Chapter 4

Velamentous cord insertion and unequal placental territories in monochorionic twins with and without twin-to-twin transfusion syndrome

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Submitted
Abstract

Objective: To determine the incidence of velamentous cord insertion and placental territory discordancy in monochorionic twins with and without TTTS.

Methods: All consecutive placentas of monochorionic twins delivered at our center between June 2002 and April 2006 were studied with vascular injection of the umbilical vessels with colored dyes. Velamentous cord insertions were recorded and placental territories were calculated by computer analysis.

Results: A total of 76 monochorionic placentas with TTTS and 63 monochorionic placentas without TTTS were studied. The incidence of velamentous cord insertion (per fetus) in the TTTS group and the no-TTTS group was 13% (20/152) and 14% (18/126), respectively (p = 0.79). Placental territory discordancy in the TTTS group and the no-TTTS group was 20% and 20% (p = 0.83). In the TTTS group, donor twins had more often a velamentous cord insertion than recipient twins (24% and 3%, respectively, p < 0.001) and smaller placental territories (44% and 56%, respectively, p < 0.001).

Conclusions: Our findings suggest that velamentous cord insertion and placental territory discordancy are not critical factors for the development of TTTS.
Introduction

Chronic twin-to-twin transfusion syndrome (TTTS) is a complication of monochorionic twin pregnancies and results from inter-twin blood transfusion via placental vascular anastomoses. Although vascular anastomoses are invariably found in almost all monochorionic placentas, only 10-15% of monochorionic twins will eventually develop TTTS. Differences in angio-architecture, amongst those the absence of arterio-arterial anastomoses, are one of the major factors involved in the development of TTTS. However, angio-architecture alone does not fully explain the pathophysiology of TTTS. Several other hypotheses on the pathophysiology of TTTS have been proposed, including utero-placental insufficiency and paradoxical activation of fetal vasoactive and humoral factors. Several authors found a higher incidence of velamentous cord insertions in TTTS placentas and hypothesized that velamentous cord insertion and unequal placental territories may lead to utero-placental insufficiency, subsequently establishing a vicious cycle resulting in the development of TTTS. However, these hypotheses were mostly unsubstantiated or based on small studies. Moreover, two recent reports show that the incidence of velamentous or marginal cord insertion is similar in monochorionic twins with and without TTTS. The objective of this study was to determine the incidence of velamentous cord insertions and placental territory discordancy in monochorionic twins with and without TTTS.

Materials and methods

All consecutive placentas of monochorionic twin pregnancies examined at our center between June 2002 and April 2006 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. The Leiden University Medical Center is a tertiary
medical center and it is the national referral center for fetal therapy in the Netherlands, including laser treatment for TTTS. Most TTTS cases referred to our center were therefore treated with laser.

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. Placental angio-architecture was studied by injecting the umbilical vessels of both cords with different colored dyes. Arteries were injected with (dark-) blue dye whereas veins were injected with orange or yellow dye. Placentas were then photographed in a plane view, and the picture was saved for computer analysis. Each fetal territory was measured by following the margins demarcated by the presence of color specific dye. Individual placental territories were measured using Image Tool for Windows version 3.0 (Image Tool, San Antonio, Texas, USA) and expressed as a percentage of the total area. The percentage of individual placental territory was calculated by dividing each individual placental territory by the sum of both territories. Placental territory discordancy was then determined by subtracting the percentage of individual placental territory from one fetus with the percentage of individual placental territory from the other fetus. The same formulas were used to determine the percentage of birth weight share per infant and inter-twin birth weight discordancy. Placentas with intrauterine fetal demise were excluded when placental maceration prohibited accurate evaluation of type of umbilical cord insertion and placental territory discordancy. Placentas of monochorionic monoamniotic pregnancies and higher multiple pregnancies were also excluded from the study.

Results of categorical variables were compared using Chi-squared test. Continuous variables were analyzed with the Independent Samples T-test. For comparisons between donors and recipients, the Paired Samples T-Test and Mc Nemar test was used. A p-value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed with SPSS for Windows version 11.0 (SPSS, Inc., Chicago, Illinois, USA).
Results

The number of consecutive monochorionic diamniotic placentas delivered and examined at our center during the study period was 161. The data required for this study could not be recorded completely for 22 placentas (nine in the TTTS-group and thirteen in the no-TTTS group) because of placental maceration caused by intrauterine fetal demise (n = 9), placental fragmentation (n = 3), placenta fixation in formalin (n = 1), loss or destruction of the placenta after delivery (n = 9). These 22 cases were excluded from further analysis. A total of 76 monochorionic placentas with TTTS and 63 monochorionic placentas without TTTS were included in the study. Mean gestational age at birth in the TTTS group and no-TTTS group was 30.8 weeks (range: 17 to 38 weeks) and 33.8 weeks (range: 25 to 38 weeks), respectively. The monochorionic pregnancies with TTTS were treated with fetoscopic laser coagulation (n = 61), amniodrainage (n = 10) or without intrauterine intervention (n = 5).

