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Chapter 3

Velamentous cord insertion in monochorionic twins with or without twin-twin transfusion syndrome: does it matter?

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ABSTRACT

Objective: To study the association between velamentous cord insertion (VCI) and different outcomes in monozygotic twins with and without twin-twin transfusion syndrome (TTTS).

Methods: We recorded the cord insertion type in all consecutive monozygotic placentas examined in two tertiary medical centers. The association between VCI and several outcomes was estimated.

Results: A total of 630 monozygotic placentas (304 with and 326 without TTTS) were studied. The incidence of VCI in the TTTS and non-TTTS group was 36.8% and 35.9%, respectively ($p=0.886$). The presence of VCI in one twin was significantly associated with lower gestational age (GA) at birth (regression coefficient -1.31 , confidence interval [CI] $-2.07, -0.56$), small for gestational age (SGA) (relative risk [RR] 1.20 , 95% CI $1.04, 1.38$), severe birth weight discordance (RR 2.39 , 95% CI $1.66, 3.45$) and intrauterine fetal demise (IUID) (RR 1.80 , 95% CI $1.26, 2.56$). The prevalence of IUID in monozygotic pregnancies without TTTS increased from 4.6% to 14.1% in the presence of VCI. In the TTTS group, the prevalence of IUID was comparable in the absence or presence of VCI. In a similar way, GA at birth was significantly lower in the presence of VCI only in the non-TTTS group.

Conclusion: Our findings suggest that VCI is not associated with the development of TTTS but increases the risk of adverse outcomes. Both VCI and TTTS independently increase the prevalence of IUID and lower GA at birth in a similar way, showing that VCI is an important indicator of adverse perinatal outcome in monozygotic twins.

Keywords

Monozygotic twins, twin-twin transfusion syndrome, velamentous cord insertion, severe birth weight discordance, intrauterine fetal demise

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a complication of monochorionic twin pregnancies and results from unbalanced inter-twin blood transfusion via placental vascular anastomoses. Although vascular anastomoses are invariably found in almost all monochorionic placentas, only 10% will eventually develop TTTS [1;2]. Differences in angio-architecture, among those the absence of arterio-arterial anastomoses, are one of the major factors involved in the development of TTTS [1-4]. However, angio-architecture alone does not fully explain the pathophysiology of TTTS [1-4]. Several other hypotheses on the pathophysiology of TTTS have been proposed, including utero-placental insufficiency and paradoxical activation of fetal vasoactive and humoral factors [3;4].

Several authors found higher incidence of velamentous cord insertions (VCI) in TTTS placentas and hypothesized that VCI may lead to utero-placental insufficiency, subsequently establishing a vicious cycle resulting in the development of TTTS [5-8]. However, these hypotheses were mostly unsubstantiated or based on small studies [5-8]. Moreover, several recent reports show that the incidence of velamentous or marginal cord insertion is similar in monochorionic twins with and without TTTS [9-11]

The objective of this study was to estimate the incidence of VCI in a large group of monochorionic twins with and without TTTS and study outcomes associated with VCI.

MATERIAL AND METHODS

All consecutive placentas of monochorionic twin pregnancies examined at the University Medical Center of Porto (Portugal) and Leiden (The Netherlands) between June 2002 and September 2012 were included in this study. Monochorionicity was confirmed after delivery by gross examination of the dividing membrane and/or histopathological examination of the placenta and the dividing membrane. Placentas were divided in a group with TTTS and a group without TTTS. TTTS was diagnosed using standard antenatal ultrasound criteria [12]. Both University hospitals are tertiary medical centers for perinatal medicine. The Leiden University Medical Center is the national referral center for fetal therapy in the Netherlands, including laser treatment for TTTS. Most TTTS cases referred to Leiden were therefore treated with laser.

Part of the placentas (n=139) included in this study were already presented in a previous report [11].

During prenatal ultrasound in TTTS twin pairs, great care was taken to define which fetus, donor or recipient, would be born first. At delivery, umbilical cords were labeled to identify the first and second-born twin. The type of abnormal umbilical cord insertion, velamentous or marginal insertion (within 1 cm of placental margin), was recorded.

