Placental cord insertion and birthweight discordance in twin pregnancies: results of the national prospective ESPRiT Study

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OBJECTIVE: The purpose of this study was to evaluate the impact of noncentral placental cord insertion on birthweight discordance in twins.

STUDY DESIGN: We performed a multicenter, prospective trial of twin pregnancies. Placental cord insertion was documented as central, marginal, or velamentous according to a defined protocol. Association of the placental cord insertion site with chorionicity, birthweight discordance, and growth restriction were assessed.

RESULTS: Eight hundred sixteen twin pairs were evaluated; 165 pairs were monochorionic, and 651 pairs were dichorionic. Monochorionic twins had higher rates of marginal ($P = .0068$) and velamentous ($P < .0001$) placental cord insertion. Noncentral placental cord insertion was more frequent in smaller twins of discordant pairs than control pairs (29.8% vs 19.1%; $P = .004$). Velamentous placental cord insertion in monochorionic twins was associated significantly with birthweight discordance (odds ratio, 3.5; 95% confidence interval, 1.3–9.4) and growth restriction (odds ratio, 4; 95% confidence interval, 1.1–14.3).

CONCLUSION: Noncentral placental cord insertion contributes to birthweight discordance in monochorionic twin pregnancies. Sonographic delineation of placental cord insertion may be of value in antenatal assessment of twin pregnancies.

Key words: birthweight discordance, placental cord insertion, twin pregnancy

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Twin pregnancies are associated with increased perinatal mortality and morbidity rates.[1] Although much of this increase in morbidity is a consequence of the increased rates of preterm delivery in twin pregnancies, there is also an independent association with growth abnormalities.[2] Studies that have evaluated perinatal outcome in twins have reported excess morbidity and death at increasing levels of birthweight discordance.[3,4]

The higher rates of adverse neonatal outcomes that are associated with discordant growth occur irrespective of gestational age at delivery and independent of small-for-gestational-age (SGA) status.[5,6] Greater degrees of growth discordance have been shown to increase the risk of intrauterine death for both the smaller and larger twin.[7-9]

Placental umbilical cord insertion site has been evaluated as a contributory factor to perinatal morbidity in singleton and twin pregnancies. In singleton pregnancies, a velamentous cord insertion is associated with obstetric complications that include prematurity, congenital anomalies, and fetal growth restriction.[10,11] A velamentous insertion is found in approximately 1% of singleton pregnancies, with an additional 7% of singleton pregnancies having a marginal cord insertion.[12]

Noncentral cord insertion is more common in twin than in singleton pregnancies.[12] In particular, monochorionic twin pregnancies have significantly higher rates of velamentous cord insertion.[13] This has been proposed as a contributory factor in the development of selective intrauterine growth restriction in monochorionic twin pregnancies; some studies show conflicting results with respect to the role of velamentous cord insertion in the cause of twin-to-twin transfusion syndrome (TTTS).[14,15]

The aim of this study was to evaluate the relative frequency of noncentral cord insertion in monochorionic and dichorionic twin pregnancies and to examine the association between noncentral cord insertion and birthweight discordance in twins.

Materials and Methods

This study was performed as a prespecified secondary analysis of the Evaluation of Sonographic Predictors of Restricted

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TABLE 1
Clinical characteristics

Variable	Monochorionic twins	Dichorionic twins	*P* value
Total, n (%)	165 (20.2)	651 (79.8)	
Mean birthweight, g[a]	2207 ± 647	2517 ± 565	.0001
Mean gestational age at delivery, wk[a]	34.7 ± 3.1	36.3 ± 2.4	.0001
Bodyweight discordance, n (%)			
>20%	32 (19.4)	109 (16.7)	.42
<5th percentile	19 (5.8)	91 (7)	.5
Twin-twin transfusion syndrome, n (%)	13 (7.8)		

[a] Data are expressed as mean ± SD.

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Growth in Twins (ESPRiT) study. ESPRiT was a multicenter, prospective, observational study of twin pregnancies that was carried out at 8 tertiary obstetric units in Ireland between May 2007 and October 2009. The primary aim of the ESPRiT study was to establish a threshold for birthweight discordance that serves as an independent predictor of adverse outcome in twin pregnancies. Institutional review board approval was obtained in each center, and participants gave written informed consent. Twin pregnancies with 2 viable fetuses that were identified from 11-22 weeks' gestation were eligible for inclusion. The principal exclusion criteria were monoamnionicity and structural or chromosomal abnormalities in either twin. Cases were excluded subsequently if an intrauterine death of 1 or both fetuses occurred at <24 weeks' gestation.

