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Influence of chorionicity and gestational age at single fetal loss on risk of preterm birth in twin pregnancy: analysis of STORK multiple pregnancy cohort

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KEYWORDS: fetal loss; preterm birth; twin pregnancy

ABSTRACT

Objective *Single intrauterine death (sIUD) in twin pregnancy is associated with a significant risk of cotwin demise and preterm birth (PTB), especially in monochorionic (MC) twins. However, it is yet to be established whether the gestational age at loss may influence the pregnancy outcome. The aim of this study was to explore the risk of PTB according to the gestational age at diagnosis of sIUD.*

Methods *This was a cohort study of all twin pregnancies booked for antenatal care in a large regional network of nine hospitals over a 10-year period. Ultrasound data were matched to hospital delivery records and to a mandatory national register for stillbirth and neonatal loss provided by the Centre for Maternal and Child Enquires. Cases with double fetal loss at the time of the scan and cases of sIUD occurring at or after 34 weeks of gestation were not included in the analysis. The relative risk (RR) of PTB at < 34, < 32 and < 28 weeks of gestation in twin pregnancies complicated by sIUD was assessed and compared with that in twin pregnancies without fetal loss. The risk of PTB at < 34 weeks was stratified according to the gestational age at diagnosis of sIUD. The risk of PTB in twin pregnancy after sIUD according to the gestational age at death was also explored.*

Results *The analysis included 3013 twin gestations (2469 dichorionic (DC) and 544 MC). Median gestational age at birth was lower in the pregnancies complicated by sIUD compared with those that were not (32.0 weeks: interquartile range (IQR), 29.0–34.3 weeks* vs *36.7 weeks: IQR, 35.0–37.6;* $P < 0.001$*) and this difference persisted when stratifying the data according to chorionicity (*$P < 0.0001$ *for both MC and DC pregnancies). The risk of PTB at < 34 weeks (RR, 4.3 (95% CI, 3.5–5.2)), < 32 weeks (RR, 6.1 (95% CI, 4.6–8.1)) and < 28 weeks (RR, 12.4 (95% CI, 6.9–22.2)) of gestation was higher in pregnancies complicated by sIUD compared with those which did not experience fetal loss. This association was observed both in MC and DC twin gestations. When compared with DC pregnancies, MC twins affected by sIUD were not at significantly increased risk of PTB before either 34, 32 or 28 weeks of gestation. The risk of PTB at < 34 weeks of gestation was higher when the sIUD occurred at a later gestational age (chi-square test for trend,* $P < 0.001$*).*

Conclusions *Twin pregnancies complicated by sIUD, regardless of the chorionicity, have a significantly higher risk of PTB at < 34, < 32 and < 28 weeks of gestation. The risk of PTB at < 34 weeks of gestation was higher when the sIUD occurred in the second half of the pregnancy. Large prospective multicenter studies with shared protocols for prenatal management are needed to ascertain the actual risk of spontaneous PTB in twin pregnancies affected by sIUD.*

INTRODUCTION

Twin pregnancies are at increased risk of perinatal mortality compared with singleton pregnancies, especially as a result of prematurity, fetal anomaly and growth restriction[1]. The overall risk of fetal death is about seven- to 10-fold higher in monochorionic (MC) than in dichorionic (DC) twin pregnancy. This increased risk is mainly attributable to the complications of placental and vascular sharing in a MC placenta, resulting in either fetal growth restriction or twin-to-twin transfusion syndrome (TTTS)[2–6]. The difference in mortality between MC and DC twins is largely because of the difference in fetal

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demise in the first half of the pregnancy, when TTTS is most likely to occur, while the survival trend after 26 weeks of gestation is relatively similar in MC and DC twins[5,6].

Single intrauterine death (sIUD) in twin pregnancy is associated with adverse pregnancy outcome, such as demise of the cotwin, preterm birth (PTB) and neurological morbidity[7,8]. Although these complications are more frequent in MC twins, in view of the peculiar vascular arrangement of placental anastomoses, they can potentially occur even in DC twins, although the reported incidence is lower in these cases[7,8].