We studied the association of VCI with several outcomes, including gestational age (GA) at birth, small for gestational age (SGA), severe birth weight discordance (BWD) (> 25%), intrauterine fetal demise (IUFD) and neonatal mortality. In the TTTS group we analyzed the association of VCI with Quintero stage. The BW discordance (in %) was calculated as $BW = [(BW \text{ larger fetus} - BW \text{ smaller fetus})/BW \text{ larger fetus}] \times 100\%$. SGA was defined as a birth weight less than 10th percentile.

We excluded monochorionic twin pregnancies with twin anemia-polycythemia sequence, twin reversed arterial perfusion, monoamniotic twins and higher multiple pregnancies. Placentas with IUFD were excluded when placental maceration prohibited accurate evaluation of type of umbilical cord insertion and placental sharing.

The fetal level data was aggregated by pair of twins, counting the number of fetuses in the pair with an outcome (SGA, IUFD, Neonatal Mortality) or exposure (VCI).

Crude and adjusted relative risks (RR) and respective 95% confidence intervals (CI) were estimated by binomial generalized linear models with log link function and Bernoulli generalized linear models with log link function for the fetal and pair level dichotomous outcome variables, respectively.

Regression coefficients and proportional odds ratio and 95% CI were estimated by linear regression and ordinal regression for the pair level continuous (GA at birth) and ordinal variable (Quintero stage), respectively.

The interaction between TTTS and VCI with different outcomes was studied. The number of fetuses with several outcomes (SGA, IUFD, Neonatal Mortality) or exposure (VCI) was aggregated (0 versus 1 or 2 twins).

$P < 0.05$ was considered to indicate statistical significance.

Statistical analyses were performed using the software R 2.12.1 and SPSS for Windows version 17.0 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

A total of 630 consecutive monochorionic diamniotic placentas were examined at our two centers and included in this study (monochorionic placentas with TTTS, $n=304$ and monochorionic placentas without TTTS, $n=326$).

The data required for this study could not be recorded completely for 67 placentas (38 in the TTTS-group and 29 in the non-TTTS group) because of placental maceration caused by intrauterine fetal demise ($n=12$ in TTTS group and $n=3$ in no-TTTS group) and loss or destruction of the placenta after delivery ($n=26$ in the TTTS-group and $n=26$ in the no-TTTS group). These 67 cases were excluded from further analysis.

Mean gestational age at birth in the TTTS group and non-TTTS group was 30 weeks (range: 15 to 38 weeks) and 33 weeks (range: 16 to 38 weeks) respectively. The mono-

chorionic pregnancies with TTTS were treated with fetoscopic laser coagulation (n=258), amniodrainage (n=24) or without intrauterine intervention (n=23). Baseline characteristics in both groups are presented in Table 1.

Table 1. Baseline characteristics in the 630 monochorionic diamniotic pregnancies

	non-TTTS group	TTTS group	P
	N (%)	N (%)	
	326 (51.7)	304 (43.3)	
Fetal level variable			
SGA (yes)			
0 twins	130 (41.1)	107 (38.8)	0.470
1 twin	121 (38.3)	119 (43.1)	
both twins	65 (20.6)	50 (18.1)	
IUFD (yes)			
0 twins	297 (91.7)	256 (84.5)	0.020
1 twin	10 (3.1)	16 (5.3)	
both twins	17 (5.2)	31 (10.2)	
Neonatal Mortality (yes)¹			
0 twins	281 (97.2)	232 (90.6)	0.003
1 twin	7 (2.4)	18 (7.0)	
both twins	1 (0.3)	6 (2.3)	
Pair level variable			
BW discordance			
<25%	237 (76.7)	127 (82.5)	0.191
>=25%	72 (23.3)	27 (17.5)	
GA at birth (weeks)	33.5 (3.9)	30.8 (4.8)	<0.001
Center			
Netherlands	241 (73.9)	285 (93.8)	<0.001
Portugal	85 (26.1)	19 (6.2)	
Quintero stage			
1	Not applicable	49 (16.2)	---
2		97 (32.0)	
3		138 (45.5)	
4		16 (5.3)	
5		3 (1.0)	

TTTS, twin-twin transfusion syndrome; SGA, small for gestational age; IUFD, intrauterine fetal demise; BW, birth weight; GA gestational age.

