Cardiovascular compromise in monochorionic twins

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CONTENTS

PART I

OVERVIEW

CHAPTER 1

GENERAL INTRODUCTION

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FETAL CIRCULATION

The development of the human heart starts early in gestation, and the fetal circulation is initiated with the beating of the heart tube at gestational day 22.[1-3] Cardiac formation and the dynamics of blood flow, or hemodynamics, are intrinsically linked. To facilitate development in the relatively hypoxemic intrauterine environment, the fetus possesses structural, physiological and functional cardiovascular adaptations that are fundamentally different from the neonate or adult.[2, 3] Hemodynamic load on cardiac tissues, which are blood pressure and wall shear stress exerted by blood flow, modulate cardiac development and are required for proper cardiac formation.[4]

David Barker first documented the relationship between infant birth weight and adult onset disease,[5, 6] followed by many reports on interaction between environment and susceptibility to disease. The contribution of the placenta to this association as a risk factor for the development of congenital heart defects (CHDs)[7, 8] has more recently been identified. The placenta is the unique organ of pregnancy that supports the growth and development of the fetus. Disruptions in placental development and function may have dramatic effects on the fetus and its development.[9]

Figure 1. Fetal circulation. (Reprinted from Sadler TW, Langman's Medical Embryology, 12th edition, Wolters Kluwer Health, 2011)

In the fetus, oxygenated blood is delivered from the placenta to the body via the umbilical vein, entering the inferior vena cava via the ductus venosus (Figure 1). The majority of this oxygenated blood passes through the right atrium into the left atrium through the foramen ovale to enter the systemic circulation, providing oxygen to the brain and myocardium. The more deoxygenated blood from the inferior and superior vena cavae passes through the right heart, pulmonary artery and ductus arteriosus to the systemic circulation. The pulmonary vascular resistance is greater than the systemic vascular resistance; blood flow from the right heart largely bypasses the lungs to perfuse the lower body and return relatively deoxygenated blood to the placenta. The placental circulation, the major determinant of right heart afterload, is generally of low resistance, whereas cerebrovascular resistance, the major determinant of left heart afterload, is highly responsive to changing conditions and autoregulatory.[10]

Fetal circulation in monochorionic twins

In monochorionic twins, fetuses have a shared circulation via placental vascular anastomoses. Under normal conditions, the feto-fetal transfusion through these anastomoses is balanced and the placental territory is equally divided. Feto-fetal and feto-placental hemodynamics are altered in case of twin-twin transfusion syndrome (TTTS) or selective fetal growth restriction (sFGR). These alterations may cause modifications in physiologic growth and maturation of the fetal heart[11, 12] and may impact the prognosis.

In TTTS, which affects 10-15% of monochorionic twin pregnancies, the intertwin blood transfusion is unbalanced leading to hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient.[13, 14] Fetal cardiovascular development in these twins is presumably influenced by genetic as well as environmental and hemodynamic factors such as blood flow, shear stress, preload and afterload. Cardiac dysfunction in TTTS mainly occurs in recipients.[15] Cardiac overload and hypervolemia in these recipient twins may result in shear stress and ventricular hypertrophy, which can cause abnormal development of the cardiac valves through a cascade of events. Right ventricular enlargement may cause severe tricuspid valve regurgitation, leading to reduced flow across the pulmonary valve, which may impair growth and development of the right ventricular outflow tract. Likewise in donor twins, hypovolemia results in decreased flow velocities, and decreased left-sided cardiac output may impair the development of the left ventricular outflow tract.[16] Ablation of the vascular anastomoses via fetoscopic laser surgery, which is the preferred treatment option for TTTS, results in acute hemodynamic changes in both the donor and the recipient fetus.

sFGR complicates another 10-15% of monochorionic twin pregnancies,[17] and is characterized by growth discordance and an unequal placental share. Altered blood flow conditions may affect cardiac development of monochorionic twins with sFGR differently, and cardiac dysfunction occurs in both the larger and the smaller co-twin, even in the absence of TTTS.[18]

Evaluation of fetal circulation

To evaluate hemodynamics of the fetal cardiac circulation and to probe pathophysiology of fetal cardiovascular diseases, Doppler and fetal echocardiography can be used.

Doppler ultrasound technology uses sound waves and is based on the Doppler shift, a physical principle of the change of ultrasound frequency when aimed at the moving object (e.g. red blood cell).[19, 20] In obstetrics, the umbilical artery, middle cerebral artery and ductus venosus are used for monitoring the physiological state of the fetus. Flow of the umbilical artery is most often quantified by the pulsatility index (PI).[21, 22] This index reflects the downstream vascular resistance by quantifying the differences between the peak systolic and the end-diastolic velocity in each cardiac cycle. A high pulsatility index indicates a high vascular impedance and possible feto-placental compromise. In extreme circumstances, the blood flow at the end of diastole may be absent or even reversed. The middle cerebral artery is used for evaluating the fetal cerebral circulation and provides information on the brain-sparing effect.[23] Information on the true velocity (peak systolic velocity, PSV) of the blood flow may also be obtained from the middle cerebral artery.[24] The ductus venosus has a central role in the distribution of highly oxygenated umbilical venous blood to the fetal heart, and its waveform is related to the pressure-volume changes in the cardiac atria. The ductus venosus can be used in the monitoring of any fetal condition that affects forward cardiac function, with decreased forward flow during atrial systole (a-wave) as the most sensitive and ubiquitous finding.[25]

In cases of suspected fetal cardiac dysfunction, echocardiography is required to identify the underlying mechanism. Next to conventional echocardiography three tools to evaluate fetal cardiac function are the myocardial performance index (MPI, also called 'Tei-index'),[26] speckle tracking[27] and color-coded Tissue Doppler Imaging (cTDI).[28] The MPI is a Doppler derived parameter of global ventricular function. The index is calculated as the sum of the isovolumetric contraction (ICT) and relaxation time (IRT) divided by the ventricular ejection time (ET). Within the index, the ICT mainly reflects systolic cardiac function and the IRT diastolic function.[26] In the 'modified' MPI method proposed by Raboisson *et al.*[29] and Hernandez-Andrade *et al.*,[30] the aortic and mitral Doppler valve-clicks are used as demarcation for the time intervals. Speckle tracking is a gray-scale based tool to assess cardiac ventricular function. The method

identifies myocardial speckle patterns on a two-dimensional B-mode ultrasound image. The speckles are recognized in the subsequent frames of a cine-loop sequence and referenced back to their position in the previous frame. Based on the data obtained, the myocardial displacement can be 'tracked' and velocity vectors can be generated. Comparison of adjacent vectors then allows to calculate the actual displacement, velocity, deformation (strain) and velocity at which deformation occurs (strain rate) in the cardiac wall.[31] Tissue Doppler Imaging (TDI) has been used since the early 1990s in adult echocardiography,[32] but is a relatively new technique in fetal echocardiography. Pulsed-wave TDI technique is similar to pulsed-wave Doppler, but focuses on lower frequency shifts, which enables measurements of the lower velocities of myocardial wall motion. Color-coded recordings are easy to obtain in a simple four-chamber view. In cTDI, the representation of myocardial velocities is superimposed on gray-scale two-dimensional or M-mode images, to indicate the direction and velocity of myocardial motion.[33]

Advances in echocardiographic technology have led to several studies that focused on fetal circulation and cardiac involvement in TTTS, and the prognostic value of these measurements, but results regarding the use of echocardiography are conflicting.

POSTNATAL CIRCULATION

The transition from intrauterine to extrauterine life requires significant biochemical, physiological, and anatomical changes at birth in a timely manner to ensure neonatal survival.[3]

The transition from fetal to postnatal circulation starts when the newborn takes the first breaths, initiating major physiological respiratory and hemodynamic changes. During the initial breaths lung liquid is cleared and air remains in the lung at the end of expiration, providing a functional residual capacity.[34] The major components of the hemodynamic transformations occur within minutes of commencing pulmonary ventilation. However, the cardiovascular transition requires hours to days to complete. The immediate consequence of the neonatal transition is the direct reversal of vascular shunts of the foramen ovale and ductus arteriosus. As the systemic vascular resistance rises and stabilizes, the pulmonary vascular resistance declines and the right-to-left shunt through the ductus arteriosus reverses to become a left-to-right shunt. The change in shunting direction will create disturbance of the blood flow. This is likely to promote and contribute to anatomical closure of the vascular shunts (foramen ovale and ductus arteriosus) separating pulmonary and systemic circulations (Figure 2).[35]

Figure 2. Neonatal circulation. (Reprinted from Sadler TW, Langman's Medical Embryology, 12th edition, Wolters Kluwer Health, 2011)

Any disruption in early development and transition can have long lasting, adverse, and sometimes fatal consequences. Failure of the normal circulatory transition after birth[36, 37] may cause persistent pulmonary hypertension of the newborn (PPHN). Severe PPHN has an estimated incidence of two per 1,000 live births,[38] and is associated with significant morbidity and mortality.[39] In PPHN, an inadequate decrease in pulmonary vascular resistance leads to a high right-ventricular pressure and the shunting of non-oxygenated blood from the pulmonary to the systemic circulation, resulting in systemic arterial hypoxemia.[39] The pathogenesis of PPHN is multifactorial,[36, 37, 40-42] and known causes of PPHN are sepsis, asphyxia, pneumonia, respiratory distress syndrome, lung hypoplasia and CHDs. Other complications during pregnancy, such as TTTS in monochorionic twins, may also influence cardiac remodeling before, during, and after the transitional period, and lead to PPHN. In TTTS, up to 70% of recipients show echocardiographic signs of anatomical or functional cardiac compromise at the time of diagnosis of TTTS, as a result of both increased pulmonary vascular resistance from vasoactive substances and volume overload.[43, 44] This chronic volume loading might cause remodeling of the pulmonary vasculature, which could result in neonatal PPHN.

Monochorionic twins are furthermore at increased risk of CHDs. The etiology is considered multifactorial, and includes genetic and environmental factors. The division of the fertilized ovum is hypothesized to be an influencing factor and a morphogenic anomaly in itself, which could lead to (cardiac) malformations.[45] The increased birth incidence of CHDs in monochorionic twins has however mostly been attributed to monochorionic placentation and TTTS, indicating an influence of hemodynamic alterations on cardiac development.[46-49] The shared placenta influences early cardiogenesis through release of vasoactive factors. Later in pregnancy, the placental intertwin vascular connections may affect fetal hemodynamics. Cord insertion sites and relative placental share are important factors, which may result in relative hypoperfusion of one twin and volume overload in the other twin. These conditions can cause CHDs, with phenotypic discordance in twin pairs.[50]

Fetoscopic laser surgery results in major cardiovascular improvement in affected twins[51-54] but does not prevent the development of subsequent cardiac defects in all cases.[55] Childhood cardiac function seems normal, but large short-term cardiac function studies after fetoscopic laser surgery are still lacking.[56] To what rate normalization of cardiac function occurs and whether cardiac function is completely normal at birth remains unknown.

AIMS AND OUTLINE OF THIS THESIS

The aims of this thesis were to study the short-term and long-term effects of fetal hemodynamic adaptations in monochorionic twin pregnancy and to elaborate on the predictive value of Doppler (echocardiographic) measurements for adverse outcomes.

Part II: Fetal circulation

This part of the thesis focusses on the effects of altered hemodynamics in TTTS. In **chapter 2** we evaluated the applicability of cTDI in the assessment of fetal cardiac function in both healthy fetuses and TTTS recipients. In **chapter 3** we explored whether fetal cardiac function parameters predict TTTS. Since compromised cardiac function contributes to the mortality rates after TTTS, we performed a systematic review and meta-analysis of the literature on the value of echocardiography and Doppler in the prediction of fetal demise after laser coagulation for TTTS in **chapter 4**. In **chapter 5** we studied the effects of hemodynamic changes in TTTS treated with fetoscopic laser surgery on neurodevelopmental outcome at the age of two.

Part III: Postnatal circulation

This part of the thesis comprises studies investigating postnatal effects of hemodynamic alterations in monochorionic twin pregnancies. In **chapter 6**, risk factors for PPHN in TTTS twins were assessed. In **chapter 7**, an updated overview of the reported birth prevalence of CHDs in liveborn monochorionic twins is presented. Since short-term cardiac function studies after laser surgery are lacking, **chapter 8** addresses the early postnatal cardiac follow-up in survivors of TTTS treated with laser surgery. Morbidity and mortality due to CHD has reduced tremendously due to early identification of cases that need postnatal intervention and due to innovations in neonatal care strategies and cardiothoracic surgery. In **chapter 9** we describe seven cases of CoA in monochorionic twins which were treated with coronary stent implantation.

This thesis finishes with a general discussion and summary of the main findings.

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PART II

FETAL CIRCULATION

CHAPTER 2

MEASUREMENT OF CARDIAC FUNCTION BY CARDIAC TIME INTERVALS, APPLICABILITY IN NORMAL PREGNANCY AND TWIN-TWIN TRANSFUSION SYNDROME

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ABSTRACT

Background: To detect early cardiac deterioration, a simple and stable tool is needed. Measurement of time intervals in a simple four-chamber view using color-coded Tissue Doppler Imaging (cTDI) is a relatively new approach to assess fetal cardiac function. The aim of this study was to evaluate the applicability of this modality and to construct reference ranges for cardiac time intervals.

Methods: We performed a prospective longitudinal cohort study in healthy fetuses. We used linear mixed models to construct age-adjusted reference ranges for shortening time (St) and lengthening time (Lt) in three cardiac regions: global heart and right and left ventricular wall. St and Lt were expressed as a percentage of the cardiac cycle. Feasibility and intra- and interobserver variabilities were evaluated. We applied the technique to twin-twin transfusion syndrome (TTTS) recipients before laser therapy to test the diagnostic performance.

Results: A total of 251 recordings were obtained from 54 healthy singletons. St decreased and Lt increased with gestational age in all regions. We found a high feasibility (99.6%) and excellent intra/interobserver variability for St (0.96/0.94) and Lt (0.99/0.96) of the global heart. Left and right ventricle performance parameters were good. In TTTS recipients, St was prolonged ($p < 0.01$) and Lt was shortened ($p < 0.01$) in all regions and the feasibility was excellent (96.6%).

Conclusions: The assessment of fetal cardiac function by measurement of cardiac time intervals is technically feasible with good reproducibility, even in difficult scanning circumstances such as TTTS. It is possible to discriminate between healthy and compromised fetuses with this technique.

INTRODUCTION

Assessment of fetal cardiac function gained much interest in the last decade. New ultrasound technologies like speckle tracking and Tissue Doppler seem promising. Conventional Doppler is increasingly used to assess cardiac function in the so-called modified myocardial performance index (MPI). However, this is mainly used in tertiary care centers in research settings. Implementation in general practice is hampered by the need for extensive training to ensure acceptable performance and reproducibility.[1, 2] Normal ranges of MPI vary widely, and despite a clear agreement about the landmarks of the time periods, interobserver agreement is often disappointing.[3-6] A simple and stable quantitative measurement of cardiac function, which is suitable for daily assessment, is not yet available. There is however a need to predict early functional deterioration of fetuses that are at risk of cardiac failure.[7]

Tissue Doppler Imaging (TDI) has been used since the early 1990s in adult echocardiography,[8] but is a relatively new technique in fetal echocardiography. Pulsed-wave TDI is similar to pulsed-wave Doppler, but focuses on lower frequency shifts, which enables measurement of lower velocities like myocardial wall motion. Color-coded recordings are easy to obtain in a simple four-chamber view. In color-coded Tissue Doppler Imaging (cTDI), the representation of myocardial velocities is superimposed on gray-scale two-dimensional or M-mode images, to indicate the direction and velocity of myocardial motion.[9]

In adults, cTDI is used as a prognostic tool in heart failure and for differentiation between constrictive pericarditis and restrictive cardiomyopathy.[10-12] In fetal echocardiography, cTDI was first described for the assessment of myocardial velocities by Paladini *et al.*,[13] in pregnancies complicated by intrauterine growth restriction or gestational diabetes.[14-18] cTDI does not differentiate between active motion and passive motion; thus, fetal or maternal movements may cause artefacts. Velocity measurements are furthermore influenced by angle of insonation and the size of the used region of interest (ROI).[19, 20] The applicability of the use of velocities in fetuses is therefore limited. In contrast, time intervals are independent of the angle of insonation and ROI size, making the use of time intervals a promising new approach for the assessment of fetal cardiac function.[15, 19] In cTDI images, change in the direction of the myocardial wall motion is visible as a nadir in the curve. We hypothesize that these nadirs can be used as transition markers to indicate the moment from shortening to lengthening of the myocardium. This might be an easy and reproducible technique to measure cardiac time intervals to express fetal cardiac function.

The aim of our study was to evaluate the applicability of cTDI in terms of feasibility and intra- and interobserver variability. We created reference curves of the shortening time and lengthening time of the myocardial wall, in specific areas in the fetal heart and the whole heart, visualized in the four-chamber view. In addition, we evaluated St and Lt in twin-twin transfusion syndrome (TTTS) recipients, who typically show compromised cardiac function, to investigate the ability to discriminate between normal and abnormal cardiac function.

METHODS

Uncomplicated singleton pregnancies were recruited in a primary care center and at our fertility department between November 2014 and December 2016. The pregnancies were dated by crown-to-rump length (CRL) measurement in the first trimester or date of conception in IVF pregnancies. Conditions that possibly influence fetal cardiac function were excluded, including maternal diabetes, pregnancy induced hypertension, pre-eclampsia, systemic lupus erythematosus, fetal heart malformations, and birth weight below the 5th percentile.

Color-coded Tissue Doppler clips were acquired using a Canon Aplio 500 with a PVT-674BT 6 MHz transducer in early second trimester and a PVT-375BT 3.5 MHz transducer in late second and third trimester. A measurement software package (Canon Medical Systems Corporation) was used for analysis. Ultrasonographic examinations were repeatedly performed between a gestational age of 16 and 36 with a monthly interval. Fetal biometry and standard 2D echocardiography were performed in each examination. In the absence of fetal movements, at least two cTDI recordings, containing five or more cardiac cycles, were stored in an apical or basal four-chamber view. Settings were optimized with the heart covering approximately 60% of the image, to obtain the highest frame rate.[20] The examinations were limited to a 15 min slot per fetus for the complete examination.

Time intervals in color-coded Tissue Doppler recordings

In images derived from cTDI, the change of direction in myocardial movement results in nadirs in the curve. Shortening time (St) was defined as the duration of myocardial motion when the ventricular wall shortens and is expressed as a percentage of the cardiac cycle. Lengthening time (Lt) was defined as the duration of myocardial motion when the ventricular wall extends and expressed as a percentage of the cardiac cycle. St and Lt are not the same as systole and diastole, which are defined by opening and closure of the semilunar valves and by not myocardial motion. Time intervals between St and Lt were noted as inter St-Lt and inter Lt-St times.

As demonstrated in Figure 1, the nadirs that delineate St and Lt were defined as the ones with the smallest angle towards the direction of shortening respectively lengthening movement. The cardiac cycle with the most appropriate delineation of the time intervals was selected and stored separately for analysis. Three ROIs were examined in each clip. A large ROI was used to evaluate global heart function. The large ROI was placed around the whole heart depicted in a four-chamber view, covering at least both ventricles. Two smaller ROI's were used to evaluate specific areas in the fetal heart: at the base of the

right ventricular wall (RV), just beneath the tricuspid valve, and at the base of the left ventricular wall, just beneath the mitral valve (LV). The smaller ROI's were placed just below the attachment of the atrioventricular valves (AV) valves at the free ventricular wall at the end of systole with the AV valves closed, to measure the base of the ventricle. The size of this ROI covered the width of myocardial wall but did not involve the AV valve.

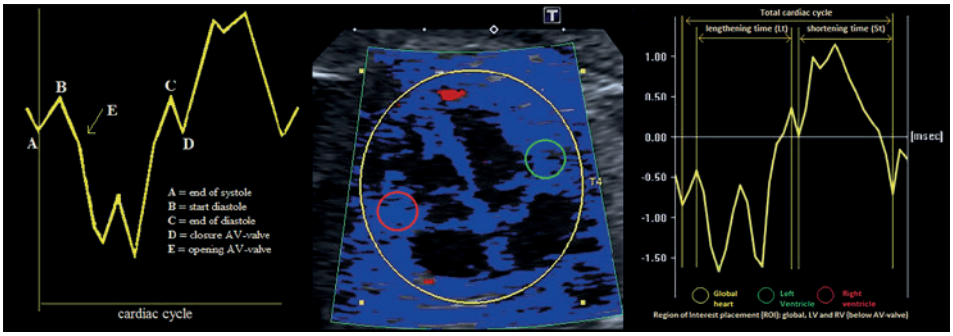

Figure 1. Schematic illustration of the cardiac cycle using cTDI, placement of regions of interest (ROI's) and demarcations of lengthening time (Lt) and shortening time (St) in the derived image

To investigate the ability to express abnormal cardiac function of this measurement, we performed cTDI measurements in all recipients with TTTS referred to our department between January 2015 and December 2016. We used the last ultrasound examination before laser therapy. Recipients may demonstrate cardiac dysfunction at time of TTTS diagnosis.[21] We stored two cTDI recordings, containing five or more cardiac cycles for analysis of the St and Lt. Because TTTS occurs mainly between 14 to 28 weeks, we compared recipients with healthy singletons within this gestational age period. Thus, the TTTS recipients were matched at the level of gestational age. All examinations were performed and analyzed by one experienced operator (S.E). For intraobserver agreement, 30 clips containing one raw cardiac cycle of the singleton group were stored and analyzed three times with a time interval of three months. For interobserver agreement, a second operator (M.G.) performed three analyses on the same 30 cardiac cycles. The mean of the three analyses of both operators was compared for interobserver agreement. Within-fetus variability was defined as agreement in three different cardiac cycles in different clips in one examination and analyzed by the same operator (S.E.). The study was approved by the medical ethical committee of the Leiden University Medical Center and all women signed informed consent.

Statistical analysis

Statistical analysis was performed with IBM SPSS 20.0 statistical package (Chicago, IL, USA). Feasibility was defined as the percentage of measurements which could be performed successfully. A measurement was noted as successful if the signal was clear enough to recognize all four nadirs. A measurement was unsuccessful in case of absent nadirs, or multiple nadirs in which the demarcation nadir could not be recognized. Baseline characteristics between healthy singletons and recipients were compared with the *t* test and Chi-square test. Intra- and interobserver agreement and within-fetus variability were quantified by the intraclass correlation coefficient (ICC). Because of the longitudinal character of this study, we used linear mixed models in which we included a random intercept per individual to account for the correlated measurements within each fetus. For each outcome variable, we evaluated whether the gestational age trend increased or decreased over time, using a mixed model with a fixed linear age effect. We used this same model to construct reference intervals for healthy singletons. To compare the means of TTTS recipients and healthy singletons, we constructed a second mixed model for each outcome including gestational age, group (healthy singleton or TTTS recipient) and the interaction between age and group as fixed effects. From this model, we estimated the mean difference between the groups at the mean observed gestational age.

RESULTS

The baseline characteristics of the healthy singletons and the TTTS recipients are depicted in Table 1. Sixty-one singletons were eligible for inclusion, but seven cases were excluded from analysis because gestational diabetes or intrauterine growth restriction developed during gestation.

Table 1. Demographic characteristics and pregnancy outcome of singletons and TTTS recipients

Characteristics	**Singletons (n = 54)**	**TTTS recipients (n = 86)**	**p-value**
Caucasian	93 2	97.0	0.17
Maternal body mass index (kg/m²)	23.3 ± 3.1	24.6 ± 4.6	0.05
Gestational age at delivery (weeks)	39.6 ± 1 4	31.5 ± 5.1	
Birth weight (grams)	3500 ± 496	1985 ± 630	
5-min Apgar score	9 ± 1	8 ± 1	
Quintero stage	n/a		
I		16.3	
II		24.4	
III		55.8	
IV		2.3	
V		1.2	
Frames per second	124 ± 22	122 ± 30	0.91

Data are presented as % or mean (+-SD). TTTS, twin-twin transfusion syndrome.

A total of 251 examinations were performed in 54 healthy singletons. Performance parameters are summarized in Table 2. Feasibility in the global heart and the right ventricular wall was excellent (99.6%/93.6%) and good in the left ventricular wall (78.1%). The mean global shortening time was 45.8% of the cardiac cycle at 16 weeks of gestation and decreased significantly to 42 4% at 36 weeks of gestation, while mean global lengthening time was 42.8% of the cardiac cycle at 16 weeks of gestation and increased to 44.6% at 36 weeks of gestation. Normal reference curves were constructed and are shown in Figure 2. The inter St-Lt and inter Lt-St time frames were noted and analysed, as shown in Table 2. While inter St-Lt appeared to be stable during gestation, inter Lt-St increased in all ROI's.

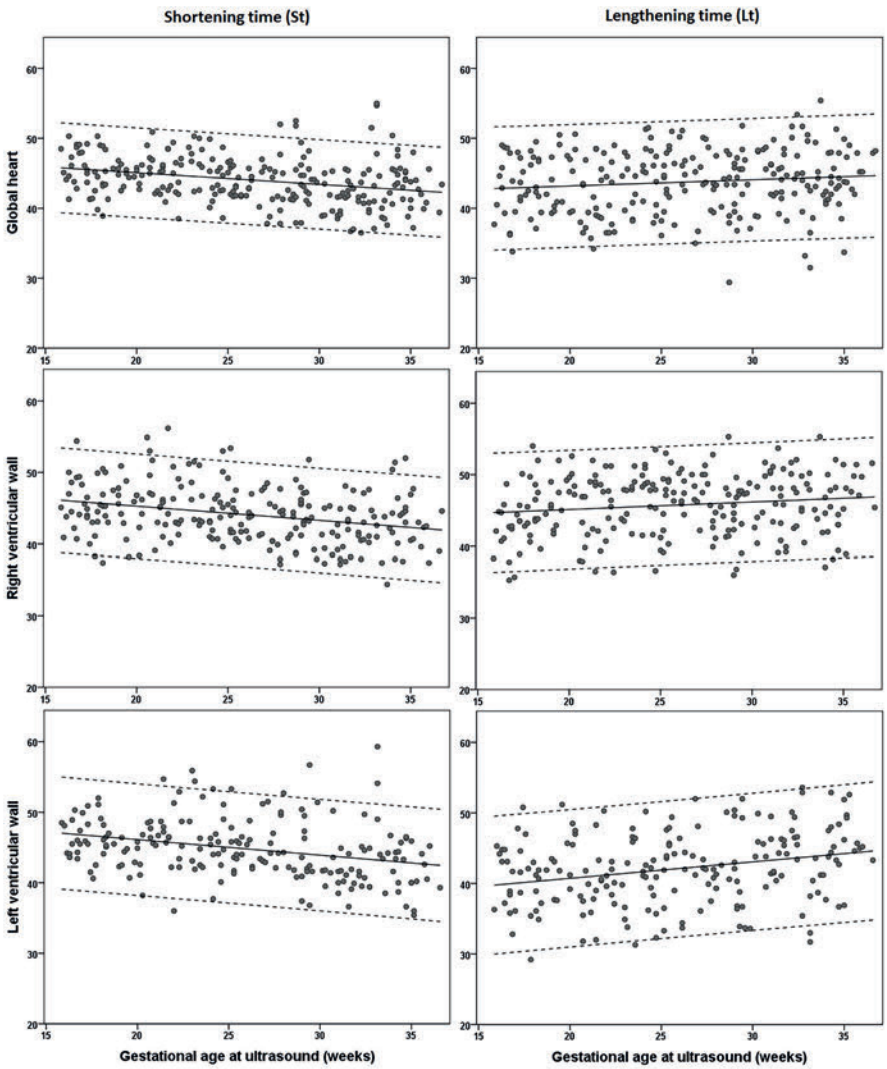

Figure 2. Reference charts for St and Lt in healthy singletons, in different ROI's of the fetal heart from 16 to 36 weeks of gestation

Table 2. Performance of cTDI in different ROI's of the fetal heart at 16 and 36 weeks of gestation

	16 weeks	**36 weeks**	**p-value**
	Mean % (SD)	**Mean % (SD)**	
Global			
St	45.8 (3.3)	42 4 (3.3)	<0.01
Lt	42.8 (4.5)	44.6 (4.5)	0.049
Inter St-Lt	9.5 (3.8)	10 2 (3.8)	0 42
Inter Lt-St	3.1 (2.2)	5.1 (2 2)	<0.01
RV			
St	46.1 (3.7)	42.1 (3.7)	<0.01
Lt	44.7 (4.3)	46.8 (4.3)	0.02
Inter St-Lt	5.8 (3.0)	6.0 (3.0)	0.88
Inter Lt-St	3.7 (2.3)	5.5 (2.3)	<0.01
LV			
St	47.0 (4.1)	42.6 (4.1)	<0.01
Lt	39.8 (5.0)	44.5 (5.0)	<0.01
Inter St-Lt	3.9 (2.6)	5.6 (2.6)	0.01
Inter Lt-St	4.0 (2.6)	5.6 (2.6)	0.01

cTDI, color-coded Tissue Doppler Imaging; ROI, region of interest; St, shortening time; Lt, lengthening time; RV, right ventricular wall; LV, left ventricular wall;

Feasibility %	Intra-CC	Inter-CC	Within-fetus variability
99.6			
	0.98	0.94	0.60
	0.99	0.96	0.56
	0.99	0.95	0.27
	0.90	0.97	0.46
93.6			
	0.94	0.76	0.47
	0.94	0.72	0.38
	0.88	0.77	0.20
	0.88	0.78	0.17
78.1			
	0.91	0.82	0.29
	0.89	0.74	0.61
	0.92	0.60	0.29
	0.86	0.74	0.19

Intra-CC, intraclass correlation coefficient for intraobserver agreement; Inter-CC, intraclass correlation coefficient for interobserver agreement.

