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Update on twin-to-twin transfusion syndrome

Christian Bamberg, Consultant in Fetal and Maternal Medicine *,
Kurt Hecher, Professor in Fetal and Maternal Medicine

University Medical Center Hamburg-Eppendorf, Department of Obstetrics and Fetal Medicine, Hamburg, Germany

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A B S T R A C T

Twin-to-twin transfusion syndrome (TTTS) is a serious complication that affects 10–15% of monochorionic multiple pregnancies. Communicating placental vessels on the chorionic plate between the donor and recipient twin are responsible for the imbalance of blood flow. There is evidence for the superiority of fetoscopic laser ablation over serial amnioreductions regarding survival and neurological outcome for stages II-IV TTTS. However, the optimal management of stage I is still debated. The “Solomon” technique showed a significant reduction in recurrent TTTS and post laser twin anemia-polycythemia sequence (TAPS) in comparison to the selective laser method without improvement in perinatal mortality or neonatal morbidity. Survival rates after fetoscopic laser surgery have significantly increased over the last 25 years. High volume centers report up to 70% double survival and at least one survivor in >90%. Long-term neurodevelopmental impairment occurs in about 10% of children after laser surgery. In this review we discuss the optimal management, innovations in laser technique, long-term neurodevelopmental outcome, and future aspects of TTTS treatment.

* Corresponding author. Department of Obstetrics and Fetal Medicine, University Medical Center Hamburg-Eppendorf, Martinistr. 52, Hamburg, 20246, Germany.
E-mail address: c.bamberg@uke.de (C. Bamberg).

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Introduction

Twin-to-twin transfusion syndrome (TTTS) occurs in monochorionic (MC) multiple pregnancies. MC twins share a single placenta and almost all cases have vascular anastomoses on the chorionic plate connecting the two fetal umbilical circulations which is the prerequisite for the development of TTTS. There are three different types of anastomoses: arterio-venous (in both directions), arterio-arterial and veno-venous. It is not completely understood why TTTS develops, but the type, number and diameter of these anastomoses determines the risk profile [1]. Approximately 10–15% of all MC twins develop TTTS [2] which usually occurs between the 16th and 26th weeks of gestation. Zhao and coworkers examined 235 MC placentas in untreated cases [3]. Color dye injection after birth was performed to investigate the prevalence, type, location and size of the placental anastomoses. The number of superficial arterio-arterial anastomoses with bidirectional blood flow between the two cord insertions was significantly lower (47%) in TTTS cases in comparison to uncomplicated cases (96%). In addition, if artery to artery connections were present in TTTS placentas the median diameter was significantly thinner and they were located more centrally in contrast to cases without TTTS. These findings highlight the unique role of the MC placenta and its vascular connections between the twins' umbilicoplacental circulations in the pathophysiology of TTTS (Fig. 1).

Diagnosis and staging of TTTS

According to the ISUOG Practice Guidelines on the role of ultrasound in twin pregnancy [4] and other guidelines [5,6] sonographic screening for TTTS should be performed every 2 weeks from 16 weeks onwards. TTTS is diagnosed by ultrasound and timely and accurate detection is essential for perinatal outcome. Severe amniotic fluid discordance is the main prenatal finding. The recipient fetus shows an increasing polyhydramnios defined as a deepest vertical pocket >8 cm before 20 weeks and >10 cm after 20 weeks of gestation. These cut offs have been defined by the Eurofoetus group (http://www.eurofoetus.org). The donor shows oligo- or anhydramnios with a deepest vertical pocket <2 cm and is stuck within its membranes to the uterine wall or placenta by the excessive polyhydramnios of the recipient. However, recently Khalil suggested modified diagnostic criteria for TTTS prior to 18 weeks' gestation [7], because a more recent study [8], which investigated the amniotic fluid volume in MC twins from the first trimester until delivery found that a deepest vertical pocket of 6 cm