¹Analysis only for the pair of twins who did not have IUFD

The incidence of VCI per twin pair (one/ both fetuses) in the TTTS group and non-TTTS group was 36.8% (112/304)/ 3.9% (12/304) and 35.9% (117/326)/ 3.4% (11/326), respectively (p=0.886). Further details on the type of umbilical cord insertion in both

groups are presented in Table 2. Two examples of monochorionic placentas with VCI are shown in figure 1 and 2 (pictures are taken after colored dye injection).

Table 2. Type of umbilical cord insertion in monochorionic pregnancies with and without Twin-twin transfusion syndrome

	non-TTTS group	TTTS group	P
	N (%)	N (%)	
	326 (51.7)	304 (43.3)	
Fetal level variable			
Velamentous cord insertion			
0 twins	198 (60.7)	180 (59.2)	0.886
1 twin	117 (35.9)	112 (36.8)	
both twins	11 (3.4)	12 (3.9)	
Marginal cord insertion			
0 twins	203 (62.3)	178 (58.6)	0.584
1 twin	94 (28.8)	99 (32.6)	
both twins	29 (8.9)	27 (8.9)	
Velamentous or marginal cord insertion			
0 twins	97 (29.8)	81 (26.6)	0.661
1 twin	171 (52.5)	169 (55.6)	
both twins	58 (17.8)	54 (17.8)	

TTTS, twin-twin transfusion syndrome



Figure 1: Monochorionic placenta with twin-twin transfusion syndrome (Quintero stage 2) treated with fetoscopic laser coagulation at 16 weeks gestational age. IUFD of ex-donor at 32 weeks. Ex-recipient twin delivered at 33 weeks.

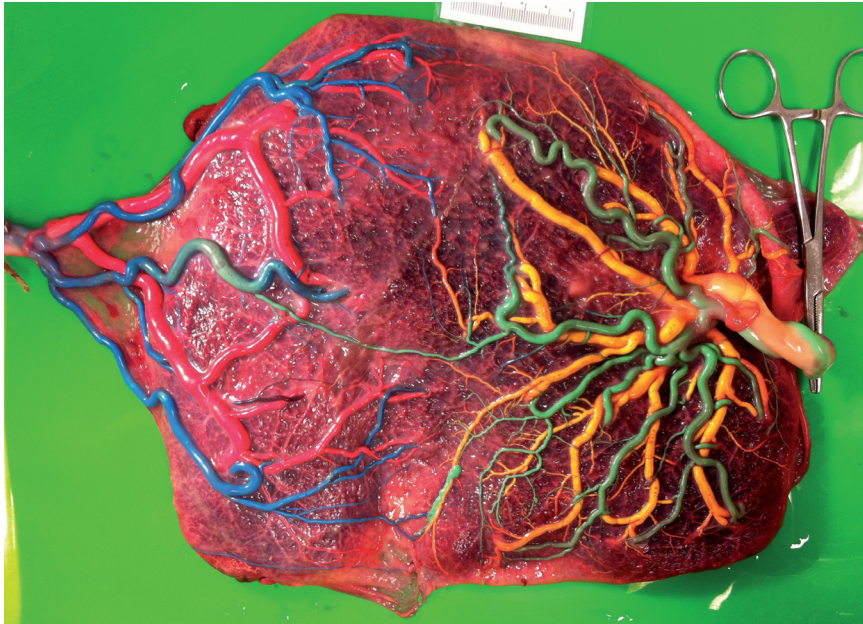


Figure 2: Monochorionic placenta with selective intrauterine growth restriction, delivered at 36 weeks gestation. Twin 1 delivered with 2040gr (placenta share on left side), twin 2 delivered with 2800gr.

