation factor to avoid the impact of the numerically large gestational weeks in the third trimester. Through this new factor, we found that increases in the gestational age at sIUD led to a shorter prolongation in gestation of the surviving twin. We know that in late pregnancy, the area of placenta is much bigger than during early pregnancy. Along with this fact, past studies have reported that placental ischemia can release various factors leading to uterine contraction. [13] This suggests that the impact on the uterus caused by a decrease in placental circulation is much bigger in later gestational ages. Therefore, the shorter prolongation in gestation of the surviving twin may be due to the effective circulating blood volume of the placenta decreasing sharply when sIUD occurs, leading to instantaneous placental ischemia-induced uterine contractions. Because the area of placenta in early pregnancy is much smaller than that in late pregnancy, the stimulation of uterine contractions caused by the decrease in placental circulation is accordingly smaller. This may explain why increases in the gestational age at sIUD leads to a shorter prolongation of gestation in the surviving twin.

A previous systematic review assessing the co-twin outcome after sIUD reported that the incidence of PTB after sIUD was 68% in MC twin pregnancies.[7] Another study reported the incidence of PTB after sIUD as being up to 66% in MC twin pregnancies.[14] However, in our study, the incidence of PTB was much higher (89.7%) than these previous studies, while the incidence of spontaneous PTB was similar to other studies.

This discrepancy may be due the higher rate of iatrogenic premature delivery at our hospital, which is a referral center responsible for difficult and critical cases in the three northeastern provinces. In addition, most of the cases of iatrogenic PTB were accompanied by maternal complications and fetal complications, which led to complex and rapid changes making iatrogenic preterm delivery inevitable.

This study is not without its limitations. Due to the retrospective design and lack of consistent documentation, potential residual confounders, such as obesity, smoking, and living environment factors, could not be properly evaluated. Autopsy and placental evaluations may also have been limited, particularly if the prolongation of gestational age was long after sIUD. On the other hand, our study offers a novel insight into the association between the gestational age at sIUD and the subsequent prolongation of gestation in the surviving twin. This insight can help clinicians to better stratify the prognoses in women experiencing sIUD in MC twin pregnancy to better support the surviving twin.

Conclusion

The gestational age of sIUD was a risk factor of preterm delivery. Increases in the gestational age at sIUD led to a shorter prolongation in gestation of the surviving twin.

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Not applicable

Disclosure of Interests

The authors declare no conflict of interest.

Contribution to Authorship

First author Jingyi Liu: Conceptualization, Methodology, Data curation, Writing-Original draft preparation.

Second author Caixia Liu: Conceptualization, Supervision.

Third author Na Shin: Writing- Reviewing and Editing.

Fourth author Na Li: Data Curation.

Fifth author Sishi Liu: Software.

Correspondence author Quan Na: Conceptualization, Writing- Reviewing and Editing

All authors accept responsibility for this paper as published.

Details of Ethics Approval

This study is a retrospective case-control study thus no ethical approval and patient consent are required.

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The authors report no conflict of interest

Contribution to Authorship

Jingyi Liu collected and analyzed the data, and was a major contributor in writing the manuscript. Na Li, Na Shin, Sishi Liu, and Caixia Liu participated in writing the manuscript and collecting data. Quan Na participated in the design of the article. All authors read and approved the final manuscript.

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