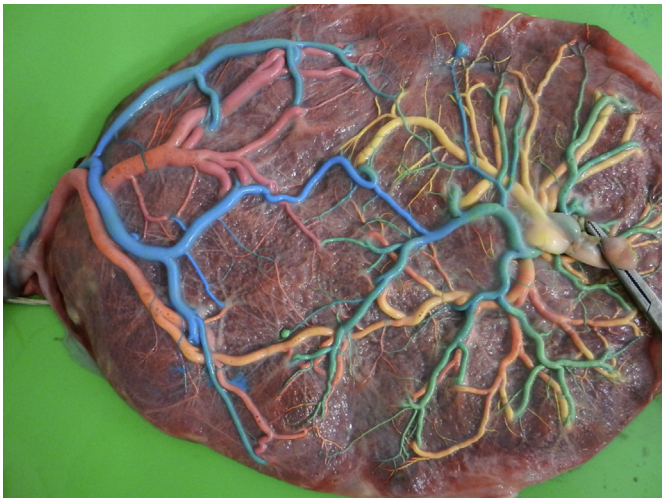

Fig. 1. MC placenta injected with colored dye illustrating all types of anastomoses: arterio-venous (AV; in both directions), arterio-arterial (AA; blue/green) and rare veno-venous (VV; red/yellow). This photo was taken at the first fetocopic laser course (Leiden University Medical Center, The Netherlands) in 2015.

represented the 90th centile and 7 cm was the 97.5th centile from 16 to 17 weeks of gestation. Consequently, a deepest vertical pocket of 6 cm before 18 weeks of gestation may be a more sensitive cut off than 8 cm. However, in cases with an anterior placenta and a deepest pool <8 cm a complete laser coagulation along the entire vascular equator may not always be feasible or at least difficult to perform.

TTTS is less common in monoamniotic twin pregnancies (prevalence 6%) [9], owing to close umbilical cord insertions and plenty of anastomoses between the two placental shares. Ultrasound findings are polyhydramnios in the common amniotic sac and discrepancy in fetal bladder filling.

Different classification systems have been described for staging of the severe TTTS. The Quintero staging system was published in 1999 and is still the most frequently used one [10]. There are five stages which are shown in Table 1.

Several limitations of the Quintero staging system have been described. For instance donor twins with a visible bladder may have abnormal Doppler findings. Two research groups from the United States, the Children's Hospital of Philadelphia (CHOP score) and the Cincinnati modification of the Quintero system incorporated additional cardiovascular parameters for the prediction of neonatal outcome [11,12]. Their intention is based on the findings, that recipients showed signs of heart failure even at early TTTS stages. Wohlmuth and coworkers reviewed the fetal cardiovascular hemodynamics in TTTS [13]. Up to 70% of recipients showed echocardiographic signs of anatomical or functional cardiac compromise. Another study showed that cardiac function of the recipient twin was abnormal, even at stage I or II [14]. In contrast, donor twins typically show normal cardiac parameters. However, from the clinical point of view the Quintero staging system is widely used, even if it does not represent a chronological order of deterioration in all cases. Intrauterine fetal death may also occur at stage I without deterioration to more advanced stages. In addition Quintero staging showed a poor prediction of neonatal outcome after laser treatment. Yamamoto and coworkers performed a longitudinal investigation of bladder filling in donors [15]. They reported by definition a visible bladder in stage I but absent voiding dynamics in almost half of the cases, meaning that the differentiation between stage I and stage II does not reflect the amount of urine production and in our opinion does not have any clinical implication. The particular aspect of TTTS I stage pregnancies will be addressed in the following chapter.

Fetoscopic laser treatment

In general, left untreated, there is a 80–90% risk for perinatal mortality due to intrauterine fetal death, miscarriage or extremely preterm delivery [16]. However, it is evidence based that in severe mid-gestational TTTS fetoscopic laser coagulation of placental vascular anastomoses is superior to serial amniodrainages. Senat and coworkers conducted a multicenter randomized controlled trial showing that in severe TTTS between 15 and 26 weeks of gestation fetoscopic laser therapy resulted in higher survival of at least one twin, higher gestational age at delivery [17] and better neurological outcomes than serial amnioreductions [17,18]. However, this study included only 11 patients with stage I disease. Therefore, the numbers are too small to draw any conclusion. According to the natural history 55–70% of pregnancies at stage I remain stable or actually regress [19,20]. A systematic review and meta-analysis suggested that the incidence of progression from stage I to more advanced stages was

Table 1
Staging of severe TTTS based on ultrasound findings (modified from Quintero [10]).

