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Ultrasound studies in monochorionic twin pregnancies : results of TULIPS: Twins and ultrasound in pregnancy studies

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Chapter 8

General discussion



Compared to human twins armadillo twin pairs are more lucky. While armadillos (Figure 1) are the only animal species with monochorionic placentation, they do not have anastomoses in their placenta and are thus not at risk for unbalanced intertwin transfusion (Professor Benirschke, personal communication 2006). This is in contrast to the human species in which about 10 to 15% of monochorionic twin pregnancies develop twin-to-twin transfusion syndrome (TTTS)^{1,2}.



Figure 1 Nine-banded armadillo (*Dasypus novemcinctus*)

TTTS in the Netherlands

The incidence of monochorionic twinning is 1 in every 400 pregnancies³. In contrast to the rate of dizygotic twinning, that varies between different populations and increases with maternal age, the rate of monochorionic twinning does not vary among different populations. With an annual birth rate of 188 000 (CBS 2005), between 47 and 67 cases of TTTS are expected in the Netherlands per year. Since 2000, fetoscopic laser coagulation of the vascular anastomoses has been performed to treat severe TTTS in the Leiden University Medical Center (LUMC), which is the national referral center for invasive fetal therapy. Results are comparable to those of specialized centers worldwide⁴. The numbers of pregnancies treated for TTTS in the LUMC have increased from 20 (2001) to 45 per year (2006) (Figure 2). This significant rise in numbers of treated cases indicates the increasing awareness of TTTS among the referring obstetricians during the past years.

The remaining gap between the expected and actual numbers of treated cases may be caused by several factors. Firstly, some of the cases may develop TTTS in the first trimester already, as we have shown in **chapter 3**. At such an early gestational age, presentation is different from the classical oligo/polyhydramnios sequence that is characteristic for the more common

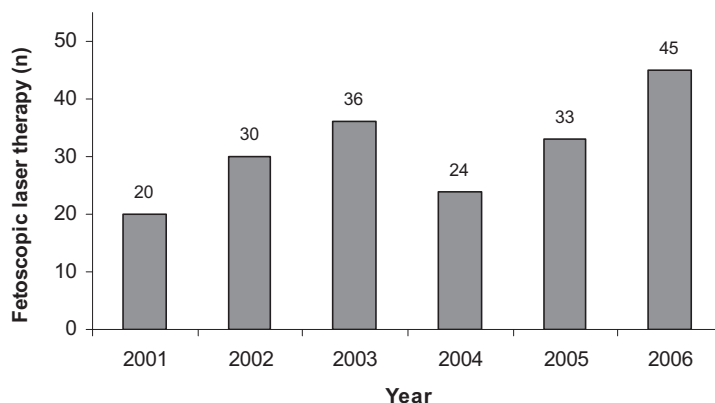


Figure 2 Number of fetoscopic laser coagulations of placental anastomoses for severe twin-to-twin transfusion syndrome in the Leiden University Medical Center

second-trimester cases. In order to timely detect all these early TTTS cases, more insight in the pathophysiology and early signs and symptoms is required. Secondly, some pregnancies may have resulted in fetal loss without even a suspicion of being caused by TTTS, because of very rapidly developing polyhydramnios followed by immature birth. Thirdly, when TTTS is diagnosed timely, patients may opt for terminating the pregnancy because of the high perinatal mortality and morbidity that is involved in severe TTTS. Fourthly, fetoscopic laser treatment is not always indicated, e.g. in mild TTTS cases or in the third trimester. This results in some patients being referred, but not being treated. Fifthly, a few patients may still be referred to Leuven (Belgium), Hamburg (Germany) or Paris (France), as was common practice in the period that fetoscopic laser treatment was not yet available in the Netherlands. Lastly, there remains the possibility that some cases are still missed, underdiagnosed or underestimated. It is understandable; the rarity of the syndrome increases the risk that TTTS is not always identified. In the Netherlands, more than 900 obstetrician-gynecologists are registered, and the number of TTTS cases annually is only around 47 to 67. Many colleagues may not encounter a case for years.

With this thesis, we hope to provide a framework including recommendations for clinical practice (**chapter 9**) that will be helpful in the prenatal management of monochorionic twins, starting from the first trimester onwards until delivery.

