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# Monochorionic placentas with proximate umbilical cord insertions: Definition, prevalence and angio-architecture

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ABSTRACT

*Introduction:* Not much is known on the definition, occurrence and characteristics of proximate umbilical cord insertions (PCI) in monochorionic (MC) placentas. 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 not treated with laser surgery were included in this study. 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 and veno-venous anastomoses in MC placentas with and without PCI was respectively 100% versus 80% ($P = .12$) and 56% versus 26% ($P = .01$). PCI may be representative of later splitting of inner cell mass.
*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.


## 1. 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.

## 2. 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

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managed with fetoscopic surgery (either laser ablation of vascular anastomoses or selective feticide) were excluded due to iatrogenic destruction of placental angioarchitecture. 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 angioarchitecture. 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 $\geq$ 8 cm before 20 weeks of gestation or $\geq$ 10 cm after 20 weeks of gestation) in the recipient and oligohydramnios (deepest vertical pocket $\leq$ 2 cm) 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 were 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.

### 2.1. 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 calculate 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.

## 3. 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 flow chart to illustrate the inclusion and exclusion of MC placentas is shown in Fig. 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. The reference range for distance between cord insertions across gestation between $16^{+0}$ and $38^{+6}$ weeks was estimated by the equation: Distance (cm) = 0.290 $\times$ 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 ($R^2$ = 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 Fig. 2. The 5th centile across gestation between $16^{+0}$ and $38^{+6}$ weeks was calculated by the equation: 0.027 $\times$ 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

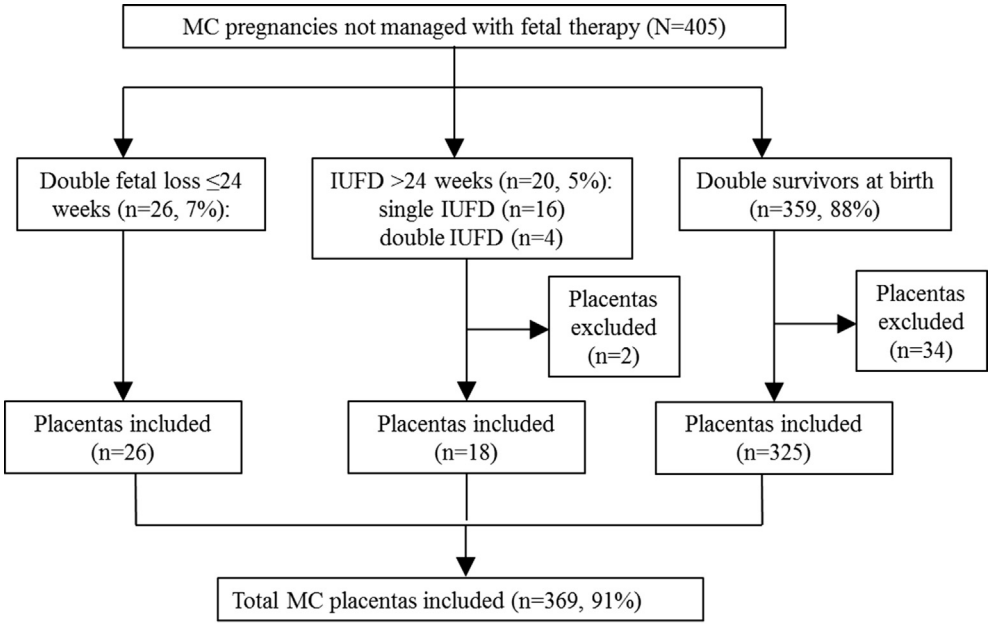


**Fig. 1.** Flow chart showing the derivation of the studied cohort.