The Significance of Placental Cord Insertion Site in Twin Pregnancy

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ABSTRACT

Objective: The aim of this study was to investigate the association between abnormal cord insertion and the development of the twin-specific complications, including birthweight discordance, selective fetal growth restriction (sFGR) and twin-to-twin transfusion syndrome (TTTS).

Methods: A single-center cohort study of twin pregnancies. Abnormal cord insertion was defined as either marginal (cord attachment site less than 2cm to the nearest margin of the placental disc) or velamentous (when the umbilical cord was attached to the membrane before reaching the placental disc with clear evidence of vessels traversing the membranes to connect with the placental disc), as described in placental pathology reports. Major structural or chromosomal abnormalities and monochorionic monoamniotic twins were not included in

the study. Information on the pregnancies, ultrasound findings, prenatal investigation and interventions was obtained from the electronic ultrasound database, while data on the placental histopathological findings, pregnancy outcomes, mode of delivery, birthweight, gestational age at delivery, and admission to the neonatal intensive care unit (NICU) were obtained from the maternity records. Categorical variables were compared by the X^2-test or Fisher's exact test, while continuous variables were compared using the t-test, analysis of variance (ANOVA) for multiple comparison and the Kruskal-Wallis test.

Results: 497 twin pregnancies, 351 (70.6%) dichorionic and 146 (29.3%) monochorionic, were included in the analysis. The incidence of birthweight discordance of 25% or more was significantly higher in pregnancies with velamentous and marginal cord insertions compared to those with normal cord insertion (24.5%, 15.2% vs 7.5%, P<0.001 and P=0.020, respectively). In pregnancies with birthweight discordance of 25% or more, the smaller twins had significantly higher prevalence of velamentous (13.8%) and marginal (34.2%) cord insertions compared to the larger twins (1.8% and 18.5%, respectively P<0.001). The smaller twins of the MCDA pregnancies showed an even higher prevalence of velamentous (29.5%) and marginal cord insertions (40.9%) compared to the larger twins (2.3% and 29.5%, respectively P<0.001). Compared to the normal cord insertion group, only velamentous insertion was significantly associated with the risk of sFGR (OR 9.24; 95% CI 2.05-58.84, P<0.001), birthweight discordance of 20% or more (OR 4.34; 95% CI 1.36-14.61, P=0.006) and 25% or more (OR 6.81; 95% CI 1.67-34.12, P=0.003) in monochorionic twin pregnancies. There was no significant association between velamentous cord insertion and TTTS (p=0.265). There was no significant association between marginal cord insertion and the development of sFGR (P=0.233), birthweight discordance of 25% or more (P=0.114) or TTTS (P=0.487). Subgroup analysis of dichorionic twins showed that abnormal cord insertion was not associated with the risk of birthweight discordance (P=0.250), sFGR (P=0.308), composite neonatal adverse outcome (P=0.637) or intrauterine death (P=0.349).

Conclusion: Monochorionic twins with velamentous cord insertion are at increased risk of birthweight discordance and sFGR. Sonographic delineation of the placental cord insertion could be of value in the antenatal stratification of twin pregnancies. Prospective studies are required to assess the value and the predictive accuracy of this potential screening marker.

INTRODUCTION

Twin pregnancies are at increased risk of perinatal and maternal mortality and morbidity.[1-4] A major contributor to the perinatal risks are complications that are specific to twin pregnancies. These include discordance of size between twins; selective fetal growth restriction (sFGR) [5-14] and complications due to monochorionic (MC) placental development, chiefly twin-to-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS) and twin reversed arterial perfusion sequence (TRAP).[15]

Anomalies of the placental insertion of the umbilical cord are more common in twin pregnancies compared to singletons.[16] Velamentous cord insertion is reported in 2% in singleton, 7% in dichorionic (DC) twin and 12% in monochorionic (MC) twin pregnancies.[17] This has been associated with unequal sharing of the placental territory which may in turn cause discordant growth.[18] In MC diamniotic (MCDA) twins, this phenomenon is thought to be a risk factor for the development of sFGR, birthweight discordance and TTTS.[19-24] Even though a number of studies have confirmed this association, others have reported conflicting results.[25-32] Therefore, the association between abnormal cord insertion, in particular velamentous insertion, and the twin-specific complications is yet to be accurately characterised. If such an association exists, sonographic delineation of the placental cord insertion could be of value in the antenatal identification of twin pregnancies at increased risk of complications.

