

Placental characteristics and complications in monochorionic twin pregnancies

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Chapter 4

Monochorionic placentas with proximate umbilical cord insertions: definition,

prevalence and angio-architecture

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Abstract

Introduction: Not much is known on the occurrence and characteristics of proximate umbilical cord insertions (PCI) in monochorionic (MC) placentas. In addition, a clear definition for PCI is lacking. The purpose of this study was to establish a reference range for the distance between cord insertions and to evaluate the prevalence and angio-architecture of MC placentas with PCI.

Methods: All MC placentas consecutively examined at our center from 2002 to 2014 were included in this study. We excluded MC placentas treated with fetoscopic surgery. The reference range of distance between cord insertions was created using the standard methodology proposed by Royston and Wright. We defined PCI as a cord insertion distance below the 5th centile.

Results and Discussion: A total of 369 MC placentas were analyzed during this study period. The 5th centile was calculated by the equation : 0.027 × gestational age (weeks) +2.91 (cm), and ranged from 3.3 to 4 cm throughout gestation. Accordingly, 18 of the 369 (5%) MC placentas fulfilled the definition criteria for PCI. PCI occurred frequently in MC monoamniotic placentas (53%, 9/17) but were rare in MC diamniotic placentas (3%, 9/352). The prevalence of arterio-arterial (AA) and veno-venous (VV) anastomoses in MC placentas with and without PCI was respectively 100% (18/18) versus 80% (281/351) (P=.12) and 56% (10/18) versus 26% (91/351) (P=.01). The proximity of umbilical cord insertions and its characteristic presence of superficial anastomoses may be a representative of the later splitting of inner cell mass in MC amniotic twins.

Conclusion: The threshold for PCI (5th centile) is approximately 4 cm throughout gestation. PCI are rare in MC diamniotic placentas, but are quite common in MC monoamniotic placentas. MC placentas with PCI are characterized by higher rates of superficial AA and/or VV anastomoses.

Keywords: Monochorionic twins, proximate cord insertions, twin-twin transfusion syndrome,

twin anemia-polycythemia sequence, growth discordance, monoamniotic.

Introduction

Several studies reported a correlation between abnormal cord insertion and adverse perinatal outcome in monochorionic (MC) twin pregnancies [1-4]. Most literature on abnormal cord insertions focuses on the presence and consequences of velamentous or marginal cord insertion. Another special type of abnormal umbilical cord insertion in MC twins, so called proximate cord insertions (PCI), occurs when the cord insertions are very near to each other [5-7]. Recent studies show that in twin-twin transfusion syndrome (TTTS) cases treated with fetoscopic laser coagulation, PCI may lead to difficulty in identifying the inter-twin vascular equator and subsequent treatment failure [8-10]. Not much is known on the occurrence and characteristics of PCI in other subgroups of MC twin pregnancies. The prevalence and characteristics of MC placentas with PCI among various subgroups of MC twins remain to be elucidated. In addition, the current definitions used for PCI are based on arbitrary assumptions and not derived from scientific analysis.

The primary aim of our study was to establish a reference range for the distance between cord insertions based on the analysis of a large cohort of MC placentas. In addition we aimed to evaluate the prevalence of PCI in different subgroups of MC twins and compare the placental angio-architecture in MC placentas with and without PCI.

