Chapter 7

Complications in Monochorionic Pregnancies

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Additional information is available at the end of the chapter

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Abstract

Monochorionic (MC) pregnancies have higher rates of fetal morbidity and mortality when compared to dichorionic (DC) ones. Therefore, the early diagnostic of chorionicity is of great importance. Monochorionic pregnancies have specific complications such as twin to twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia polycythemia sequence (TAPS), and twin reversed arterial perfusion sequence (TRAPS). MC pregnancies have several unique and serious complications that contribute to a perinatal mortality rate of 11%. The pathophysiology of most of these complications is related to the placental angio-architecture, and it results from an unbalanced perfusion between the fetuses. The screening of TTTS starts in 16 weeks with a sonographic follow-up every 2 weeks. In the last decade, there was an improvement in the treatment of TTTS. With the advent of the fetoscopic laser photocoagulation (FLPC), there was a drastic increase in the survival rate of the fetuses with TTTS when compared with serial amnioreduction. Besides that, in TRAPS, fetoscopic procedures such as cord occlusion improve the outcome of the normal fetus. We will also discuss sFGR and its classification and management. The aim of this chapter is to review the most important complications in MC pregnancies.

Keywords: monochorionic, twin to twin transfusion syndrome, TTTS, twin anemia polycythemia sequence, TAPS, selective fetal growth restriction, multiple pregnancy

1. Introduction

Multiple pregnancies are the result of one of the three possibilities: a fertilization of two or more oocytes from different spermatozoids, a single fertilization followed by a splitting of the zygote, or a combination of both [1]. These pregnancies have an increased risk of several complications for both mother and fetuses, such as diabetes mellitus, hypertensive disorders associated with pregnancy, preeclampsia, anemia, hyperemesis, hemorrhage, and cesarean

delivery [2–5] in the maternal side and higher risk of fetal anomalies, fetal demise, neonatal death [6], and preterm birth in the fetal side [7].

It is known that monochorionic (MC) pregnancies have higher rates of fetal morbidity and mortality when compared to dichorionic (DC) ones [1, 8, 9]. Besides that, the MC pregnancies have specific complications such as the twin to twin transfusion syndrome (TTTS), the selective fetal growth restriction (sFGR), the twin anemia polycythemia sequence (TAPS), and the twin reversed arterial perfusion sequence (TRAPS). Most of these complications can be managed and treated in order to decrease the fetal morbimortality.

2. Importance of multiple pregnancy

In the last years, the rate of multiple pregnancies has raised all over the globe. In the USA, it rose from 18.9in 1980 to 33.4 twins per 1000 births in 2016. The twin birth rates were higher in black women, followed by non-Hispanic white women. The triplet and high-order multiple birth rate has decreased about 48% in the last 8 years, from 193.5 in 1998 to 101.4 twins per 100.000 births in 2016 [7]. This decrease in high-order multiple pregnancies illustrates the reproductive medicine societies' strategies for reducing the risk of high-order pregnancies, like single-embryo transfer and multifetal pregnancy reduction [10–12].

In England, there is also an increase in multiple births. From 1998 to 2016, the multiple maternity rate rose from 14.4 to 15.9 twins per 1000 births. Since 1993, women aged 45 and over have consistently recorded the highest multiple maternity rate. These changes in the multiple pregnancy rates are due to the increase in ART. It is estimated that in vitro fertilization (IVF) conceptions are 11 times more likely to result in a multiple birth than natural conceptions. In 2014, 16% of IVF pregnancies resulted in multiple birth, with nearly 19,000 IVF babies born in the UK in 2014 [13].

This trend was largely attributed to an elevated amount of dizygotic pregnancies, without significant variations in monozygotic births over the past few decades. The dizygotic twinning rate is affected by many factors such as race, previous multiple pregnancy, maternal age and parity, lifestyle, season, use of fertility drugs and treatments, genetics, and others [14–16].

The high number of multiple births impacts directly in rate of preterm birth and low birthweight. Data from 2016 show that among twin pregnancies, 59.9% are born before complete 37 weeks of gestation, while in singletons, only 8% are preterm births. In singleton births, 6.4% were born with weight less than 2500 g. This percentage is 55.4 in twins and more than 95% in triplets [7].

3. Complications

The MC pregnancies have several unique and serious complications that contribute to a perinatal mortality rate of 11% [17, 18]. The pathophysiology of most of these complications is related to the placental angio-architecture [19]. Placental anastomoses are described since the 1600s.

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The term "third circulation" that represents an "area of transfusion" and the potential harmful effect of vascular connections between the fetuses was first described by Schatz in 1896 [20]. In 1965, Naeye [21] identified the effect of chronic nutritional deprivation on the size of organs in one twin while appreciating that transfusion to the other increased the hemoglobin concentration and hematocrit, with subsequent cardiomyopathy and hypertension. Since then, several authors have proposed diagnosis criteria and different kinds of treatments of the MC pregnancy problems. In this session, the main complications of the MC gestations will be discussed.

3.1. Twin to twin transfusion syndrome

One of the first suggestions of this disease in history lies in a Dutch painting from 1617 named the Early-Deceased Children of Jacob de Graeff and Aeltge Boelens that illustrates two children. One of them is pale and the other plethoric (**Figure 1**). Twin to twin transfusion syndrome is one of the main complications that occurs in about 10–15% of the MC pregnancies with an overall incidence of 3 in 10,000 pregnancies [22, 23].

If left untreated, TTTS mortality rates are about 70–100%. Perinatal mortality is the result of either miscarriage or very preterm delivery as a consequence of severe polyhydramnios and uterine distention or fetal demise due to severe cardiovascular disturbances [24, 25].

Figure 1. The Dutch painting the Early-Deceased Children of Jacob de Graeff and Aeltge Boelens shows two male twins: one pale and the other plethoric.

3.1.1. Pathophysiology

The pathophysiology underlies in the placental angio-architecture which is characterized by individual placental territory size, cord insertion location, and the quantity, size, and direction of intertwin anastomoses which are the most important factors in the pathogenesis because when unbalanced, they may cause hemodynamic changes that end in TTTS [26].

All MC placentas have intertwin anastomoses that are formed in the first trimester. They are important because they allow transfer of volume, red blood cells, vasoactive substances, and hormones. There are three type of intertwin anastomoses, and their flow may be unidirectional or bidirectional. Arteriovenous (AV) anastomoses are unidirectional but they exist in both directions (from donor to recipient or from recipient to donor). AV anastomoses end in a shared cotyledon where the arterial villous circulation of one twin links to the venous villous return of the other at the level of the intervillous space. Artery-to-artery (AA) and vein-to-vein (VV) are more superficial and bidirectional anastomoses (**Figure 2**). The flow direction depends on the types of connection, vessel calibers, and the pulse pressure. TTTS results from an unbalanced chronic perfusion from donor to recipient twin across placental anastomoses. This blood transfer is more likely in those placentas with more AV anastomoses and a lack of superficial balancing AA or VV anastomoses or when these bidirectional anastomoses are unusually small [26, 28].