Intraobserver agreement within a cardiac cycle was good for the global heart and the RV and LV (St 0.98/0.94/0.91 and Lt 0.99/0.94/0.89). Interobserver agreement was excellent for the global heart (St 0.94 and Lt 0.96) and reasonable for the RV (St 0.76 and Lt 0.72) and LV (St 0.82 and Lt 0.74). The intraclass correlation coefficient for within-fetus variability varied between 0.17 and 0.61 in all ROIs, reflecting high variability of the heart cycle within the same fetus. Mean frame rate (frames per second) was 98, with a standard deviation of 35 frames per second. Lower frame rates were associated with advanced gestational age.

Baseline characteristics for TTTS recipients were comparable with healthy singletons (Table 1). In 86 recordings of recipients at time of TTTS diagnosis, feasibility was 96.6% for global ROI, 94 2% for RV and 70.0% for LV. Lengthening time was significantly shortened, and shortening time significantly prolonged, in all ROI's (Table 3 and Figure 3).

Table 3. Singletons versus recipients at time of TTTS diagnosis, in different ROI's of the fetal heart in the second trimester

	Singletons Mean % (SD)	**Recipients Mean % (SD)**	**Mean Difference[a] (CI)**	**p-value**
Global				
St	44.9 (2.7)	48.3 (4.7)	3.0 (1.9 - 4.1)	<0.01
Lt	43 4 (4.5)	37.6 (5.3)	5.6 (4.1 - 7.0)	<0.01
Inter St-Lt	8.1 (4.0)	9.7 (4.7)	1.7 (0 4 - 2.8)	0.01
Inter Lt-St	3.7 (2.3)	4.3 (2.5)	0.8 (0.0 - 1.5)	0.04
RV				
St	45 2 (2.7)	49.0 (7.5)	3.1 (1 2 - 5.0)	<0.01
Lt	45.6 (4 2)	37.2 (7.1)	8.1 (6.3 - 9.9)	<0.01
Inter St-Lt	5.3 (3.1)	8.3 (2.5)	2.8 (1.7 - 4.0)	<0.01
Inter Lt-St	3.7 (2.3)	4 4 (3.0)	0 4 (-1.2 - 0.4)	0.30
LV				
St	45.8 (3.6)	48.9 (7.5)	3.1 (1.8 - 4 4)	<0.01
Lt	41 2 (4.9)	34.8 (5.7)	6.1 (4.3 - 7.9)	<0.01
Inter St-Lt	4.3 (2.5)	10 4 (3.7)	6.0 (4.9 - 7.1)	<0.01
Inter Lt-St	4.3 (2.5)	5.8 (4.1)	1.5 (0.3 - 2.6)	0.01

TTTS, twin-twin transfusion syndrome; ROI, region of interest; St, shortening time; Lt, lengthening time; RV, right ventricular wall; LV, left ventricular wall; CI, confidence interval.
[a]Mean difference between recipients and singletons at 21 weeks of gestation

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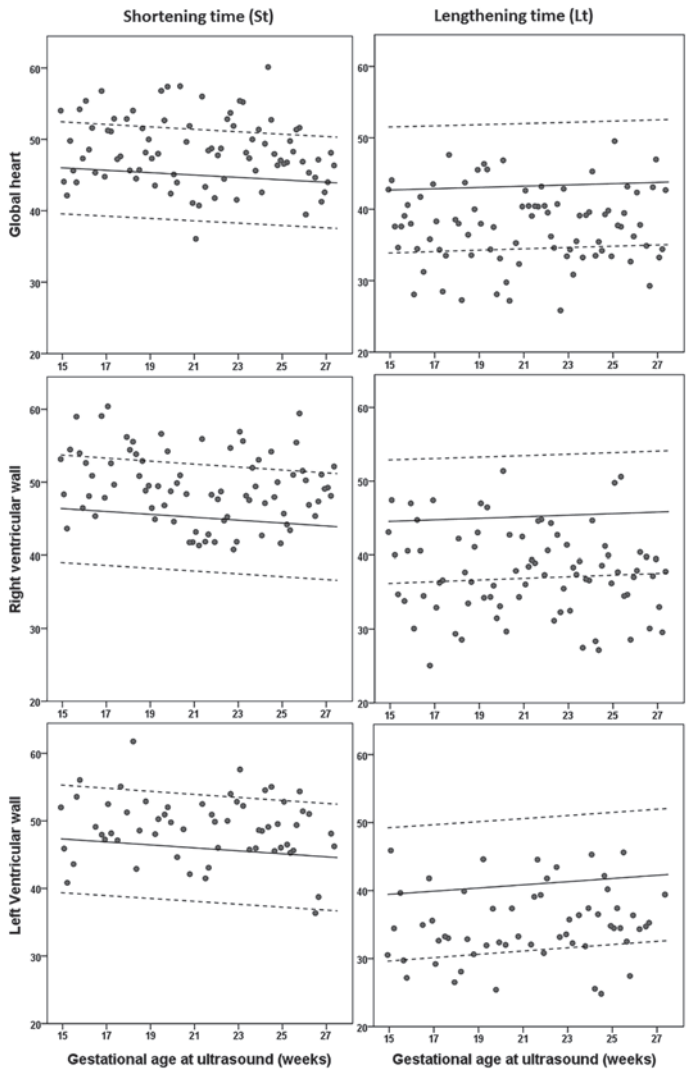

Figure 3. Scatterplots for recipients at time of TTTS diagnosis versus singletons reference curves in different ROI's of the fetal heart from 16 to 28 weeks of gestation

DISCUSSION

In this study, we introduce a new approach to assess fetal cardiac function through the measurement of time intervals of the myocardial wall motion in a simple four-chamber view using cTDI. Lengthening time and shortening time of the fetal heart show a slight increase, respectively decrease, with advancing gestation. Feasibility and intra- and interobserver agreement were shown to be excellent in the global heart ROI. The high feasibility (96.6%) in difficult circumstances like TTTS, with polyhydramnios and abundant fetal movements of the recipient, indicates that this approach is simple and robust. Lt was shortened and St prolonged in TTTS recipients compared to healthy singletons, reflecting the discriminative ability of this new parameter.

Currently, the MPI is the most used method to assess fetal cardiac function. MPI is considered a consistent cardiac marker which becomes altered in early stages of chronic hypoxia or cardiac overload.[22] MPI implementation in routine assessment has several limitations. First, MPI is a pulsed-wave Doppler-derived index of isovolumetric time intervals (IRT/ICT) and ejection time (ET), and ventricular inflow and outflow are ideally measured in the same cardiac cycle. For left MPI measurement, a combined flow velocity waveform recording of mitral valve and aorta outflow can be obtained in the same sample volume, but these recordings require considerable expertise of the operator in image acquisition and correct recording of the Doppler tracing. The anatomy of the tricuspid valve and pulmonary artery, however, precludes recording of both valves within the same Doppler sample gate in the right ventricle, which is the dominant ventricle in fetal circulation. Therefore, right MPI can only be calculated from two separate recordings, which affects feasibility and reproducibility. As a result, normal ranges of both left and right MPI vary widely and interobserver agreement is disappointing.[3-6] Another difficulty in MPI measurements is the caliper placement in the Doppler waveforms to calculate the time intervals. This seems to be resolved with the development of automated MPI systems which removes the subjectivity of manual caliper placement, but authors acknowledge that ultrasound image acquisition remains a potential source of variability, even for highly trained operators.[23, 24] Contrary, the cTDI recordings described in this study are easy to obtain because only a recording of the four-chamber view is needed. The four-chamber view is easy to acquire and is part of every routine obstetric ultrasound examination. The placement of the ROI is simple and fast, which makes this technique applicable in daily obstetrical care in the future.

The measurement of cardiac time intervals in cTDI is a relatively new approach in fetal echocardiography.[15] Willruth *et al.*[19] concluded that time intervals can be analyzed with a high accuracy, irrespective of what ROI size is used. They described IRT, ICT, and ET

retrieved by cTDI, comparable to these parameters in Doppler-derived MPI. Interobserver agreement in this study was low, probably because the closure and the opening of the cardiac valves are not easy to recognize in the signal. In our approach of the analysis of the same signal, cardiac time intervals are marked by myocardial wall motion and not by the movement of the blood. Instead of ET, which represents blood volume shift and is marked by cardiac valve clicks, we propose to evaluate St, which reflects the time the myocardium actually contracts. By definition St will be longer than ET because the myocardium first starts to contract, and with increased intraventricular pressure the semilunar valve opens, and the ejection of blood starts. Lt is prolonged in the same manner (Figure 1). Consequently, the inter St-Lt and inter Lt-St are shorter than the isovolumetric time intervals. As shown in Table 2, the inter-shortening-lengthening time as well as the inter-lengthening-shortening time show a large standard deviation in all ROIs which we attribute to measurement error caused by the current frame rates. Therefore, the value of inter St-Lt, respectively, and Lt-St in individual measurements is limited.

However, this approach of the analysis of cTDI signal results in an excellent feasibility and intra- and interobserver agreement for global heart function, which is better than currently used techniques to assess fetal cardiac function. This is explained by the simplicity of the large ROI placement and the easy recognition of the nadirs in the curve. We observed that wall motion in the smaller ROIs is less consistent and several smaller nadirs may be visible, which results in a larger interobserver variability. We observed that the LV shows lower feasibility scores compared to the RV. Previous studies show lower volume shifting and less ventricular wall displacement in the left ventricle compared to the right ventricle in fetal life,[15, 25, 26] which might explain the nadirs to be less clear, which results in lower feasibility scores and reproducibility.

In contrast to intra- and interobserver agreement, within-fetus variability in our study was high in all areas of the fetal heart. We hypothesize that the high within-fetus variability can be attributed to beat-to-beat (BTB) variability, which is a physiological phenomenon mediated by the autonomic nervous system. This hypothesis is consistent with a recently published study by Maheshwari *et al.*,[27] which showed that MPI time intervals have a BTB variability which is comparable with the fetal heart rate variability. BTB variability is well established in various Doppler flow measurements, and the occurrence of physiological changes as possible contributors to measurement variation is mentioned before in studies assessing repeatability.[28, 29]

Recipients in TTTS show abnormal cardiac function, and it is suggested earlier that cardiac profiling can be an aid in early management of TTTS.[30, 31] Our study shows deviations in mean cardiac time intervals with a shortened Lt, prolonged St and prolonged inter St-Lt

in recipients, which confirms findings of abnormal MPI and prolonged isovolumetric contraction time.[32, 33] The within-fetus variability in normal fetuses, together with the overlap of the results in TTTS recipients with the normal values, makes distinction in TTTS difficult. Care should be taken, and further research is needed to determine the diagnostic accuracy of cTDI. The feasibility rates in the TTTS recipients are, however, exceptionally high compared to the current techniques, as it is known that the retrieval of Doppler recordings in TTTS is difficult because of the polyhydramnios and the abundant fetal movements of the recipient. A feasibility rate of 96.6% proves that this method is simple and fast. Future studies are planned by our group to elucidate the possible role of cTDI in monitoring monochorionic twins.

To investigate the ability to discriminate between normal and abnormal cardiac function, recipient twins were matched for gestational age to healthy singletons. The lack of a control group of uncomplicated twins is a limitation of our study. It is, however, well accepted that reference charts of healthy singletons are compared to complicated monochorionic twins. In the previous studies in the field of fetal cardiology, speckle tracking-derived fetal cardiac function and modified MPI measurements in recipient twins were compared to normal singleton fetuses.[24, 34, 35] Uncomplicated (monochorionic) twins are generally not used as a control group, since twin pregnancies cannot be considered normal because of their complexity and high risk of complications.

In conclusion, the proposed technique presents a promising new approach to assess fetal cardiac function. Recordings are easy to obtain and feasibility and inter- and intraobserver agreement are excellent for global heart function, even in difficult scanning circumstances as in TTTS recipients. Therefore, this technique is potentially useful in daily practice, because it can be applied in only a four-chamber view. Furthermore, this approach seems promising in the detection of abnormal heart function, but further research in pathological pregnancies is needed.

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CHAPTER 3

CARDIAC TIME INTERVALS AND MYOCARDIAL PERFORMANCE INDEX FOR PREDICTION OF TWIN-TWIN TRANSFUSION SYNDROME

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ABSTRACT

Objectives: To explore whether intertwin discordance in myocardial performance index (MPI) or cardiac time intervals enables the prediction of twin-twin transfusion syndrome (TTTS) in monochorionic diamniotic (MCDA) pregnancies with amniotic fluid discordance.

Methods: Prospective cohort study of MCDA pregnancies with amniotic fluid discordance ≥ 4cm. Serial ultrasound examinations consisted of evaluation of amniotic fluid, fetal Dopplers and fetal cardiac function.

Results: We included 21 'pre-TTTS' (group I), 18 selective fetal growth restriction (sFGR, group II) and 20 uncomplicated MCDA twin pairs (group III). Group I had a higher intertwin difference in left ventricle (LV) MPI and right ventricle (RV) MPI compared to group II and III. The intertwin difference in global heart relaxation time was significantly higher in group I compared to group III. Future recipient twins had significantly higher relaxation times of the global heart and RV and lower contraction times of the global heart and RV compared to the 'expected recipients' in group II and III.

Conclusions: Intertwin discordance in LV-MPI and RV-MPI differentiate between TTTS and MCDA pregnancies with transient discordant amniotic fluid volume. Cardiac time intervals identify future recipient twins. The clinical utility of cardiac time intervals and MPI should be investigated in large prospective studies.

INTRODUCTION

Improved prediction of twin-twin transfusion syndrome (TTTS) is needed to identify pregnancies that will benefit most from expert follow-up.[1] Early detection of TTTS allows for referral of patients to a fetal therapy center where laser surgery can be performed. Complications may be prevented with early detection and appropriate treatment. 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.[2, 3]

Previous attempts to find improved methods to stratify the risk for TTTS include different measures of fetal cardiac dysfunction. In a study by Zanardini *et al.*[4] in 100 uncomplicated monochorionic twin pregnancies at 18 weeks' gestation the myocardial performance index (MPI) assessed by Tissue Doppler Imaging in the left ventricle of the future recipient showed a cut-off > 0.52 to detect more than 90% of subsequent TTTS cases, for a false-positive rate of 10%.[4] In this study however, the analysis was done based on the MPI of the future recipient twin, whereas, at baseline, both twins are supposed to have still normal amniotic fluid levels and it would therefore be impossible to foretell which of the twins will become the recipient. It would be more useful to predict which pregnancy will develop TTTS, from a cohort of pregnancies with some amniotic fluid difference ('pre-TTTS'). Wohlmuth *et al.*[5] attempted to discriminate between 'pre-TTTS' and monochorionic diamniotic (MCDA) controls using ventricular strain. No differences in right or left ventricular strain discordance between 'pre-TTTS' and MCDA controls were found.[5] As we believe that cardiac function is already compromised in 'pre-TTTS', modalities with better test characteristics than ventricular strain, such as the MPI and measurement of cardiac time intervals[6] by color-coded Tissue Doppler Imaging (cTDI), may be able to discriminate between normal and abnormal cardiac function.[4, 7, 8]

The aim of this prospective study was therefore to explore whether intertwin discordance in MPI or cardiac time intervals by cTDI in MCDA pregnancies with amniotic fluid difference not yet fulfilling TTTS criteria could distinguish future TTTS pregnancies from those only affected by discordant growth or discordant amniotic fluid volume without TTTS.

METHODS

This study was a single center prospective cohort study performed at the Leiden University Medical Center (LUMC) between January 2015 and March 2017. The LUMC is the national referral center for fetal therapy. In this study, all consecutive patients attending our monochorionic twin pregnancy clinic and patients that were referred to our center for the suspicion of TTTS were included. In case of amniotic fluid discrepancy, the frequency of ultrasound examination was at least twice per week. We excluded monoamniotic pregnancies, triplets and cases with congenital anomalies (including acquired right ventricular outflow tract obstruction [RVOTO]) or twin anemia polycythemia sequence (TAPS)[9]. The study was approved by the medical ethical committee of the LUMC (NL 45251.058.13).

Each ultrasound examination consisted of amniotic fluid evaluation (deepest vertical pocket), fetal Dopplers and evaluation of fetal cardiac function. Fetal biometry was measured every two weeks. Selective fetal growth restriction (sFGR) was defined as: estimated fetal weight (EFW) of one twin < 3rd percentile or at least two of four contributory parameters (EFW of one twin < 10th percentile, abdominal circumference of one twin < 10th centile, EFW discordance ≥ 25%, and umbilical artery pulsatility index of the smaller twin > 95th percentile).[10] TTTS was diagnosed using standard European diagnostic ultrasound criteria,[11] and pregnancies were staged prospectively according to the Quintero staging system.[12] If TTTS criteria were not (yet) fulfilled, 'pre-TTTS' was defined as an intertwin amniotic fluid discordance ≥ 4 cm. 'Future TTTS' pregnancies were those which progressed to TTTS stage 1 or higher (group I). 'sFGR' pregnancies were those diagnosed with sFGR and who never progressed to TTTS (group II). 'Uncomplicated' MCDA pregnancies never fulfilled the criteria of the beforementioned groups (group III). In group III the amniotic fluid discordance remained stable or decreased. The 'expected recipient' was the fetus with the largest deepest vertical pocket, the 'expected donor' was the fetus with the smallest deepest vertical pocket (in sFGR also the smallest fetus).

Fetal echocardiography was performed by two experienced sonographers (M.G. and S.E) using a Canon Aplio 500 (Canon Medical Systems Corporation, Tochigi, Japan) with a PVT-674BT 6 MHz transducer in early second trimester and a PVT-375BT 3.5 MHz transducer in late second trimester. The left ventricle (LV)-MPI and right ventricle (RV)-MPI were obtained with pulsed-wave Doppler, in the absence of fetal movements. LV-MPI was measured according to the Mod-MPI technique of Hernandez-Andrade *et al*.[13] Briefly, the isovolumetric contraction (ICT) and isovolumetric relaxation (IRT) times were obtained by measuring the time interval between the closure of the atrioventricular valve and its subsequent opening in the next cardiac cycle (atrioventricular valve

time). In the left ventricle, the ejection time (ET) was measured from the opening to the closure of the mitral valve. Mod-MPI was calculated as (ICT+IRT)/ET. In the right ventricle measurements were obtained separately for the tricuspid and pulmonary valves due to the right-sided valves' anatomical configuration. RV-MPI was calculated as (isovolumetric time - ET)/ET. Discrepant fetal heart rate was not an exclusion criterion, since large fluctuations in fetal heart rate could potentially be part of underlying pathological processes.[14, 15] Additionally, cTDI clips containing five or more cardiac cycles in the absence of fetal movements, were stored in an apical or basal four-chamber view. Three regions of interest (ROIs) were examined in each clip, according to our previously described technique.[6] A large ROI was used covering the whole heart to evaluate global heart function. Two small ROI's were used to evaluate the RV wall and the LV wall just above the atrioventricular valves. In images derived from cTDI, the change in direction of myocardial movement results in nadirs in the curve (Figure 1). Shortening time (St) was defined as the duration of myocardial motion during ventricular contraction. Lengthening time (Lt) was defined as the duration of myocardial motion during ventricular relaxation or expansion. Both St and Lt were expressed as a percentage of the total duration of one cardiac cycle. Measurements were performed without blinding to twin pairing or pregnancy outcome.

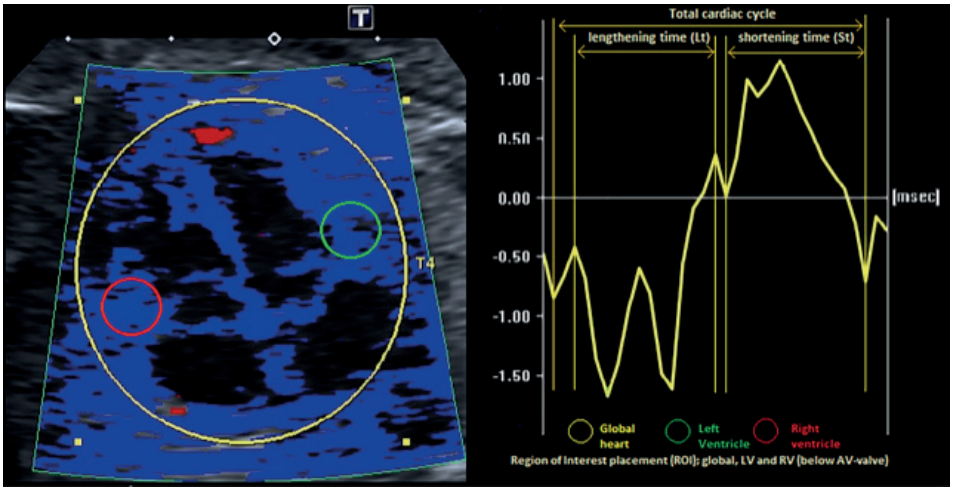

Figure 1. Schematic illustration of the cardiac cycle using cTDI, placement of regions of interest (ROI's) and demarcations of lengthening time (Lt) and shortening time (St) in the derived image. Adapted from 'Measurement of cardiac function by cardiac time intervals, applicability in normal pregnancy and twin-to-twin transfusion syndrome' by S J. Eschbach *et al.*, 2018, Journal of Echocardiography. Copyright 2018, The Authors.

Statistical analysis

Intertwin discordances of MPI measurements and cardiac time intervals were calculated as 'expected recipient' minus 'expected donor'. Individual measurements and intertwin discordances were compared between 'future TTTS' and 'sFGR' and between 'future TTTS' and 'uncomplicated' twins using the one-way ANOVA. Consecutive ultrasound examinations of one twin pair were included in the analysis, if available. Best cut-off points were identified by analysis of the receiver-operating characteristics (ROC) curve. To maximize both sensitivity and specificity, the Youden's J-statistic was applied (sensitivity + specificity - 1).[16] Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$.

RESULTS

A total of 59 MCDA pregnancies with 'pre-TTTS' were included. 21 pregnancies were allocated to group I: pre-TTTS that evolved to TTTS, all treated by laser. Growth discordance pre-laser was present in 14 of 21 twin pairs. The disease severity according to Quintero stages was distributed as follows: Stage I n = 5; Stage II n = 9; Stage III n = 7. The median gestational age at laser was 17+6 weeks (interquartile range 15+4 to 20+1). 18 pregnancies were allocated to group II: pregnancies only complicated by sFGR, of which 9 were Gratacos stage I, 3 were Gratacos stage II and 6 were Gratacos stage III. The remaining 20 pregnancies were allocated to group III: no sFGR, no TTTS, no TAPS, amniotic fluid discordance remained stable or decreased. A total of 111 ultrasound scans were available. The median gestational age at first ultrasound was 30 ± 4 years in group I, 30 ± 5 years in group II and 31 ± 5 years in group III. The mean body mass index (BMI) of mothers was 25 (21 - 28) kg/m2 in group I, 25 (22 - 28) kg/m2 in group II and 26 (23 - 28) kg/m2 in group III. 67% of patients in group I was nulliparous, compared to 59% in group II and 74% in group III.

Myocardial performance index by pulsed-wave Doppler

Group I (future TTTS) had a higher intertwin difference in LV-MPI and RV-MPI compared to group II (sFGR) and group III (uncomplicated), but a statistically difference was only found between group I and III. Compared to group III, the intertwin discordance in LV-MPI and RV-MPI in group I was twice as large (0.15 vs. 0.08, p = 0.03 and 0 25 vs. 0.12, p = 0.02). Comparing group I with both group II + III showed similar results (Table 1). Individual MPI measurements were not statistically significant different across future TTTS stages in group I (data not shown). Pregnancies that evolved into a higher TTTS stage showed a larger intertwin difference in RV-MPI (Stage 1: 0.06, Stage 2: 0.26 and Stage 3: 0.36, p = 0.001).

Cardiac time intervals by color-coded Tissue Doppler Imaging

Overall contraction times were higher and relaxation times were lower in future recipients (group I), compared to the 'expected recipient' in group II or III. The intertwin difference in global heart relaxation time (dGlobal RT) was significantly higher in group I compared to group III. Future recipient twins had significantly higher relaxation times of the global heart, right ventricle and left ventricle compared to the 'expected recipients' in group II + III. Future recipient twins had significantly lower contraction times of the global heart and right ventricle compared to the 'expected recipients' in group II + III (Table 2).

Table 1. Myocardial performance index

Parameter	Group I (TTTS)	Group II (sFGR)	Group III (Uncomplicated)	Group II + III (no TTTS)
LV-MPI donor	0.50	0.51	0.57*	0.53
LV-MPI recipient	0.58	0.58	0.61	0.60
dLV-MPI	0.15	0.10	0.08*	0.09*
RV-MPI donor	0.53	0.51	0.55	0.53
RV-MPI recipient	0.64	0.64	0.62	0.63
dRV-MPI	0 25	0.18	0.12*	0.15*

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; LV, left ventricle; MPI, myocardial performance index; d, delta; RV, right ventricle.
* $p < 0.05$, compared to Group I.

Table 2. Cardiac time intervals using cTDI

Parameter	Group I (TTTS)	Group II (sFGR)	Group III (Uncomplicated)	Group II + III (no TTTS)
Global Ct donor	44%	44%	45%	44%
Global Ct recipient	49%	46%*	45%*	45%*
dGlobal Ct	7.1%	4 4%	6.8%	5.5%
Global Rt donor	46%	44%	44%	44%
Global Rt recipient	37%	41%*	43%*	42%*
dGlobal Rt	11.6%	6.3%*	7.7%	6.9%*
RV Ct recipient	51%	45%*	45%*	45%*
RV Rt recipient	37%	45%*	44%*	45%*

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; Ct, contraction time; d, delta; Rt, relaxation time; RV, right ventricle; LV, left ventricle.
* $p < 0.05$, compared to Group I.

Cut-off values

The best cut-off point for each parameter was identified from its ROC curve to assess its predictive value in MCDA pregnancies an amniotic fluid difference ≥ 4 cm. Tables 3 to 5 give the predictive performance of cardiac parameters, for the subsequent development of TTTS. The chance of TTTS was higher in case of lower values of relaxation times (Rt).

Table 3. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group II + III (no-TTTS)

Parameter	Cut-off	Sensitivity	Specificity
dLV-MPI	0.13	63 4%	76.9%
dRV-MPI	0.21	66.7%	78.6%
Global Ct recipient	48.2%	70.8%	72.3%
Global Rt recipient	40.0%	58 2%	75.0%
dGlobal Rt	9.9%	64.3%	79 4%
RV Ct recipient	49.9%	65 2%	81.5%
RV Rt recipient	38.7%	87.0%	73.9%

TTTS, twin-twin transfusion syndrome; d, delta; LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; Ct, contraction time; Rt, relaxation time.

Table 4. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group II (sFGR)

Parameter	Cut-off	Sensitivity	Specificity
Global Ct recipient	48.2%	71.8%	73.1%
Global Rt recipient	35 2%	92.3%	50.0%
dGlobal Rt	9.9%	64.3%	88.9%
RV Ct recipient	49.9%	65 2%	88.0%
RV Rt recipient	38.7%	96.0%	73.9%

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; Ct, contraction time; Rt, relaxation time; d, delta; RV, right ventricle.

Table 5. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group III (uncomplicated)

Parameter	Cut-off	Sensitivity	Specificity
dLV-MPI	0.09	72.7%	73.3%
dRV-MPI	0.21	66.7%	83.3%
Global Ct recipient	47.8%	70.8%	72 4%
Global Rt recipient	40.0%	65.5%	75.0%
RV Ct recipient	49.8%	65 2%	75.9%
RV Rt recipient	40.8%	76.9%	82.6%

TTTS, twin-twin transfusion syndrome; d, delta; LV, left ventricle; RV, right ventricle; Ct, contraction time; Rt, relaxation time.

DISCUSSION

We assessed the MPI and cardiac time intervals in MCDA twins with discordant amniotic fluid. In this exploratory analysis we have found that intertwin discordance in LV-MPI and RV-MPI may help to differentiate between future TTTS and MCDA pregnancies with discordant amniotic fluid volume without TTTS. Using cardiac time intervals measured by cTDI clinicians at tertiary care centers can furthermore identify future recipient twins and differentiate between future TTTS and sFGR and uncomplicated MCDA pregnancies. Identifying recipient twins may especially help in cases where the cardiac function of the 'stuck' donor or extremely small fetus cannot be assessed, and intertwin discordance cannot be estimated.

The increased intertwin discordance in cardiac parameters in future TTTS twins found in this study is in line with a previous study where impaired ventricular strain was found in pre-recipient twins.[5] The development of unbalanced intertwin transfusion seems to be associated with early signs of cardiac function changes.