Materials and methods

All consecutive MC placentas examined at the Leiden University Medical Center from July 2002 to October 2014 were included in this study. MC pregnancies managed with fetoscopic surgery (either laser ablation of vascular anastomoses or selective feticide) were excluded due to iatrogenic destruction of placental angio-architecture. We also excluded placentas due to damage caused by manual placental removal, fixation in formalin or when the insertion site of umbilical cord was damaged preventing accurate measurements and evaluation of placental angio-architecture. We divided the MC placentas into 5 subgroups including: 1.) normal MC; 2.) TTTS treated conservatively with amnioreduction or expectant management; 3.) spontaneous twin anemia-polycythemia sequence (TAPS); 4.) growth discordance and 5.) monoamniotic (MA). Normal MC twin pregnancies were defined as uneventful MC twin pregnancies. Diagnosis of TTTS was based on the internationally accepted criteria: polyhydramnios (deepest vertical pocket \geq 8cm before 20 weeks of gestation or \geq 10cm after 20 weeks of gestation) in the recipient and oligohydramnios (deepest vertical pocket \leq 2cm) in the donor [11]. Diagnosis of spontaneous TAPS was based of prenatal criteria depending on Doppler ultrasound measurements or postnatal criteria using hematological tests as previously reported [12]. Growth discordance was defined as inter-twin birth-weight discordance \geq 25%.

MC placentas were examined and routinely injected using colored dye according to a protocol described before [13]. Pictures of the injected placenta were then taken using a high-resolution digital camera and a measuring-tape was placed on the placenta to allow various measurements on the digital picture. Examination, classification and injection was performed by 2 of the authors (D.Z., E.L.).

After placental injection, distance between both cord insertions was measured. We defined PCI as a cord insertion distance below the 5th centile. We also measured the ratio between insertion distance and placental diameter by dividing the longest placental diameter by the distance between cord insertions. We recorded the type of umbilical cord insertion as (para-) central, marginal or velamentous. Velamentous cord insertion was defined as a cord directly inserted into the amniotic membrane instead of placental parenchyma and marginal cord insertion was defined as a cord insertion site within 1 cm of the plate edge. We

recorded the number and type of anastomoses. Arterio-arterial (AA) and veno-venous (VV) anastomoses were classified as superficial anastomoses and arterio-venous (AV) anastomoses were classified as deep anastomoses. All measurements were performed using Image J 1.45s (Image J, National Institute of Health, USA). Part of the placental data was included in previous studies to map the localization of vascular anastomoses on placental plate surface and compare the placental characteristics between different forms of TAPS [14, 15].

Information on perinatal outcome was documented for each case in a dedicated database, including gestational age at birth, birth weight and perinatal death (either fetal demise or neonatal death).

The primary aim of our study was to estimate the cut-off value for PCI against gestational age. We also compared the prevalence of PCI in various subgroups of MC twins and studied the characteristics of MC placentas with and without PCI.

Statistics

The gestational age-specific reference range of distance between cord insertions was generated according the standard methodology described by Royston and Wright [16]. Briefly, polynomial least-squares regression was applied to estimate the mean curve of distance between cord insertions in function of gestational age at birth and to calculated scaled absolute residuals. The standard deviation (SD) curve was estimated by the polynomial least-squares regression of the scaled absolute residuals. A centile curve was calculated using the formula: centile = mean + $K \times$ SD (K is the corresponding centile of the normal distribution). Independent-samples t test or Mann-Whitney U test was adapted to compare continuous variables. Chi-square or Fisher's exact test was used to analyze categorical variables, where appropriate. A P value <.05 was considered to show the

statistical significance. SPSS Statistics v20.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Results

A total of 405 MC placentas not treated with fetoscopic laser surgery were delivered or shipped to our center for examination during this study period. Thirty-six (9%) cases could not be injected due to damage of cord insertion site (n=16), severely damaged placentas (n=10), placentas fixed in formalin (n=6), severe maceration (n=2) and TRAP (n=2). The remaining 369 (91%) placentas were injected and analyzed, including 197 (53%) normal MC, 48 (13%) TTTS treated with amnioreduction or managed expectantly, 26 (7%) spontaneous TAPS, 81 (22%) growth discordance and 17 (5%) MA. A detailed flowchart to illustrate the inclusion and exclusion of MC placentas is shown in Figure 1.

In the TTTS group, 44% (21/48) were stage 1, 27% (13/48) were stage 2, 23% (11/48) were stage 3 and 6% (3/48) were stage 4. Half of the TTTS cases (n=24) were treated with amnioreduction, while the other half were managed expectantly. Baseline characteristics of these 5 subgroups are summarized in Table 1. The distances between the cord insertions ranged from 0 to 34 cm.