The aim of this study was to investigate if there is an association between abnormal cord insertion in twin pregnancies, with the development of twin-specific complications: birthweight discordance, sFGR and TTTS.

METHODS

This was a retrospective cohort study in a tertiary referral center from 2000 to 2016. The inclusion criteria were twin pregnancies delivering at St. George's Hospital with available placental histopathological examination reports which met the criteria suggested by Hubinont et al.[33] The exclusion criteria included fetuses with known major congenital anomalies or aneuploidy and MC monoamniotic (MCMA) pregnancies. Information on the pregnancies, ultrasound findings, prenatal investigation and interventions were obtained from the electronic database (ViewPoint 5.6.8.428, ViewPoint Bildverarbeitung GmbH, Weßling, Germany) in the Fetal Medicine Unit, St George's Hospital. Information on the placental histopathological findings, pregnancy outcomes, mode of delivery, birthweight, gestational age at delivery, and admission to the neonatal intensive care unit (NICU) were obtained from the maternal or newborn health records.

The placental cord insertion site was categorized into three groups: marginal, velamentous and normal.[34] Marginal insertions were diagnosed when the cord attachment site was less than 2.0 cm to the nearest margin of the placental disc; and velamentous insertions when the umbilical cord was attached to the membrane before reaching the placental disc, with clear evidence of vessels traversing the membranes to connect with the placental disc. All other cord insertion sites (central, paracentral, eccentric, etc.) which were more than 2cm from the nearest edge of the placental disc, were considered as normal. Chorionicity was confirmed with microscopic evaluation of the placental membranes (T-Zone). Placentas were grouped according to the presence of abnormal cord insertion (marginal or velamentous). Marginal cord insertion group was defined as the presence of marginal insertion in one or both of the fetuses with the absence of velamentous insertion. Velamentous cord insertion group was defined as velamentous insertion in one or both of the fetuses irrespective of the contralateral cord insertion.

Birthweight discordance was calculated by subtracting the weight of the smaller twin from the weight of larger twin and then dividing by the weight of larger twin, expressed as a percentage. The gestational age-specific Z-score of birthweight was calculated using the formula derived from INTERGROWTH-21.[35] sFGR was diagnosed when the birthweight of one of the twins was below the 10th centile for gestational age and there was at least 25% birthweight discordance between the neonates.[15] Pregnancies complicated by TTTS Quintero stage II or higher were treated with laser photocoagulation of the anastomosing placental vessels.[36] Composite neonatal adverse outcome was 5-minute Apgar score of less than 7, or admission to neonatal care unit.

Statistical Analysis

Data are presented as median and interquartile ranges (IQR) for continuous data and as n (%) for categorical variables. Categorical variables were compared by X^2-test or Fisher's exact test. Normal distribution assumptions of each variable were tested with Shapiro-Wilk test and quantile-quantile (Q-Q) plots. Group analysis of continuous variables with a normal distribution was performed using the t-test or analysis of variance (ANOVA) for multiple comparison. The analysis of continuous variables with non-normal distribution was performed using Kruskal-Wallis test. For discrete data with binary outcomes, contingency tables were formed and the associations were tested with Fisher's exact test and the odds ratios with 95% confidence intervals (CIs) were reported. Since most of the studied outcomes were binary, a power analysis was made assuming a modest 15% difference in the prevalence of birthweight discordance between groups. In order to test for this assumption with a ratio of 1:3 between monochorionic and dichorionic twins in the study cohort, at least 118 MCDA and 276 dichorionic pregnancies were required (Power: 80%, alpha: 0.05). All significance tests were two-tailed. P values less than 0.05 were considered statistically significant for all analyses.

The analysis was performed using the RStudio Software (Version 1.00.136, RStudio®, Inc.).

Literature Review

We conducted a literature review using MEDLINE database between the years 1990 and 2017. The search terms representing the participants ('twin') were combined with association terms (cord' OR 'insertion'). Studies reporting on the placental cord insertion in twin pregnancy and its association with pregnancy outcome were included in order to construct a review table.

