Cardiovascular compromise in monochorionic twins

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PART IV

SUMMARY AND DISCUSSION

CHAPTER 10

GENERAL DISCUSSION

During pregnancy, the fetus depends on nutrients and oxygen transferred across the placenta into the umbilical vein. An adequate placental circulation is vital for the development of the fetus and for the formation of a functional cardiovascular system. A fetus possesses the ability to adapt to different hemodynamic loading conditions. Although these adaptive circulatory changes are necessary to sustain intrauterine life, they are thought to modify the development of the cardiovascular system and 'program' the fetus for cardiovascular morbidities later in life. The idea that blood flow in itself exerts physical forces that play important roles in the vascular pathophysiology was first postulated over a century ago by Thoma.[1] His experiments demonstrated that blood vessels morphologically remodel over time and either widen or regress, in order to adapt to the amount of flow they receive. A possible explanation of this phenomenon is that vessels remodel and change in size in response to shear stress.[2]

Studies into the human fetal cardiovascular physiology are essential to our understanding of normal fetal development, as well as to the evaluation of fetal disease. Modalities to evaluate fetal hemodynamics include Doppler ultrasound and fetal echocardiography. Tools used in this thesis to assess cardiac function include the myocardial performance index (MPI, also called 'Tei-index'),[3] speckle tracking[4] and color-coded Tissue Doppler Imaging (cTDI).[5]

cTDI is a relatively new Doppler derived tool, in which recordings are easy to obtain in a simple four-chamber view. It focusses on lower frequency shifts, which enables measurements of the lower velocities of myocardial wall motion. Our research group has introduced a promising new approach to assess fetal cardiac function through the measurement of time intervals of the myocardial wall motion with cTDI (chapter 2, Figure 1). Time intervals are independent of the angle of insonation and region of interest (ROI) size, and feasibility and inter- and intraobserver agreement are excellent for global heart ROIs. This technique is potentially useful in daily obstetrical care, but future research should be conducted to investigate its discriminative ability and diagnostic accuracy.

THE INFLUENCE OF HEMODYNAMIC DISTURBANCES IN MONOCHORIONIC TWINS

Fetuses in monochorionic twin pregnancies experience specific hemodynamic challenges. Vascular anastomoses in the shared placenta allow for transfusion of blood from one fetus to the other. In the majority of monochorionic twin pregnancies, feto-fetal transfusion is balanced and the placental territory is equally divided. In case of twin-twin transfusion syndrome (TTTS) or selective fetal growth restriction (sFGR), fetal hemodynamics are altered. The circulation of the recipient or larger twin becomes hyperdynamic due to hypervolemia and/or increased cardiac output. The donor or smaller twin will have a decreased cardiac output due to hypovolemia or hypoperfusion.

Accurate assessment of fetal hemodynamics and quantification of cardiovascular compromise is needed to gain insight into the developmental processes in monochorionic twin pregnancies. With this thesis we aimed to study the short-term and long-term effects of fetal hemodynamic adaptations in monochorionic twin pregnancy, and to answer the question whether Doppler (echocardiographic) measurements have a predictive value for adverse outcomes.

Fetal cardiovascular hemodynamics in twin-twin transfusion syndrome

In the event of TTTS, recipient and donor twins are confronted by extremely different cardiac loading conditions in utero; hemodynamics that are even further imbalanced by ablation of the vascular anastomoses in fetoscopic laser surgery. Disturbance of the fragile equilibrium can ultimately lead to cardiovascular decompensation as well as to profound disturbance of brain perfusion. Both twins are therefore at risk for the development of cardiac (functional) abnormalities, intrauterine fetal demise (IUFD), persistent pulmonary hypertension of the newborn (PPHN) and neurodevelopmental impairment (NDI). In the next paragraphs we will discuss the new evidence we have gathered regarding the possible relationship between cardiovascular compromise in TTTS twins and the beforementioned adverse events.

