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Thesis mentor: Aleks Finderle, MD, PhD, Assistant Professor

The graduation thesis was graded on _____ in _____, before the Committee composed of the following members:

1. Tea Štimac, MD, PhD, Associate Professor (President of the Committee)
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3. Alemka Brnčić -Fischer, MD, PhD, Associate Professor

The graduation thesis contains 39 pages, 6 figures, 4 tables, 49 references.

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List of abbreviations and acronyms:

AA – Arterio-arterial

ANP – Atrial natriuretic peptide

ART – Assisted reproductive technologies

AO – Aorta

AV – Arterio-venous

AV – Atrioventricular

β-hCG – β-human chorionic gonadotropin

BNP – Brain natriuretic peptide

CHOP – Children's Hospital of Philadelphia

CfDNA – Cell-free DNA

CL – Cervical length

CRH – Corticotropin-releasing hormone

CRL – Crown-rump length

CVS – Chorionic villus sampling

DC – Dichorionic

DCDA – Dichorionic diamniotic

DVP – Deepest vertical pocket

FGR – Fetal growth restriction

FSH – Follicle-stimulating hormone

FLPC – Fetoscopic laser photocoagulation

GIFT – Gamete intrafallopian transfer

IVF – In vitro fertilization

LH – Luteinizing hormone

LV – Left ventricle

MCDA – Monochorionic diamniotic

MCMA – Monochorionic monoamniotic

MPI – Myocardial performance index

MC – Monochorionic

NEC – Necrotizing enterocolitis

NT – Nuchal translucency

PA – Pulmonary artery

PAPP-A – Pregnancy-associated plasma protein A

PROM – Premature rupture of membranes

RAAS – Renin-angiotensin-aldosterone system

RV – Right ventricle

RVOTO – Right ventricular outflow obstruction

SF – Shortening fraction

SFLPC – Selective fetal laser photocoagulation

TAPS – Twin anemia-polycythemia sequence

TORCH – Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex viruses

TR – Tricuspid regurgitation

TRAP – Twin reversed arterial perfusion

TTTS – Twin-Twin transfusion syndrome

VV – Veno-venous

1. INTRODUCTION

Twin pregnancies, characterized by the simultaneous development of two embryos within the uterus, can be categorized into two main types: monochorionic and dichorionic. Monochorionic twin pregnancies occur when a single fertilized egg splits into two embryos, resulting in twins that share a single placenta. This shared placental structure distinguishes monochorionic twins from their dichorionic counterparts, who typically have separate placentas, although these placentas can sometimes fuse. The shared placenta in monochorionic twins creates a unique environment with intricate vascular connections between the fetuses. These vascular anastomoses, while providing a vital link between the twins, can also pose significant risks, particularly if there are unidirectional arteriovenous anastomoses, leading to the development of Twin-Twin Transfusion Syndrome (TTTS) and other complications.

TTTS is a severe and potentially life-threatening condition that impacts 10-15% of monochorionic twin pregnancies. It occurs when the blood flow between the twins becomes unbalanced due to the shared vessels in the placenta. In TTTS, one twin, known as the donor, transfers blood to the other twin, the recipient. This unequal exchange results in the donor twin becoming hypovolemic and growth-restricted, while the recipient twin experiences hypervolemia and associated complications. The recipient twin's increased blood volume can lead to heart failure and other cardiac issues, whereas intrauterine growth restriction or even fetal demise can affect the donor twin.

Early diagnosis and intervention are critical in managing TTTS to improve outcomes for both twins. Regular and detailed ultrasound monitoring is essential for detecting the condition at its onset. Treatment options such as fetoscopic laser photocoagulation aim to correct the blood flow imbalance by coagulating the abnormal vascular connections in the placenta. Another approach, amnioreduction, involves removing excess amniotic fluid from the recipient twin to alleviate the pressure and symptoms associated with polyhydramnios.

Despite advances in medical technology and treatment strategies, TTTS remains a complex and challenging condition with significant implications for fetal and neonatal health. The prognosis for affected twins varies depending on the severity and timing of the intervention. Continued research and improvements in clinical practice are essential to enhance the understanding and management of TTTS.

2. AIMS AND OBJECTIVES

The primary aim of this thesis is to investigate TTTS within the context of MC twin pregnancies. Initially, this thesis will provide an overview of different types of twinning and the methods used to diagnose them. Following this, the discussion will delve into the complications associated with monochorionic twin pregnancies, with a specific focus on TTTS. This exploration will encompass understanding the pathophysiology, diagnostic methods, treatment options, and associated outcomes of TTTS.

First and foremost, it is critical to ascertain the frequency and risk factors linked to TTTS in pregnancies involving monochorionic twins. This involves analyzing statistical data on the incidence of TTTS in order to identify important elements that have a significant impact in the syndrome's development. By understanding these risk factors, healthcare providers can better anticipate and monitor pregnancies at higher risk for TTTS, enabling earlier intervention and potentially improved outcomes.

Secondly, this thesis aims to explore the pathophysiological mechanisms underlying TTTS. This includes investigating the role of shared placental vessels and the types of vascular anastomoses that lead to the development of the syndrome, as well as the involvement of the renin-angiotensin-aldosterone system (RAAS). We can gain additional information regarding the course of TTTS and its effects on fetal health and development by looking into these mechanisms.

Another critical objective is to review and evaluate current diagnostic criteria and staging systems for TTTS. This involves assessing the effectiveness of various ultrasound markers and other diagnostic tools in the early detection of TTTS. Additionally, the thesis will analyze different staging systems used to classify the severity of TTTS, such as the Quintero staging system, and their implications for treatment planning. Improving these diagnostic approaches is crucial for effective management.

Furthermore, this thesis will evaluate the treatment options available for managing TTTS. This includes discussing various interventions, such as fetoscopic laser photocoagulation, amnioreduction, and other emerging therapies. By comparing the outcomes and effectiveness

of these different treatment modalities, valuable insights can be provided into the best practices for managing TTTS and improving fetal outcomes.

Lastly, this thesis aims to assess the complications and prognosis associated with TTTS. This entails assessing the twins , both the donor and recipient in terms of their short- and long-term health outcomes, as well as identifying potential complications that may arise from TTTS and its treatment. Understanding these aspects will help healthcare providers develop more comprehensive care plans for affected pregnancies.

In summary, by addressing these objectives, this thesis aims to contribute to the existing knowledge on TTTS and enhance clinical practices for managing this complex condition in monochorionic twin pregnancies.

3. LITERATURE REVIEW

3.1 Overview of Twin Pregnancies

In humans, spontaneous twin pregnancies are relatively rare, occurring with a frequency of approximately 1 in 80 pregnancies. This frequency decreases exponentially with the number of fetuses, following Hellin's rule. According to this rule, the frequency of triplet births is the square of the frequency of twin births ($1/80^2$, or 1 in 6,400), and the frequency of quadruplet births is the cube of the frequency of twin births ($1/80^3$, or 1 in 512,000). (1)

The incidence of twin and multiple pregnancies has significantly increased in recent years. There are two primary causes for this increase. Firstly, the average age of pregnant women has increased. As maternal age increases, ovarian sensitivity to gonadotropins decreases, causing the pituitary gland to release more luteinizing hormone (LH) and follicle-stimulating hormone (FSH). This increase in hormone production stimulates more follicles to mature, thus increasing the likelihood of multiple ovulations and fertilizations. Secondly, there is a more frequent use of pharmacological therapies, such as Clomiphene Citrate and Gonadotropins, to stimulate ovulation, as well as the growing use of assisted reproductive techniques. The impact of these factors may vary depending on the type of pregnancy (monozygotic or dizygotic) and the population studied. Monozygotic twins are generally not influenced by maternal age or fertility

treatments. In contrast, dizygotic twins and their incidence is more directly affected by the aforementioned factors. (2)

Contrary to popular belief, most iatrogenic twin pregnancies result from simple ovulation induction treatments rather than assisted reproduction techniques. By limiting the number of embryos or oocytes transferred, both in vitro fertilization (IVF), which has a 3.5% risk of multiple pregnancies, and gamete intrafallopian transfer (GIFT), which has a 5% risk, effectively control the risk factors for multiple pregnancies. These techniques generally result in low-order multiple pregnancies, such as twins. However, for anovulatory patients treated with Clomiphene or Gonadotropins to induce mono-ovulation, or for couples with unexplained infertility undergoing intrauterine insemination or timed intercourse preceded by the induction of 2-4 follicles (the so-called "superovulation" induction), the risk of multiple pregnancies is, at least theoretically, uncontrollable. (3,4)

Multiple pregnancies constitute approximately 2-3% of all births and they can manifest in two primary forms: monozygotic and dizygotic. The latter, accounting for approximately 70% of all twin pregnancies, arises from the simultaneous fertilization of two distinct oocytes by two separate spermatozoa. This process results in the formation of two embryos, each possessing its own set of genetic characteristics. Conversely, monozygotic twin pregnancies, which account for 30% of all pregnancies, result from a single spermatozoon fertilizing a single oocyte to produce a single zygote. In general in the twinning process, subsequent to fertilization, the zygote undergoes division, resulting in the generation of two embryonic entities with identical genetic composition. This division may occur at various stages of embryonic development, leading to distinct forms of monozygotic twinning, such as dichorionic diamniotic (DCDA), monochorionic diamniotic (MCDA), and monochorionic monoamniotic twins (MCMA), each with its own set of obstetric and perinatal considerations. (5)

MONOZYGOTIC TWINS

Monozygotic twins, often referred to as identical twins, originate from a single oocyte that undergoes fertilization with a single spermatozoon, resulting in the formation of a zygote. Subsequent to fertilization, the zygote undergoes division, leading to the emergence of two distinct embryos with nearly identical genetic structure. It's notable that monozygotic twins share not only identical genetic structure but also the same sex. However, there is currently no

conclusive evidence pointing to heritability or environmental factors influencing the occurrence of monozygotic twinning.