RESULTS

The study cohort included 518 twin pregnancies. After excluding 21 pregnancies that had major structural (n=4) or chromosomal abnormalities (n=16), and TRAP sequence (n=1), 497 twin pregnancies (351 DC and 146 MC) were included in the analysis. Of these 497, the cord insertion was marginal in 170 (34.2%), velamentous in 50 (10.1%) and normal in 277(55.7%) cases. The prevalence of abnormal cord insertion was significantly higher in MC (n=97, 66.4%), when compared to DC twin pregnancies (n=123, 35.0%) (P<0.001). Marginal cord insertions were reported in 69 (47.2%) of the MC and 101 (28.8%) of the DC twin pregnancies, while velamentous cord insertion was seen in 28 (19.1%) and 22 (6.2%), respectively.

The study cohort included 48 twin pregnancies with birthweight discordance of 25% or more, 41 with sFGR and 35 with TTTS (table 1). Twin pregnancies with velamentous cord insertion, compared to those with normal cord insertion, had significantly higher median birthweight discordance (10.78%; IQR 6.27-24.59% vs 9.69%; IQR 4.68-17.71%, P=0.033) and birthweight discordance of 25% or more (24.0% vs 7.6%, P<0.001) (Table 1). The birthweight absolute Z-score difference between the twins was also significantly higher in twin pregnancies with velamentous cord insertion compared to those with normal cord insertion (0.95; IQR 0.48-1.10 vs 0.70; IQR 0.34-1.29, P=0.019) (Table 1). The birthweight of both the smaller and the larger twins were significantly lower in pregnancies with velamentous insertion compared to those with normal cord insertion (P=0.018 and P<0.001, respectively) (Table 1). The gestational age at delivery was significantly lower in abnormal cord insertion groups (both velamentous and marginal insertion) when compared to twin pregnancies with normal cord insertion (P=0.004 and P=0.003, respectively) (Table 1).

There was an association between birthweight discordance of 25% or more and the type of placental cord insertion (Figures 1 and 2). In twins with discordance, there was significantly higher prevalence of velamentous (13.8%) and marginal (34.2%) cord insertions in the smaller twin of the pair when compared to the larger twin of the pair (1.8% and 18.5%, respectively P<0.001) (Figure 1). The smaller twins of discordant MCDA pregnancies showed an even higher prevalence of velamentous (29.5%) and marginal cord insertion (40.9%) compared to the larger twins (2.3% and 29.5%, respectively P<0.001) (Figure 2). In MCDA twin pregnancies, the incidence of composite neonatal adverse outcome was also significantly higher in the abnormal vs the normal cord insertion groups (70.0% vs 53.0%, P=0.046) (Table 2). There was no significant difference in the frequency of TTTS between

abnormal and normal cord insertions (P=0.999) (Table 2). In DC twins, there were no significant differences in sFGR between those with abnormal vs normal cord insertion (10.5 vs 7.0%, P=0.308); nor in the birthweight discordance (12.1 vs 7.8%, P=0.250, Table 2).

Compared to the normal cord insertion group, only the velamentous insertion was significantly associated with the risk of sFGR (OR 9.24; 95% CI 2.05-58.84, P<0.001), birthweight discordance of 20% or more (OR 4.34; 95% CI 1.36-14.61, P=0.007) and 25% or more (OR 6.81; 95% CI 1.67-34.12, P=0.003) (Table 3). There was no significant association between velamentous cord insertion and TTTS (p=0.591). There was no significant association between marginal cord insertion and the development of sFGR (P=0.233), birthweight discordance of 25% or more (P=0.114) or TTTS (P=0.487) in MC twins.

The literature search yielded 118 citations. After exclusion of the studies by reviewing the abstracts, 13 studies reporting on the association of cord insertion site with either sFGR, birthweight discordance or TTTS in MCDA twin pregnancies were retrieved. Data from these studies were used to construct a review table (Table 4). The published literature consistently reported a significant association between abnormal cord insertion, in particular velamentous insertion, and inter-twin birthweight discordance of 20% or 25% and sFGR in MCDA twin pregnancies.[18-21,28,30,37,39] The studies report inconsistent results as to whether or not velamentous cord insertion is associated with TTTS.[22,24,29,38-42]

DISCUSSION

Our results demonstrate a significant association between abnormal cord insertion and birthweight discordance in twins overall, and this is most noticeable in MCDA twins: here velamentous insertion was associated with the development of sFGR, significant birthweight discordance (≥25% or ≥20%), but not with the development of TTTS. The smaller twin in a pregnancy with birthweight discordance of 25% or more was more likely to have an abnormal cord insertion than the larger twin; or either twin in a pregnancy with birthweight discordance less than 25%. The cord insertion site did not have a significant association with adverse pregnancy outcomes in DC twins. In MCDA twin pregnancies the literature consistently reports a significant association between abnormal cord insertion, in particular velamentous insertion, and birthweight discordance (≥25% or ≥20%) and with sFGR. This is not the case in TTTS for which the studies have reported inconsistent results.

