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Title: Teaching and quality control in fetoscopic surgery
Issue Date: 2015-05-13

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The research described in this thesis was performed at the Department of Obstetrics of the Leiden University Medical Center, the Netherlands

ISBN 9789461089687

Cover: Stephan van Oppenraaij, Studio OOenO reclamemakers, Joanne Verweij
Placenta and fetus developed by Remie Bakker, www.manimalworks.nl
Layout and printing: Gildeprint, Enschede
Illustrations general introduction: Amanda Gautier, www.gautierillustration.com

The publication of this thesis was financially supported by:

Ten Holter Noordam advocaten
Stichting IDB te Voorschoten
Chipsoft
Afdeling Verloskunde LUMC
Afdeling Neonatologie LUMC
Afdeling Kindergeneeskunde LUMC
BMA BV (Mosos)
Wetenschapsfonds Hagaziekenhuis
Hoytema stichting

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 13 mei 2015
klokke 13.45 uur

door

Suzanne Hendrika Philomena Peeters

geboren te Dordrecht
in 1985

PROMOTIECOMMISSIE

Promotor:	Prof. Dr. D. Oepkes
Co-promotores:	Dr. E. Lopriore
	Dr. J.M. Middeldorp
Overige leden:	*Prof. Dr. M.C. De Ruiter*
	Prof. Dr. F.W. Jansen
	Prof. Dr. L. Lewi (University Hospitals KU Leuven, België)

CONTENTS

Part 1

General introduction

1. TWIN PREGNANCIES

Around 1% of all pregnancies are twin gestations. Approximately 70% of twin pregnancies are non-identical twins (dizygotic); the other 30% are identical (monozygotic) twins. Dizygotic twins result from the fertilization of two eggs, and apart from a few exceptions, have separate placentas and separate inner (amnion) and outer (chorion) membranes. Each fetus is supplied by its own placenta. Therefore, by definition, dizygotic twins are dichorionic (DC) (e.g. have two placentas).

In monozygotic twinning, one zygote (fertilized egg) splits into two separate embryos, ultimately forming two (identical) individuals. Placentation in monozygotic twins depends on the timing of separation. If cleavage occurs before day 3 post-conception, both twins have separate placentas and each twin has its own chorionic and amniotic membranes.[1] Such twins are often indistinguishable from dizygotic twins, at least on ultrasound and by placental examination.

In the majority of monozygotic twins (70-75%), cleavage occurs within 3-8 days and twins share one single placenta, one single chorionic membrane but they have separate amniotic sacs. These twins are called monochorionic (MC) diamniotic twins. Division after 8 days results in monochorionic monoamniotic (MA) twins (sharing one placenta and one amniotic sac). MA pregnancies are rare and account for 1-5% of all monozygotic twin pregnancies.[2-4] Except for some sporadic cases[5,6] all MC pregnancies are monozygotic. (Figure 1)

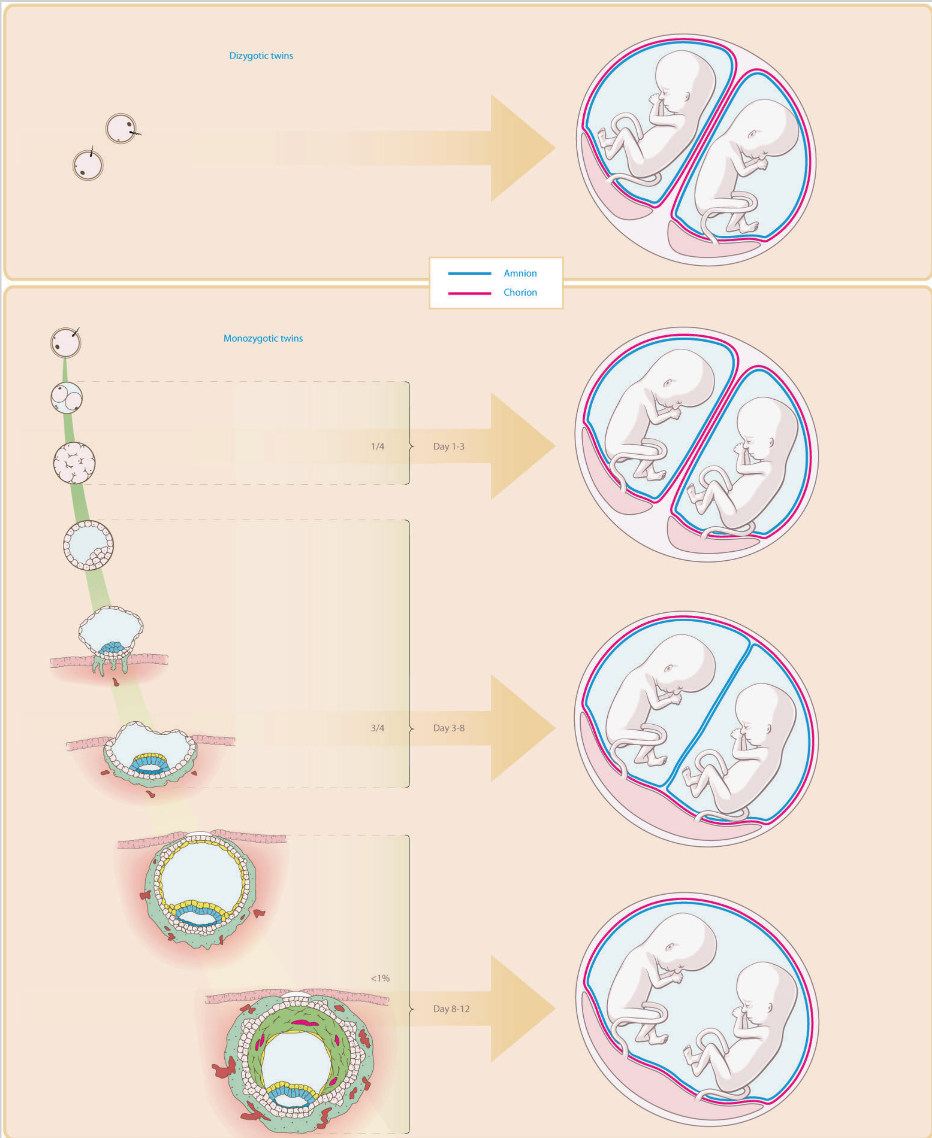

Figure 1. Dizygotic twins versus monozygotic twins resulting in dichorionic (DC) and monochorionic (MC) twins

Chorionicity (whether or not twins share a placenta), rather than zygosity, determines the outcome of twin pregnancies. MC twins have a two times higher risk on adverse perinatal outcome compared to DC twins and four times higher compared to singletons.[7,8] Some complications can only occur in twins that share a placenta, therefore ultrasound examination, preferably in the first trimester, to determine the number of placentas and amniotic sacs is crucial.

Problems that occur exclusively in MC pregnancies arise from the blood vessels that connect the circulations of both twins, called vascular anastomoses. These vascular anastomoses are present in virtually all MC twin placentas, and almost never occur in DC placentas. Three different types of vascular anastomoses can be identified: unidirectional artery to vein anastomoses (AV) and the superficial bidirectional artery-to-artery (AA) and vein to vein (VV) anastomoses. (Figure 2) Intertwin transfusion through these vascular anastomoses can lead to various complications including twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS) and twin reversed arterial perfusion (TRAP).

Figure 2. Placenta injected with colored dye illustrating the different types of vascular anastomoses

2. TWIN-TWIN TRANSFUSION SYNDROME

TTTS is a condition that complicates 10% of MC pregnancies.[8,9] This syndrome is the result of an unbalanced exchange of blood through the vascular anastomoses at the placental surface. This imbalance occurs when blood flow from one twin through unidirectional AV anastomoses is insufficiently compensated by blood flow through AV anastomoses in the opposite direction or through bidirectional superficial AA or VV anastomoses. This imbalance creates a transfusion from one twin (the donor) to the other twin (the recipient). The number, size and type of anastomoses play an important role in the development of TTTS.[10,11]

The transfusion causes the donor twin to have decreased blood volume resulting in decreased urinary output, leading to a low level of amniotic fluid (oligohydramnios). The blood volume of the recipient twin is increased, which causes a higher than normal urinary output, which leads to excess amniotic fluid (polyhydramnios) and can strain the fetal heart and eventually can lead to heart failure. (Figure 3)

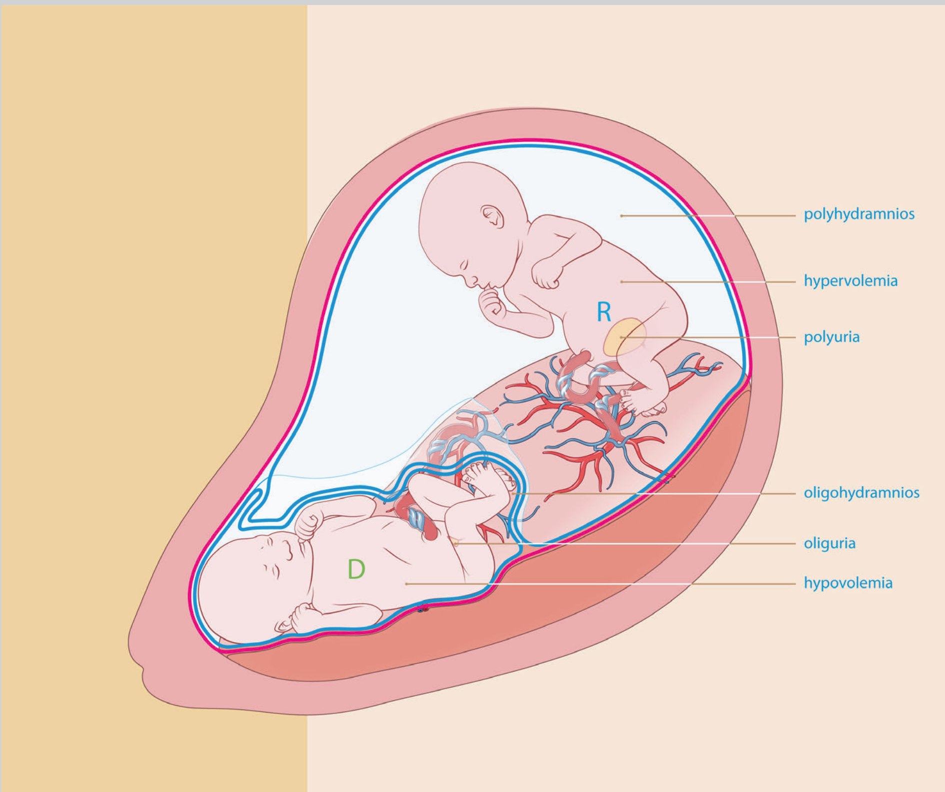

Figure 3. Twin-twin transfusion syndrome. (TTTS) D is donor, R is recipient

TTTS carries a high risk of adverse perinatal outcome due to miscarriage, intrauterine death or premature birth. The polyhydramnios in turn may cause the rupture of membranes, contractions, cervical shortening and immature or premature birth. If not treated, mortality rates in TTTS may be as high as 80 to 100%.[12-14] Treatment options for TTTS include symptomatic treatment with amniodrainage (draining of excess amniotic fluid through a needle that is passed into the sac of the recipient to reduce the symptoms caused by polyhydramnios) or causal treatment with fetoscopic laser coagulation of the vascular anastomoses. First choice treatment is laser coagulation.[12,15-17] (Figure 4)

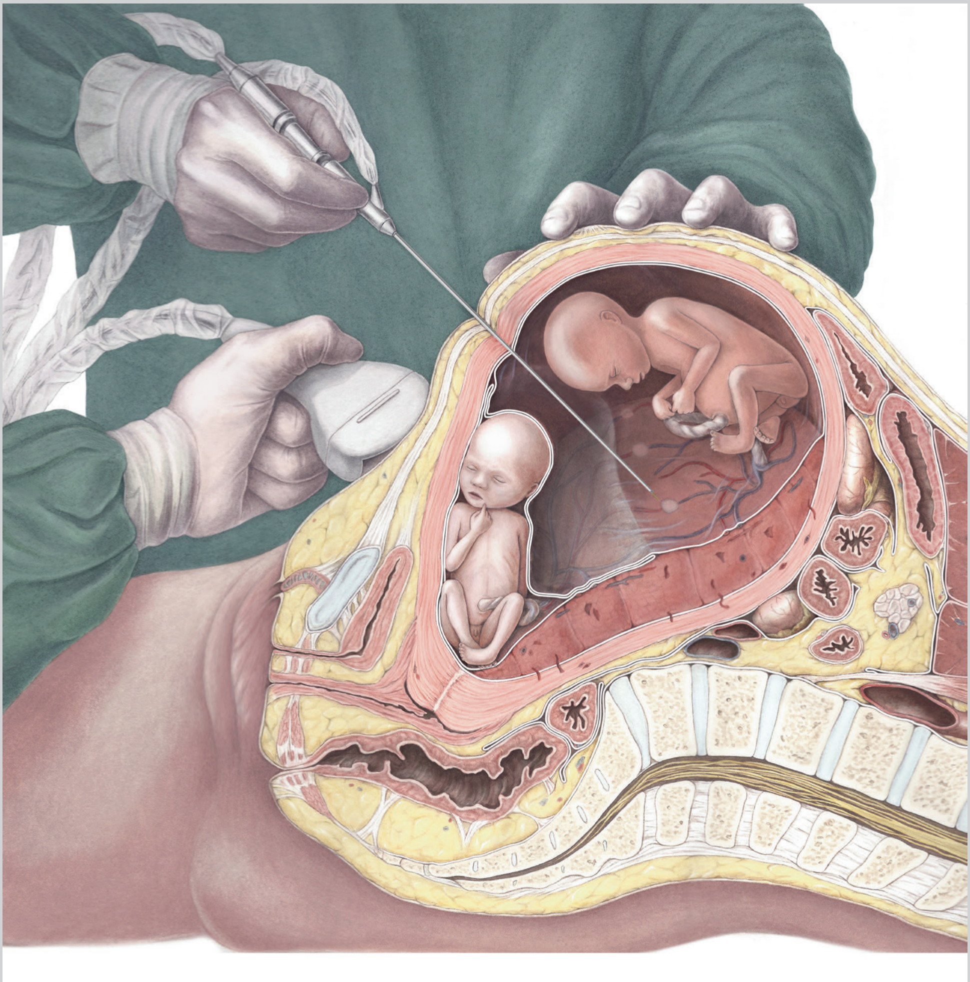

Figure 4. Fetoscopic laser coagulation of vascular anastomoses

3. LASER THERAPY

Fetoscopic laser coagulation is a technique used to separate the fetal circulations by coagulating the connecting vessels with a laser beam. (Figure 4) The surgeon introduces a small fetoscope into the amniotic cavity of the recipient twin, identifies the vascular equator (place where the vascular anastomoses meet) and attempts to laser them one by one. By coagulation of all vascular anastomoses the underlying cause of the disease is addressed through a single intervention.