The division's time is particularly significant for the later growth and categorization of monozygotic twins. Specifically:

- Division occurring between the 1st and 3rd days post-fertilization results in Dichorionic Diamniotic (DCDA) twins, constituting approximately 1/3 of monozygotic twin cases.
- When division takes place between the 4th and 8th days post-fertilization, after the trophoblast has differentiated, Monochorionic Diamniotic (MCDA) twins develop. This subtype comprehends approximately 2/3 of all monochorionic pregnancies.
- Division between the 9th and 12th days post-fertilization, following amniotic sac differentiation, gives rise to Monochorionic Monoamniotic (MCMA) twins, representing a rare occurrence comprising approximately 1% of all monochorionic pregnancies.
- In extremely rare cases where division occurs after the 12th day post-fertilization, conjoined twins may develop.

DIZYGOTIC TWINS

Dizygotic twins, commonly known as fraternal twins, arise from the fertilization of two separate oocytes by two distinct spermatozoa. As a result, these twins may share the same sex or have different sexes, with a distribution of approximately 25% male-male, 25% female-female, and 50% female-male pairs. Genetically, they resemble typical siblings, sharing about 50% of their genetic material. The occurrence of dizygotic twinning can be influenced by various factors, including hereditary predisposition, ethnic background, and advanced maternal age due to elevated levels of gonadotropins. Additionally, the use of fertility treatments such as follicle-stimulating hormone (FSH), clomiphene citrate, or assisted reproductive technologies (ART) may increase the likelihood of dizygotic twinning. Dizygotic twins are typically dichorionic-diamniotic (DCDA), and although the placentas of dizygotic twins may fuse, they do not share vascular connections. (2,6,7)

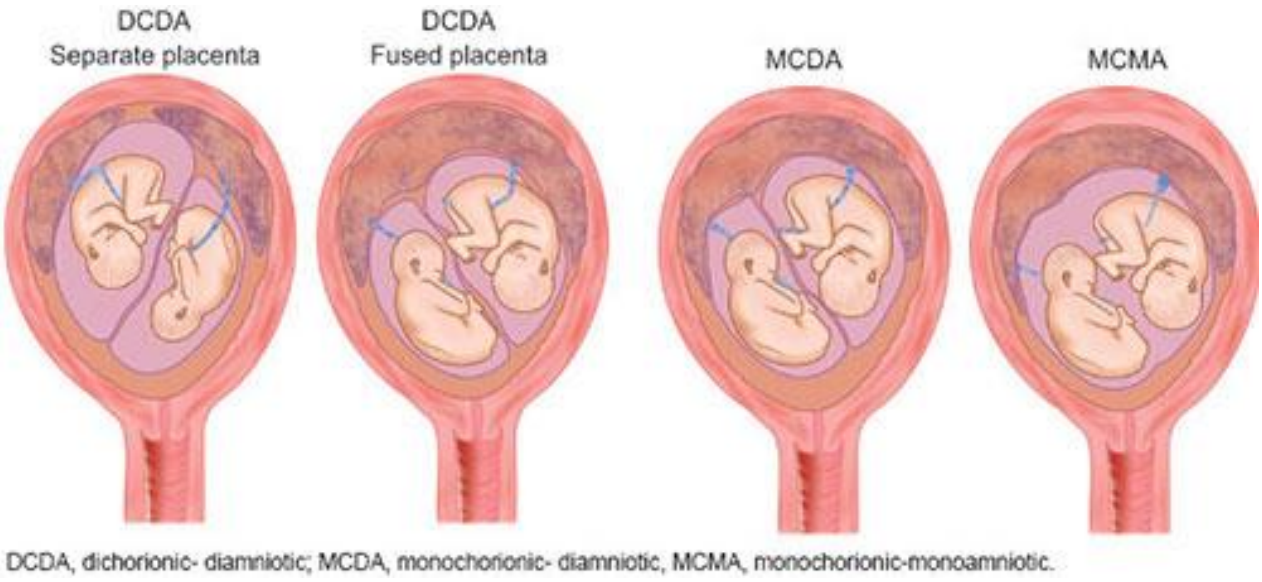

Figure 1: Placentation of twins

3.2 Diagnosis of chorionicity and amnionicity in twin pregnancies

Twin pregnancies represent a significant clinical challenge due to their high-risk nature, necessitating a thorough diagnostic approach to determine chorionicity and amnionicity. This is particularly crucial considering that monozygotic twin pregnancies carry an even greater risk compared to dizygotic twins.

Early ultrasound assessment before 13 weeks + 6 days gestation is of greatest importance, as delayed evaluation may increase the risk of diagnostic misclassification by up to 10%. During the initial ultrasound examination typically conducted around 7 to 8 weeks, the primary focus lies in determining the number of embryos present. However, it is after the 7-9th weeks of gestation that the ability to determine chorionicity, amnionicity, and the number of placentas significantly improves. Diagnostic ultrasound markers such as the "lambda" sign, resembling a triangular chorion between the intertwin membranes, serve as a reliable indicator of dichorionic pregnancies. Conversely, the "T sign," characterized by a 90° angle connecting the two amnions, signifies a monochorionic pregnancy.

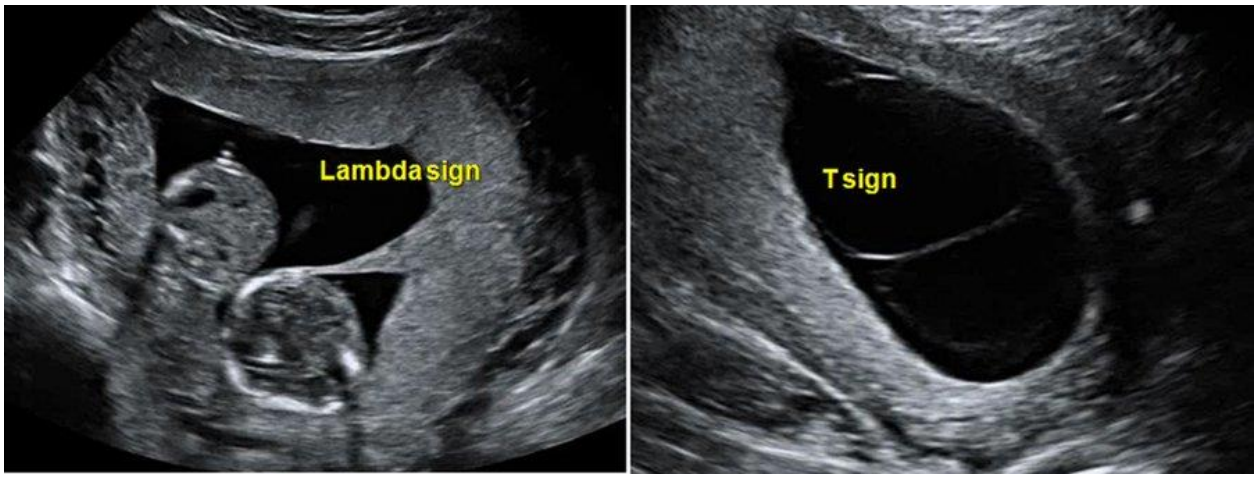

Figure 2: “Lambda” and “T” sign in ultrasound diagnostics of chorionicity

In addition to the "lambda" and "T signs," other diagnostic markers aid in distinguishing between DC and MC twin pregnancies. For instance, the thickness of the chorion serves as a reliable indicator; a membrane thickness equal to or greater than 1.9mm suggests a dichorionic pregnancy, while a thickness less than 1.9mm indicates a monochorionic pregnancy. Moreover, the identification of membrane layers on ultrasound is crucial. In dichorionic pregnancies, three distinct layers are typically observed: two amniotic membranes with a chorionic layer in between. Conversely, monochorionic pregnancies exhibit only two layers consisting of two amniotic membranes.

The number of placentas and gestational sacs are also important diagnostic indicators in twin pregnancies. Firstly, the presence of two placentas strongly suggests a dichorionic pregnancy, as each fetus typically has its own placenta. Conversely, a single placenta usually indicates a monochorionic pregnancy, where both fetuses share a single placental mass.

Similarly, the number of gestational sacs provides valuable information. In a DC pregnancy, where each fetus possess its individual amniotic sac, the presence of two gestational sacs is expected. On the other hand, in a monochorionic pregnancy, where both fetuses share the same chorionic and amniotic sacs, only one gestational sac is typically observed. Determining the sexes of the fetuses can also provide valuable diagnostic information. Dizygotic twins, characterized by different sexes, strongly suggest a dichorionic pregnancy.