Interpretation of the study findings and comparison with existing literature

Our results are consistent with the published literature, which reports a significant association between velamentous cord insertion and the risk of significant inter-twin size discordance and sFGR in MCDA twin pregnancies. [18-21,28,30,37,39]. The association between velamentous cord insertion and adverse pregnancy outcome in twin pregnancy was thought to be due to the fact that velamentous cord insertion is more prone to compression, which is likely to reduce the blood flow leading to hemodynamic instability.[29] We did not observe a similar association between marginal cord insertion and the risk of significant inter-twin size discordance and sFGR in MCDA twin pregnancies. Furthermore, our data suggest that velamentous cord insertion was not significantly associated with TTTS. However, our analysis might be underpowered to address this question. Nevertheless, the published literature also reports inconsistent results on the relationship between abnormal cord insertion and TTTS.[29,40] Large multicenter prospective studies have reported no association between velamentous cord insertion and the development of TTTS.[18,20,22]

Clinical and research implications

Birthweight discordance is a major determinant of perinatal outcome in twin pregnancies, irrespective of the chorionicity.[43,44] Although a certain degree of discordance in fetal growth is invariably present in all twin pregnancies, large inter-twin weight discordances have been associated with stillbirth, neonatal death, preterm birth, respiratory distress and admission to NICU.[10,44-50] In view of the association between abnormal cord insertion, in particular velamentous cord insertion in MCDA twins, and the risk of sFGR and severe inter-twin birthweight discordance, this finding could represent a marker to identify those pregnancies at highest risk early in pregnancy. Therefore, sonographic delineation of the placental cord insertion, which could be best performed early in pregnancy, could be of value in the stratification of the risk of fetal growth disroders in twin pregnancies and triggering closer antenatal surveillance in those at higher risk.

In the UK, a recently published national guideline focusing on the management of MC twin pregnancy has implied an association between abnormal cord insertion and TTTS, quoting the studies Umur et al., Zhao et al., de Villiers et al., and Chang at al.,[51-54] However, of those cited studies, only De Villiers et al. reported an association between TTTS and abnormal cord insertion, despite the fact that the association reported in the paper was non-significant. The other studies did not report on the cord insertion site. This association is backed by a study by De Paepe et al. but most of the studies suggest a non-significant association between velamentous cord insertion and the development of TTTS.[18,20,22,28] A large multicenter study is required to address this question robustly. Meanwhile, a meta-analysis, particularly one using individual patient data, could be useful to address this controversial issue.

Despite the fact that our findings demonstrate an association between the velamentous cord insertion in MCDA twins and the risk of sFGR, a large prospective screening study is needed to investigate whether routine use of placental cord insertion can be a useful screening marker for adverse pregnancy outcome in twin pregnancies. More importantly, it would be important to delineate how this knowledge would alter the current management of these pregnancies. International guidance recommends regular ultrasound scans of MC pregnancies every 2 weeks from 16 weeks.[15] The finding of velamentous cord insertion is unlikely to increase or decrease this frequency.

Strengths and limitations

The strengths of our study include the relatively large number of cases, secondly the application of robust criteria for the inclusion of the placental pathology reports, thirdly minimizing the inter-observer variability or bias in reporting the placental pathology as all cases were examined and reported in a single institution, and finally the consistent findings with the published literature.

The main limitation is its retrospective design with its inherent risk of selection bias and the high prevalence of complicated pregnancies and abnormal cord insertions. Although this would potentially have overemphasized the effect of abnormal insertion on adverse pregnancy outcomes, our results, for the most part, were in accordance with the published literature. This could simply reflect the high risk nature of the pregnancies delivering at our center. St. George's Hospital is a tertiary referral center for the care of complicated twin pregnancies and our sample is likely not representative of the general population – meaning we observe a higher prevalence of abnormal cord insertions and adverse outcomes than expected. Conversely, the rate of sFGR was lower than expected but this may be explained by the fact that we have used strict criteria for the definition of sFGR as recommended by recent guidelines.[15] We note the low number of intrauterine demise in our cohort, which could also be due to selection bias, which could have resulted from the fact that we have included the pregnancies which delivered at our centre, and fulfilled the quality control criteria for placental pathological examination.

