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

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ABSTRACT

Background: Single intrauterine death (sIUD) in twin pregnancies is associated with a significant risk of co-twin 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 the diagnosis of sIUD.

Methods: A cohort study of all twin pregnancies from a large regional network of 9 hospitals over a ten-year period. Ultrasound data was matched to hospital delivery records and a mandatory national register for perinatal losses (CMACE). Cases with double fetal loss at the time of the scan were not included in the analysis. The cumulative rates of PTB before 34, 32 and 28 weeks of gestation was assessed in pregnancies which did vs those which did not experience sIUD. The risk of PTB was stratified according to the gestational age at the diagnosis of sIUD.

Results: The analysis included 3013 twin gestations (2469 DC and 544 MC) . Median gestational age at birth was lower in the pregnancies complicated by sIUD compared to those which were not (32.0 weeks, IQR 29.0-34.3 vs 36.7 weeks, IQR 35.0-37.6; p<0.001) and this

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difference persisted when stratifying the analysis according to chorionicity ($p<0.0001$ for both MC and DC pregnancies). The risk of PTB before 34 weeks (RR: 4.3, 95% CI 3.5-5.2), before 32 weeks (RR: 6.1, 95% CI 4.6-8.1) and before 28 weeks (RR: 12.40, 95% CI 6.9-22.2) was higher in pregnancies complicated by a sIUD compared to those which did not experience any fetal loss. This association was observed both in MC and DC twin gestations. When compared to DC pregnancies, MC twins affected by sIUD were not at significantly increased risk of PTB either before 34, 32 or 28 weeks of gestation. The risk of PTB before 34 weeks of gestation was higher when the sIUD occurred at a later gestational age (Chi-square test for trend, $p<0.001$).

Conclusion: Twin pregnancies complicated by sIUD, regardless of the chorionicity, have a significantly higher risk of PTB before 34, 32 and 28 weeks of gestation. The risk of PTB before 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 to singleton, especially due to prematurity, fetal anomalies and growth restriction[1]. The overall risk of death is about seven to ten-fold higher in monochorionic (MC) compared to dichorionic (DC) twin pregnancies. This increased risk is mainly attributed 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 due to the difference in fetal 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) is associated with adverse pregnancy outcome, such as the demise of the co-twin, preterm birth (PTB) and neurological morbidities[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 their incidence has been reported to be lower[7,8].

A previous systematic review assessing the outcome of the co-twin following sIUD has reported that the rate of PTB was 68% (95% CI 56.7–78.5) in MC and 54% (95% CI 41.5–66.9) in DC twin pregnancies[8]. However, the small number of the included cases per each study, lack of stratification according to the gestational age at birth or gestational age at the sIUD, and the wide heterogeneity in the perinatal management in the included studies hinder the ability to extrapolate accurate results 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 the gestational age at birth or gestational age at the sIUD, after single fetal loss 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 period of ten years since 2000. All women registering for routine antenatal care by 11 weeks of gestation were considered suitable for the analysis. Scan data were obtained by a computerized search from each hospital's obstetric ultrasound computer database, while the outcome details were obtained from their computerized maternity records. These two databases were crosschecked to ensure full data capture of all twin pregnancies during the study period. All data included in the analysis was collected prospectively but analysed retrospectively. Ethical approval for this retrospective study was obtained from the local research ethics committee.

Fetal loss was defined as any spontaneous death occurring from 14 weeks of gestation. Pregnancies affected by twin-to-twin transfusion syndrome, terminations of pregnancy, fetal or chromosomal abnormalities, pregnancies of unknown chorionicity, monochorionic 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 gestations 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 (HC) 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 monochorionic twins had two additional scans at around 16-17 and 18-19 weeks specifically to identify early features of twin-to-twin transfusion syndrome (TTTS). If TTTS was suspected, women were referred to the local tertiary centre for assessment for fetoscopic laser ablation of the placental interconnecting vessels. Ultrasound scan was performed every 4 weeks in dichorionic twins, and every 2 weeks in monochorionic twins until 24 weeks, and every 3-4 weeks afterwards.

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

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

All calculations were performed using StatsDirect version 3 (StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2013) and GraphPad Prism version 7 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com). Statistical significance was set at $p<0.05$. All p values 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 previously described[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 to 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 ~~566~~ 544 MC) available for the analysis, consisting in 65 (44 DC and 21 MC) pregnancies with sIUD and ~~2959~~ 2948 (2425 DC and 523 MC) with no fetal loss.

There were 68 IUD in 65 pregnancies, including three cases where a single loss was follow by co-twin death during pregnancy, all occurring in DC pregnancies. These 3 pregnancies were not included in the computation of PTB.

The incidence of IUD was significantly higher in MC twins (3.9%, 21/544) compared to 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 the pregnancies complicated by sIUD compared to those which were not (32.0 weeks, 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 before 34, 32 and 28 weeks of gestations occurred in 66.1%, 48.4% and 19.4% (of twin pregnancies with sIUD (Table 1). The risk of PTB before 34 weeks (RR: 4.3, 95% CI 3.5-5.2), before 32 weeks (RR: 6.1, 95% CI 4.6-8.1) and before 28 weeks (RR: 12.40, 95% CI 6.9-22.2) was significantly higher in pregnancies complicated by a sIUD compared to those which did not experience any fetal loss. When stratifying the analysis according to chorionicity, the incidence of PTB before 34, 32 and 28 weeks of gestations was 61.9%, 47.6% and 19.1% in MC pregnancies, while it was 68.3%, 48.8% and 19.5% in DC gestations (Table 1). In MC pregnancies, the risk of PTB before 34, 32 and 28 weeks of gestations was significantly higher in the pregnancies complicated by sIUD (RR 3.0, 95% CI 2.1-4.4, 4.9, 95% CI 2.9-8.2, and 7.7, 95% CI 2.7-21.5, respectively). The equivalent figures in DC pregnancies were 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 <34, <32 and <28 weeks of gestation, respectively (Table 1). When compared to DC pregnancies, MC twins affected by

sIUD were not at significantly increased risk of PTB either before 34, 32 or 28 weeks of gestation (Table 2).

