TITLE: The vascular equator in monochorionic twin placentas

Word count: Abstract 249 – main text 1677 – discussion 395 – tables 1 – figures 2

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ABSTRACT

Introduction: We aim to examine the location of the vascular equator according to the umbilical cord insertions in monochorionic twin placentas according to the site of the cord insertions.

Methods: We included two prospective series of monochorionic twin placentas of patients included in the first trimester between 2004 and 2008, and between 2016 and 2019. We injected the placentas after birth and divided them into three groups, with respectively concordant (eccentric-eccentric, marginal-marginal, and velamentous-velamentous), intermediate (eccentric-marginal and marginal-velamentous) and discordant (eccentric-velamentous) cord insertions. For each unidirectional anastomosis, we determined the cord-anastomosis ratio and then calculated the mean ratio per placenta in each group. We also calculated the deviation from the midline in all groups.

Results: 202 placentas were included. In concordant placentas, the mean cord-anastomosis ratio was 0,966 [0,916 – 1,016]. In placentas with intermediate discordance, the mean ratio was 0,879 [0,824 – 0,940] and in discordant placentas it was 0,791 [0,703 – 0,887] ($p < 0,001$). In concordant placentas, the equator was in the middle of the cord insertions with an average deviation of 0,1 [-0,1 – 0,3] cm. In the intermediate placentas, the equator deviated on average 0,5 [0,2 – 0,7] cm and was displaced from the middle towards the most central cord insertion. In discordant placentas, this effect was even more pronounced with an average displacement of 1,0 [0,5 – 1,5] cm.

Discussion: In concordant placentas, the vascular equator lies in the middle between both cord insertions. In intermediate and discordant placentas, the equator is closer to the more central cord insertion.

KEY WORDS

Monochorionic, placenta, vascular equator, TTTS, fetoscopy

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HIGHLIGHTS

- Monochorionic placentas can have concordant, intermediate or discordant cord insertions
- In concordant placentas, the equator is situated in the middle between the cords
- In intermediate placentas, the equator deviates towards the most eccentric cord
- In discordant placentas, this deviation increases
- There is a large variability of anastomoses within and between placentas
- This information can be useful when planning fetoscopic laser surgery

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INTRODUCTION

In monochorionic diamniotic (MCDA) twin pregnancies, both twins share the same placenta. They have a higher risk of complications compared to dichorionic pregnancies because most MCDA placentas have vascular anastomoses that connect the two fetal circulations. Through these anastomoses, the twins continuously exchange blood. An imbalance in blood flow may lead to twin-to-twin transfusion syndrome (TTTS) [1], which occurs in about 10% of all MCDA twin pregnancies. If left untreated, TTTS leads to a high risk of loss through miscarriage, preterm delivery, or intrauterine fetal death [2].

At present, fetoscopic laser coagulation of all the anastomoses along the vascular equator is the best treatment for TTTS, resulting in better survival and neurological outcomes for both fetuses [3]. Optimal visualization of the vascular equator during surgery is essential because residual anastomoses can cause severe complications such as twin anemia-polycythemia sequence or recurrent TTTS [4]. Therefore, trocar insertion perpendicular to the vascular equator is essential to achieve good visualization and ablation of all anastomoses.

The location of the vascular equator cannot be seen on ultrasound scan but is presumed to be precisely in the middle between the two cord insertions, which can be visualized by ultrasound. We determine the site of trocar insertion based on the location of the placenta, the recipient and donor sac, and the assumption that the equator lies in the middle of the cord insertions. However, there is minimal evidence to support this assumption. We, therefore, aim to examine the location of the equator relative to the cord insertions in a series of MCDA twin placentas according to the cord insertion site in the placenta.

MATERIALS AND METHODS

We included placentas from two prospective studies in this analysis. The first was the EuroTwin2Twin project, for which we collected monochorionic twin placentas between February 2004 and October 2008 within the Fifth Framework Program of the European Commission (#QLG1-CT-2002-01632,

EuroTwin2Twin). Between August 2016 and November 2019, we examined monochorionic twin placentas as part of the TWINSHARE study (ClinicalTrials.gov Identifier: NCT03024918). These studies received ethical committee approval from the University Hospitals Leuven. In both studies, patients with an ongoing MCDA twin pregnancy diagnosed between 11.0 and 14.0 weeks in the University Hospitals Leuven were invited to take part. As part of these prospective cohort studies, referring physicians sent the placenta after birth in a dry container for injection studies.