Conclusions

In summary, velamentous cord insertion in twin pregnancies overall, but more specifically in MCDA twins, is associated with the risk of sFGR and significant inter-twin birthweight discordance. Sonographic delineation of the placental cord insertion in the first trimester could be of value in early risk assesmet for subesquent fetal growth disorders in twins. Prospective studies are needed to assess the value and the predictive accuracy of this potential screening marker.

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FIGURE LEGENDS

Figure 1. The distribution of twin pregnancies and their fetuses according to the inter-twin birthweight discordance of 25% or more and the type of placental cord insertion in all twin pregnancies.

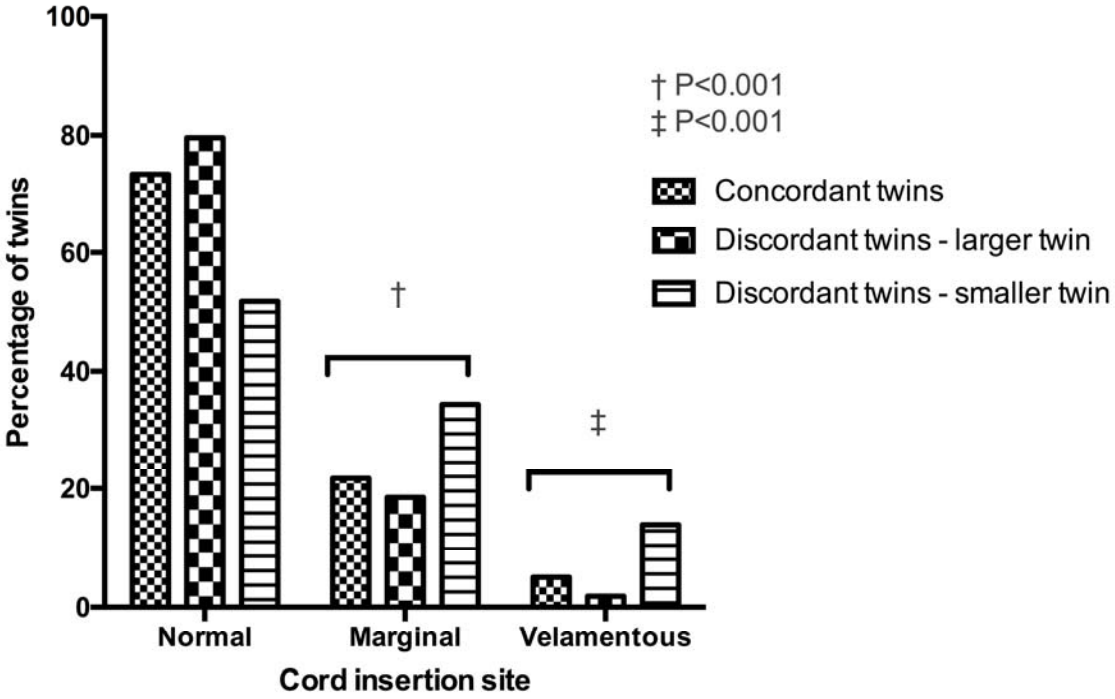
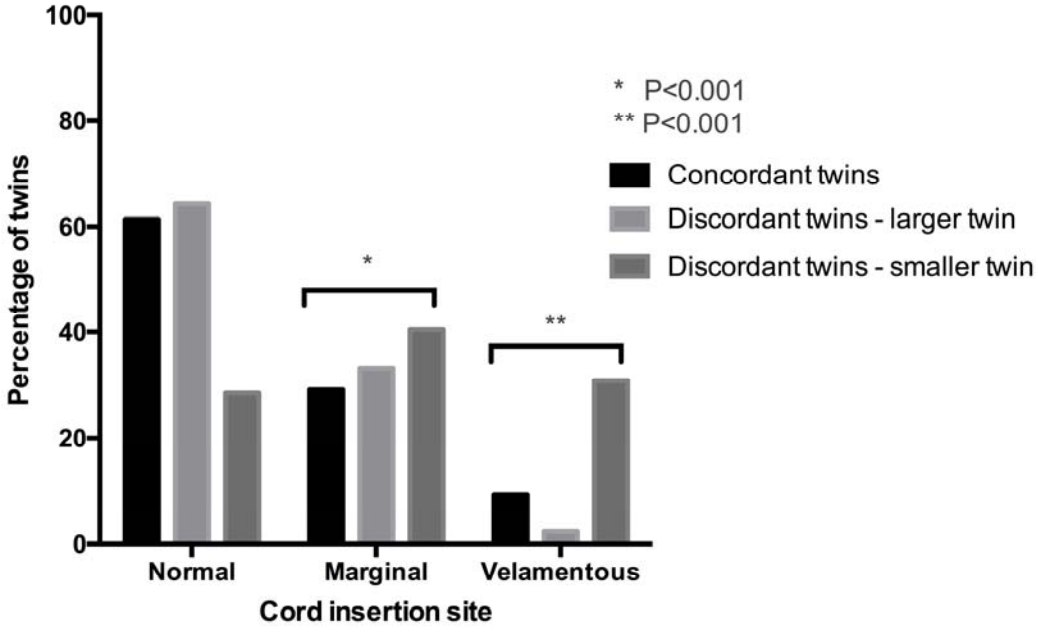