Risk factor analysis showed that the presence of VCI in one twin was significantly associated with lower GA at birth (regression coefficient -1.46, CI -2.21, -0.07), SGA (RR 1.16 95% confidence interval [CI] 1.01, 1.34), severe BWD (RR 3.14 95% CI 1.97, 5.02) and IUFD (RR 1.76 95% CI 1.24, 2.94). We found no association between the presence of VCI and neonatal mortality (RR 1.25 95% CI 0.66, 2.34) or higher Quintero stage (proportional OR 1.02 95% CI 0.65, 1.58). The presence of VCI in both twins revealed a significant association with lower GA at birth (regression coefficient -2.24 CI -4.15, -0.32) and IUFD (RR 2.37 95% CI 1.10, 4.37), but not with SGA (RR 1.10 95% CI 0.74, 1.52) severe BWD (RR 2.60 95% CI 0.87, 7.77), neonatal mortality (RR 0.80 95% CI 0.04, 3.62) and higher Quintero stage (proportional OR 0.78 95% CI 0.27, 2.33). These associations continue to occur after adjustment for Center. Results of univariate and multivariate risk analysis are presented in Table 3.

Our results also showed significant interaction between TTTS and VCI when we considered IUFD and GA at birth. The prevalence of IUFD (in at least one twin) in monochorionic pregnancies without TTTS increased from 4.6% to 14.1% in the presence of VCI. In the TTTS group, the prevalence of IUFD was comparable in the absence or presence of VCI (15.1% and 16.1%, respectively). The GA at birth was similar in the non-TTTS group with VCI and the TTTS without VCI (32 and 31 weeks, respectively) compared with 34 weeks for the non-TTTS group without VCI. For this outcome as well, the GA at birth significantly lowers in the presence of VCI but only in the non-TTTS group (Table 4).

Table 3. Association between Velamentous cord insertion and several outcomes

OUTCOME	Crude RR (95%CI)	Adjusted RR (95%CI) ¹
SGA		
0 twins with VCI	Ref	Ref
1 twin with VCI	1.16 (1.01, 1.34)	1.20 (1.04, 1.38)
both twins with VCI	1.10 (0.74, 1.52)	1.20 (0.80, 1.61)
Severe BWD		
0 twins with VCI	Ref	Ref
1 twin with VCI	3.14 (1.97, 5.02)	2.39 (1.66, 3.45)
both twins with VCI	2.60 (0.87, 7.77)	2.06 (0.93, 4.59)
IUFD		
0 twins with VCI	Ref	Ref
1 twin with VCI	1.76 (1.24, 2.94)	1.80 (1.26, 2.56)
both twins with VCI	2.37 (1.10, 4.37)	2.46 (1.14, 4.56)
Neonatal Mortality²		
0 twins with VCI	Ref	Ref
1 twin with VCI	1.25 (0.66, 2.34)	1.20 (0.63, 2.25)
both twins with VCI	0.80 (0.04, 3.62)	0.74 (0.04, 3.40)
	Crude regression Coefficient (95%CI)	Adjusted regression Coefficient (95%CI) *
GA at birth (weeks)		
0 twins with VCI	Ref	Ref
1 twin with VCI	-1.46 (-2.21, -0.07)	-1.31 (-2.07, -0.56)
both twins with VCI	-2.24 (-4.15, -0.32)	-2.00 (-3.92, -0.09)
	Proportional Odds Ratio (95%CI)	Proportional Odds Ratio (95%CI)
Quintero stage³		
0 twins with VCI	Ref	Ref
1 twin with VCI	1.02 (0.65, 1.58)	0.94 (0.60, 1.46)
both twins with VCI	0.78 (0.27, 2.33)	0.68 (0.23, 2.06)

RR, relative risk; VCI, velamentous cord insertion; SGA, small for gestational age; BWD, birth weight discordance; IUFD, intrauterine fetal demise; GA gestational age.

¹Adjusted for Center

²Analysis only for the pair of twins who did not have IUFD

³Analysis only for the pair of twins who did have TTTS

Table 4. Interaction between Twin-twin transfusion syndrome and Velamentous cord insertion to Intrauterine fetal demise and Gestational age at birth (weeks)

IUID	non-TTTS group		TTTS group		P for Interaction
	0 twins N (%)	at least 1 twin N (%)	0 twins N (%)	at least 1 twin N (%)	
With VCI					
0 twins	187 (95.4)	9 (4.6)	152 (84.9)	27 (15.1)	0.027
1/both twins	110 (85.9)	18 (14.1)	104 (83.9)	20 (16.1)	
GA at birth (weeks)	non-TTTS group		TTTS group		P for Interaction
	mean (SD)		mean (SD)		
With VCI					
0 twins	34.4 (2.8)		31.0 (4.7)		0.014
1/both twins	32.1 (4.9)		30.4 (5.6)		

TTTS, twin-twin transfusion syndrome; IUID, intrauterine fetal demise; VCI, velamentous cord insertion; GA gestational age.