Table 1 Baseline ch	iaracteristics in	the various su	ubgroups of M	C placentas					
	Nor	mal MC	TTTS		TAPS	sIUG	R	MA gi	dno.
	u)	i=197)	(n=48))	n=26)	(n=8	1)	(n=1	[7]
GA at birth – week	a 35.3 (;	32.3-36.4)	29.6 (27.6-35	3.5) 33.2 ((31.0-35.0)	33.9 (29.8	8-35.8)	32.0 (29.	0-33.7)
BW – gram ^a	2250 (1	1701-2650)	1448 (1128-2)	021) 1820 (1434-2134)	1561 (101	5-2135)	1720 (108	8-2070)
BWD - % ^a	9.7 (4.4-15.3)	15.8 (8.1-24	.3) 19.5	(9.6-29.6)	31.7 (27.8	8-38.3)	5.6 (2.0	-20.6)
Cesarean - n (%)	2	4 (28)	22 (46)	1	11 (42)	49 (6	1)	14 (8	82) ^b
Table 1 ^ª Denotes media Table 2 Characteris	in (IQR). ^b Three ca tics of various 1.	ises were manag types of MC p	ed with vaginal d	elivery due to fe	stal demise in or	ne twin			
	Normal MC	TTTS	TAPS	sIUGR	MA	P_1	P_2	P ₃	P_4
	(n=197)	(n=48)	(n=26)	(n=81)	(n=17)	Value	Value	Value	Value
PCI n (%)	7 (4)	0	0	2 (2)	9 (53)	.37	.62	.62	<.01
Distance– (cm) ^a	17 (13-21)	18 (14-21)	18(13-24)	15 (11-19)	3 (1-6)	.40	.23	<.01	<.01
Ratio– % ^a	63 (49-76)	70 (61-80)	69(59-81)	61 (50-71)	22 (9-31)	.02	<.05	.84	<.01
VCI– n (%) ^b	84 (21)	29 (30)	6 (12)	58 (36)	1 (3)	90.	.14	<.01	.01
Table 2 ^a Denotes media	n (IQR). ^b Refers tc	o the type of cor	d insertion per fe	tus. PCI: Proxima	ate cord insertic	ons Distance:	Distance be	tween cord i	nsertions.

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Figure 1 Flow chart showing the derivation of the studied cohort.



Figure 2 Scatter plot of distance between cord insertions across gestation and estimated reference range with curves of various centiles.

The reference range for distance between cord insertions across gestation between 16^{+0} to 38^{+6} weeks was estimated by the equation: Distance (cm) = 0.290 × gestational age (GA) (weeks) + 6.720 (R^2 = 0.04, P = .00). The curve fitting SD was as follows: SD (cm) = $0.134 \times GA$ (weeks) + 1.943 (R² = 0.04, P = .00). The 5th, 10th, 50th, 90th and 95th centile lines were calculated using the *K* value of -1.96, -1.28, 0, 1.28, and 1.96, respectively and are shown in Figure 2. The 5th centile across gestation between 16^{+0} to 38^{+6} weeks was calculated by the equation: 0.027 × GA (weeks) +2.912 (cm) (yielding a range from 3.3 cm to 4.0 cm). A total of 18 of the 369 MC placentas fulfilled the criteria for PCI. The distances between the cord insertions ranged from 0 to 34 cm. The reference range for distance between cord insertions across gestation between 16^{+0} to 38^{+6} weeks was estimated by the equation: Distance (cm) = $0.290 \times \text{gestational age (GA) (weeks)} + 6.720 (R^2 = 0.04, P = .00)$. The curve fitting SD was as follows: SD (cm) = $0.134 \times GA$ (weeks) + 1.943 (R² = 0.04, P = .00). The 5th, 10th, 50th, 90th and 95th centile lines were calculated using the K value of -1.96, -1.28, 0, 1.28, and 1.96, respectively and are shown in Figure 2. The 5th centile across gestation between 16^{+0} to 38^{+6} weeks was calculated by the equation: 0.027×10^{-10} GA (weeks) +2.912 (cm) (yielding a range from 3.3 cm to 4.0 cm). A total of 18 of the 369 MC placentas fulfilled the criteria for PCI. Further analysis showed that PCI occurred frequently in MA placentas (53%, 9/17) but were rare in normal MC (4%, 7/197), TTTS (0%, 0/48), TAPS (0%, 0/26) and growth-discordance (2%, 2/81) placentas, respectively. Additional placental characteristics in the 5 subgroups of MC placentas are reported in Table 2. Two examples of MC placentas with PCI are shown in Figure 3 and 4.