A previous systematic review assessing the outcome of the cotwin following sIUD reported that the rate of PTB was 68% in MC and 54% in DC twin pregnancies[8]. However, the small number of cases included per study, lack of stratification according to gestational age at birth or at sIUD, and the wide heterogeneity in perinatal management in the included studies hinder the ability to extrapolate accurate results in order to enable individualized management or counseling in these complicated pregnancies.

The aim of this study was to ascertain the risk of PTB, stratified according to gestational age at diagnosis of sIUD in a large cohort of twin pregnancies.

METHODS

This was a retrospective cohort study of all twin pregnancies booked for antenatal care in nine hospitals in the Southwest Thames Obstetric Research Collaborative (STORK), over a 10-year period from 2000. All women up to 11 weeks of gestation registering for routine antenatal care were considered suitable for the analysis. Scan data and outcome details were obtained from each hospital by electronic search of their ultrasound computer databases and computerized maternity records, respectively. The two databases were cross-checked to ensure full data capture of all twin pregnancies during the study period. All data included in the analysis were collected prospectively but analyzed retrospectively. Ethical approval for this retrospective study was obtained from the local Research Ethics Committee.

Fetal loss was defined as spontaneous death occurring after 14 weeks of gestation. Pregnancies affected by TTTS, termination of pregnancy and fetal or chromosomal abnormality, and pregnancies of unknown chorionicity, MC monoamniotic and high-order multiple gestations were excluded from the analysis. Pregnancies complicated by miscarriage occurring before 24 weeks, those with double fetal loss at the time of the initial diagnosis and sIUD beyond 34 weeks of gestation were also excluded.

Gestational age was determined by the crown–rump length of the larger twin at the 11–14-week scan or by head circumference if assessed after 14 weeks' gestation[9,10]. Chorionicity was determined by ultrasound evaluation according to the presence of the lambda or T signs and confirmed after birth[11]. A routine fetal structural survey was carried out at 18–22 weeks, and all MC twins had two additional scans at around 16–17 and 18–19 weeks specifically in order to identify early features of TTTS. If TTTS was suspected, women were referred to the local tertiary center for assessment for fetoscopic laser ablation of the placental interconnecting vessels. Ultrasound examination was performed every 4 weeks in DC twins and every 2 weeks in MC twins until 24 weeks, and every 3–4 weeks thereafter.

Ultrasound and outcome data were matched to a mandatory national register for stillbirth and neonatal loss provided by the former Centre for Maternal and Child Enquires (CMACE). In accordance with the CMACE regulations, patient identifiers, such as name, hospital number and date of birth, were not made available to the researchers. Primary outcome was the incidence of PTB, whether secondary to spontaneous or iatrogenic delivery. Secondary outcome was the occurrence of cotwin demise after sIUD.

The relative risk (RR) of PTB at < 34, < 32 and < 28 weeks of gestation in the pregnancies complicated by sIUD was compared with the RR in uncomplicated pregnancies. A subgroup analysis according to chorionicity was also performed. Finally, the risk of PTB at < 34 weeks of gestation after sIUD was explored according to the gestational age at death using three time windows (14–19 weeks, 20–25 weeks and 26–32 weeks) and compared using the chi-square test for trends.

All calculations were performed using StatsDirect version 3[12] and GraphPad Prism version 7 for Windows[13]. Statistical significance was set at $P < 0.05$. All values of P were two-tailed.

RESULTS

The study cohort included 3117 twin pregnancies (605 MC and 2512 DC). The general characteristics of the STORK population have been described previously[4,6]. The cumulative rate of fetal loss was 5.7% (95% CI, 4.9–6.5%). The rate of fetal loss was higher in MC compared with DC twin pregnancies (103/605 *vs* 74/2512; odds ratio (OR), 6.8 (95% CI, 4.9–9.3); $P < 0.0001$). This discrepancy in mortality was a result of the difference in the survival trend in early gestation, while there was no statistically significant difference from 24 to 34 weeks' gestation ($P = 0.08$). After exclusion of miscarriages, pregnancies affected by TTTS, sIUD at or beyond 34 weeks of gestation and double fetal losses, there were 3013 twin gestations (2469 DC and 544 MC) available for analysis, consisting of 65 (44 DC and 21 MC) pregnancies with sIUD and 2948 (2425 DC and 523 MC) without fetal loss.