DISCUSSION

This is the largest study reporting on the difference in velamentous cord insertion and discordant placental share between monochorionic twin placentas with and without TTTS. We found that the rate VCI in monochorionic placentas with and without TTTS was almost identical. Our findings refute a possible causative relationship between VCI and the development of TTTS.

VCI are rare in singleton placentas (2%) and far more common in dichorionic (7%) and particularly in monochorionic twin placentas (12%) [13]. The high incidence of VCI in monochorionic twin placentas is thought to result from a “battle” for space between each twin’s placental shares, a competition process also called trophotropism [14-16]. VCI are associated with smaller placental mass and lower birth weights [14;15;17;18].

In monochorionic twinning, VCI have also been related to the development of TTTS. In a study of 38 monochorionic placentas, Fries *et al* [5] reported a significantly higher prevalence of VCI in TTTS placentas than in non-TTTS placentas, respectively 32% (7/22) and 9% (5/54) ($p < 0.01$). In view of this finding, Fries *et al* proposed an etiologic role for VCI in the development of TTTS [5]. As a VCI can be easily compressed, Fries *et al* suggested that TTTS could result from hemodynamic instability due to reduced blood flow to the donor twin with a VCI. However, the number of placentas studied was small. Moreover, 3 of the 38 (8%) monochorionic pregnancies were monoamniotic. This probably represents a selection bias, as placental angio-architecture, type of umbilical cord insertion and incidence of TTTS are known to be different in monoamniotic and diamniotic monochorionic pregnancies [19]. In a study of 60 monochorionic placentas, Machin [6]

reported that roughly 30% of twins with velamentous or marginal cord insertion have TTTS, whereas only 6% (1/17) of twins without velamentous or marginal cord insertion develop TTTS. However, exact data on the number of placentas with TTTS was not mentioned. Contrarily, in a study of 58 monochorionic twin pregnancies, Bajoria reports similar frequencies of VCI in TTTS and non-TTTS twins (16% and 19% respectively) [10]. In a recent study of 89 consecutive monochorionic placentas, De Paepe *et al* also found a similar prevalence of velamentous or marginal cord insertion in TTTS and non-TTTS placentas (37% and 36% respectively) [9]. In another (unpublished) series of 90 monochorionic placentas, Taylor *et al* also found equally high incidence VCI in TTTS and non-TTTS placentas (53% and 52% respectively) [20]. In a study of 139 placentas, Lopriore *et al* also reported a similar incidence of VCI in the groups with and without TTTS (13% versus 14%, respectively) [11]. The wide range of reported incidence of VCI in the various studies is remarkable, ranging from 6% to 53%. There are several reasons that could explain the discrepancy in results, such as different ways of counting and reporting the data (VCI per pair or per fetus), subjectivity in defining VCI and small number of placentas included in some studies.

From the risk factor analysis, we found four outcomes to be associated with the presence of VCI in one twin, including lower GA at birth, SGA, severe BWD and IUFD. These associations continue to occur after adjustment for Center. We failed to find a correlation between the presence of VCI and neonatal mortality or higher Quintero stage.

In our study, the presence of VCI in one twin is significantly associated with SGA and severe BWD. This study is in agreement with previous studies showing that VCI are associated with smaller birth weights and severe BWD [6;14;15;18]. Up to 21% of monochorionic twin pregnancies are complicated by severe BWD even in the absence of TTTS (selective intrauterine growth restriction, sIUGR) [21]. While its pathogenesis remains incompletely understood the development of sIUGR is generally attributed to aberrant placental characteristics. The higher frequency of peripheral cord insertion and uneven placental sharing has been well documented [6;18;22]. These findings are in accordance with previous reports. However, our results show that the presence of VCI in both twins is not associated with severe BWD which seems easy to understand, but, surprisingly, the presence of VCI in both twins is not significantly associated with SGA status as well. To our knowledge, this is the first study which differentiates the presence of VCI in one and both fetuses during the analysis of different outcomes. More studies are necessary to understand these differences.