Stage	Poly-/Oligohydramnios	Absent bladder in donor	[a]Severely abnormal Doppler findings in UA and/or DV	Hydrops	Demise
I	+	−	−	−	−
II	+	+	−	−	−
III	+	+	+	−	−
IV	+	+	+	+	−
V	+	+	+	+	+

[a] Defined as at least one of the following: umbilical artery (UA) absent or reversed enddiastolic flow (ARED), negative A-wave ductus venosus (DV).

27% and the pooled overall survival was 79%, 77%, 68% and 84% if managed expectantly, by amnioreduction, laser if there was progression and laser as first-line treatment, respectively [21]. Therefore, many fetal medicine centers offer conservative management and close monitoring at stage I to avoid unnecessary interventions. However, the North American Fetal Therapy Network reported that 60% of conservatively managed stage I cases progressed and only fetoscopic laser surgery was protective against double fetal loss or very preterm delivery before 26 + 0 weeks [22]. Due to the lack of evidence the research group from Paris initiated the TTTS stage I trial in 2010, an international randomized study comparing conservative management versus immediate laser surgery (http://clinicaltrials.gov/ct2/show/NCT01220011). Inclusion criteria were TTTS stage I according to the Eurofoetus criteria between 16 + 0 and 26 + 6 weeks of gestation. The women were randomly assigned to primary laser within 72 h or conservative management with weekly follow-up. In the conservative management group, in cases with progression to stage II or higher, the occurence of severe maternal discomfort due to polyhydramnios, or cervical shortening <15 mm, laser was performed. The primary outcome was overall intact survival at 6 months after birth. Unfortunately, very recently this study has been closed for poor recruitment. At the moment, we are awaiting the analysis from the population which has so far been randomized and a concomitant registry of not randomized cases.

It is consensus that all vascular anastomoses should be ablated during the fetoscopic laser procedure (Fig. 2). However, this raises the question, whether all connecting vessels can be identified and coagulated [23]. It has been reported that after standard fetoscopic laser technique, patent anastomoses were seen in up to one third of the placentas [24]. Therefore, a new laser method, called the "Solomon" technique, was developed. After identifying and coagulating the anastomoses, a thin line was drawn with the laser from one placental edge to the other connecting the laser dots. The rationale of this method is to ablate the entire vascular equator and minimize the risk of residual anastomoses that are not visible by naked eye. In a RCT the standard selective laser method was compared with the Solomon technique [25]. 274 women were randomly assigned, of whom 139 were treated with the Solomon technique and 135 received standard treatment. The new technique was associated with a significant reduction of recurrent TTTS and post laser twin anemia-polycythemia sequence (TAPS)

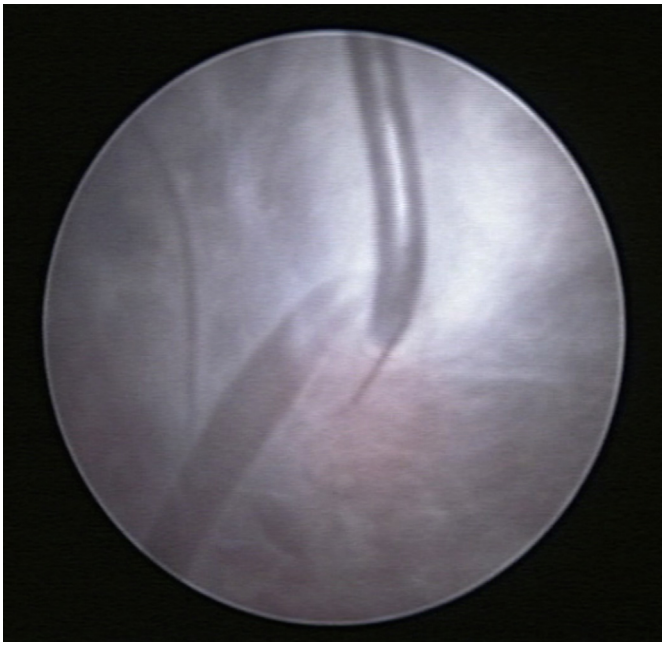

Fig. 2. Typical arterio-venous (AV) anastomosis on the placental surface during fetoscopy. The vessel at 12 o'clock is the darker donor's artery, the vessel coming in at 7 o'clock is the lighter recipient's vein.