First-trimester ultrasound examination

As outlined in **chapter 1**, monochorionicity can be diagnosed with a 100% sensitivity and 99% specificity in the first trimester of pregnancy^{5,6}. While postnatally the gold standard for determining chorionicity is microscopic examination of the intertwin dividing membrane⁷, prenatally, the visualization of a “T” sign at the intertwin membrane-placental junction in the first trimester

of pregnancy should be considered the gold standard. The presence of a single placental mass, that was previously thought to be present in every monochorionic twin pregnancy, cannot be considered a reliable criterion. As we have shown in **chapter 2**, 3% of monochorionic twins have two placental masses. Concordance of fetal gender, another factor supposed to be mandatory in monochorionic twins, cannot be reliably determined in the first trimester of pregnancy. Moreover, multiple cases of sex-discordant or dizygotic monochorionic twins have recently been reported, especially after assisted reproductive technology⁸⁻¹². The thickness of the intertwin membrane is not a useful tool, since it does not distinguish sufficiently between the two types of twins and its measurement is associated with high intra- and interobserver variability¹³.

In view of the severe hemodynamic intertwin complications associated with monochorionicity, prenatal care of monochorionic twinning demands special attention of the obstetrician, starting from the first trimester onwards until birth. Although most cases of TTTS are identified in the second trimester of pregnancy, we and others¹⁴⁻¹⁷ have shown that TTTS may occur in the first trimester already. This is the reason why early surveillance is of importance.

We have diagnosed TTTS at 11 weeks of gestation, one of the earliest cases reported thus far (**chapter 3**). The only finding was an increased nuchal translucency in one of the twins. Another (unpublished) case in our series presented at 14 weeks with differences in amniotic fluid compartments and discordant bladder filling. This patient was successfully treated with fetoscopic laser therapy at 15 weeks of gestation. These new insights about the very early onset of TTTS and the vascular anastomoses on monochorionic twin placentas that may cause (double) fetal death or neurological damage¹⁸, even in the first trimester of pregnancy, are important to be aware of. This knowledge may be used in the counseling of patients pregnant with monochorionic twins that are complicated by single increased nuchal translucency, early intertwin discordance for amniotic fluid or bladder filling, or early intrauterine fetal death.

Timely detection

Although most monochorionic twin pregnancies have an uneventful course, the risks of perinatal complications are increased as compared to dichorionic and singleton pregnancies. From the moment a monochorionic twin pair has been diagnosed, patients must be informed that their pregnancy is considered to be high-risk. The 10 to 15% chance of developing TTTS is to be explained as the major problem. It is of importance to outline clearly the clinical symptoms of TTTS, such as a rapidly increasing girth or premature contractions. Patients must be encouraged to contact their obstetrician immediately if they are worried, and should then be scheduled for ultrasound examination the same day. Despite the anxiety that may be aroused with this detailed information, we have shown in **chapter 4** that explicit patient instructions can be crucial for the timely detection of TTTS.

Prevention of TTTS would deliver the best results regarding perinatal mortality and morbidity; however, this is currently not feasible. To treat TTTS is second-best and has been shown to improve perinatal survival significantly. In the LUMC, fetoscopic laser coagulation of the placental vessels is the first-line treatment in TTTS cases detected between 15 and 26 weeks. Since the outcome has been shown to be significantly better if the syndrome is treated in Quintero Stages 1-2 compared to Stages 3-4^{4,19}, attention has been increasingly paid to the early diagnosis of TTTS.

To date, TTTS diagnosis is solely based on prenatal ultrasound criteria. However, the optimal frequency of ultrasound examination during pregnancy in order to detect TTTS timely has not yet been determined. Without being evidence based, a program of at least biweekly ultrasound examinations is recommended by most specialized clinics^{3,20,21}. In **chapter 4**, we have shown that combined use of biweekly sonography and maternal symptom monitoring results in timely diagnosis of TTTS. The use of subjective maternal symptoms together with the objective medical tools for diagnosing TTTS seems to be a well-functioning approach. Obviously, we do realize that the lack of a control group in our study is a potential weakness. However, it was deemed unethical to compare our "best practice" protocol of biweekly ultrasound examinations to a less intensive program of prenatal monitoring. Nevertheless, information on how to manage monochorionic twins is urgently needed and we think our study contributes valuable data on this information gap.