3.1.2. Clinical manifestations of TTTS

The principal clinical feature in TTTS is hypervolemia in the recipient and hypovolemia in the donor twin that may progress to cardiovascular impairment, hydrops, and fetal death. In the

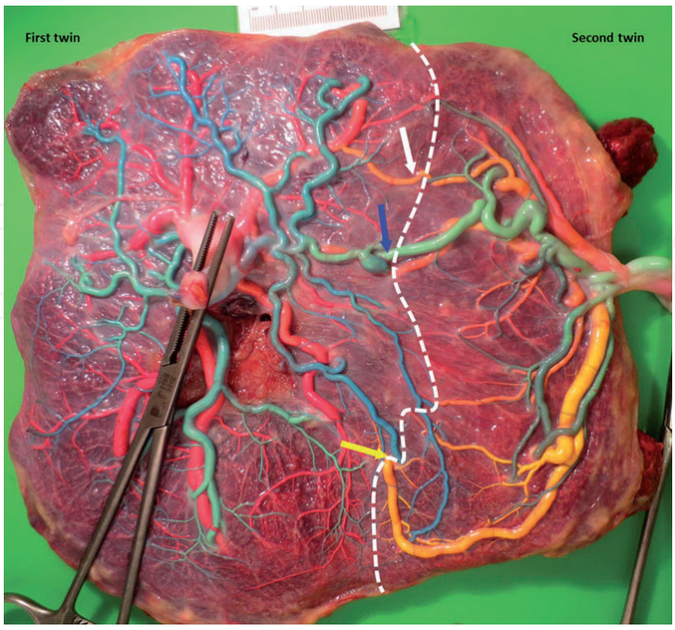

Figure 2. Monochorionic placenta of not complicated twin pregnancy. The blue, white, and yellow arrows represent AA, VV, and AV anastomoses, respectively. Adapted from twin research and human genetics, Zhao et al. [27].

first trimester, diagnosis is difficult, since the amniotic fluid is usually normal in both fetuses. Some sonographic markers such as discordance in nuchal translucency thickness (NT) and abnormalities in ductus venosus (DV) may be early signs of TTTS, but they have a low predictive value [29–31]. The sonographic manifestations usually may be noted as early as 16 weeks of gestation, but they can appear in the third trimester as well. TTTS manifestations are rare after 28 weeks of gestation.

In the second trimester, the oligohydramnios in the donor twin, as well as the polyhydramnios in the recipient twin, can easily be noted by ultrasound examination. The donor becomes hypovolemic; therefore, renal perfusion decreases. This hypoperfusion activates the renin-angiotensin system (RAS), producing vasoconstriction, oliguria, and oligohydramnios. As the disease progresses, the fetus becomes anuric and gets "stuck" against the uterine walls (**Figure 3**). The circulation becomes hyperdynamic with an increased vascular resistance in the fetus and in the placenta, leading to fetal growth restriction (FGR), cerebral redistribution, and abnormal arterial Doppler assessment. The recipient twin becomes hypervolemic and, by myocardial stretching, releases atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which are also biomarkers associated with heart failure. Elevated levels of these biomarkers and troponin are found in the amniotic fluid of the recipient, suggesting the presence of myocardial damage [26, 32, 33]. Despite the hypervolemia, vascular resistance in the recipient twin is increased. This hypertension is attributed to vasoactive mediators such as endothelin and also a paradoxically high level of renin. The source of endothelin and renin is probably partly from the placenta and partly from the donor via the vascular communications [34, 35]. These changes in fetal hemodynamics may cause a progressive cardiomyopathy that increases the heart size, reduces the myocardial compliance, and causes atrioventricular valvar regurgitation and abnormal venous Doppler findings. Several studies show that in early Quintero stages or even before the diagnostic of TTTS, the cardiac function in the recipient twin may be impaired [36–38]. A recent study noted that in the recipient twin, left ventricular filling pressures are elevated and systolic function is decreased before abnormalities in the

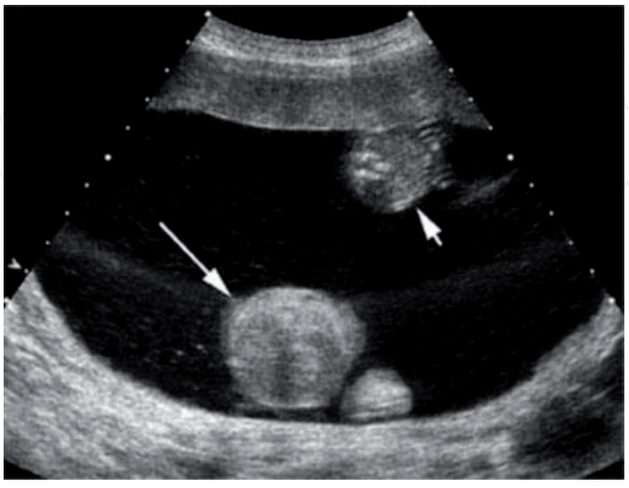

Figure 3. Two fetal abdomens. The smaller one (short arrow) is stuck in the anterior uterine wall and has no amniotic fluid. The bigger fetus (long arrow) has polyhydramnios. Adapted from: https://radiologykey.com/complications-of-multiple-gestations/.

right heart become apparent. They also described an improvement after fetoscopic laser photocoagulation (FLPC) in these fetuses [38].

In the third trimester, fetal discordance in amniotic fluid and growth may occur, increasing uterine distension and causing shortened cervical length and preterm birth. Also, the mirror syndrome, a rare condition that presents itself as a sudden maternal edema, loss of renal and cardiac function, hypertension, and fetal hydrops, may appear in women with TTTS [26, 39, 40].

There is another rare form of TTTS described as "acute peripartum TTTS" which is defined as the intertwin hemoglobin difference at birth >8 g/dl. Since it is a rare condition (2.5% of all the MC pregnancies), there are a few studies and the pathogenesis remains unclear. Some studies says that in theory, acute fetal blood loss from the donor twin into the circulation of the recipient twin may occur as a result of variations in blood pressure due to uterine contractions or fetal positions [41].

3.1.3. Diagnostic criteria and staging

In the past, TTTS was diagnosed at the time of birth based on neonatal criteria that included a growth discordance of 15–20% associated with discordant cord or neonatal hemoglobin concentrations of ≥5 g/dl [42]. In 1992, another study showed that these criteria are present in other conditions such as uteroplacental insufficiency, infection, and malformations and therefore should not be used as diagnostic criteria for TTTS [43].

The screening for TTTS should begin with an early ultrasound in order to confirm the chorionicity. The first trimester scan should be performed to look for morphology abnormalities and discordance in the NT measurement, abnormalities in the DV, and even crown-rump length discordances [44]. Unlike dichorionic pregnancies, where ultrasound can be performed every 4 weeks until the end of the second trimester, monochorionic pregnancies should be examined by ultrasound every 2 weeks beginning in the 16th week. An analysis of fetal growth, amniotic fluid deepest vertical pocket (DVP), umbilical artery pulsatility index (UA-PI), medium cerebral artery pulsatility index (MCA-PI), and peak systolic velocity (MCA-PSV) should be obtained [45, 46]. Besides that, a fetal echocardiography should be performed, since cardiac abnormalities are the most common defect in MC pregnancies. The fetal growth and the MCA-PSV are important parameters in the differential diagnosis of sFGR and TAPS, respectively. The early diagnosis is extremely important, since it allows timely treatment with FLPC.