Study subjects underwent serial sonographic assessment of biometric parameters and multivessel Doppler ultrasound studies. Outcome data that were collected included maternal and obstetric characteristics, delivery and birthweight outcomes, and perinatal morbidity and mortality data.

Placental examination was carried out in the Pathology Department of the delivery hospital according to a defined study protocol. Formalin fixation of the placentas was carried out as per local practice in the delivery hospital. All placentas had chorionicity confirmed with gross and histologic examination of the intertwin membrane. Placental cord insertion site for each twin was recorded as central, marginal, or velamentous. *Marginal cord insertion* was defined as cord insertion at the edge of the placental disc. *Velamentous insertion* was defined as umbilical cord insertion into the membranes that are remote from the placental disc. All other cord insertions were defined as *central*.

All birthweights were recorded, and twins were recorded as SGA when their birthweight was <5th percentile for gestational age. Birthweight discordance was calculated as the absolute difference in birthweight between the twins and was expressed as a percentage of the weight of the larger twin. For the purposes of this analysis, *significant birthweight discordance* was defined as a difference in birthweight of >20%.

The overall distribution of cord insertion sites was compared between monochorionic and dichorionic twin pregnancies. The rate of each type of cord insertion was compared between twins that were SGA and those whose birthweight was appropriate for gestational age. To evaluate the association with birthweight, discordant twins were divided into 3 groups: the lighter twins of birthweight-discordant pairs, the heavier twins of birthweight-discordant pairs, and twins with birthweight discordance <20% (concordant). Prospective risk of SGA status and birthweight discordance with marginal and velamentous cord insertion was calculated.

Statistical analyses were performed with SAS software (version 9.1; SAS Institute Inc, Cary, NC). Relative frequencies were compared with the use of the chi-squared test. The paired Student *t* test was used to analyze continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate risks and the uncertainty around the risk estimates. A probability value of $< .05$ was considered statistically significant.

Results

One thousand twenty-eight twin pregnancies were recruited at 8 tertiary level centers in the ESPRiT study; 1001 patients completed the study and delivered at 1 of the 8 participating study centers. In 165 cases, the placentas were lost to follow up. In a further 20 cases, placental examination was completed, but the umbilical cord insertion site was not possible to determine or failed to be recorded. This left 816 twin pairs with data available for analysis. Table 1 outlines the clinical characteristics of this cohort: 20.2% of the pairs (n = 165) were monochorionic diamniotic, and 79.8% of the pairs (n = 651) were dichorionic. Monochorionic twins were delivered at a mean gestational age of 34.7 weeks, compared with 36.3 weeks' gestation for dichorionic twins. Mean birthweight was significantly lighter in the monochorionic cohort when compared with the dichorionic cohort ($P = .0001$); however, the proportion of SGA infants was similar in both groups ($P = .5$). Birthweight discordance of ≥20% was present in 17.3% of twin pregnancies. There was no significant difference in the frequency of birthweight discordance between monochorionic and dichorionic twin pregnancies; 7.8% of the monochorionic twin pregnancies (n = 13) in this cohort were affected by TTTS.

Overall, 20% of the 1632 individual twins (n = 327) in the study had noncentral cord insertion demonstrated on placental pathologic examination. Rates of marginal and velamentous cord insertion were 15.3% (n = 250) and 4.7%

(n = 77), respectively. When the results were stratified by chorionicity, monochorionic twin pregnancies had significantly higher rates of noncentral cord insertion when compared with dichorionic twin pregnancies (OR, 2.2; 95% CI, 1.7–2.9). The difference was significant for both marginal and velamentous cord insertion sites (Table 2).

Noncentral cord insertion sites were significantly more common in the smaller twins of birthweight-discordant pairs when compared with both their larger cotwins and twins with concordant birthweights ($P = .0025$; Figure 1). Birthweight discordance was associated significantly with both marginal ($P = .03$) and velamentous cord insertion ($P = .003$), when evaluated within the entire cohort.

Within the cohort of 165 monochorionic twin pregnancies, there were 32 cases of significant birthweight discordance (19.4%). Of these, 50% of the smaller twins (n=16) from birthweight-discordant pairs had a noncentral umbilical cord insertion. Velamentous cord insertion was documented in 9.4% of monochorionic twins and was significantly more frequent (21.9%) in smaller twins of birthweight-discordant pairs than in larger cotwins or concordant control infants (9.3% and 7.9%, respectively; $P = .007$; Figure 2).