Indeed, while determining chorionicity is relatively straightforward, discerning amnionicity poses a greater challenge in twin pregnancies. To determine amnionicity, clinicians typically search for the presence of a thin intertwin amniotic membrane. If such a membrane is observed,

it suggests diamniotic twins, indicating that each fetus has its own amniotic sac. Conversely, the absence of a discernible intertwin amniotic membrane suggests a monoamniotic pregnancy, where both fetuses share a single amniotic sac.

In instances where the intertwin amniotic membrane is not readily discernible during ultrasound assessments, caution must be exercised in excluding a DCDA pregnancy. This vigilance is justified as it is possible for one of the twins to be affected by severe oligohydramnios, potentially resulting in adhesion of the membrane to the affected twin. This circumstance raises concerns regarding the development of TTTS, a condition wherein one twin experiences an excessive influx of blood while the other encounters a deficiency. Further explanations on twin-twin transfusion syndrome will be provided in subsequent sections, encompassing its pathophysiology, diagnostic criteria, and therapeutic interventions.

Another important diagnostic marker is the count of yolk sacs. In monoamniotic pregnancies, only one yolk sac is typically observed. Conversely, in diamniotic pregnancies, two yolk sacs are generally present.

A further technique to identify a monochorionic monoamniotic pregnancy is to look for cord entanglement using color Doppler ultrasonography. This technique utilizes Doppler technology to visualize the blood flow within the umbilical cords of the fetuses. Cord entanglement, where the umbilical cords of the twins become intertwined, is a characteristic feature of monochorionic monoamniotic pregnancies.

The meticulous and repetitive diagnostic evaluations essential in twin pregnancies, particularly for determining chorionicity and amnionicity, play a critical role due to the complexities involved. This is especially significant in rare scenarios like MCMA twins, which pose heightened risks for both maternal and fetal well-being. These evaluations, typically employing several ultrasound assessments are crucial for early identification and management of potential complications, ultimately ensuring optimal outcomes for both mother and babies. (8-10).

3.3 Other diagnostic tests in twin pregnancies

In addition to establishing chorionicity, amnionicity, and zygosity, conducting further diagnostic tests is crucial in multiple pregnancies. Given the heightened risk of complications,

congenital abnormalities, and specific syndromes associated with multiple pregnancies, these tests require a careful approach similar to that of singletons but with increased attention. Early gestational age determination using crown-rump length (CRL) is essential for twin pregnancies. It guides prenatal care, detects growth discrepancies, and informs delivery timing. According to guidelines, it is recommended to conduct aneuploidy screening at 11 to 13 weeks and 6 days of gestation. This screening, known as the combined test, involves assessing various factors including nuchal translucency (NT), serum β-human chorionic gonadotropin (β-hCG), and pregnancy-associated plasma protein A (PAPP-A). In the case of dichorionic pregnancies, the combined test is performed for each fetus separately. However, in monochorionic pregnancies, the risk assessment is based on the pregnancy as a whole rather than on individual fetuses. (11) Additionally, cell-free DNA (cfDNA) testing involves analyzing maternal blood, which contains DNA fragments from the placenta, for the screening of aneuploidy. This test offers a higher detection rate than the combined test, as it can detect chromosomal abnormalities with higher accuracy. (9)

In multiple pregnancies, serum screening for genetic anomalies may not be as reliable as it is for singletons. If the combined test yields a positive result, more accurate but invasive options such as chorionic villus sampling (CVS) and amniocentesis are available for detecting genetic abnormalities. During these procedures, a sample can be obtained from one sac in monochorionic pregnancies. However, in dichorionic pregnancies, samples must be collected from both sacs for a comprehensive assessment. Cordocentesis, typically performed after 18 weeks gestation, directly samples fetal blood from the umbilical cord, providing additional information when other tests such as amniocentesis and CVS yield inconclusive results. (11)

In twin pregnancies, vigilant screening for fetal abnormalities is imperative due to increased risk, especially in monozygotic twins. These risks include a spectrum of conditions such as gastrointestinal wall defects, neural tube abnormalities, neurological conditions, cleft palates, and cardiac defects. Therefore, meticulous anatomical examination, including thorough assessment of all fetal body structures and particularly the four chambers of the heart during ultrasound evaluations, is essential. Moreover, because twins are more likely to suffer from growth restriction, it is crucial to continuously observe the amount of amniotic fluid in each sac during the second trimester. This necessitates specific evaluations such as measuring the deepest vertical pocket (DVP), assessing umbilical artery pulsatility by Doppler ultrasound, and examining the condition of the fetuses' bladder, also using ultrasound. (12) Additionally,

monitoring the mother's cervical length (CL) throughout pregnancy is vital. Mothers carrying twins face an elevated risk of cervical insufficiency, which can precipitate in preterm delivery. Cervical length is frequently measured by transvaginal ultrasonography, especially in women with short cervixes. (11,13)

3.4 Complications associated with twin pregnancies

Complications in twin pregnancies surpass those in singleton pregnancies significantly, leading to elevated rates of mortality and morbidity for both the mother and the fetuses. The maternal mortality rate is notably doubled compared to those carrying singletons. This heightened risk is attributed to various factors including hypertensive disorders, gestational diabetes, postpartum hemorrhage, anemia, placental abruption, and numerous other complications. (14)

Similarly, fetuses in twin pregnancies face substantially greater risks compared to singletons, with a markedly increased likelihood of preterm birth. Compared to singletons, twins are still more likely to suffer from necrotizing enterocolitis and intraventricular hemorrhage even if they are born at the same gestational age. Moreover, twins are more predisposed to experience fetal growth restrictions, intrauterine death, cerebral palsy, and congenital abnormalities. Additionally, they are susceptible to specific complications unique to multiple pregnancies, which will be further elucidated in subsequent discussions.

In addition to the mentioned risks, it's important to note that monochorionic pregnancies carry even higher mortality and morbidity rates compared to dichorionic pregnancies. In fact, the mortality and morbidity rates in monochorionic pregnancies are three to five times higher than in dichorionic pregnancies. (15,16)

Twin pregnancies, particularly in cases of monochorionicity, show an increased incidence of complications, such as:

- Fetal growth restriction (FGR): FGR stands as a prominent contributor to morbidity and mortality rates among twins, presenting a significantly heightened risk compared to singletons. In fact, the likelihood of FGR occurring in twins is approximately ten times greater than in singleton pregnancies. This condition occurs when one or both fetuses are below the 10th percentile for their gestational age. FGR can be classified into two types: symmetrical which is the less common form (20-30%) and affects all growth parameters uniformly. It typically arises

from congenital anomalies, TORCH infections, maternal diseases, or substance abuse, and it manifests early in pregnancy. And asymmetrical FGR which is more common (70-80%), this form usually results from placental insufficiency and appears later in pregnancy. It is characterized by a reduction in one or more specific parameters measured during the ultrasound. To assess FGR, we perform ultrasound biometry, focusing on measurements such as biparietal diameter, head circumference, and especially abdominal circumference, which is the most reliable indicator. Additionally, we evaluate the amniotic fluid volume. If the ultrasound indicates fetal anomaly or polyhydramnios, we then investigate potential causes, such as aneuploidy, genetic syndromes, and infections. Following the exclusion of these variables, we use Doppler ultrasonography to assess the blood flow in the middle cerebral artery and umbilical artery. A positive Doppler result typically indicates that FGR is due to placental insufficiency. (17-19)

- Fetal malformations: Twin pregnancies exhibit a twofold increased risk of fetal malformations compared to singleton pregnancies. This elevated risk persists within twins, with a particularly heightened incidence observed in monochorionic twins compared to dichorionic twins, where the risk is doubled. Among the range of observed malformations, common occurrences encompass cardiovascular anomalies, central nervous system anomalies, genitourinary and digestive system anomalies, alongside musculoskeletal abnormalities. (20)
- Miscarriage and fetal loss: Twins have a higher risk of miscarriage and fetal loss, with monochorionic twins being particularly vulnerable. The probability of early fetal loss in MC twins is ten times greater than in DC twins. (21)
- Preterm delivery and perinatal mortality: Twins have a higher likelihood of premature delivery due to various factors such as increased uterine distension and cervical insufficiency. Additionally, certain biochemical agents, including corticotropin-releasing hormone (CRH) from the larger placental mass and fetal lung surfactant protein A, which increases uterine contractility, play a role. These factors contribute to increased chance of delivering prematurely with subsequent increase in perinatal mortality rate in twins that is three times higher than in singletons. More specifically, 10% of twin pregnancies end in delivery before 32 weeks, and around half of twin pregnancies end in delivery before 37 weeks. (22)
- Twin-twin transfusion syndrome (TTTS): discussed in detail in the next chapter.
- Twin reversed arterial perfusion sequence (TRAP): Twin reversed arterial perfusion (TRAP) sequence is a rare complication occurring in approximately 1-2% of monochorionic twin pregnancies. It is characterized by one twin with a normal cardiovascular system and the other, known as the acardiac twin, which lacks direct vascular connections to the placenta and survives

only through retrograde arterial perfusion from the “pump” twin. The fetal circulations are interconnected by arterioarterial placental anastomoses, allowing blood to flow retrogradely from the “pump” twin to the acardiac twin. This situation places a significant burden on the heart of the healthy twin, potentially leading to heart failure and a perinatal mortality rate of 35 to 55%. Pathologically, the TRAP sequence is related to calcified, aberrant villi and a widespread thrombotic vasculopathy that affects the chorionic plate's blood vessels. Doppler ultrasonography is used to establish the diagnosis as it may indicate that the acardiac twin's umbilical artery has reversed flow. The acardiac twin invariably has a mortality rate of 100%, making close monitoring of the healthy twin crucial to reduce mortality risks. The degree of weight discordance between the twins correlates with increased mortality risk. The risk of perinatal mortality is directly proportional to the weight of the acardiac fetus. Treatment involves radiofrequency ablation to separate the abnormal vascular connections between the twins. (23)