In 1999, Quintero et al. standardized the diagnostic criteria and classification system of TTTS (**Table 1**) [47]. The diagnosis is made when a discordance in the DVP of the twins is visualized. The DVP of the donor twin should be <2 cm; meanwhile the DVP of the recipient, before 20 weeks, should be >8 cm, and after 20 weeks, it should be >10 cm in the European criteria and > 8 cm in the US criteria. The fetal bladders should also be evaluated since there might be a discordance in the size of the fetal bladders (larger in the recipient and smaller in the donor). It is worth reminding that weight discordance is not a diagnostic criterion for TTTS, but it also can be noted in the ultrasound examination.

Stage	Sonographic findings
I	DVP > 8 cm in the recipient* and < 2 cm in the donor twin
II	Absent bladder filling in the donor
III	Critically abnormal Doppler studies of either fetus**
IV	Hydrops of either fetus
V	Intrauterine fetal demise of either fetus

*Before 20 weeks the universal cutoff is 8 cm, and between 21 and 26 weeks, the cutoff is 8 cm in the USA and 10 cm in Europe.

**Absent-reverse diastolic flow in the umbilical artery and/or absent/reverse flow in the ductus venosus or pulsatile flow in the umbilical vein.

Table 1. TTTS staging system. Adapted from Journal of Perinatology, Quintero et al. [44].

There are some critics about it because this staging system is not progressive (e.g., stage I can go to stage IV without passing through stages II and III) [45], and it does not correlate well with survival chance in twins treated with FLPC [48]. Nevertheless, these criteria are the most used to classify TTTS.

3.1.4. Management of TTTS

The natural history of TTTS shows high rates of fetal morbidity and mortality. The perinatal death in some series of cases is about 70–100%, depending on the stage of disease [26]. In stage I, it is known that nearly 70% of the pregnancies remain stable or regress, but in 5% of cases of stages I or II, there is fetal death of one or both twins without warning. Besides that, only 30% of pregnancies managed expectantly have double survivors. In the other stages, mortality increases and treatment is necessary [49]. There are several ways to manage TTTS, which include FLPC, amnioreduction, selective reduction, and pregnancy termination.

The FLPC is the preferred option because its outcomes are better when compared to serial amnioreduction [50, 51]. For stage I, there is no consensus regarding the use of FLPC, so the cases should be individualized [52]. For stages II to IV, FLPC of placental anastomoses is the primary treatment between 16 and 26 weeks of gestation. In 2004, Senat et al. have shown that the mortality rate of fetuses treated with FLPC when compared with serial amnioreduction is significantly lower (RR 0.71; 95% CI 0.55; 0.92). This study also showed a decreased risk of intraventricular hemorrhage and neurological impairment in the laser group. Probably it is because there is a higher rate of prematurity in the amnioreduction group [51]. The procedure consists in inserting a fetoscope in the amniotic sac of the recipient, locating the donor twin and the intertwin membrane, coagulating (with Nd:YAG or diode laser) the intertwin anastomoses along the placental vascular equator, and, after that, removing amniotic fluid from the recipient sac [26, 51].

The quality of fetoscopy images in the early 1990s, when the first FLPC for TTTS was performed, was not good; therefore, the vascular anastomoses were not so easy to identify. The so-called nonselective technique for vessel coagulation was proposed [53]. This technique

consisted in coagulating all of the vessels that crossed the intertwin membrane. It did not attempt to differentiate anastomotic from non-anastomotic vessels but rather to catch as many anastomoses as possible (**Figure 4**). With the development of new techniques and advance in fetoscopy technology, another approach was proposed: the selective fetoscopic laser photocoagulation (SFLP) [54, 55]. In this method, the vascular equator is visualized and only intertwin anastomoses are coagulated. This technique differs from the "nonselective" FLPC because the equator does not always coincide with the membrane; therefore, not all the vessels that cross the intertwin membrane should be coagulated; thus, theoretically, more placental tissue will be available for the donor twin after the procedure (**Figure 4**). In 2000, Quintero et al. compared the SFLP with the "nonselective" FLPC and found that the selective method yielded superior results, with survival of at least 1 infant in 83% of patients against 61% in the "nonselective" group [56]. The order of anastomoses coagulation was also studied. Some authors claim that the sequential method, which is a technique where the AV (donor to recipient) are coagulated before the VA, improves the survival rate of both fetuses [57–59] and the survival rate of at least on fetus [58–60]. A recent meta-analysis showed that there may be an improved double neonatal survival as well as a decreased donor and recipient fetal demise with the use of the sequential technique, although all the studies are small and underpowered to confirm the hypothesis [61]. Although the SFLP improved neonatal outcomes, there is about 18% of surgical failure, defined as postoperative symptomatic patent anastomoses (**Figure 5**) [62–65], which could result in several complications such as recurrent TTTS (7–9%) [61, 65], TAPS (13–16%) [66, 67], and fetal death. This is a very delicate situation, because

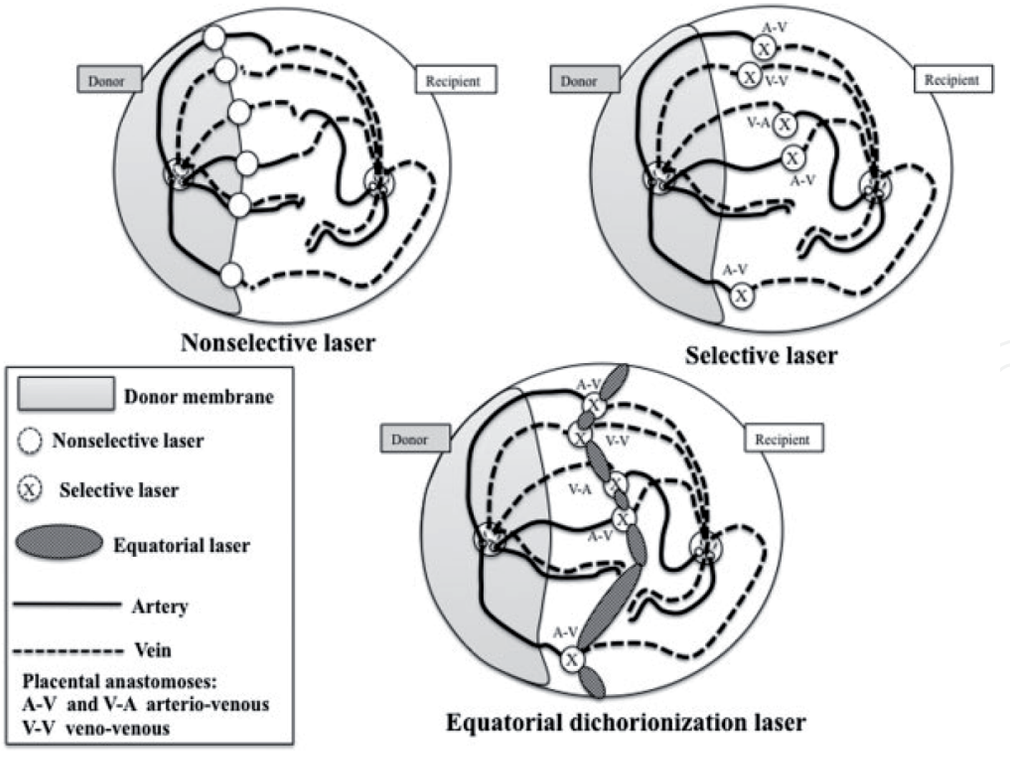

Figure 4. Types of fetoscopic laser techniques in the treatment of TTTS. The nonselective method coagulates all vessels crossing the intertwin membrane. SFLP occlude anastomoses where they occur, sparing placental tissue of the donor. The equatorial laser dichorionization or Solomon technique separates the fetal circulations by coagulating the vascular equator. Adapted from Am J Perinatol. Benoit et al. [26].