Of the 165 pairs of monochorionic twins in the study cohort, there were 13 cases of TTTS, which was a rate of 7.8%. There was no difference in the frequency of marginal or velamentous cord insertion in monochorionic twins with TTTS when compared with those without TTTS (Table 3). Marginal cord insertions were found in 19.2% (n = 5) and 22.8% (n = 68) of TTTS and non-TTTS cases, respectively. The frequency of velamentous cord insertion was 7.7% for those with TTTS (n = 2), compared with 9.7% for those without (n = 29). The distribution of noncentral cord insertion sites in those twins with TTTS was equal between donor and recipient twins.

In dichorionic twin pregnancies, there was a trend toward increased rates of noncentral placental cord insertion among smaller twins ($P = .051$). The frequency of marginal cord insertion in smaller twins was 18.3%, compared with 15.6% in larger cotwins, and 12.9% in the cohort with concordant birthweight ($P = .10$). Velamentous cord insertion was observed in 5.5% of smaller birthweight-discordant twins, 2.8% of larger birthweight-discordant twins, and 3.4% of concordant twins ($P = .18$).

The association between noncentral cord insertion and intrauterine growth restriction was evaluated by comparing frequencies of central, marginal, and velamentous cord insertion on those twins who were SGA and those who were appropriate-sized for gestational age (Table 4). Overall 57.9% of SGA monochorionic twins (n = 11) had a noncentral cord insertion site. Statistically higher frequencies of both marginal and velamentous cord insertions were found in SGA monochorionic twins, when compared with ap-

TABLE 2
Placental cord insertion site: relative frequency according to chorionicity

Variable	Monochorionic twins, n (%)	Dichorionic twins, n (%)	*P* value[a]
Central	226 (68.5)	1079 (82.9)	
Noncentral	104 (31.5)	223 (17.1)	< .0001
Marginal	73 (22.1)	177 (13.6)	.0068
Velamentous	31 (9.4)	46 (3.5)	< .0001

[a] χ^2 test.

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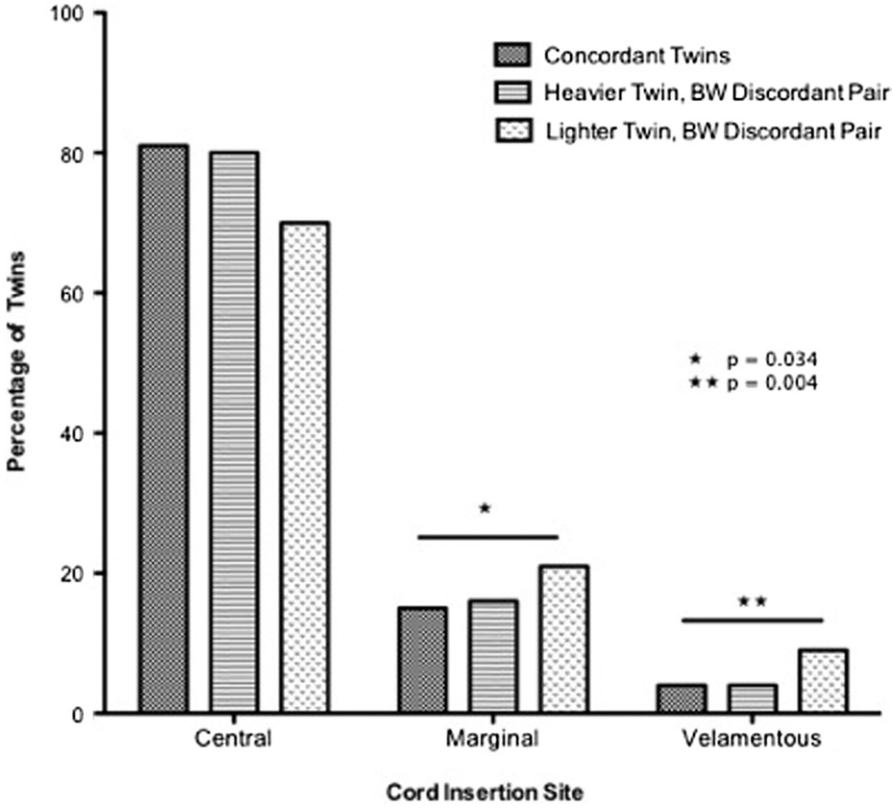
FIGURE 1
Placental cord insertion site of all twins



Birthweight (*BW*)-discordant pairs vs heavier twin, birthweight pairs, and concordant twins.