With this treatment, perinatal outcome improved compared to serial amniodrainage, (drainage of the excess amniotic fluid without adressing the cause of the problem; the vascular anastomoses) however, results are still far from optimal. After laser therapy survival rates of both fetuses reach 35-67%.[12,18-22] Among the surviving children, 4–16% have signs of cerebral injury and 6–18% have neurodevelopmental complications.[23-26]

The goal of fetoscopic laser surgery is to coagulate all anastomoses. However, in up to 4-33% of treated pregnancies, some intertwin vascular connections remain patent.[27-31] These remaining connections, called residual anastomoses, are associated with severe complications such as TAPS (13%) or recurrent TTTS (14%).[32,33] A modified laser technique; the Solomon technique, was developed to minimize the occurrence of residual anastomoses. (Figure 5)
The rationale of the Solomon technique is coagulation of the whole vascular equator from one placenta margin to the other (drawing a line). Recently, a large randomized controlled trial showed that the Solomon technique significantly reduced the risk on TAPS and recurrent TTTS.[33,34]

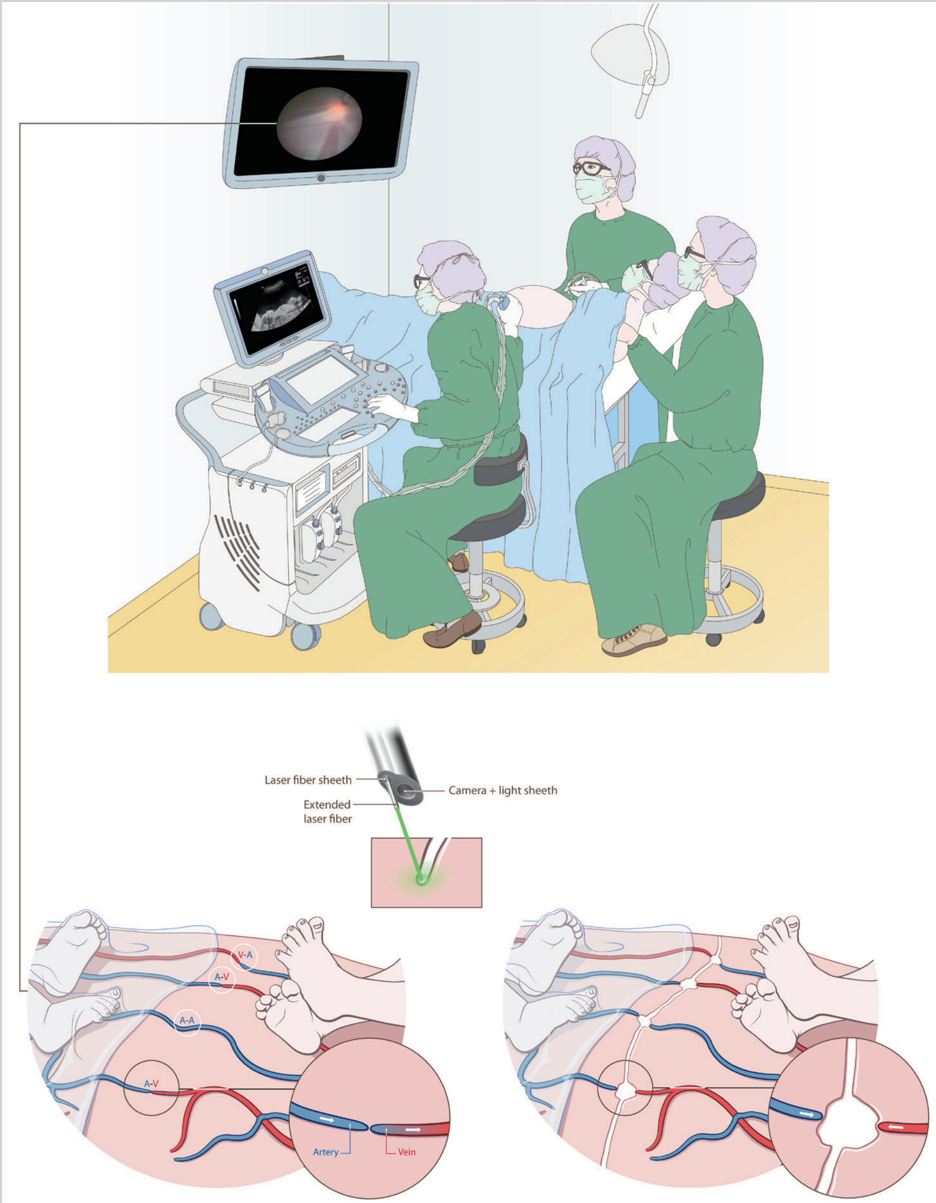

Figure 5. Fetal therapy team during operation and vascular anastomoses before and after laser coagulation using Solomon technique

4. LEARNING CURVE

It has only been 25 years since fetoscopic surgery was performed for the first time and nowadays it is still offered in a limited number of highly specialized Maternal Fetal Medicine (MFM) centers around the world. Recently published series from even the most experienced groups still show a high percentage of single or double fetal loss, and a mean gestational age at birth of around 32 weeks.[21,22] In this thesis we evaluate outcomes of the pioneers in fetal therapy in the beginning years compared to current performance. Since 2000, over 600 MC twin pregnancies complicated by TTTS have been treated with fetoscopic laser surgery in the Leiden University Medical Center (LUMC). The LUMC is one of the eight tertiary care centers in the Netherlands, and serves as the national referral center for fetal therapy. Per year 60-70 patients are treated with laser surgery.
With the acceptance of laser surgery as the best treatment, an increasing number of centers offering this procedure are expected. There is concern that a more widespread use of this technique, at least temporarily, will lead to less favourable outcomes due to learning curve impacts and small numbers. Since TTTS is rare, and both the surgical procedure as well as careful selection of cases and optimal timing of treatment is complex, concentration of care in specialized MFM centers has been advocated.
The concept of a "learning curve" is being used increasingly in surgical training and education to denote the process of gaining knowledge and improving skills.[35,36] An often-arising question in all types of surgery is the actual number of procedures an individual operator has to perform to achieve satisfactory outcomes and results. In principle, novice surgeons are assumed to perform surgery less safely and efficiently than more experienced colleagues at the peak of their career.[37]
In addition, there are hardly any studies that address monitoring of performance among experienced operators in fetoscopic surgery. In other (surgical) areas this topic is extensively studied since assessment of performance can improve quality of care.[38] Without the use of quality monitoring systems, substandard care and errors may easily be underestimated.
Therefore in this thesis we aim to investigate the learning curves and evaluate performance of individual operators in fetoscopic surgery.

Several authors initially documented treatment criteria and laser techniques[39,40] and (minor) modifications have been introduced through the years.[31,41-43] Today, quite substantial differences appear to exist between centers in their specific approaches, instrumentation and guidelines for accepting patients for laser surgery, making it difficult to compare results between centers.

As in many fields of medicine and in particular in surgery, concentration of care for highly specialized procedures has been recommended,[44,45] and the relationship between surgical volume and operative outcome was investigated.[46,47] Performance by high-volume surgeons and at high-volume hospitals is associated with reduction in morbidity and lower costs.[48,49] In this thesis we aim to identify the differences in practice of fetal therapy centers and relate this to center volume.

5. CHALLENGING MONOCHORIONIC PREGNANCIES

Fetoscopic laser therapy, although quite effective, is associated with high risk of complications.[43,50,51] Complications that occur in the first week after fetoscopic laser surgery include miscarriage, premature rupture of membranes immediately after intervention, placental abruption and intrauterine fetal death. Late complications include preterm premature rupture of membranes before 32 weeks gestations, fetal demise, recurrence of TTTS and TAPS and neonatal death.

Some surgeries are more challenging than others. In this thesis we concentrate on the following subgroups with TTTS; monoamniotic (MA) pregnancies, pregnancies with unintentional perforation of the intertwin dividing membranes and triplets.

Spontaneous MA pregnancies are rare and account for 1% of all monozygotic conceptions.[2,3,52] The perinatal loss rate in MA twins varies from 8 to as high as 42%.[53,54,55] High perinatal loss rates have been attributed mainly to umbilical cord entanglement, intertwin transfusion syndromes, discordant fetal abnormalities or growth and preterm birth.[2,56,57]

Due to close proximity of the umbilical cord insertions and absence of amniotic membrane separating the two cords, entanglement (with the cords forming a knot) occurs in almost all MA pregnancies. During labor and birth compression on either of the cords by pulling the knot may lead to discontinuation of the blood flow, and is suspected to be the cause of double intrauterine fetal demise. Fetal sonographic surveillance and preterm caesarean section as mode of delivery is advised. In some of these cases antenatal surgical interventions become necessary. In this thesis we aim to review relevant aspects of fetal surgical interventions in complicated MA pregnancies.

As with all invasive procedures, perioperative complications of laser surgery itself increase the risk of adverse outcome.[58] One of these complications is unintentional perforation of the intertwin dividing membranes (e.g. the plane of separation between the two twins by the amniotic membranes), thereby creating an iatrogenic MA twin pregnancy.

Some of the complications of spontaneous MA may also occur in iatrogenic MA pregnancies. Clinical implications of iatrogenic MA twins, and optimal management strategies in these pregnancies, have not yet been established. Since perforation is not always detected during or directly after surgery, this diagnosis can be missed easily, unless specific attention is given to its features during follow up examinations. If rupture of the intertwin membranes is suspected, pregnancies are often monitored more closely, hospitalization after viability is considered and a preterm cesarean section is scheduled between 32 and 34 weeks' gestation to prevent cord accidents. (Figure 6) Uncomplicated MC twin pregnancies after laser surgery are often allowed to continue to around 36 weeks. Therefore, in this thesis we study if this group of MC pregnancies treated with laser therapy was associated with lower gestational age at birth, with concomitant adverse effects on neonatal morbidity.

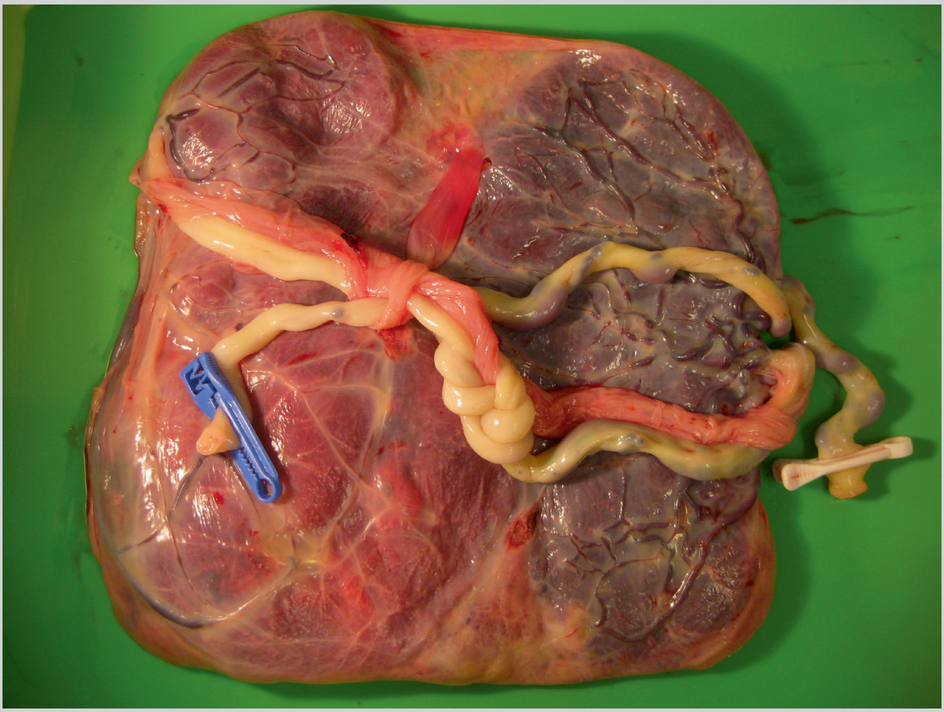

Figure 6. Iatrogenic monoamniotic (MA) placenta with knot in the umbilical cords

TTTS is not only seen in MC twins, it can also occur in higher order multiple pregnancies such as triplet gestations. Management options depend on the type of placentation; triplet pregnancies can be trichorionic (i.e. 3 fetuses with separate placentas and amniotic cavities), dichorionic (DC) (i.e. monochorionic twins and a singleton with a separate placenta) or monochorionic (MC). (i.e. 3 fetuses with one shared placenta and three amniotic cavities) The prognosis of TTTS in MC triplets is considered to be different from DC triplets and has been reported to be severe, with higher rates of mortality and preterm birth, despite intervention.[59,60] Although technically more challenging, fetoscopic surgery is feasible in triplets. In this thesis we compare perinatal outcome of MC and DC triplets with TTTS.

6. STANDARDIZED TREATMENT AND TRAINING

It is clear that fetoscopic surgery is restricted to a few highly specialized surgeons. However, coming years more fetal surgery will be performed. It is expected that new centers that start to perform fetal therapy will exhibit a learning curve and require guidance in learning the procedure. To ensure that the level of expertise is maintained, an evidence based training curriculum and continuous process of reporting and monitoring of outcomes is required.

Standardized surgical training programs for fetoscopic surgery are nonexistent. Since definitions of errors and inadequate technique are lacking, educators often base their teaching on personal experience and individual preferences. In this thesis we focus on the development of evidence-based guidelines for fetoscopic laser treatment of TTTS.

Learning skills from an experienced mentor will always continue to play a significant role in training. However, there is an increasing need for a standardized evidence-based tool to train and evaluate trainees. In this thesis we develop and a procedure-specific evaluation tool for fetoscopic laser surgery.

As for any other procedure it seems logical to offer appropriate training and supervise early practice. Since fetoscopic procedures are performed on an infrequent basis, the surgeon in training is forced into a lengthy and expensive stay in a (often distant) fetal therapy center to accumulate at least some hands-on experience. Even large fetal treatment centers have limited numbers of cases, and animal models are lacking, therefore teaching and training this procedure is challenging.

In addition, ethical concerns are raised about teaching basic skills on a patient, when alternatives are available. Skills acquired on box trainers [61,62] and virtual reality trainers[63,64] are transferable to surgery on real patients. Simulator training may bypass the early learning curve, which is known to be associated with an higher rate of complications.[65] Therefore we investigate if a standardized training curriculum using a high fidelity simulator can contribute to retaining high standards and quality of care in fetal therapy. (Figure 7)

Figure 7. Simulator model for fetal therapy

7. OUTLINE OF THIS THESIS

Teaching and quality control in fetoscopic surgery

Fetoscopic surgery is a surgical technique that is used to treat fetus(es) that are still inside the pregnant uterus. Coming years, more fetoscopic surgery will be performed. The most commonly performed procedure is laser surgery for twin-twin transfusion syndrome.

This thesis shows learning curves for this procedure and current practice in relation to technical aspects and pregnancy outcomes. We show how to monitor performance and address specific subgroups in which laser surgery can be more complicated. Since teaching and training in fetoscopic surgery is challenging, we create and validate an evidence-based evaluation tool for the laser procedure. To conclude, we develop a standardized training curriculum with a high fidelity simulator model.

Part I. General introduction

Part II. Learning curve and current practice

Chapter 1 – Learning curve and ongoing quality control for fetoscopic laser coagulation in TTTS. Using the cumulative sum analysis this study assesses the learning curves and monitored ongoing performance of four operators performing fetoscopic laser therapy.

Chapter 2 – Global survey on laser surgery for TTTS. In this study we evaluate the differences between international fetal centers in their treatment of TTTS by fetoscopic laser therapy.