Worldwide, the MPI technique is gaining popularity and the number of articles on cardiac function as measured by MPI is increasing, but even study groups that have invested extensive research efforts into MPI acknowledge the limitations in reproducibility.[7, 17] Furthermore, most studies in the literature are focused mainly on fetal cardiac function in monochorionic pregnancies already complicated by TTTS. Due to the limited number of articles investigating 'pre-TTTS', and the fact that results regarding the utility of the MPI and other cardiac parameters to predict TTTS are conflicting, cardiac parameters are currently not used in the risk stratification of TTTS. In this study, the intertwin difference in LV-MPI and RV-MPI were found to be predictors for TTTS, with a specificity of approximately 80%. Higher MPI values found in the larger twin in sFGR may be explained by an increase in cardiac output and potentially a hyperdynamic circulation, as a result of perfusion of the placenta of the smaller one via arterio-arterial (AA) anastomoses. This resembles a milder form of the situation observed in monochorionic twins with an acardiac fetus.[18]

The results of our study furthermore show that Tissue Doppler is even more sensitive to detect subtle cardiac dysfunction compared to conventional Doppler. In line with findings of our previous study where recipient twins could be discriminated from uncomplicated monochorionic twins,[6] we have found decreased contraction times and increased relaxation times in the future recipient twins. The right ventricular relaxation time in the 'expected recipient' showed a high sensitivity (87%) to detect the future TTTS recipient. Right ventricular contraction time in the 'expected recipient' shows a good

specificity of 82%. The clinical problem of dealing with a large fluid discrepancy in a selective growth-restricted twin pair may furthermore be overcome using cardiac time intervals, since the future TTTS can be differentiated from sFGR by identification of the future recipient twin as shown by data in Tables 2 and 4.

Using both indices (MPI and cardiac time intervals using cTDI), follow-up could be planned with a larger interval. This could allow a significant reduction in the number of ultrasounds and prevent unnecessary travels to a fetal therapy center far from home. However, the safety of this approach needs to be validated in larger prospective studies.

There are limitations to this study. Our study cohort consists partly of monochorionic twins referred to our center for the suspicion of TTTS, which could have introduced a selection bias. We have used the modified MPI technique to improve reproducibility, however, reproducibility of (manual) measurement of MPI is known to be still limited. This study includes a limited number of patients. The clinical applicability of our measurements therefore have be confirmed by large prospective (multicenter) studies. Multiple comparisons performed in this study may have increased the likelihood of statistically significant differences resulting from random rather than systematic variation. Correction for multiple testing is however a subject of debate, and is not always advised if study aims have an exploratory nature.[19, 20]

CONCLUSIONS

Fetal cardiac function evaluation improves early detection of TTTS. If referring hospitals are able to stratify between future TTTS and MCDA pregnancies with transient amniotic fluid differences, unnecessary hospital visits or referrals (important in countries with large travelling distances) may be avoided, and pregnant women who are likely to develop TTTS will benefit from timely expert follow-up. The potential utility of cardiac time intervals and MPI in the triage of amniotic fluid discordance should be confirmed in large prospective (multicenter) studies, validating our estimated cut-off points. Furthermore, automatized measurements are needed since measurements of MPI or cardiac time intervals require expert hands and are time consuming.

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CHAPTER 4

THE VALUE OF ECHOCARDIOGRAPHY AND DOPPLER IN THE PREDICTION OF FETAL DEMISE AFTER LASER COAGULATION FOR TTTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

This study aimed to investigate the value of echocardiography and Doppler before fetoscopic laser coagulation for twin-twin transfusion syndrome (TTTS) in the prediction of intrauterine fetal demise (IUFD). We performed a systematic review and meta-analysis to compare preoperative parameters between fetuses with and without demise after laser surgery. Eighteen studies were included. Recipient twins have an increased risk of demise in case of preoperative absent/reversed flow (A/REDF) in the umbilical artery (odds ratio [OR] 2.76, 95% confidence interval [CI] 1.78-4 28), absent or reversed a-wave in the ductus venosus (OR 2.32, 95% CI 1.70-3.16) or a middle cerebral artery peak systolic velocity > 1.5 multiples of the median (MoM) (OR 7.59, 95% CI 2.56-22.46). In donors, only A/REDF in the umbilical artery (OR 3 40, 95% CI 2.68-4.32) and absent or reversed a-wave in the ductus venosus (OR 1.66, 95% CI 1.12-2 47) were associated with IUFD. No association was found between donor-IUFD and preoperative myocardial performance index (MPI). Two studies found an association between abnormal MPI and recipient demise. With this study, we have identified a set of preoperative Doppler parameters predictive of fetal demise after laser surgery. More research is needed to assess the utility of preoperative echocardiographic parameters such as the MPI in predicting IUFD.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) complicates approximately 10-15% of monochorionic twin pregnancies and results from unbalanced intertwin transfusion through placental vascular anastomoses, which impacts cardiovascular loading conditions.[1, 2] If left untreated, the overall perinatal mortality can be as high as 90% to 100%.[3, 4] Fetoscopic laser coagulation of placental anastomoses significantly improves the dual twin survival rate to 64% to 70% and the survival rate of at least one survivor to 85% to 92%.[5, 6] Survival after surgery is determined by a combination of post-laser intrauterine fetal demise (IUFD) and non-viable delivery. Compromised cardiac function is thought to contribute significantly to the mortality rates after TTTS.[7] Cardiac (functional) abnormalities, most commonly observed in recipients[8-10] are, however, not taken into account in the disease severity classification by Quintero.[11] The diagnosis of TTTS is made by ultrasound and encompasses the presence of concurrent polyhydramnios in the recipient and oligohydramnios in the donor twin.[12] Since fetuses with cardiac compromise are more likely to die in utero, assessment of fetal cardiac function prior to laser surgery might help in staging disease severity.

Several studies have focused on fetal circulation and cardiac involvement in TTTS and the prognostic value of these measurements. The objective of this systematic review and meta-analysis was to determine the capability to predict IUFD after fetoscopic laser coagulation with echocardiography and Doppler before surgery.

METHODS

Search strategy

This systematic review was performed using the PRISMA methodology.[13] Relevant articles were identified using electronic databases (Pubmed, Embase, Web of Science and Cochrane). Publications from January 1990 to July 2018, written in English and containing the search terms related to twin-twin transfusion syndrome, fetoscopic laser coagulation, prediction of fetal demise and ultrasonography were included. The final search was performed on 1 October 2018. Two reviewers (M.G. and S.E.) screened titles and abstracts independently for relevance. If a title or abstract seemed relevant, full text was retrieved and assessed for inclusion. Selected articles were cross-referenced. Disagreement was resolved by consensus between the two reviewers. Studies were excluded from the analysis if no ultrasound had been performed prior to laser surgery or IUFD was not an endpoint of the study. IUFD was defined as fetal demise at any time after laser surgery and before onset of labor.

Quality assessment

Study quality and risk of bias was assessed by the two reviewers using the Hayden bias rating tool,[14] as suggested by the Cochrane Collaboration. With this tool the risk of bias was assessed in 6 domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Each of the 6 potential bias domains was rated as having high, moderate, or low risk of bias. Low methodological quality was not an exclusion criterion.

Data extraction

One reviewer (M.G) extracted relevant information from the selected articles. The following data were extracted from the selected articles and tabulated: first author, year of publication, study design, country of origin, number of patients, type of fetoscopic laser surgery (selective laser photocoagulation of communicating vessels [SLPCV] or the Solomon technique)[5], operationalization of primary outcome and outcome measurement and the incidence of IUFD in cases and controls (2 x 2 tables). If possible, deaths attributable to pregnancy loss before 24 weeks gestation or termination of pregnancy were excluded from the analyses.

Statistical analysis

Statistical analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Odds ratios (ORs) and their 95% confidence intervals (CIs) were used as effect sizes for meta-analysis of dichotomous data. Heterogeneity between studies was examined with the inconsistency square

(I^2) statistics, with between-study heterogeneity at $I^2 \geq 50\%$ and $p \geq 0.05$.[15] In case of heterogeneity, a random effects model was used.[16] Otherwise, or in case of limited studies to reliably estimate between study variability, a fixed effect model was used. We performed meta-analyses and constructed forest plots to examine the effect of abnormal Doppler flow velocity waveforms (FVWs) on IUFD with separate analyses for recipients and donors. Absent and reversed end-diastolic flow (A/REDF) in the umbilical artery (UA) were combined in one group. Likewise, absent or reversed a-wave in the ductus venosus (DV) were combined in one group. Parameters measured in the same twin were used for the analyses (i.e. umbilical artery Doppler in the recipient twin in relation to recipient IUFD).

RESULTS

The search resulted in 473 articles, of which 18 were included in this study (Figure 1). The study characteristics are summarized in Table 1. Quality assessment is summarized in Table 2.

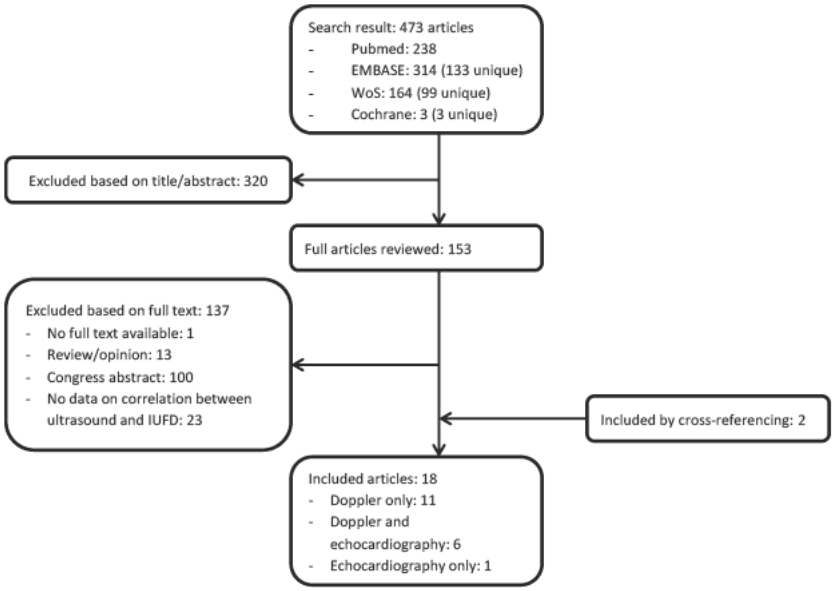

Figure 1. Flow chart demonstrating results of systematic review

Overall IUFD

Five studies report on fetal demise in the first 24 hours after surgery. An IUFD rate of 12% for donors and 8% for recipients was reported.[17-21] If the period was extended to the first week after laser surgery the mortality rates increased to 17% and 15%, respectively.[19, 20, 22] In studies including all fetal deaths before onset of labor, 23% of donor twins and 17% of recipient twins died in utero.[19, 21, 23-33] In the early years of fetoscopic laser coagulation (1998-2008) these rates were 29% and 21%. These rates improved to 19% and 13%, respectively, in the following decade (2008-2018).

Doppler ultrasonography

Three studies were excluded from the meta-analysis[19, 33, 34] because abnormal Doppler FVWs were not analyzed in relation to IUFD,[19, 33] or only time-interval variables of the DV FVW were analyzed.[34] Since the number of included studies was too small for reliable assessment of between-study variance, a fixed effect model was used throughout.

We estimated the prevalence of abnormal Doppler FVWs in both donors and recipients prior to laser surgery. Of all fetuses, both alive and demised, 25.3% of donors and 6.2% of recipients had A/REDF in the UA prior to laser surgery. Abnormal DV FVW was found in 9.7% of donors and 28.3% of recipients. In 6.9% of donors and 35.6% of recipients pulsations in the umbilical vein were present. An elevated middle cerebral artery peak systolic velocity (MCA-PSV) prior to surgery was reported in 7.9% of donor twins and 2.4% in recipient twins.

Variables associated with fetal demise in recipient twins were: A/REDF in the UA, absent or reversed a-wave in the DV and MCA-PSV > 1.5 multiples of the median (MoM; Figure 2). Pulsatile flow in the umbilical vein was seen in over one-third of recipients but this did not increase the risk of recipient IUFD (OR 1.50, 95% CI 0.98-2.29). In donors, only A/REDF in the umbilical artery and absent or reversed a-wave in the DV were associated with IUFD (Figure 3). An elevated MCA-PSV in the donor almost doubled the risk of demise, but this finding did not reach significance (OR 1.91, 95% CI 0.97-3.76). Three studies reported the odds of donor demise for AEDF and REDF in the UA separately.[28-30] All three studies concluded that REDF in the UA was the strongest predictor of donor demise. Many studies included in this review were underpowered to detect a difference in IUFD rate of donors and recipients with abnormal DV FVW. No study except for the study by Ishii *et al.*[26] found a significant association between preoperative abnormal DV FVW and donor demise. By pooling the data in this meta-analysis, we were able to find an association between abnormal DV FVW and an increased risk of IUFD of both donors and recipients.

In the included studies, additional variables were also investigated. Kontopoulos *et al.*[27] showed that the proportion of time in the cardiac cycle spent in AEDF (%AEDF) was significantly higher in patients with IUFD of the donor as compared to surviving donors (36.5% vs. 29.6%, p = 0.01). In a recent study by Delabaere *et al.*[20] with 111 patients, donors with early fetal demise (less than 7 days after laser surgery) had a lower MCA-pulsatility index (PI) (1.43 vs 1.65, p = 0.02), a higher UA-PI (2.03 vs 1.59, p = 0.05) and a lower cerebroplacental ratio (0.81 vs 1.11, p = 0.01) as compared to donors who survived the first week after surgery. Two other studies were not able to confirm these findings.[21, 29]

Table 1. Article characteristics

	Author (year) Country	Design	Multi-/ singlecenter	Patients	Type of FLS
1	Ville (1998) UK	P	M	132	SLPCV
2	Zilulnig (1999) Germany	P	S	121	SLPCV
3	Martinez (2003) USA	P	S	110	SLPCV
4	Cavicchioni (2006) France	R	S	120	SLPCV
5	Ishii (2007) Japan	P	M	55	SLPCV
6	Kontopoulos (2007) USA	P	S	401	SLPCV
7	Kontopoulos (2009) USA	P	S	189	SLPCV
8	Skupski (2010) USA	R	M	466	SLPCV
9	Trieu (2012) France	R	S	86	N/A
10	Eixarch (2013) Spain	P	S	215	SLPCV
11	Gapp-Born (2014) France	P	S	105	Both
12	Tachibana (2015) Germany	R	S	107	SLPCV
13	Snowise (2015) USA	P	S	166	Solomon
14	Patel (2015) USA	R	S	369	SLPCV
15	Eschbach (2016) Netherlands	R	S	288	Both
16	Finneran (2016) USA	R	S	53	SLPCV
17	Leduc (2017) Canada	R	S	105	Both
18	Delabaere (2018) Canada	R	S	111	Both

FLS, fetoscopic laser surgery; IUFD, intrauterine fetal demise; P, prospective; M, multicenter; SLPCV, selective laser photocoagulation of communicating vessels; UA, umbilical artery;

Time of IUFD	Doppler measurements	Echocardiography	Included in meta-analysis
Before onset of labor	UA	No	UA
Before onset of labor	UA, DV	No	UA
Unspecified	UA, DV, UV, MCA	Yes	UA, DV, UV
Before onset of labor	UA, DV	No	UA, DV
Before onset of labor	UA, DV, UV	No	UA, DV, UV
Unspecified (donor)	UA, %UA	No	UA
<24 h after FLS	MCA	No	MCA-PSV
Before onset of labor	UA, DV, UV	Yes	UA, DV, UV
<7 d after FLS	MCA	No	MCA-PSV
<7 d after FLS	UA, DV, MCA	Yes	UA, MCA-PSV, DV
Unspecified (recipient)	-	Yes	-
<2 d after FLS	DV (time intervals)	No	-
Before onset of labor (donor)	UA, DV, MCA	No	UA, DV
<24 h after FLS (recipient)	UA	No	UA
SFD before onset of labor	UA, DV, UV	No	UA, DV, VU
<7 d after FLS	-	Yes	-
Unspecified	UA	Yes	UA
<7 d after FLS	UA, DV, MCA	Yes	UA, DV, MCA-PSV

S, single center; DV, ductus venosus; MCA, middle cerebral artery; UV, umbilical vein; R, retrospective; h, hours; PSV, peak systolic velocity; N/A, not applicable; d, days; SFD, single fetal demise.

Table 2. Risk of bias in six domains based on the Hayden bias rating tool

	Variable	Study participation	Study attrition
1	Ville (1998)	Moderate	Low
2	Zilulnig (1999)	Moderate	Low
3	Martinez (2003)	Low	Low
4	Cavicchioni (2006)	Moderate	Low
5	Ishii (2007)	High	Low
6	Kontopoulos (2007)	Moderate	Low
7	Kontopoulos (2009)	Moderate	Low
8	Skupski (2010)	Low	Low
9	Trieu (2012)	Low	Low
10	Eixarch (2013)	Low	Low
11	Gapp-Born (2014)	Low	Low
12	Tachibana (2015)	Low	Low
13	Snowise (2015)	Low	Low
14	Patel (2015)	Moderate	Low
15	Eschbach (2016)	Low	Low
16	Finneran (2016)	Moderate	Low
17	Leduc (2017)	Moderate	Low
18	Delabaere (2018)	Low	Low

	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
	Low	Moderate	Moderate	Low
	Low	Moderate	Moderate	Low
	Low	Moderate	High	Low
	Moderate	Low	Low	Low
	Low	Low	Moderate	Low
	Low	Moderate	High	Moderate
	Low	Low	Low	Low
	Moderate	Low	Low	Low
	Low	Moderate	Low	Low
	Low	Low	Low	Low
	Low	Low	Low	Low
	Low	Low	High	Low
	Low	Low	Low	Low
	Low	Low	High	Low
	Low	Low	Low	Low
	Moderate	Low	Low	Low
	Moderate	Low	High	Low
	Low	Low	Moderate	Low

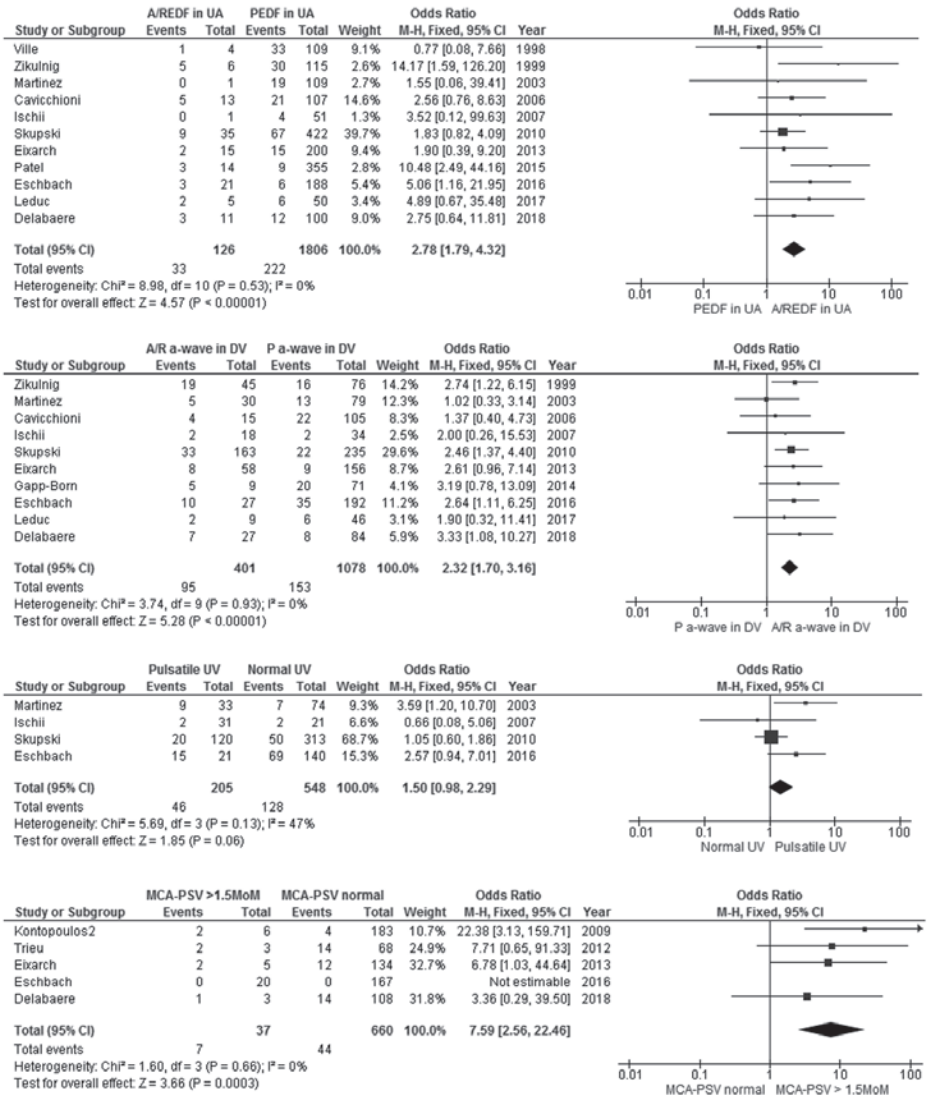

Figure 2. Doppler flows in the recipient twin. PEDF or A/REDF in UA, positive or absent/reversed end-diastolic flow in the umbilical artery; P or A/E a-wave in DV, positive or absent/reversed a-wave in the ductus venosus; UV, umbilical vein; MCA-PSV, middle cerebral artery-peak systolic velocity

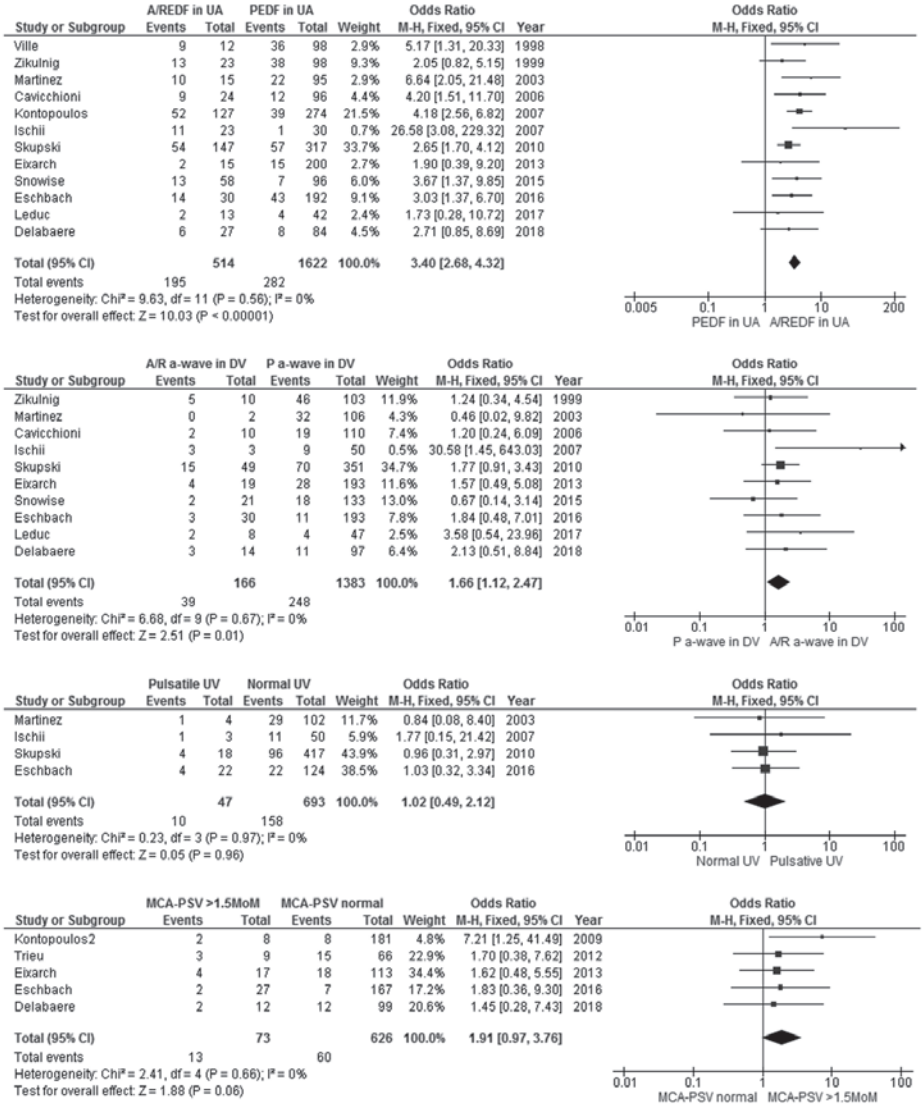

Figure 3. Doppler flows in the donor twin. PEDF or A/REDF in UA, positive or absent/reversed end-diastolic flow in the umbilical artery; P or A/E a-wave in DV, positive or absent/reversed a-wave in the ductus venosus; UV, umbilical vein; MCA-PSV, middle cerebral artery-peak systolic velocity

Results of individual studies on echocardiography in relation to IUFD

In seven studies echocardiographic findings were analyzed in relation to IUFD.[19-21, 28, 29, 32, 33] We could only perform a meta-analysis on atrioventricular regurgitation. The presence of this finding was not associated with a higher risk of either donor (OR 1.34, 95% CI 0.39-4.62) or recipient demise (OR 1.20, 95% CI 0.79-1.83).[20, 21, 28]

The substantial methodical heterogeneity prevented the construction of other forest plots, we therefore present a summary of outcomes for other echocardiographic parameters. Five studies assessed the preoperative myocardial performance index (MPI) as a separate parameter,[19, 20, 29, 32, 33] of which two report an increased risk of recipient demise.[20, 33] In a study of 105 recipients,[33] the risk of recipient demise was four times higher if the MPI *z* score was above a cut-off *z* score of 1.645, which corresponds to the 95th percentile ($p < 0.01$). After adjustment for gestational age and placental localization, there was no increased risk (OR 3.09, 95% CI 0.94-9.30, $p = 0.06$). In the most recent study by Delabaere *et al.*,[20] demised recipients had a higher mean MPI of the right ventricle (RV-MPI) as compared with survivors after adjustment for gestational age at laser surgery (unadjusted $p = 0.07$, adjusted $p = 0.02$). The three remaining studies did not find an association between preoperative MPI and postoperative recipient demise.[19, 29, 32] The results are therefore conflicting. An association between preoperative MPI and donor-IUFD was absent in all studies.

In three studies, the Children's Hospital of Philadelphia (CHOP) score[35] (a sum of 12 cardiovascular parameters, including the MPI) was analyzed in relation to IUFD.[20, 28, 33] A CHOP score above 5 is generally considered as abnormal. Interestingly, only a CHOP score ≥ 3 was associated with recipient demise (40% with a score ≥ 3 vs 13% with a score < 3, $p < 0.01$)[33] and a score > 5 was not.[20] In the study of 466 TTTS cases, 'global cardiac dysfunction' was included in the analysis, a factor defined as an abnormal MPI, ventricular dyskinesia, abnormal ejection fraction, abnormal CHOP score (or other measure of cardiac dysfunction; exact cut-off values for separate parameters were not stated). The presence of "global cardiac dysfunction" prior to surgery did not increase the risk of either donor or recipient demise.[28]

In a small study by Leduc *et al.*[32] of 55 treated pregnancies the aortic isthmus flow velocity patterns were assessed. The isthmic systolic index,[36] which reflects the relative performances of the right and left ventricle, measured in recipients before laser, was associated with recipient IUFD ($p = 0.04$).

DISCUSSION

In this systematic review and meta-analysis we found an association between preoperative Doppler FVWs and IUFD after fetoscopic laser coagulation. Fetal echocardiographic parameters such as the MPI appear not to be associated with fetal demise after laser coagulation. Results from studies investigating echocardiographic parameters do almost reach significance however, possibly indicating lack of power in these studies. The conflicting results regarding the use of echocardiography in the prediction of demise prevented us from building a prediction model including both Doppler and echocardiographic parameters.

We have shown an IUFD rate of 19% for donors and 13% for recipients in the last decade. Improved survival after laser surgery may reflect a learning-curve effect of the operators,[6, 37] who gain more experience with this procedure globally. Furthermore, evolution of the technique[38] and developments and improvements in ultrasonographic monitoring may play a role. The investigation of these factors on fetal survival rates fell outside of the scope of this article.