Only the placentas of pregnancies resulting in the live birth or stillbirth of both twins were included in the analysis.⁵ Placentas too compromised for injection or stored in formalin were excluded. Placentas of pregnancies with single fetal demise remote from delivery (>48 hours) were excluded because of placental maceration of the part of the demised twin. Further, we excluded placentas of pregnancies that did not have any or only bidirectional anastomoses, as it is not possible to identify the exact meeting point in artery-to-artery and vein-to-vein anastomoses. Placentas treated with fetoscopic laser surgery were excluded as well, as this procedure destroys the anastomoses on the placental surface. We catheterized the placentas and injected them with colored dye, as described previously [1,5]. After injection, we took a digital photograph perpendicular to the chorionic surface.

For each placenta, the umbilical cord insertions of each twin were classified to be either velamentous (umbilical cord insertion in the fetal membranes instead of the parenchyma), eccentric (>2cm from the placental edge) or marginal (< 2cm from the placental edge). We marked all unidirectional arterio-venous (AV) and veno-arterious (VA) anastomoses on the placental surface as the meeting point between the artery and vein on the vascular equator (Figure 1). An operator with experience in placental injection identified the anastomoses for each placenta.

Afterwards, we divided the placentas into three groups. The first group had concordant umbilical cord insertions, defined as all placentas with either two eccentric, two marginal, or two velamentous insertions. The second group had intermediate cord insertions, defined as all placentas with one eccentric and one marginal or one marginal and one velamentous insertion. Finally, the third group had discordant cord insertions, defined as one eccentric and one velamentous insertion.

For each placenta, the course of the vascular equator was determined by the line connecting all anastomoses. For each anastomosis, we then measured the distance from the more central insertion to the anastomosis, as well as the distance from the more peripheral insertion to the anastomosis, and calculated the ratio of these distances. In concordant placentas, we assessed whether one insertion was more central than the other, and if not, we calculated the ratio of the distance from the cord of the firstborn twin and the distance from the cord of the second twin.

For both groups, we compared the mean cord-anastomosis ratio per placenta using generalized estimating equation analysis, correcting for clustering of the anastomoses within placentas after transformation on the logarithmic scale. Log transformation was used to correct for skewed data. If the vascular equator is genuinely in the middle of both cord insertions, we expect the mean cord-anastomosis ratio per placenta to be equal to 1. If the equator is closer to the most central cord, the ratio will be less than 1. Likewise, an equator closer to the more peripheral cord will result in a ratio more than 1. From these ratios, we also calculated the deviation of the equator from the midline between both cord insertions in centimeter. Positive values indicate a deviation towards the more eccentric cord insertion, while negative values represent a deviation towards the more marginal cord insertion.

RESULTS

During the combined study periods, 371 monochorionic twins delivered. 93 (26%) placentas were not returned for examination. Another 76 (21%) placentas were excluded: 25 because of laser surgery, 21 because of single intrauterine fetal demise, 14 because of extensive damage, 14 because of the absence of visible unidirectional anastomoses, one because of a common cord insertion and one because of storage in formalin. This left 202 of the 371 placentas (54%) available for analysis. The mean gestational age at delivery was 34 weeks $\pm$ 3 weeks, and the range was 15 to 40 weeks. Seven placentas were delivered before viability and another four after double intra-uterine demise. The remaining 191 placentas resulted from double livebirths, with a mean birth weight of the larger

twin of 2348 ± 518 grams, and 2042 ± 534 grams for the smaller twin. The average birth weight discordance was 13 ± 10 %.

The cord insertions were concordant in 74 placentas (37%), intermediate in 111 (55%), and discordant in 17 placentas (8%). The detailed distribution of the cord insertions is presented in Table 1. The mean number of anastomoses per placenta was 7 ± 4 , with a range of 1 to 20.