- Neurologic disorders: Cerebral palsy is eight times more common in twins than in singletons, especially in monochorionic twins. This increased risk is due to imbalanced blood flow in the placental anastomoses, leading to ischemia. (24)
- Gastrointestinal diseases such as necrotizing enterocolitis: Necrotizing enterocolitis (NEC) is more common in infants who are small for gestational age, and thus, its incidence is higher in twins. Pathologically, this increased risk is thought to be related to changes in fetal circulation caused by placental anastomoses, leading to episodes of hypovolemia. This hypovolemia can contribute to the development of the necrosis, edema, and hemorrhage characteristic of NEC. (25)

Regarding the mother, there is a higher risk of:

- Hypertensive disorders: Women pregnant with twins are at a significantly higher risk of developing hypertensive disorders. Specifically, if they are primigravida, they have a fivefold increased likelihood of experiencing such conditions compared to those carrying singletons. For multigravida women, the risk is ten times higher with twin pregnancies than with singletons. (24)
- Placental abruption and post-partum hemorrhage: Mothers carrying twins face a 1-2% risk of experiencing placental abruption, compared to a 0.38-1% risk in those with singleton pregnancies. Additionally, women with twin pregnancies have a 2 to 4 times higher likelihood of developing postpartum hemorrhage than those with singletons. (26,27)

- Gestational diabetes: Between 3% and 9% of mothers carrying twins may develop gestational diabetes. This arises because pregnancy naturally induces heightened insulin resistance, and when expecting twins, the pancreas may struggle to meet the increased demand. (28)
- Anemia: In women expecting twins, there is a notable rise in maternal blood volume compared to that in a single pregnancy. Consequently, this increase leads to a decrease in hemoglobin concentration. (24)
- Maternal mortality: Maternal mortality rates are twice as high in pregnancies with twins compared to singleton pregnancies. (24)

3.5 Specific complication of monochorionic twin pregnancies: Twin-Twin Transfusion Syndrome (TTTS)

TTTS is a serious and distinct complication of MC twin pregnancies. The unequal distribution of blood flow in monochorionic twins can result in a variety of vascular complications given that they share a single placenta with interconnected blood arteries. Although all MC twins have placental vascular anastomoses, TTTS arises from an imbalance in these vascular connections, resulting in one twin receiving less blood from the placenta (the donor) and the other receiving more blood (the recipient). TTTS is a relatively common complication in MC twins, that typically appears in the second trimester, between the 15th and 25th weeks of gestation. This condition causes a significant disparity in blood flow between the twins. The donor twin suffers from oligohydramnios and oliguria, while the recipient twin experiences polyhydramnios, which can lead to cardiac issues and fetal hydrops. In recent years, there have been significant advancements in the treatment of TTTS, improving outcomes for affected pregnancies. However, severe short and long-term complications can still occur. These complications mainly include cardiac, renal, and neurological impairments, resulting from the unequal distribution of oxygen and nutrients between the twins. Despite therapeutic improvements, managing TTTS remains challenging due to the complex nature of the disease and its potential impacts on fetal development. (29-31)

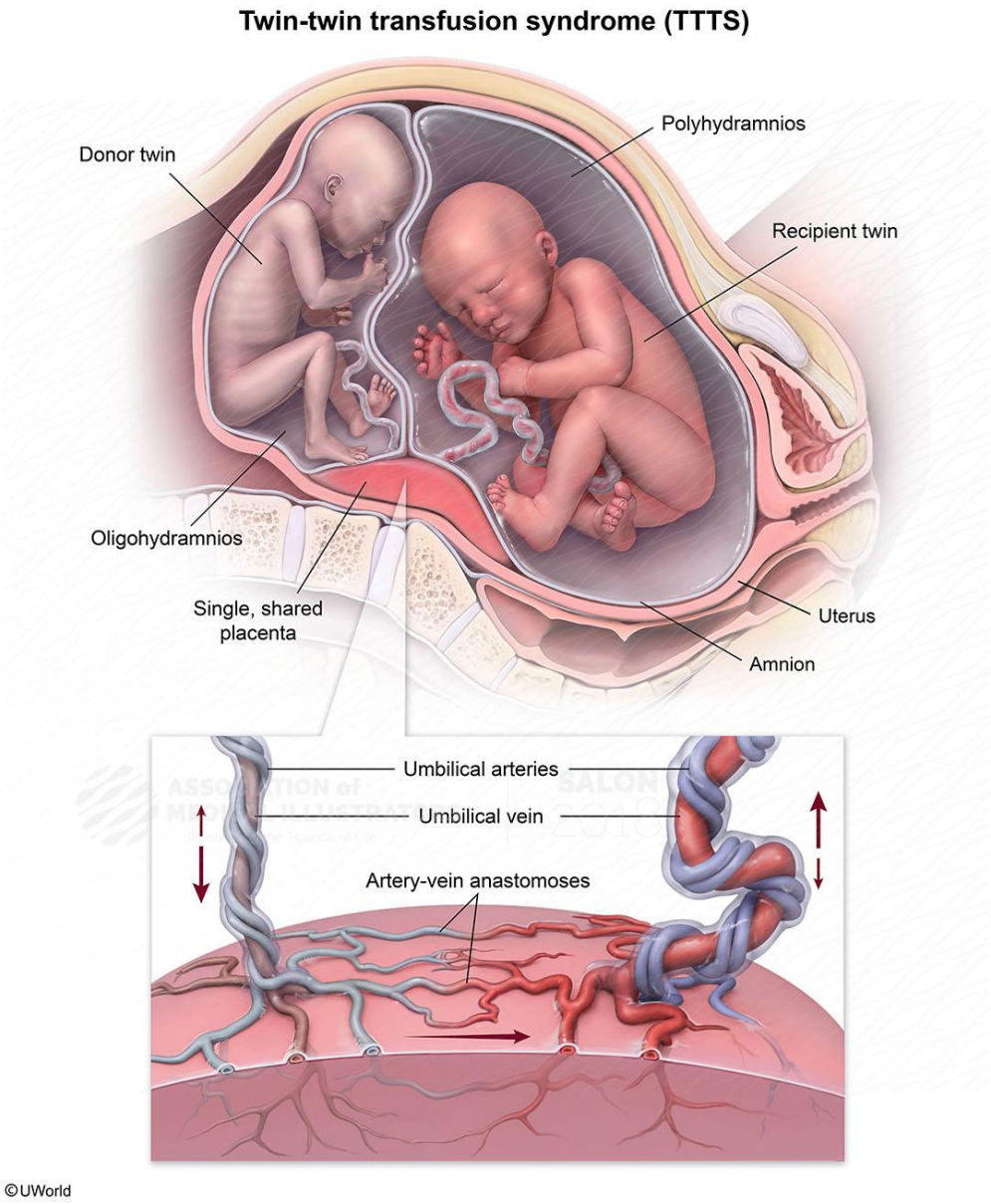

Figure 3: Twin-twin transfusion syndrome (TTTS)

3.5.1 Prevalence, risks and outcomes

TTTS affects approximately 1 in 2000 pregnancies, or 10% to 15% of all monochorionic pregnancies. While it primarily manifests in MCDA twins due to the shared placenta and vascular connections, TTTS has been exceptionally rare in MCMA twin pregnancies. This syndrome is responsible for 17% of perinatal mortality in twin pregnancies. Without treatment, TTTS has an alarmingly high mortality rate of 80% to 100%. Even with intervention, there remains a significant risk of complications, both due to TTTS itself and the high likelihood of

preterm delivery, which is the most common complication, occurring in about 27% to 44% of cases.

Other frequent complications include respiratory distress syndrome (27% to 62%), renal failure (5% to 7%), necrotizing enterocolitis (3% to 4%), pulmonary hypertension (3%), and severe intraventricular hemorrhage (4% to 34%). These complications highlight the severe impact TTTS can have on neonatal health, largely due to the uneven distribution of blood flow and the consequent disparities in oxygen and nutrient supply between the twins. (29,32,33)

3.5.2 Pathophysiology

In monochorionic twin pregnancies, the placental angioarchitecture includes several types of vascular anastomoses that are crucial for balancing blood flow between the twins. These connections, which facilitate the exchange of blood, are categorized into arterio-venous (AV), arterio-arterial (AA), and veno-venous (VV) anastomoses.