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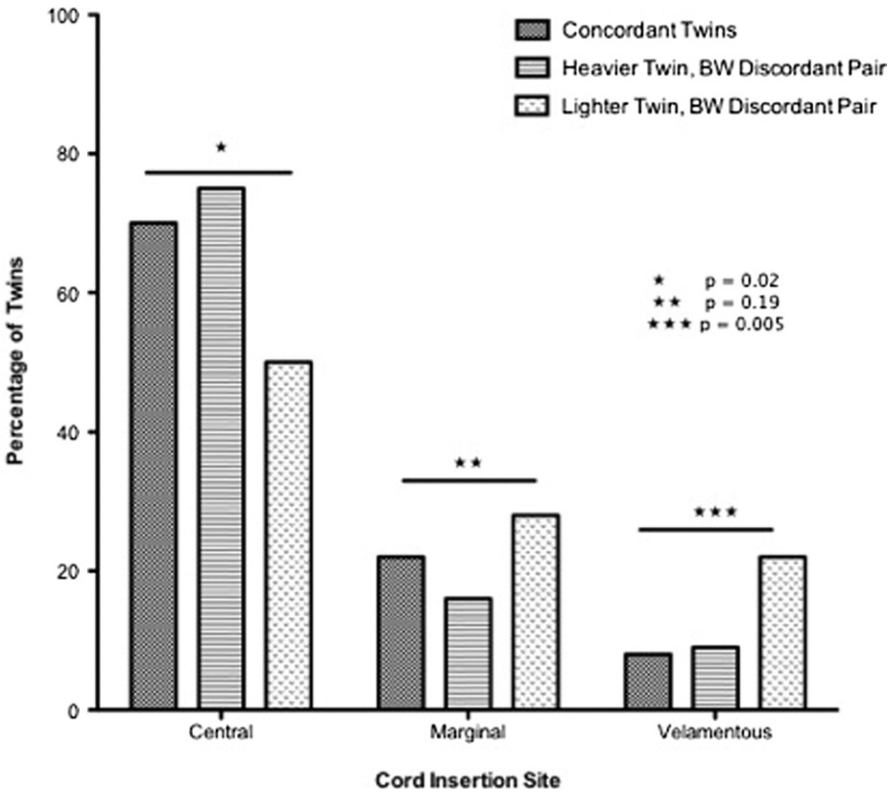
FIGURE 2
Placental cord insertion site of monochorionic twins



Lighter twin, birthweight (*BW*)-discordant pairs vs heavier twin, birthweight-discordant pairs, and concordant twins.

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propriately grown infants. Within the dichorionic cohort, no association was found between cord insertion site and SGA status.

Evaluation of the risk of birthweight discordance for a fetus with noncentral cord insertion gave an overall OR of 1.8 (95% CI, 1.2–2.6). This risk increased with monochorionicity (OR, 2.4; 95% CI, 1.1–5.0) and with the combination of monochorionicity and a velamentous cord insertion (OR, 3.5; 95% CI, 1.3–9.4; Table 5). The OR for birthweight <5th percentile for gestational age in monochorionic twins with a noncentral cord insertion is 3.22 (95% CI, 1.26–8.27). A velamentous cord insertion further increases this OR to 4.03 (95% CI, 1.14–14.3).

Comment

Twin pregnancies pose a unique challenge to obstetric management and are associated with markedly increased rates of perinatal morbidity.[1] This is particularly true of monochorionic twin pregnancies.[16] Growth discordance is associated independently with adverse outcomes,[6] and identification of factors that contribute to growth abnormalities in these pregnancies may improve antenatal risk stratification, with the institution of intense fetal surveillance in high-risk cases.

There are multiple putative mechanisms for discordant growth in twin pregnancies, which differ according to chorionicity. Studies that have evaluated placental factors have suggested that unequal placental sharing and abnormalities of umbilical cord insertion contribute to growth discordance in monochorionic twin pregnancies. An association with noncentral umbilical cord insertion and birthweight discordance in dichorionic twins has been reported less consistently.[13-15,17-19] Most published studies have been retrospective with those prospective studies that selectively have evaluated risk in monochorionic twins only.