(Table 2). Perinatal mortality and severe neonatal morbidity did not differ significantly between the two groups. Using color dye injection residual anastomoses were not significantly reduced ($p = 0.12$) in the placentas of the Solomon group (19%) in comparison to the standard group (30%) in the initial study. This is in contrast to a secondary analysis of the trial which reported a significant reduction ($p = 0.04$) of residual anastomoses after the use of the Solomon technique (19% vs 34%) [26]. In the subgroup of cases in which laser surgery was recorded as complete by the surgeon, an even larger reduction of residual anastomoses was seen: 12% in the Solomon group compared with 32% in the standard group ($p < 0.01$). Even if the procedure time in the Solomon group was identical with the standard group, the total amount of laser energy was approximately twofold higher (9275 J verus 4933 J; $p < 0.0001$). The authors recommended that in the absence of any adverse effects compared with the standard coagulation technique, surgeons may consider performing the Solomon method. Concerns remain whether lasering of healthy placental tissue between the anastomoses is justified resulting in an increased extent of placental injury [27]. Furthermore, Quintero et al. [28] and Chmait et al. [29] observed fewer patent anastomoses, namely 3.5% and 5%, respectively, using the selective laser technique. In addition, very recently an increased risk of placental abruption after Solomon laser treatment was reported [30]. In this retrospective study 287 cases with selective laser coagulation were compared to 86 cases after the introduction of the Solomon technique in 2012. Perinatal surviving was significantly higher in the Solomon group as compared to the selective procedure (77% vs 54%, $p < 0.001$). However, the risk of placental abruption was significantly higher with the Solomon method than in the selective group (14% vs 3%, OR 13.5, 95% CI 3.7–49.2). The authors concluded that one possible explanation could be a more extensive tissue damage of the thinner areas at the placenta edges. In our clinical experience we favour the partial Solomon technique by coagulating an area of neighboring anastomoses along the vascular equator to avoid unnecessary sacrifying of placental tissue where no vessels are detectable on the chorionic plate (Fig. 3a, b, c) (Fig. 4).

There is some evidence that laser treatment in TTTS before 16 and after 26 weeks is feasible, safe and may improve the perinatal outcome [31,32]. The arguments for and against laser therapy are summarized in Table 3.

Table 2
Primary outcome of the Solomon trial [25].

	Solomon group (n = 137)	Standard group (n = 135)	OR (95% CI)
1-month postnatal survival:			
At least one surviving neonate	116/137 (85%)	117/135 (87%)	0.85 (0.43–1.68)
Double survival	87/137 (64%)	81/135 (60%)	1.16 (0.71–1.89)
Recurrent TTTS	2/137 (1%)	9/135 (7%)	0.21 (0.04–0.98)
Post laser TAPS	4/137 (3%)	21/135 (16%)	0.16 (0.05–0.49)

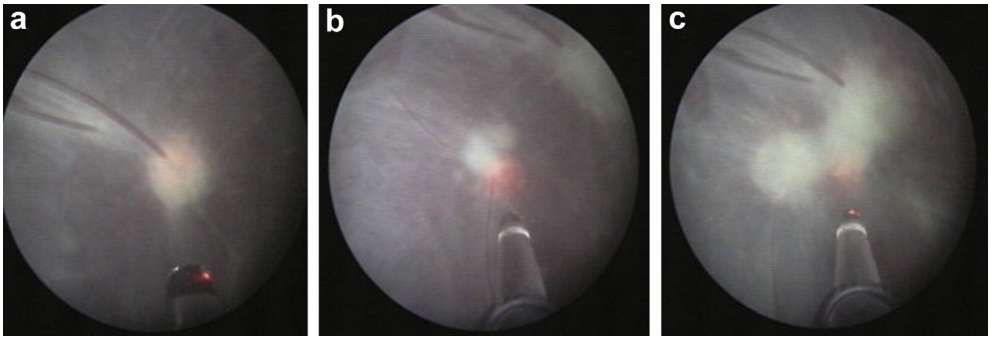

Fig. 3. a/b/c: Area of anastomoses and application of the partial Solomon technique (continous coagulation line between the laser dots).