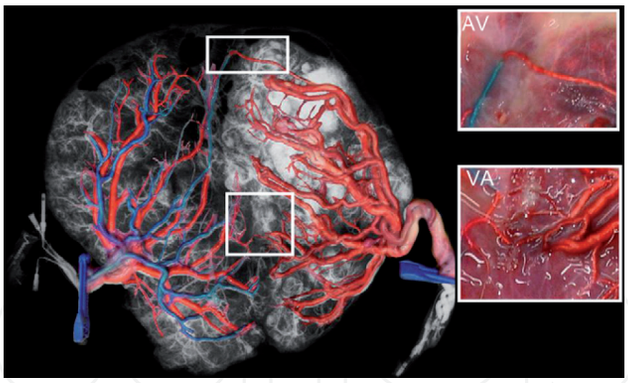

Figure 5. Digitally modified image of placenta with recurrent TTTS with missed AV and VA anastomoses. Adapted from Am J Obstet Gynecol. Lewi et al. [62].

repeating the procedure is more difficult for several reasons such as the size of the uterus and the fetuses. Furthermore, it is associated with an overall perinatal survival rate of 50% [67].

Recently, a new fetoscopic technique in which superficial coagulation of microvasculature on the chorionic plate between ablated anastomotic sites following SFLP was described [68] (**Figure 4**). Some authors compared the SFLP with this new technique in cohort studies and showed a trend toward the latter group [69, 70]. A subsequent randomized trial by Slaghekke et al. compared this new approach called the Solomon technique *versus* the SFLP and found no difference in the overall survival rates. However, a decrease in recurrent TTTS and TAPS after the procedure was observed in the Solomon group (4 vs. 21%) [66].

The main early complications of laser photocoagulation are unintentional septostomy in 8–12%, premature rupture of membranes (PROM) in about 1–9%, and amnion dehiscence (membrane separation) in 5–10% of cases.

The time of delivery in cases of laser photocoagulation varies between 31 and 34 weeks and most of them (60–80%) are not elective. The most common indication is the onset of labor followed by nonreassuring fetal testing and PROM. The mode of delivery is usually by cesarean section, in 57–70% of cases [26, 51, 60, 69, 70].

Unfortunately, in low-income countries, the laser therapy is not widely known and there are no teaching facilities. One Brazilian study showed the initial experience of a single center and found a single twin and both twins' survival rate 1 month after birth is 87.5 and 45.8%, respectively. These reported data are in line with those obtained in major centers worldwide, considering the learning curves and infrastructures [71]. In order to extend the range of the laser therapy to all the MC pregnancies, more teaching centers should be opened, and telemedicine should be used to aid low-income places to achieve the excellence in fetoscopy techniques.

3.1.5. Perinatal outcomes after treatment

The perinatal outcomes after the use of SFLP or Solomon technique are very satisfactory. Baschat et al. [70] found that the double survival rates at 6 months of age were 68% in the Solomon group and 50% in the SFLP. Ruano et al. [69] showed an overall neonatal survival rate from 61.8% in the SFLP group to 86.5% when Solomon technique was used. This difference

could be due to the increased experience with fetoscopic laser in general and not to the use of the Solomon technique. In the only randomized trial, the single twin and both twins' survival rates after 1 month in the SFLP were 87% and 60%, while in the Solomon group these rate were 85% and 64%, respectively [66].

The neurologic outcomes in the neonatal period following laser procedures, such as intraventricular hemorrhage, periventricular leukomalacia, cerebral white matter cysts, ventricular dilatation, and cerebral atrophy, range from 8 to 18% [51, 72, 73]. The long-term neurodevelopmental outcomes vary between 3 and 12% for cerebral palsy and 4 and 18% for neurodevelopmental impairment [73]. In one study, the neurodevelopmental scores in preterm-born children treated with laser therapy for TTTS were similar in preterm-born DC children, suggesting that prematurity has the main role in the neurologic impairment in fetus treated with laser photocoagulation [74]. Other authors have suggested risk factors for poorer neurodevelopmental outcomes [75, 76]. Lopriore et al. analyzed 212 pregnancies treated with fetoscopic laser surgery and found that advanced gestational age at laser surgery, low gestational age at birth, low birthweight, and high Quintero stage are risk factors of poor neurological development at 2 years of age [76].

Several studies report a rapid cardiac function recovery in the recipient and in the donor twin [36, 38, 77–80]. The coagulation of vascular anastomoses stops the volume exchange, as well as the vasoactive mediators, allowing cardiac output, cardiac size, valvular regurgitation, and ventricular inflow to normalize in the recipient twin in about half of the cases [38, 77]. The donor twin shows an increase in left ventricular filling pressure and cardiac output, which can temporarily cause a relative volume overload. It can worsen the cardiac function and cause ductus venosus alterations and even hydrops; however, these changes tend to disappear by 2 to 4 weeks after the laser procedure [79, 81, 82].

There are other types of treatment, such as septostomy. This procedure increases the risk of severe complications like cord entanglement and disruption of the membrane. This procedure has generally been abandoned [64, 83]. The selective reduction is another therapeutic option that tries to improve the outcome of the surviving twin whenever there is an imminent risk of spontaneous intrauterine death of one fetus. It can be performed either by ultrasound-guided vascular embolization or cord clamping through fetoscopy. A maximum of 50% survival is reached and most services have not supported this technique [68].

The fetoscopic laser coagulation is the gold standard treatment in stage II to stage IV TTTS affected pregnancies; the SFLP and Solomon technique are the best options for lowering the mortality and morbidity in theses fetuses. For Quintero stage I, there is not enough data that favors laser surgery, and more powered studies should be done comparing it to other kinds of treatment; therefore, the treatment for this stage has to be individualized.

3.2. Selective intrauterine growth restriction

Selective intrauterine growth restriction happens in 10–25% of MC gestations and it considerably increases perinatal morbidity and mortality [84–86]. The diagnostic criteria for sFGR differ among clinicians; therefore, it is hard to compare the findings of existing studies, to

combine their results, or to establish robust evidence-based management. The pathophysiology in sFGR in MC and DC twins seems to be different. While DC sFGR have conventionally been managed as FGR in a singleton pregnancy, MC twin pregnancies sFGR is thought to result mainly from an unequal placental share. In most cases the origin is in the placental territory discrepancy (**Figure 6**). Vascular anastomoses between both fetuses intrinsically justify IUGR, and one twin receives better oxygenated blood [87].