We found that A/REDF in the UA, absent or reversed a-wave in the DV and MCA-PSV > 1.5 MoM increases the risk of recipient-IUFD. Abnormal UA FVW, present in only 6% of recipients, may result from placental compression by increased intra-amniotic pressure due to massive polyhydramnios or, alternatively, from poor cardiac function. A suggested theory is that poor myocardial contractility as a result of recipient hypervolemia and cardiac overload, result in an insufficient generated blood pressure to propel the blood forward in the UA throughout diastole.[20] The theory that poor cardiac function causes A/REDF flow in the umbilical artery in recipient twins is further supported by the finding that recipient twins with abnormal UA FVW always have abnormal venous FVW of the umbilical vein, ductus venosus, or both.[18] More than one-third of recipients had a pulsatile umbilical vein preoperative, which could also indicate cardiac overload. This parameter was however not statistically significant associated with recipient demise. The mechanism underlying the association between increased MCA-PSV and IUFD in recipients is not entirely clear. Increased cardiac output resulting from the hypervolemic status of these fetuses, which is responsible for cardiomegaly and hypertrophy in some TTTS cases, could also elevate the blood velocity in the cerebral arteries. These changes have also been shown in fetuses with congenital heart disease[39] or intrauterine growth restriction.[40] Another suggested explanation is decreased fetal oxygenation due to placental interstitial edema which increases MCA blood velocity through autoregulation in the absence of low hemoglobin.[29, 41]

In donors, only A/REDF in the UA and absent or reversed a-wave in the DV were found to be associated with donor-IUFD. In these twins, the mechanism leading to hemodynamic changes appears to differ from the pathophysiology in recipient twins. Abnormal UA FVW occurs in a quarter of donors prior to laser surgery. If present, the odds of demise are 3.4 times higher as compared to fetuses who have a normal UA FVW. It reflects both placental insufficiency (maldevelopment and unequal sharing) and fetal hypotension secondary to the hemodynamic imbalance in TTTS. Three studies showed that REDF in the UA is a stronger predictor of donor-IUFD than AEDF.[28-30] It is suggested that reversed UA flow reflects placental insufficiency in a greater degree and that it is not amenable to improvement following restoration of volume status.[29] Abnormal venous FVW in donor twins may be explained by either cardiac decompensation due to severe placental insufficiency or hypovolemia as a result of the TTTS. The relative hypervolemia after occlusion of vascular anastomoses may increase the afterload and cause acute transient impaired cardiac function which attributes to a higher chance of donor demise after surgery. Elevated MCA-PSV prior to surgery is reported in 8% of donor twins. In monochorionic twins, unbalanced net intertwin blood transfusion may lead to TTTS, but also to twin anemia polycythemia sequence (TAPS). In TAPS, there is a chronic and slow transfusion of blood from the donor to the recipient twin through extremely small anastomoses.[42] This process leads to an anemic donor and polycythemic recipient. Two to eight percent of TTTS cases may have preoperative signs of TAPS,[43] which may explain the increased MCA-PSV in donors prior to laser surgery. Although there was a tendency for donor twins with an elevated MCA-PSV to die more frequently in utero after surgery this finding did not reach statistical significance.

The question whether echocardiographic parameters should be included in the TTTS staging system remains unanswered. Most studies investigating the association between assessment of cardiac function and IUFD include neonatal demise instead of fetal demise as their endpoint.[44-49] A large amount of data reflecting cardiac function had therefore been excluded from this systematic review. Furthermore, the limited amount of available reports on the value of a detailed cardiovascular assessment in the prediction of fetal survival provide discordant results. Three out of five studies did not find any genuine correlation with IUFD.[19, 29, 32] The lack of correlation between severity of cardiac disease and intrauterine demise is not explained so far. The low reproducibility and repeatability indices of the MPI and a high degree of expertise needed to perform MPI or CHOP score measurements may be important factors. Very precise recordings and manual placement of calipers are needed for MPI calculations. For the left ventricle, the Doppler cursor is placed between the mitral valve and aortic valve, and both mitral inflow and aortic outflow can be visualized on the same trace. Measurement of the RV-MPI is further complicated because the right ventricular inflow

and outflow cannot be visualized in one plane and thus not in the same trace. Published normal ranges for different gestational ages demonstrate a wide variation,[50-54] probably because a standardized method has not been established. While automation of these measurements will remove the human factor on measurement error, experience is still required to be able to acquire the correct Doppler waveform successfully.[55, 56] The lack of correlation may also be explained by the effectiveness of laser surgery for improving recipient cardiac function. Other variables associated with laser surgery such as premature rupture of membranes, unequal placental share and preterm delivery become the predominant determinants of fetal mortality after correction of the hemodynamic imbalance.

To our knowledge, this is the first review and meta-analysis of pre-operative echocardiography and Doppler in the prediction of IUFD after fetoscopic laser surgery. To maximize our sample size, we included all studies which investigated fetal demise before birth, not only early-IUFD (< 7 days). Other causes of demise such as placental insufficiency or IUGR could therefore have influenced our results, even though the majority of IUFD after laser occurs in the first week after laser surgery.[7, 21, 26] There are also other limitations to this study. Most studies are single center reports. Half of the reports are retrospective studies. In all but one study[30] selective coagulation was used for all or for a proportion of cases. It is known that incomplete laser coagulation is a risk factor for recurrent TTTS or post-laser TAPS and therewith for possible subsequent fetal demise.[57] Finally, we did not include fetal growth discordance, selective fetal growth restriction (sFGR) or TAPS prior to laser surgery in this study. Future large-scale prospective studies could allow for multivariate analysis into the interference of sFGR and TAPS on fetal echocardiography and Doppler parameters for IUFD. Incorporating signs of sFGR or TAPS, but also factors such as Quintero stage, hydrops and gestational age at TTTS diagnosis, into a prediction model together with the beforementioned Doppler parameters could be useful in daily clinical care in cases where the risk of fetal demise turns out to be high, to spend additional counseling time on cord occlusion as a back-up plan if laser surgery seems technically challenging. A prediction model could also be useful in future clinical trials investigating innovations in treatment of TTTS.

In conclusion, we have identified a set of preoperative Doppler parameters predictive of fetal demise after fetoscopic laser coagulation. Recipient twins have an increased risk of demise in case of preoperative abnormal FWV of the UA, DV and MCA. In donor twins, only abnormal FVW of the UA and DV are associated with IUFD after surgery. The utility of preoperative parameters that reflect cardiac function such as the MPI in predicting IUFD remains unclear.

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CHAPTER 5

PERIOPERATIVE FETAL HEMODYNAMIC CHANGES IN TWIN-TWIN TRANSFUSION SYNDROME AND NEURODEVELOPMENTAL OUTCOME AT TWO-YEARS OF AGE

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ABSTRACT

Objective: To investigate whether perioperative fetal hemodynamic changes in twin-twin transfusion syndrome (TTTS) are associated with neurodevelopmental impairment (NDI) at two-years.

Methods: Doppler parameters of three sonograms (day before, first day after and one week after laser surgery for TTTS) were assessed for correlation with neurodevelopmental outcome at two-years (2008-2016). NDI was defined as: cerebral palsy, deafness, blindness, and/or a Bayley-III cognitive/motor developmental test-score > 2 SD below the mean.

Results: Long-term outcome was assessed in 492 TTTS survivors. NDI was present in 5% (24/492). After adjustment for severe cerebral injury (present in 4%), associated with NDI were: middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the median (MoM) one day after surgery (odds ratio [OR] 4.96, 95% confidence interval [CI] 1.17-21.05, p = 0.03), a change from normal umbilical artery pulsatility index (UA-PI) pre-surgery to UA-PI > p95 post-surgery (OR 4.19, 95% CI 1.04-16.87, p = 0.04), a change from normal to MCA-PSV > 1.5 MoM (OR 4.75, 95% CI 1.43-15.77, p = 0.01).

Conclusion: Perioperative fetal hemodynamic changes in TTTS pregnancies treated with laser are associated with poor neurodevelopmental outcome. Prospective research on the cerebrovascular response to altered hemodynamic conditions is necessary to further understand the cerebral autoregulatory capacity of the fetus in relation to neurodevelopmental outcome.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies and is caused by an unbalanced blood flow between the donor and recipient twin. The risk of fetal death is approximately 90% if left untreated.[1] The best possible outcome is achieved with fetoscopic laser surgery of the vascular anastomoses, which has an overall survival rate of 74-87%.[2, 3] In TTTS survivors, the incidence of neurodevelopmental impairment (NDI) is on average 10%.[4] Possible risk factors for NDI are advanced gestational age (GA) at intervention, advanced TTTS stage, lower GA at birth, lower birth weight and severe neonatal cerebral injury.[4, 5]

Hemodynamic changes in fetuses may cause fetal developmental abnormalities, for example malformation of cortical development.[6] In case of single fetal demise in monochorionic twin pregnancies, 26% of co-twins suffer from severe cerebral injury,[7] which is thought to be caused by acute fetal exsanguination into the low pressure circulation of the demised fetus through the placental vascular anastomoses. In TTTS, ablation of the vascular anastomoses also results in hemodynamic changes in both the donor and the recipient fetus, with a possible effect on the fetal brain. Whether there is a direct effect on neurodevelopment is unknown. One study showed that a post-laser cerebroplacental ratio[8] < 1.0 was a risk factor for slightly lower developmental test-scores at the age of two.[9]

The aim of this study was to evaluate perioperative fetal hemodynamic changes in TTTS pregnancies treated with fetoscopic laser coagulation (FLC) in relation to neurodevelopmental outcome at the age of two in a large consecutive cohort of TTTS survivors.

METHODS

The Leiden University Medical Center (LUMC) serves as the national referral center for fetal therapy in the Netherlands. Surviving children of consecutive monochorionic twin pregnancies with TTTS treated with fetoscopic laser surgery between March 2008 and April 2016 were eligible for this study. Details on the laser technique at our center[8, 10] and short-term outcome results have previously been reported.[11] The selective laser technique was applied between January 2008 and March 2008. From March 2008 until July 2012 either the selective or the Solomon technique was used, as part of the Solomon trial.[2] After conclusion of the trial, the Solomon technique became the standard technique for all procedures. For this study we retrieved antenatal and neonatal data from our databases. The study was approved by the institutional review board of the LUMC.

Antenatal parameters

TTTS was diagnosed using standard European diagnostic ultrasound criteria[12] and pregnancies were staged prospectively according to the Quintero staging system.[13] We recorded GA at laser surgery, TTTS stage, antenatal and/or postnatal twin anemia polycythemia sequence (TAPS), recurrence of TTTS and fetal demise of the co-twin. The presence of TAPS was identified according to previously published criteria.[14] Doppler parameters of three antenatal sonograms (day before laser surgery, first day after laser surgery and approximately one week after laser surgery) were obtained and evaluated for abnormalities in: umbilical artery (UA) pulsatility index (UA-PI) and end-diastolic velocity (UA-EDV), middle cerebral artery PI (MCA-PI) and peak systolic velocity (MCA-PSV), and pattern of the ductus venosus (DV). UA Doppler was defined as abnormal when EDV was absent or reversed, or the PI was above the 95th percentile (> p95).[15] Blood flow during the atrial contraction in the DV was classified as normal (positive a-wave) or abnormal (absent or reversed a-wave). MCA-PSV was converted to multiples of the median (MoM), and > 1.5 MoM was considered abnormal.[16] The cerebroplacental ratio (CPR) was calculated by dividing MCA-PI by UA-PI. An abnormal CPR was categorically defined at < 1.0.[17]

Postnatal parameters

The following neonatal data were recorded: GA at birth, birth weight and severe cerebral injury. Small for gestational age (SGA) was defined as birth weight < p10. Severe neonatal cerebral injury was defined as at least one of the following: intraventricular hemorrhage ≥ Grade III,[18] cystic periventricular leukomalacia ≥ Grade II,[19] ventricular dilatation ≥ 97th percentile,[20] porencephalic cysts or arterial or venous infarction detected on cerebral imaging.

Since 2008, TTTS survivors have been routinely assessed in our long-term follow-up outpatient clinic at the age of two, corrected for prematurity (two years after the estimated date of delivery). Previous results on neurodevelopmental outcome up to 2016 have been reported.[5, 21] In short: a standardized follow-up evaluation included a physical and neurological examination and an assessment of cognitive and motor development with use of the Dutch version of the Bayley Scales of Infant and Toddler Development III (Bayley-III).[22] NDI was defined as the presence of: cerebral palsy (≥ Grade II),[23] deafness, blindness, and/or a Bayley-III cognitive or motor developmental test-score > 2 SD below the mean.

Statistical analysis

Data are reported as n (%), mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Baseline characteristics were compared with the use of the Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. An analysis of risk factors (perioperative Doppler parameters) possibly predicting adverse long-term outcome (NDI) was conducted using univariate and multivariate logistic regression models with a generalized estimated equation (GEE) module to account for the effect that observations of twin pairs are not independent. The multivariable model included variables that showed a significant association in the univariable analysis. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$. P values were adjusted for multiple hypotheses testing using the false discovery rate (FDR) correction (FDR threshold of 0.1).[24]

RESULTS

During the study period, 398 consecutive TTTS pregnancies were treated with fetoscopic laser surgery. 119 pregnancies were excluded (no follow-up n = 51 (13%), double fetal/neonatal death n = 50 (13%), incomplete follow-up n = 16 (4%), Tay Sachs disease n = 1, neurofibromatosis type I n = 1). Of the remaining 279 pregnancies, 492 children were enrolled in this study.

Table 1 presents the baseline characteristics and Table 2 presents the perinatal characteristics of the children included in this study. Extreme prematurity (< 28 weeks gestation) occurred in 26 out of 279 (9.3%) pregnancies. NDI was detected in 24/492 survivors (4.9%, 95% CI 3.3-8.9). Among the perinatal characteristics, only severe cerebral injury, detected in 21/492 (4.3%, 95% CI 2.8-8 4) live-born neonates, was significantly associated with the occurrence of NDI (OR 17.15, 95% CI 6.24-47.20). Severe cerebral injury was detected in 8/24 (33%) cases with NDI and in 13/468 (3%) cases without NDI (p < 0.001). Of the twins with NDI, two donors (2/12) and six recipients (6/12) had severe cerebral injury, of whom one donor was suspected of intracranial hemorrhage on ultrasound and MRI after FLC. There was no difference in GA at laser, TTTS stage, incomplete laser, fetal demise of the co-twin, GA at birth or birth weight between cases with NDI and those without. Pregnancies of three of the cases with NDI (two donors and one recipient) were complicated by post-laser TAPS, with reversal of the intertwin transfusion (the former TTTS donor was the TAPS recipient and vice-versa).

Table 1. Perinatal characteristics of 279 TTTS pregnancies treated with laser surgery

Characteristics	**Value**
Gestational age at laser surgery (weeks)	20.0 (17.4 - 22.6)
TTTS stage	
I	32 (12)
II	91 (33)
III	149 (53)
IV	7 (3)
TAPS or recurrent TTTS	33 (12)
Fetal demise of co-twin	51 (18)
Gestational age at birth (weeks)	33.1 (30.3 - 36.0)

Data are presented as median (IQR) or n (%). TTTS, twin twin transfusion syndrome; TAPS, twin anemia polycythemia sequence.

Table 2. Characteristics of 492 TTTS survivors

Characteristics	**NDI**	**No NDI**	**p-value**
	(n = 24)	**(n = 468)**	
Recipient	12 (50)	232 (50)	0.97
GA at laser surgery (weeks)	20.3 (17.5 - 23.2)	20.0 (17.4 - 22.6)	0.75
TTTS stage			
I	3 (13)	57 (12)	1.00
II	10 (42)	149 (32)	0.32
III	10 (42)	250 (53)	0.26
IV	1 (4)	12 (3)	0.48
TAPS	3 (13)	50 (11)	0.48
Recurrent TTTS	1 (4)	6 (1)	0.30
Fetal demise of co-twin	2 (8)	49 (11)	1.00
GA at birth (weeks)	32.3 (30.0 - 34.6)	33.1 (30 4 - 35.9)	0.33
37-40	3 (13)	33 (7)	0.41
33-37	7 (29)	220 (47)	0.09
26-33	12 (50)	207 (44)	0.58
24-26	2 (8)	8 (2)	0.08
Birth weight (grams)	1655 (1260 - 2051)	1822 (1350 - 2293)	0.27
Small for gestational age	11 (46)	201 (43)	0.78
Severe neonatal cerebral injury	8 (33)	13 (3)	**<0.001**

Data are presented as median (IQR) or n (%). TTTS, twin-twin transfusion syndrome; NDI, neurodevelopmental impairment; TAPS, twin anemia polycythemia sequence.

Table 3. Analysis of hemodynamic risk factors for neurodevelopmental impairment

		NDI
		(n = 24)
Absent/reversed UA EDV	Pre-surgery	1 (5)
	Day 1	0 (0)
	Week 1	1 (5)
UA PI > p95	Pre-surgery	1 (6)
	Day 1	2 (15)
	Week 1	4 (20)
Change UA from normal to PI to > p95		4 (27)
MCA PSV > 1.5 MoM	Pre-surgery	1 (5)
	Day 1	5 (36)
	Week 1	4 (24)
Change MCA PSV from normal to > 1.5 MoM		6 (43)
MCA PI < p5	Pre-surgery	3 (21)
	Day 1	1 (8)
	Week 1	2 (12)
CPR < 1.0	Pre-surgery	8 (50)
	Day 1	3 (27)
	Week 1	1 (6)
Absent/reversed DV a-wave	Pre-surgery	1 (5)
	Day 1	1 (10)
	Week 1	1 (5)

Data are presented as n (%). NDI, neurodevelopmental impairment; OR, odds ratio; FDR, false discovery rate; CI, confidence interval; UA, umbilical artery; EDV, end-diastolic velocity;

The main study findings are summarized in Table 3. After correction for multiple hypotheses testing, NDI was associated with MCA-PSV > 1.5 MoM the first day after surgery and a change from normal UA-PI to UA-PI > p95 and normal MCA-PSV to MCA-PSV > 1.5 MoM after laser. When adjusted for severe cerebral injury, these parameters remained statistically significant. An MCA-PSV > 1.5 MoM the first day after surgery, detected in five cases, increased the risk of NDI almost five times (OR 4.96, 95% CI 1.17-21.05, p = 0.03). Pre-surgery, these five infants had normal MCA-PSV Dopplers. Of the NDI cases, 27% had a normal UA-PI prior to laser and an abnormal UA-PI after surgery (first day after or after one week), which increased the risk of NDI four times

No NDI (n = 468)	Crude OR (95% CI)	FDR- adjusted p value
54 (12)	0.38 (0.07 - 2.06)	0.58
19 (5)	0.0	1.00
11 (3)	2 20 (0.34 - 14.50)	0.69
47 (12)	0.50 (0.07 - 3.75)	0.77
18 (5)	3 29 (0.77 - 14.11)	0.31
33 (8)	3 27 (1.15 - 9.33)	0.11
20 (7)	5 23 (1.62 - 16.89)	**0.04**
23 (6)	1.32 (0.30 - 5.86)	0.95
25 (8)	6.49 (2.06 - 20 46)	**0.01**
20 (5)	5 47 (1.32 - 22.63)	0.10
28 (10)	6.22 (2.12 - 18.23)	**0.02**
123 (34)	0.59 (0.17 - 2.02)	0.73
83 (29)	0.16 (0.02 - 1.28)	0.28
70 (18)	0.63 (0.12 - 3 29)	0.83
156 (45)	0.99 (0.40 - 2 45)	1.02
81 (31)	1.06 (0 29 - 3.84)	1.04
80 (22)	0.20 (0.01 - 2.47)	0.50
61 (15)	0.69 (0.15 - 3.20)	1 27
49 (16)	0.76 (0.12 - 4.72)	0.97
16 (4)	1.17 (0.11 - 12.98)	1.06

PI, pulsatility index; MCA, middle cerebral artery; PSV, peak systolic velocity; MoM, multiples of the median; CPR, cerebroplacental ratio; DV, ductus venosus.

(OR 4.19, 95% CI 1.04-16.87, p = 0.04). A change from normal MCA-PSV to MCA-PSV > 1.5 MoM (either one day or one week after FLC) occurred in 43% of children with NDI, and increased the risk of NDI almost five times (OR 4.75, 95% CI 1.43-15.77, p = 0.01). Abnormal UA-PI and MCA-PSV were equally distributed between recipients and donors. One of six fetuses with an MCA-PSV > 1.5 MoM after laser surgery developed TAPS, the remaining five fetuses had only transient increased MCA-PSV without evidence of TAPS.

DISCUSSION

This study shows that perioperative fetal hemodynamic changes in TTTS pregnancies treated with laser surgery are associated with poor neurological outcome. Hemodynamic changes, leading to increased MCA-PSV or UA-PI after laser surgery, were found to be a risk factor for NDI. Since 5% of children were affected by NDI, we advise routine long-term follow-up for all TTTS twins, especially for those with deterioration of Doppler flows.

The fetal hemodynamic changes in TTTS pregnancies undergoing laser surgery has been the subject of debate in a few studies.[8, 25-28] In only one small cohort, studying 99 children, a correlation was found between an abnormal post-laser cerebroplacental ratio and long-term developmental outcomes.[8] Data from our study further increases the awareness regarding the potential relationship between fetal perioperative hemodynamic changes and NDI.

It has been suggested that the temporary elevation in MCA-PSV is a benign condition.[28] An elevated MCA-PSV may however reflect fetal anemia, as part of a TTTS/TAPS spectrum, at time of diagnosis. Fetal anemia may result in a hypoxic environment and may have a deteriorating effect on fetal brain development. The mechanism underlying the elevated MCA-PSV in the recipient post-laser in the absence of TAPS is not fully understood. Possibly, there is a period of (mal)adaptation in these fetuses, resulting in increased brain vulnerability. Another suggestion is that amnioreduction, which is performed to relieve pressure at the end of the laser surgery, leads to the so called 'placental steal phenomenon'.[29] Brief episodes of hemodynamic imbalance, which may cause hyper- and hypoperfusion of the fetal brain, might result in (transient) cerebral lesions that remain undetected by routine monitoring techniques.[26] In the group without NDI, the majority of fetuses had a normal UA-PI and MCA-PI post-laser, indicating normal autoregulation. There was a trend towards higher rates of abnormalities of UA-PI and MCA-PI post-laser in NDI cases, possibly reflecting insufficient autoregulatory capacities in these fetuses. This hypothesis is supported by results from the study by Delabaere *et al.*,[20] in which cases with fetal demise had a higher mean UA-PI and lower mean MCA-PI, indicating a detrimental effect of cerebroplacental redistribution. Even though the number of SGA fetuses was similar between NDI and no-NDI cases, we cannot rule out a possible effect of fetal growth restriction (and therefore an increased UA-PI) on neurodevelopment.[31] Future prospective studies investigating the cerebrovascular response to altered hemodynamic conditions and its effect on neurodevelopment are necessary to further understand the cerebral autoregulatory capacity of the mid-trimester human fetus.

In accordance with a recent report from our group,[21] we did not find an association between TTTS stage, incomplete laser, fetal demise of the co-twin or GA at birth and NDI, factors previously thought to be associated with NDI. The lack of correlation between GA at birth and NDI can be explained by improvement in neonatal intensive care treatment for premature neonates in combination with the low absolute number of TTTS survivors with severe NDI.

The primary strength of this study lies in the number of TTTS survivors to identify risk factors for neurodevelopment. The use of an extensive dataset with perioperative Doppler parameters and perinatal variables allowed for a robust assessment of risk factors. All pre-operative and post-operative sonograms were performed by a limited number of sonographers experienced in the management of monochorionic twin pregnancies. Routine neonatal cerebral imaging was performed to rule out severe cerebral injury. And lastly, neurodevelopmental assessments were conducted by independent and experienced personnel. Despite these strengths, our findings may be limited by several factors. This was a retrospective study, although the data were collected prospectively. Ultrasound data were not complete in all cases. Prenatal detailed neurosonography or fetal MRI is not routinely performed at our center; possible transient cerebral abnormalities could, therefore, not be ruled out. The question remains whether cerebral injury occurred during pregnancy, as a result of the TTTS or FLC, or after delivery. Another important limitation of long-term follow-up studies, including ours, is the inability to obtain 100% inclusion. However, less than 15% was lost to follow-up, which is lower than generally encountered in the literature. Even though this study includes a large number of subjects, the absolute number of NDI cases was still limited. Furthermore, a control group of uncomplicated monochorionic or dichorionic twins was not available. Although generally applied in twin studies,[8, 32, 33] the cut-off value of < 1.0 for abnormal CPR results from studies in singletons.[17, 34] And lastly, the follow-up evaluation was at two-years of age. Although this age allows for strong cognitive, language, personal-social and motor assessment, some developmental problems become more apparent at a later age such as attention-deficit disorder or speech language problems.[35]

CONCLUSIONS

Our study indicates that perioperative fetal hemodynamic changes in TTTS twins treated with laser surgery are associated with poor neurological outcome. We advise routine long-term follow-up for all TTTS twins, especially for those with signs of hemodynamic deterioration after laser surgery. Parents can be informed that the risk of neurodevelopmental impairment at two-years of age is approximately 5%. Since 4% of the children were affected by severe cerebral injury, large prospective studies are required to examine the impact of preoperative fetal cranial imaging and progressive changes on neurodevelopment after laser surgery.

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PART III

POSTNATAL CIRCULATION

CHAPTER 6

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN IN TWIN-TWIN TRANSFUSION SYNDROME: A CASE-CONTROL STUDY

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ABSTRACT

Background: Persistent pulmonary hypertension of the newborn (PPHN) is associated with severe morbidity and mortality. Twin-twin transfusion syndrome (TTTS) is suggested to increase the risk of PPHN.

Objectives: To describe the incidence of PPHN in TTTS twins and to identify risk factors in TTTS twins for the development of severe PPHN.

Methods: Cases with severe PPHN were extracted from our monochorionic twin database (2002-2016). Severe PPHN was defined as severe hypoxemia requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment, confirmed by strict echocardiographic criteria. A case-control comparison within TTTS survivors was conducted to identify risk factors for PPHN.

Results: The incidence of PPHN in TTTS twins was 4% (24/598, 95% confidence interval [CI] 2.7-5.9%) and 0 4% (2/493, 95% CI 0.1-1.5%) in uncomplicated monochorionic twins (odds ratio [OR] 10.3, 95% CI 2 4-43.9, p = 0.002). Two risk factors were independently associated with PPHN: severe prematurity (OR 3.3, 95% CI 1.0-11.4) and recipient status (OR 3.9, 95% CI 1 4-11.0). In TTTS recipients, another risk factor for PPHN is anemia at birth (OR 7 2, 95% CI 1.8-29.6).

Conclusion: Clinicians caring for neonates with TTTS should be aware of the 10-fold increased risk of PPHN compared to uncomplicated monochorionic twins. PPHN occurs more often in case of premature delivery and in recipient twins, particularly in the presence of anemia at birth. As the development of severe PPHN is difficult to predict, we advise that all TTTS twins should be delivered in a tertiary care center with iNO treatment options.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is the result of failure of the normal circulatory transition after birth. An inadequate decrease in pulmonary vascular resistance (PVR) leads to a high right-ventricular pressure and the shunting of non-oxygenated blood from the pulmonary to the systemic circulation, resulting in systemic arterial hypoxaemia.[1] Severe PPHN has an estimated incidence of two per 1,000 live births[2] and is associated with significant morbidity and mortality.[1]

The pathogenesis of PPHN is multifactorial and includes maternal and neonatal causes. There is an increased risk in the infants of mothers with asthma, diabetes or obesity, and in case of fetal exposure to certain drugs.[3] Known effects are the early closure of the ductus arteriosus due to exposure to non-steroidal anti-inflammatory drugs,[4] and pulmonary vascular remodeling due to exposure to selective serotonin re-uptake inhibitors.[5, 6]

Another cardiovascular disorder that is suggested to increase the risk of PPHN is twin-twin transfusion syndrome (TTTS).[7, 8] TTTS affects 10-15% of monochorionic twin pregnancies and results from unbalanced intertwin blood transfusion through placental vascular anastomoses, that leads to hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient.[8, 9] Two small case series reported an incidence of severe PPHN of 26-30/1,000 TTTS newborns, most of which were recipients.[10, 11] Up to 70% of recipients show echocardiographic signs of anatomical or functional cardiac compromise at the time of diagnosis of TTTS, as a result of both increased PVR from vasoactive substances and volume overload.[12, 13] This chronic volume loading might cause remodeling of the pulmonary vasculature, which could result in neonatal PPHN.

The objectives of this study were to describe the incidence of PPHN in TTTS twins and to identify risk factors for the development of PPHN in TTTS survivors, and in recipient twins in particular.

METHODS

All live born monochorionic twins (single or double live births) delivered at our center between March 2002 and September 2016 were eligible for this study. The Leiden University Medical Center (LUMC) is the national referral center for TTTS in the Netherlands. All monochorionic twins admitted to our neonatal intensive care unit (NICU) are prospectively entered into a dedicated medical database, as described previously.[10] We excluded triplets, acardiac twins, twin pairs with spontaneous twin anemia polycythemia sequence (TAPS) or selective fetal growth restriction (defined as a birth weight discrepancy > 25%), twin pairs in which selective feticide was performed, neonatal demises, and those with a major structural heart defect (including right ventricular outflow tract obstruction) or severe lung hypoplasia.

We searched our database for all neonates who were affected by severe PPHN. Severe PPHN was defined as severe hypoxemia (PaO_2 < 37.5-45 mmHg in a FiO_2 of 1.0) requiring mechanical ventilation and inhaled nitric oxide (iNO) treatment. A diagnosis of PPHN was only reached if right-to-left shunting in the ductus arteriosus was observed on echocardiography in the absence of a structural heart defect or severe lung hypoplasia.[14] Echocardiography is performed routinely in all infants admitted to our NICU with severe hypoxemia and the suspicion of PPHN. In order to make a clear distinction between primary PPHN and PPHN secondary to lung injury and prolonged mechanical ventilation in extreme premature neonates with bronchopulmonary dysplasia, our study included only cases of PPHN detected on the first day of life.