Chapter 3 – Review of literature on survival after fetoscopic laser surgery in TTTS comparing the outcomes of early years of practice with current practice.

Part III. Challenging monochorionic pregnancies

Chapter 4 – Case series and review of the literature on antenatal surgical interventions in MA pregnancies complicated by TTTS, TRAP, discordant anomalies, or request for elective reduction.

Chapter 5 – In this study we evaluate management and outcome of pregnancies treated with laser surgery for TTTS complicated by iatrogenic rupture of the intertwin dividing membranes compared to those with intact intertwin membranes.

Chapter 6 – In this study we evaluate outcome of monochorionic triplets complicated by feto-fetal transfusion syndrome. We compare monochorionic triplets with dichorionic triplet and perform a review of the literature.

Part IV. Model for training laser therapy

Chapter 7 – Study on the essential steps of the laser procedure for TTTS. Using the Delphi methodology we create an evidence based evaluation instrument to assess fetal surgeons.

Chapter 8 – In this study we assess reliability and construct validity of an evaluation instrument that can be used for technical skills assessment and feedback in training fetal surgeons.

Chapter 9 – We conducted a randomized controlled trial to evaluate the effect of a standardized simulator training for fetoscopic laser surgery.

Part V. Summary

Part VI. General discussion

In the summary and general discussion the most important findings of this thesis are outlined and future perspectives are given.

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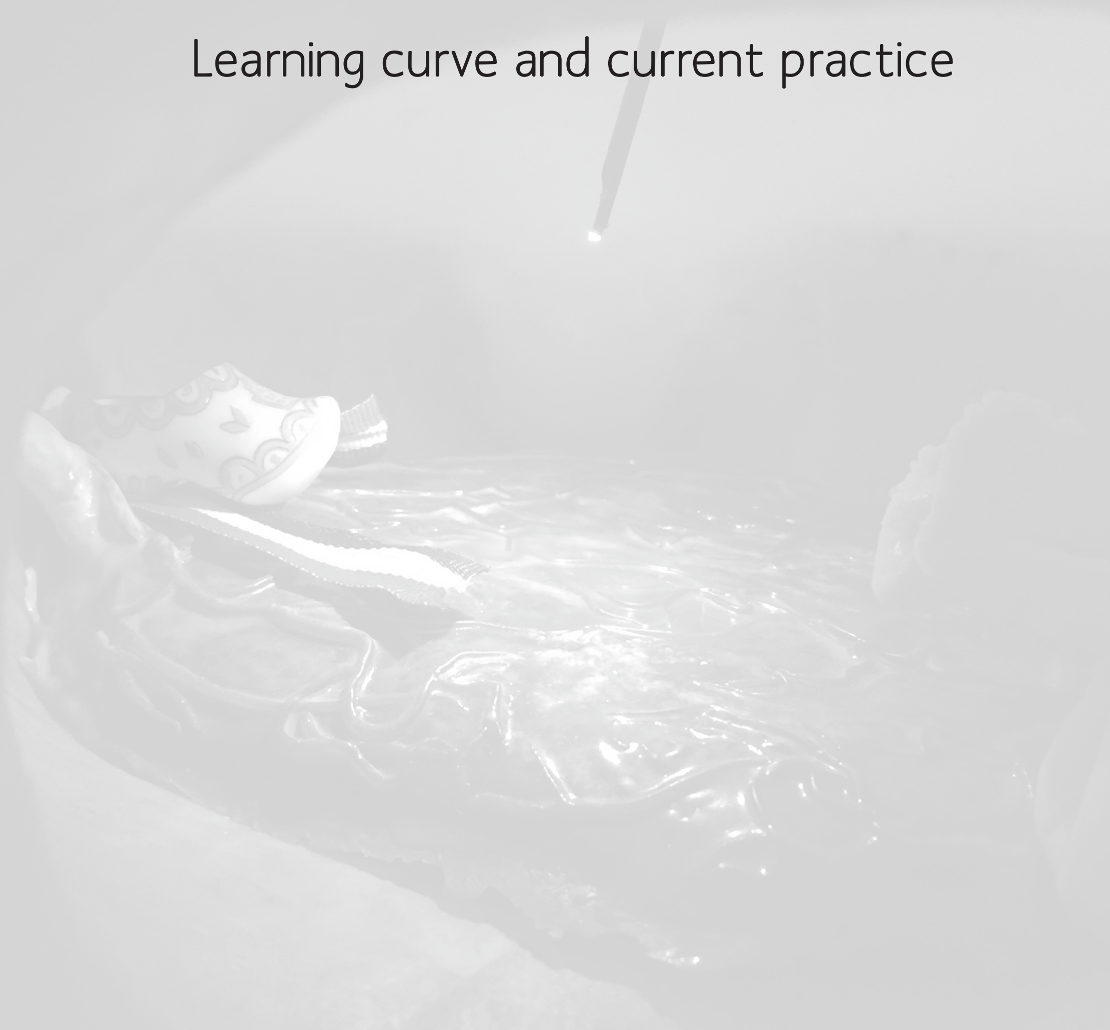
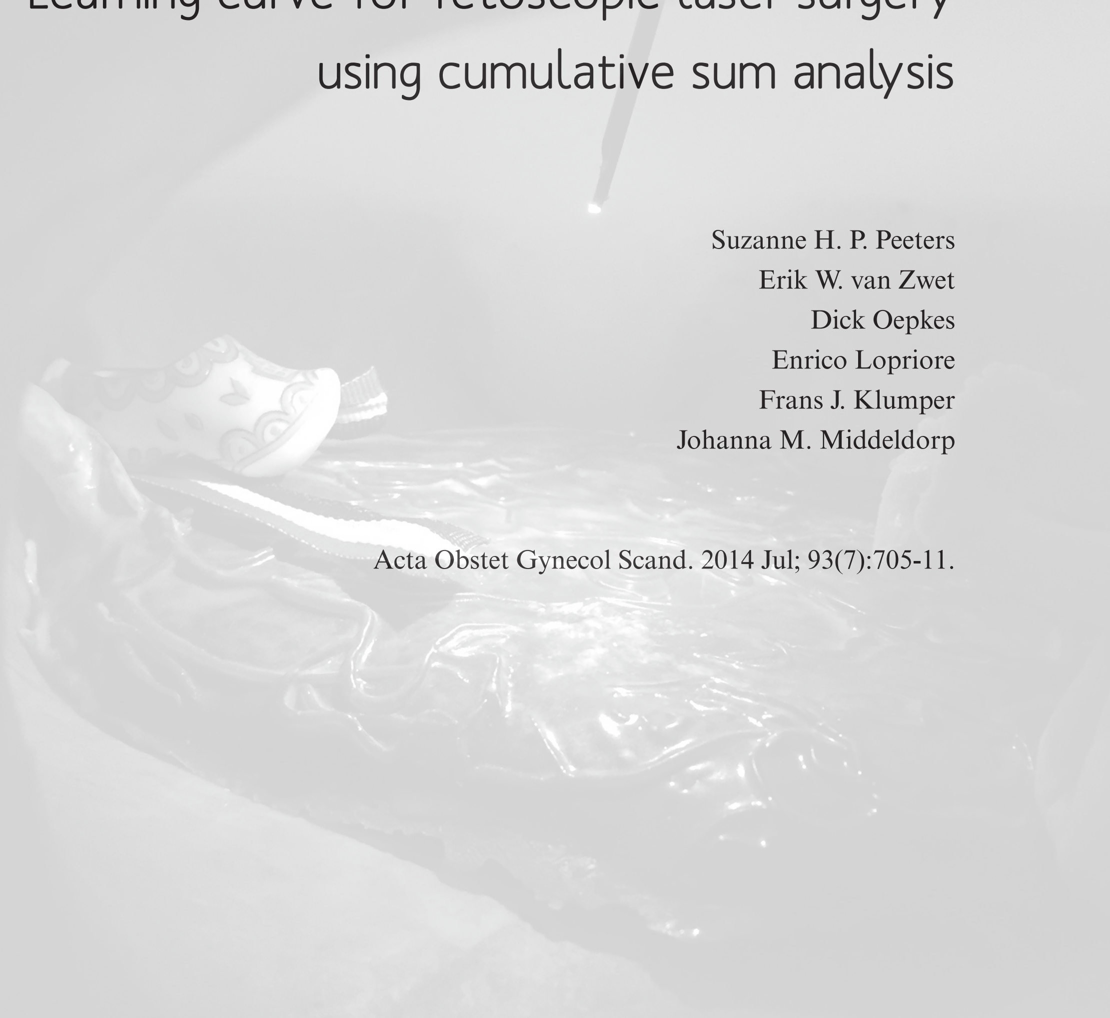
Part II

Learning curve and current practice



Chapter 1

Learning curve for fetoscopic laser surgery using cumulative sum analysis



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ABSTRACT

Objective. To identify a learning curve and monitor operator performance for fetoscopic laser surgery for twin-to-twin transfusion syndrome using cumulative sum analysis.

Design. Retrospective cohort study.

Setting. National tertiary referral center for invasive fetal therapy.

Population. A total of 340 consecutive monochorionic pregnancies with twin-to-twin transfusion syndrome treated with fetoscopic laser coagulation between August 2000 and December 2010.

Methods. A learning curve was generated using learning curve cumulative sum analysis and cumulative sum methodology to assess changes in double survival across the case sequence. Laser surgery was initially performed by two operators, joined by a third and fourth operator after 1 and 2 years, respectively.

Main outcome measures. Individual operator performance, double perinatal survival at 4 weeks.

Results. Overall survival of both twins occurred in 59% (201/340), median gestational age at birth was 32.0 weeks. Cumulative sum graphs showed that level of competence for double survival for the operators was reached after 26, 25, 26, and 35 procedures, respectively. Two operators kept their competence level and continued to improve after completing the initial learning process; two others went out of control at one point in time, according to the cumulative sum boundaries. A difference in learning effect was associated with number of procedures performed annually and previous experience with other ultrasound-guided invasive procedures.

Conclusions. This study shows that all operators reached a level of competence after at least 25 fetoscopic laser procedures and confirms the value of using the cumulative sum method both for learning curve assessment and for ongoing quality control.

INTRODUCTION

Mastering the skills necessary to perform surgical procedures with success, ease, and safety represents a learning curve for each surgeon. The learning curve itself ultimately represents the acquisition of competency, which affords an understanding of a new technique, technical modifications to the technique and improvements in support staff and perioperative care.

Learning curve patterns may vary depending on the type of surgical procedure, choice of outcome measurements[1], and from one surgeon to another.[2] Surgical training programs commonly prescribe a certain length of time or number of procedures performed to certify operators as proficient. A common question is: what is the actual number of procedures an individual operator has to perform to achieve satisfactory outcome results? The course of performance of an individual or group of surgeons can be plotted over time. In principle, novice surgeons are assumed to perform surgery less safely and efficiently than more experienced colleagues at the peak of their career.[3]

Although there is growing interest in tracking individual surgical outcome, traditional monitoring tools generally fail to consider the gradual learning process of starting surgeons. Cumulative sum (CUSUM) analysis is a graphical method for quality control to show changes in individual surgical performance. This technique is increasingly used as a management tool in medicine for competence monitoring.[4] The learning curve CUSUM (LC-CUSUM) test has been proposed to determine when a surgeon reaches a predefined level of performance while learning a new procedure.[5]

Twin-to-twin transfusion syndrome (TTTS) is one of the most common major complications of monochorionic twin pregnancies and carries a high risk of perinatal mortality and morbidity.[6] Fetoscopic laser coagulation is the treatment of choice [8,9] and with an increasing number of centers offering this procedure there is concern that, at least temporarily, less favorable outcomes will be seen because of learning curve effects. Identifying a learning curve for laser surgery is a logical step in the progression of incorporating this technique into the surgeons' armamentarium of procedures available in highly specialized Maternal–Fetal Medicine centers.[10]

We aim to use the CUSUM methodology to define the learning curve and monitor operator performance for fetoscopic laser coagulation.

MATERIAL AND METHODS

At the Leiden University Medical Center, the national referral center for invasive fetal therapy, a retrospective study was performed on prospectively collected data on all monochorionic twin pregnancies with TTTS treated by fetoscopic laser coagulation of vascular anastomoses between August 2000 and December 2010. Inclusion criteria for laser surgery were: monochorionic pregnancy, gestational age between 13 and 28 weeks, TTTS Quintero stage 1 with severe clinical symptoms of polyhydramnios, or TTTS Quintero stage ≥2. For this analysis, cases were not included if mothers were clinically in labor at time of diagnosis (n = 17). None of the other pregnancies were excluded once the fetoscope had been introduced into the amniotic cavity, even if laser coagulation was not possible. Details on the procedure were previously reported (11).

All surgeons eligible for training and performing fetoscopic laser surgery were experienced maternal–fetal medicine specialists with an academic career focusing on fetal medicine. Preconditions for training included extensive knowledge and experience in fetal medicine, expertise in diagnostic procedures including highest level of ultrasound, amniocentesis, chorionic villus sampling, and fetal blood sampling. All fetal surgeons were well-trained gynecologic laparoscopists.

Laser surgery was initially performed by two operators, joined by a third and fourth operator after 1 and 2 years, respectively. In the initial stage each procedure was attended by at least two operators; however, only one was performing the fetoscopy and laser surgery, others could observe and help to determine vascular anastomoses. Two procedures were performed by a foreign operator in the first year of laser therapy and excluded for learning curve analyses.

The technique that was used for the laser procedure underwent minor adjustments through the years, similar for all operators. Some of the women (n = 84) included in this study also participated in the randomized Solomon trial (www.trialregister.nl; NTR1245). The data on obstetric and neonatal outcomes were derived from medical charts. Demographic characteristics, details on the fetoscopic surgery, further interventions, and outcomes were prospectively collected in our fetal database. Pregnancy outcomes included survival up to 4 weeks after birth, intrauterine fetal demise and preterm delivery.

All surgeries were classified as failed or successful. Criteria for classifying a procedure as failed were: fetal loss of one or both twins and the occurrence of perinatal death within 28 days after the procedure. For this analysis, double perinatal survival, defined as survival up to 4 weeks of age, was chosen as a primary outcome. Individual prior experience with other ultrasound guided invasive procedures, such as intrauterine blood transfusion, chorionic villus sampling, and amniocentesis per operator was assessed. Individual performance with fetoscopic laser coagulation was analyzed by describing the number of procedures performed in consecutive years and the corresponding success rates.

Statistical analysis

For each surgeon, two types of CUSUM charts were constructed, to assess the learning curve and to monitor performance according to the number of successful procedures;[5,12] these are described in more detail in Appendix S1. A CUSUM score was computed from the successive outcomes, with successes yielding an increase in the score and failures yielding a decrease in score. In graphs, CUSUM scores are plotted on the y-axis against the consecutive number of procedures on the x-axis. The horizontal limit lines in CUSUM-graphs determine the spacing between unacceptable (H0) and acceptable (H1) boundaries, i.e. the null and alternative hypotheses. Once the score has reached a predefined level (L), the test rejects the null hypothesis in favor of the alternative and performance is deemed acceptable. In LC-CUSUM graphs the learning phase is completed when limit "L1" is crossed with accumulation of successive scores. CUSUM scores are then reset at 0 before starting the monitoring phase.