In concordant placentas, the mean cord-anastomosis ratio was 0,966 [0,916 – 1,016]. In placentas with intermediate discordance, the mean ratio was 0,879 [0,824 – 0,940] and in discordant placentas it was 0,791 [0,703 – 0,887], indicating that the equator was significantly closer to the more central cord insertion ($p < 0,001$). The mean distance between the cord insertions was $13,7 \pm 0,7$ cm in the concordant group, $16,1 \pm 0,4$ cm in the intermediate group, and $18,3 \pm 1,2$ cm in the discordant group. In concordant placentas, the equator was in the middle of the cord insertions with an average deviation of 0,1 [-0,1– 0,3] cm. In the intermediate placentas, the equator deviated on average 0,5 [0,2 – 0,7] cm and was displaced from the middle towards the most central cord insertion. In discordant placentas, this effect was even more pronounced with an average displacement of 1,0 [0,5 – 1,5] cm.

Figure 2 shows a scatterplot of the ratios of all the anastomoses per placenta in all three groups, demonstrating a high variability within and between placentas.

DISCUSSION

In fetoscopic laser treatment for TTTS, ablation of all the anastomosis across the vascular equator is the most critical determinant for treatment success. Adequate trocar insertion perpendicular to the vascular equator is therefore essential. We assume the equator to lie in the middle of the cord insertions, but until now, there has not been any evidence to support this assumption. In this study, we found that in concordant placentas, the vascular equator lies indeed in the middle between the cord insertions. In intermediate and discordant placentas, the equator was, on average, 0,5 cm and 1,0 cm displaced from the middle towards the more central cord insertion. It appears as though the

deviation increases with increasing discordance between the insertions. This information can help optimize and standardize the procedure for trocar insertion, leading to better visualization of all the anastomoses and potentially better treatment outcomes. However, we have also demonstrated a high variability within and between placentas regarding the location of individual anastomoses. Because of this high variability, surgeons always need to be aware of the possibility of abnormal vessels that deviate from the expected equator.

Our study is the first to describe the location of the vascular equator relative to the cord insertions. We analyzed placentas from MCDA twin pregnancies recruited in the first trimester, creating a representative sample of the general population. We found a mean of 7 anastomoses per placenta, which is comparable with findings in other studies [6,7]. The distribution of cord insertions in our population was similar to findings from other MCDA twin cohorts [8]. We have a relatively small subgroup of discordant placentas but were able to demonstrate a significant effect nevertheless. Unfortunately, there is an unavoidable selection bias since placentas treated with fetoscopic laser surgery for TTS and placentas with single fetal demise were excluded. These placentas were excluded for technical reasons, as we can no longer evaluate the anastomoses. However, we have no reason to assume that the equator would be located differently in these types of placentas.

In conclusion, our findings support the assumption that in concordant placentas, the vascular equator lies in the middle of the cord insertions. However, in intermediate and discordant placentas, the equator is displaced towards the more central cord insertion and this deviation increases with increasing discordance. This evidence is useful in selecting the entry for trocar insertion during fetoscopic laser surgery.

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212 **Table 1: Distribution of the cord insertions for each group**

213

Type of concordance	Cord insertions	Number of placenta's (N=202)
Concordant	Both eccentric	36
	Both marginal	38
	Both velamentous	0
Intermediate	Marginal – eccentric	100
	Marginal – velamentous	11
Discordant	Eccentric – velamentous	17

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FIGURE LEGEND

Figure 1: Digital photograph of placentas after color dye injection.

Figure 1a shows a placenta with concordant (eccentric) umbilical cord insertions. Figure 1b shows a placenta with discordant (marginal and eccentric) cord insertions. Yellow lines indicate the cord-anastomoses distances. Blue lines indicate the distance between cord insertions.

Figure 2: Scatterplot of the log(ratio) of individual anastomoses per placenta.

Scatterplot of the log(ratio) of individual anastomoses per placenta in concordant (Figure 2a), intermediate (Figure 2b) and discordant (Figure 2c) placentas. The number of each placenta is indicated on the X-axis and each dot represents an individual anastomosis. The green lines indicate the mean log(ratio) in each group and blue lines represent the 95% confidence interval. We used log(ratio) for the statistical analysis to correct for the skewed data when using ratios. Log (ratio) 0 indicates the middle between both cord insertions. Positive values indicate a deviation towards the more marginal insertion, while negative values indicate a deviation towards the more eccentric insertion. There is a large variability within and between placentas.

Figure

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