Cardiac abnormalities

Fetoscopic laser surgery ensures cardiovascular improvement in affected twins, but our studies show that it does not prevent the occurrence of cardiac defects at birth. The prenatal diagnosis of a congenital heart defect (CHD) in multiple pregnancy can, however, be challenging. We have found a low prenatal detection rate of 21% in case of TTTS (chapter 8), explained by the impaired image acquisition due to the polyhydramnios, in combination with the often excessive movements of the recipient twin and the 'stuck', anhydramniotic donor. Our studies showed that the focus should

not only lie on the notably enlarged heart of the recipient twin. We provide evidence that also a large number of donors is affected by cardiac abnormalities. In addition to an increased risk of pulmonary stenosis, we have found that donors are at an increased risk of left-sided defects such as bicuspid aortic valves and critical coarctation of the aorta (CoA). Clinicians have to take this into account when presenting the good news that the performed laser surgery has been successful in preventing demise, and tell the parents that expert echocardiographic follow-up should rule out any (acquired) anomalies. If a cardiac anomaly is absent however, results from our large prospective follow-up study may reassure parents that cardiac function normalizes after laser and is already normal at birth. Our results indicate an influence of hemodynamic alterations on cardiac development in monochorionic twins. The etiology of CHDs is, however, considered to be multifactorial. To what extent the twinning process, a morphogenic anomaly in itself, is responsible for the development of (other) cardiac anomalies remains a question.

Intra-uterine fetal demise

In our meta-analysis we have found an association between abnormal preoperative Doppler flow velocity waveforms and post-laser IUFD (chapter 4). Even though our results may not be surprising since abnormal Dopplers pre-laser correspond with advanced TTTS stage, the findings could be used in a future study with the aim to build a prediction model for IUFD. A large multicenter study, with comparable expertise and hardware, could allow for multivariate analyses into the interference of sFGR and twin anemia polycythemia sequence (TAPS), but also factors such as Quintero stage, hydrops and gestational age at TTTS diagnosis, on fetal echocardiography and Doppler parameters for IUFD. If the risk of demise can be predicted with reasonable accuracy, additional counseling time should be spent on cord occlusion as a back-up plan if laser surgery seems technically challenging. Better understanding of the underlying pathophysiology of TTTS, and knowledge on which fetuses are at high risk for demise, may also help in the development of strategies to protect the twins during laser surgery. In addition to timely referral by clinicians in referral centers, adequate training of fetal surgeons, and technical developments, we could investigate options to stabilize the fetal circulation before and during laser surgery, in order to decrease the fetuses' vulnerability to acute preload and afterload changes. At this time, only pre-laser administration of nifedipine has been reported as a possible agent to improve recipient survival, without benefit for the donor twin.[6, 7] Digoxin has been used in the setting of stage IV TTTS but its effectiveness has never been studied systematically. Whilst the potential of nifedipine needs to be confirmed in a randomized controlled trial, it raises the potential for adjuvant medical treatments to assist or improve current treatment.

Neurodevelopmental impairment

We conducted the first large study into the association between perioperative hemodynamic changes in TTTS twins treated with laser surgery and neurodevelopmental outcome at the age of two (chapter 5). We have found that hemodynamic alterations are not only associated with IUFD or the development of cardiac defects, but may also contribute to poor neurological outcome. In our cohort, 4% of TTTS infants were affected by severe cerebral injury, and 5% were affected by NDI. The exact pathophysiology of these brain lesions remains unclear. Moreover, (transient) cerebral lesions could remain undetected by routine monitoring techniques. In a study by Van Aertsen *et al.*[8] third trimester MRI detected a brain lesion after laser surgery for TTTS in 9% of pregnancies. The authors state that the prevalence of brain lesions detected by MRI is higher compared to prenatal ultrasonography alone, making MRI a useful adjunct to detect antenatal brain lesions in twin pregnancies after in utero treatment for TTTS. In most countries such as the Netherlands, however, fetal MRI is not routinely performed after laser. Furthermore, the number of brain lesions detected after laser surgery does not necessarily correlate with the number of postnatal lesions or outcome at the age of two. For now, MRI remains only indicated in cases with suspected brain lesions on ultrasound, or as part of a research protocol.

Fetuses that have experienced large perioperative hemodynamic alterations are at higher risk for NDI, but the mechanism to exactly how or when cerebral injury occurs is not explained so far. Did it occur during pregnancy, as a result of the TTTS or laser surgery, or after delivery due to prematurity? To answer this question, we need a large prospective study into peri-operative risk factors, fetal neurosonography before and after laser, and pre- and postnatal MRI, in relation to neurodevelopmental outcomes at the age of two. Moreover, future research could be conducted into the potential of giving magnesium or other potential neuroprotective agents at the time of laser surgery. Neuroprotective agents have been shown to decrease the incidence of cerebral palsy in preterm delivery, but possibly all women with TTTS will benefit from prophylactic administration of such agents even if preterm delivery is not thought to be an immediate risk.