Control limits decide whether performance is unacceptable. In this study an "expert level" was calculated, to define acceptable and unacceptable boundaries as input for the CUSUM analysis, based on three of the largest recently published studies[6,13,14] and the only randomized controlled trial on fetoscopic laser therapy in TTTS.[9] Combining outcomes of these recent studies with survival rates of 67%,[13] 54%,[14] and 57%,[6] respectively, we calculated the "expert level" to be a mean survival of both twins at 4 weeks after delivery of 59% (H1: $p = 0.59$). The unacceptable boundary was set as 36% (H0: $p = 0.36$).[9]

The CUSUM score emits a signal in case of persistent deviation towards a deterioration or improvement in performance; by reaching either lower (H0) or upper (H1) limits. Conversely, the performance is assumed to be acceptable as long as the CUSUM score remained within the limits. The thresholds L1 (for competence) and L2 (for incompetence) are set differently. As it is likely that performance will be less successful during the learning phase, and to minimize the probability that performance of an operator who is not yet competent is noted as acceptable; L1 = 3.4. To quickly identify suboptimal performance of an operator who already completed the learning phase; L2 = 2.5.

Factors that may influence the outcome of the procedure such as gestational age, Quintero stage, placenta localization, and introduction technique were compared for all procedures performed by each operator by using chi-squared test and one-way analysis of variance. Taking these patients' risk factors into consideration, all CUSUM scores were calculated based on risk-adjusted case failure. Therefore operative failures in high-risk patients are not as visually significant on the CUSUM chart as they would be in low-risk patients. A p-value ≤0.05 was considered to indicate statistical significance.

Statistical analysis was performed with IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA). No ethics approval was required for this study.

RESULTS

In total, 340 monochorionic pregnancies treated with fetoscopic laser coagulation were included in this study. Characteristics and outcomes of all treated pregnancies sorted by procedures per operator are described in Table 1. Operator 1 performed significantly more combined open laparoscopy for anterior placenta in the starting years of fetoscopy.[15] Other possible confounding factors, such as Quintero stage and placenta localization, were not significantly different between all operators, nonetheless high-risk patients (i.e. advanced Quintero stage, anterior placenta) were identified to calculate adjusted-risk CUSUM scores. Secondary analysis of preoperative characteristics over the consecutive years showed no significant differences. Overall perinatal survival rates of at least one twin and double survival were 86% (294/340) and 59% (201/340), respectively.

Survival rate at birth, including triplet pregnancies, was 76% (528/690), equally divided among recipient twins in 72% (244/340) and donor twins in 75% (256/340). Neonatal death occurred in 21 neonates [from 19 pregnancies, 6% (19/340)]. Delivery occurred before 24 weeks in 11% (36/340), before 28 weeks in 18% (61/340), before 32 weeks in 41% (139/340), and before 34 weeks in 57% (194/340) of pregnancies. Ten triplet pregnancies were treated, all were dichorionic triamniotic triplets. In five triplets, all children survived at birth, in the five other cases single intrauterine fetal demise occurred. One former recipient died within 4 weeks after birth. Figure 1 shows the number of procedures performed per individual operator and fetal outcome using LC-CUSUM and CUSUM plots. The graphical data demonstrate a range of time over which competence was attained and kept. Operators 1 and 2, starting at almost the same time in 2000, had similar learning curves. The learning phase of operators 1 and 2 ended after procedure 26 and 25, respectively, demonstrated by crossing the L1 threshold. For operator 1 an alarm was set at the 95th procedure (red circle), indicating inadequate performance. The performance of operator 2 remained in between alarms and therefore performance was deemed adequate. Operator 3 finished the learning curve after 26 procedures; however, after setting stricter boundaries, performance became unacceptable after the 38th procedure because of accumulated failures. Performance improved directly hereafter, as shown by the dotted line in the plot. Operator 4, starting 2 years after the first operator was declared competent after 35 procedures and remained competent. In Table 2, number of procedures performed, individual success rates and previous experience with ultrasound-guided procedures are summarized.

	All pregnancies (n = 340)	Operator 1 (n = 110)	Operator 2 (n = 109)	Operator 3 (n = 72)	Operator 4 (n = 49)	*p*-value
Gestational age at laser surgery (week), median (range)	20+0 (13+4-29+4)	19+6 (13+4-29+4)	20+1 (14+3-27+4)	20+4 (14+4-29+0)	19+6 (14+5-25+6)	0.48
Gestational age at birth (weeks), median (range)	32+0 (15+6-41+2)	31+6 (18+0-40+0)	32+2 (15+0-41+2)	31+6 (16+4-40+6)	31+5 (17+0-39+1)	0.88
Preterm birth <24 weeks gestational age, n (%)	36 (11)	13 (12)	7 (6)	11 (15)	5 (10)	
Quintero stage I, n (%)	35 (10)	13 (12)	7 (6)	7 (9)	8 (16)	0.11
Quintero stage II, n (%)	109 (32)	43 (39)	31 (28)	22 (31)	13 (27)	
Quintero stage III, n (%)	181 (53)	46 (42)	68 (62	40 (56)	27 (55)	
Quintero stage IV, n (%)	15 (5)	8 (7)	3 (4)	3 (4)	1 (2)	
Placental localization posterior, n (%)	187 (55)	50 (45)	58 (53)	47 (65)	32 (65)	0.09
Placental localization anterior, n (%)	137 (40)	55 (50	44 (40)	22 (31)	16 (33)	
Placental localization lateral, n (%)	16 (5)	5 (5)	7 (7)	3 (4)	1 (2)	
Percutaneous insertion, n (%)	304 (89)	83 (75)	104 (95)	69 (96)	48 (98)	0.01
Laparotomy, n (%)	10 (3)	6 (6)	2 (2)	2 (3)	0 (0)	
COLFAP, n (%)	26 (8)	21 (19)	3 (3)	1 (1)	1 (2)	

Table 1: Characteristics of 340 pregnancies complicated by twin-to-twin transfusion syndrome and treated with laser surgery sorted by operator.
Legend: COLFAP, combined laparoscopy and fetoscopy in cases with completely anterior placenta.

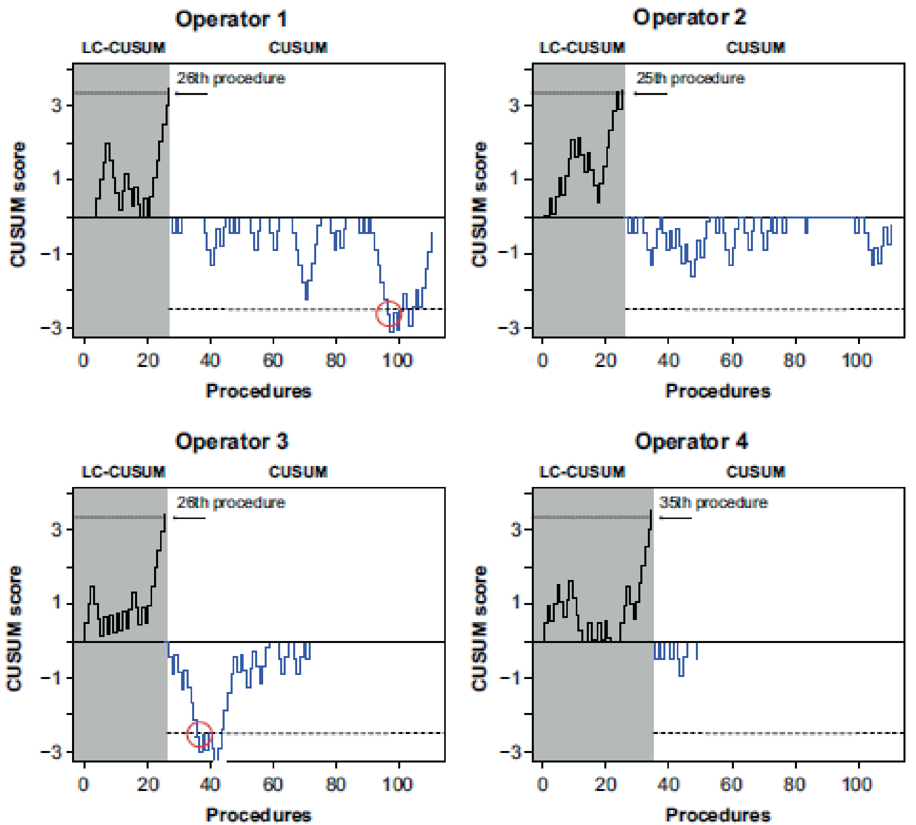

Figure 1

The individual learning curve cumulative sum (LC-CUSUM) and cumulative sum (CUSUM) plots for fetoscopic laser coagulation in twin-twin transfusion syndrome in four operators representing double survival at 4 weeks.

Legend: The consecutive number of performed procedures on the x-axis is plotted against the actual CUSUM value on the y-axis. LC-CUSUM and CUSUM scores are plotted in terms of the successive procedures, evaluating performance by double survival. LC-CUSUM is applied until acceptable performance has been reached and CUSUM is used thereafter to ensure that adequate level is maintained. For the LC-CUSUM (black line), as long as the score remains below the limit "L1" (dotted line), the operator is not considered proficient; when the LC-CUSUM score crosses this limit, the operator has completed the learning phase. For the CUSUM (blue line), as long as the score remains under the limit, the operator is considered to maintain an acceptable performance. The dotted blue lines represent the CUSUM score from operators that showed unacceptable performance as a result of a peak in failure rate (red circle) during their CUSUM monitoring phase.

Operator	Period	Procedures (n)	At least one survivor		Double survival		Annual procedures (mean number)	Previous experience (years)*
			n	%	n	%		
Operator 1	Aug 2000 to Dec 2010	110	94	85	66	60	11	9
Operator 2	Dec 2000 to Dec 2010	109	100	92	69	63	11	8
Operator 3	Jan 2002 to Dec 2010	72	58	81	40	56	8	3
Operator 4	Oct 2002 to Dec 2010	47	42	89	26	53	7	3
Total procedures	Aug 2000 to Dec 2010	340	294	86	201	59	34	na

Table 2 Operator's success and experience.
Legend: *Determined as experience with other ultrasound-guided invasive procedures (intraperitoneal transfusion, chorionic villus sampling and/or amniocentesis).

DISCUSSION

Our study shows an increase in survival rates with growing operator experience, using an LC-CUSUM method to assess individual learning curves. In addition, the CUSUM analysis for continuous monitoring of individual performance proved both feasible and highly insightful. The number of procedures required to reach an adequate level of performance ranged between 26 and 35 in our four operators. The minimal individual variation in learning profiles may be explained by the "group" learning effect, by influence of general expertise and exchange of experience.
Two operators showed a peak in failure rate during their CUSUM monitoring phase. Such an event may have multiple explanations, which cannot be inferred from the CUSUM analysis but requires in depth analysis of the procedures itself, such as difference in technical details with other operators, and particular case mix during this period. This is an illustrative example of the use of CUSUM plots for monitoring of performance among experienced operators, a practice which these operators continued beyond the study period. In particular, CUSUM enables almost real-time evaluation, in contrast to other less sophisticated methods, such as annual or 3-monthly reports. The use of CUSUM prevents potentially hazardous delay in taking action to improve outcome. In the case of real-time assessment one should consider monitoring and coaching these operators according to the LC-CUSUM standards, until they again reach acceptable levels of performance. However, awareness of underperformance alone may already improve outcomes.
Due to the retrospective design of this study, ongoing CUSUM scores were plotted and rapid recovery was demonstrated within a short time. The difference in learning curves between all operators was probably the result of operator 4. Operator 4 reached a level of competence after 35 procedures. The slow initial accrual of cases by operator 4 could certainly have contributed to the upward trend of the CUSUM curve for these first 35 procedures. Operators 1 and 2 performed approximately 12 procedures per year, whereas operator 4 started off performing only four cases annually, although often supervised by an experienced colleague. Compared with the other operators, also previous experience with other ultrasound-guided invasive procedures was considerably different for operator 4. During analysis of preliminary results of this study in 2010 we already noted this effect and assured that surgeries were more equally divided among operators by making logistical changes in our clinic. Equal division of the number of procedures performed by each operator annually should be taken into account in case of learning curve assessment of rare procedures such as laser surgery in TTTS.

To optimize the learning curve in our center, in the initial phase each procedure was attended by at least two operators. In addition, all treated cases were discussed monthly in a multidisciplinary setting, with exchanging of ideas and suggestions for improvement of technique and prevention of complications. Another most helpful tool, in our view, was the systematic evaluation of each treated placenta through careful placental injection of colored dye.[16]

The learning curve in our series represents the improvement of both the operators, from experience and practice, and the performance of the entire team at managing pregnancies involving TTTS. Teamwork, discussion (including international audits),[17] stimulation, controllability, and continuity may be beneficial factors. Previous authors have shared their opinion on a learning curve for fetoscopic laser coagulation in TTTS. Julian De Lia, the pioneer of laser surgery in TTTS, describes that the end of his learning curve was reached after 33 procedures, although without further explanation.[18] Hecher et al. reported a learning curve of 75 procedures and found a significant increase in perinatal survival over time.[19] Defining a learning curve with a predefined number of cases fails to take into account that individual operators may not achieve proficiency with a fixed sample size. Papanna et al. used similar LC-CUSUM and CUSUM analysis to determine the learning curve for three operators, reaching a level of competence after 60, 21, and 21 procedures, respectively.[20] However, this study did not include risk adjustment for high-risk patients, which may highly influence the slope of the CUSUM plots. Results of our center with four operators showed similar pregnancy outcomes as published series with one operator[19] and the presumed disadvantage of dilution of procedures does not seem to exist in our unit, likely due to the team approach.

Case selection, by either treating predominantly high risk or low-risk cases during the learning phase, may bias learning curve results. This effect should be taken into account during assessment of competence. Setting appropriate thresholds for acceptable and unacceptable performance is difficult. In this study we used literature-based expert levels, but an alternative may include historical data from the own unit with advantage of having comparable case-mix. Likewise, the choice of design parameters for CUSUM is critical to its performance, other surgical parameters such as operating time or presence of residual anastomoses may be useful endpoints to classify the operation as successful or failed. One of the limitations in this study is that the effect on an individual learning curve by assisting another operator was not measured. This however may have a positive influence on individual expertise levels. This effect was described by Kolkman et al., who showed that mentor traineeship can accelerate the learning curve of advanced laparoscopic procedures.[21] The other attributable effect that was not measured included the extent of the operators' experience with obstetric ultrasound, invasive fetal diagnostic and therapeutic procedures, and endoscopy prior to starting laser therapy. These skills probably contributed to a steeper individual learning curve.

In summary, this study evaluated the learning curve for fetoscopic laser coagulation as an example of minimal invasive intrauterine treatment. CUSUM analysis is well suited to the assessment of procedures with a binary outcome, but accurate and appropriate standards of practice must be determined before assessment to ensure the correct identification of underperformance. A prospective study would be able to evaluate the value of the CUSUM technique as a continuous audit system, allowing urgent real-time feedback to improve the quality of surgery. Determination of an accurate learning curve, as well as evaluation of individual surgeons, will be of great value with relevance to other procedures to decrease medical error and substandard performance, and to improve quality.