Figure 2. The distribution of twin pregnancies and their fetuses according to the inter-twin birthweight discordance of 25% or more and the type of placental cord insertion in monochorionic diamniotic twin pregnancies.



	Normal cord insertion (n=277)	**Marginal insertion (n=170)**	**Velamentous insertion (n=50)**	**P values***
Maternal age in years, median (IQR)	33.00 (30.00-36.00)	34.00 (29.00-36.00)	35.00 (30.75-37.00)	0.791
Gestational age at delivery in weeks, median (IQR)	36.43 (34.57-37.57)	35.86 (32.86-37.07)†	35.57 (31.75-37.00)†	0.187
Cesarean delivery, n (%)	188 (67.9)	122 (71.8)	38 (76.0)	0.430
Pregnancies conceived via assisted reproduction techniques, n (%)	96 (34.7)	45 (26.5)	18 (36.0)	0.169
Monochorionic diamniotic twin pregnancies, n (%)	49 (17.7)	69 (40.6)†	28 (56.0)†	0.511
Self reported ethnic origin -Caucasian, n (%) -Black, n (%) -Asian, n (%) -Other, n (%)	 -174 (63.5) -34 (12.4) -27 (9.9) -39 (14.2)	 -98 (58.3) -30 (17.9) -17 (7.1) -28 (16.7)	 -32 (64.0) -6 (12.0) -2 (4.0) -10 (20.0)	0.241
Birthweight discordance (%), median (IQR)	9.7 (4.7-17.7)	12.2 (4.5-20.2)	10.8 (6.3-24.62)†	0.472
Birthweight discordance ≥20%, n (%)	50 (18.1)	42 (24.7)	16 (32.0)†	0.708
Birthweight discordance ≥25%, n (%)	21 (7.6)	26 (15.3)†	12 (24.0)†	0.428
Birthweight of the larger twin in grams, median (IQR)	2510 (2068-2800)	2383 (1899-2793)	2190 (1603-2497)†	0.281

Birthweight of the smaller twin in grams, median (IQR)	2220 (1750-2550)	2220 (1604-2660)	1995 (1270-2436)†	0.027
Absolute Z score difference, median (IQR)	0.70 (0.34-1.29)	0.92 (0.32-1.57)	0.95 (0.48-2.10)†	0.528

Table 1. Comparison of the study groups according to the umbilical cord insertion site. Data are presented as median and interquartile range.

IQR: interquartile range, The comparison between each of the marginal cord insertion group and the velamentous cord insertion group with the twin pregnancies with normal placental cord insertion was performed using the Mann-Whitney or Chi-Square test († P<0.05), * Three group comparison was performed using Kruskal-Wallis or Chi-Square test."

Table 2. Adverse pregnancy outcome according to the cord insertion site and the chorionicity.