Persistent pulmonary hypertension of the newborn

Awareness of the fetal physiology is also relevant for many aspects of postnatal circulatory care. At birth, infants transition to newborn life by means of complex cardiovascular changes to ensure neonatal survival. Cardiac adaptation in TTTS can cause remodeling of the pulmonary vasculature, which may result in failure of the transition and lead to PPHN. With the data presented in chapter 6, we hope to raise awareness about the 10-fold increased risk of PPHN in (treated) TTTS twins compared to uncomplicated monochorionic twins.

Selective fetal growth restriction and fetal hemodynamic alterations

In monochorionic twin pregnancies complicated by sFGR, altered blood flow conditions affect cardiac development in both twins differently, and cardiac dysfunction occurs in both the larger and the smaller twin. sFGR cases can have a large amniotic fluid difference, not yet meeting the diagnostic criteria for TTTS, but indicating a form of hemodynamic imbalance in these pregnancies (chapter 3).

A higher risk for long-term neurological or cognitive impairment in monochorionic twins with sFGR or with a large birth weight discordance is found, if compared to uncomplicated monochorionic or dichorionic twins, with a disadvantage for the smaller twin.[9] As for congenital heart defects, we have found an increased rate of critical CoA and pulmonary stenosis in sFGR compared to uncomplicated monochorionic twins. In chapter 9 seven cases of coarctation of the aorta (CoA) in monochorionic twins are presented; all were the smaller twin of monochorionic pairs complicated by sFGR. Narrowing of the aortic arch may occur secondary to the hemodynamic disturbances (decreased perfusion and decreased left-sided cardiac output). An interesting finding of this study was that three of the larger co-twins had pulmonary stenosis. The association between TTTS and right ventricular outflow tract obstruction (RVOTO) has been reported extensively, but reports of RVOTO along with other complications in monochorionic twins are sparse. In sFGR, the larger twin perfuses a variable proportion of the placenta of the smaller one, mainly via arterio-arterial (AA) vascular anastomoses. This involves by definition an increase in cardiac output and potentially a hyperdynamic circulation in the larger twin, resembling a milder form of the situation observed in monochorionic twins with an acardiac fetus. The myocardial adaptation to the hyperdynamic circulation in the larger twin may eventually result in pulmonary stenosis.

IS THE QUINTERO SYSTEM ENOUGH?

Fetal medicine specialists have tried to find prognostic factors, including cardiac parameters, of outcomes in monochorionic twin pregnancies. The use of more advanced functional parameters has increased our knowledge of pathophysiology in TTTS, but do they help to predict and manage the disease?

Since 1999 TTTS is staged according to the Quintero staging system,[10] a system based on the evaluation of amniotic fluid, bladder filling and fetal Dopplers. The Quintero staging system does not provide information on prognosis nor does it predict IUFD or NDI. To date, no tool is available to reliably predict the development of TTTS in advance. From a pathophysiological perspective the cardiovascular system is likely affected early in the disease pathogenesis. And even though compromised cardiac function is thought to contribute significantly to the mortality rates after TTTS, cardiac (functional) abnormalities are not taken into account in this disease severity classification system. Over time specific cardiovascular staging systems have been proposed including the Children's Hospital of Philadelphia (CHOP) score[11] and the Cincinnati staging system,[12] in addition to the use of general cardiovascular wellbeing staging systems such as the cardiovascular profile score (CVPS).[13] Several attempts to include fetal ultrasound-based cardiac parameters in the risk stratification of disease did, however, not influence current management of TTTS so far. We have found that intertwin discordance in left ventricle MPI and right ventricle MPI may help to differentiate between future TTTS and pregnancies with discordant amniotic fluid volume that do not develop into TTTS (chapter 3). Using cardiac time intervals measured by cTDI, future recipient twins can be identified and future TTTS can be discriminated from sFGR and uncomplicated monochorionic twin pregnancies. Possibly, Tissue Doppler is more sensitive to detect subtle cardiac dysfunction compared to conventional Doppler.