ACKNOWLEDGEMENTS

We gratefully acknowledge Dr. I.L. van Kamp and Dr. I.T. Lindenburg, Department of Obstetrics and Dr. R. Wolterbeek, Department of Biostatistics at the Leiden University Medical Center for their contributions to the statistical analysis.

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APPENDIX 1.

CUSUM methodology

The cumulative sum (CUSUM) methodology is a graphical method to assess changes in individual surgical performance (1). CUSUM sequentially tests the null hypothesis that the process is in control, i.e. its mean is equal to a given target. Thus, it detects when the process changes to an out of control state. The learning curve CUSUM (LC-CUSUM) was developed based on two one-sided test procedures where the null hypothesis is that the process is out of control (2).

We introduced a null- and alternative hypothesis, but it should be stressed that a CUSUM analysis itself is not a hypothesis test. Irrespective of the level of expertise of the trainee, his or her CUSUM will eventually cross the threshold. Hence, the null hypothesis is always rejected and the probability of a type I error (α) is 1. Consequently, the probability of a type II error (β) is 0 (3). For this reason, the performance of a CUSUM procedure must be quantified differently.

Biau et al. recommended using simulation of average run lengths (ARL) (4). A simulated cohort of surgeons is used in which each surgeon was assumed to have a probability of making an error in a single case. The cumulated score for each case in the series was calculated until it crossed the terminating barrier L1, or until the maximum number of cases was reached. The run length is therefore defined as the number of cases until threshold L1 is crossed. This is a random variable, whose distribution depends on the skill of the surgeon. The ARL under H0 and H1 is sometimes used to quantify the performance of the CUSUM procedure. However, since the distribution of the run length is highly skewed, we prefer the Median Run Length (MRL).

Ideally, we would like the MRL to be very short under H1 (if operator is underachieving this will easily be detected), and very long under H0 (since it is likely that performance will be less successful while in the learning phase, if MRL under H0 is long, the probability of declaring a surgeon competent who in fact is not becomes small). By raising or lowering the threshold L1 we can change the MRL, but increasing the MRL under H0 means also increasing it under H1.

We used a Monte Carlo simulation (10,000 runs) to determine the MRL for our set of parameters. We found:

MRL for competence under H0: (p=0.36) 263
MRL for competence under H1: (p=0.59) 23

When a surgeon has been declared "competent" everything is turned around and (starting from zero) a CUSUM is constructed for:

H0: p=0.59 and H1: p=0.36

Now we continue on-going monitoring of performance until the CUSUM crosses a pre-defined limit L2=2.5 When that happens, the performance is discussed with the surgeon and possibly remedial actions are taken. Again, we computed the MRL:

MRL for incompetence under H0: (p=0.36) 89
MRL for incompetence under H1: (p=0.59) 15

We can turn a CUSUM into a hypothesis test, by choosing a fixed number 'n' and rejecting the null hypothesis if the threshold is crossed before the n-th case. In our case, we choose n=30, since this is a generally accepted number of procedures after which the learning curve should be completed (5;6). For the learning phase we found the probability of a type I error (α) is 0.05 and the power (1- β) 0.72. Therefore according to this analysis the probability to reject the hypothesis that performance is unacceptable, when performance is indeed unacceptable is low and the probability to reject the hypothesis that performance is unacceptable when in fact it is acceptable is high.

For the second phase, we found that the probability of a type I error is 0.17 and the power 0.87.

LC-CUSUM holds the feature that a barrier at 0 cannot be crossed and the score remains at 0 if the operator accumulates successive failures. In this way a starting surgeon will not have to compensate unnecessarily for the accumulated failures when starting a procedure. Since the performance of the surgeon is out of control at the beginning, an upper limit indicating this inadequate procedure is unnecessary. After an operator crossed boundary 'h' he or she has reached a level of competency and further performance is monitored with a CUSUM test.

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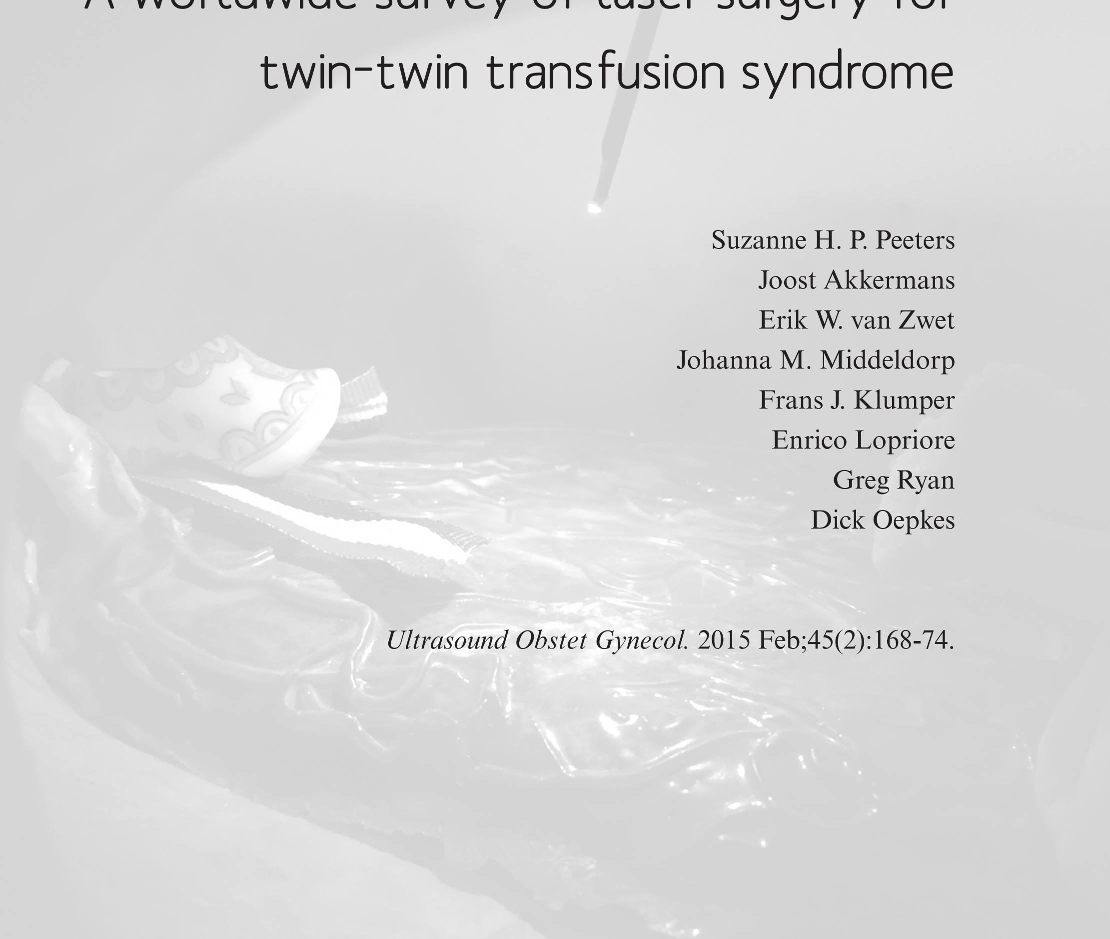
Chapter 2

A worldwide survey of laser surgery for twin-twin transfusion syndrome



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Ultrasound Obstet Gynecol. 2015 Feb;45(2):168-74.

ABSTRACT

Objective. To evaluate differences between international fetal centers in their treatment of twin–twin transfusion syndrome (TTTS) by fetoscopic placental laser coagulation.

Methods. Fetal therapy centers worldwide were sent a web-based questionnaire. Participants were identified through networks and through scientific presentations and papers. Questions included physician and center demographics, treatment criteria, operative technique and instrumentation. Laser treatment was compared between low-volume (< 20 procedures/year) and high-volume (≥ 20 procedures/year) centers. Data were analyzed using descriptive statistics.

Results. Of 106 fetal therapy specialists approached, 76 (72%) from 64 centers in 25 countries responded. Of these, 48% (31/64) of centers and 63% (48/76) of operators performed fewer than 20 laser procedures annually. Comparison of low- and high-volume centers showed differences in technique, gestational age limits for treatment and geography. High-volume centers more often used the Solomon technique and applied wider gestational age limits for treatment. Europe and Asia had more high-volume centers, whereas South America, the Middle East and Australia had mainly low-volume centers.

Conclusion. This survey revealed significant differences between fetal centers in several aspects of fetoscopic placental laser therapy for TTTS. Increasing awareness of TTTS, and of laser coagulation as its preferred treatment, will lead to an increase in centers offering this modality, especially in Asia, Africa, South America and the Middle East. Considering the rarity of TTTS and the relative complexity of the procedure, developing international guidelines for techniques, instrumentation and suggested minimum volumes per center may aid in optimizing perinatal outcome.

INTRODUCTION

Since the acceptance of laser coagulation of placental vascular anastomoses as the best treatment for twin–twin transfusion syndrome (TTTS), perinatal morbidity and mortality associated with this condition have substantially reduced.[1] However, results are still far from ideal, with overall mortality rates varying from 26% to 48% and significant attendant complications, such as iatrogenic preterm prelabor rupture of membranes, extremely premature delivery, twin anemia–polycythemia sequence (TAPS) and recurrence of TTTS.[2,3]

Fetoscopic surgery is now routinely offered in fetal medicine centers across the world. Since TTTS is relatively rare and the surgical procedure is quite complex, concentration of care in these specialized centers has been advocated.[4] Several authors have documented the treatment criteria and techniques[5,6] and (minor) modifications to the technique have been made over the years,[3,7,8] but as yet no literature that systematically documents the specific implementation of fetal therapy worldwide exists.

With the economic growth in developing countries, an increasing number of centers wishing to offer this procedure is expected. This raises some concern that a more widespread use of laser treatment may, at least temporarily, lead to less favorable outcomes owing to 'learning-curve' effects.[9,10] Because of the absence of uniform guidelines, centers base their practice on personal and mentor experience and individual preferences. Without the use of quality-monitoring systems, substandard care and errors may easily be underestimated. Therefore, we advocate the development of evidence-based guidelines for fetoscopic laser treatment of TTTS.

Today, differences appear to exist between centers in their specific approaches, instrumentation and guidelines for accepting patients for laser surgery, making it difficult to compare results between centers. With this international survey, we hope to take an important first step in the process of developing evidence-based international guidelines by evaluating differences between international fetal centers in their treatment of TTTS by fetoscopic placental laser coagulation.

METHODS

A participant database of e-mail addresses was created from the International Fetal Medicine and Surgery Society (IFMSS), the North American Fetal Therapy Network and the Eurofetus group. Furthermore, in 2013 fetal therapists were approached at the

IFMSS annual meeting in Jerusalem and at the International Conference of Prenatal Diagnosis and Therapy in Lisbon. Finally, fetal therapists who published on intrauterine therapeutic procedures indexed in *PubMed* were contacted. From this database, a list of 106 fetal medicine specialists was generated.

The specialists identified were asked to participate in an anonymous survey if they were actively involved in the evaluation and treatment of pregnancies complicated by TTTS. A web-based questionnaire was sent by e-mail between May and August 2013. Reminders were sent out to non-responders or responders with incomplete survey responses every 2 weeks up to 3 months after the initial invitation. E-mail addresses of all potential participants were linked to a unique key to track automatically responses and match blindly respondents from the same center.

The survey was designed *de novo* and consisted of three domains: specialist and center-specific demographics, laser technique for TTTS and instrumentation. Questions were generated through a discussion of fetal therapy specialists of the Leiden University Medical Center, Leiden, The Netherlands and the Fetal Medicine Unit of the Mount Sinai Hospital, University of Toronto, Toronto, Canada. The demographics included type of practice, geographical location, experience, number of TTTS cases evaluated and treated per year and number of fetal surgeons per center (Appendix S1). The technique domain of the survey consisted of questions on inclusion and exclusion criteria for laser therapy, anesthesia, entry technique, laser technique, cerclage and amnioreduction policy and postpartum placenta color-dye injection (Appendix S2). The instrumentation section of the survey consisted of questions regarding the fetoscopes and operating sheaths used in different clinical situations and the types of laser used (Appendix S3). The questionnaire gathered both quantitative and qualitative data from categorical, multiple choice and open-ended questions. A free-text field accompanied all questions to gather additional information and comments from the participants. The survey was pretested for face validity before distribution by an expert panel of five experienced colleagues. Survey entries were not eligible if the respondent did not perform laser treatment for TTTS.The total response rate was based on the number of fully completed eligible surveys.

The data were exported into an Excel spreadsheet (MS Office 2010; Microsoft Corp.,Mountain View, CA, USA) and descriptive statistics were undertaken using SPSS 20 v. 20.0 (IBM Corp., Armonk, NY, USA).

Data were analyzed per respondent and per center. For the center analysis, responses from operators from the same center were grouped. When discrepancies existed, the mean was used in numerical variables and in the case of categorical data; the centers' predominant answer was used.

For additional analysis, all centers were categorized into two groups depending on the number of laser procedures performed annually. Centers that performed ≥20 procedures annually were considered 'high-volume' centers and compared with 'low-volume' centers performing<20 procedures per year. Continuous variables are reported as mean (SD) or median (range); group differences were compared using the Mann–Whitney *U*-test or independent Student's *t*-test. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate, and *P*≤0.05 was considered to indicate statistical significance.

2

RESULTS

Of 106 fetal therapy specialists approached, 76 (72%) responded. In total, 64 centers from 25 countries participated. Most centers were located in North America (*n*=22 (34%)) and Europe (*n*=19 (30%)) (Figure 1).

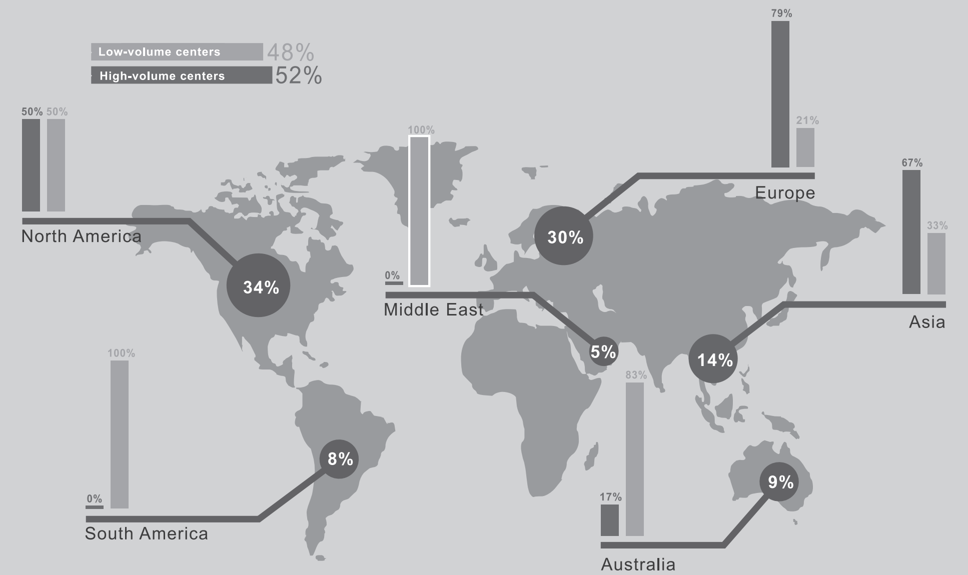

Figure 1
Geographical location of respondents and corresponding distribution of low-volume (n=31, 48%) ( ) vs high-volume (n=33, 52%) ( ) fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

The majority (80%) were based in university medical centers. Figure 2 shows the annual mean number of laser procedures carried out per center and the total number of laser procedures per geographical area. Thirty-one (48%) centers performed <20 procedures per year and were classified as low volume, compared with 33 (52%) that were classified as high volume. Forty-eight (63%) fetal therapists who responded performed <20 procedures per annum and 59 (78%) were older than 45 years of age and had a median of 20 (range, 4–37) years' experience in their field of practice. They had a median of 9 (range, 0.5–25) years' experience with laser procedures in TTTS. Almost all performed other twin-pregnancy related invasive procedures. Table 1 describes the demographics of the respondents. No significant differences in geographic distribution existed between responders and non-responders.