The following data concerning TTTS were retrieved from the database: Quintero stage at diagnosis, recipient or donor status, type of treatment for TTTS (expectant management/ amniodrainage/ fetoscopic laser surgery [FLS]/ selective feticide), gestational age (GA) at the time of FLS and the occurrence of post-laser TAPS. A diagnosis of TTTS was based on standard European diagnostic ultrasound criteria.[15] The following neonatal data was recorded: GA at birth, anemia at birth requiring a red blood cell transfusion within 24 hours postpartum, and perinatal asphyxia. Perinatal asphyxia was defined as the presence of ≥ 3 of the following criteria: non-reassuring cardiotocogram patterns, umbilical cord artery pH < 7.10 and base deficit ≥ 16 mmol/L or lactate > 10 mmol/L, a 5-min Apgar score of < 5, failure to achieve spontaneous breathing 5 min after birth, and the onset of multiple organ failure. In TTTS cases, the status of the donor or the recipient was recorded according to the status in utero, and remained registered as such, also in post-laser TAPS cases. Therefore, in case of reversal of the intertwin transfusion after laser (in post-laser TAPS cases), the initial recipient was still recorded as the recipient after birth.

Statistical analysis

First, an analysis was performed to estimate the incidence of PPHN in both TTTS and uncomplicated monochorionic twins. Second, a case-control comparison was conducted to identify risk factors for PPHN in neonates with TTTS. TTTS neonates with PPHN were considered as cases and those without PPHN were considered as controls. Since recipient twins are already known to be at an increased risk of PPHN, we also performed risk analyses within the subgroup of recipients. The data were analyzed using SPSS v23 (IBM, USA) and reported as n (%) or median (interquartile range [IQR]). An analysis of risk factors possibly predicting PPHN was conducted using univariate and multivariate logistic regression models with a generalized estimating equation approach to account for the fact that observations of twin pairs are not independent. The following potential predictors for severe PPHN were studied in a univariable logistic regression model: Quintero stage, recipient status (compared with donor), treatment for TTTS, GA at the time of FLS, post-laser TAPS, severe prematurity (GA at birth < 32 weeks), anemia at birth, and perinatal asphyxia. The multivariate logistic regression model included all variables that showed a significant association in the univariate analyses. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). The level of significance was set at $p < 0.05$. This study was approved by the Medical Ethics Committee of the LUMC.

RESULTS

A total of 1,347 live born monochorionic twins were delivered in our obstetrical department and admitted to our NICU between March 2002 and September 2016. A total of 1,091 newborns were included for analyses; 598 were TTTS twins and 493 were uncomplicated monochorionic twins (Figure 1). A total of 39 TTTS twins and 10 uncomplicated monochorionic twins were single survivors after the fetal demise of the co-twin. Severe PPHN occurred in 26 of the 1,091 (2.4%) liveborn monochorionic twins. The incidence of severe PPHN was 4% (24/598, 95% CI 2.7-5.9%) in the TTTS twins and 0.4% (2/493, 95% CI 0.1-1.5%) in the uncomplicated monochorionic twins (OR 10.3, 95% CI 2.4-43.9, p = 0.002).

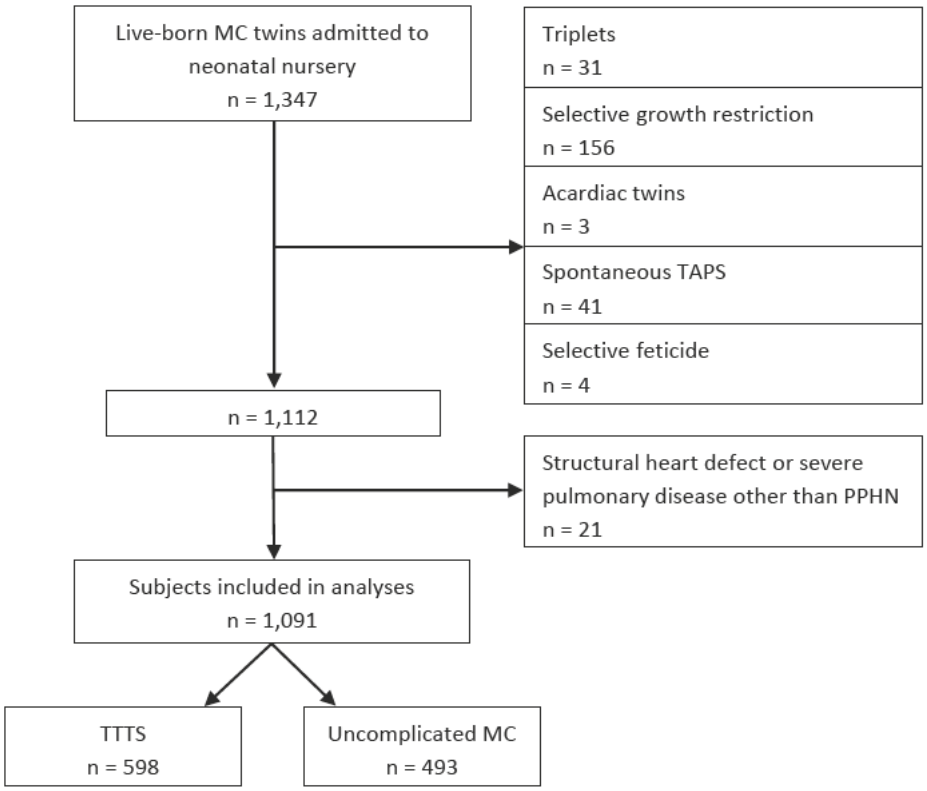

Figure 1. Flow chart showing the derivation of the study population. TAPS, twin anaemia polycythaemia sequence; MC, monochorionic

Table 1 shows possible risk factors for PPHN in TTTS newborns. The 24 TTTS newborns with PPHN were considered as cases and the 574 without PPHN as controls. We found no differences in Quintero stage at diagnosis, type of TTTS treatment, GA at the time of FLS, post-laser TAPS, or the occurrence of asphyxia between cases and controls. More recipients were affected by PPHN than donors; 75% of twins in the group of TTTS twins with PPHN were recipients versus 49% in the group without PPHN (OR 3.1, 95% CI 1.3-7.3). PPHN occurred more often in cases of severe prematurity (83 vs. 43%; OR 6.7, 95% CI 2.2-20.0) and with anemia at birth (25 vs. 8%; OR 3.8, 95% CI 1 4-10.4). The multivariable model only confirmed a significant independent association between PPHN and severe prematurity (OR 3.3, 95% CI 1.0-11 4) and recipient status (OR 3.9, 95% CI 1.4-11.0). The median length of the period from FLS to birth was 2 weeks less in the group with PPHN (10 vs. 12 weeks; crude OR 1.82 for each week younger, 95% CI 1.7-1.9, p = 0.006). In the TTTS recipients, post-laser TAPS (indicating incomplete FLS) contributed to a higher risk of PPHN in the univariate analysis (35 vs. 13% of recipients treated by FLS; OR 3.8, 95% CI 1 4-10.4). No difference in GA at the time of FLS was found. We found an independent association between PPHN and severe prematurity (OR 4.4, 95% CI 1.4-13.7) and between PPHN and anemia at birth (OR 7 2, 95% CI 1.8-29.6). One third of anemic ex-recipients developed PPHN (Table 2).

Table 3 shows the characteristics of all PPHN cases. All PPHN cases with post-laser TAPS were anemic at birth, demonstrating a reversal of the intertwin transfusion after laser. One (untreated) recipient was anemic because of acute peri-mortem transfusion after the intrauterine demise of the donor twin.

Table 1. Possible risk factors associated with PPHN in TTTS newborns

Risk factors	**PPHN (n = 24)**	**No PPHN (n = 574)**
Quintero stage		
I	4 (17)	103 (18)
II	8 (33)	169 (29)
III	11 (46)	270 (47)
IV	1 (4)	30 (5)
V	0 (0)	2 (0)
Recipient status	18 (75)	283 (49)
Treatment		
Fetoscopic laser surgery	21 (88)	496 (86)
Amniodrainage	1 (4)	47 (8)
Expectant management	2 (8)	31 (5)
GA at laser, weeks	19 (17 - 21)	20 (18 - 23)
Post-laser TAPS	6 (29[a])	65 (13[a])
Gestational age at birth		
< 32 weeks	20 (83)	246 (43)
≥ 32 weeks	4 (17)	328 (57)
Anemia at birth	6 (25)	46 (8)
Asphyxia	1 (4)	4 (1)

Data are presented as n (%) or median (IQR). PPHN, persistent pulmonary hypertension of the newborn; OR, odds ratio; CI, confidence interval; GA, gestational age;
[a] In TTTS twins treated by FLS.

Table 2. Possible risk factors associated with PPHN in TTTS recipients

Risk factors	**PPHN (n = 18)**	**No PPHN (n = 283)**
GA at laser, weeks	19 (17 - 21)	20 (18 - 23)
Post-laser TAPS	6 (35[a])	32 (13[a])
Gestational age at birth		
< 32 weeks	14 (78)	118 (42)
≥ 32 weeks	4 (22)	165 (58)
Anemia at birth	6 (33)	13 (5)

Data are presented as n (%) or median (IQR). PPHN, persistent pulmonary hypertension of the newborn; OR, odds ratio; CI, confidence interval; GA, gestational age;
[a] In TTTS twins treated by FLS.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
	-	0.86	-	-
	3.1 (1.3 - 7.3)	**0.01**	3.9 (1 4 - 11.0)	**0.01**
	-	0.77	-	-
	0.9 (0.8 - 1.0)	0.20	-	-
	2.5 (1.0 - 6.5)	0.06	-	-
	6.7 (2.2 - 20.0)	**<0.01**	6.0 (1.9 - 19.1)	**<0.01**
	3.8 (1.4 - 10.5)	**0.01**	3.3 (1.0 - 11 4)	0.06
	6.2 (0.6 - 64 4)	0.13	-	-

TAPS, twin anemia polycythemia sequence.

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
	0.9 (0.8 - 1.1)	0 25	-	-
	3.8 (1 4 - 10.4)	**0.01**	1.4 (0.4 - 4.9)	0.64
	4.9 (1.6 - 15.1)	**0.01**	4.4 (1 4 - 13.7)	**0.01**
	10.4 (3.4 - 32.2)	**<0.01**	7 2 (1.8 - 29.6)	**0.01**

TAPS, twin anemia polycythemia sequence.

Table 3. PPHN cases in TTTS and uncomplicated monochorionic twin pregnancies

	Donor or Recipient	Quintero stage	Treatment	GA at laser, weeks
1	Recipient	Q2	FLS	23
2	Recipient	Q2	FLS	18
3	Recipient	Q2	FLS	19
4	Recipient	Q3	FLS	19
5	Recipient	Q2	FLS	20
6	Recipient	Q3	FLS	27
7	Recipient	Q3	FLS	16
8	Recipient	Q3	FLS	18
9	Recipient	Q1	FLS	17
10	Recipient	Q2	FLS	17
11	Recipient	Q1	FLS	21
12	Recipient	Q2	FLS	16
13	Recipient	Q3	FLS	23
14	Recipient	Q3	FLS	18
15	Recipient	Q3	FLS	16
16	Recipient	Q4	FLS	20
17	Recipient	Q3	FLS	20
18	Donor	Q2	FLS	19
19	Donor	Q3	FLS	18
20	Donor	Q2	FLS	17
21	Donor	Q3	FLS	23
22	Recipient	Q1	Expectant	-
23	Donor	Q1	Expectant	-
24	Donor	Q3	Amniodrainage	-
25	Normal MC	-	-	-
26	Normal MC	-	-	-

GA, gestational age; TAPS, twin anemia polycythemia sequence; Q, Quintero stage; FLS, fetoscopic laser surgery; alive, alive at time of discharge/transfer to secondary care center; MC, monochorionic twin.

GA at birth, weeks	Post-laser TAPS	Anemia at birth	Outcome
26	Yes	Yes	Neonatal death
27	Yes	Yes	Alive
27	No	No	Alive
27	No	No	Alive
28	Yes	Yes	Neonatal death
28	No	No	Neonatal death
28	No	No	Alive
28	No	No	Alive
29	No	No	Alive
29	No	No	Alive
30	No	No	Alive
31	No	No	Alive
31	No	No	Alive
33	Yes	Yes	Neonatal death
33	No	No	Alive
33	Yes	Yes	Alive
33	No	No	Alive
27	No	No	Alive
28	No	No	Alive
29	No	No	Alive
29	No	No	Alive
29	-	Yes	Alive
24	-	No	Neonatal death
30	-	No	Neonatal death
30	-	No	Alive
32	-	Yes	Alive

DISCUSSION

In our cohort of TTTS twins, the incidence of severe PPHN requiring iNO at birth was increased 10-fold compared to in monochorionic twins without TTTS (4 vs. 0.4%). This study confirms the previously noted association between PPHN and TTTS, although the incidence of 4% was slightly higher than the previously reported incidence of 2.6-3%.[10, 11] Differences across studies may be due to methodological differences including variations in the criteria for PPHN and small sample sizes. The strict diagnostic criteria for severe PPHN in our study and the large sample size meant that the incidence could be estimated more accurately.

We found two risk factors that were independently associated with severe PPHN: a younger GA at birth and a recipient status. Previous studies already identified recipient twins as being at an increased risk of PPHN.[10, 11] The relatively high incidence of PPHN in TTTS found in this study, particularly in preterm deliveries and in recipients, could have several explanations. First, preterm delivery and severe anemia are common problems in TTTS.[16, 17] Severe anemia is often present in TTTS cases after incomplete laser surgery due to persistent intertwin blood transfusion through residual anastomoses. Severe anemia at birth may lead to acute hypoxia, which leads to vascular remodeling and increased PVR[18] that result in PPHN. The association with severe prematurity and PPHN is less clear. Although the incidence of PPHN in premature newborns is thought to be lower than in term or near-term newborns,[19] a recent study showed a higher risk of PPHN in late preterm infants than in term infants.[20] In TTTS twins, preterm birth comprises a higher risk of PPHN. Importantly, association does not mean causation. As the GA at laser was similar in the cases and the controls, and prematurity correlated strongly with PPHN, a shorter period from FLS to birth could also explain the higher risk of PPHN observed. In our cohort, the median length of this period was two weeks less in the group with PPHN. It might take several months for damaged pulmonary vasculature to recover from high volume-load damage, so an early birth could lead to high PVR and PPHN. Other factors linked to preterm birth such as premature prolonged rupture of the membranes, inflammation due to chorioamnionitis, or perinatal sepsis may be related to the development of PPHN. This could also explain the increased occurrence of PPHN in recipients after FLS, as these twins are at increased risk of iatrogenic rupture of the membranes, chorioamnionitis, and sepsis.[21, 22] Unfortunately, due to the retrospective nature of this study, we did not systematically record the presence of these factors.

Another explanation for the high incidence is based on the cardiac adaptation to TTTS. In TTTS, cardiac function is especially compromised in recipients. Chronic volume loading causes remodeling of the pulmonary vasculature, which contributes to the development of PPHN.[12, 13] Although cardiac function usually improves within a few weeks after FLS, abnormalities of the pulmonary vasculature may persist despite complete laser surgery being performed, and this could lead to PPHN. As an analogy, right ventricular outflow tract obstruction also occurs in recipients despite complete laser surgery and can result in abnormal development of the pulmonary valve and subsequent pulmonary stenosis or atresia.[24] In cases of incomplete laser surgery and the existence of residual anastomoses, the cardiac burden may be prolonged. As shown in this study, incomplete laser surgery was identified as a risk factor for PPHN in TTTS recipients, with one-third of the recipients who were anemic at birth developing PPHN after post-laser TAPS. We propose a 'double hit theory' for anemic recipients after post-laser TAPS: the baseline increased risk of PPHN due to increased PVR is further increased by acute hypoxia as a result of anemia at birth. Therefore, in cases of detected or suspected post-laser TAPS, clinicians should be aware of the extremely increased risk of PPHN in anemic recipients.

We found an increased incidence of PPHN in donors (2%) versus in uncomplicated MC twins (0.4%) or all live births (0.2%). In donor twins, cardiac output is reduced as a result of hypovolemia. Since cardiac output is essential in determining systemic oxygen transport, hypovolemia could cause hypoxia and lead to pulmonary endothelial adaptation.[18] We excluded twin pairs with a birth weight discrepancy of > 25%, so the supposed hypothesis of a higher risk of PPHN as a result of lower arginine levels in growth-restricted donors[25, 26] cannot be substantiated by this study.

This study has certain strengths and limitations. The LUMC is the national referral center for TTTS in the Netherlands. As a result, a large database of TTTS twins has been created, in which rare outcomes can be investigated. Nevertheless, the absolute number of PPHN cases was still relatively small, so some of the risk factor analyses may be underpowered. We only included severe PPHN cases, since such infants require prompt treatment. Mild PPHN cases without the need for iNO treatment were not included. No additional prenatal findings were recorded, e.g. flow velocities over the aorta and pulmonary artery. These findings might predict the development of PPHN and could be a subject of further research.

CONCLUSIONS

Clinicians caring for neonates with (treated) TTTS should be aware of the 10-fold increased risk of PPHN compared to in uncomplicated monochorionic twins. PPHN occurs more often in recipients and after premature delivery. As the development of severe PPHN is difficult to predict, we advise that all TTTS twins should be delivered in a tertiary care center with iNO treatment options.

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CHAPTER 7

CONGENITAL HEART DEFECTS IN MONOCHORIONIC TWINS:
A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Monochorionic (MC) twins are at an increased risk of developing congenital heart defects (CHDs) compared to singletons and dichorionic twins. The development of acquired CHDs in this specific group of twins is associated with twin-twin transfusion syndrome (TTTS). We performed a systematic review and meta-analysis to provide an overview of the reported birth prevalence of CHDs in liveborn MC twins with and without TTTS. Twelve studies were included in this review. Compared to the reference population, MC twins were 6.3 times more likely to be born with a CHD (59.3 per 1,000 liveborn twins; relative risk [RR] 6.3, 95% confidence interval [CI] 4 4-9.1), and TTTS twins had a 12-fold increased risk of having a CHD at birth (111.3 per 1,000 live births; RR 12.4, 95% CI 8.6-17.8). The increased incidence of CHDs can mainly be attributed to the risk of right ventricular outflow tract obstruction (35/1,000 TTTS twin live births vs. 0.5/1,000 singleton live births). We recommend an expert fetal echocardiogram in all MC twins, follow-up scans in the event of TTTS, and a postnatal cardiac evaluation in all TTTS survivors.

INTRODUCTION

Congenital heart defects (CHDs) represent the most common human birth defect, having a birth prevalence of 7-9 per 1,000 singleton live births.[1, 2] CHDs are more common in twin pregnancies with a reported prevalence of approximately 20 in 1,000 live births. Monochorionic (MC) twins are at an even higher risk compared to dichorionic (DC) twins.[2] A systematic review and meta-analysis of four studies conducted in 2007 showed a 9-fold increase in CHD risk in MC twins[3] compared to singletons.

The development of acquired CHDs in MC twins is associated with twin-twin transfusion syndrome (TTTS).[4] TTTS complicates 10-15% of MC twin pregnancies and results from unbalanced blood flow from one twin (donor) to the other twin (recipient) via placental vascular anastomoses.[5, 6] The birth prevalence of MC twins with a CHD may be influenced by the improved survival rates for MC twins over the last decade, especially for those treated for TTTS.[7] The literature has been significantly expanded and more up-to-date population prevalence rates have been published.[1] The aim of this systematic review and meta-analysis was to provide an updated overview of the reported birth prevalence of CHDs in liveborn MC twins with and without TTTS.

METHODS

Search strategy

This systematic review was performed using the PRISMA methodology.[8] Relevant articles were identified using electronic databases (Pubmed, Embase, Web of Science, and Cochrane) on 17 January 2019, using search terms related to 'monochorionic twins' and 'congenital heart defects'. The search was limited to original research papers with English abstracts. No time restriction for publication dates was used. All titles and abstracts were screened for study population (live born MC twins), type of CHD, and birth prevalence. Papers focusing on etiology, prenatal diagnosis, prognosis, or animal research were excluded. Two reviewers (M.G. and A.S) screened titles and abstracts independently for relevance. If a title or abstract seemed relevant, full text was retrieved and assessed for inclusion. Articles were eligible if the number of liveborn MC twins affected by CHD could be determined from the published data, there was postnatal confirmation of the CHD, and chorionicity was determined. Selected articles were cross-referenced. Disagreement was resolved by consensus.

Quality assessment

Study quality and risk of bias was assessed by the two reviewers using the Hayden bias rating tool,[9] as suggested by the Cochrane Collaboration. With this tool the risk of bias was assessed in six domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). Each of the six potential bias domains was rated as having high, moderate, or low risk of bias. Low methodological quality was not an exclusion criterion.

Data extraction

Two reviewers (M.G. and A.S.) extracted the relevant information from the selected articles. The following study characteristics were extracted from the selected articles and tabulated: first author, year of publication, time period during which the study was performed, country, study design (retrospective or prospective), determination of chorionicity, number of live births, number of patients with CHD, birth prevalence of total CHDs, and prevalence of common CHD subtypes: right ventricular outflow tract obstruction (RVOTO), ventricular septal defect (VSD), atrial septal defect (ASD), coarctation of the aorta (CoA), aortic stenosis (AS), tetralogy of Fallot (TOF), and transposition of the great arteries (TGA).

Statistical analysis

Statistical analyses were performed using MS excel for Windows (Microsoft Corporation, Redmond, Washington, DC, USA) and Review Manager 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Relative risks (RRs) and their 95% confidence intervals (CIs) were used as effect sizes for the meta-analysis of dichotomous data. Heterogeneity between studies was examined with the inconsistency square (I^2) statistics, with between-study heterogeneity at $I^2 \geq 50\%$ and $p \geq 0.05$.[10] In case of heterogeneity a random effects model was used.[10] The population risk of CHDs was based on the study by Van der Linde *et al*.[1]

RESULTS

The systematic literature search yielded 3,029 citations, of which 2,736 were excluded by review of the title or abstract. Full manuscripts were retrieved for the remaining 293 studies and a total of 12 articles (n = 3,136 live born twins) were included in the review (Figure 1, Table 1).[12-23] Eight studies had a prospective design. Six studies included MC twin pregnancies complicated by TTTS only. Four studies only described the prevalence of RVOTO. There was some overlap between the cohorts of Lopriore *et al.*,[18] Hack *et al.*[14] and Eschbach *et al.*[13]

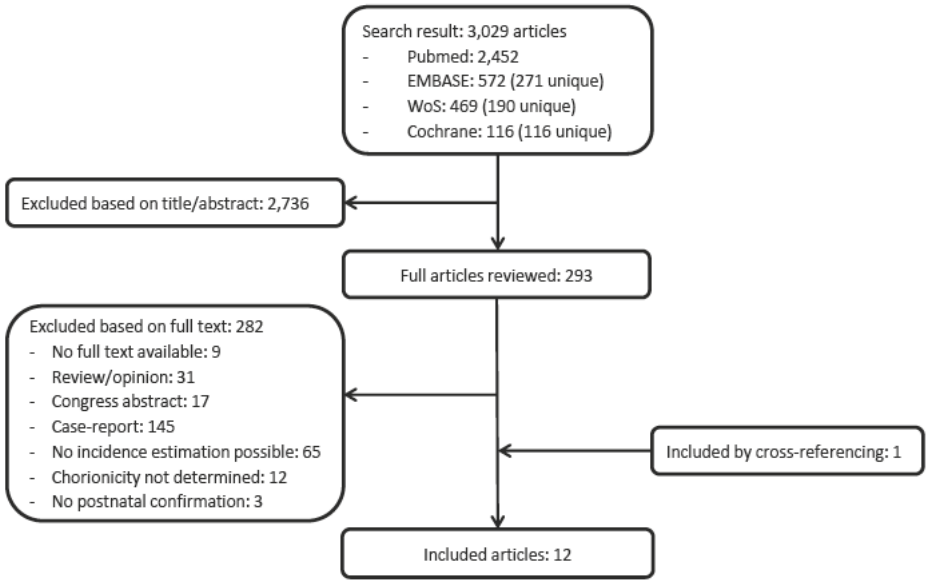

Figure 1. PRISMA diagram for study selection. WoS, Web of Science

Quality assessment is summarized in Table 2. To judge the overall risk of bias in each study, it is not recommended to use a summated score for the overall study quality.[9] In the included studies there was a low to moderate risk of bias in the majority of domains. Some studies did not report on their diagnostic tests; prognostic factor measurement was therefore rated as 'high risk of bias'. There was a high risk of bias in the outcome measurement in the study by Hack *et al.*[14] since the authors only recorded the presence of congenital heart malformations without mentioning whether the method and setting of their investigations to diagnose a CHD was the same for all study participants.

In the study population of 3,136 liveborn twins, 185 CHDs were identified. The prevalence of CHDs in MC twins was 59.3 per 1,000 live births (95% CI 50.5-69.4). In MC twins with and without TTTS, the prevalence of CHDs per 1,000 live births was 111.3 (95% CI 87.3-140.9) and 53.4 (95% CI 44.2-64.5), respectively. Compared to the population prevalence of 9.1 per 1,000 live births,[1] MC twins were 6.3 times more likely to be born with a CHD than infants in the general population (RR 6.3; 95% CI 4 4-9.1). TTTS twins were almost 2.5 times more likely to have a CHD than non-TTTS twins (RR 2.4; 95% CI 1.6-3.5). Compared to singletons, TTTS twins had a 12-fold increased risk of having a CHD at birth (RR 12 4, 95% CI 8.6-17.8) (Figure 2).

Quintero's classification to stage TTTS severity has been applied since 2000;[24] studies investigating patient cohorts prior to 2000 therefore do not report Quintero stages. Hidaka *et al*.[16] describes one TTTS case (Quintero stage 2) where the donor appeared to have CoA after birth. Three of the studies report on the Quintero stage distribution in the study population. In the first study from 2007,[18] with a CHD prevalence of 5.4% in TTTS twins, the Quintero stage distribution was: 17% stage I, 37% stage II, 41% stage III, 4% stage IV. In the second study from 2011,[21] with a CHD prevalence of 15.5%, the Quintero stage distribution was: 10% stage I, 22% stage II, 50% stage III, 18% stage IV. In the third study from 2014,[23] with a CHD prevalence in TTTS twins of 8.9%, 30% of pregnancies were Quintero stage I, 40% stage II, 21% stage III, 1% stage IV, and 7% stage V. Eschbach *et al*.[13] found that 82% of RVOTO cases were staged as Quintero stage III or IV, compared to 43% of cases without RVOTO (p = 0.07).

The reported birth prevalence of the CHD subtypes in all MC twins (per 1,000 live births) was: VSD, 25.9 (95% CI 20.2-33.2); RVOTO, 22.3 (95% CI 17.6-28.4); ASD, 13.6 (95% CI 9.7-19.1); CoA, 2.1 (95% CI 0.9-5.0); AS, 2.6 (95% CI 1.2-5.6); TOF, 0.9 (95% CI 0.2-3.1), and TGA, 0.9 (95% CI 0 2-3.1). The prevalence of TOF and TGA was similar to the prevalence in singletons (both 0.3 per 1,000 singleton live births). All other subtypes had a higher prevalence ($p < 0.05$). The type of CHD with the largest relative risk (RR 70; 95% CI 27-179, $p < 0.001$) in TTTS twins was RVOTO (35/1,000 vs. 0.5/1,000 singleton live births).

Table 1. Article characteristics

	Year	Author	Country	Time period	Design
1	1996	Cincotta	UK	1994-1995	P
2	1998	Simpson	USA	1992-1997	P
3	2001	Lougheed	Canada	1994-1998	R
4	2002	Karatza	UK	1997-2000	P
5	2006	Herberg	Germany	1995-1997	P
6	2007	Hadika	Japan	2000-2006	P
7	2007	Lopriore	Netherlands	2002-2005	P
8	2009	Hack	Netherlands	2000-2007	R
9	2011	Pruetz	USA	2009-2010	P
10	2013	Pettit	USA	1996-2003	R
11	2014	Springer	Austria	2002-2012	R
12	2016	Eschbach	Netherlands	2004-2015	P

CHDs, congenital heart defects; P, prospective; TTTS, twin-twin transfusion syndrome; RVOTO, right ventricular outflow tract obstruction; R, retrospective; MC, monochorionic.