The question whether echocardiographic parameters should be included in the TTTS disease severity staging system remains unanswered. The lack of correlation between severity of cardiac disease and IUFD may be explained by, next to the difficulty of measurement such as the MPI, the effectiveness of laser surgery for improving cardiac function. Other variables associated with laser surgery, and accounting for the vast majority of long-term morbidity related to monochorionicity at large, such as preterm premature rupture of membranes (PPROM), unequal placental share and preterm delivery, become the predominant determinants of fetal mortality after correction of the hemodynamic imbalance. Future research should focus on prevention of complications such as iatrogenic PPROM, and subsequent preterm birth. A potential noninvasive treatment option for TTTS could be high-intensity focused ultrasound (HIFU), but its

feasibility, safety and efficacy have yet to be determined.[14] Until (3D) ultrasound placental mapping of all vascular anastomoses is possible, technical improvements such as flexible mini-fetoscopes may increase the chance of visualization of the vascular equator and the possibility of ablation of the anastomoses using minimal energy, thereby minimizing the placental damage and lowering the risk of PPROM.[15]

The ultimate goal is accurate prediction of the syndrome, followed by a preferably noninvasive treatment with minimal complications. If referring hospitals are able to stratify between future TTTS and uncomplicated monochorionic twin pregnancies, unnecessary hospital visits or referrals (important in countries with large travelling distances) may be avoided, and cases who are likely to develop TTTS will benefit from expert follow-up. Early detection of TTTS allows for advising of patients to travel to a facility where laser surgery is performed. The preceding events of TTTS are however underexplored and the pathophysiological triggers involved in the transition from balanced to unbalanced intertwin transfusion resulting in TTTS remain largely unknown. There are some early prenatal ultrasound criteria available for risk estimation regarding the development of TTTS (intertwin discordance of crown-to-rump length, nuchal translucency and ductus venosus flow velocity waveform), but these have the disadvantage of poor positive predictive values.[16, 17] The potential utility of cardiac time intervals and MPI in the triage of amniotic fluid discordance should be investigated in large (multicenter) studies, validating our estimated cut-off points (chapter 3). Furthermore, automatized measurements are needed since measurements of MPI or cardiac time intervals require expert hands and are time consuming. If TTTS can be predicted in cases with an amniotic fluid discordance based on cardiac parameters, we could investigate whether these cases could benefit from early laser treatment in a future randomized controlled trial.

IMPLICATIONS FOR COUNSELING AND CARE OF MONOCHORIONIC TWIN PREGNANCIES

Future parents of monochorionic twins worry not only about survival of both twins, but also about the future health and quality of life of their children. In making clinical decisions in a complicated course of a monochorionic twin pregnancy, clinicians should be able to counsel based on the best available evidence regarding the consequence of specific complications. In the next paragraphs we will discuss what our new insights could mean for the management of monochorionic twin pregnancies. We do acknowledge that the access to specialized care differs across the world, preventing the implementation of our recommendations in countries with little access to health care. In an ideal world we would manage monochorionic twins via a standard protocol, including fetal Dopplers, echocardiography and neurosonography, with prospective collecting of data for research purposes and for control of treatment outcome. If every monochorionic twin is assessed for wellbeing in a routine setting, advanced TTTS disease and other adverse outcomes may possibly be prevented. We present some of the largest studies to date, but the absolute number of adverse events is still small. To guide future clinical practice, implementing a core outcome set for TTTS and sFGR within future research studies is required to ensure that the results of all studies can be compared, contrasted and combined.

Cardiovascular surveillance in monochorionic twins

Results from this thesis underline the importance of cardiovascular surveillance in monochorionic twin pregnancies. Our data support the recommendations of the American Institute of Ultrasound in Medicine that monochorionic twin pregnancy should be considered an indication for fetal echocardiography at mid-gestation.[18] Detailed fetal echocardiography by a well-trained team of fetal specialists is mandatory for all monochorionic twins to confirm normal anatomy or to perform a comprehensive investigation if abnormalities are suspected. Knowledge on the specific lesions that can be encountered, including those that may evolve, are compulsory. Prenatal diagnosis, counseling and tailored care of pregnancy in case of CHD should take place in a tertiary referral center with neonatal cardiothoracic facilities. In case of uncomplicated monochorionic twin pregnancy clinicians should carefully examine both neonates at birth and refer for echocardiography in case of suspected CHD or PPHN.