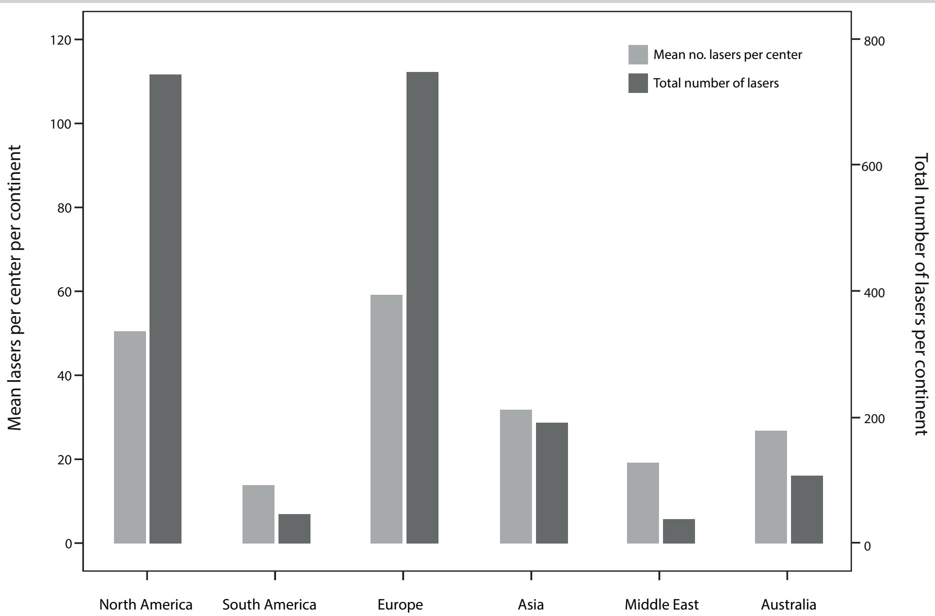

Figure 2
Total number of reported annual laser procedures ( ) according to geographical area and corresponding mean number of procedures per center ( ) in fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

Characteristic	Value
Gender	
Male	58 (76)
Female	18 (24)
Age	
< 36 years	—
36–45 years	17 (22)
46–55 years	38 (50)
≥ 56 years	21 (28)
Medical specialty	
Maternal–fetal medicine	72 (95)
Pediatric surgery	4 (5)
Years of experience with invasive obstetric procedures	18 (13–23)
Years of experience with laser therapy	9 ± 4.6
Laser procedures performed/year	
0–10	22 (29)
11–20	27 (36)
21–30	11 (14)
31–40	8 (11)
41–50	3 (4)
≥ 50	5 (7)

Data are given as *n* (%), median interquartile range or mean ± SD.

Table 1 Demographic characteristics of study population of 76 fetal therapy specialists

For anterior placentae, the median lower gestational age (GA) limit for laser surgery treatment was 16+0 weeks (31/64; 48%), ranging from 14+0 to 20+0 weeks and the median upper limit was 26+0 weeks (31/64; 48%), ranging from 22+0 to 32+0 weeks. For posterior placentae, the median lower GA limit was 16+0 weeks (34/64; 53%), ranging from 14+0 to 20+0 weeks, and the median upper limit was also 26+0 weeks (31/64; 48%), ranging from 24+0 to 32+0 weeks. Fifteen of the centers (23%) offered laser surgery before 16 weeks and 22 (34%) after 26 weeks' gestation.

The majority of centers preferred operating with the patient under local anesthesia with or without intravenous (IV) sedation (*n*=38 (59%)). In five (8%) of the centers, general anesthesia was the preferred form of anesthesia. The majority of procedures were performed in a general operating room (*n*=45 (70%)). Thirteen centers (20%) had a dedicated fetal surgery room and six (9%) a dedicated obstetric operating room available. Direct percutaneous trocar insertion was the preferred entry type in 50 (78%) centers and the Seldinger technique was preferred in 12 (19%) centers, although in three of the latter it was specified that, in certain circumstances, the direct percutaneous technique

was used; minilaparotomy was used in two (3%) centers as their preferred technique for trocar insertion. Cervical cerclage was never performed in the same session as the laser procedure in 20 (31%) of the centers and the majority considered cerclage only in cases with cervical shortening or dilatation (*n*=43 (67%)). Cerclage was part of the standard treatment procedure in only one center.
Table 2 presents the center-specific differences.

Irrespective of the placental location, selective laser coagulation, in which all true anastomoses crossing the vascular equator are coagulated, was the preferred technique in 26 (41%) centers. A sequential technique, first lasering arteriovenous anastomoses from donor to recipient, and aiming to minimize hemodynamic fluctuation, was used in 33 (52%) cases that had a posterior placenta and 30 (47%) that had an anterior placenta. The Solomon laser technique, i.e. lasering the complete vascular equator, was used in 18 (28%) cases that had a predominantly posterior placenta and in 15 (23%) cases that had an anterior placenta. Eleven (17%) centers combined sequential and Solomon techniques. Almost half of the responding centers (*n*=29 (45%)) used placental dye injection postnatally to assess completeness of the laser procedure.

A diode laser was used in 36 (56%) of the centers and a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in 23 (36%). Four (6%) centers used both diode and Nd:YAG lasers, and one center used potassium titanyl phosphate (KTP) laser in selected cases. Scope diameter used in procedures under 16 weeks' gestation ranged from 1.0 mm (3 Fr) to 3.8 mm (11 Fr), with 51% between 1.0 mm and 1.4 mm (4 Fr). Sheath diameter used in procedures under 16 weeks' gestation ranged from 1.0 mm to 3.8 mm, with 46% between 3.0 mm (9 Fr) and 3.4 mm (10 Fr). In procedures after 16 weeks' gestation, scope diameter ranged from 1.0 mm to 3.8 mm, with 57% between 2.0 mm (6 Fr) and 2.4 mm (7 Fr). Sheath diameter used in procedures after 16 weeks' gestation ranged from 2.0 mm to 4.0 mm (12 Fr), with 58% between 3.0 mm and 3.4 mm.

Characteristic	All (*n* = 64)	Type of center High-volume (n = 33)*	Low-volume (n = 31)†	*P*
Anesthesia				0.020
Local with/without sedation	38 (59)	23 (70)	15 (48)	
Regional (epidural/spinal)	19 (30)	8 (24)	11 (35)	
General anesthesia	5 (8)	—	5 (16)	
Other (50% local, 50% regional)	2 (3)	2 (6)	—	
Entry type				0.263
Percutaneous via direct trocar insertion	50 (78)	28 (85)	22 (71)	
Percutaneous via Seldinger technique	12 (19)	5 (15)	7 (23)	
Minilaparotomy	2 (3)	—	2 (6)	
Laser type				0.682
Diode	36 (56)	19 (58)	17 (55)	
Nd:YAG	23 (36)	10 (30)	13 (42)	
KTP	1 (2)	1 (3)	—	
Both Nd:YAG and diode	4 (6)	3 (9)	1 (3)	
GA upper limit > 26 + 0 weeks				
Anterior placenta	18 (28)	12 (36)	6 (19)	0.130
Posterior placenta	22 (34)	14 (42)	8 (26)	0.162
GA lower limit < 16 + 0 weeks				
Anterior placenta	12 (19)	7 (21)	5 (16)	0.603
Posterior placenta	15 (23)	8 (24)	7 (23)	0.875
Solomon laser technique				
Anterior placenta	15 (23)	11 (33)	4 (13)	0.054
Posterior placenta	18 (28)	13 (39)	5 (16)	0.039
Sequential laser technique				
Anterior placenta	30 (47)	16 (48)	14 (45)	0.790
Posterior placenta	33 (52)	18 (55)	15 (48)	0.622
Amnioreduction				1.000
Until DVP 4 cm	4 (6)	2 (6)	2 (6)	
Until DVP 6 cm	38 (59)	19 (58)	19 (61)	
Until DVP 8 cm	21 (33)	11 (33)	10 (32)	
Other	1 (2)	1 (3)	—	
Cerclage policy				0.891
Never	20 (31)	10 (30)	10 (32)	
Always	1 (2)	—	1 (3)	
When dilatation or shortening	43 (67)	23 (70)	20 (65)	
BMI limit exclusion for laser	4 (6)	2 (6)	2 (6)	1.000
Laser in MC twins with severe growth discordance	28 (44)	17 (52)	11 (35)	0.196
Short cervix not an exclusion for laser treatment	37 (58)	22 (67)	15 (48)	0.139
Placental dye injection	29 (45)	15 (45)	14 (45)	0.981

Data are given as *n* (%).

* High-volume defined as centers carrying out ≥ 20 laser procedures/year.

†Low-volume defined as centers carrying out < 20 laser procedures/year.

BMI, body mass index; DVP, deepest vertical pocket; GA, gestational age; KTP, potassium titanyl phosphate (laser); MC, monochorionic; Nd:YAG, neodymium-doped yttrium aluminum garnet (laser).

Table 2 Fetal therapy center-specific differences, including comparison of high- vs low-volume centers

Short cervical length was not considered as a contraindication to laser treatment in 37 (58%) centers, nor was a large maternal body mass index (*n*=60 (94%)). A previous amnioreduction was a contraindication for laser in four (6%) centers and triplet pregnancies were a contraindication in six (9%) of the centers. In 35 (55%) centers selective termination of pregnancy via cord occlusion was offered as a first-line alternative to laser therapy in cases of TTTS. Of the 29 centers that did not offer termination of pregnancy, five stated that they could not offer this owing to legal restrictions. In monochorionic twins with severe growth discordance, defined as an estimated fetal weight below the 10th percentile in the smaller twin and above the 10th percentile in the larger one[11] in the absence of diagnostic criteria for TTTS, laser therapy was offered as a first-line treatment in 28 (44%) centers.

We identified 33 high-volume and 31 low-volume centers, based on whether they performed ≥20 or <20 procedures annually, respectively. A striking difference between the two groups was their geographic location, low-volume centers being more frequently located in South America, Australia and the Middle East (P<0.01) (Figure 1). The number of fetal surgeons per center was higher in high-volume centers than in low-volume ones (P=0.03). Data on the annual number of procedures performed per center, with respect to the number of fetal surgeons per center, are presented in Figure 3. Anesthetic technique was quite different between the groups (P=0.02), general anesthesia being used as first choice in only five (16%) of the low-volume centers. For posterior placentae, high-volume centers more frequently used a Solomon laser technique (in some centers combined with a selective sequential technique) than did low-volume centers (39% (13/33) *vs* 16% (5/31), respectively) (P=0.04). GA limits for treatment were less strict in the high-volume centers, with an upper limit of >26+0weeks in 42% (14/33), compared with 26% (8/31) in the low-volume centers, but these results were not statistically significantly different (P=0.16).
Comparisons between high- and low-volume centers are presented in detail in Table 2.

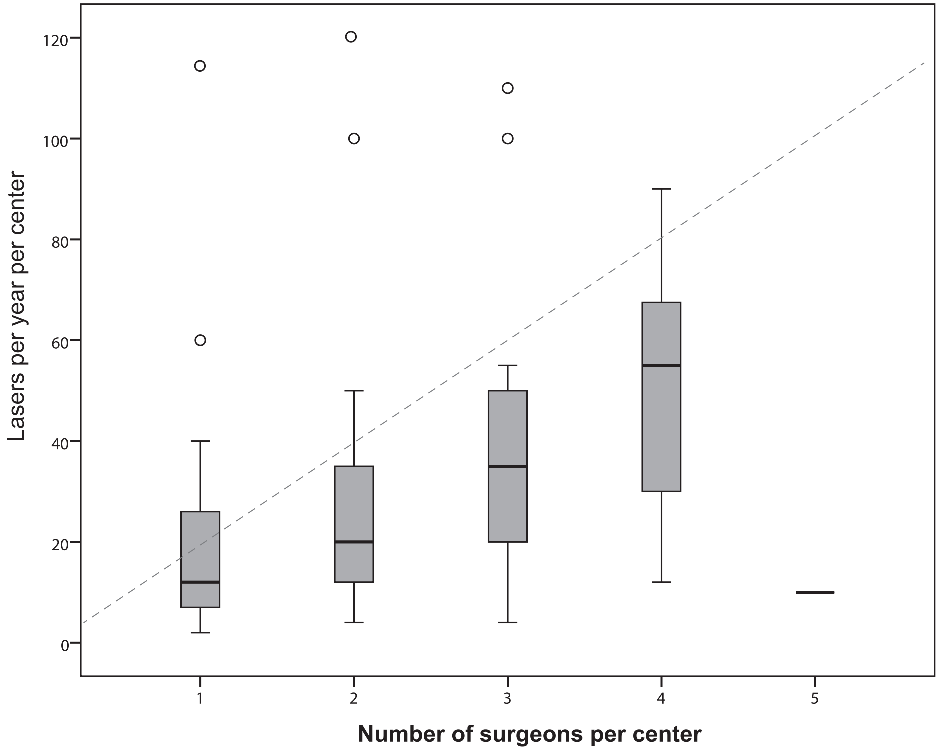

Figure 3
Box-and-whisker plots of number of surgeons per fetal therapy center according to number of procedures performed annually in centers offering laser treatment for twin–twin transfusion syndrome. Boxes represent median and interquartile range, whiskers are range excluding outliers and circles are outliers.

DISCUSSION

This is the first study to identify and compare differences in fetal therapeutic techniques and protocol for TTTS between centers worldwide. We demonstrate considerable variations in patient characteristics, instrumentation and techniques, which appear to be, at least partially, related to the volume of patients treated and geographical circumstances of the centers.

Throughout the world, different criteria for laser therapy are used among established fetal medicine centers. In particular, there are differences in GA limits and cervical length at which laser therapy is offered. Differences in patient selection, referral and treatment options may significantly affect perinatal outcome data. These variations hamper the interpretation and comparability of results from single centers.

Sixty-three percent of fetal therapists and 48% of centers perform <20 procedures per annum. Even though there is limited evidence concerning the ideal number of procedures that should be performed to maintain high-quality results[10], many studies have investigated the relationship between hospital volume data and postoperative surgical outcomes in other fields of surgery. Better outcomes have been reported in high-volume institutions for high-risk procedures.[12–14] 'Learning-curve' and monitoring studies show that approximately 20–30 procedures per year (per operator) are needed to maintain a requisite skill level.[9,10]. To optimize surgical outcomes and to decrease the incidence of medical error, we propose the implementation of a continuous audit system, allowing timely feedback at each center. If fewer surgical procedures are performed annually, lower-volume centers will be at risk of late recognition of substandard care or the incidence of complications.