The overall incidence of velamentous cord insertion per fetus in all monochorionic twin pregnancies was 13% (37/278). Type of umbilical cord insertion and difference in placental territories between the TTTS group and no-TTTS group are presented in Table 1. Examples of monochorionic placentas with velamentous cord insertion and unequal placental territories are shown in figures 1, 2, 3 and 4 (pictures are taken after colored dye injection).

<table>
<thead>
<tr>
<th></th>
<th>TTTS group (n = 76 placentas)</th>
<th>no-TTTS group (n = 63 placentas)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velamentous cord insertion – no (%)a</td>
<td>20 (13%)</td>
<td>18 (14%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Marginal cord insertion – no (%)a</td>
<td>49 (33%)</td>
<td>33 (26%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Velamentous or marginal cord insertion – no (%)a</td>
<td>69 (45%)</td>
<td>52 (41%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Placental territory discordancy - %b</td>
<td>20 ± 14</td>
<td>20 ± 15</td>
<td>0.83</td>
</tr>
<tr>
<td>Placental territory discordancy &gt; 20% - no (%)</td>
<td>31 (41%)</td>
<td>25 (40%)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

a Refers to the type of cord insertion per fetus
b Value given as mean ± SD
FIGURE 1  Monochorionic placenta without TTTS. Twin 1 has a velamentous cord insertion and a placental territory of 36%, whereas twin 2 has a central cord insertion and a placental territory of 64%.

FIGURE 2  Monochorionic placenta without TTTS. Twin 1 has a velamentous cord insertion and a placental territory of 21%, whereas twin 2 has a paracentral cord insertion and a placental territory of 79%.
Velamentous cord insertion and unequal placental territories in TTTS

FIGURE 3  Monochorionic placenta with TTTS treated with fetoscopic laser surgery. Twin 1 (ex-recipient) has a central cord insertion and a placental territory of 73%. Twin 2 (ex-donor) has a velamentous cord insertion and a placental territory of 27%.

FIGURE 4  Monochorionic placenta with TTTS treated with amniodrainage. Twin 1 (donor) has a marginal cord insertion and a placental territory of 47%, whereas twin 2 (recipient) has a velamentous cord insertion and a placental territory of 53%.
Type of abnormal umbilical cord insertion, placental territory discordancy and birth weight difference between donor and recipient twins in the TTTS group are presented in Table 2.

Differences between monochorionic twins with and without velamentous cord insertion are presented in Table 3.

**TABLE 2** Type of umbilical cord insertion, birth weight and individual placental territories in donor and recipient twins with TTTS.

<table>
<thead>
<tr>
<th></th>
<th>Donor (n = 76)</th>
<th>Recipient (n = 63)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velamentous cord insertion – no (%)$^a$</td>
<td>18 (24%)</td>
<td>2 (3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Marginal cord insertion – no (%)$^a$</td>
<td>30 (39%)</td>
<td>19 (25%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Velamentous or marginal cord insertion – no (%)$^a$</td>
<td>48 (63%)</td>
<td>21 (28%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight – gb$^b$</td>
<td>1547 ± 723</td>
<td>1763 ± 739</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Birth weight share – %$^b$</td>
<td>46 ± 6</td>
<td>54 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Individual placental territory - %$^b$</td>
<td>44 ± 11</td>
<td>56 ± 11</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

$^a$ Refers to the type of cord insertion per fetus
$^b$ Value given as mean ± SD

**TABLE 3** Differences between twins with and without velamentous cord insertion.

<table>
<thead>
<tr>
<th></th>
<th>Velamentous insertion$^a$ (n = 38)</th>
<th>No velamentous insertion$^a$ (n = 240)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth– weeks$^b$</td>
<td>30.7 ± 5.1</td>
<td>32.4 ± 4.4</td>
<td>0.036</td>
</tr>
<tr>
<td>Birth weight – gb$^b$</td>
<td>1454 ± 672</td>
<td>1914 ± 755</td>
<td>0.001</td>
</tr>
<tr>
<td>Individual placental territory - %$^b$</td>
<td>36 ± 10</td>
<td>52 ± 11</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

$^a$ Refers to the type of cord insertion per fetus
$^b$ Value given as mean ± SD
Discussion

In this large single center study we report on the difference in velamentous cord insertion and discordant placental territories between monochorionic twin placentas with and without TTTS. We found no difference in velamentous cord insertion between monochorionic placentas with and without TTTS. 