Besides the importance of second-trimester ultrasound examination, we would like to underline that TTTS and other complications in monochorionic twin pregnancies may occur after 26 weeks of gestation as well²². Intensive prenatal care should therefore be started early in pregnancy and continued until delivery. This infers biweekly scanning for symptoms of TTTS until term, even during the third trimester of pregnancy.

Pre-symptomatic markers

Besides the transformation of an existing, "best practice" program for monitoring monochorionic twin pregnancies into a scientifically sound concept, we also aimed at identifying sonographic markers that could forecast the development of TTTS and enable timely diagnosis and subsequent timely treatment of TTTS (**chapter 4**). We showed the deepest vertical pocket of amniotic fluid to be a TTTS predictor. Polyhydramnios in the one sac without accompanying oligohydramnios in the other must be considered an important warning sign, possibly indicative of the development of TTTS later in pregnancy. In our study, absent or diminished fetal bladder filling and intertwin differences in fetal growth did not precede the ultimate diagnosis of TTTS. We were also unable to show differences between TTTS cases and non-TTTS cases in Doppler studies performed prior to the scan revealing TTTS. Increased nuchal translucency thickness²³, eventually combined with abnormal flow patterns in the ductus venosus (DV)²⁴, folding of

the intertwin membrane²³, and the sonographic absence of arterioarterial anastomoses²⁵ have been shown to be valuable in the prediction of future TTTS. Nuchal translucency thickness and folding of the intertwin membrane could however not be identified as TTTS predictors, nor did the DV show abnormal flow in any of the fetuses in our study. These different findings may be related to our relatively small sample size. Therefore, although our own results suggest otherwise, we still think that the observation of these previously investigated TTTS predictors should alert obstetricians and should thus lead to increased surveillance possibly leading to timely TTTS detection. It should be realized, however, that absence of these factors does not guarantee that TTTS will not develop.

Fetoscopic laser therapy

Once TTTS has been diagnosed, parents are counseled on all five different treatment modalities available: the natural history of “wait and see”, termination of pregnancy (if gestational age is under 24 weeks), selective feticide, serial amniodrainage, and fetoscopic laser coagulation of the placental anastomoses. In our series, none of the patients have chosen one of the first two options. As outlined before, a selection bias may already have occurred at the referring clinic. The results of the study performed by Senat *et al.*¹⁹, in which chances of fetal survival were higher and neonatal morbidity lower after fetoscopic laser treatment compared to amniodrainage, are used in our counseling. All referred patients had a strong preference for fetoscopic laser coagulation. Selective feticide is performed in situations of irreversible fetal damage, like intracranial bleeding, in order to save the co-twin. This option is also used as a first- or second choice in some cases at Quintero Stage 4 and technical difficulties which limit complete laser occlusion of all vascular anastomoses.

Although laser therapy has resulted in better outcome than any other treatment tried thus far, it should be realized that even in the best series at least one of the twin babies is lost in approximately 50% of affected pregnancies (269 pregnancies with ≤ 1 survivor in 534 pregnancies)^{4,19,26-28}. Neurological impairment hits another 5 to 17%²⁹⁻³² of survivors. Is this “as good as it gets^{33?}” The outcome of laser therapy remains suboptimal because of a high rate of persistence, recurrence or even reversal of TTTS, as well as the occurrence of twin anemia-polycythemia sequence, that may occur due to incomplete ablation or recanalization of anastomoses³⁴⁻³⁷. This may implicate a continuous burden for the fetal volume loading of both donor and recipient twin. With the increasing popularity of laser ablation as first-line treatment for TTTS, attention should therefore not only be shifting towards early diagnosing TTTS, but also to the follow-up of the fetal hemodynamics of both twins after laser therapy. Ultrasound examination, Doppler and echocardiography are the indicated tools to do so.

Doppler in TTTS

Doppler ultrasound examination is a useful tool to detect and follow-up fetal hemodynamic changes in TTTS. In **chapter 5**, we have shown that donor twins experience a state of transient volume overload and that the cardiac function of recipients improves after laser therapy for TTTS. These findings confirm studies by others³⁸⁻⁴². New and intriguing findings in our study were the changes in cerebral and renal blood flow after laser therapy for TTTS. These are interesting results in view of the neurological morbidity among TTTS survivors that is still reported despite laser treatment²⁹⁻³². In addition, in TTTS treated conservatively, up to 30% of donors suffer from renal failure and/or renal tubular dysgenesis due to chronic volume depletion and renal hypoperfusion *in utero*⁴³⁻⁴⁵. In our study, however, the changes in the middle cerebral artery (MCA) and renal artery (RA) that were found were not associated with long-term neurological or renal sequelae. These new insights can be used in clinical practice for the counseling of parents in TTTS cases with abnormal flow in the MCA and RA.