In a retrospective analysis of 447 twin pairs, Hanley et al[17] found that velamentous cord insertion did not predict birthweight discordance in dichorionic twins but was associated with a 13-fold increase in risk of discordance among monochorionic twins. Conversely, Victoria et al[18] retrospectively evaluated 382 twin pregnancies with respect to growth discordance and placental disease. *Umbilical cord abnormalities*, which were defined as velamentous cord insertion and single umbilical artery, were compared between concordant, mildly discordant, and severely discordant twin pairs. In both dichorionic and monochorionic pregnancies, umbilical cord abnormalities were significantly more frequent in the smaller twins of severely discordant twin pairs than in mildly discordant or concordant twin pairs.

These retrospective studies that evaluated the impact of cord insertion site are supported by 2 prospective studies in monochorionic twins. De Paepe et al[15] evaluated placental characteristics in 216 monochorionic twins without TTTS. Higher rates of velamentous cord insertion were documented among the 36 discordant pairs in this study. The 22% rate of velamentous cord insertion that was found in birthweight-discordant monochorionic twins in this study was comparable with the rate of velamentous cord insertion in smaller twins of birthweight-discordant pairs in our study. This study also reported significantly increased frequencies of unequal placental sharing in birthweight-discordant twins. This provides a putative explanation for the mechanism of birthweight discordance in the presence of an abnormal placental cord insertion.

Machin[19] evaluated 60 monochorionic placentas and found marginal or velamentous cord insertion to be associated with an increased risk of significant birthweight discordance. The rate of velamentous cord insertion in the cohort studied by Machin was extremely high at 45%. The fact that this is significantly higher than the rates that are found in our study and in other published studies indicates that the study sample may not have

been representative of the general monochorionic twin population. Although the results of the study by Machin support the findings of our study, our study represents an unselected cohort of twins; therefore, our results are applicable to any population of twin pregnancies.

We performed a large, multicenter, prospective study of 861 twin pregnancies (135 monochorionic and 651 dichorionic) and found abnormal placental umbilical cord insertion to be associated significantly with discordant growth. We documented high rates of both marginal and velamentous cord insertions in twin pregnancies. Compared with reported frequencies of noncentral cord insertion in singleton pregnancies,[12] marginal cord insertion was noted approximately twice as often (15.3% vs approximately 7%) in the twin pregnancies; in our study with velamentous cord insertion, it was approximately 5 times more frequent (4.7% vs approximately 1%). The rates of velamentous cord insertion in our study are somewhat lower than the rates that were reported in a large cohort of twin placentas that were evaluated by Sato and Benirschke.[20] In their cohort of 389 monochorionic twins, the rate of velamentous cord insertion was 12%; 7.3% of the 780 dichorionic twins in their study had a velamentous cord insertion. The differences in rates in the 2 studies may be attributable to the fact that, because theirs was a retrospective study, Sato and Benirschke may have had a higher proportion of complicated twin pregnancies, because these placentas are more likely to be retained for pathologic examination.

Overall in our study cohort, the risk of birthweight discordance of ≥20% was 80% higher for twins with a noncentral cord insertion site. This increase was observed both in twins with a marginal cord insertion and twins with a velamentous cord insertion site, although the risk of growth discordance was markedly greater with the latter. The excess of noncentral umbilical cord insertions that were found in the smaller twins of birthweight-discordant twin pairs in our study was driven by the very high rate of velamentous cord insertions in birthweight-discordant monochorionic twins. However, we did not find a similar relationship between umbilical cord insertion and growth discordance in dichorionic twin pregnancies. Similarly, the association between noncentral cord insertion and growth restriction, as defined by birthweight of <5th percentile for gestational age, was observed only in monochorionic twin pregnancies.

The results of this study point to a role for velamentous cord insertion in the cause of growth restriction in monochorionic twin pregnancies. Because there was no difference noted in the relative rates of marginal and velamentous cord insertion in TTTS and non-TTTS monochorionic twin pregnancies, it would appear that this effect is independent of the role of TTTS in birthweight discordance. The study by Sato and Benirschke[20] evaluated the role of fetal vessel thrombi in the cause of growth discordance in monochorionic twin pregnancies. They concluded that thrombi were observed more frequently in placentas with a velamentous cord insertion. The increased risk of fetal vessel thrombi in these cases may be an etiologic factor in the increased rates of birthweight discordance and fetal growth restriction that were observed in monochorionic twins with a velamentous placental cord insertion site. The association between velamentous cord insertion and unequal placental sharing, as studied by De Paepe et al,[15] provides a further possible explanation for the association that we have found between velamentous cord insertion and birthweight discordance.