Velamentous cord insertions are rare in singleton placentas (2%) and far more common in dichorionic (7%) and particularly in monochorionic twin placentas (12%)\(^n\). The high incidence of velamentous cord insertions 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\(^26;198;199\). Velamentous cord insertions are associated with smaller placental mass and lower birth weights\(^26;198;200;201\).

In monochorionic twinning, velamentous cord insertions have also been related to the development of TTTS. In a study of 38 monochorionic placentas, Fries \(^89\) et al reported a significantly higher prevalence of velamentous cord insertion in TTTS placentas than in no-TTTS placentas, 32% (7/22) and 9% (5/54), respectively (p < 0.01). In view of this finding, Fries et al proposed an etiologic role for velamentous cord insertion in the development of TTTS\(^89\). As a velamentous inserted cord 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 velamentous inserted cord. 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\(^60\).

In a study of 60 monochorionic placentas, Machin\(^90\) 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 report similar frequencies of velamentous cord insertion in TTTS and no-TTTS twins (16% and 19%, respectively)\(^196\). 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 no-TTTS placentas (37% and 36%, respectively). In another (unpublished) series of 90 monochorionic placentas, Taylor et al also found equally high incidence of velamentous cord insertion in TTTS and no-TTTS placentas (53% and 52%, respectively). Our findings are in agreement with the findings of Bajoria, De Paepe et al and Taylor et al and challenge the existence of a causative relationship between velamentous cord insertion and the development of TTTS.

This study also shows a similar frequency of placental territory discordancy in monochorionic placentas with and without TTTS. Only a few studies have expanded on the relationship between placental asymmetry and development of TTTS. In a small uncontrolled study of 9 monochorionic pregnancies, Bruner et al speculated that TTTS may result from asymmetrical placental insufficiency; according to this hypothesis, placental vascular anastomoses may become functional and lead to TTTS when resistance to placental perfusion reaches a threshold. In a study of 89 monochorionic placentas, De Paepe et al found uneven placental distribution (defined as greater than 25% discordance between the two placental territories) more frequently in TTTS placentas than in no-TTTS placentas (73% and 24%, respectively, p < 0.005). However, in the same study, De Paepe et al found a similar incidence in abnormal cord insertion. We, as well as others, have found that velamentous cord insertions are associated with smaller placental territories and smaller birth weights. If estimations of placental territories were performed by rough approximation, an obvious bias may have been introduced. In contrast, we used computer analysis to calculate placental territories. Our findings are in agreement with a recent study of 133 monochorionic placentas from Quintero et al, showing similar frequencies of placental territory discordancy in monochorionic placentas with TTTS and without TTTS. Similar placental territory discordancy in TTTS and no-TTTS placentas suggests that a causal relationship between unequal placental territories and the development of TTTS is highly improbable. Finally, this study shows a significant difference in placentation between
donor twins and recipient twins with TTTS. We found that donor twins are more likely to have a velamentous or marginal cord insertion and smaller placental territories than recipient twins. In a study of 71 TTTS placentas, Quintero et al also found significant differences in individual placental territories between donor twins and recipient twins (44% versus 55%, respectively, $p < 0.001$), in agreement with our results. In contrast, in a smaller study of 32 TTTS placentas, Bajoria found no difference in velamentous or marginal cord insertions between donor and recipient twins (65% versus 59%, respectively).

Our findings suggest an association between abnormal cord insertion, smaller placental territories and being a donor in TTTS. The cause of this high frequency of abnormal cord insertion and smaller placental territory in donor twins is not known. Placental formation is directly related to placental angiogenesis. Various factors, such as vascular endothelial growth factors and fibroblast growth factors, as well as vascular flow are suggested to play an important role in placental vascularization. We speculate that abnormal cord insertion and smaller placental territories in donors are not a cause but a consequence of TTTS. As the donor twin becomes hypovolemic, vascular perfusion of its placental territory diminishes resulting in a decrease in villous and capillary surface areas. This process may then lead to a reduced expansion of placental cotyledons, particularly those on the outer-side of the donor’s placenta, resulting in a smaller placenta with a marginal or velamentous inserted cord. Cotyledons from the donor’s placenta that are also perfused through anastomoses by the recipient have a greater probability to remain intact. Fetal hypovolemia and placental hypoperfusion in donors may also explain the difference in vascular distribution patterns between donors and recipients found in the study by De Paepe et al.

In conclusion, our findings show that the frequency of velamentous cord insertion and placental territory discordancy is similar in TTTS and no-TTTS monochorionic twins, challenging the notion of a causative relationship with the development of TTTS.