Anastomoses known as arterio-venous (AV) connect one twin's arterial supply to the other twin's venous drainage. They are found more deeply and are usually unidirectional. Notably, they exhibit high resistance—up to 20 times more than AA anastomoses. This intricate network links the arterial and venous ends of each fetus in a capillary network within the villi of the chorionic plate.
Conversely, bidirectional and superficial arterio-arterial (AA) and veno-venous (VV) anastomoses enable balanced blood flow between the twins. These anastomoses have low resistance and they can become unidirectional if there is a change in blood pressure. This bidirectional nature typically facilitates a balanced exchange of blood, preventing significant discrepancies in blood volume between the twins. (33,34)

However, in the case of TTTS, there is a significant imbalance due to the absence or scarcity of AA and VV anastomoses and the presence of usually one or more deep AV anastomoses. Furthermore, blood flow changes can be chronic, as in TTTS, or sudden, as in co-twin demise, which is the death of one of the fetuses.

Research indicates that the presence of arterio-arterial (AA) anastomoses detected through Doppler ultrasound reduces the probability of developing TTTS ninefold.

One study showed that 70% of twins with TTTS had a single deep AV anastomosis and a very small number of AA and VV anastomoses, whereas uncomplicated monochorionic (MC) pregnancies typically had multiple anastomoses, particularly those superficial ones. (32)
Studies have demonstrated that uncomplicated MC pregnancies generally have more anastomoses than TTTS pregnancies, suggesting that a higher number of AA, VV, and AV anastomoses provides a protective balance of blood flow between the twins. (29,32)
This also explains why TTTS occurs more frequently in MCDA twins and not in MCMA twins. Although very rare, TTTS has been documented in MCMA twins. The different angioarchitecture of the placenta of MCMA twins, which includes a greater number of both deep and superficial anastomoses, particularly AA and VV anastomoses, supports the idea that a higher number of these connections helps maintain blood flow balance and prevents TTTS. (35,36)

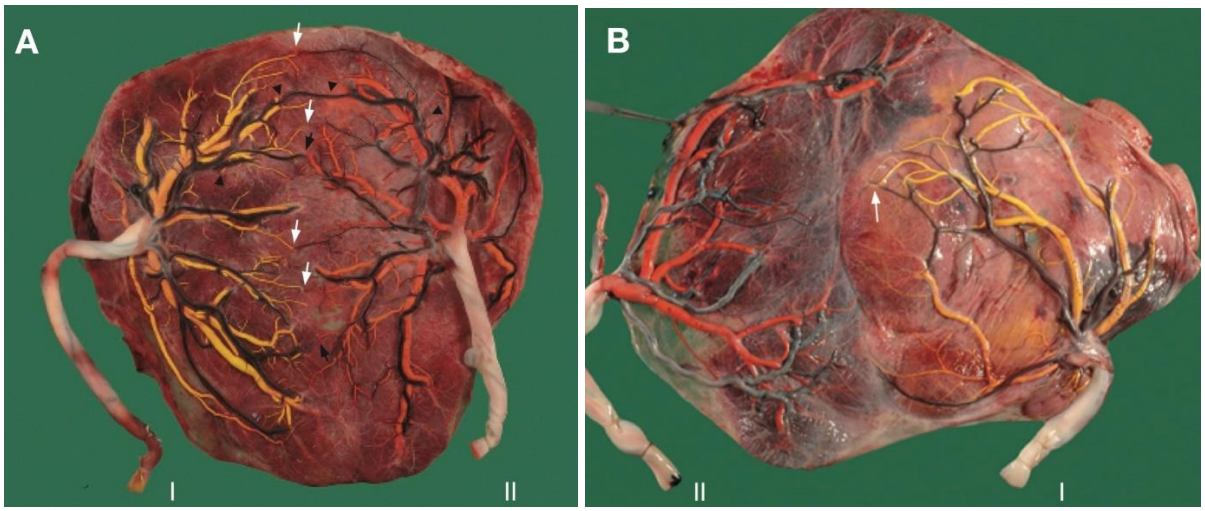

Figure 4: placenta of MCDA twins without TTTS. There is an AA anastomosis (black arrowheads) and several AV anastomoses in both directions (white and black arrows). (A). Placenta of MCDA twins with TTTS. Only a small AV anastomosis is present (white arrow). The recipient part of the placenta is dark and the donor part is pale. (B)

Understanding the complex interplay of placental anastomoses in monochorionic twin pregnancies is essential for predicting and managing conditions like TTTS. This chapter researches the significance of these vascular connections and their implications for the development and management of TTTS, highlighting the importance of a comprehensive understanding of placental angioarchitecture in ensuring favorable pregnancy outcomes.

In addition to changes in placental angioarchitecture, another crucial pathophysiological factor is the fetal adaptive response, particularly the renin-angiotensin-aldosterone system (RAAS). After discussing the imbalance in blood flow between the twins, it is important to consider the consequences of this condition. As mentioned, the donor twin becomes oliguric and develops oligohydramnios, while the recipient twin experiences polyhydramnios.

For the donor twin, decreased blood volume leads to reduced renal perfusion. This hypoperfusion increases the risk of renal dysgenesis due to tubular degeneration, loss of glomeruli, and cell apoptosis. To compensate, the RAAS is activated to restore normal volume, causing vasoconstriction that further worsens blood flow to the kidneys and placenta. This exacerbates the donor twin's oliguria, oligohydramnios, and restricted fetal growth.

On the other hand, the recipient twin experiences polyhydramnios and hypervolemia, which typically downregulates the RAAS system. However, studies have found that recipient twins often exhibit elevated levels of renin and angiotensin II, along with kidney lesions characteristic of hypertensive microangiopathy. This paradox initially suggested that renin might be transferred from the donor twin to the recipient. However, this theory was discredited due to the short half-lives of renin (up to 90 minutes) and angiotensin II (approximately 4 minutes), making sustained transfer via the generally slow blood flow unlikely.

Recent research proposes a new theory involving a placental RAAS system, suggesting that the recipient twin is exposed to RAAS components synthesized within the placenta. This theory is supported by findings that both donor and recipient twins show similarly elevated levels of renin and angiotensin II. This discovery provides significant insights into the pathophysiology of TTTS, explaining why both twins exhibit increased RAAS components despite having opposite clinical features. The hypothesis of a placental RAAS system explains the simultaneous presence of high RAAS components in both twins, resolving the apparent contradiction and highlighting the complexity of TTTS. This new understanding underscores the importance of the placental environment in the disease's progression and offers potential avenues for targeted therapeutic interventions. (32,37,38)

Additionally, it has been demonstrated that recipient twins have higher concentrations of endothelin-1 and natriuretic peptides, including brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP).

These markers were found to be double the amount in recipient twins compared to donor twins and were even higher in those recipients who also exhibited fetal hydrops. These substances are indicators of cardiac disorders and are consistent with the clinical findings in recipient twins. Moreover, they correlate with the amount of amniotic fluid present in the twins, underscoring their significance. The evidence presented above indicates that these vasoactive mediators are important factors in the pathophysiology of TTTS, since they contribute to the twins' differences in blood flow and fluid regulation. (32)

3.5.3 Clinical picture

As discussed in the previous chapter, the clinical presentation of twins affected by TTTS is markedly different between the donor and recipient. The donor twin exhibits oliguria, hypovolemia, oligohydramnios, and fetal growth restriction. In contrast, the recipient twin displays hypervolemia, polyuria, and polyhydramnios.
This chapter will now delve into more specific findings, particularly those involving the cardiovascular system of the twins.

The donor twin, compared to the recipient twin, presents with a much milder cardiovascular profile. Abnormal echocardiography findings are rare in donor twins. However, a common issue is decreased renal perfusion, which, as previously mentioned, leads to tubular degeneration, loss of glomeruli, and cell apoptosis, potentially resulting in renal dysgenesis. Nevertheless, the persistent hypovolemia and hypoperfusion in donor twins lead to endothelial dysfunction and chronic activation of the RAAS, which can damage the arterial system and cause vascular stiffness. Despite these issues, cardiac functions, including both ventricular and valvular functions, are typically preserved in the donor twin.