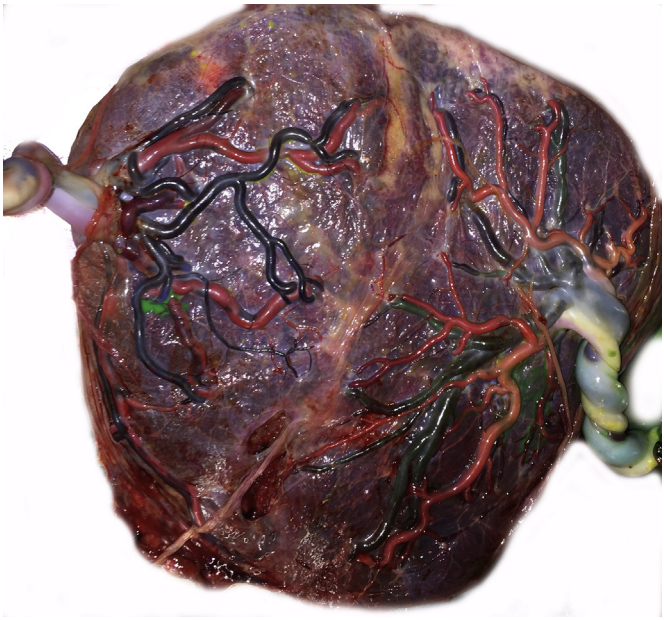

Fig. 4. A MC placenta with TTTS treated with fetoscopic laser coagulation. We performed a partial Solomon technique. In the upper part we drew a line connecting the laser dots. In the lower part there were no connecting vessels, therefore we did not coagulate the entire vascular equator.

Outcomes

In 2015 Akkermans and coworkers published a systematic review comprising 25 years of fetoscopic laser coagulation in TTTS [34]. They summarized the outcome of 3868 women included in 34 studies and mentioned a large variation between the different fetal medicine centers in terms of case load and outcome. However, mean survival of both twins and of least one twin significantly increased from 35% to 65% and 70%–88%, respectively. The mean gestational age at birth of all series was 32.4 ± 1.3 weeks.

Recently, we published the largest single center experience for laser coagulation [35]. We reported the perinatal outcome of 1020 consecutive pregnancies with severe midgestation TTTS with a practically 100% follow up (1019/1020). During the study period (January 1995 to March 2013) the yearly caseload more than doubled from 43 to 91 patients and fetal survival of both twins increased significantly from 50% in the first group of 200 cases to 69.5% in the last group of 220 cases ($p = 0.018$), reaching a plateau after 600 procedures. There was no significant trend of at least one surviving twin with an increase from 80.5% to 91.8% ($p = 0.072$). We found a mean gestational age at delivery with at

Table 3
Pros and cons regarding early and late laser surgery in TTTS (modified from Baud et al. [33]).

	Early TTTS (<16 weeks)	Late TTTS (>26 weeks)
Prevalence	2.5%	4–8%
In favour of laser surgery	- Feasible - Perinatal outcome comparable to conventional laser therapy between 16 and 26 weeks	- Delay delivery and recovery in utero - Trend for better neonatal outcome
Against laser therapy	- Amnion–chorion not fused - Increased risk of PPROM rate within 1 week of laser - Hypothetic spontaneous regression	- Turbid amniotic fluid - Larger placental vessels, difficult to coagulate