In total, there were 68 intrauterine deaths in the 65 pregnancies with sIUD, including three cases in which a single loss was followed by cotwin death during pregnancy, all occurring in DC pregnancies. These three pregnancies were not included in the computation of PTB.

Table 1 Incidence of preterm birth (PTB) at < 34, < 32 and < 28 weeks of gestation in 21 monochorionic (MC) and 41 dichorionic (DC) twin pregnancies complicated by single intrauterine death (sIUD), compared with twin pregnancies without fetal loss (controls)

PTB	*sIUD (n = 62)** *(% (n/N) (95% CI))*	*Controls (n = 2948)* *(% (n/N) (95% CI))*	*RR (95% CI)*	P
All twin pregnancies				
< 34 weeks	66.12 (41/62) (53.0–77.7)	15.50 (457/2948) (14.2–16.9)	4.27 (3.5–5.2)	< 0.001
< 32 weeks	48.39 (30/62) (35.5–61.4)	7.90 (233/2948) (7.0–8.9)	6.12 (4.6–8.1)	< 0.001
< 28 weeks	19.35 (12/62) (10.4–31.4)	1.56 (46/2948) (1.1–2.1)	12.40 (6.9–22.2)	< 0.001
MC twins				
< 34 weeks	61.9 (13/21) (38.4–81.9)	20.65 (108/523) (17.3–24.4)	3.00 (2.1–4.4)	< 0.001
< 32 weeks	47.62 (10/21) (25.7–70.2)	9.75 (51/523) (7.3–12.6)	4.88 (2.9–8.2)	0.001
< 28 weeks	19.05 (4/21) (5.4–41.9)	2.49 (13/523) (1.3–4.2)	7.66 (2.7–21.5)	0.001
DC twins				
< 34 weeks	68.29 (28/41) (51.9–81.9)	14.39 (349/2425) (13.0–15.9)	4.75 (3.8–6.0)	< 0.001
< 32 weeks	48.78 (20/41) (32.9–64.9)	7.50 (182/2425) (6.5–8.6)	6.50 (4.6–9.2)	< 0.001
< 28 weeks	19.51 (8/41) (8.8–34.9)	1.36 (33/2425) (0.9–1.9)	14.34 (7.1–29.1)	< 0.001

*Three cases affected by loss of cotwin (all DC pregnancies) were excluded from analysis. RR, relative risk.

Table 2 Incidence of preterm birth (PTB) at < 34, < 32 and < 28 weeks of gestation in 21 monochorionic (MC) and 41 dichorionic (DC) twin pregnancies complicated by single intrauterine death (sIUD), according to chorionicity

PTB	*MC (n = 21)* *(% (n/N) (95% CI))*	*DC (n = 41)* *(% (n/N) (95% CI))*	*RR (95% CI)*	P
< 34 weeks	61.9 (13/21) (38.4–81.9)	68.29 (28/41) (51.9–81.9)	0.91 (0.6–1.3)	0.626
< 32 weeks	47.62 (10/21) (25.7–70.2)	48.78 (20/41) (32.9–64.9)	0.98 (0.6–1.7)	0.931
< 28 weeks	19.05 (4/21) (5.4–41.9)	19.51 (8/41) (8.8–34.9)	0.98 (0.3–2.9)	0.965

RR, relative risk.

The incidence of IUD was significantly higher in MC twins (3.9%, 21/544) compared with DC twin pregnancies (1.9%, 47/2469) with an OR of 2.0 (95% CI, 1.2–3.4; $P < 0.006$).

The median gestational age at birth was significantly lower in pregnancies complicated by sIUD compared with those which were uncomplicated (32.0 weeks: interquartile range (IQR), 29.0–34.3 *vs* 36.7 weeks: IQR, 35.0–37.6; $P < 0.001$) and this difference persisted when stratifying the analysis according to chorionicity ($P < 0.0001$ for both MC and DC pregnancies).