The recipient twin presents a significantly more intricate cardiovascular profile, which can potentially lead to fatal outcomes. Hypervolemia induces volume overload, stretching the myocardium and resulting in cardiac hypertrophy in 18 to 49% of cases, making it the most prevalent feature. Additionally, tricuspid regurgitation occurs in 35 to 50% of cases, mitral regurgitation in 13 to 15%, and an increased cardiothoracic ratio is observed in approximately 47% of cases. As the severity progresses, worsening cardiac hypertrophy can also lead to pulmonary stenosis, which, over time, may culminate in right ventricular outflow tract obstruction, occurring in 9% of cases. (32-34,38,40)

Maternal symptoms, while not very specific, are also observable. Among these, weight gain occurs in 76% of cases, stomach pain in 58%, and swelling in an equal percentage. Additionally, abdominal circumference increases rapidly due to the larger amount of amniotic fluid present. Other symptoms may include decreased fetal movement, abdominal cramps and contractions, leg edema, and dyspnea. However, it remains uncertain whether these symptoms are attributable to TTTS, other common complications, or the inherently high-risk nature of monochorionic pregnancies. (39)

3.5.4 Diagnosis and stages of TTTS

To diagnose TTTS, certain criteria must be met. These include confirming monochorionicity and assessing amniotic fluid levels via ultrasound. In TTTS, one twin typically exhibits polyhydramnios, defined as a deepest vertical pocket of at least 8 centimeters, while the other twin demonstrates oligohydramnios, with a deepest vertical pocket of less than 2 centimeters. Additionally, it is crucial to examine the fetal bladder: the donor twin's bladder may be very small or non-visible, while the recipient twin's bladder often shows a clear increase in size. (32,33)

When assessing amniotic fluid and chorionicity, it is crucial to examine carefully, as severe hypovolemia in the donor twin can cause the amniotic membrane to adhere to the twin, potentially misleading the ultrasound interpretation as monoamnionicity. This condition, known as “stuck twin” syndrome, generally indicates a poor prognosis. (36)

Additionally, observing growth discordance between the twins can provide important clues. If the difference in growth exceeds 20%, it is significant and warrants further investigation for other indicators that confirm TTTS.

In Doppler flowmetry ultrasound, it is essential to examine the umbilical artery, umbilical vein, ductus venosus, peak systolic velocity, and middle cerebral artery. The umbilical artery is particularly important for predicting the likelihood of fetal hydrops. Critically abnormal Doppler findings include reversed or absent end-diastolic velocity in the umbilical artery, pulsatile flow in the umbilical vein, and reversed flow in the ductus venosus. Additionally, assessing the middle cerebral artery is valuable for predicting periventricular leukomalacia, a common complication in TTTS. (43,44)

Other useful markers for predicting TTTS during the first trimester of pregnancy include the E/A ratio. This ratio compares the blood flow peak in early diastole (E) and the blood flow peak in late diastole caused by atrial contraction (A). It provides insight into the heart's diastolic function and helps identify potential issues with the tricuspid valve. (41)

Additional markers for diagnosing TTTS include nuchal translucency (NT) discordance of more than 20%, which indicates different volumes between the twins. It is also crucial to monitor for cardiac involvement and if there is pleural or pericardial effusion, particularly in the recipient twin. This ultrasound check-up should be performed every two weeks to promptly detect any complications. Furthermore, it is important to look for signs of fetal hydrops, which signify a severe stage of the disease. Fetal hydrops can manifest as ascites and edema of the skin on the scalp and/or abdomen. (41,42,44)

It is also important to consider a hemoglobin level discordance of more than 5 g/dL, although this alone cannot be used as a diagnostic factor for TTTS. Additionally, MRI can be utilized in the second trimester to provide more detailed information about fetal complications, as it does not involve radiation. However, MRI is not commonly used as a standard diagnostic imaging tool. (32,43)

Four different staging systems are available for categorizing the severity of TTTS, each with its own variations. The Quintero classification is the most widely utilized, followed by the Cincinnati classification, the Cardiovascular Profile Scoring (CVPS) classification, and finally the Children's Hospital of Philadelphia (CHOP) classification. (32)

QUINTERO CLASSIFICATION

Table 1: Quintero classification

Stages	Donor bladder	Amniotic fluid Donor/Recipient	Doppler wave forms	Other
I	Visible	Oligohydramnios/ polyhydramnios	Normal	/
II	Not visible	Oligohydramnios/ polyhydramnios	Normal	/

III	Visible or not visible	Oligohydramnios/ polyhydramnios	Abnormal	/
IV	/	/	/	Fetal hydrops or abdominal ascites
V	/	/	/	Demise of either fetus

The Quintero classification is essential for tracking disease progression in TTTS; however, it has limitations as it does not consider survival rates. Typically, more advanced stages indicate a poorer prognosis. The classification overlooks factors such as growth discordance between the twins, Doppler flowmetry ultrasound findings, and fetal echocardiography results. Despite its widespread use, physicians should recognize these omissions and ensure that these factors are separately and carefully evaluated. (32,34,35,42)

CINCINNATI CLASSIFICATION

Table 2: Cincinnati classification

Stage	Donor	Recipient	Recipient cardiomyopathy
I	Oligohydramnios (deepest vertical pocket <2cm)	Polyhydramnios (deepest vertical pocket >8 cm)	No
II	Bladder not visible	Bladder visible	No
III	Abnormal doppler	Abnormal doppler	None
IIIA			Mild
IIIB			Moderate
IIIC			Severe
IV	Hydrops	Hydrops	
V	Death	Death	
Variables			
Cardiomyopathy	Mild	Moderate	Severe
AV regurgitation	Mild	Moderate	Severe
RV/LV thickness[a]	>2 + Z-score	>3 + Z-score	>4 + Z-score

MPI	>2 + Z-score	>3 + Z-score	Severe biventricular dysfunction

Abbreviations: AV, atrioventricular; MPI, myocardial performance index, RV/LV, right ventricle, left ventricle. Z-score – standard deviation.

[a] normal value for RV: 0.32±0.08 and normal value for LV: 0.33 ± 0.05

The Cincinnati classification is a valuable alternative for assessing TTTS as it incorporates fetal echocardiography and accounts for various severities of cardiomyopathy. This comprehensive approach provides a more detailed understanding of the condition, allowing for better evaluation and management of the disease. (32)

CARDIOVASCULAR PROFILE SCORING (CVPS) CLASSIFICATION

Table 3: Cardiovascular profile scoring (CVSP) classification

Findings	Normal (2 points each)	1-Point deduction	2-Point deduction
Hydrops fetalis	None	Ascites; pleural and pericardial effusion	Skin edema
Venous doppler	Normal	Ductus venosus atrial systolic reversal	Umbilical venous pulsations
Cardiothoracic ratio	<0.35	>0.35 and <0.5	>0.5
Cardiac function	Ventricular SF >0.28 and valve regurgitation	SF <0.28 or TR or semilunar valve regurgitation	TR plus dysfunction or any mitral regurgitation
Arterial doppler	Normal	Absent end-diastolic flow in the umbilical artery	Reverse end-diastolic flow in the umbilical artery

Abbreviations: SF-shortening fraction; TR-tricuspid regurgitation.

The Cardiovascular Profile Score (CVPS) classification typically consists of 10 points, with deductions made for encountered pathologies. This staging system stands out for its inclusion of fetal echocardiography, Doppler flowmetry ultrasound, and assessment of fetal hydrops. It serves as a valuable tool in predicting survival rates in cases of TTTS. (32)

CHILDREN'S HOSPITAL OF PHILADELPHIA (CHOP) CLASSIFICATION

Table 4: Children's hospital of Philadelphia (CHOP) classification

Recipient	0 point	1 point	2 points
Ventricular findings			
Cardiac enlargement	None	Mild	>Mild
Systolic dysfunction	None	Mild	>Mild
Ventricular hypertrophy	None	Present	
Valve function			
Tricuspid regurgitation	None	Mild	>Mild
Mitral regurgitation	None	Mild	>Mild
Venous doppler findings			
Tricuspid valve inflow	2 Peaks	1 Peak	
Mitral valve inflow	2 Peaks	1 Peak	
Ductus venous	All forward	Decreased atrial contraction	Reversal
Umbilical vein	No pulsations	Pulsations	
Great vessels findings			
Outflow tracts	PA>AO	PA=AO	PA<AO, RVOTO
Pulmonary insufficiency	Absent	Present	
Donor twin			
Umbilical artery	Normal	Decreased diastole	Absent or reverse end-diastolic flow

Abbreviations: AO-aorta; PA-pulmonary artery; RVOTO-right ventricular outflow obstruction.