least one liveborn of 33.7 ± 3.2 weeks. After introduction of the 30° fetoscope with Albarran steering lever to deflect the laser fiber for anterior placentas in the year 2001 the double-survival rate was independent from placental location without a significant difference between anterior and posterior placentas. Interestingly, the success rates for survival of both twins of a trainee and an experienced surgeon were not significantly different. We believe that the absent learning curve effect in our study population of the trainee surgeon may be explained by a hands-on training and starting with easier cases with posterior placentas. Furthermore, immediate take-over by the lead surgeon if complications occurred and final check whether all anastomoses had been closed was guaranteed. We concluded that concentration of laser treatment in national and international specialized high-volume fetal medicine centers improves double survival rates. Technical developments and an experienced team which supervises hands-on training contribute to this success. These results are in agreement with the findings of Stirnemann and colleagues [36] presenting the follow up of 1017 out of 1092 cases (93%) after TTTS treatment with percutaneous fetoscopic laser between 2000 and 2016. The overall survival of at least one twin was 84% and both twins survived in 53%. During the study period dual survival increased from 42% to 66%, highlighting the improvement in perinatal outcomes. Gestational age at surgery <17 weeks was a significant risk factor for PPROM.

Another important aspect are neurodevelopmental follow-up studies in survivors. Fetal brain lesions following laser surgery may be depicted by prenatal ultrasound or MRI. The lesions may be ischemic or hemorrhagic and the prevalence is approximately 2% (equally distributed in donors and recipients). Significant risk factors are recurrent TTTS and post laser TAPS following incomplete laser surgery [37]. Van Klink et al. showed that severe cerebral injury at birth was independently associated with neurodevelopment impairment at 2 years of age [38]. Schou et al. investigated the prevalence of severe neurodevelopment impairment (cerebral palsy, bilateral blindness and/or deafness, severe cognitive and/or motor delay) in children at the age of 2 years after fetoscopic laser surgery for TTTS [39]. 9 out of 86 children (10.5%) were affected. It is important to know that follow-up studies reported varying rates of cerebral palsy and neurodevelopment impairment in TTTS treated cases with laser surgery. This may be due to different methodology, heterogeneity within small case series and lack of uniform outcome criteria. Van Klink summarized 13 studies and found a prevalence of 6.1% for cerebral palsy and 9.8% neurodevelopmental impairment [40]. Preterm delivery was an independent risk factor for neurodevelopmental impairment after laser treatment [41]. Other important risk factors were increased gestational age at intervention, higher Quintero stage, perinatal severe cerebral injury and low birthweight [38,42].

Twins with TTTS have the highest risk for congenital heart defects in comparison to uncomplicated MC twins and singletons. The prevalence of heart disease in children after laser therapy was investigated in cohort studies. Herberg and coworkers found in six (9.7%) out of 62 survivors at the age of 10 years a structural heart defect [43]. Pulmonary stenosis was the main finding and detected in 5 cases, both in former recipient and donor twins.

A detailed review of long-term outcomes for MC twins after laser therapy in TTTS has been published recently, including neurodevelopmental and cardiovascular outcomes, growth, renal function and ischemic events [44]. Furthermore, potential effects of intrauterine programming on later life have to be taken into account.

Future directions

We should keep in mind, that fetoscopic laser treatment is still an invasive procedure with some non-negligible risks. Research focuses on prevention of complications, such as iatrogenic preterm rupture of membranes and consecutive miscarriage and preterm birth, which on the other hand is also a complication of TTTS itself, owing to the massive polyhydramnios. Another aspect is the optimal point of entry for the fetoscope, which may be challenging in cases with an extensive anterior placenta. Chmait et al. have recently shown that trocar insertion particularly in the lateral lower uterine segment was associated with an increased risk of preterm rupture of membranes within 21 days after the procedure [45]. In addition, Petersen et al. retrospectively reviewed 673 fetoscopic laser cases from 6 centers according to port sizes [46]. An increasing access diameter was associated with preterm birth

before 28 weeks, but neither with preterm rupture of the membranes or birth <4 weeks nor with latency from laser to birth. Cervical length was critically associated with obstetrical outcomes.