The finding of RA pulsatility index (PI) significantly being decreased in TTTS recipients, may be interesting to use in clinical practice. The hypervolemic status is thought to cause increased renal flow (by means of decreased RA PI) in order to eliminate excess fluid. In monochorionic twins presenting with polyhydramnios without accompanying oligohydramnios, this decreased RA PI in recipients may be used as a novel tool for the detection of future TTTS cases. As shown in **chapter 4**, we have identified isolated polyhydramnios as a TTTS predictor. Adding the measurement of the RA PI may improve the early identification of pregnancies at increased risk for TTTS. Cases with only polyhydramnios and no hemodynamic involvement would be distinguished from those with polyhydramnios and increased RA flow. We speculate that the latter group, with disturbed hemodynamics already, may develop into a full blown TTTS sooner or later and should therefore be monitored even more closely. However, as long as no studies have been performed to test this hypothesis, frequent ultrasound examinations remain indicated in all monochorionic twins with single polyhydramnios.

TTTS and the fetal heart

In **chapters 6 and 7** of this thesis, we have focused on the cardiac consequences of TTTS and laser therapy for both donor and recipient twins. It has been shown, that cardiac malformation rates in monochorionic twins with and without TTTS are significantly higher than in the general population^{46,47}. The recipient fetuses are most commonly affected. The mechanisms behind this increased rate of cardiac disease remain unidentified; however, both increased preload and afterload are likely to be involved. Primarily, volume overload due to the placental vascular anastomoses in monochorionic twins causes high cardiac output (CO) in the recipient twin. A secondary effect, in reaction to this increased volume loading and sheer wall stress,

is that vasoconstrictive hormones, such as endothelin-1⁴⁸, are released. Consequently, cardiac afterload increases, leading to right ventricular hypertrophy^{46,49,50}, presenting sonographically as an increased cardiothoracic ratio. In **chapter 6**, we have shown that cardiothoracic ratios of recipient twins in TTTS before therapy are significantly increased compared to donors and non-TTTS monochorionic twins. This is probably due to recipients being most often affected by prenatal cardiac compromise^{47,51-55}. With this study, we have shown that a simple measurement like the cardiothoracic ratio may provide us with information that leads to the same conclusions as the far more complex echocardiographic examination.

After having performed laser therapy for TTTS, fetal volumes are expected to normalize and to become equally distributed^{40,42}. In **chapter 7** we have shown that CO of donors and recipients after laser therapy are comparable and remain so during gestation. We also found, however, that median CO/kg in donors and recipients after laser treatment was significantly higher as compared to singletons. This rise in CO after laser therapy was a striking result and has not been published before.

Increased CO is known to occur due to either increased preload or decreased afterload, or a combination of both. However, since we found an increased CO *after* successful laser treatment, which should normalize fetal volumes^{40,42}, the model of increased preload as causal factor for the rise in CO seems less likely. It seems more plausible to link the rise in CO after laser therapy with decreased afterload. Theoretically, the common single monochorionic placenta with inter-twin vascular connections may be related to a greater number of placental vessels as compared to singletons, leading to a much lower shared placental resistance of monochorionic twins as compared to normal singletons, resulting in a decreased afterload and a rise in CO.

This model of decreased afterload, however, seems not compatible with several studies that have shown increased levels of endothelin-1⁴⁸ and angiotensin II⁵⁶⁻⁵⁸ in the recipient's circulation, causing *increased* afterload. In view of the results of our study in **chapter 7**, we speculate that raised concentrations of circulating peptides are present, however, apparently without immediate effect on fetal CO. If the released hormones would act properly in TTTS fetuses, all recipients would show systemic hypertension. Although fetal and neonatal hypertension have been described anecdotally^{57,59}, a recent study at our institution could not detect significant differences in systolic blood pressure of donors and recipients born after fetoscopic laser therapy⁶⁰. Moreover, endothelin-1 levels in donor and recipient twins were similar in this study⁶⁰.