Several possible limitations to our study are acknowledged. The number of placentas that did not undergo examination raises the possibility that there is an overrepresentation of complicated twin pregnancies in our sample. However, the proportions of monochorionic and dichorionic twin pregnancies and the rates of both birthweight discordance and

TABLE 3
Frequency of noncentral cord insertion in twin-twin transfusion syndrome

Variable	Twin-twin transfusion syndrome, n (%)	No twin-twin transfusion syndrome, n (%)	*P* value[a]
Cases	13	152	
Cord insertion site			
Central	19 (73.1)	207 (68.1)	.76
Marginal	5 (19.2)	68 (22.4)	.9
Velamentous	2 (7.7)	29 (9.5)	.75

[a] Twin-twin transfusion syndrome.

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TABLE 4
Association between cord insertion site and growth restriction

Twins	Appropriate for gestational age, n (%)	Small for gestational age, n (%)	*P* value[a]
Monochorionic			
Marginal	66 (21.2)	7 (36.8)	.03
Velamentous	27 (8.7)	4 (21.1)	.02
Dichorionic			
Marginal	163 (13.4)	14 (15.5)	.54
Velamentous	41 (3.4)	5 (5.5)	.26

[a] χ^2 test.

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TABLE 5
Risk of birthweight discordance and small-for-gestational-age status according to cord insertion site

	Birthweight discordance			Birthweight <5th percentile		
Cord insertion site	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
All twins						
Central[a]	1.0			1.0		
Noncentral	1.8	1.2–2.6	.0025	1.55	0.9–2.4	.04
Marginal	1.6	1.1–2.5	.0344	1.4	0.9–2.3	.18
Velamentous	2.5	1.3–4.6	.0037	2.02	0.9–4.2	.05
Dichorionic twins						
Central[a]	1.0			1.0		
Noncentral	1.6	0.9–2.5	.052	1.3	0.8–2.2	.32
Marginal	1.5	0.9–2.6	.105	1.2	0.6–2.1	.54
Velamentous	1.8	0.7–4.4	.188	1.7	0.6–4.4	.26
Monochorionic twins						
Central[a]	1.0			1.0		
Noncentral	2.4	1.1–5.0	.0179	3.2	1.3–8.3	.01
Marginal	1.8	0.8–4.4	.159	2.9	1.0–8.3	.03
Velamentous	3.5	1.3–9.4	.0077	4.0	1.1–14.3	.02

CI, confidence interval.

[a] Reference value.

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SGA status are comparable, in the cohort of 816 twins reported here, with the entire cohort of 1001 twin pregnancies that completed the ESPRiT study. The fact that all placental examinations were not carried out in a single laboratory is another potential source of bias. However, the nature of the placental examination variable that was studied here (cord insertion site) should limit any potential bias in this regard.

The utility of sonographic assessment in the determination of the cord insertion site has been examined in singleton and twin pregnancies. Di Salvo et al[21] compared prenatal sonographic examination and postnatal histopathologic findings with respect to umbilical cord insertion in 38 singleton and 8 twin pregnancies. Forty-nine of the 54 cord insertion sites were delineated correctly with ultrasound scanning, with an overall sensitivity and specificity of antenatal ultrasound finding of 69% and 100%, respectively. The ability of a combination of gray-scale and color Doppler ultrasound scans to identify velamentous cord insertion was evaluated prospectively by Sepulveda et al[22] in 832 singleton pregnancies. They determined that velamentous cord insertion could be determined reliably with prenatal sonography, with successful visualization of the placental cord insertion site in 99% of cases.

Antenatal surveillance in twin pregnancies aims to identify those pregnancies that are at an increased risk of complications. Although sonographic estimation of fetal weight is known to be a reliable tool in the prediction of birthweight, there is an acknowledged margin of error of up to 20%. Therefore, the addition of other sonographic predictors of birthweight discordance (such as placental umbilical cord insertion site) may be useful in risk stratification and planning of surveillance and management of twin pregnancies.

In summary, this is one of the largest prospective studies to date to evaluate the risk of birthweight discordance that is associated with noncentral cord insertion in monochorionic and dichorionic twin pregnancies. We have found the cord insertion site to be associated with discordant growth and intrauterine growth restriction in monochorionic twin pregnancies. A similar association was not demonstrated in dichorionic twins. Sonographic evaluation of cord insertion site should be considered in the antenatal assessment of twin pregnancies with the finding of a noncentral cord insertion prompting more intensified antenatal fetal surveillance. However, further prospective examination of the accuracy of antenatal ultrasound imaging in this setting is warranted. ■

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