In this study we also found that the presence of VCI was significantly associated with increased IUFD. Perinatal mortality and morbidity is higher in monochorionic twin pregnancies than in dichorionic twin pregnancies [23]. The higher mortality in MC twins is attributed to the effects of placental morphologic characteristics. Placental vascular anastomoses, unequal placental sharing and abnormalities in umbilical cord insertions

are associated with fetal growth and BWD, the latter being a major contributor to unfavorable perinatal outcome in MC twins [18]. Placental cord insertion has been reported as an indicator for adverse perinatal outcome. [5;6;24] Our findings are in agreement with previous reports. However, in this study, the prevalence of IUFD increases in the presence of VCI, but only in the non-TTTS group. Our results showed a significant interaction between TTTS and VCI for IUFD. The prevalence of IUFD (in at least one twin) in monochorionic pregnancies without TTTS increased from 4.6% to 14.1% in the presence of VCI (in one or both twins). In the TTTS group, the prevalence of IUFD was comparable in the absence or presence of VCI (15.1% and 16.1%, respectively). In a similar way, the GA at birth significantly lowers in the presence of VCI but only in the non-TTTS group.

Antenatal surveillance in monochorionic twins aims to identify those pregnancies that are at an increased risk of complications. Therefore, the knowledge and addition of ultrasound predictors of adverse outcome (such as VCI) may be useful in risk stratification and management of twin pregnancies.

The value of ultrasound assessment in the determination of the umbilical cord insertion in first trimester has been examined in singleton and twin pregnancies. Di Salvo et al [25] compared prenatal ultrasound examination and postnatal histopathologic findings with respect to umbilical cord insertion with an overall sensitivity and specificity of 69% and 100%, respectively. In a prospective study, Sepulveda et al [26] determined that VCI could be determined reliably with prenatal ultrasound in 99% of cases.

Several possible limitations to our study are acknowledged. The number of placentas that did not undergo examination because of placental maceration caused by IUFD raises the possibility of selection bias. More studies are necessary to clarify this issue. In a future research perspective, a prospective study using ultrasound in the determination of the umbilical cord insertion at first trimester would be useful in the determination of the incidence of VCI in monochorionic twins with and without TTTS. 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 (umbilical cord insertion) should limit any potential bias in this regard.

In conclusion, our findings show that the frequency of VCI is similar in TTTS and non-TTTS monochorionic twins, challenging the notion of a causative relationship with the development of TTTS. However, in this study, VCI increases the risk of several adverse outcomes, such as SGA status, severe BWD, IUFD and lower GA at birth. We also found that both VCI and TTTS independently increase the prevalence of IUFD and lower GA at birth in a similar way, showing that VCI is an important indicator of adverse perinatal outcome in monochorionic twins. This point underscores the need for first trimester prenatal detection of VCI and increased surveillance in these twins, even in the absence of TTTS.