A future aim is the development of a non invasive treatment for TTTS. High-intensity focused ultrasound (HIFU) has already been used for twin reversed arterial perfusion sequence (TRAP) [47]. This case report described the successful cessation of blood supply to the acardius acranius by HIFU for the first time. Recently, a case series of six TRAP patients using HIFU has been published [48]. In three cases blood vessels to the acardiac twin were occluded, but two patients had fetal demise of the pump twin. In animal models HIFU has been used and placental vascular flow was occluded in 28 of 30 targets and histological examination confirmed occlusion in 24 [49]. This in vivo sheep model seems to be promising. However, its effectiveness and safety in human pregnancies has still to be assessed. An essential prerequisite is the development of an ultrasound or MRI based placental mapping of all vascular anastomoses before the procedure. Until then continous technical improvements such as flexible mini-fetoscopes may increase the chance of visualization of the whole vascular equator in anterior placentas, especially in cases where anastomoses are close to insertion site of the fetoscope.

Unfortunately, many cases of TTTS worldwide are still left untreated. A global survey of 64 centers of fetal therapy units offering laser treatment for TTTS identified 33 high-volume (>20 procedures annually) and 31 low-volume (<20 procedures annually) units, respectively [50]. The investigators found a striking difference between the two groups in terms of the geographic location. Low-volume centers were more frequently located in South America, Australia and the Middle East ($p < 0.01$). In contrast, 79% of the 19 European fetoscopic centers were high volume units. Therefore, some regions may have difficulties to establish and run high volume centers offering laser treatment in TTTS. Meanwhile, international collaborations with the goal to provide timely access to treatment is a main challenge.

There are some early prenatal ultrasound criteria available for risk estimation regarding the development of TTTS (intertwin discordance of crown rump length, nuchal translucency, and ductus venosus flow velocity waveforms), but these have the disadvantage of poor positive predictive values [51,52]. We have focused on the umbilical coiling index in TTTS cases (unpublished data) and performed a prospective study using three-dimensional ultrasound with color Doppler imaging of the umbilical cord in untreated TTTS cases. In 65 recipients and 56 donors coiling index could be quantified at the day of laser surgery. The mean coiling index of recipient twins was significantly higher than of donors. Discordance of the umbilical cord coiling in TTTS may reflect the recipients' hyper- and the donors' hypovolemia. Future studies are needed to evaluate whether intertwin first trimester coiling index discordance may act as an early predictor for TTTS.

Conclusion

In conclusion, fetocopic laser coagulation is the gold standard for treatment of severe TTTS at midgestation (16–26 weeks). There is some evidence, that early and late laser interventions are feasible and may improve the outcome. Some fetal medicine centers offer conservative management with close surveillance at stage I TTTS. However, shortening of the cervix, maternal discomfort and increasing polyhydramnios are criteria to perform laser treatment. Since the introduction of fetoscopic laser surgery for TTTS 25 years ago, perinatal mortality decreased significantly. High-volume centers are able to achieve 70% double twin survival and survival of at least one twin in >90% of cases after fetoscopic laser treatment. To achieve this laser therapy should be centralized in specialized centers performing at least 20 procedures per surgeon annually. Prospective registration and standardised long-term outcome studies are important [53].

It will be interesting if non invasive treatment for TTTS will be feasible in the future. Meanwhile technical progress in terms of flexible scopes may improve the visualization and coagulation of all anastomoses.

Conflict of interest

None of the authors has a conflict of interest.

Practice points

- Women carrying a MC pregnancy should be informed about the clinical symptoms of TTTS (rapid increase of uterine size, preterm contractions, back pain)
- Every MC twin pregnancy should be monitored by ultrasound fortnightly for a timely diagnosis of TTTS
- Fetoscopic laser surgery is the first line treatment of severe TTTS because the effectiveness of this therapy is evidence based and addresses the underlying cause.
- Centralization of intrauterine surgery is mandatory because high-volume fetal medicine centers performing laser surgery show the highest survival rates.
- The "Solomon" technique is a promising method, but larger studies regarding complications and long-term follow-up are needed.

Research agenda

- Standardised long-term follow up studies.
- Reduction of prematurity and consecutive neurodevelopment impairment.
- Development of new technologies such as HIFU (depending on placental imaging modalities) and flexible scopes.
- Identification of early predictors for the development of TTTS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2018.12.011.

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