The Children's Hospital of Philadelphia (CHOP) classification combines nine fetal echocardiography pathological findings with four ultrasound pathological findings. While each of the four classifications offers valuable insights, it's important to note that they all have limitations, with Quintero classification having the most. There is no definitive evidence to determine the superiority of one classification over the others. Therefore, it is recommended to

consider all available classifications to ensure a comprehensive diagnostic approach to TTTS. (32)

3.5.5 Treatment of TTTS

AMNIOREDUCTION

Amnioreduction was the first proposed treatment for TTTS, primarily aimed at alleviating maternal symptoms caused by excessive amniotic fluid and prolonging the pregnancy to avoid preterm delivery, since PROM is the most common complication of TTTS. This procedure involves inserting a fine needle under ultrasound guidance to monitor the depth and location. The needle is used to drain the excess amniotic fluid into a collection bag, while the amniotic pressure is measured using a water manometer at the needle tip. The volume of fluid removed varies significantly among patients, typically ranging from 700 ml to 4500 ml. There are no strict guidelines on the exact amount of fluid to be drained, as it depends on the individual patient's condition and her excess fluid volume. The general approach is to reduce the amniotic fluid pressure, guided by the deepest vertical pocket on ultrasound. This procedure usually doesn't last more than 30 minutes. Survival rates for amnioreduction vary widely due to the limited number of patients in studies. One study reported survival rates ranging from 37% to 83%, while another found rates between 53% and 78%. Overall, this treatment helps improve blood flow between the twins, promoting a better equilibrium and enhancing their chances of survival. But it is advised for moderate stages of TTTS and the problem is that often this procedure has to be retaken since the accumulation of amniotic fluid will happen again probably. Other complications after this procedure are placental abruption and infection, however they occur rarely. (32,45)

MICROSEPTOSTOMY

Microseptostomy is a procedure in which a hole is created in the intertwin membrane to allow fluid to flow from the polyhydramniotic twin to the oligohydramniotic twin. This technique can be employed when amnioreduction has failed, to avoid repeating the amnioreduction procedure. The primary risk associated with microseptostomy is the potential enlargement of the hole, which can lead to a large septostomy or, in rare cases, complete disruption of the intertwin membrane, resulting in the twins becoming monoamniotic. Due to these risks, microseptostomy is not commonly used. Other potential complications are similar to those seen with

amnioreduction, such as placental abruption and infection, although these are infrequent. The survival rate following microseptostomy is approximately 65%. (32)

FETOSCOPIC LASER PHOTOCOAGULATION (FLPC)

FLPC, the first-line treatment for TTTS, involves ablating all of the vascular anastomoses with ultrasound guidance in a minimally invasive procedure. The process begins by administering local anesthesia to the mother, followed by a small incision to insert the cannula. The intertwin membrane can be located by orienting the scope along an imaginary line that connects the two locations where the umbilical cord inserts into the donor twin at a right angle to its longitudinal axis. Once the intertwin membrane is identified, the laser is positioned directly on the targeted vessel at a 90-degree angle, approximately 1 to 2 centimetres from the anastomosis. The laser is then fired, and successful ablation is confirmed when the vessel turns white. Due to potential interference from fetal and maternal movements, breathing, or placental positioning, achieving this outcome often requires three or four attempts. After completing the ablation, the amniotic fluid is drained until the deepest vertical pocket measures approximately 5 to 6 centimetres. In cases where the cervix is less than 15 millimeters in length, indicating a risk of cervical insufficiency, a cervical cerclage is recommended prior to the laser procedure. The entire process typically lasts about one hour; however, longer durations can increase the likelihood of complications. Following the procedure, patients are usually discharged after one to two days but must return to the hospital for weekly check-ups to monitor for any potential complications.

FLPC is considered the first-line treatment for TTTS due to the proven Doppler ultrasound changes observed after the procedure. However, it carries several complications, including a higher risk of premature rupture of membranes (PROM), with a 23% risk attributed in part to the larger size of the fetoscope. Additional risks include the possibility of the laser ablating normal anastomoses, which can increase the donor twin's risk of placental insufficiency, and the potential for missing abnormal anastomotic vessels, thereby inadequately treating TTTS.

Compared to non-selective laser coagulation, which has a survival rate of 61%, selective fetal laser photocoagulation (SFLPC), which targets only abnormal anastomoses, has shown an 83% survival rate for at least one twin. Non-selective fetal laser coagulation involves ablating all blood vessels that traverse the intertwin membrane. Despite this approach, deep anastomoses can be missed in approximately 20% of cases, making the procedure complex and necessitating performance by highly experienced practitioners. Consequently, experts recommend combining

selective and non-selective fetal laser coagulation for optimal outcomes. The rate of neurodevelopmental impairment following this treatment is reported to be as high as 11% according to one study. This procedure is advised for patients classified from Stage II to Stage IV TTTS, though there is no consensus on the optimal therapy for Stage I patients. Compared to amnioreduction, fetoscopic laser coagulation offers a more durable solution when all pathological anastomoses are accurately visualized and ablated, whereas amnioreduction typically requires repetition. (32,37,43,46)

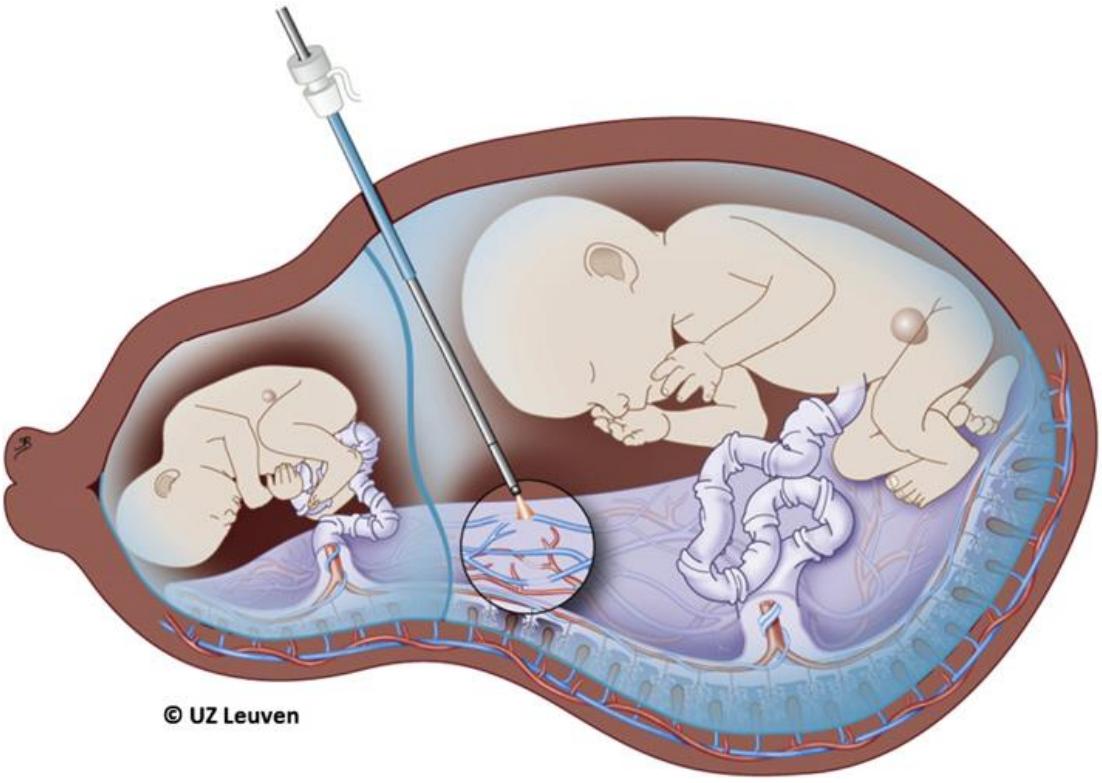

Figure 5: Fetoscopic laser coagulation in TTTS

FETOSCOPIC CORD COAGULATION

This treatment is reserved for extremely severe cases when there is no chance of survival for the recipient twin due to advanced cardiomyopathy. It is also indicated in situations where fetoscopic laser coagulation of the anastomotic vessels has been unsuccessful, resulting in the death of one twin. In such cases, the receiving twin's umbilical cord is cut, thereby sacrificing the recipient twin in order to safeguard the donor twin. Although this prognosis is largely dependent on the twins' gestational ages at the time of the surgery, the survival probability for the remaining twin can reach 80%. Several studies have indicated that the donor twin experiences complete re-establishment of amniotic fluid volume in 95% of cases. In spite of

that, ethical questions have been raised by experts regarding the sacrifice of one twin in this procedures for TTTS treatment. (32)

SEQUENTIAL TREATMENT

The sequential treatment approach, as proposed by the Fetal Care Center of Cincinnati, is tailored to individual patients based on echocardiography and Doppler ultrasound findings. Patients presenting before the 24th week of gestational age without severe cardiovascular abnormalities (classified from stage I to stage IIIA) are recommended to undergo amnioreduction as the first-line therapy, supplemented by regular echocardiography assessments. Conversely, patients under 24 weeks gestational age with severe cardiac abnormalities (stage IIIB, IIIC, or IV) are advised to undergo fetoscopic laser photocoagulation. For patients beyond the 24th week of gestational age, amnioreduction is suggested unless the condition is particularly severe. This approach is favored due to the relatively lower invasiveness of amnioreduction compared to fetoscopic laser coagulation. By initially opting for the least invasive treatment option suitable for the severity of the condition, the sequential approach aims to optimize patient outcomes while minimizing risks. If initial treatments prove unsuccessful, more invasive interventions are considered as necessary steps in the management process. (32)

3.5.6 Complications and prognosis of TTTS

One complication that can arise after the treatment of TTTS is twin-anemia polycythemia sequence (TAPS), in which one twin becomes anemic while the other develops polycythemia. Unlike TTTS, TAPS does not present with amniotic fluid abnormalities such as oligohydramnios or polyhydramnios. TAPS typically involves the persistence of residual unidirectional microanastomoses. This condition can occur following fetoscopic laser photocoagulation, with reported incidences ranging from 2% to 16%. Another study indicates that approximately 33% of cases exhibit these residual microanastomoses. TAPS tends to develop more gradually than TTTS and, notably, the mother does not experience any symptoms. Additionally the twin with polycythemia is at an increased risk of thrombotic events. The Leiden staging system, which uses Doppler ultrasonography to measure blood flow in the middle cerebral artery and is similar to the Quintero classification, provides the basis for TAPS diagnosis. In cases of TAPS, there is typically a discordance in blood flow, with the anemic twin exhibiting faster than normal flow and the polycythemic twin displaying slower than

normal flow. Consequently, it is imperative for mothers who have undergone fetoscopic laser coagulation to attend regular check-ups to monitor middle cerebral artery blood flow using Doppler ultrasound. There are no specific guidelines for the treatment of TAPS. However, potential management strategies include watchful waiting, intrauterine transfusion, and laser therapy. The Solomon technique, a novel approach, involves coagulating the vascular equator of the placenta and represents one such laser treatment option. Regular monitoring and individualized treatment plans are crucial for managing this condition effectively. (40,46)