Chorionicity determination	Study population	Number of liveborn twins (TTTS)	Number of CHDs
TTTS diagnosis	14 TTTS pregnancies	22	2/10 recipients RVOTO, donors 0
Examination placenta postpartum	12 TTTS pregnancies	22	3/10 recipients RVOTO, donors 0
TTTS diagnosis	73 TTTS pregnancies	146	6/73 recipients RVOTO, donors 0
Examination placenta postpartum	136 MC twin pregnancies (47 TTTS)	226 (60)	9/226 MC twins, no-TTTS 4/166, TTTS 5/60
TTTS diagnosis, all treated with fetoscopic laser	73 TTTS pregnancies	89	10/89 MC twins
Examination placenta postpartum	87 MC twin pregnancies (1 TTTS)	174 (2)	11/174 MC twins
Examination placenta postpartum	101 MC twin pregnancies (46 TTTS)	161 (74)	6/161 MC twins, no-TTTS 2/87, TTTS 4/74
First trimester ultrasound scan and/or examination placenta postpartum	98 MCMA twin pregnancies (6 TTTS)	164 (unknown)	7/164 MC twins
TTTS diagnosis, all treated with fetoscopic laser	50 TTTS pregnancies	84	13/84 MC twins
Examination placenta postpartum	482 MC twin pregnancies (48 TTTS)	926 (83)	69/926 MC twins, no-TTTS 55/843, TTTS 14/83
First trimester scan, and TTTS treated with fetoscopic laser	381 MC twin pregnancies (70 TTTS)	754 (135)	39/754 MC twins, no-TTTS 27/619, TTTS 12/135
TTTS diagnosis, majority treated with fetoscopic laser	485 TTTS pregnancies	368 (368 recipients)	11/368 recipients RVOTO

Table 2. Quality scores based on the Hayden bias rating tool

	Variable / study	Study participation	Study attrition	Prognostic factor measurement
1	Cincotta	Moderate	Moderate	High
2	Simpson	Low	Low	Low
3	Lougheed	Moderate	Moderate	High
4	Karatza	Low	Low	Low
5	Herberg	Low	Low	Low
6	Hadika	Moderate	Moderate	High
7	Lopriore	Low	Low	Low
8	Hack	Low	High	Moderate
9	Pruetz	Low	Low	Moderate
10	Pettit	Low	Low	Moderate
11	Springer	Low	Moderate	Low
12	Eschbach	Low	Moderate	Low

	Outcome measurement	Study confounding	Statistical analysis and reporting
	Moderate	Low	Low
	Low	Low	Low
	Moderate	Low	Moderate
	Low	Low	Moderate
	Low	Low	Low
	Low	Low	Low
	Low	Low	Low
	High	Low	Moderate
	Low	Low	Low
	Low	Low	Low
	Moderate	Low	Moderate
	Moderate	Low	Low

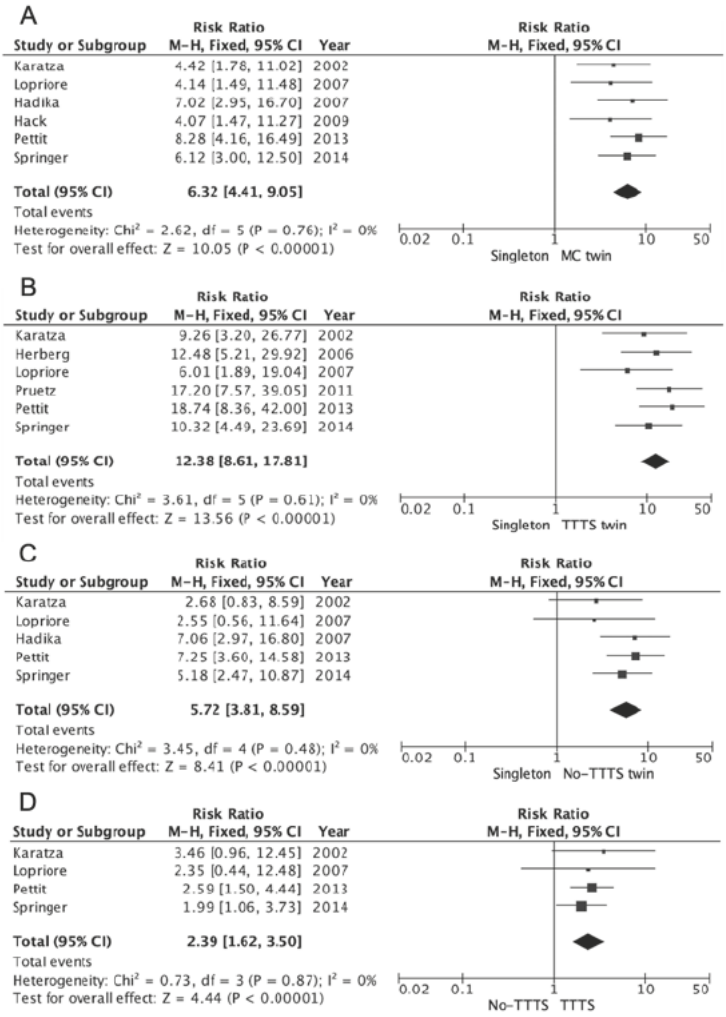

Figure 2. Risk of CHDs in MC twins with and without TTTS. A: MC twins vs. singletons, B: MC twins with TTTS vs. singletons, C: MC twins without TTTS vs. singletons, D: MC twins with TTTS vs. MC twins without TTTS. Risk ratios with 95% confidence intervals (CIs) were calculated by a fixed effect model. The pooled risk ratio is represented by a black diamond, where diamond width corresponds to 95% CI bounds.

DISCUSSION

With this systematic review and meta-analysis, we estimated the prevalence of CHD in MC twins to be 59 per 1,000 live births, which is over 6 times higher as compared to singleton live births. In TTTS survivors the risk is even higher, with a 12-fold increased risk compared to singletons. The estimated prevalence in these neonates is 111.3 per 1,000 live births. Therefore, we recommend an expert fetal echocardiogram in all MC twins at mid-gestation. In the event of TTTS, a second prenatal fetal echocardiogram around 30-32 weeks should be performed to rule out any acquired defects such as RVOTO, and a postnatal echocardiogram in all survivors may be considered.

The estimated prevalence rates and relative risks in this study are lower than those previously reported by Bahtiyar *et al*.[3] There may be several explanations for this. First, the present study involves over five times the number of live birth MC twins, which enabled us to estimate the birth prevalence of CHD in MC twins with and without TTTS more precisely, and which possibly reduced the risk of selection bias. Second, we excluded stillbirths. The inclusion of stillborn fetuses would have elevated the prevalence of CHD. Finally, lower relative risks were calculated due to the use of the generally accepted population prevalence of CHDs of 9.1 per 1,000 live births[1] instead of the lower rates from the cohorts of Wren *et al*.[25] or Ferenc *et al*.[26]

Twin birth rates have increased over the last decades due to the increasing maternal age and the extensive use of assisted reproductive technology (ART).[27, 28] ART increases not only the number of dizygotic but also the number of monozygotic twins. In MC twins, which are all monozygotic, the division of the fertilized ovum is hypothesized to be an influencing factor which could contribute to primary structural cardiac anomalies.[29] ART itself is also considered a risk factor for CHDs.[30, 31] However, the increased incidence of acquired CHDs in MC twins has mostly been attributed to MC placentation and TTTS, indicating an influence of hemodynamic alterations on cardiac development. We found an increased risk of the most prevalent subtypes of CHDs (VSD, RVOTO, ASD, CoA, and AS) in MC twins compared with singletons, although this should be interpreted with caution due to the low numbers of some CHDs, particularly CoA and AS. However, this finding possibly supports the hypothesis of the influence of hemodynamic factors in the development of CHDs, which is furthermore supported by the fact that defects such as TOF, for which genetic influences are thought to be more important in development, are equally prevalent in MC twins and singletons. Previous studies suggest that more severe TTTS is associated with cardiac defects,[4, 32, 33] possibly indicating an effect of a larger hemodynamic imbalance. This finding could not be supported by this

meta-analysis since only a small number of studies report on the Quintero stage distribution,[18, 21, 23] and in only one study the disease severity was analyzed in relation to CHD prevalence.[13]

Fetoscopic laser surgery, as a curative treatment for TTTS ensures cardiovascular improvement in affected twins,[34-36] but does not prevent the occurrence of cardiac defects at birth in all cases, as shown by this study. Cardiac adaptation in TTTS mainly occurs in recipients.[23, 37] Cardiac overload and hypervolemia in these twins may result in shear stress and ventricular hypertrophy, which can cause abnormal development of the cardiac valves through a cascade of events. Shear stress causes endothelial changes, and right ventricular hypertrophy and severe tricuspid valve regurgitation lead to diminished flow across the right ventricular outflow tract, which may impair growth and development of the right ventricular outflow tract. These processes can lead to RVOTO, which is found in approximately 3.5% of recipients (this study). It is suggested that since valve development is not completed at the beginning of the second trimester, fetuses who experience TTTS earlier in gestation are more frequently affected by RVOTO.[13] Less reported, but still clinically important, is the coexistence of CoA and TTTS, which seems to be more frequently seen in donors than in recipients.[38] The underlying mechanism leading to CoA is not fully understood. A proposed explanation is the reduced flow theory, which suggests that the narrowing of the aortic arch develops secondary to hemodynamic disturbances.[39] Decreased flow may occur as the result of decreased left-sided cardiac output of the donor twin in TTTS due to hypovolemia, or in the case of ventricular outflow tract obstruction.[40]

Improved echocardiographic techniques are likely to substantially account for the increased detection rate of cardiac lesions. In the last decade there has been a shift towards a diagnosis before birth. In expert hands, prenatal detection rates of CHD in multiple pregnancies can be as high as 88%.[41] However, in the case of TTTS, the CHD detection rates are reported to be as low as 42.9% in recipient twins and 16.7% in donor twins.[21] Possible explanations for the low detection rates are the polyhydramnios in combination with the excessive movements of the recipient twin and the 'stuck' anhydramniotic donor, which both severely impair image acquisition and the detection of CHD. Therefore, next to the detection of possible acquired valvular pathology, follow-up fetal echocardiograms are warranted after TTTS treatment, when scanning conditions normalize, to rule out missed structural anomalies at earlier scans. An accurate diagnosis is critical in determining the requirement of immediate (postnatal) treatment, predicting the course of (surgical) repair, and for the counseling the parents about the prognosis.

This study has certain limitations. There are only a few studies with a large sample size available. Comparison of prevalence rates of all CHD subtypes between MC twins with and without TTTS and between MC twins and singletons are therefore limited. We found a high incidence of CHDs in MC twins, especially in the TTTS population, but it is possible that many milder forms of CHDs that are present in twins without TTTS and in singletons are missed or underdiagnosed, which could lead to an underestimation of the CHD prevalence in these infants. In this review, hospital-based studies were included which could have resulted in upwardly biased estimates of prevalence compared to national registries. Our data do not reflect the CHD prevalence at mid-gestation, since (selective) feticide cases and studies without postnatal follow-up were excluded. We do not think, however, that the inclusion of the (limited number of) feticide cases would have changed our results significantly. Despite these limitations, our results do suggest a significant burden of CHDs in MC twins that can have important neonatal implications. Future studies should determine whether there is still a need to perform postnatal echocardiography in all TTTS twins.

CONCLUSIONS

There is still a large burden of CHDs in MC twins with and without TTTS. We recommend an expert fetal echocardiogram in all MC twins, follow-up scans in the event of TTTS, and a postnatal cardiac evaluation in all TTTS survivors.

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CHAPTER 8

EARLY POSTNATAL CARDIAC FOLLOW-UP OF SURVIVORS OF TWIN-TWIN TRANSFUSION SYNDROME TREATED WITH FETOSCOPIC LASER COAGULATION

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ABSTRACT

Objective: To assess the cardiac function and prevalence of congenital heart defects (CHD) in twin-twin transfusion syndrome (TTTS) survivors.

Study design: Prospective follow-up of TTTS-pregnancies treated with laser surgery (2015-2018). Echocardiography was performed one day and one month after birth (corrected for prematurity). Results were compared to a control group of age-matched uncomplicated monochorionic twin pairs at one month.

Results: 89 TTTS (168 neonates) and 9 control pregnancies (18 neonates) were enrolled. CHD birth prevalence was 9 2% (8/87) in recipients and 13.6% (11/81) in donors (p = 0.37). Four of 19 (21%) were detected prenatally, all pulmonary stenosis. Donors had lower aortic peak velocities compared with recipients at day one (0.66 ± 0.15 m/s vs 0.71 ± 0.19 m/s, p = 0.04) and one month (1.04 ± 0.21 m/s vs 1.11 ± 0.18 m/s, p = 0.02), but not compared to controls.

Conclusion: CHD prevalence in TTTS survivors is high, with a low prenatal detection of minor abnormalities. Follow-up fetal echocardiograms and a postnatal echocardiogram should be offered.

INTRODUCTION

Monochorionic (MC) twins are at increased risk of congenital heart defects (CHDs).[1] The development of CHD can partly be attributed to twin-twin transfusion syndrome (TTTS),[2, 3] which affects 10-15% of MC pregnancies and carries an 12-fold increased risk of CHD as compared to singletons.[4] Fetoscopic laser coagulation (FLC), as the curative treatment for TTTS, results in major cardiovascular improvement in affected twins,[3, 5-7] but does not prevent the development of subsequent cardiac defects in all cases.[8] There are only a few reports on the effect of TTTS on postnatal cardiac function, and the majority are focused on cardiac function later in childhood.[5, 9-12] Childhood cardiac function seems normal, but large short-term cardiac function studies after FLC are still lacking.[13] To what rate normalization of cardiac function occurs and whether cardiac function is completely normal at birth remains unknown.

As monochorionic twins complicated by TTTS are at high risk for CHD, a detailed postnatal echocardiogram may be an advantage for early detection of CHD and might improve neonatal management. With this study we aimed to assess cardiac function and postnatal CHD prevalence in TTTS survivors to determine if a postnatal echocardiogram in all TTTS survivors is necessary.

METHODS

This was a prospective follow-up study of TTTS survivors after FLC, recruited from a cohort of monochorionic twin pregnancies with TTTS consecutively operated between January 2015 and August 2018 at the Leiden University Medical Center (LUMC). The LUMC is the national referral center for fetal therapy in The Netherlands. A group of age-matched healthy MC twin pairs without TTTS born at the LUMC during the study period was used as a control group. Monochorionic triplets (n = 8) were excluded.

In all cases a comprehensive preoperative ultrasound examination was performed to confirm the TTTS diagnosis and to assess fetal cardiac anatomy. TTTS severity was classified according to the Quintero staging system.[14] Details on the laser technique (either with or without the Solomon technique)[15] at our center and short-term outcome results have previously been reported.[16] All patients in this study were treated with the Solomon technique. Standard echocardiographic assessments of the cardiac anatomy were obtained using a Canon Aplio 500 (Canon Medical Systems Corporation). Cardiac abnormalities detected at follow-up scans were recorded. Prenatal right ventricular outflow tract obstruction (RVOTO) was classified as functional pulmonary atresia (absence of forward flow across the pulmonary valve with an exclusive reverse direction of flow in the ductus arteriosus), pulmonary stenosis (turbulent flow with a peak systolic velocity of > 1 m/s), or isolated pulmonary insufficiency (reversed flow from main pulmonary artery entering the right ventricle).[17]

The following antenatal and neonatal data were recorded: gestational age (GA) at laser surgery, Quintero stage, GA at birth, birth weight and diagnosis of Persistent Pulmonary Hypertension of the Newborn (PPHN). PPHN was defined as severe hypoxemia (PaO_2 < 37.5-45 mm Hg in a FiO_2 of 1.0) requiring mechanical ventilation and inhaled Nitric Oxide (iNO) treatment. Diagnosis of PPHN was only reached if right-to-left shunting in the ductus arteriosus was observed by echocardiography, in the absence of a structural heart defect or severe lung hypoplasia.[18]

Postnatal echocardiography using a Vivid E9 or S6 (GE Healthcare, Wauwatosa, WI, USA) was performed according to the guideline of the American Society of Echocardiography[19] in the first days of life (if born in the LUMC) and at the age of one month (corrected for prematurity). Standard echocardiographic assessments of the cardiac anatomy and Doppler velocimetry were obtained. Pulmonary stenosis was diagnosed by pulsed-wave Doppler and was defined as mild (peak velocity < 3 m/s), moderate (peak velocity 3-4 m/s) or severe (peak velocity > 4 m/s). An existing atrial septal defect (ASD) was considered small (> 3 mm to < 6 mm), moderate (≥ 6 mm and < 8 mm) or large (≥ 8 mm).[20]

An ASD < 3 mm was defined as a persistent foramen ovale (PFO) and considered as a non-pathological cardiac finding.[21] The images and cine loops were stored as raw data for offline analysis.

Offline analysis

Analyzes were performed using EchoPAC software (GE Healthcare, Wauwatosa, WI, USA) by using the apical four-chamber view. Left ventricular (LV) and right ventricular (RV) diastolic performance were assessed by measurements of peak early-wave velocity (E) (in m/s) and peak atrial contraction wave velocity (A) (in m/s) from spectral Doppler tracings at the tip of the mitral and tricuspid valve. The E/A ratio was calculated. The peak velocity, mean systolic flow velocity and the velocity time integral (VTI) across the aortic and pulmonic valve were measured using pulsed-wave Doppler. In addition, Tissue Doppler Imaging (TDI) was performed at the LV lateral wall, the interventricular septum (IVS) and the RV free wall. Longitudinal myocardial velocity curves were obtained by placing the cursor at the basal part of each region. Subsequently, peak systolic velocities (s') and peak early (e') and late diastolic velocities (a') were assessed in each myocardial velocity curve. The mean of three good-quality waveforms was used for all analyses. LV and RV global longitudinal strain were obtained from the apical four-chamber view using speckle-tracking strain analysis, as previously described and according to the international guidelines.[22, 23] The interventricular septum was included in the LV strain analysis.

In TTTS survivors, aortic dimensions were measured. Echocardiographic measurements included the aortic annular diameter, aortic root, sinotubular junction, ascending aorta, proximal transverse arch, distal transverse arch, aortic isthmus and the distance between the left common carotid and left subclavian arteries. To eliminate the effect of weight and body size, the distal transverse arch/ascending aorta ratio, carotid-subclavian artery index and isthmus/ascending aorta ratio were calculated.[24]

Statistical analysis

Data are reported as n (%), mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. For comparisons between donors and recipients we used univariate regression models with a generalized estimated equation (GEE) module to account for the effect that observations of twin pairs are not independent. Linear regression analysis was used to compare TTTS twins to uncomplicated MC twins. No adjustment was made for multiple comparisons, and results should be interpreted accordingly. Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$. The population risk of CHDs was based on the study by Van der Linde *et al*.[25]

RESULTS

During the study period 173 consecutive TTTS pregnancies were treated by FLC. Fetal echocardiography revealed no cardiac anomalies in donor twins. The only CHD detected in recipient twins was RVOTO. Prenatal RVOTO was detected in 23 out of 173 recipient twins (13.3%); pulmonary atresia n = 7, pulmonary stenosis (PS) n = 6, pulmonary insufficiency (PI) n = 10. One recipient showed pulmonary valve calcification. In 8 cases abnormal flow velocity wave form across the pulmonary valve (PV FVW) became apparent after FLC. In 17 cases the PV FVW normalized before birth (in one case the pregnancy was terminated because of intracranial abnormalities in the co-twin). Three recipients with PI demised after FLC.

Of the 173 TTTS pregnancies, 148 had at least one survivor. The 25 other pregnancies resulted in double demise (n = 3), inviable delivery (n = 20) or termination of pregnancy (n = 2). Of the 148 pregnancies, 89 (168 neonates) agreed to participate in this follow-up study. Echocardiography at day one was performed in 121 neonates and at the age of one month in 143 neonates. The baseline characteristics are depicted in Table 1. Median birth weight was similar between recipients and donors (2,001 g vs. 1,814 g, p = 0.10). The second echocardiogram was performed 11 weeks after delivery (range 9-14 weeks) in TTTS twins and and 9 weeks after delivery (range 7-11 weeks) in uncomplicated MC twins. At 44 weeks the weight of TTTS twins was 4,271 g, as compared to 4,486 g in uncomplicated MC twins (p = 0.23). PPHN occurred in three infants (1.8%), all three were recipient twins (3 of 87, 3.4%). Nine uncomplicated MC pregnancies (18 neonates) were enrolled for the second echocardiogram.

Postnatal structural heart disease

The prevalence of CHD (Table 2) in TTTS twins was 11.3% (19/168, 95% CI 7.4-37.7), which was considerably higher than the population prevalence of 0.9% (RR 12 4, 95% CI 7.8-19.9). A heart defect was detected in 9 2% (8/87) of recipients and in 13.6% (11/81) of donors (p = 0.37) PS was the most frequently diagnosed defect, detected in 4 2% of TTTS survivors (7/168), of whom five were recipients (five of 87, 5.7%) and two were donors (two of 81, 2.5%). In donors, also three ventricular septal defects (VSDs), three ASDs and three bicuspid aortic valves (BAVs) were detected. There was no family history of bicuspid aortic valves. Two BAV cases were really bi-leaflet. One case appeared functionally bi-leaflet at birth with minimal aortic insufficiency, with a normal follow-up scan (which was not performed as part of this study). Three recipients had a VSD. Two recipients had severe PS, one of whom required balloon valvuloplasty at day 20 and at the age of 7 months. The other recipient with severe PS suffered from a severe infection and died at day 4 before surgery could be performed. Three recipients and two donors had mild valvular stenosis, which

did not require intervention so far. These infants with mild PS had normal velocities across the pulmonary valve at birth, but mildly increased velocities at one month. The prenatal detection rate of CHD was 21% (4/19). The donor twin group had a prenatal detection rate of 0%, compared with a detection rate of 50.0% (4/8) in the recipient twin group, which were all PS cases. All ASDs (n = 6), BAVs (n = 3) and VSDs (n = 3) and three mild PS (two donors and one recipient) were undiagnosed before birth. The two other recipients with mild PS had transient increased PV FVW and pulmonary valve calcifications post-FLC.

Table 1. Baseline characteristics of the 89 TTTS pregnancies

Characteristics	Value
Maternal age (years)	30 (4.5)
Maternal BMI (kg/m²)	24 (19 - 30)
Nulliparous	41 (46)
Quintero stage	
I	16 (18)
II	35 (39)
III	34 (38)
IV	4 (5)
GA at laser (weeks)	19.3 (16.7 - 21.9)
Number of neonates	168 (87 recipients)
Single survivor	8 (9)
GA at birth (weeks)	33.7 (31.3 - 36.1)
Birth weight (grams)	1924 (606)

Data are presented as the median (IQR), mean (SD) or n (%). TTTS, twin-twin transfusion syndrome; BMI, body mass index; GA, gestational age.

Table 2. Prevalence of CHD in TTTS twins and prenatal findings

	Recipient	Donor	Prenatally diagnosed
Number of infants	87	81	-
CHD	8 (9 2)	11 (13.6)	4/19 (21.1)
Pulmonary stenosis	5 (5.7)	2 (2.5)	4/7 (57.1)
VSD	0	3 (3.7)	0
ASD	3 (3 4)	3 (3.7)	0
Bicuspid AoV	0	3 (3.7)	0

Data are presented as n (%). CHD, congenital heart defect; VSD, ventricular septum defect; ASD, atrial septum defect; AoV, aortic valve.

Postnatal myocardial function

The only within-twin-pair differences in Doppler echocardiography at day one (Table 3) were a lower peak velocity across the aortic valve (AoV) (0.66 ± 0.15 m/s vs 0.71 ± 0.19 m/s, p = 0.04) and lower mean velocity across the AoV (0.43 ± 0.10 m/s vs 0 47 ± 0.13 m/s, p = 0.04) in donors as compared with recipients. Neonates with BAV had a non-significantly lower velocity across the AoV compared to TTTS twins without BAV (0.63 m/s vs 0.67 m/s, p = 0.55). At birth none of the four PS cases had increased velocities across the pulmonary valve (PV). Two neonates with pulmonary atresia had minimal or no antegrade flow across the PV. One neonate had turbulent flow across the valve without increased velocities. Another showed only pulmonary valve calcifications. Diastolic function was similar between donors and recipients and all measures were within the upper level of published normal ranges.[26] Overall donors showed a trend towards lower myocardial motion velocities as compared to recipients, but the only significant differences were lower velocities of late myocardial relaxation (a' wave) at the RV wall and early myocardial relaxation (e' wave) at the basal interventricular septum as measured with TDI. After exclusion of twins with CHD, only the a' wave at the RV wall remained significantly different between donors and recipients (0.073 ± 0.017 cm/s vs 0.067 ± 0.013 cm/s, p = 0.02).

At the age of one month (Table 4), donors had persisting lower velocities across the AoV compared with recipients (1.04 ± 0.21 m/s vs 1.11 ± 0.18 m/s, p = 0.02), but not compared to MC controls (1.10 ± 0.14 m/s, p = 0.19). The maximum velocity across the AoV in infants with BAV was 0.92 m/s compared to 1.08 m/s in TTTS infants without BAV (p = 0.18). Neonates with PS had higher velocities across the PV compared to TTTS twins without (1.81 m/s vs. 0.98 m/s). Tissue Doppler derived velocities differed between donors and MC controls in velocities of late myocardial relaxation (a') at the RV wall and early myocardial relaxation (e') at the LV wall.

Aortic dimensions

The results of echocardiographic measurements of the aorta can be found in Table 5 and 6. Donors had significantly smaller dimensions of the aortic annulus, aortic root, sinotubular junction and ascending aorta compared with recipients. After adjustment for weight (since cardiac dimensions are weight dependent), there were no statistically significant differences. Measurements of the aortic arch were similar between donors and recipients. The distal transverse arch/ascending aorta ratio, carotid-subclavian artery index and isthmus/ascending aorta ratio were smaller in donors compared with recipients, but these results did not reach statistical significance.

Table 3. Cardiac variables in TTTS twins day one postpartum

		Recipient	Donor	R – D
		Mean (SD)	**Mean (SD)**	**p-value**
Doppler echocardiography				
Pulmonary valve	Vmax (m/s)	0.72 (0.188)	0.73 (0.132)	0.92
	Vmean (m/s)	0.51 (0.136)	0.51 (0.096)	0.67
	VTI (m)	0.10 (0.031)	0.10 (0.023)	0.99
Aortic valve	Vmax (m/s)	0.71 (0.193)	0.66 (0.147)	**0.04**
	Vmean (m/s)	0.47 (0.130)	0 43 (0.099)	**0.04**
	VTI (m)	0.09 (0.026)	0.08 (0.021)	0.23
Mitral valve	E (m/s)	0.45 (0.128)	0 45 (0.112)	0.76
	A (m/s)	0.45 (0.121)	0 41 (0.093)	0.08
	E/A ratio	1.01 (0 236)	1.08 (0.351)	0.16
Tricuspid valve	E (m/s)	0.43 (0.116)	0 41 (0.134)	0.24
	A (m/s)	0.49 (0.097)	0 46 (0.105)	0.15
	E/A ratio	0.88 (0.376)	0.89 (0.531)	0.93
Tissue Doppler velocities				
Right ventricle	s' (m/s)	0.049 (0.0011)	0.049 (0.0111)	0.78
	e' (m/s)	0.066 (0.0239)	0.064 (0.0224)	0.65
	a' (m/s)	0.072 (0.0163)	0.067 (0.0136)	**0.04**
Left ventricle	s' (m/s)	0.032 (0.0109)	0.030 (0.0104)	0.17
	e' (m/s)	0.043 (0.0163)	0.041 (0.0177)	0.45
	a' (m/s)	0.040 (0.0174)	0.040 (0.0164)	0.87
Septal	s' (m/s)	0.033 (0.0083)	0.033 (0.0019)	0.82
	e' (m/s)	0.047 (0.0151)	0.042 (0.0107)	**0.03**
	a' (m/s)	0.047 (0.0125)	0.044 (0.0096)	0.12
Deformation measurements				
LV global longitudinal strain (%)		-13.4 (2.56)	-12.8 (3.21)	0.39
RV global longitudinal strain (%)		-15.5 (4.78)	-15 2 (3.93)	0.80

R, recipient; D, donor; Vmax, maximum velocity; Vmean, mean velocity; VTI, velocity time integral; E, early filling velocity; A, late filling velocity; s', ventricle contraction; e', ventricle relaxation; a', atrial contraction measured with TDI; LV, left ventricle; RV, right ventricle.