3.2.1. Diagnostic criteria and staging

Since many authors have proposed different diagnostic criteria, in 2017, the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) published a guideline for the sFGR diagnostic. It is defined as a condition in which one fetus has estimated fetal weight (EFW) < 10th centile and the intertwin EFW discordance is >25%. EFW discordance is calculated by the following formula: (weight of larger twin – weight of smaller twin) × 100)/weight of larger twin [45]. This weight discordance was proposed by an expert consensus, mainly based on data that show that an 18% EFW discordance reflects poorer outcomes both in DC and MC pregnancies [88]. Curiously, the charts used to monitor the fetal growth should be the same as those used in singleton pregnancies [45, 89], although specific multiple pregnancy charts are available [90]. However, there is a reduction in fetal growth in twin compared with singleton pregnancy, particularly in the third trimester. The key question for clinicians is whether this difference in growth represents adaptation or restriction [91]. Once the diagnosis is made, a detailed anomaly scan and screening for viral infections (cytomegalovirus, rubella, and toxoplasmosis) should be made. Amniocentesis may also be required to exclude chromosomal abnormalities as a cause of FGR [45, 92].

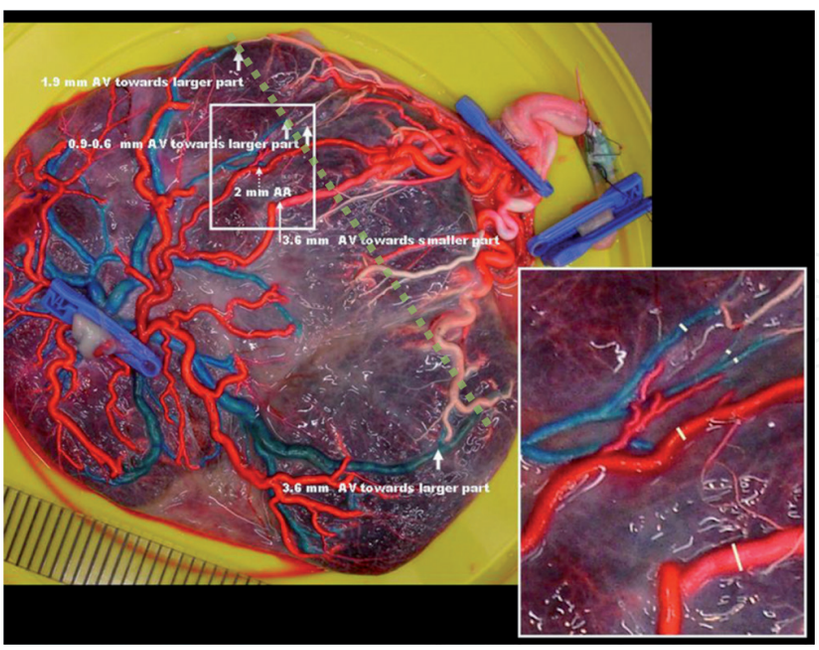

Figure 6. Macroscopic photograph demonstrates the measurement of the vascular anastomoses. There is a 2-mm arterioarterial anastomosis (dashed arrow) and 5 AV anastomoses (arrows). A macroscopic placental surface discordance is also visible (green dashed line: Vascular equator). Adapted from Am J Obstet Gynecol. Lewi et al. [86].

In order to follow up the sFGR pregnancies, as well as in singleton pregnancies, umbilical artery Doppler waveforms and UA-PI are accessed. In pregnancies complicated with sFGR, there are particularities in the umbilical artery Doppler probably because of the variability in the intertwin vascular anastomoses resistance [93, 94]. Three patterns are observed in the umbilical artery Doppler: positive end-diastolic flow, absent or reversed end-diastolic flow (AREDF), and intermittent absent or reversed end-diastolic flow (iAREDF) [95]. The latter pattern though is to result from the presence of transmitted waveforms from the larger into the smaller twin's cord due to the existence of placental large AA anastomoses (**Figure 6**) [93–95]. Based on these three Doppler types, Gratacós et al. proposed a three-stage classification system of the sFGR fetuses. In stage I, the umbilical artery in the smaller twin has a positive end-diastolic flow; in stage II, there is an AREDF; and stage III is characterized by iAREDF (**Figure 7**) [95].

The stage I prognosis is better, with an overall intrauterine mortality rate of 3–4% and a 97% rate of intact survival-free from neurological complications according to two recent meta-analyses. The neonatal morbidity, defined as abnormal brain imaging, respiratory distress syndrome (RDS), admission to the neonatal intensive care unit (NICU), or retinopathy of prematurity (ROP), was reported in about 9% of newborns. The neurologic outcome in this stage seems to be better when compared to the others as well as the gestational age at delivery [84, 93–95, 97]. Stage II sFGR has a poorer prognostic. It is reported that these fetuses tend to have a high risk of hypoxic deterioration and consequently overall, single, and double intrauterine death rates of 16.6%, 8.2%, and 10.4% of cases managed expectantly [97] and a 21% perinatal mortality [84]. The double survival rate in this stage is about 25% [98]. The iAREDF pattern has an intrauterine mortality rate similar to stage II. The overall, single, and double intrauterine death occurred in 13.2%, 7.2%, and 5.5% of cases managed expectantly although this stage is more unpredictable than the others [86, 93, 95, 97, 98]. Some ultrasound markers can be used as adverse predictors such as ductus venosus Z score [98], velamentous cord insertion (**Figure 8**) [99, 100], and weight discordance. A recent meta-analysis found that, in MC twin pregnancies, excluding cases affected by twin to twin transfusion syndrome, twins with birthweight discordance ≥25% were at higher risk of intrauterine death (OR 3.2, 95%CI, 1.5–6.7) and neonatal

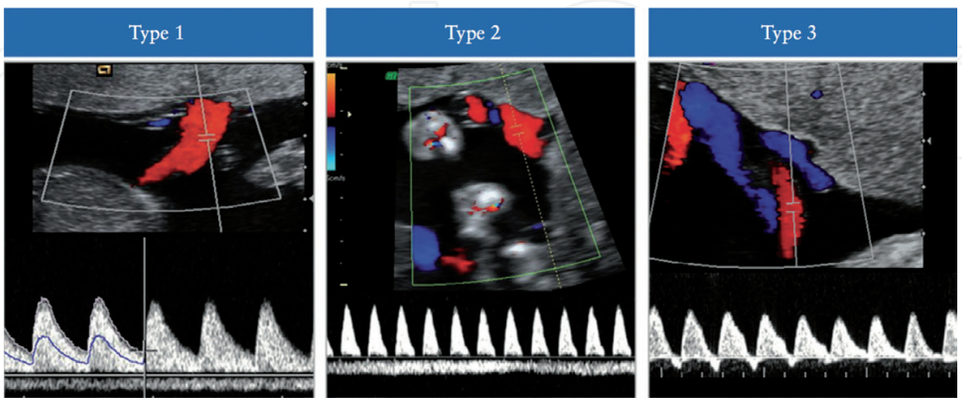

Figure 7. Classification of selective fetal growth restriction in monochorionic twin pregnancy. In type I, the umbilical artery Doppler waveform has positive end-diastolic flow, while in type II there is absent or reversed end-diastolic flow (AREDF). In type III there is a cyclical/intermittent pattern of AREDF. Extracted from ISUOG. https://www.isuog.org/uploads/assets/uploaded/b4ce0129-a7e8-40a9-8543c4243fb7638f.pdf [45].