REFERENCE LIST

- [1] Huber A, Hecher K. How can we diagnose and manage twin-twin transfusion syndrome? *Best Pract Res Clin Obstet Gynaecol* 2004;18:543-56.
- [2] Lewi L, Van Schoubroeck D, Gratacos E, Witters I, Timmerman D, Deprest J. Monoamniotic diamniotic twins: complications and management options. *Curr Opin Obstet Gynecol* 2003;15:177-94.
- [3] Lopriore E, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Twin-to-twin transfusion syndrome: from placental anastomoses to long-term neurodevelopmental outcome. *Curr Pediatr Rev* 2005;1:191-203.
- [4] Galea P, Jain V, Fisk NM. Insights into the pathophysiology of twin-twin transfusion syndrome. *Prenat Diagn* 2005;25:777-85.
- [5] Fries MH, Goldstein RB, Kilpatrick SJ, Golbus MS, Callen PW, Filly RA. The role of velamentous cord insertion in the etiology of twin-twin transfusion syndrome. *Obstet Gynecol* 1993;81:569-74.
- [6] Machin GA. Velamentous cord insertion in monoamniotic twin gestation. An added risk factor. *J Reprod Med* 1997;42:785-89.
- [7] Saunders NJ, Snijders RJ, Nicolaides KH. Therapeutic amniocentesis in twin-twin transfusion syndrome appearing in the second trimester of pregnancy. *Am J Obstet Gynecol* 1992;166:820-24.
- [8] Bruner JP, Anderson TL, Rosemond RL. Placental pathophysiology of the twin oligohydramnios-polyhydramnios sequence and the twin-twin transfusion syndrome. *Placenta* 1998;19:81-6.
- [9] De Paepe ME, DeKoninck P, Friedman RM. Vascular distribution patterns in monoamniotic twin placentas. *Placenta* 2005;26:471-75.
- [10] Bajoria R. Vascular anatomy of monoamniotic placenta in relation to discordant growth and amniotic fluid volume. *Hum Reprod* 1998;13:2933-40.
- [11] Lopriore E, Sueters M, Middeldorp M, et al. Velamentous cord insertion and unequal placental territories in monoamniotic twins with and without twin-to-twin-transfusion syndrome. *Am J Obstet Gynecol* 2007;196:159.e1-159.e5.
- [12] Wittmann BK, Baldwin VJ, Nichol B. Antenatal diagnosis of twin transfusion syndrome by ultrasound. *Obstet Gynecol* 1981;58:123-27.
- [13] Sato Y, Benirschke K. Increased prevalence of fetal thrombi in monoamniotic-twin placentas. *Pediatrics* 2006;117:e113-e117.
- [14] Loos RJ, Derom C, Derom R, Vlietinck R. Birthweight in liveborn twins: the influence of the umbilical cord insertion and fusion of placentas. *BJOG* 2001;108:943-48.
- [15] Benirschke K, Masliah E. The placenta in multiple pregnancy: outstanding issues. *Reprod Fertil Dev* 2001;13:615-22.
- [16] Machin GA. Why is it important to diagnose chorionicity and how do we do it? *Best Pract Res Clin Obstet Gynaecol* 2004;18:515-30.
- [17] Victoria A, Mora G, Arias F. Perinatal outcome, placental pathology, and severity of discordance in monoamniotic and dichorionic twins. *Obstet Gynecol* 2001;97:310-15.
- [18] Hanley ML, Ananth CV, Shen-Schwarz S, Smulian JC, Lai YL, Vintzileos AM. Placental cord insertion and birth weight discordancy in twin gestations. *Obstet Gynecol* 2002;99:477-82.
- [19] Umur A, van Gemert MJ, Nikkels PG. Monoamniotic-versus diamniotic-monoamniotic twin placentas: anastomoses and twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2003;189:1325-29.
- [20] Jain V, Fisk NM. The twin-twin transfusion syndrome. *Clin Obstet Gynecol* 2004;47:181-202.
- [21] Ortibus E, Lopriore E, Deprest J, et al. The pregnancy and long-term neurodevelopmental outcome of monoamniotic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. *Am J Obstet Gynecol* 2009;200:494.e1-494.e8
- [22] De Paepe ME, Shapiro S, Young L, Luks FI. Placental characteristics of selective birth weight discordance in diamniotic-monoamniotic twin gestations. *Placenta* 2010;31:380-6

- [23] Hack KE, Derks JB. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. *BJOG* 2008;115: 58–67
- [24] Hack KE, Nikkels PG, Koopman-Esseboom C, Derks JB, Elias SG, Van Gemert MJ, Visser GH. Placental characteristics of monochorionic diamniotic twin pregnancies in relation to perinatal outcome. *Placenta* 2008;29:976–81
- [25] Di Salvo DN, Benson SB, Laing FS, Brown DL, Frates MC, Doubilet PM. Sonographic evaluation of the placental cord insertion site. *AJR Am J Roentgenol* 1998;170:1295-8
- [26] Sepulveda W, Rojas I, Robert JA, Schnapp C, Alcalde JL. Prenatal detection of velamentous insertion of the umbilical cord: a prospective color Doppler ultrasound study. *Ultrasound Obstet Gynecol* 2003;21:564–9

