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## Cardiovascular compromise in monochorionic twins

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### Citation

Gijtenbeek, M. (2021, July 7). *Cardiovascular compromise in monochorionic twins*. Retrieved from <https://hdl.handle.net/1887/3195073>

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**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



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**Title:** Cardiovascular compromise in monochorionic twins

**Issue Date:** 2021-07-07



# PART I

OVERVIEW



# CHAPTER 1

# GENERAL INTRODUCTION



Partly adapted from: Gijtenbeek M, Haak M. Congenital Heart Disease in Monozygotic Twins. In: Matias A, Blickstein I, editors. Developmental and Fetal Origins of Differences in Monozygotic Twins. 1. London, United Kingdom: Elsevier; 2020.



## 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.<sup>1-3</sup> 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.<sup>2-3</sup> 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.<sup>4</sup>

David Barker first documented the relationship between infant birth weight and adult onset disease,<sup>5-6</sup> 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)<sup>7-8</sup> 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.<sup>9</sup>

**Figure 1.** Fetal circulation. (Reprinted from Sadler TW, Langman's Medical Embryology, 12<sup>th</sup> 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.<sup>10</sup>

### **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<sup>11, 12</sup> 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.<sup>13, 14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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,<sup>17</sup> 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.<sup>18</sup>

### 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).<sup>19, 20</sup> 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).<sup>21, 22</sup> 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 fetoplacental 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.<sup>23</sup> Information on the true velocity (peak systolic velocity, PSV) of the blood flow may also be obtained from the middle cerebral artery.<sup>24</sup> 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.<sup>25</sup>

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'),<sup>26</sup> speckle tracking<sup>27</sup> and color-coded Tissue Doppler Imaging (cTDI).<sup>28</sup> 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.<sup>26</sup> In the 'modified' MPI method proposed by Raboisson *et al.*<sup>29</sup> and Hernandez-Andrade *et al.*,<sup>30</sup> 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.<sup>31</sup> Tissue Doppler Imaging (TDI) has been used since the early 1990s in adult echocardiography,<sup>32</sup> 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.<sup>33</sup>

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.<sup>3</sup>

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.<sup>34</sup> 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).<sup>35</sup>

**Figure 2.** Neonatal circulation. (Reprinted from Sadler TW, Langman's Medical Embryology, 12<sup>th</sup> 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<sup>36, 37</sup> may cause persistent pulmonary hypertension of the newborn (PPHN). Severe PPHN has an estimated incidence of two per 1,000 live births,<sup>38</sup> and is associated with significant morbidity and mortality.<sup>39</sup> 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.<sup>39</sup> The pathogenesis of PPHN is multifactorial,<sup>36, 37, 40-42</sup> 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.<sup>43, 44</sup> 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.<sup>45</sup> 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.<sup>46-49</sup> 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.<sup>50</sup>

Fetoscopic laser surgery results in major cardiovascular improvement in affected twins<sup>51-54</sup> but does not prevent the development of subsequent cardiac defects in all cases.<sup>55</sup> Childhood cardiac function seems normal, but large short-term cardiac function studies after fetoscopic laser surgery are still lacking.<sup>56</sup> 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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