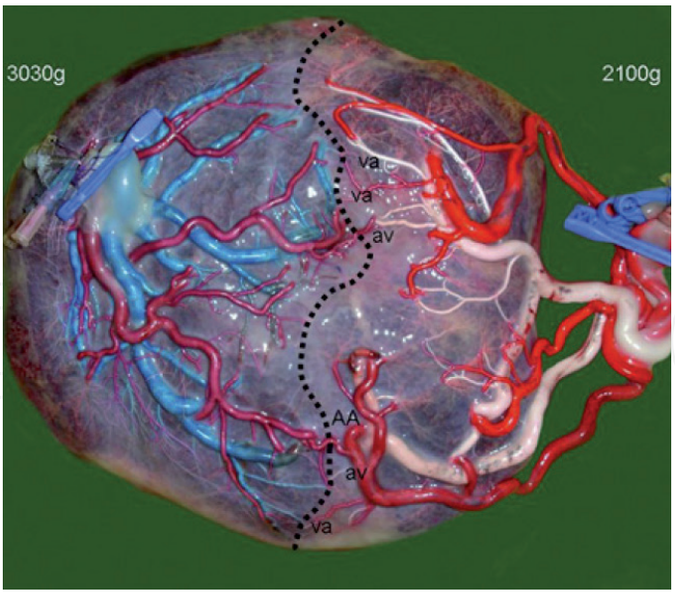

Figure 8. Monochorionic placenta with velamentous cord insertion in the smaller twin side. AV and VA anastomoses are seen and on big AA anastomoses. Adapted from Am J Obstet Gynecol. Lewi et al. [96].

death (OR 4.66, 95% CI, 1.8–12.4) compared with controls [101]. Gratacós et al. [93] found a 15% unexpected intrauterine death rate in the smaller twin on stage III sFGR compared with 2.6% and 0 in stages I and II, respectively. On the other hand, other authors show a better prognosis. Rustico et al. [102] showed a 0% rate in double fetal death at stage III as well as better rates in overall survival and lower neonatal death in the smaller twin (8% and 62%, respectively).

3.2.2. Management of sFGR

When sFGR presents with an umbilical artery positive end-diastolic flow, the prognosis is good, and therefore it is a consensus that the expectant management based on a weekly fetal growth and UA-PI evaluation should be done to look for progression to more severe stages which can occur in up to 25% of cases. For stages II and III, several studies compared SFLP with cord occlusion or expectant management, but there are not powered studies to support a gold standard treatment. In a retrospective study with 142 stage II sFGR fetuses treated with SFLP, there was survival rate of the smaller, larger, and both twins of 38.7, 67.6, and 34.5%, respectively. The survival rate of at least one twin was 71.8% [103]. When compared to expectant management, SFLP for stage III sFGR showed a higher overall intrauterine death (14.5 vs. 36%, respectively) as well as a higher death rate in the smaller twin which is 19% for the expectant group and 66% for the SFLP group [104]. Other prospective trial with ten pregnant women with sFGR stages II or III and oligohydramnios treated with SFLP showed that only three newborns of the restricted group survived and all of the newborns in the larger twin group were well and alive at 28 days of age [105].

Cord occlusion of the smaller twin is an option for early diagnosed sFGR, when the spontaneous death of the restricted fetus is most likely to happen, but it is the most difficult decision for the parents to make since they give up the life of one child to protect the other. Chalouhi et al.

[106] found a 90% survival rate in the larger twin after cord occlusion and a 4.5% neurologic complication rate which is much lower than the 26% rate when a spontaneous intrauterine death occurs [107].

The sFGR treatment is not yet defined. Several factors should be evaluated together with parents such as weight discordance, time of diagnosis (early vs. late), hemodynamic state of the restricted fetus at the time of diagnosis, and the will to protect the larger twin since the adverse outcomes are very low after a cord occlusion [94]. If FLPC or expectant management is elected, parent counseling should be made regarding complications and outcomes to both fetus.

3.3. Twin anemia polycythemia sequence

The placental angio-architecture is responsible for most of the complications in MC pregnancies. The intertwin vascular anastomoses have a key role in the pathogenesis of TTTS and sFGR. In 2007, a new MC pregnancy complication was described by Lopriore et al. [108] that involves a discordance in postnatal hemoglobin and hematocrit levels, a difference in neonate reticulocyte levels, and small AV anastomoses in the placenta after colored dye injection (**Figure 9**). This condition was named twin anemia polycythemia sequence. TAPS happens when blood from one twin is slowly transfused to the other by small AV anastomoses at a 5–15 ml/ 24 h rate [108]. Unlike TTTS, there is a less acute and well-compensated intertwin transfusion process leading to a discordance in hemoglobin levels without hemodynamic or amniotic fluid alterations [110]. The reticulocyte levels are also increased in the donor newborn and decreased in the recipient, which differ from other acute diseases, such as acute peripartum TTTS [41]. Another characteristic of TAPS is that after colored dye injection in MC placentas after TAPS, AA anastomoses are observed in about 11% and all of them are small (<1 mm). In comparison, the incidence of AA anastomoses in uncomplicated MC pregnancies and TTTS pregnancies is 80 and 25%, respectively [111, 112], which suggests that AA anastomoses protect against TAPS and TTTS. The maternal side of the TAPS placenta also shows an important color difference. The donor side is more white than the recipient side that shows a plethoric aspect like the respective twin (**Figure 10**) [113].

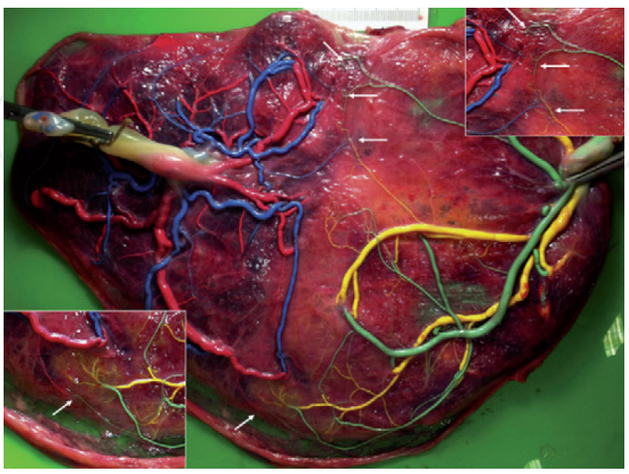

Figure 9. TAPS placenta after colored dye injection (blue or green for arteries and pink or yellow for veins). The white arrows indicate the small AV and VA anastomoses. Adapted from placenta. de Villiers et al. [109].