Table 4. Cardiac variables in TTTS twins and uncomplicated MC twins one month postpartum

		Recipient	**Donor**
		Mean (SD)	**Mean (SD)**
Doppler echocardiography			
Pulmonary valve	Vmax (m/s)	1.00 (0.240)	1.02 (0 292)
	Vmean (m/s)	0.71 (0.152)	0.71 (0.198)
	VTI (m)	0.14 (0.036)	0.14 (0.038)
Aortic valve	Vmax (m/s)	1.11 (0.177)	1.04 (0 208)
	Vmean (m/s)	0.73 (0.111)	0.70 (0.136)
	VTI (m)	0.14 (0.026)	0.13 (0.030)
Mitral valve	E (m/s)	0.95 (0.187)	0.95 (0.185)
	A (m/s)	0.79 (0.140)	0.78 (0 230)
	E/A ratio	1.08 (0 418)	1.33 (0.672)
Tricuspid valve	E (m/s)	0.70 (0.178)	0.71 (0.194)
	A (m/s)	0.63 (0 238)	0.61 (0.149)
	E/A ratio	1.06 (0.581)	1.00 (0.391)
Tissue Doppler Imaging			
Right ventricle	s' (m/s)	0.096 (0.0173)	0.092 (0.0215)
	e' (m/s)	0.152 (0.0467)	0.149 (0.0496)
	a' (m/s)	0.112 (0.0271)	0.096 (0.0306)
Left ventricle	s' (m/s)	0.056 (0.0128)	0.054 (0.0152)
	e' (m/s)	0.096 (0.0300)	0.090 (0.0290)
	a' (m/s)	0.070 (0.0220)	0.072 (0.0273)
Septal	s' (m/s)	0.056 (0.0104)	0.055 (0.0100)
	e' (m/s)	0.095 (0.0233)	0.092 (0.0263)
	a' (m/s)	0.077 (0.0215)	0.071 (0.0163)
Deformation measurements			
LV global longitudinal strain (%)		-13.6 (3.23)	-13.4 (3.33)
RV global longitudinal strain (%)		-18.6 (5.39)	-19 2 (4.28)

R, recipient; D, donor; C, control; Vmax, maximum velocity; Vmean, mean velocity; VTI, velocity time integral; E, early filling velocity; A, late filling velocity;

Control	R – D	R – C	D – C
Mean (SD)	p-value	p-value	p-value
1.05 (0.226)	0.52	0.44	0.66
0.73 (0.133)	0.90	0.48	0.54
0.14 (0.028)	0.67	0.86	0.56
1.10 (0.135)	**0.02**	0.97	0.19
0.76 (0.094)	0.10	0.38	0.11
0.15 (0.027)	0.06	0.51	0.15
0.89 (0.136)	1.00	0.30	0 25
0.82 (0.148)	0.74	0.41	0.65
1.08 (0.151)	0.34	0.85	0 49
0.79 (0.244)	0.37	0.10	0 20
0.70 (0.159)	0.89	0.38	0.17
0.98 (0.160)	0.71	0.72	0.92
0.093 (0.0117)	0 25	0.48	0.85
0.163 (0.0447)	0.69	0.28	0.18
0.127 (0.0233)	0.16	0.16	**0.04**
0.056 (0.0109)	0 42	0.78	0.73
0.108 (0.0286)	0 23	0.10	**0.02**
0.073 (0.0197)	0.63	0.54	0.76
0.058 (0.0078)	0 48	0.31	0.17
0.103 (0.0259)	0.51	0.13	0.10
0.080 (0.0243)	0 23	0.68	0 42
-13.2 (3.14)	0.61	0.44	0.85
-20 2 (6.00)	0 45	0.40	0.70

E/A, early/late filling velocity measured with blood flow Doppler; s', ventricle contraction; e', ventricle relaxation; a', atrial contraction measured with TDI; LV, left ventricle; RV, right ventricle.

Table 5. Aortic dimensions in TTTS survivors day one postpartum

	Recipient	Donor	p-value
Aortic annulus (mm)	5 42	5.18	**<0.01**
Aortic root (mm)	7.63	7.40	0.06
Sinotubular junction (mm)	6.22	5.89	**<0.01**
Ascending aorta (mm)	6.52	6 27	**0.01**
Proximal transverse arch (mm)	5.86	6.12	0.25
Distal transverse arch (mm)	5 23	5.37	0.51
Aortic isthmus (mm)	4.78	4.51	0.34
Distance between left common carotid and left subclavian arteries (mm)	2.57	2.67	0.39
Distal transverse arch/ascending aorta ratio	0.814	0.791	0.60
Carotid-subclavian artery index	2.286	2.195	0.53
Isthmus/ascending aorta ratio	0.759	0.713	0.10

Table 6. Aortic dimensions in TTTS survivors one month postpartum

	Recipient	Donor	p-value
Aortic annulus (mm)	7.40	7.32	**<0.01**
Aortic root (mm)	10.35	10.14	**0.01**
Sinotubular junction (mm)	8.65	8 43	**0.01**
Ascending aorta (mm)	9.03	8.99	0.06
Proximal transverse arch (mm)	7.84	7.64	0.15
Distal transverse arch (mm)	7.05	6.77	0.32
Aortic isthmus (mm)	6.22	5.89	0.32
Distance between left common carotid and left subclavian arteries (mm)	3.13	3.15	0.64
Distal transverse arch/ascending aorta ratio	0.773	0.771	0.97
Carotid-subclavian artery index	2.454	2.350	0.93
Isthmus/ascending aorta ratio	0.744	0.726	0 47

DISCUSSION

The main findings of the present study were a high birth prevalence of structural CHD (11.3%) after FLC and a low prenatal detection rate. Both recipient and donor twins were at risk of a CHD, with a prevalence of 9.2% and 13.6% respectively. We found an increased prevalence of PS, ASD, VSD and BAV. The only significant functional echocardiographic parameter was a lower peak aortic velocity in donor twins compared with recipient twins, but not compared to controls. To rule out any CHD in both recipient and donor twins, we therefore advise follow-up fetal echocardiograms and a postnatal echocardiogram.

Fetal cardiovascular development is influenced by genetic as well as environmental and hemodynamic factors such as blood flow, shear stress, preload and afterload.[8] In the event of TTTS, recipient and donor twins experience extremely different cardiac loading conditions in utero. Ventricular hypertrophy in recipients is suggested to be a consequence of hemodynamic changes, increased cardiac afterload, and the exposure to abnormal concentrations of vasoactive mediators such as endothelin-1, renin and angiotensin II.[27] Myocardial hypertrophy and increased systemic afterload can result in insufficient closure of the pulmonary valve, resulting in pulmonary insufficiency and eventually bidirectional flow in the ductus arteriosus.[17] Further deterioration of cardiac function with progression of the TTTS, may cause functional pulmonary atresia with no right ventricular outflow.

FLC improves cardiac function, and the PV FVW normalizes in over two thirds of cases, in the absence of irreversible anatomical changes to the pulmonary valve. Isolated pulmonary insufficiency, previously suggested to be a mild anomaly,[17] resulted in fetal demise in three cases in this study. In donor twins the occurrence of PS can be attributed to the postinterventional deterioration of cardiac function secondary to an acute increase in afterload after FLC.[28, 29] It is furthermore suggested that the increased rate of postnatal ASDs in recipient twins may result from increased right-to-left shunting at the atrial septum secondary to right ventricular dysfunction and tricuspid regurgitation.[30]

The increased prevalence of BAV in donors is a new finding with clinical importance, since it may result in aortic valvular stenosis and/or regurgitation and endocarditis later in life.[31, 32] It may be explained by hypovolemia and decreased cardiac output.[8] This explanation is supported by the lower aortic Doppler peak velocity in donor twins as compared with recipient twins, which suggests persistent reduced cardiac output in these twins. Karatza *et al.*[33] furthermore showed that recipient twins had higher aortic peak velocities than donors at time of TTTS. Whether decreased velocities in donors as compared with recipients have any clinical relevance should be the topic of further

research. As suggested by Van den Boom *et al.*,[34] donors are also at increased risk of other left-sided defects such as aortic coarctation due to decreased circulatory volume.[35] We hypothesized that due to decreased cardiac output and decreased aortic peak velocity during pregnancy until the early neonatal period, donor twins have smaller aortic arches even in the absence of true aortic coarctation. This study did not have the power to detect true differences in aortic dimensions, however.

Our results are in accordance with earlier prospective studies that showed a prevalence of 9-16%[30, 36] and equal CHD rates in recipients and donors.[30] The low prenatal detection rate of 21% in our study is explained by, firstly, the difficult scanning conditions in TTTS due to the combination of polyhydramnios of the recipient twin and the 'stuck' anhydramniotic donor. Second, minor defects (ASDs and small VSDs) and BAVs are considered undetectable before birth. And last, three infants who subsequently developed neonatal pulmonary stenosis, which became apparent one month after birth, had a normal fetal pulmonary valve morphology and velocity during pregnancy and at birth. In the study by Pruetz *et al.* the fetal CHD detection rates in case of TTTS was 42.9% in recipient twins and 16.7% in donor twins.[30] Postnatal echocardiograms in this study were, however, only performed in a select group of patients. Minor defects could therefore be left undetected in this study and the true prenatal detection rate may be lower. The low prenatal detection rate, 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 fetal and neonatal echocardiograms.

This study has strengths and limitations. First, this is the largest short-term prospective follow-up study to date, with a control group of age-matched unaffected MC twins at the age of one month. Since there is a limited number of studies into cardiac function in (premature) newborns,[37] the use of MC twins as a control group is superior to a control group of singletons or comparison to reference values from the literature. Second, we studied infants at the age of one month, corrected for prematurity, to eliminate the response to hemodynamic, hormonal, and biochemical stressors at birth. And last, this is the first study in which the Solomon technique was used in all cases. This technique is known for lower TTTS recurrence rates and improved survival and neonatal outcome.[15] In studies in which the selective approach was used, results may also have been influenced by an unstable hemodynamic environment after laser surgery if residual anastomoses were present. There are also limitations to this study. Because routine neonatal echocardiography was not performed in referring hospitals, we choose to exclude patients who did not undergo an echocardiogram as part of this study. This could have introduced a selection bias, which may have upwardly biased the prevalence

of PS. Inclusion of sparse echocardiography data from other centers, with different scanning protocols, could however have introduced large variation in the data. Our control group of monochorionic twins is small, our results must therefore be interpreted with caution. And last, multiple comparisons performed in this study may have increased the likelihood of statistically significant differences resulting from random rather than systematic variation. Correction for multiple testing is however a subject of debate, and is not always advised if study aims have an exploratory nature.[38, 39]

CONCLUSIONS

Data from this study support the recommendations of the American Institute of Ultrasound in Medicine that MC twin pregnancy should be considered an indication for fetal echocardiography.[40] To rule out any CHD in both recipient and donor twins, follow-up fetal echocardiograms should be performed and a postnatal echocardiogram should be offered to all TTTS survivors.

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CHAPTER 9

CRITICAL COARCTATION OF THE AORTA IN SELECTIVE FETAL GROWTH RESTRICTION AND THE ROLE OF CORONARY STENT IMPLANTATION

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ABSTRACT

Introduction: Monochorionic twins are at increased risk of congenital heart defects (CHDs). Up to 26% have a birth weight < 1,500 g, a CHD requiring neonatal surgery, therefore, poses particular challenges.

Objective: To describe pregnancy characteristics, perinatal management, and outcome of monochorionic twins diagnosed with critical coarctation of the aorta (CoA).

Methods: We included monochorionic twins diagnosed with critical CoA (2010-2019) at two tertiary referral centers, and we systematically reviewed the literature regarding CoA in monochorionic twins.

Results: Seven neonates were included. All were the smaller twin of pregnancies complicated by selective fetal growth restriction. The median gestational age at birth was 32 weeks (28-34). Birth weight of affected twins ranged 670-1,800 g. One neonate underwent coarctectomy at the age of one month (2,330 g). Six underwent stent implantation, performed between day 8 and 40, followed by definitive coarctectomy between 4 and 9 months in four. All seven developed normally, except for one child with neurodevelopmental delay. Three co-twins had pulmonary stenosis, of whom one required balloon valvuloplasty. The literature review revealed ten cases of CoA, all in the smaller twin. Six cases detected in the first weeks after birth were treated with prostaglandins alone, by repeated transcatheter angioplasty or by surgical repair, with good outcome in two out of six.

Conclusions: CoA specifically affects the smaller twin of growth discordant monochorionic twin pairs. Stent implantation is a feasible bridging therapy to surgery in these low birth weight neonates.

INTRODUCTION

Monochorionic twins are six times more likely to be born with a congenital heart defect (CHD) compared to singletons.[1] All subtypes of CHD are more common in monochorionic twins, except for tetralogy of Fallot and transposition of the great arteries.[1] Coarctation of the aorta (CoA) as an isolated congenital abnormality in monochorionic twins is predominantly found in donor twins with twin-twin transfusion syndrome (TTTS).[2, 3] Donor twins are usually the smaller twin in their set, which leads to the question whether other factors related to fetal growth also contribute to the development of CoA. Up to 26% of monochorionic twins have a birth weight less than 1,500 g.[4] In these very low birth weight (VLBW) infants, a critical CHD, such as critical CoA, poses particular challenges. In term neonates with a normal birth weight, the treatment of choice of critical coarctation of the aorta is surgical repair, usually by resection and extended end-to-end anastomosis. This treatment results in excellent long-term survival with low morbidity. In most centers the role of catheter interventions by balloon angioplasty or stent implantation is restricted to the resolution of re-coarctation. Catheter interventional therapy in neonates is used as bailout option in patients with poor left ventricular function or other severe comorbidities. In VLBW infants the role of catheter intervention might be different as the surgical risks and frequency of re-coarctation will increase.

In the present study we report the pregnancy characteristics, perinatal management, and outcome of monochorionic twins who were diagnosed with critical CoA at two tertiary referral centers for complicated monochorionic pregnancies, and we systematically review the literature regarding CoA in monochorionic twins.

METHODS

Case series

A tertiary multicenter retrospective study was performed at the University Hospitals Leuven, Belgium, and Leiden University Medical Center, the Netherlands. We have identified monochorionic twins who were born in one of the two tertiary referral centers and were diagnosed with critical CoA between 2010 and 2019.

The following fetal and perinatal variables were collected: time of diagnosis and type of selective fetal growth restriction (sFGR), fetal abnormalities on prenatal ultrasound, gestational age (GA) at birth, birth weight and placental share. sFGR was defined as an estimated fetal weight < 10th percentile of one twin with intertwin discordance of ≥ 25%[5, 6] and classified according to the classification system of Gratacós.[5] A detailed fetal anomaly scan was performed at mid-gestation. A third trimester anomaly scan was only performed in case of suspicion of fetal abnormalities at earlier scans, or in case of TTTS. Fetal CoA was suspected when there was ventricular disproportion in a four-chamber view, the left ventricle being significantly smaller than the right ventricle. Placentas were routinely injected with color dye according to our previously reported protocol,[7] and placental territory was calculated by dividing the placental territory of the larger twin by the placental territory of the smaller twin.[8]

Postnatal echocardiography was performed in case of clinical signs and symptoms such as a cardiac murmur, diminished pulsations at the lower extremities, or if pulmonary hypertension was suspected. CoA was defined as a local constriction with an increased velocity across the aortic isthmus measured by pulsed-wave doppler, and diastolic forward flow across the aortic isthmus. In cases with dubious echo findings under prostaglandin treatment, the drug was discontinued and the patient closely monitored and repeatedly studied by echocardiography to depict the typical findings. For this study we collected ultrasound and echocardiographic findings, time of diagnosis of CoA, type of treatment postpartum, number of interventions, age and weight of the infant at time of intervention, time to surgery and, if applicable, long-term developmental outcomes. We also collected data on perinatal outcome and long-term outcome of the co-twin.

Systematic literature review

Relevant articles were identified using electronic databases (Pubmed, Embase, Web of Science, and Cochrane) on September 30, using search terms related to 'monochorionic twins' and 'coarctation of the aorta'. The search was limited to papers written in English. No time restriction for publication dates was used. One reviewer (M. Gijtenbeek) screened titles and abstracts for relevance. If a title or abstract seemed relevant, the full

text was retrieved and assessed for inclusion. Selected articles were cross-referenced. Studies were excluded if the twins with CoA had additional extracardiac anomalies or if birth weight could not be retrieved from the data. The following data were extracted from the selected articles and tabulated: first author, year of publication, pregnancy complications, gestational age at birth, birth weight, time of diagnosis, type of treatment, outcome and development of the co-twin.

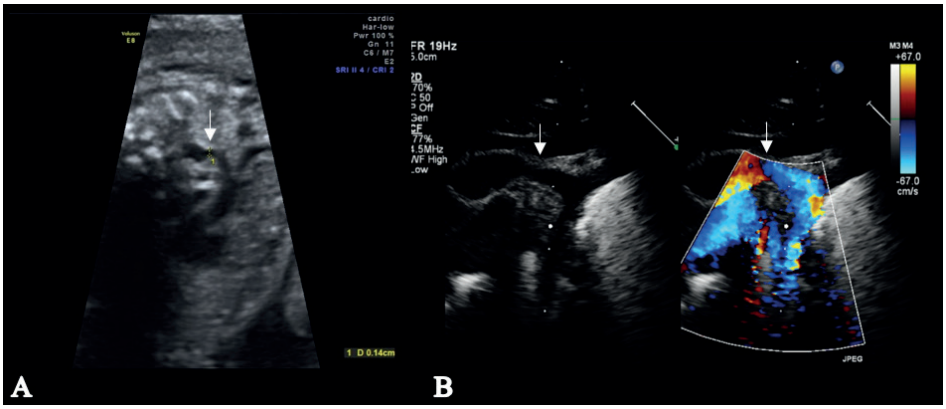

Figure 1. Ultrasound image of case 2. A: 28 weeks' gestation, B: after birth. Arrows indicate the coarcted segment

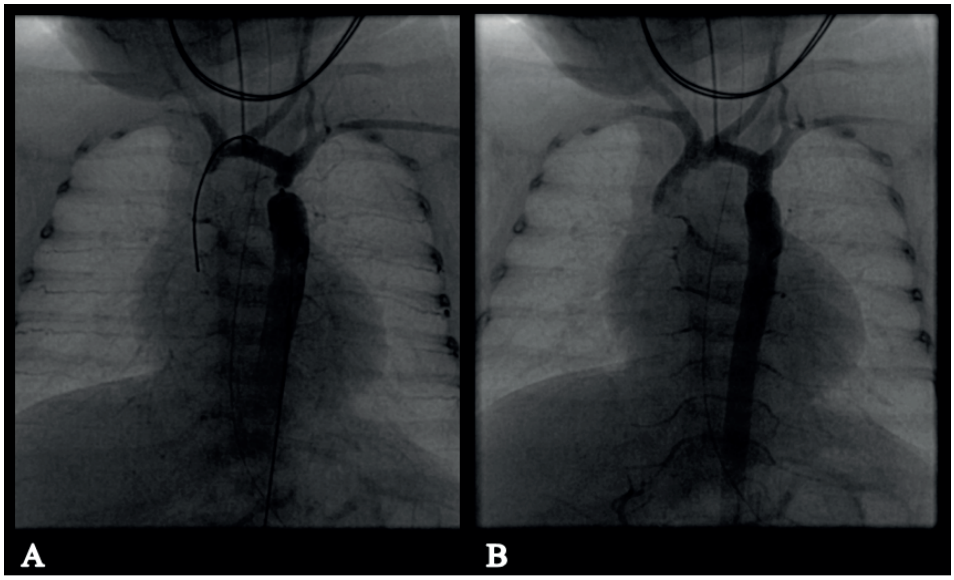

Figure 2. Intraoperative images of case 3. A: Pre-intervention, B: Status post stent implantation

RESULTS

During the study period, seven monochorionic diamniotic twins were diagnosed with critical CoA, of whom six underwent coronary stent implantation as bridging therapy to surgery. All seven were diagnosed with sFGR during pregnancy. sFGR type 1 (positive umbilical artery end-diastolic flow) was diagnosed in two cases, type 2 (persistent absent or reversed umbilical artery end-diastolic flow) in one case and type 3 (intermittent absent or reversed umbilical artery end-diastolic flow) in four cases. None of the cases had TTTS. All seven had discordant amniotic fluid at some point in pregnancy, but the discordance never fulfilled the criteria for TTTS. In Case 4 at 17 weeks, there was a difference in middle cerebral artery peak systolic velocity with 32 cm/s in the smaller twin (1.37 multiples of the median) and 17 cm/s in the larger twin (0.73 multiples of the median), suggestive of twin anemia polycythemia sequence (TAPS), which resolved spontaneously at 20 weeks' gestation. The affected twin in Case 1 had borderline ventriculomegaly, with a normal fetal brain MRI at 28 weeks. In two cases (Cases 2 and 6) CoA was suspected antenatally (Figure 1). Case 5 showed left/right asymmetry in the four-chamber view, which was attributed to adaptation in FGR. All cases were hospitalized between 27 and 33 weeks' gestation for in-patient monitoring, including a course of corticosteroids for fetal lung maturation. All were delivered by cesarean section, of which three were emergency deliveries because of an abnormal heart rate pattern in the smaller twin. The median GA at birth was 32 weeks (28-34). Birth weight of the affected twins ranged from 670 to 1,800 g. The placentas showed gross unequal sharing with little individual territory for the smaller twin, except for the placenta of the case with early TAPS.

All infants, except for Case 4, were treated intravenous prostaglandin E (PGE) treatment to keep the arterial duct open. PGE was stopped in two cases because of suspected pulmonary hemorrhage (Cases 1 and 3) and pulmonary edema (Case 1). Two other cases experienced hypotension (Case 5) or sepsis-like syndrome (Case 6) resulting from prolonged PGE treatment. One twin, born at 34 weeks' gestation with a birth weight of 1,630 g (co-twin 2,475 g), underwent coarctectomy via thoracotomy at the age of one month (2,330 g) and a balloon dilatation of a re coarctation at the age of 2.5 months.

The other six neonates underwent coronary stent implantation, of whom individual patient characteristics and outcomes are depicted in Table 1. In Case 5, balloon angioplasty on day 18 (1,040 g) via the right carotid artery was performed, which was not effective. In all six cases, coronary stent placement was performed because of unbalanced hemodynamic situation with systemic hypoperfusion and pulmonary overflow. Median age and weight at stent implantation was 29 days (8-40) and 1,735 g

(1,075-2,700), respectively (Figure 2). Stent implantation was performed via sternotomy (Cases 1 and 6), or percutaneously via the femoral artery (Cases 2, 3 and 4) or carotid artery (Case 5). Heparin and conotrope was administered to Case 3 because of femoral artery thrombosis. No other complications of stent placement occurred. Cases 1 and 5 had a percutaneous balloon dilatation of the stent at 3 months (2,580 g) and 10 months (8,500 g), respectively. In Case 6, two coronary stents were placed via sternotomy together with banding of the pulmonary artery and clipping of the duct. At the age of two months (3,008 g), a percutaneous balloon dilatation of the stent, a stent-in-stent placement proximal in the CoA, and a balloon dilatation of pulmonary artery banding were performed. Four infants had definitive surgical correction via thoracotomy at 6 months (4-9) and weight 5,150 g (4,430-6,080); two infants were still awaiting coarctectomy. Two patients suffered from pneumonia post-surgery (Cases 2 and 3).

All seven infants developed normally (9 months - 9 years), except for one child with neurodevelopmental delay. One infant had a mildly delayed motor development at the age of one year, which was attributed to visual impairment because of areolar atrophy of the macula.

Three of the larger co-twins had a form of pulmonary stenosis: one twin had symptomatic pulmonary valve stenosis that required balloon valvuloplasty at the age of two months, two twins had peripheral pulmonary artery stenosis that was managed conservatively. All co-twins had a normal development and cardiac function at follow-up visits.

Table 1. Results

	Case 1	**Case 2**
Fetal characteristics	sFGR type 3 (15 w)	sFGR type 3 (15 w)
	Brain-MRI normal (28 w)	A: CoA; B: PS (28 w)
Obstetrical outcome		
GA at birth (w + d)	28 + 4	32 + 4
BW (percentile)	A: 670 g (1st)	A: 1,800 g (17th)
	B: 1,055 g (7th)	B: 2,150 g (71st)
Placental share	13% / 87%	15% / 85%
Postnatal outcome A		
Age at diagnosis	5 d	Prenatal
PDA with PGE	Yes	Yes
Age at stent	29 d	28 d
Weight at stent	1,075 g	2,700 g
Stent size (mm)	3x8	4.5x12
Age at surgery	9 mo	6 mo
Weight at surgery	5,000 g	6,080 g
Follow-up	2 y: mild delay motor development; 8 y: normal cardiac function	6 y: delayed mental development; 7 y: normal cardiac function
Postnatal outcome B		
Diagnosis	RDS	Dilated ascending aorta, peripheral PS
Follow-up	2 y: normal development	6 y: delayed language development; 7 y: normal cardiac function

sFGR, selective fetal growth restriction; w, weeks; TAPS, twin anemia polycythemia sequence; A, affected twin, B, co-twin; PS, pulmonary stenosis; DV, ductus venosus; LV/RV, left/right ventricle; PLVCS, persistent left vena cava superior; CoA, coarctation of the aorta;

Case 3	Case 4	Case 5	Case 6
sFGR type 3 (25 w)	sFGR type 1, TAPS (17 w)	sFGR type 1 (23 w)	sFGR type 1 (16 w)
A: absent DV; B: PS (25 w)	TAPS spontaneous resolved (20 w)	A: LV/RV asymmetry (26 w)	A: PLVCS, CoA (20 w)
Brain-MRI normal (30 w)		sFGR type 2 (27 w)	A: hypoplastic arch, VSD (29 w)
32 + 2	34	28 + 1	34
A: 1,190 g (1st)	A: 1,530 g (1st)	A: 780 g (10th)	A: 1,380 g (1st)
B: 1,630 g (6th)	B: 2,280 g (44th)	B: 1,466 g (94th)	B: 2,160 g (27th)
-	32% / 68%	19% / 81%	25% / 75%
1 d	40 d	11 d	Prenatal
Yes	No	Yes	Yes
30 d	40 d	22 d	8 d
1,750 g	2,410 g	1,210 g	1,719 g
4.7x8	4x8	4.5x13	4x8 and 4.5x12
5.5 mo	4 mo	N/A	N/A
5,300 g	4,430 g	N/A	N/A
6 y: normal development and cardiac function	4 y: normal development and cardiac function	1 y: mild delay motor development; 19 mo: awaiting repair	9 mo: awaiting repair
Pulmonary valve stenosis, 30 d: balloon dilatation	11 mo: repair of isolated palatoschisis	RDS	Peripheral PS
8 y: normal development and cardiac function	3 y: normal development	1 y: normal development	9 mo: normal development

VSD, ventricle septum defect; GA, gestational age; d, day(s); BW, birth weight; g, grams; PDA, patent ductus arteriosus; PGE, prostaglandin E; mo, month(s); g, gram(s); N/A, not applicable; y, year(s); RDS, respiratory distress syndrome.

Table 2. Summary of monochorionic twins with discordant CoA reported in the literature

	Author (year)	Pregnancy complications	GA at birth (w)	BW (g)	BW co-twin (g)	Time of diagnosis
1	Driver (1960)	None	-	2,200	2,300	5.5 months
2	Morgan (1968)	?	-	2,155	3,289	5 years
3	Morgan (1968)	?	-	2,523	2,835	5 years
4	Hidaka (2007)	TTTS (donor)	28	712	1,060	Postnatal
5	van den Boom (2010)	TTTS (donor)	27	725	1,200	Postnatal
6	van den Boom (2010)	TTTS (donor)	28	850	1,180	Day 65
7	van den Boom (2010)	TTTS (donor)	25	713	937	Day 4
8	van den Boom (2010)	TTTS (donor)	33	1,520	2,490	Postnatal
9	Al-Ammouri (2015)	TTTS?	30	900	1,550	Day 5
10	Moldovan (2015)	TTTS?	31	950	1,700	2 weeks

GA, gestational age; w, weeks; BW, birth weight; g, grams; TTTS, twin-twin transfusion syndrome; PGE, prostaglandin E; IVH, intraventricular hemorrhage; PPHN, persistent pulmonary hypertension of the newborn;

	Treatment	Follow-up	Co-twin
			Normal development
	8 weeks after diagnosis surgical repair	1 year after surgery: alive and well	Normal development
	None		Normal development
	PGE	Pulmonary hemorrhage and renal failure; died on day 4	Normal development
	Day 22 surgical repair	IVH, 9 months: mild residual stenosis of the distal aorta, spastic diplegia and cortical blindness	PPHN, died after 25 h
	Day 67 surgical repair	Discharged at 5 weeks corrected GA	Chronic lung disease and PDA without treatment
	Day 13 surgical repair of CoA and PDA	Chronic lung disease, poor growth	Dysplastic aortic valve; died after 24h
	PGE for 1 day	Hypoplastic distal aortic arch, no focal coarctation; MRI showed extensive PVL	PPHN, Ebstein anomaly with PS; balloon septostomy + valve repair
	Day 7 balloon angioplasty, day 47 balloon angioplasty	13 months: no signs of re-coarctation	Normal development
	Surgical correction at 2 months (2,000 g)	Severe ROP	Bilateral grade III IVH, bilateral ventriculomegaly, intracranial hypertension; VP drain

PDA, patent ductus arteriosus; CoA, coarctation of the aorta; PVL, periventricular leukomalacia; PS, pulmonary stenosis; ROP, retinopathy of prematurity; VP, ventriculoperitoneal

Systematic literature review

The search resulted in 145 articles. After the removal of 48 overlapping results, 97 abstracts and titles were screened. Full texts of 21 articles were assessed in detail. Review articles (n = 2), congress abstracts (n = 3), articles with non-isolated cases (n = 4), articles from which the birth weight or exact number of twins with CoA could not be retrieved (n = 5), and articles not written in English (n = 1) were excluded. The remaining six articles were case reports, case series, or cohort studies.[2, 3, 9-12]

The six articles described 10 cases of monochorionic twins with discordant CoA (Table 2). Four twins had TTTS, all were treated by amnioreduction. In two other cases (9-10) TTTS diagnosis was uncertain (no mentioning of Quintero staging). Both were treated by immediate delivery of twins because of fetal distress, with a significant birth weight discordance. The median birth weight of affected twins was 925 g (712-2,523); all were the smaller twin in their set. Four cases of CoA were detected after more than two months, of whom two underwent a coarctectomy with good cardiac outcome. In six cases, critical CoA was detected in the first weeks after birth (Cases 4 to 10). Case 4 and 8 were treated with PGE alone, of whom one died after four days, and the other infant had extensive periventricular leukomalacia on MRI. Case 9 had two angioplasties with normal outcome. Three cases had surgical correction of the CoA, of whom one developed severe neurological problems, and another suffered from chronic lung disease and poor growth.