Concentration of care for this highly specialized procedure has been advocated,[4] although geographical circumstances can justify the need for low-volume centers, since timely referral and treatment are associated with improved dual-twin survival and decreased neurodevelopmental delay.[15] However, Tchirikov et al.[16] showed that the advantages of state-of-the-art laser treatment in a specialized medical center outweigh the risks of long distance (air) transportation for TTTS patients. Since laser coagulation has been shown to be the treatment of choice for TTTS, the benefits of offering it, albeit in lower-volume centers, must be carefully weighed against offering only amnioreduction. In certain parts of the world, and for some patients, referral to larger, more experienced centers for laser treatment may not be possible.

Regardless of the number of fetal surgeons or number of procedures performed, infrastructure in the management of TTTS is of major importance. Success rates depend on performance of the entire team in the management of TTTS patients, as well as post-procedure follow-up by referring specialists. Teamwork, discussion (including international audits), stimulation and continuity may be factors that could help to optimize outcomes.

Since laser therapy was first introduced, several modifications have been described. Improvements in instrumentation and laser technique seem to have improved the success rate of placental dichorionization and thereby decreased the rate of subsequent complications. The use of smaller instruments to prevent iatrogenic damage to the membranes has been proposed once the learning curve has been overcome.[17] Recently an international randomized trial showed that complete coagulation of the vascular equator using the Solomon technique reduces the risk of recurrent TTTS and TAPS.[3]

In 55% of fetal medicine centers selective termination is available as an option, but it is not clear whether this should be offered routinely, or only in specific situations (such as in cases of discordant lethal anomalies or a moribund cotwin). In some centers selective termination is not possible, often because of legal restrictions. Whether or not this modality is available obviously influences several of the outcome parameters, hampering comparison between centers.

Currently in the USA the Food and Drug Administration only permits the use of the Karl Storz fetoscopic set for the treatment of TTTS between the GA limits of 16 and 26 weeks. This restricts the USA centers in using wider GA limits for treating TTTS or using laser treatment for other indications such as discordant growth restriction and TAPS.

Interestingly, we found that despite the lack of evidence for its efficacy, a large proportion (44%) of centers offer laser therapy for severe discordant growth restriction without evidence of TTTS. Before this new treatment option becomes assimilated into our therapeutic armamentarium, we suggest that it be evaluated as a matter of urgency by an appropriately powered, international, multicenter randomized controlled trial.

Our study has some limitations. Despite the use of fetal medicine networks to select participants, small start-up centers might not have been included in this survey. However, with a response rate of 72% (76/106) of fetal medicine specialists at the forefront of fetal therapy, we think that the majority of centers are well represented. For this study, the number of questions was limited and we relied on self-reporting of respondents, rather than documentation of their practice. The study reflects current practice and is of value in generating hypotheses and identifying areas for future research, but cannot be used as a guideline, thus our results should be interpreted with caution.

It should be borne in mind that many cases of TTTS worldwide go untreated, emphasizing the importance of ongoing education regarding TTTS. This study may serve as a starting point for further discussion regarding the optimal treatment strategies for TTTS and may provide a means of evaluating current therapeutic practices for patients with TTTS. Future studies should focus on the development of evidence-based guidelines for a standardized approach to the provision of laser treatment for TTTS.

ACKNOWLEDGEMENTS

We would like to thank all participants and participating centers for sharing invaluable data about their practice. This research is supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organization for Scientific Research (NWO) and which is partly funded by the Ministry of Economic Affairs.

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Chapter 3

25 years of fetoscopic laser coagulation in twin-twin transfusion syndrome: a systematic review

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Submitted

ABSTRACT

Background. The aim of this study was to assess the perinatal outcome of pregnancies with TTTS treated with laser therapy over the past 25 years and in relation to different techniques used in this time period.

Data Sources. A systematic review of studies reporting on perinatal outcome according to the MOOSE guidelines was conducted. MEDLINE, Embase and Cochrane databases were systematically searched. Comparisons were made in respect to time period, laser technique and Quintero stages.

Results. In total 34 studies reporting on 3.868 monochorionic twin pregnancies were included. Mean survival of both twins increased from 35% to 65% (p=0.012) and for at least one twin from 70% to 88% (p=0.009) over the past 25 years. Mean gestational age at birth remained stable over the years at 32 weeks' gestation. Also we showed a significantly improved perinatal survival with the evolution of the laser technique from non-selective to selective, selective sequential and the Solomon technique (p=0.010).

Discussion. Since the inception of laser therapy for TTTS more than two decades ago, perinatal survival improved significantly. Improved outcome is associated with several factors including evolution of the laser technique, learning curve effect, better referral and improved early neonatal care.

INTRODUCTION

Monochorionic (MC) twin pregnancies are at a 10% risk of developing twin-twin transfusion syndrome (TTTS),[1,2] due to vascular anastomoses on a shared placenta. Before De Lia et al. proposed fetoscopic laser coagulation of the placental vessels in 1990,[3] serial amnioreduction was considered the only treatment option of polyhydramnios, the most prominent feature of TTTS. Serial amnioreduction was associated with mortality rates up to 60%, a median gestational age at delivery around 28 weeks, and up to 50% severe neurodevelopment impairment in survivors.[4]

Survival significantly improved after the introduction of laser coagulation, by addressing the cause of the problem, making it the accepted treatment of choice for TTTS.[5] However, results are still far from satisfactory, with mortality rates varying from 20% to 48%, and significant complications including iatrogenic preterm premature rupture of membranes (PPROM)[6] resulting in preterm delivery before 32 weeks gestation, twin anemia-polycythemia sequence (TAPS),[7] recurrence or reversal of TTTS[8] and adverse long-term neurodevelopmental outcome in 6-18% of survivors.[9]

Since the first publications on fetoscopic laser surgery, several technical modifications have been described. Coagulation of all vessels crossing the intertwin membrane was abandoned because it led to unnecessary placental loss.[10] In 1998, Quintero et al. introduced the selective laser coagulation technique.[11] This technique, which was rapidly adopted by most fetal therapy centers, aims to save as much functioning placenta tissue as possible by coagulating only true inter-twin vascular anastomoses, instead of every vessel crossing the membranous equator. In 2007 the same group proposed the sequential selective laser coagulation technique.[12]

Sequential selective laser is an adaptation whereby anastomoses are coagulated in a specific order. The aim is to obliterate the anastomoses in a sequence that allows, at least partly, an intraoperative correction of the hypoperfusion of the donor and hyperperfusion of the recipient. This is achieved by first closing the arteriovenous anastomoses from donor to recipient, starting with the largest ones, followed by the closure of the vein-to-artery anastomoses, (e.g. the vessels with a blood flow towards the donor) as the last part of the procedure. In 2008 the Solomon trial[13] was started, introducing a new adaptation to the selective technique. The rationale of the Solomon technique is coagulation of the whole vascular equator from one placenta margin to the other. With the Solomon technique, all laser spots are connected by drawing a laser line, minimizing the chance of residual anastomoses. The study showed that this technique was associated with significantly less residual anastomoses, thereby reducing the risk for TAPS and recurrence of TTTS.

This study focuses on perinatal outcome after laser therapy over the past 25 years, and the impact of the above-mentioned changes in laser treatment strategies on these outcome results. We systematically reviewed all published series since the inception of laser treatment of TTTS with respect to survival, gestational age at birth and procedural or post-operative complications in relation to the time and the laser technique used.

Data Sources

Before conduct of the systematic review a detailed protocol that included the search strategies, inclusion and exclusion criteria, outcome parameters, and methods of statistical analysis was created. This systematic review of literature was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[14], and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[15] where applicable.

Literature Search

An initial literature search on survival after laser coagulation for TTTS was conducted in MEDLINE, Embase and the Cochrane Library using PubMed and OVID search engines without restriction on the language or type of publication. Keywords and free text searches were performed with combinations of the following keywords: survival, perinatal survival, twin-to-twin transfusion syndrome, TTTS, twin-twin transfusion syndrome, fetofetal transfusion, placental anastomoses, laser, laser therapy, laser ablation, SLPCV, SQLPCV, sequential laser, selective laser, fetoscopy, FLOC and photocoagulation. Additionally, reference sections of eligible studies were hand-reviewed for potential eligible studies. Our search included articles published up to May 2014 that reported on pregnancy outcomes after fetoscopic laser coagulation of placental vascular anastomoses.

Inclusion and Exclusion Criteria

Randomized trials and comparative studies, as well as prospective and retrospective case-series were considered eligible for inclusion. Reasons for exclusion were studies with insufficient or overlapping data, letters, conference abstracts, review articles and case reports.

Selection and Data Extraction

All references were independently screened by two reviewers (J.A. and S.H.P.) Disagreement on eligibility of a study was resolved by discussion until consensus was reached. Studies presenting data on twin pregnancies with confirmed monochorionicity by first trimester ultrasound, affected by TTTS according to the Eurofoetus criteria[16], or the Quintero criteria[17] treated with fetoscopic laser coagulation of vascular anastomoses were included.

Studies were selected when presenting at least the number of patients treated and either survival rate of both twins, survival rate of one twin, survival rate of at least one twin or gestational age at birth. Other important parameters were complications, such as PPROM, gestational age at laser and laser technique used. In the sporadic event that study results contained also outcomes of triplets (e.g. monochorionic twins affected by TTTS and a singleton) we used the perinatal outcome results of the twins for analysis.

To prevent double counting of cases, we excluded studies reporting outcomes from pregnancies that were treated in overlapping years with other published series from the same centers.

Differences in dual survival, single survival and at least one survival, as well as gestational age at birth were analyzed on a timeline. Five-year intervals were chosen to analyze studies over time. For categorization we used the year the study was concluded as a cut-off value. Survival was analyzed per laser technique used in the series to show the impact of the proposed technical adaptations of the laser treatment. Furthermore, we combined results of all series reporting on survival results per Quintero stage to evaluate stage-based outcome.

Statistical Analysis

Continuous variables were reported as the median (range) or mean (SD), for synthesis of data medians (range) were recalculated as means (SD) using the method described by Hozo et al.[18]

Results of multiple groups were compared using analysis of variance (ANOVA) statistics. Results of categorical variables were compared using Fisher exact test or $\chi 2$ test, as appropriate. Student *t* test was used to compare normally distributed values between 2 groups. The Mann-Whitney U test was used to compare nonparametric variables. A p value <0.05 was considered to indicate statistical significance.

Statistical analysis was performed using SPSS (IBM SPSS Statistics 20 for Windows, New York: IBM, 2011.) and MS Excel (Microsoft Excel 2010. Redmond, Washington: Microsoft, 2010). Being a literature review, no approval from our Ethics Committee was needed before performing this study.

RESULTS

Flow of study inclusion

Figure 1 shows a flow diagram according to the Quality of Reporting of Meta-analyses-statement[15] with the total number of citations retrieved by the search strategy and the number included in the review. After full-text analysis a total of 34 studies were included in the time-based analysis.[10,12,13,19-49] Twelve studies[5,50-60] presented data overlapping other series of which three presented data relevant for either the technique, or stage based analysis.[56,59,60] These three studies did not overlap other series in stage-based or technique-based analyses and were included in our analysis.

Study Characteristics

The characteristics of all included studies are shown in table 1. One of the studies enrolled was a randomized controlled trial;[13] there were 13 prospective single center cohort studies,[10,12,19-21,23-27,29,31,33] 18 retrospective single center cohort studies,[28,30,32,34-45,47,48,60] two prospective multicenter cohort studies[22,59] and three retrospective multicenter cohort studies.[46,49,56]

The studies were from United States, Belgium, Australia, Canada, Spain, Poland, Italy, Taiwan, Germany, The Netherlands, Denmark, United Kingdom, France, Japan, Mexico, Brazil, China and Chile. The primary outcomes; perinatal survival of at least one or both twins and gestational age at birth, were well defined in all included studies.

There were three non-English language articles.[35,36,41] Language skills of the authors and co-workers (Chinese) were sufficient to analyze the articles.

Three authors described their series in two separate cohorts in order to display their learning curve.[21,40,43] Eight studies compared different (adaptations of) laser techniques.[12,13,21,22,31,47,49,59] Baud et al. compared outcomes of early, late and conventional selective laser surgery defined as performed before 17 weeks gestation, after 26 weeks gestation and between 17 and 26 weeks.[48]

For the stage-based analyses we replaced the Quintero stage I cases from the study by Middeldorp et al.[26], with the series of Wagner et al.[60] from our center to have the most current non-overlapping results. Furthermore the series of Quintero et al. was replaced by the study of Chmait et al. for this analysis because of overlap and the latter presenting more data.

For the overlapping series of Nakata et al.[59] and Murakoshi et al.[42], we used the latter for the time-based analysis and the selective series from Nakata for the technique-based analysis. For the study of Liu et al. it was unclear what technique was used and therefore it was excluded in the technique-based analysis.[41]

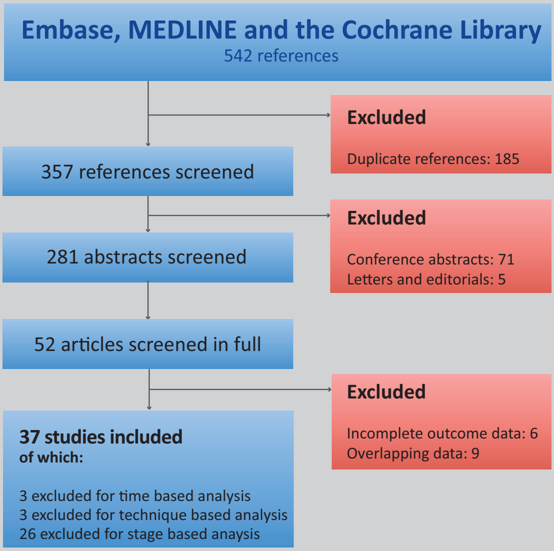

Figure 1 Flow chart of study selection according to the MOOSE guideline.

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Author and year	N	Inclusion period	Type of study	Dual survival (%)	GA at birth (weeks mean/SD)	Comments
De Lia 1995	26	1988-1994	Prospective single center cohort	35	32.2 (2.8)	
Ville 1995	45	1992-1994	Prospective single center cohort	36	35.0 (3.8)	
De Lia 1999	67	1995-1998	Prospective single center cohort	57	30.0 (5.0)	
Hecher 2000 ¥*	200	1995-1999	Prospective single center cohort	48	34.0 (2.7)	Early versus late series to show learning curve effect
Quintero 2000 ¥*	89	1994-1999	Prospective multicenter cohort	39	32.0 (2.5)	Non-selective laser versus selective laser
Gray 2006 ≠	31	2002-2003	Prospective single center cohort	39	34.0 (4.5)	
Huber 2006 ≠	200	1999-2003	Prospective single center cohort	60	34.3 (2.9)	
Ierullo 2007	77	2002-2006	Prospective single center cohort	40	NA	
Middeldorp 2007 ≠	100	2000-2004	Prospective single center cohort	58	33.0 (3.7)	
Quintero 2007 ¥	193	2003-2005	Prospective single center cohort	65	33.7 (4.0)	Sequential laser versus standard selective laser
Sepulveda 2007 ≠	33	2003-2006	Prospective single center cohort	27	32.0 (3.8)	
Stirneman 2008	287	1999-2005	Retrospective single center cohort	42	32.0 (3.6)	
Cincotta 2009 ≠	100	2002-2007	Prospective single center cohort	66	31.0 (3.2)	
Nakata 2009 ¥	52	2002-2006	Prospective multicenter cohort	50	32.0 (4.2)	Excluded for time based analysis but included for technique based analysis due to overlap.
Ruano 2009 ≠	19	2006-2008	Retrospective single center cohort	26	32.1 (3.0)	
Wagner 2009 ≠	20	2000-2007	Retrospective single center cohort	65	33.0 (5.0)	Excluded for time and technique based analysis but included for stage based analysis due to overlap.
Chmait 2010 ¥	99	2006-2008	Prospective single center cohort	68	32.2 (4.5	Sequential laser versus standard selective laser
Meriki 2010 ≠	75	2003-2008	Retrospective single center cohort	60	32.0 (2.7)	
Morris 2010	164	2004-2009	Prospective single center cohort	38	33.2 (1.3)	
Yang 2010	30	2002-2008	Retrospective single center cohort	60	32.0 (4.0)	
Chmait 2011 ≠	680	2002-2010	Retrospective multicenter cohort	67	32.3 (4.4)	Excluded for time and technique based analysis but included for stage based analysis due to overlap.