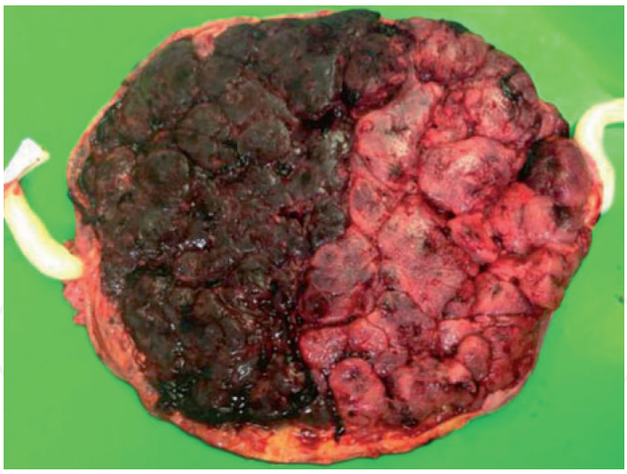

Figure 10. Maternal side of the TAPS placenta showing the difference in color between the plethoric share of the recipient (left side of the placenta) and the anemic share of the donor (right side of the placenta). Adapted from twin research and human genetics. Tollenaar et al. [113].

TAPS may occur spontaneously or post-laser surgery. The prevalence of spontaneous TAPS is about 1.6–5% [18, 68, 114], while post-laser TAPS occurs in 3–16% [66], depending on the technique used. The possible pathophysiology for the latter is the inability to identify all AV anastomoses, therefore leaving some small AV anastomoses without coagulation. The Solomon trial showed a significant decrease in post-laser TAPS in the placental dichorionization group, supporting this hypothesis [66].

3.3.1. Diagnostic criteria and classification

TAPS can be diagnosed either antenatally or postnatally. Antenatal diagnosis (**Table 2**) is based in MCA-PSV measurement in both fetuses showing an increased velocity in the anemic and a decreased velocity in the polycythemic twin. The most used criteria of TAPS diagnosis are an MCA-PSV > 1.5 MoM for the donor twin and <1.0 MoM for the recipient twin [111, 115]. Slaghekke et al. analyzed 43 twin pregnancies complicated by TAPS and found that a MCA-PSV > 1.5 MoM correlated with anemia (hemoglobin levels >5 SD below the mean) with a 94% sensitivity, a 74% specificity, a 76% positive predictive value, and a 94% negative predictive value. In the same study, MCA-PSV ≤ 1.0 MoM correlated with polycythemia (hemoglobin levels >5 SD above the mean) with a 97% sensitivity, a 96% specificity, a 93%

Antenatal criteria	**Postnatal criteria**
Donor MCA-PSV ≥ 1.5 MoM	Intertwin hemoglobin difference > 8 g/dl
AND	**AND 1 of the following**
Recipient MCA-PSV ≤ 1.0 MoM	Reticulocyte count ratio > 1.7
	Placenta with only small (diameter < 1 mm) vascular anastomoses

Table 2. Antenatal and postnatal diagnostic criteria for TAPS. Adapted from ultrasound Obstet Gynecol. Slaghekke et al. [111].

positive predictive value, and a 99% negative predictive value [115]. In some TAPS cases, other ultrasound findings have been reported. The first one is the difference in placental thickness, and echodensity on ultrasound examination was detected [110]. Another ultrasound finding described in TAPS is the so-called starry sky liver [116] which is characterized by clearly identified portal venules and diminished parenchymal echogenicity. More studies are needed to further investigate the validity and significance of these antenatal ultrasound findings for the diagnosis of TAPS.

The postnatal criteria (**Table 2**) can be used when TAPS is not diagnosed by MCA Doppler. It is based on the finding of discordant hemoglobin levels (Hb difference > 8.0 g/dl) associated with an increased intertwin reticulocyte count ratio > 1.7 that is pathognomonic for TAPS and placental evidence of only small vascular anastomoses [111, 117].

The classification for TAPS was proposed by Slaghekke et al. in 2010 [111] based on the difference in hemoglobin levels postnatally (**Table 3**).

3.3.2. Management of TAPS

There is no optimal treatment for TAPS. Options include expectant management and early delivery; intrauterine transfusion (IUT) in the donor, with or without partial exchange transfusion (PET) in the recipient; selective feticide; and fetoscopic laser surgery.

Expectant management is made with closing ultrasound monitoring with serial MCA-PVS evaluation and an early delivery when necessary. It leads to a 75 to 83% survival rate [111, 118].

Another kind of treatment is IUT that can be performed intravascularly or intraperitoneal. It seems the latter may be superior to intravascular intrauterine transfusions because it is technically easier and can be performed as early as 15 weeks [119]. Although this method is commonly used, it is a palliative option, since it temporarily meliorates the donor anemia. Furthermore, the raise in blood viscosity in the recipient twin can lead to embolic complications [67]. These complications can be managed by partial exchange transfusion (PET) that decreases the viscosity of the blood of the polycythemic recipient. The perinatal survival rate in some studies is generally good, reaching 85–100% [111, 118].

Antenatal stage	Doppler ultrasound
Stage I	MCA-PSV donor >1.5 MoM and MCA-PSV recipient <1.0 MoM, without other signs of fetal compromise
Stage II	MCA-PSV donor >1.7 MoM and MCA-PSV recipient <0.8 MoM, without other signs of fetal compromise
Stage III	As stage I or II, with cardiac compromise of donor, defined as critically abnormal flow*
Stage IV	Hydrops of donor
Stage V	Intrauterine demise of one or both fetuses preceded by TAPS

*Critically abnormal Doppler is defined as absent or reversed end-diastolic flow in umbilical artery, pulsatile flow in the umbilical vein, and increased pulsatility index or reversed flow in ductus venosus.

Table 3. Antenatal TAPS classification. Adapted from Ultrasound Obstet Gynecol. Slaghekke et al. [111].

The only causal treatment for both spontaneous and post-laser TAPS is laser surgery. It is technically more difficult because of the absence of polyhydramnios and a stuck twin, which makes the visualization of the vascular equator more challenging as well as the size of anastomoses, which is difficult to visualize during fetoscopy [111]. The results in small studies are satisfactory, with a survival rate of 94–100% [111, 118, 120, 121] and an apparent improvement in perinatal outcome by prolonging pregnancy and reducing respiratory distress syndrome [117].

The TAPS management should be made after evaluation of different factors, including TAPS stage, gestational age, and the clinician experience in the different types of treatments. In early stages, TAPS can be managed expectantly. If gestational age is below 26–28 weeks, laser treatment should be considered [113]. When laser treatment is not possible, IUT should be considered. When repeated IUT is expected or in case of severe polycythemia in the recipient, PET of the recipient can be done.