An accurate prenatal diagnosis of a heart defect is critical in determining the requirement of immediate postnatal treatment, predicting the course of (surgical) treatment and assessing the prognosis of the defect. Furthermore, a correct diagnosis is essential to enable parents to make informed decisions regarding the management options in the

current pregnancy. These include: continuation of pregnancy, selective termination of the affected twin and in some occasions, termination of the complete pregnancy. The management does not only depend on disease severity and likely outcomes of the affected twin, but also on the risks to the normal twin, involved with possible medical interventions. Selective termination gives parents the option of discontinuing the life of a fetus with a potentially poor long-term outcome, but even in serious cardiac conditions differentiation of poor outcomes is not always possible. As we have learned, acquired CHDs such as RVOTO may be transient, and critical CoA may have stent implantation as a valid treatment option. Selective feticide furthermore comes with a significant risk of PPROM and immature labor as well, with the risk of losing both twins.

Care for pregnancies complicated by TTTS

At time of TTTS diagnosis, a comprehensive assessment of both fetuses should include biometry, arterial and venous Dopplers and evaluation of cardiac function. The low prenatal detection rate of CHDs in TTTS twins as demonstrated in chapter 8, and the fact that RVOTO may evolve even after delivery and can become apparent after postnatal decrease in pulmonary vascular resistance, highlights the importance of caution in counseling in early pregnancy and the need for serial echocardiograms. Next to the detection of possible acquired valvular pathology, follow-up fetal and neonatal echocardiograms are warranted after TTTS treatment, when scanning conditions normalize, to rule out missed structural anomalies at earlier scans.

Since TTTS twins are at increased risk of PPHN, and the development of PPHN is difficult to predict, we advise that all TTTS twins should be delivered in a tertiary care center with inhaled Nitric Oxide (iNO) treatment options. In the absence of conclusive clinical trials determining the optimal clinical management of clinical presentations of the preterm infant such as PPHN, treatment decisions in the neonatal intensive care unit (NICU) frequently rely on applying knowledge of physiology and pathophysiology to identify optimal therapy.

The perinatal event most strongly associated with NDI in monochorionic twins is the demise of one twin, followed by severe NDI in 26% of co-twins.[19] Key benefit of fetoscopic laser surgery is separation of the fetal circulations prior to IUFD of a twin and thereby preventing the subsequent cerebral injury. In 5% of TTTS survivors however, infants are still hampered by NDI. Our study indicates that perioperative fetal hemodynamic changes in TTTS twins treated with laser surgery may contribute to poor neurological outcome (chapter 5). We therefore advise both fetal and neonatal neurosonography, and routine long-term follow-up of all TTTS twins, especially for those with signs of hemodynamic deterioration after laser surgery.

Care for pregnancies complicated by sFGR

Antenatal surveillance in sFGR is not only mandatory to ascertain the condition of the smaller twin, but to assess fetal wellbeing of both twins, since both twins in sFGR are at risk of CHDs. Moreover, examining the heart of the smaller twin may be extremely difficult due to the small cardiac size. We therefore want to stress the importance of dedicated fetal echocardiography and postnatal surveillance in twin pregnancies complicated by sFGR.

Up to 26% of monochorionic twins have a birthweight less than 1,500 g.[20] A critical CHD such as CoA poses particular challenges in these very low birth weight infants. It may leave parents with difficult choices such as selective termination in case of early diagnosis or palliative care when born with critical heart disease. Our case series (chapter 9) presents new possibilities for treating infants with critical CoA. We have demonstrated that primary coronary stent implantation is a feasible bridging therapy to surgery. Stent implantation can lead to postponement of surgery, and consequently higher infants' weight at definitive surgery.

FINAL CONCLUSION

With the studies described in this thesis, we were able to investigate cardiovascular compromise in complicated monochorionic twin pregnancy in great detail. The results are the next step in prediction of disease and adverse outcomes, and help in the management of monochorionic twin pregnancies.

All clinicians caring for monochorionic twins should perform an echocardiogram at mid-gestation and should carefully examine both neonates at birth. In case of abnormal perioperative fetal Dopplers in TTTS, we should be aware of the increased risk of IUFD and NDI. In all surviving TTTS twins, but also in sFGR twins, cardiac abnormalities should be ruled out by follow-up fetal and neonatal echocardiography. Routine long-term follow-up should be available to all TTTS twins, since TTTS may also have an impact beyond the perinatal phase.

Both cTDI and MPI are potentially valuable techniques which can be used in the risk stratification in monochorionic twins, but future prospective studies are needed to validate our results. We should join forces with other fetal therapy centers in order to create large cohorts with core outcome sets, and to facilitate implementation of cardiac function measurements, with the ultimate aim of improving both short- and long-term outcomes in monochorionic twins.

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