Despite recent advancements in both diagnostic and therapeutic procedures TTTS, many of these treatments still carry significant consequences. While the previous chapter offered a detailed examination of these complications, a concise overview is provided below. Premature rupture of membranes (PROM) is the most common complication and poses a significant risk. Cardiovascular abnormalities are also common, including ventricular hypertrophy, pulmonary stenosis, and right ventricular outflow tract obstruction. Additionally, atrial and ventricular septal defects are frequently observed. (32,43)

Learning disabilities and reduced physical development can also occur, primarily due to premature delivery. Along with an elevated risk of acute kidney injury shortly after delivery and possible progression to chronic kidney failure, these infants also face an increased risk of chronic illnesses including diabetes and hypertension. (31,46,48) The risk of brain injury is high, with intraventricular hemorrhage, periventricular leukomalacia, and cerebral palsy being significant concerns. These conditions can lead to long-term neurodevelopmental impairments. (31,32,47)

Respiratory issues, including asthma and bronchopulmonary dysplasia, may also manifest. (43) Ophthalmologic problems, particularly retinopathy, and an increased risk of hearing loss are additional complications. Fetal hydrops poses a heightened risk, and ischemic limb conditions or gastrointestinal tract atresia, as well as necrotizing enterocolitis, are serious concerns. These complications underscore the complexity and risks associated with the treatment of TTTS, highlighting the need for careful monitoring and comprehensive post-treatment care. (31,32,43)

4.DISCUSSION

The incidence of TTTS is increasing, largely due to the rise in multiple pregnancies resulting from assisted reproductive technologies (ART) and the trend of growing maternal age. This increase necessitates enhanced diagnostic and treatment strategies to manage TTTS effectively. Diagnosing TTTS primarily relies on ultrasound techniques, identifying key indicators such as oligohydramnios and polyhydramnios in the twins. Doppler ultrasound is crucial for assessing blood flow patterns and early detection and staging of TTTS. Four staging systems are commonly used to classify TTTS severity, with the Quintero staging system being the most widely adopted method today.

Treatment strategies for TTTS have evolved significantly. Fetoscopic laser photocoagulation (FLPC) has emerged as the preferred intervention. This procedure involves the ablation of shared placental vessels to normalize blood flow between the twins. Studies have shown that FLPC improves survival rates and reduces neurological complications in surviving twins. However, FLPC carries risks, including PROM, preterm labor, and the possibility of incomplete laser ablation requiring repeat procedures.

A further therapeutic approach called amnioreduction includes draining excessive amniotic fluid from the recipient twin's sac in order to minimize polyhydramnios and alleviate mother discomfort. While amnioreduction provides temporary relief and delays TTTS progression, it does not address the underlying vascular connections and is less effective long-term compared to laser photocoagulation. Other treatments, such as fetoscopic cord coagulation or microseptostomy in severe cases, are also being explored, though they come with ethical and medical considerations.

Despite advancements, TTTS continues to pose significant risks, including preterm labor, neurological impairments, and long-term developmental issues in survivors. Many studies are conducted on small patient groups, leading to unclear data on treatment effectiveness and highlighting the need for more extensive studies on monochorionic twins. The limitations of current staging systems in predicting outcomes and guiding treatment effectively, coupled with the invasive nature of FLPC and its associated risks, mean that not all TTTS cases can be managed optimally.

From the literature reviewed, it is evident that while we have made significant strides in understanding and treating TTTS, ongoing research is essential to refine these methods and improve outcomes further.

5. CONCLUSION

TTTS represents a critical concern in the management of monochorionic twin pregnancies. The condition's pathophysiological complexity, characterized by an abnormal blood flow distribution between the donor twin and recipient twin, leads to a range of severe complications. The donor twin experiences hypovolemia, oliguria, and growth restriction due to reduced blood supply. In contrast, because of the increased blood flow, the recipient twin has cardiomegaly, polyuria, and hypervolemia. These complications underscore the importance of vigilant prenatal care and timely intervention.

Early diagnosis through detailed ultrasound monitoring and the use of staging systems like the Quintero classification are essential in guiding treatment decisions and improving outcomes. The role of ultrasound in identifying key markers of TTTS, such as polyhydramnios and oligohydramnios, or in severe cases the "stuck twin" phenomenon, is crucial for detecting TTTS at an early stage and intervening before the condition progresses.

Fetoscopic laser photocoagulation (FLPC) has revolutionized the treatment landscape for TTTS, offering a targeted approach to correcting the vascular imbalances that drive the syndrome. This procedure has improved survival rates and reduced the incidence of severe neurological outcomes, making it the preferred treatment option for many cases of TTTS. However, FLPC is not without risks; the potential for complications such as preterm labor and incomplete ablation, where some anastomoses are missed, necessitates a high level of expertise and experience.

Despite advancements in diagnosis and treatment, TTTS continues to pose significant challenges. The condition's inherent unpredictability and potential for long-term complications highlight the need for ongoing research and refinement of management protocols. Comprehensive postnatal follow-up is vital to address any developmental issues and ensure the long-term health of both twins.

This thesis has aimed to provide a detailed exploration of TTTS, drawing from current literature and clinical practices. By enhancing the understanding of TTTS and its management, healthcare providers can improve care for monochorionic twin pregnancies, ultimately ensuring better health outcomes. Continued advancements in ultrasound technology and a deeper understanding of placental vascular architecture are essential for further improving diagnostic accuracy and treatment outcomes for TTTS. Through ongoing research and collaboration among medical professionals, it is hoped that more refined and effective strategies will emerge, reducing the morbidity and mortality associated with this challenging condition.

6. SUMMARY

TTTS is a severe complication characterized by an imbalance in blood flow between the donor and recipient twins and it affects 10% to 15% of MC twin pregnancies. This imbalance arises due to the presence of abnormal vascular connections in the shared placenta, leading to one twin (donor) having insufficient blood and the other (recipient) receiving excess blood. Consequently, the donor twin often experiences oligohydramnios and growth restrictions, while the recipient twin suffers from polyhydramnios and potential cardiac pathologies.

The thesis explores the pathophysiology, diagnosis, and treatment of TTTS, highlighting the importance of early detection and intervention. The pathophysiology involves the presence of AV anastomoses, which are typically deep and unidirectional, creating a significant imbalance in blood flow between the twins. The presence of AA and VV anastomoses, which are more superficial and bidirectional, can mitigate this imbalance but are often scarce in TTTS cases.

Early diagnosis through detailed ultrasound monitoring is crucial. Key markers such as polyhydramnios and oligohydramnios, identified through staging systems like the Quintero classification and others, are vital for the early detection of TTTS. These systems guide the intervention process and improve treatment outcomes. The preferred treatment, fetoscopic laser photocoagulation (FLPC), aims to ablate the connecting vessels to balance the blood flow. While FLPC has significantly improved outcomes, it carries risks, including the potential for complications such as preterm birth, cardiac, renal, and neurological impairments, as well as missed anastomoses.

Despite advancements in diagnosis and treatment, TTTS remains a challenging condition. Ongoing research and refinement of management protocols are essential to improve long-term health outcomes for affected twins. This emphasizes the need for continuous advancements in therapeutic techniques and prenatal care strategies.

Key words: twin pregnancies, monochorionic twins, twin-twin transfusion syndrome (TTTS), vascular anastomoses, ultrasound diagnosis, fetoscopic laser photocoagulation (FLPC)

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8.CV

Katia Babin, born on October 21, 1997, in Trieste, Italy, began her academic journey at a local primary school, where she developed a keen interest in learning. She continued her education at a scientific high school, actively participating in the European Youth Parliament, which broadened her horizons and enhanced her critical thinking skills.

Katia subsequently began her medical studies in English at the University of Rijeka. From her first year, she pursued numerous internships in the Department of Orthopedics, gaining valuable hands-on experience. Her dedication to expanding her medical knowledge took her twice on exchange programs through the CROMsic initiative: first to Greece, where she worked in the Gynecology Department, and later to Finland, where she delved into Cardiology. Between her fifth and sixth year, Katia undertook an internship in Seoul, South Korea, in Gynecology, where she discovered a deep passion for the field and decided to specialize in it. These exchanges not only enriched her medical expertise but also exposed her to diverse cultures and perspectives. Most recently, Katia participated in the Erasmus Blended Program in Maribor, designed for students aspiring to specialize in Gynecology. This experience further solidified her commitment to her chosen field, equipping her with advanced knowledge and a broader understanding of different medical practices.