3.4. Twin reversed arterial perfusion sequence

Twin reversed arterial perfusion sequence resulting in an acardiac twin is a rare condition and occurs in 1:35,000 births or 1% of all monozygotic twins [122]. It consists in one health twin (the "pump" twin) and one acardiac mass which is perfused by the other fetus' heart. This acardiac twin most often has an underdeveloped head and upper body and impressive edema also mostly of the upper body. In some cases, there might be fetal movements. In rare cases, a rudimentary pulsating cardiac structure may be seen. It is though that the VV and AA bidirectional anastomoses are responsible for the perfusion of the acardiac fetus. One study analyzed the TRAPS placenta and found big AA anastomoses as well as veins in direct continuity with each other. They also noted that umbilical cords were attached, with insertion adjacent to each other [123]. The blood from the pump twin flows through the umbilical artery to the umbilical artery of the acardiac twin and then it flows back to the recipient twin through the umbilical vein. The returning blood bypasses the placenta and returns to the pump twin via VV anastomoses, without passing through the placenta. This condition may cause a hyperdynamic circulation and progressive high output cardiac failure in the pump twin causing fetal death in about half of cases if not treated [122, 124, 125].

The diagnostic is made by turning on the color Doppler and showing the inverse direction of blood flow in the aorta of the acardiac twin [92] (**Figure 11**). TRAPS is usually diagnosed in the 11–13 weeks scan or even in the early endovaginal ultrasound [126–128]. Given the fact that 50% of pump twin dies if expectant management is made and that in 33% of the TRAPS pregnancies diagnosed at the first trimester the healthy twin dies before 18 weeks [123, 129], several intrauterine interventions have been tested in order to improve the perinatal outcomes. The overall survival of the treatment methods is similar among several studies and varies between 71 and 86% [130–134]. The methods used to manage TRAPS are cord ligation; monopolar, bipolar, or laser cord coagulation; and fetoscopic laser coagulation of placental anastomoses. However, intrafetal techniques such as intrafetal laser ablation and intrafetal radiofrequency ablation (RFA) are preferred because, when compared to cord occlusion

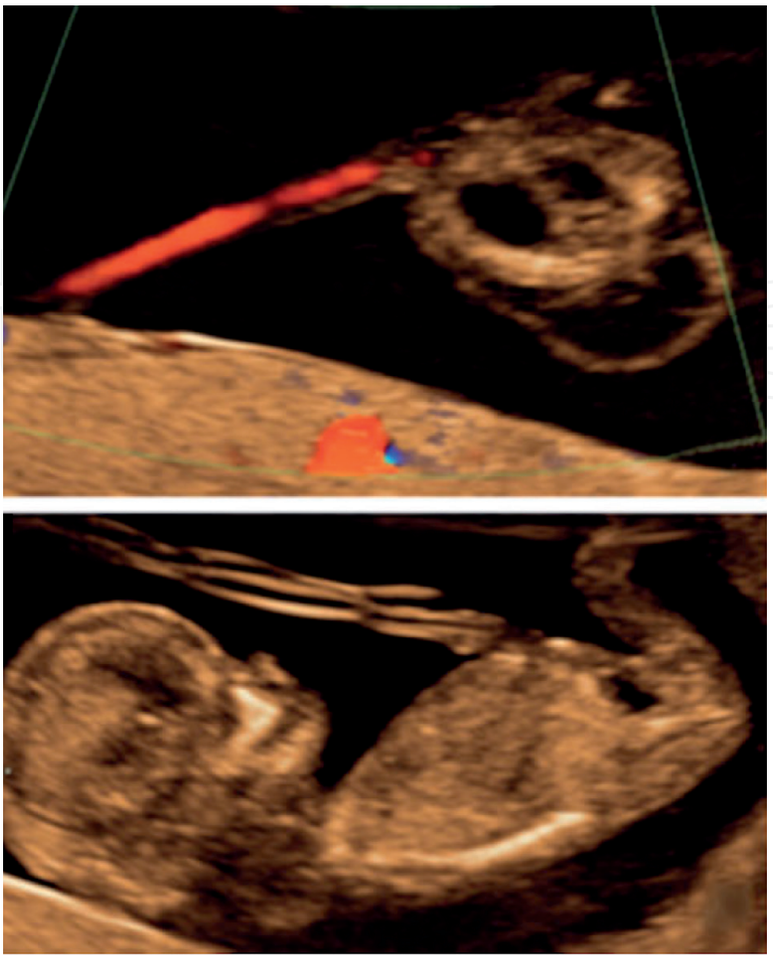

Figure 11. Upper image: Acardiac twin with retrograde flow in the umbilical cord. Lower image: Normal recipient twin. Adapted from ultrasound Obstet Gynecol. Pagani et al. [124].

techniques, they are associated with a lower technical failure rate (13 vs. 35%), lower rate of preterm birth or rupture of membranes before 32 weeks (23 vs. 58%), and higher rate of clinical success (77 vs. 50%) [135].

There are some doubts about the optimal time to do the treatment. Performing any procedure before the obliteration of the coelomic cavity increases the risk of talipes and miscarriage [136]; therefore, most of the authors perform the intervention between 13 and 16 weeks [124]. In one study in which the median gestational age at intervention (intrafetal laser ablation) was 13.2 weeks, there was a 41% mortality rate in the first 72 h after the procedure; therefore, surgery before 13 weeks of gestation should be avoided [136]. Some studies showed that expectant management could be offered in special cases. Jelin et al. [125] found a 100% survival when the acardiac twin had less than 50% of the pump twin's weight. Other studies suggested that discordance between crown-rump length of the pump twin and upper pole-rump length of the TRAP twin could be potential predictors of pregnancy outcome [137].

The optimal approach should be an early diagnosis and a proper parental counseling and an intrafetal intervention, by laser or RFA in 13–16 weeks. The expectant management could be considered if the TRAP twin is smaller (about half the size) than the pump twin.

4. Conclusion

Monochorionic pregnancies are at a great risk of complications such as preterm birth, fetal and neonatal death, and neurological injury. The early sonographic screening is extremely important to diagnose some of the most important complications which can lead to death of one or both siblings. It should begin in the first trimester, where the confirmation of chorionicity should be done and the search for potential predictors of adverse outcomes such as NT discordance should be accessed. Some complications such as TRAPS can be diagnosed and managed in this period. Beginning in the 16th week, a biweekly detailed ultrasound examination is extremely important since it can detect early stages of TTTS, sFGR, and TAPS. Most of these complications can be treated in the mid-trimester improving the survival rate of one or both fetuses.

The fetoscopic approach is the main method to manage MC twin complications and should be available in specialized fetal medicine centers with trained staff to perform the laser surgery. Several laser techniques have been tested in the last years and the improvement in the outcomes is clear. Although the results are satisfactory, the complication rates, such as PROM and unintentional septostomy, are still relatively high as well as the both twins' survival rate.

Future directions in the management of TTTS are likely to involve refinements in the prediction of the disease, clarification of the optimum frequency of surveillance, technique of laser therapy, prediction of adverse outcome after treatment, and development of other vascular ablative techniques.

Although the treatment efficacy is rapidly improving in big centers, in most parts of the world, there is a lack of specialized centers and trained personnel. In order to achieve an optimal management in MC pregnancy complications, it is important to improve the early screening and diagnosis and the referral system, mainly in low-income countries.

Conflict of interest

There are no conflicts of interest in this chapter.

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