Figure 3 Monochorionic diamniotic placenta with growth discordance (delivery at 35 weeks' gestation, birth weight of 1st and 2nd twin is 3340 grams and 2415 grams, respectively) with proximate cord insertions (≤ 4 cm). Green stars and white stars denote the cord insertions of the first and second twin, respectively. AA and VV anastomoses are indicated with blue and yellow arrows, respectively.

Figure 4: Monoamniotic placenta (delivery at 32 weeks' gestation; birth weight of 1st and 2nd twin is 2210 grams and 2218 grams, respectively) with proximate cord insertions. Green stars and white stars denote the cord insertions of the first and second twin, respectively. AA and VV anastomoses are indicated with blue and yellow arrows, respectively. The inserted picture shows the detailed distance between cord insertions (bottom right).

Table 3 Placental characteristics in MC twins with and without proximate cord

insertions

	PCI (n=18)	No-PCI (n=351)	P value
AV present – n (%)	18 (100)	350 (100)	1.00
AA present – n (%)	18 (100)	264 (80)	.12
VV present – n (%)	10 (56)	91 (26)	.01
VCI – n (%) ^a	1 (3)	177 (25)	.02

Table 3^a Denotes the type of cord insertion per fetus.

Characteristics (angioarchitecture and type of cord insertion) of MC placentas with and without PCI are shown in Table 3. The prevalence of AA anastomoses in MC placentas with and without PCI was 100% (18/18) versus 80% (281/351), respectively, P=.12. The prevalence of VV anastomoses in MC placentas with and without PCI was 56% (10/18) and 26% (91/351), respectively, P<.01.

Discussion

This is the first study establishing a reference range for the distance between umbilical cord insertions across gestational age. The reference range and associated equations were based on the evaluation of 369 MC placentas. We defined PCI as a distance between the cords insertions lower than the 5th centile. Accordingly, the cut-off value for PCI ranged from 3.3 to 4.0 cm across gestation. This cut-off value is slightly lower than the 5 cm cut-off used in previous studies [7, 17]. However, the 5 cm cut-off value was based on arbitrary assumptions and not derived from scientific analysis. We propose that a lower cut-off set at 4 cm would be more appropriate. In addition, since the range of the 5th centile varied only slightly throughout gestation (from 3.3 to 4 cm), we suggest that the use of a fixed cut-off set at 4 cm might be easier to use in daily practice instead of a gestational-age-dependent equation. This study also shows that the prevalence of PCI in various subgroups of MC diamniotic placentas is low (0-4%) whereas in the subgroup of MC monoamniotic placentas PCI are quite common (53%). The significant proximity of umbilical cord insertions may be a representative of the later splitting of inner cell mass in MA twin gestations (around 8-12 days after fertilization) compared to MC diamniotic twin gestations (around 4-8 days after fertilization). The short distance between cord

insertions in MA placentas is reported to be one of the main causal factors leading to the ubiquitous entanglement of umbilical cords [7, 18].