PTB at < 34, < 32 and < 28 weeks of gestation occurred in 66.1%, 48.4% and 19.4%, respectively, of twin pregnancies with sIUD (Table 1). The risk of PTB at < 34 weeks (RR, 4.3 (95% CI, 3.5–5.2)), < 32 weeks (RR, 6.1 (95% CI 4.6–8.1)) and < 28 weeks (RR, 12.40 (95% CI, 6.9–22.2)) was significantly higher in pregnancies complicated by a sIUD compared with those which did not experience fetal loss. When stratifying the analysis according to chorionicity, the incidence of PTB at < 34, < 32 and < 28 weeks of gestation was, respectively, 61.9%, 47.6% and 19.1% in MC pregnancies and 68.3%, 48.8% and 19.5% in DC gestations (Table 1). In MC pregnancies, the risk of PTB at < 34, < 32 and < 28 weeks of gestation was significantly higher in the pregnancies complicated by sIUD (respectively: RR, 3.0 (95% CI, 2.1–4.4); RR, 4.9 (95% CI, 2.9–8.2); and RR, 7.7 (95% CI, 2.7–21.5)) compared with those which were uncomplicated. The equivalent risk in DC pregnancies was 4.8 (95% CI, 3.8–6.0), 6.5 (95% CI, 4.6–9.2) and 14.3 (95% CI, 7.1–29.1) for PTB at < 34, < 32 and < 28 weeks of gestation, respectively (Table 1). When compared with DC pregnancies, MC twins affected by sIUD were not at significantly increased risk of PTB before either 34, 32 or 28 weeks of gestation (Table 2).

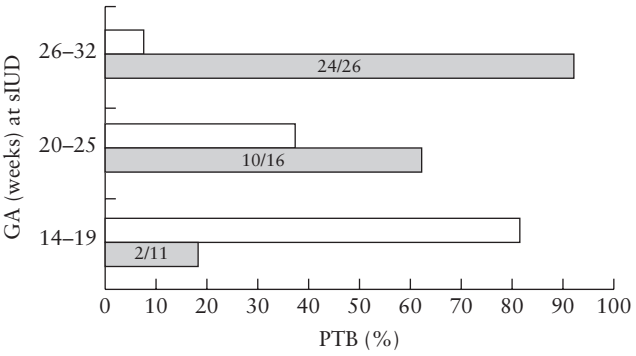

Figure 1 Prevalence of preterm birth (PTB) before 34 weeks of gestation in twin pregnancies complicated by a single intrauterine death (sIUD) at 14–19, 20–25 and 26–32 weeks of gestation (GA). □, no PTB; ■, PTB.

The risk of PTB at < 34 weeks of gestation was significantly higher when sIUD occurred at a later gestational age (chi-square test for trend, $P < 0.001$). When stratifying the analysis according to chorionicity, this trend persisted ($P = 0.03$ for MC twins and $P = 0.01$ for DC twins). The risk of PTB at < 34 weeks was significantly higher if the sIUD occurred at 26–32 weeks compared with occurrence at 14–19 weeks (24/26 *vs* 2/11; RR, 5.1 (95% CI, 1.9–18.0)) or at 20–25 weeks of gestation (24/26 *vs* 10/16; RR, 1.5 (95% CI, 1.1–2.4)) (Figure 1).

DISCUSSION

The findings from this study demonstrate that twin pregnancies complicated by sIUD are at increased risk of PTB at < 34, < 32 and < 28 weeks of gestation. The risk of PTB after sIUD was similar in MC and DC twin pregnancies, irrespective of the gestational age at death. Finally, the risk of PTB at < 34 weeks of gestation was higher when sIUD occurred in the second half of the pregnancy, when compared with occurrence in earlier gestation.

PTB after sIUD in twin pregnancy may result from spontaneous preterm labor or iatrogenic delivery as a result of clinicians' concerns about the risk to the cotwin, especially in the case of MC pregnancy. A previous systematic review assessing the cotwin outcome after sIUD reported that the incidence of PTB after sIUD was 68% (95% CI, 56.7–78.5) in MC and 54% (95% CI, 41.5–66.9) in DC twin pregnancies[8]. The overall risk of PTB did not change with chorionicity (OR, 1.1 (95% CI, 0.34–3.51), $P = 0.9$). However, some of the included studies were very small (ranging from two to 18 pregnancies). Furthermore, the included studies covered a relatively wide time interval in which management of twin pregnancies after sIUD was likely to have changed, especially among different centers. When exploring the effect of gestation on the association between sIUD and PTB, the authors reported that the risk of prematurity at 28–33 weeks of gestation was increased in MC compared with DC twins (OR, 4.96 (95% CI, 1.6–15.8)). In the present study, the risk for PTB was higher when the sIUD occurred later in gestation, both in MC and in DC twin pregnancies. This finding should be interpreted with caution because it might be related to iatrogenic delivery rather than to spontaneous preterm labor induced by the sIUD, although in the STORK centers it was not common clinical practice to expedite delivery in the case of sIUD, except in cases with signs of impending fetal compromise, such as abnormal cardiotocogram (CTG) or fetal Doppler. Furthermore, the lack of a difference between MC and DC pregnancies would indicate that iatrogenic birth was not implemented on the basis of chorionicity. There has been a long-standing regional policy of expectant management with monitoring in these pregnancies, unless indications for intervention exist.