The finding of increased CO after laser therapy may also be explained as follows. As shown by Herberg *et al.*⁴⁷, the frequency of congenital heart disease in TTTS survivors after laser therapy is comparable to that after serial amnioreduction⁴⁶, although a lower frequency was expected after causal treatment. This suggests that factors very early in pregnancy may lead to cardiac remodeling that cannot be corrected by fetoscopic laser therapy. From around 28 days after fertilization, vascular communication between the two embryos via the placenta is possible⁶¹.

This very early onset of intertwined vascular transfusion may initiate a process of cardiovascular remodeling. Irreversible fetal changes may already have occurred before laser therapy, which may have resulted in severely altered fetal circulations that are beyond regulatory control. The persistence of increased CO, as well as the increased frequency of congenital heart defects despite laser therapy, may be reflections of these permanently changed cardiovascular systems.

Besides the increased CO that we found to exist in donors and recipients after fetoscopic laser therapy for TTTS, we also found significantly increased diameters of the great artery diameters compared to singletons (**chapter 7**). This finding is in line with the cardiomegaly in donors and recipients after laser therapy that was shown in **chapter 6**. The increased CO after causal treatment may therefore well be related to fetal cardiomegaly. The opposite relation, however, may be true as well. It might be hypothesized that, with two fetal circulations connected, a bigger circulating volume is involved in monozygotic twinning as compared to singletons. It has been acknowledged, that blood flow plays a critical role in the development of heart valves, chambers, and arteries⁶². For example, ascending aorta and pulmonary artery stenosis are known to be caused, at least partly, by diminished blood flow^{63,64}. Simultaneously, the accompanying great vessel often shows an increased diameter as a result of redistribution of flow, meaning an increase of contralateral intracardiac flow⁶⁵, suggestive of an accelerated growth of the great arteries in cases of abnormal and chronic rise in CO. In this view, assuming that an increased amount of blood volume is pumped through all placental and fetal vessels starting shortly after fertilization, it would possibly lead to enhanced growth of the great arteries.

The increase of cardiothoracic ratios (**chapter 6**) and median CO/kg (**chapter 7**) in donors after laser therapy are of special interest, since the literature reports no or little cardiac pathology among donor fetuses^{43,44,46,52,53}. Indeed, donors experience a period of volume overload after laser therapy and the same cascade of cardiovascular remodeling as occurs in recipients before laser treatment may then be initiated. Timing, duration and amount of volume loading in donors after laser therapy may however be different from recipients, which may explain the fetal heart sizes and CO of donors remaining smaller than those of recipients. Our studies suggest that labeling donors as not being at risk for cardiac involvement and disease is not necessarily true. Two recent papers have shown that surviving donor twins may suffer from complications due to vascular stiffness and raised cardiac afterload after birth, which has been associated with adult onset of cardiovascular disease such as hypertension and ischemic heart disease^{66,67}.

It is reassuring that, in the literature, the incidence of prenatal congestive heart failure (55% of recipients) was much higher than the incidence of congenital heart disease after birth (13.7% of recipients)⁴⁷. This illustrates the remarkable adaptive capacity of the fetal heart. Intrauterine cardiac failure may apparently be reversed during fetal life or shortly after birth.

This is an important finding that should be mentioned in the counseling of parents. Prenatal cardiac failure apparently has a good chance to disappear after birth. However, in view of the increased prevalence of congenital heart disease and right ventricular outflow tract obstruction that still exists among surviving recipients and to a lesser extent among donors, it remains of importance to have postnatal echocardiography performed.

Conclusion

In conclusion, knowledge about monochorionic twinning and its complications such as TTTS is crucial for clinicians participating in the care of pregnant women and for children born as monochorionic twins. With the studies described in this thesis, we aimed at designing a framework that is helpful in providing high quality prenatal care for monochorionic twins. A first-trimester scan to establish chorionicity is vital and should be followed by biweekly ultrasound examinations and patient instructions. Specific “guidelines” that may be used both before and after fetoscopic laser treatment for TTTS are provided in the recommendations for clinical practice (**chapter 9**).

We hope that the studies presented in this thesis will contribute to increased awareness of the potential problems and optimization of management of this unique subset of pregnancies: the monochorionic twins.

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