This study also compared the angio-architecture in MC twin placentas with and without PCI. Interestingly, we found that MC placentas with PCI are characterized by a higher incidence of superficial AA (100%) and VV (56%) anastomoses. The cause of the higher rate of superficial anastomoses in MC placentas with PCI is not known and could also be related to the later splitting of inner cell mass. Previous studies showed that the blood flow in superficial AA anastomoses is bidirectional and reduce the inter-twin fluid disequilibrium [19, 20]. The presence of AA anastomoses may thus have a protective effect and be beneficial in cases with PCI, such as reduced risk of TTTS development [19]. The exact role and effect of VV anastomoses in MC placentas is not clear. Although Denbow et al argued that VV anastomoses may increase the perinatal mortality [21], several other studies reported no association between perinatal mortality and VV anastomoses [5-7].

Antenatal detection of umbilical cord insertion site has been steadily achieved with the advance in ultrasound technology [25]. The accuracy of ultrasound examination in the diagnosis of PCI has however not been studied yet. The clinical implication of antenatal detection of PCI also requires further investigation.

The main limitation of our study, besides its retrospective nature, is the relative small number of cases with PCI preventing further analyzing the clinical significance of PCI. Our data should therefore be interpreted with care. Larger studies are required to assess the correlation between clinical outcome and PCI. Ideally, the design of these larger studies should be prospective and start with ultrasound examination in the first trimester of pregnancy. In addition, our data should be also interpreted with caution due to the inclusion bias of MC twin pregnancies. The majority of TTTS cases examined at our center are treated with fetoscopic laser surgery and these cases were excluded from this study. In a previous study in TTTS cases managed with fetoscopic laser surgery at our center, we reported a 2% (4/252) rate of PCI [9], which is in accordance with the rate of PCI in TTTS cases managed conservatively in this study.

In conclusion, PCI are rare in MC diamniotic placentas, but occur frequently in MC monoamniotic placentas. MC placentas with PCI are characterized by high rates of AA and VV anastomoses. Larger studies are needed to understand the clinical implications of PCI. Based on our analysis, we propose to set "≤4cm" as the fixed cut-off value of PCI and this cut-off should be used in future studies on PCI in MC twins to increase the homogeneity and uniformity between the various studies.

References

[1] Hanley ML, Ananth CV, Shen-Schwarz S, Smulian JC, Lai YL and Vintzileos AM. Placental cord insertion and birth weight discordancy in twin gestations. Obstet Gynecol. 2002;99(3):477-82.

[2] Fries MH, Goldstein RB, Kilpatrick SJ, Golbus MS, Callen PW and Filly RA. the role of velamentous cord insertion in the etiology of twin-twin transfusion syndrome. Obstet Gynecol. 1993;81(4):569-74.

[3] Machin GA. Velamentous cord insertion in monochorionic twin gestation - An added risk factor. J Reprod Med. 1997;42(12):785-9.

[4] Costa-Castro T, De Villiers S, Montenegro N, Severo M, Oepkes D, Matias A and Lopriore E. Velamentous cord insertion in monochorionic twins with or without twintwin transfusion syndrome: Does it matter? Placenta. 2013;34(11):1053-8.

[5] Nikkels PG, Hack KE and van Gemert MJ. Pathology of twin placentas with special attention to monochorionic twin placentas. J Clin Pathol. 2008;61(12):1247-53.

[6] Hack KE, Nikkels PG, Koopman-Esseboom C, Derks JB, Elias SG, van Gemert MJ and Visser GH. Placental characteristics of monochorionic diamniotic twin

pregnancies in relation to perinatal outcome. Placenta. 2008;29(11):976-81. [7] Hack KE, van Gemert MJ, Lopriore E, Schaap AH, Eggink AJ, Elias SG, van den Wijngaard JP, Vandenbussche FP, Derks JB, Visser GH and Nikkels PG. Placental characteristics of monoamniotic twin pregnancies in relation to perinatal outcome.

Placenta. 2009;30(1):62-5.

[8] Gandhi M, Papanna R, Moise K, Popek E, Johnson A and Moise KJ, Jr. Treatment of twin-twin transfusion syndrome with proximate umbilical cord insertions. J Ultrasound Med. 2011;30(8):1151-5.