The risk of PTB before 34 weeks of gestation was significantly higher when the 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 and $p=0.01$ for DC twins, respectively). The risk of PTB before 34 weeks was significantly higher if the sIUD occurred at 26-32 compared to either at 14-19 (24/26 vs 2/11, RR 5.1, 95% CI 1.9-18.0) or 20-25 weeks of gestation (24/26 vs 10/16, RR 1.5, 95% CI 1.1-2.4) (Figure 1).

DISCUSSION

Summary of the study findings

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

Interpretation of the study findings and comparison with published literature

PTB after sIUD in twin pregnancies may result from spontaneous preterm labor or iatrogenic delivery due to clinicians' concerns about the risk to the co-twin, especially in case of MC pregnancies. A previous systematic review assessing the co-twin 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 2 to 18 pregnancies). Furthermore, the included studies covered a relatively wide time interval (from 1999 to 2009), in which management of twin pregnancies after sIUD was likely to change, especially among different centers. When exploring the effect of gestation on the association between sIUD and PTB, the authors reported the risk of prematurity at 28-33 weeks of gestation was increased in MC compared to 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 DC twin pregnancies. This figure should be interpreted with caution because it might be related to iatrogenic delivery rather than spontaneous preterm labor induced by the sIUD, although in the STORK centers it was not common clinical practice to expedite delivery in case of sIUD except in cases with signs of impending fetal compromise, such as abnormal CTG or fetal Dopplers. Furthermore, the lack of a difference between MC and DC pregnancies would indicate that iatrogenic birth was not implemented on the basis of chorionicity. It has been a long-standing regional policy of expectant management with monitoring in these pregnancies, unless there are indication for interventions.

Clinical and research implications

The occurrence of a sIUD in a twin pregnancy may have a profound impact on the surviving twin. Several adverse events, such as PTB, co-twin 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 co-twin[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[12-14]. 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 sequalae on the surviving fetus, although it is linked to an increased risk of co-twin IUD in MC pregnancies[12,13.]

Interestingly, the incidence of sIUD is lower in DC compared to MC twin pregnancies[8]. Despite this, they are still at higher risk for adverse perinatal outcome compared to 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. In DC twins, conservative management with fortnightly fetal surveillance and delivery at or close to term represents the most likely option for sIUD occurring in the first trimester of pregnancy. 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 obstetrics complications, elective preterm delivery of the surviving co-twin is not indicated[17].

Management of MC twin pregnancies complicated by sIUD poses peculiar prognostic dilemma. Prophylaxis with corticosteroids is indicated in view of the high rate of spontaneous PTB occurring after the IUD due to either fetal compromise of the surviving twin or spontaneous PTB. Optimal gestational age at delivery in case of sIUD occurring in the second or third trimester has not been determined yet and the majority of these pregnancies are currently delivered within few weeks after sIUD due to clinicians' concern. However, it should be kept in mind that immediate delivery after sIUD has not been proven to reduce the burden of the associated neonatal morbidities, while to expose the surviving co-twin to the risks associated with prematurity[16].

Strengths and weaknesses

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 which was shared by the participating centers. Delivery of the surviving co-twin soon after the diagnosis of sIUD was not recommended unless signs of impending fetal demise, such as abnormal CTG or Dopplers were detected. A major limitation of the current study is the lack of stratification between spontaneous and iatrogenic PTB, due to the retrospective nature of the study. However, this was also a limitation of a previously published systematic review exploring the co-twin outcome after sIUD in twin pregnancies[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.

Conclusions

Twin pregnancies complicated by sIUD, regardless of the chorionicity, have a higher risk of PTB before 34, 32 and 28 weeks of gestation. The risk of PTB before 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 the optimal management of these pregnancies.

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Table 1. Preterm birth (PTB) in twin pregnancies complicated by a single intrauterine death (sIUD) compared to those which were uncomplicated

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

***: 3 cases affected by the loss of the co-twin (all DC pregnancies) excluded from the analysis.**

Table 2. Preterm birth (PTB) in twin pregnancies complicated by a single intrauterine death (sIUD) according to chorionicity

PTB	Monochorionic twin pregnancies (n=21)	Dichorionic twin pregnancies (n=41)	RR (95% CI)	p-value
PTB<34 weeks	61.9 (95% CI 38.4-81.9) (13/21)	68.29 (95% CI 51.9-81.9) (28/41)	0.91 (0.6-1.3)	0.626
PTB<32 weeks	47.62 (95% CI 25.7-70.2) (10/21)	48.78 (95% CI 32.9-64.9) (20/41)	0.98 (0.6-1.7)	0.931
PTB<28 weeks	19.05 (95% CI 5.4-41.9) (4/21)	19.51 (95% CI 8.8-34.9) (8/41)	0.98 (0.3-2.9)	0.965

Figure legends

Figure 1. Prevalence of PTB in twin pregnancies with sIUD occurring at different gestational age windows.