Five out of 10 co-twins had an uneventful neonatal period and follow-up. Two infants died, one suffered from PPHN and the other had a dysplastic aortic valve. One co-twin had Ebstein's anomaly with pulmonary stenosis, which required balloon septostomy and valve repair.

DISCUSSION

This case series shows that sFGR in monochorionic twin pregnancies can be accompanied by critical CoA, which specifically affects the smaller twin. In these low birth weight infants, stent implantation is a feasible bridging therapy to surgery.

The estimated prevalence of CoA in monochorionic twins is 2.1 per 1,000 live births,[13] which is considerably higher than the population prevalence of 0.34 per 1,000 singleton live births.[14] There are a few case series available describing this defect in monochorionic twins,[2, 3, 9-12, 15-18] and CoA as an isolated congenital abnormality in monochorionic twins has been associated with TTTS.[2, 3] The underdevelopment of the aortic arch in donor twins is possibly explained by (chronic) hypovolemia and decreased left-sided cardiac output.[19] The donor twins in these case reports were the smaller twin in their set, which leads to the question of whether factors related to fetal growth also contribute to the development of CoA. All our cases affected the smaller twin of a monochorionic pair with sFGR, and none had TTTS. In an unselected cohort of monochorionic twin pregnancies,[20] there were 64 liveborn twin pairs with a birth weight of more than 25%. Of these 64, three growth restricted twins were diagnosed with a critical CoA, leading to an estimated incidence of about 5%.

Altered blood flow conditions affect cardiac development of monochorionic twins with sFGR differently, and cardiac dysfunction occurs in both the larger and the smaller co-twin even in the absence of TTTS.[21] In TTTS, the renin-angiotensin system is activated, and the renal secretion of renin is upregulated because of the chronic hypovolemia in the donor twin.[22, 23] It has been suggested that renin is activated in both the larger and the smaller twin in sFGR as well, with or without the presence of TTTS.[24] Unequally shared placentas in twins without TTTS usually have large arterio-arterial (AA) anastomoses, a larger net flow over arterio-venous (AV) anastomoses, and a larger diameter of all anastomoses.[25] The characteristics of umbilical artery Doppler flow are strongly influenced by the pattern of these intertwin vascular connections, and the predominant direction and magnitude of blood flow interchange via placental anastomoses may vary accordingly. Fetuses with positive umbilical artery diastolic flow are generally considered to have a favorable prognosis, fetuses with persistent absent or reversed end-diastolic flow have been reported to have a high risk of hypoxia and fetal demise.[5] Since four of the seven cases in this study had intermittent absent or reversed umbilical artery end-diastolic flow, we hypothesize that highly unstable fetal hemodynamics may contribute to the development of cardiovascular abnormalities. In the smaller twin in sFGR, without signs of TTTS, narrowing of the aortic arch may occur secondary to the hemodynamic disturbances (decreased perfusion and decreased left-sided cardiac

output).[26] Two of our cases with critical CoA had positive umbilical artery end-diastolic flow, suggesting that only chronic hypovolemia may already have an effect on cardiac development.

Interestingly, three of the larger twins in our study had pulmonary stenosis of whom one required balloon valvuloplasty. The larger twin perfuses a variable proportion of the placenta of the smaller one, mainly via AA anastomoses. This involves by definition an increase in cardiac output and potentially a hyperdynamic circulation, resembling a milder form of the situation observed in monochorionic twins with an acardiac fetus.[27] The myocardial adaptation to the hyperdynamic circulation in the larger twin may result in pulmonary stenosis.[28]

In previous reports of CoA in VLBW donor twins,[2, 3] the defect was treated with prostaglandins alone, by repeated transcatheter angioplasty or by surgical repair. In VLBW infants, surgical treatment carries a substantial risk for morbidity and mortality[29, 30] and is preferably postponed until 3 kg with prostaglandins. In our experience, the results of surgical coarctation repair at 1.5 kg are disappointing with a high risk of early critical re-coarctation. 'Rescue-stenting' of the re-coarctation can then be offered, followed by surgical reintervention with stent excision later in life. This redo surgery carries a risk of complications such as vocal cord paralysis or phrenic nerve paralysis. Prolonged treatment with PGE to postpone surgery is also associated with a high risk of complications, such as respiratory depression, hypotension, sepsis, and hemorrhage. In fact, in our series PGE treatment was discontinued because of complications in four out of six cases. In six out of seven patients prostaglandin therapy was insufficient to gain weight and postpone surgery, and the clinical condition demanded earlier treatment. Balloon angioplasty as bridging therapy to surgery can be performed in case of localized coarctation with otherwise well-developed aortic arch. In case of long-segmented aortic arch hypoplasia balloon angioplasty will not be useful, and balloon dilatation before 6 months of age has a recurrence rate over 50%.[31, 32]

In our experience it is difficult to maintain an acceptable hemodynamic balance in children with left heart obstructive lesions and duct dependent systemic circulation requiring PGE therapy. Pulmonary vascular resistance will drop in the first weeks after birth, and this process occurs earlier in the premature infant.[33] As a result, these children will develop pulmonary overflow and insufficient systemic circulation with clinical signs of heart failure and risk of necrotizing enterocolitis. To minimize these risks in twin pairs with discordant growth that are usually delivered between 32 and 34 weeks gestation, primary coronary stent implantation may be a feasible bridging therapy to surgery,[34, 35] which we have shown with this case series. Stent implantation

can lead to a longer postponement of surgery, and consequently higher infants' weight at surgery.[34] Stent implantation does carry a substantial risk of complications, such as carotid or femoral artery trauma or thrombosis. In our study however, only one patient had a complication of the stent implantation. In newborns where a very small stent is implanted, re-coarctation is likely to occur. In our series, three patients needed a (balloon)dilatation of the stent, procedures that went uneventful. Four infants received uncomplicated surgical correction by thoracotomy, a procedure that may be more challenging than primary surgical correction. All six infants treated by stent implantation had a good cardiac outcome, two were still awaiting definitive repair. Unfortunately, there are no controlled studies yet to decide on the best treatment for the rare cases of critical coarctation of the aorta in VLBW infants.

Long-term neurodevelopment was favorable in the majority of twins. It is known that the risk of long-term neurological or cognitive impairment in monochorionic twins with sFGR or with a large birth weight discordance is higher compared to uncomplicated monochorionic or dichorionic twins, with a disadvantage for the smaller twin.[36] In our cohort, six of the seven growth restricted twins had a normal neurodevelopment. Even though the numbers in this study are small, the presence of a critical CoA in addition to the growth restriction, does not seem to increase the risk of neurodevelopmental impairment in monochorionic twins.

CONCLUSIONS

CoA appears to specifically affect the smaller twin of a growth discordant monochorionic twin pair. Stent implantation is a feasible bridging therapy to surgery in these low birth weight neonates. Larger co-twins are also at risk for cardiac anomalies arising from cardiac overload, namely pulmonary stenosis. Our findings underline the importance of dedicated fetal echocardiography and postnatal surveillance in twin pregnancies complicated by sFGR.

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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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CHAPTER 11

SUMMARY

This thesis discusses cardiovascular compromise in complicated monochorionic twin pregnancy, with special emphasis on short- and long-term effects of hemodynamic adaptations.

Part I comprises the general introduction of this thesis. In **part II** we evaluated fetal hemodynamics and cardiac function in monochorionic twins with twin-twin transfusion syndrome (TTTS) in order to predict the outcomes of these pregnancies. **Part III** describes the postnatal effects of hemodynamic alterations in monochorionic twin pregnancies.

PART II: FETAL CIRCULATION

In **chapter 2** we assessed fetal cardiac function in healthy singletons and TTTS recipients by measurement of cardiac time intervals using color-coded Tissue Doppler Imaging (cTDI). We used linear mixed models to construct age-adjusted reference ranges for shortening time (St) and lengthening time (Lt) in three cardiac regions: global heart and right and left ventricular wall. St decreased and Lt increased with gestational age in all regions. We found a high feasibility (99.6%) and excellent intra/interobserver variability for St (0.96/0.94) and Lt (0.99/0.96) of the global heart. Left and right ventricle performance parameters were good. In TTTS recipients, St was prolonged ($p < 0.01$) and Lt was shortened ($p < 0.01$) in all regions as compared to healthy singletons, and the feasibility was excellent (96.6%). With the technique of cTDI it is possible to discriminate between healthy and compromised fetuses.

In **chapter 3** we present a prospective study in which monochorionic twins with an amniotic fluid discordance ≥ 4 cm underwent serial ultrasound examinations. Each examination consisted of evaluation of the amniotic fluid (deepest vertical pocket), fetal Dopplers and fetal cardiac function. We have found that intertwin discordance in myocardial performance index (MPI) of both the left and right ventricle of the heart may help to differentiate between future TTTS and pregnancies with discordant amniotic fluid volume without TTTS. Using cardiac time intervals measured by cTDI clinicians can furthermore identify future recipient twins and differentiate between future TTTS and selective fetal growth restriction (sFGR) and uncomplicated monochorionic twin pregnancies.

In **chapter 4** a systematic review and meta-analysis of the literature on the value of echocardiography and Doppler in the prediction of intrauterine fetal demise (IUFD) after laser coagulation for TTTS is presented. We found that absent or reversed end-diastolic flow (A/REDF) in the umbilical artery (UA), absent or reversed a-wave in the ductus

venosus and middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the median (MoM) increases the risk of recipient-IUFD. In donors, only A/REDF in the UA and absent or reversed a-wave in the ductus venosus were found to be associated with donor-IUFD. The limited amount of available reports on the value of a detailed cardiovascular assessment in the prediction of fetal survival provided discordant results.

In **chapter 5** we investigated the possible relationship between perioperative hemodynamic changes and neurodevelopmental outcomes at two-years of age in 492 TTTS survivors. Neurodevelopmental impairment (NDI) was present in 5% of survivors. After adjustment for severe cerebral injury (detected in 4% of the children), the following parameters were associated with NDI: MCA-PSV > 1.5 MoM one day after surgery, a change from normal umbilical artery pulsatility index (UA-PI) pre-surgery to UA-PI > p95 post-surgery and change from normal to increased MCA-PSV. This study indicates that perioperative hemodynamic changes in TTTS twins treated with laser surgery may contribute to poor neurological outcome.

PART III: POSTNATAL CIRCULATION

In **chapter 6** the incidence of persistent pulmonary hypertension of the newborn (PPHN) in TTTS was described and risk factors for the development of PPHN in TTTS survivors were identified in a case-control study. Severe PPHN occurred in 26 of the 1,091 (2.4%) liveborn monochorionic twins. The incidence of severe PPHN was 10-fold increased in TTTS twins compared to monochorionic twins without TTTS (4% vs. 0 4%). Two risk factors were independently associated with severe PPHN: a younger gestational age (GA) at birth and a recipient status. In TTTS recipients, post-laser twin anemia polycythemia sequence (TAPS) (indicating incomplete fetoscopic laser surgery) contributed to a higher risk of PPHN in the univariate analysis, and an independent association with severe prematurity and anemia at birth was found. We propose a 'double hit theory' for anemic recipients after post-laser TAPS: the baseline increased risk of PPHN due to increased pulmonary vascular resistance is further increased by acute hypoxia as a result of anemia at birth.

In **chapter 7** an updated overview of congenital heart defects (CHD) in monochorionic twins is presented with a systematic review and meta-analysis. In this review 12 studies were included. Compared to the reference population, monochorionic twins were 6.3 times more likely to be born with a CHD (59.3 per 1,000 live born twins). TTTS twins had a 12-fold increased risk of having a CHD at birth (111.3 per 1,000 live births). The increased incidence of CHDs can mainly be attributed to the risk of right ventricular outflow tract obstruction (35/1,000 TTTS twin live births vs. 0.5/1,000 singleton live births).

In **chapter 8** we assessed cardiac function and postnatal CHD prevalence in 168 TTTS survivors. The main findings of the study were a high prevalence of structural CHD (11.3%) after fetoscopic laser coagulation and a low prenatal detection rate (21%). Both recipient and donor twins were at risk of a CHD, with a prevalence of 9.2% and 13.6% respectively. Pulmonary stenosis was the most frequently diagnosed defect in 4.2% of TTTS survivors (seven of 168), of whom five were recipients (five of 87, 5.7%) and two were donors (two of 81, 2.5%). In donors, also three ventricular septal defects, three atrial septal defects and three bicuspid aortic valves were detected. The only significant functional echocardiographic parameter was a lower peak aortic velocity in donor twins compared with recipient 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. In this study, one neonate underwent coarctectomy at the age of one month (2,330 g), six underwent stent implantation as bridging therapy to surgery. All seven developed normally, except for one child with neurodevelopmental delay. Three of the larger twins had pulmonary stenosis of whom one required balloon valvuloplasty. An additional systematic literature review revealed ten cases of monochorionic twins with discordant CoA, where the affected twin was the smaller baby. Six cases of critical CoA detected in the first weeks after birth were treated with prostaglandins alone, by repeated transcatheter angioplasty or by surgical repair, with good outcome in two out of six.

CHAPTER 12

NEDERLANDSE SAMENVATTING

De ontwikkeling van het hart en de foetale circulatie of hemodynamiek zijn nauw met elkaar verbonden. Hemodynamische veranderingen tijdens een zwangerschap kunnen daarom van invloed zijn op de ontwikkeling van het hart. Om de foetale circulatie te beoordelen kan men gebruik maken van Doppler en foetale echocardiografie.

Monochoriale tweelingen hebben een gezamenl jke circulatie via vaatverbindingen op het placentaoppervlak. Foetoplacentaire hemodynamische veranderingen kunnen optreden in het geval van complicaties tijdens monochoriale tweelingzwangerschappen, zoals het tweeling-transfusie syndroom (TTS) en selectieve foetale groeirestrictie (sFGR). In het geval van TTS, wat voorkomt in 10-15% van de monochoriale tweelingzwangerschappen, ontstaat er door een ongebalanceerde uitwisseling van bloed een hypovolemie en oligohydramnion in de donor en een hypervolemie en polyhydramnion in de ontvanger/ recipiënt. sFGR treedt op in 10-15% van de monochoriale tweelingzwangerschappen en wordt gekarakteriseerd door een groeidiscrepantie en een ongelijke placentaverdeling. De aangepaste hemodynamiek in deze zwangerschappen kan een verschillend effect hebben op de cardiale ontwikkeling van de grote en kleine foetus, ook zonder dat er aanwijzingen zijn voor TTS.

Tijdens de transitie van de foetale naar de postnatale circulatie verdwijnen de foetale shunts en is er een sterke toename in de systemische vaatweerstand. Door deze stijging in de systemische vaatweerstand daalt de pulmonale vaatweerstand. Bij een falende transitie van de circulatie na de geboorte kan persisterende pulmonale hypertensie van de neonaat (PPHN) optreden. Door een inadequate daling in de pulmonale vaatweerstand ontstaat er een hoge rechter-ventrikeldruk en shunting van zuurstofarm bloed van de pulmonale naar de systemische circulatie, waardoor er hypoxemie optreedt. Oorzaken voor PPHN zijn onder andere sepsis, asfyxie en blootstelling aan bepaalde medicijnen. Andere complicaties tijdens de zwangerschap zoals TTS kunnen mogelijk zorgen voor cardiale aanpassingen, de transitie beïnvloeden, en zo ook bijdragen aan het ontstaan van PPHN.

Bij de geboorte hebben monochoriale tweelingen een verhoogde kans op congenitale hartafwijkingen. De ontwikkeling van hartafwijkingen is geassocieerd met TTS. Foetoscopische laser coagulatie, de standaard behandeling van TTS, zorgt voor een verbetering van de overleving en de foetale cardiovasculaire conditie, maar neemt niet de gehele kans op hartafwijkingen weg. Voorts heeft tot 26% van de monochoriale tweelingen een geboortegewicht van < 1.500 g, waardoor de chirurgische behandeling van een hartafwijking zoals coarctatio aortae (CoA) zeer risicovol kan zijn.

In dit proefschrift worden de aanpassingen van de foetale cardiovasculaire hemodynamiek in het geval van gecompliceerde monochoriale tweelingzwangerschappen besproken, met speciale aandacht voor de korte en lange termijn effecten van deze aanpassingen. **Deel 2** van dit proefschrift omvat studies waarin wij hebben gekeken naar de foetale hemodynamiek en hartfunctie in monochoriale tweelingen met TTS om zo de uitkomsten van deze zwangerschappen te voorspellen. In **deel 3** beschrijven we de postnatale cardiopulmonale uitkomsten in monochoriale tweelingen.

DEEL 2: FOETALE CIRCULATIE

In **hoofdstuk 2** hebben we de hartfunctie van zowel gezonde eenlingen als TTS recipiënten bekeken. Met color-coded Tissue Doppler Imaging (cTDI) werden tijdsintervallen van de hartcyclus gemeten (zie Figuur 1 in hoofdstuk 2). Met linear mixed models zijn er voor de zwangerschapsduur-gecorrigeerde referentie curves van shortening time (St) en lengthening (Lt) gecreëerd in 3 cardiale regio's: globale hart en rechter en linker ventrikelwand. St nam af en Lt nam toe met de zwangerschapsduur in alle regio's. We vonden een hoge *feasibility* (99,6%) en uitstekende *intra/inter-observer variability* voor St (0,96/0,94) en Lt (0,99/0,96) van het globale hart. De parameters voor het linker en rechter ventrikel waren goed. In TTTS recipiënten, St was langer ($p < 0.01$) en Lt was korter ($p < 0.01$) in alle regio's vergeleken met gezonde eenlingen, en de *feasibility* was uitstekend (96,6%). Met cTDI is het mogelijk om te discrimineren tussen gezonde en cardiaal belaste foetussen.

In **hoofdstuk 3** presenteren we een prospectieve studie waarin monochoriale tweelingen met een vruchtwaterverschil van ≥ 4 cm meerdere echo-onderzoeken ondergingen. Elk onderzoek bestond uit het beoordelen van het vruchtwater (diepste verticale pocket), foetale Doppler metingen en analyse van de foetale hartfunctie. Uit dit onderzoek blijkt dat het verschil in myocardial performance index (MPI) tussen beide foetussen, van zowel het linker als het rechter ventrikel, mogelijk differentieert tussen toekomstige TTS en ongecompliceerde monochoriale tweelingzwangerschappen. Met behulp van de cardiale tijdsintervallen gemeten met behulp van cTDI kunnen clinici in tertiaire ziekenhuizen mogelijk ook toekomstig recipiënten identificeren en differentiëren tussen TTS, sFGR en ongecompliceerde monochoriale tweelingen.

Hoofdstuk 4 bevat een samenvatting en meta-analyse van de literatuur betreffende het nut van echocardiografie en Doppler in het voorspellen van intra-uteriene vruchtdood (IUVD) na laser coagulatie voor TTS. Deze studie liet zien dat er een verhoogde kans op IUVD van de recipiënt was in het geval van afwezige of reversed einddiastolische flow

(A/REDF) in de arteria umbilicalis, afwezige of reversed a-wave in de ductus venosus of een arteria cerebri media pieksnelheid > 1,5 Multiples of the Median (MoM). Donoren hadden alleen een verhoogde kans op IUVD in het geval van A/REDF in de arteria umbilicalis of afwezige of reversed a-wave in de ductus venosus. Het beperkte aantal artikelen waarin gekeken werd naar de relatie tussen gedetailleerde cardiovasculaire metingen en IUVD lieten tegenstrijdige resultaten zien.

In **hoofdstuk 5** worden perioperatieve hemodynamische veranderingen gerelateerd aan de motorische en cognitieve ontwikkeling op de leeftijd van 2 jaar in 492 kinderen behandeld met laser coagulatie vanwege TTS. Een ernstig ontwikkelingsprobleem of 'neurodevelopmental impairment' (NDI) was gedetecteerd in 5% van de kinderen. Na correctie voor ernstige cerebrale schade (in 4% van de kinderen gezien met behulp van een schedelecho), kwamen de volgende risicofactoren voor NDI naar voren: arteria cerebri media pieksnelheid > 1,5 MoM, een verandering van normale arteria umbilicalis bloedstroompulsaliteit of 'pulsatility index' (PI) voor de operatie naar een verhoogde PI boven de 95^{e} percentiel na de operatie en een verandering van een normale arteria cerebri media pieksnelheid naar een pieksnelheid > 1,5 MoM. Deze studie laat zien dat de perioperatieve veranderingen in TTS zwangerschappen kunnen bijdragen aan slechte neurologische uitkomsten.

DEEL 3: POSTNATALE CIRCULATIE

In **hoofdstuk 6** wordt er gekeken naar de incidentie en risicofactoren van PPHN in levend geboren TTS tweelingen. Ernstige PPHN kwam voor in 26 van de 1.091 (2,4%) monochoriale tweelingen. Het risico op ernstige PPHN was 10 maal hoger in TTS tweelingen vergeleken met monochoriale tweelingen zonder TTS (4% versus 0.4%). Twee risicofactoren waren onafhankelijk geassocieerd met het krijgen van ernstige PPHN: een kortere zwangerschapsduur bij de geboorte en recipiënt-zijn. Uit de univariate analyse kwam naar voren dat een tweeling anemie polycythemie sequentie (TAPS) na laser (duidend op een incomplete laser) een hogere kans op PPHN geeft in TTS recipiënten. In TTS recipiënten was er tevens een onafhankelijke relatie tussen PPHN en ernstige prematuriteit en anemie bij geboorte. Wij stellen een '*double hit theory*' voor anemische recipiënten na post-laser TAPS voor: het initieel verhoogde risico op PPHN door verhoogde pulmonale vaatweerstand is verder verhoogd door acute hypoxie ten gevolge van anemie bij geboorte.

In **hoofdstuk 7** wordt er door middel van een systematische literatuurstudie en meta-analyse een actueel overzicht gegeven van congenitale hartafwijkingen in monochoriale tweelingen. Er werden in totaal 12 studies geïncludeerd. Vergeleken met

de referentiepopulatie hadden monochoriale tweelingen en 6,3 maal zo hoge kans om geboren te worden met een congenitale hartafwijking (59,3 per 1.000 levendgeborenen). TTS tweelingen hadden een 12 maal zo hoge kans (111,3 per 1.000 levendgeborenen). De verhoogde kans op hartafwijkingen kan met name worden toegeschreven aan de verhoogde kans op obstructie van de rechter ventrikel uitstroombaan (35/1.000 TTS tweelingen versus 0,5/1.000 eenlingen).

In **hoofdstuk 8** wordt er gekeken naar cardiale functie en geboorteprevalentie van hartafwijkingen in 168 TTS overlevenden. De belangrijkste bevindingen van deze studie z jn een hoge prevalentie van hartafwijkingen (11,3%) na TTS laser en een lage prenatale detectiegraad (21%). Zowel recipiënten als donoren hebben een risico op hartafwijkingen, met een prevalentie van respectievelijk 9,2% en 13,6%. Pulmonalisstenose werd met 4,2% het vaakst gedetecteerd (zeven van de 168); v jf van de zeven waren ex-recipiënt. In ex-donoren werden ook drie ventrikelseptumdefecten, drie atriumseptumdefecten en drie bicuspide aortakleppen gedetecteerd. De enige significante functionele echocardiografische parameter was een lagere pieksnelheid over de aortaklep in donoren vergeleken met recipiënten.

In **hoofdstuk 9** worden zeven casus beschreven van monochoriale tweelingen met kritieke CoA. Alle zeven waren de kleinste van een tweeling met sFGR. In deze studie werd één neonaat behandeld middels coarctectomie op de leeftijd van 1 maand (2.330 g), zes werden behandeld middels stentimplantatie als overbruggingsoptie tot de operatie. Alle zeven, behalve één met een neurologische ontwikkelingsachterstand, ontwikkelden normaal. Drie van de grotere 'co-twins' hadden een pulmonalisstenose, waarvan er één een ballondilatatie nodig had. Een aanvullend systematisch literatuuronderzoek liet 10 casus van monochoriale tweelingen met discordante CoA zien, allen de kleinste van een tweelingpaar. Zes casus waarbij het defect in de eerste weken na de geboorte was gedetecteerd werden behandeld met alleen prostaglandines, met herhaalde angioplastiek of met chirurgie, met een goede uitkomst in twee van de zes.

PART V

LIST OF ABBREVIATIONS
LIST OF CO-AUTHORS AND THEIR AFFILIATIONS
LIST OF PUBLICATIONS
ABOUT THE AUTHOR
DANKWOORD

LIST OF ABBREVIATIONS

AC	Abdominal circumference
AEDF	Absent end-diastolic velocity
AS	Aortic stenosis
ASD	Atrial septal defect
AV	Atrioventricular
CoA	Coarctation of the aorta
CHD	Congenital heart defect
CHOP	Children's Hospital of Philadelphia
CI	Confidence interval
CPR	Cerebroplacental ratio
CRL	Crown-to-rump length
cTDI	Color-coded Tissue Doppler Imaging
CTG	Cardiotocogram
DV	Ductus venosus
DVP	Deepest vertical pocket
EFW	Estimated fetal weight
ET	Ejection time
FDR	False discovery rate
FLC	Fetoscopic laser coagulation
FLS	Fetoscopic laser surgery
FMH	Fetomaternal hemorrhage
FVW	Flow velocity waveform
GA	Gestational age
GEE	Generalized estimated equation
Lt	Lengthening time
LUMC	Leiden University Medical Center
LV	Left ventricle
I^2	Inconsistency square
ICT	Isovolumetric contraction time
iNO	Inhaled nitric oxide
IQR	Interquartile range
IRT	Isovolumetric relaxation time
IUFD	Intrauterine fetal demise
IUT	Intrauterine transfusion
MC	Monochorionic
MCA	Middle cerebral artery
MoM	Multiples of the median

MPI	Myocardial performance index
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
OR	Odds ratio
PGE	Prostaglandin E
PI	Pulsatility index
PPHN	Persistent pulmonary hypertension of the newborn
PPROM	Preterm premature rupture of membranes
PVR	Pulmonary vascular resistance
PV	Pulmonary valve
PSV	Peak systolic velocity
REDF	Reversed end-diastolic velocity
ROC	Receiver-operating characteristics
ROI	Region of interest
RR	Relative risk
RV	Right ventricle
RVOTO	Right ventricular outflow tract obstruction
SD	Standard deviation
sFGR	Selective fetal growth restriction
SLPCV	Selective laser photocoagulation of communicating vessels
St	Shortening time
SVR	Systemic vascular resistance
TAPS	Twin anemia polycythemia sequence
TDI	Tissue Doppler Imaging
TGA	Transposition of the great arteries
TOF	Tetralogy of fallot
TTTS	Twin-twin transfusion syndrome
UA	Umbilical artery
VLBW	Very low birth weight
VSD	Ventricular septal defect

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ABOUT THE AUTHOR

Manon Gijtenbeek werd op 12 april 1989 in stuitligging geboren in het Holyziekenhuis te Vlaardingen.

In 2006 behaalde zij het HAVO diploma en in 2007 het VWO diploma aan het Groen van Prinsterercollege in Vlaardingen. Daarna begon zij aan de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Na het behalen van haar propedeuse in het 1e jaar is zij gestart met de NIHES researchmaster 'Clinical Epidemiology'. Manon heeft haar masterthesis geschreven over de vroege ontwikkeling van de hersenblaasjes onder leiding van prof. dr. R.P.M. Steegers-Theunissen. Intussen groeide de interesse voor de Verloskunde & Gynaecologie en behaalde zij het Structureel Echoscopisch Onderzoek (SEO) examen in 2011. In 2012 studeerde zij af als epidemioloog A.

Met een voorliefde voor vakken met een acuut karakter werkte Manon tijdens de studie met veel plezier op de Spoedeisende Hulp van het Erasmus MC en de Acute Hulp van het Sophia Kinderziekenhuis, was zij secretaris van de Spoedeisende Hulp Studenten Organisatie (SEHSO) en ging zij voor een keuze-coschap Spoedeisende Hulp geneeskunde naar Paramaribo, Suriname. Naast de coschappen werkte Manon als echoscopist voor verschillende verloskundigenpraktijken in de regio Rotterdam. In 2015 studeerde Manon *cum laude* af in de Geneeskunde, waarna zij werkte als arts-assistent Verloskunde en Gynaecologie in het Maasstad Ziekenhuis te Rotterdam.

Na een klein jaar begon Manon in 2016 als arts prenatale geneeskunde op de afdeling Verloskunde en Foetale Therapie in het Leids Universitair Medisch Centrum (LUMC). Daar deed zij tevens onderzoek onder leiding van dr. M.C. Haak en prof. dr. D. Oepkes. In 2017 solliciteerde zij voor de opleiding, waarna het traject werd voortgezet als 'arts in opleiding tot specialist en klinisch onderzoeker' (AIOSKO). Na een mooie reis door Midden-Amerika is zij april 2020 gestart met de opleiding tot gynaecoloog in het HAGA ziekenhuis (opleider drs. A.H. Feitsma). Op dit moment is z j bezig met het academische deel van haar opleiding in het LUMC (opleider dr. M. Sueters).

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