[9] Zhao DP, Peeters SH, Middeldorp JM, Klumper FJ, Oepkes D and Lopriore E. Laser surgery in twin-twin transfusion syndrome with proximate cord insertions. Placenta. 2013.

[10] Lewi L, Jani J, Blickstein I, Huber A, Gucciardo L, Van Mieghem T, Done E, Boes AS, Hecher K, Gratacos E, Lewi P and Deprest J. The outcome of monochorionic diamniotic twin gestations in the era of invasive fetal therapy: a prospective cohort study. Am J Obstet Gynecol. 2008;199(5).

[11] Senat MV, Deprest J, Boulvain M, Paupe A, Winer N and Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004;351(2):136-44.

[12] Slaghekke F, Kist WJ, Oepkes D, Pasman SA, Middeldorp JM, Klumper FJ, Walther FJ, Vandenbussche FP and Lopriore E. Twin anemia-polycythemia sequence:

diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther. 2010;27(4):181-90.

[13] Lopriore E, Slaghekke F, Middeldorp JM, Klumper FJ, van Lith JM, Walther FJ and Oepkes D. Accurate and simple evaluation of vascular anastomoses in

monochorionic placenta using colored dye. J Vis Exp. 2011;(55):e3208.

[14] Zhao DP, de Villiers SF, Slaghekke F, Walther FJ, Middeldorp JM, Oepkes D and Lopriore E. Prevalence, size, number and localization of vascular anastomoses in monochorionic placentas. Placenta. 2013;34(7):589-93.

[15] de Villiers SF, Slaghekke F, Middeldorp JM, Walther FJ, Oepkes D and Lopriore E. Placental characteristics in monochorionic twins with spontaneous versus post-laser twin anemia-polycythemia sequence. Placenta. 2013; 34(5):456-9.

[16] Royston P and Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound in Obstetrics and Gynecology. 1998;11(1):30-8.

[17] Zhao DP, Peeters SH, Middeldorp JM, Klumper FJ, Oepkes D and Lopriore E. Laser surgery in twin-twin transfusion syndrome with proximate cord insertions. Placenta. 2013;34(12):1159-62.

[18] Su LL. Monoamniotic twins: diagnosis and management. Acta Obstet Gynecol Scand. 2002;81(11):995-1000.

[19] Umur A, van Gemert MJ, Nikkels PG and Ross MG. Monochorionic twins and twin-twin transfusion syndrome: the protective role of arterio-arterial anastomoses. Placenta. 2002;23(2-3):201-9.

[20] Denbow ML, Taylor M, Cox P and Fisk NM. Derivation of rate of arterio-arterial anastomotic transfusion between monochorionic twin fetuses by Doppler waveform analysis. Placenta. 2004;25(7):664-70.

[21] Denbow ML, Cox P, Taylor M, Hammal DM and Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. Am J Obstet Gynecol. 2000;182(2):417-26.

[22] Hack KEA, Nikkels PGJ, Koopman-Esseboom C, Derks JB, Elias SG, van Gemert MJC and Visser GHA. Placental Characteristics of Monochorionic Diamniotic Twin Pregnancies in Relation to Perinatal Outcome. Placenta. 2008;29(11):976-81.

[23] Ortibus E, Lopriore E, Deprest J, Vandenbussche FP, Walther FJ, Diemert A, Hecher K, Lagae L, De Cock P, Lewi PJ and Lewi L. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. Am J Obstet Gynecol. 2009;200(5):494 e1-8.

[24] Adegbite AL, Castille S, Ward S and Bajoria R. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. Am J Obstet Gynecol. 2004;190(1):156-63.

[25] Sepulveda W, Rojas I, Robert JA, Schnapp C and Alcalde JL. Prenatal detection of velamentous insertion of the umbilical cord: a prospective color Doppler ultrasound study. Ultrasound Obstet Gynecol. 2003;21(6):564-9.