The occurrence of sIUD in a twin pregnancy may have a profound impact on the surviving twin. Several adverse events, such as PTB, cotwin death and neurological morbidities of the surviving fetus, have been reported in these pregnancies[8]. Gestational age at loss and chorionicity are the two main determinants of perinatal outcome in the surviving cotwin[8]. sIUD can occur at any time during pregnancy, although its prevalence is higher during the early embryonic period, a phenomenon known as vanishing twin syndrome, which can affect up to about 29% of twin pregnancies[14–16]. The reason for the embryonic loss and the actual magnitude of this phenomenon are yet to be ascertained. However, vanishing twin syndrome is not associated with long-term sequelae for the surviving fetus, although it is linked with an increased risk of cotwin intrauterine death in MC pregnancy[14,15].

The incidence of sIUD was lower in DC compared with MC twin pregnancy[8]. Despite this, DC twin pregnancies with sIUD are still at higher risk for adverse perinatal outcome compared with uncomplicated DC gestations[8]. Management of twin pregnancies affected by sIUD is challenging as the evidence is sparse and is mainly derived from small series with different protocols of antenatal management[17,18]. In DC twins in which sIUD occurs in the first trimester of pregnancy, conservative management with fortnightly fetal surveillance and delivery at, or close to, term should be the favored option. For sIUD occurring after viability, prophylaxis with corticosteroids is also indicated in view of the high rate of spontaneous PTB. However, in the absence of spontaneous PTB or obstetric complications, elective preterm delivery of the surviving cotwin is not indicated[19].

Management of MC twin pregnancies complicated by sIUD poses a particular prognostic dilemma. Prophylaxis with corticosteroids is indicated in view of the high rate of spontaneous PTB occurring after intrauterine death as a result of either fetal compromise of the surviving twin or spontaneous PTB. Optimal gestational age at delivery in the case of sIUD occurring in the second or third trimester has not yet been determined and the majority of these pregnancies are currently delivered within a few weeks following sIUD because of clinicians' concern. However, it should be borne in mind that immediate delivery after sIUD has not been proven to reduce the burden of the associated neonatal morbidity, while it exposes the surviving cotwin to the risks associated with prematurity[20].

The STORK cohort studied here is one of the largest twin pregnancy cohorts of known chorionicity to be validated against both a concomitant delivery database and a mandatory national register of stillbirths and neonatal deaths. The strengths of the study are represented by its large sample size and the common protocol for prenatal management of twin pregnancies shared by the participating centers. Delivery of the surviving cotwin soon after the diagnosis of sIUD was not recommended unless signs of impending fetal demise, such as abnormal CTG or Doppler, were detected. A major limitation of the current study is the lack of stratification between spontaneous and iatrogenic PTB, as a result of the retrospective nature of the study. However, this was also a limitation of a previously published systematic review exploring the cotwin outcome after sIUD in twin pregnancy[8]. Another limitation of our study is the lack of data on maternal characteristics, which are potential risk factors for adverse pregnancy outcome, such as PTB.

In conclusion, twin pregnancies complicated by sIUD, have a higher risk of PTB at < 34, < 32 and < 28 weeks of gestation, regardless of the chorionicity. The risk of PTB at < 34 weeks of gestation was higher when the sIUD occurred in the second half of the pregnancy. Large prospective multicenter studies with shared protocols for prenatal management are needed to ascertain the actual risk of spontaneous PTB in twin pregnancies complicated by sIUD and their optimal management.

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