	Normal cord insertion (n=277)	**Abnormal cord insertion (n=220)**	**P value**
Monochorionic diamniotic twin pregnancies (n=146) (49 Normal cord insertion and 97 Abnormal cord insertion)			
Twin-to-twin transfusion syndrome, n (%)	12 (24.5)	23 (23.7)	1.000
Selective fetal growth restriction, n (%)	1 (2.0)	11 (11.3)	0.049
Birthweight discordance ≥25%, n (%)	2 (4.1)	13 (13.4)	0.093
Composite adverse outcome, n (%)	26 (53.1)	68 (70.1)	0.046
Intrauterine death, n (%)	1 (2.0)	3 (3.1)	1.000
Dichorionic twin pregnancies (n=351) (228 Normal cord insertion and 123 Abnormal cord insertion)			

Selective fetal growth restriction, n (%)	16 (7.0)	13 (10.6)	0.308
Birthweight discordance ≥25%, n (%)	18 (7.9)	15 (12.2)	0.250
Composite adverse outcome, n (%)	81 (35.6)	51 (41.5)	0.637
Intrauterine death, n (%)	0 (0)	1 (0.8)	0.349

Table 3. The association between abnormal placental cord insertion and selective fetal growth restriction, twin-to-twin transfusion syndrome, and birthweight discordance in monochorionic diamniotic twin pregnancies

	Velamentous cord insertion Odds ratio (95% CI)	**P value**	**Marginal cord insertion Odds ratio (95% CI)**	**P value**
Selective fetal growth restriction	9.24 (2.05-58.84)	<0.001	2.37 (0.55-14.38)	0.233
Birthweight discordance ≥25%	6.81 (1.67-34.12)	0.003	2.68 (0.75-12.11)	0.114
Birthweight discordance ≥20%	4.34 (1.36-14.61)	0.007	2.01 (0.77- 5.60)	0.136
Twin-to-twin transfusion syndrome	1.36 (0.40-4.42)	0.591	0.67 (0.24-1.84)	0.487

CI=confidence interval

Table 4. The literature summary of the association between abnormal cord insertion in monochorionic diamniotic (MCDA) twin pregnancies and the development of birthweight discordance, selective fetal growth restriction (sFGR) and twin-to-twin transfusion syndrome (TTTS)

First author and year	Number of MCDA twin pregnancies	Birthweight Discordance	Twin to twin transfusion syndrome	Selective fetal growth restriction
Costa-Castro et al 2016 [22]	513	-	OR 1.06 (95% CI 0.76-1.48)	-
Cambiaso et al 2016[18]	374	Birthweight Discordance (≥25%), OR 1.63 (95% CI 0.94-2.85)	-	-
Yonetani et al 2015[24]	357	-	OR 1.07 (95% CI 0.37-2.72)	-
Lopriore et al 2012[37]	47	Birthweight Discordance (≥25%), OR 2.88 (95% CI 1.14-7.48)	-	-
Kent et al 2011[20]	165	Birthweight Discordance (>20%), OR 3.41 (95% CI 1.00-11.07)	OR 0.79 (95% CI 0.08-3.98)	OR 1.88 (95% CI 0.40-7.18)
De Paepe et al 2010[28]	216	Birthweight Discordance (>20%), OR 4.13 (95% CI 1.77-9.56)	-	-

First author and year	Number of MCDA twin pregnancies	Birthweight Discordance	Twin to twin transfusion syndrome	Selective fetal growth restriction
De Paepe et al 2010[40]	218	-	OR 5.27 (95% CI 2.05-14.61)	-
Hack et al 2008	296	Birthweight Discordance (>20%), OR 1.28 (95% CI 0.77-2.13)	-	-
Lopriore et al 2007[41]	139	-	OR 0.89 (95% CI 0.39-2.02)	-
Fick et al 2006 [39]	644	Birthweight Discordance (>20%), OR 1.60 (95% CI 0.93-2.87)	-	-
Hanley et al 2002[21]	84	Birthweight Discordance (≥20%) OR 13.59 (95% CI 3.25-71.01)	-	-
Machin et al 1997 [30]	60	Birthweight Discordance (≥20%), OR 2.37 (95% CI 0.61 – 11.42)	-	-
Fries et al. 1993[29]	38	-	OR 7.19 (95% CI 1.27-49.28)	-

First author and year	Number of MCDA twin pregnancies	Birthweight Discordance	Twin to twin transfusion syndrome	Selective fetal growth restriction
Our study	146	Birthweight Discordance ≥25%: OR 6.81 (95% CI 1.67-34.12)	OR 1.36 (95% CI 0.40-4.42)	OR 9.24 (95% CI 2.05-58.84)