Delabaere 2011	49	2006-2008	Retrospective single center cohort	59	32.0 (2.6)	Article in French
Hernandez-Andrade 2011	35	2008-2009	Retrospective single center cohort	49	32.0 (3.7)	Article in Spanish
Lombardo 2011	70	2000-2010	Retrospective single center cohort	59	32.1 (NA)	
Tchirikov 2011	80	2006-2011	Retrospective single center cohort	78	33.8 (3.2)	Use of 1mm optic versus 2mm optic
Weingertner 2011	100	2004-2010	Retrospective single center cohort	52	32.6 (3.8)	
Chang 2012 *	44	2005-2010	Retrospective single center cohort	50	30.6 (5.9)	
Liu 2012	33	2003-2010	Retrospective single center cohort	52	31.0 (6.0)	Excluded in technique based analysis due to unclear technique. Article in Chinese
Murakoshi 2012 ≠	152	2002-2010	Retrospective single center cohort	63	33.0 (NA)	
Rustico 2012 *	150	2004-2009	Retrospective single center cohort	41	32.1 (2.2)	
Sundberg 2012 ≠	55	2004-2010	Retrospective single center cohort	35	34.8 (4.0)	
Swiatkowska-Freund 2012	85	2005-2010	Retrospective single center cohort	45	32.0 (2.5)	
Valsky 2012	334	2006-2009	Retrospective multicenter cohort	68	33.2 (3.0)	GA at laser 16-26 weeks versus >26 weeks
Baschat 2013 ¥	147	2005-2011	Retrospective single center cohort	60	32.6 (3.5)	Selective laser versus Solomon laser
Baud 2013	325	1999-2012	Retrospective single center cohort	63	31.3 (4.0)	GA at laser <16 weeks versus 16-26 weeks versus >26 weeks.
Ruano 2013 ¥	102	2010-2012	Retrospective multicenter cohort	65	31.6 (4.4)	Selective laser versus Solomon laser
Slaghekke 2014 ¥	272	2008-2012	Multicenter RCT	62	32.3 (3.3)	Selective laser versus Solomon laser

Table 1 Included studies in the review. *These studies described more series over different time periods and were split up in the time-based analyses. ¥These studies described comparisons between different techniques. ≠These studies described their outcome results per Quintero stage.GA= gestational age.

Primary Outcome

A total of 3.868 women with a MC twin pregnancy complicated by TTTS treated with fetoscopic laser coagulation were included in the time-based analysis, the sample size per study ranged from 19 to 334 women. The median time span of study inclusion for all studies was 4 years (interquartile range (IQR): 2-6).

Mean gestational age at time of surgery was 20.9 weeks (±1.9).

Combining all series, the mean perinatal survival of both twins, one twin and at least one twin were respectively 53.7% (SD 14.8), 29.5% (SD 10.5) and 83.2% (SD 8.3). Overall survival of fetuses was 5.348/7.736 (69.1%). Figure 2 displays a timeline of the average perinatal survival of all studies based on their study period.

For both twins, survival rates significantly increased from 35% (1990-1995) to 65% (2010-2014) (p=0.012) and survival rates for at least one twin significantly increased from 70% (1990-1995) to 88% (2010-2014)(p=0.009). No significant change in survival of one twin was seen between 1990-1995 (35%) and 2010-2014 (23%)(p=0.248).

The overall mean gestational age at birth of all series was 32.4 weeks (SD 1.3). Figure 2 shows a timeline of the mean gestational age at birth of all studies. Gestational age at birth did not change in time for the included series (p=0.226).

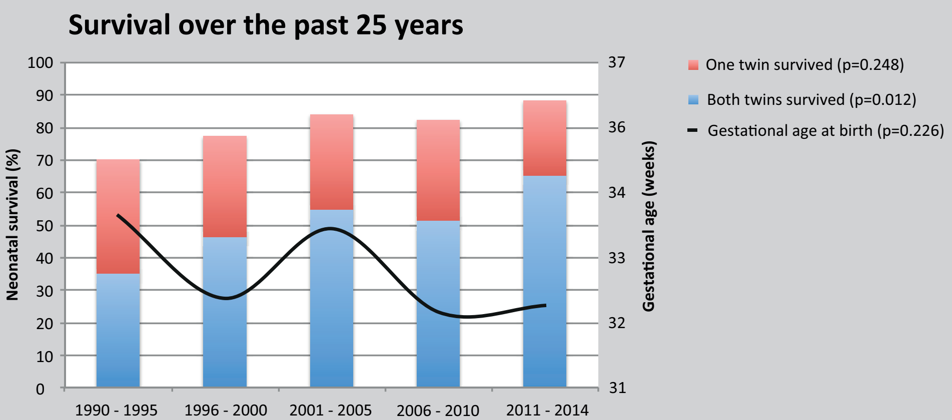

Figure 2 Survival results over a 25-year period of laser therapy for TTTS and mean gestational age at birth development.

Laser Technique

Thirty-four studies clearly specified their laser technique and eight of these studies compared two groups for which different laser techniques were used.[12,13,21,22,31,47,49,59] These groups were analyzed separately resulting in 42 subgroups describing survival results for

different laser techniques. The non-selective laser technique was used in five series,[10,19-22] 28 series used the selective laser technique,[12,21-40,43,44,46-49,59] selective sequential technique was used in six series[12,13,31,42,45,59] and three series used the Solomon technique.[13,47,49]
Figure 3 shows the results on perinatal survival for each technique. Survival of both twins improved significantly (p=0.010) over the course of introduction of new or modified techniques to the detriment of survival of only one twin (p=0.028). Overall a gradual improvement of survival at least one twin is seen for newer techniques (p=0.004).

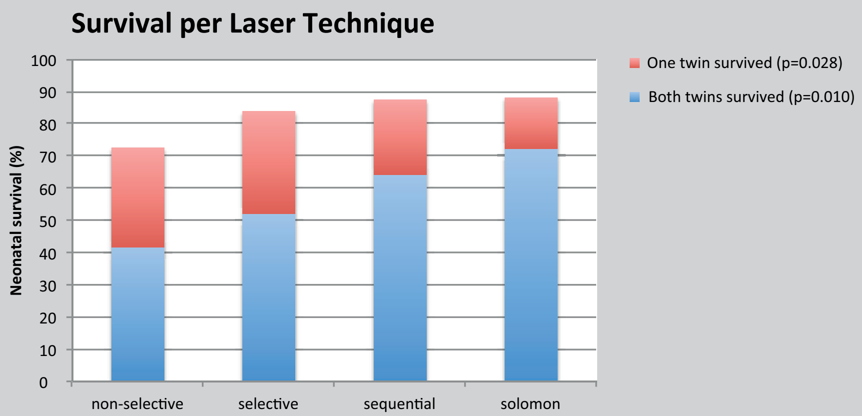

Figure 3 Laser technique based perinatal survival results

Quintero Stage

Eleven series reported perinatal survival by Quintero stage with a combined number of 1.451 pregnancies.[23,24,26,27,29-32,42,44,56,60] Most series presented data for Quintero stage I to IV (n=6).[24,26,32,42,44,56] Three studies presented data for stages II to IV.[23,27,29] Ruano et al.[30] only reported on stages III and IV, and Wagner et al.[60] only reported on stage I TTTS. The results for combined stage based outcomes after laser treatment are shown in figure 4. Although a trend was seen in decrease of survival with higher stages, no significant differences exist between Quintero stages in respect to survival of both twins (p=0.072), only one twin (p=0.081) or at least one twin (p=0.277).

Complications

Reports on post-treatment complications after laser therapy were not readily available in all studies. Only 12 (33%) of the included studies reported data on PPROM. Definitions ranged from '<37 weeks gestation' to 'within 7 days after fetoscopy' making comparison of these results impossible.[13,28,30,32,33,36,37,39,40,43,47,48]

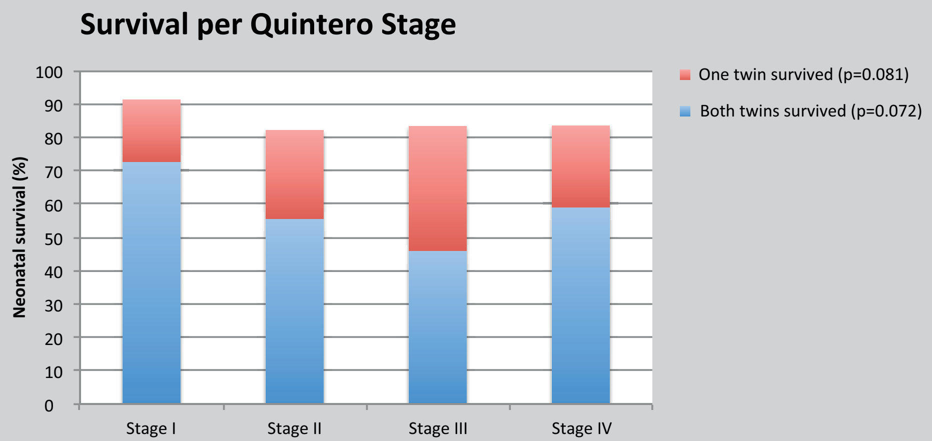

Figure 4 Quintero stage based perinatal survival results of 1.451 laser treated MC pregnancies.

DISCUSSION

In this review of all published series reporting on outcomes after fetoscopic laser treatment for TTTS, we found a significant improvement of survival of both twins and at least one twin over the past 25 years. This study also shows a significant improvement in survival of both twins with the more recently developed laser techniques. In 1990, De Lia et al. published the first results of fetoscopic laser therapy as an alternative for serial amnioreduction for the treatment of TTTS.[3] Since then the technique has undergone a variety of modifications.

There are several hypotheses to explain the improvement in perinatal survival after laser treatment in time. First of all, adaptations in laser technique such as indicated above are likely to affect survival, however the only way to demonstrate this true effect is to perform a randomized controlled trial adequately powered for perinatal survival.

Secondly, an important factor affecting treatment results is the learning curve effect. In principle, novice surgeons are assumed to perform surgery less safely and efficiently than more experienced colleagues. A learning curve represents the improvement of both the operators, from experience and practice, and, equally as important, the performance of the entire team at managing pregnancies with TTTS. Better teamwork, multidisciplinary discussion with colleagues from the neonatology department (including international audits), stimulation, controllability, and continuity may have been beneficial factors.[58]

Furthermore, since laser therapy has been accepted as the preferred treatment option knowledge and awareness in remote centers not offering this highly specialized treatment, has grown. Increased awareness may have resulted in improved timely referral and decreasing number of cases with advanced disease and poor outcomes.

With the acceptance of laser surgery as the best treatment thus far, over the years increasing number of centers started to offer this procedure. Since TTTS is rare, and both the surgical procedure as well as careful selection of cases and optimal timing of treatment is complex, concentration of care in specialized MFM centers has been advocated. With the most recent survival rates as a benchmark, (real time) monitoring and quality control are essential to prevent that a more widespread use of this technique, at least temporarily, leads to less favourable outcome due to learning curve effects and small numbers.

The finding that newer techniques have better perinatal survival results could be attributable to a true improvement in the technique. However this effect could be positively affected by the fact that new techniques are, in general, introduced and adopted sooner by the more experienced therapists after completion of their learning curve and thus likely perform better. Another important factor influencing this improved survival is based on case selection in series comparing two techniques which was evident in some studies on the sequential laser technique.[61]

With this study we hope to set a benchmark level, which established and starting centers can use to compare their individual results with. Regular structural reflection on ones' own practice is essential to prevent late detection of suboptimal performance. If less favorable outcomes are noticed, a quality cycle including further education, supervision of practice and improvement of learning environment should be initiated. We encourage starting up centers, as well as established centers, to share their performance for peer review and publish their series in order to keep updating the benchmark for other centers.[62]

Reviewing the Quintero stage-based outcome after laser treatment showed a non-significant trend in decreased survival of both twins with progression of stage, except for stage IV disease. We hypothesize that this could be explained by the low number of stage IV cases per series and possible case selection of high-risk cases by more experienced therapists.

Unfortunately, data on post treatment complications such as TAPS, recurrent TTTS or PPROM, were often not available in the reported studies or lacked uniform definitions. Iatrogenic PPROM is generally assumed to be one of the most important causes of premature delivery after laser therapy.[6] To gain better insight in the important complications of laser treatment it is imminent that we use systematic methods of reporting. Incidences are low and knowledge is largely based on small series. In order to conduct systematic reviews in these areas definitions need to be uniform when it comes to perinatal survival (e.g. alive at 28 days after birth), PPROM (e.g. before 32 weeks gestation), TAPS and recurrent TTTS.

This study has some limitations. Our findings could be influenced by publication bias. Centers that are still in their learning curve, or otherwise have less favorable results might be hesitant to publish their series when they underperform compared to the published series of established centers.

The past decades have also shown significant improvements regarding (early) neonatal care resulting in overall better outcomes after preterm birth.[63-65] The effect of the above mentioned factors are very difficult to quantify and should be taken into account when interpreting the results of this study.

Another limitation is the inclusion of series that have a large time span of data collection. This might have decreased the differences in survival over time when later series include the learning curve phase of the center. Evaluation of technical or other adaptations of surgical techniques using historic controls is hampered by bias caused by increasing experience over time, the learning curve effect and improved neonatal care.

Treatment of TTTS yielded a fair improvement in perinatal survival with the introduction of laser surgery over two decades ago. This review shows a significant increase in perinatal survival since then. Combining all published series, as a benchmark, perinatal survival of at least one twin after laser therapy can be achieved in 83% of pregnancies, and survival of both twins in 54% of pregnancies. The median gestational age at delivery in these series was 32.4 weeks. Nevertheless, we believe significant improvement opportunities prevail and we see challenges in improving instrumentation and technology for the treatment of TTTS to increase survival of both twins and, almost equally important, in prolonging pregnancies beyond 34 weeks' gestation. Survival and short-term neonatal morbidity should not be the only goals. The ultimate goal should be "disease-free survival" and focus on reducing the rate of neurodevelopmental impairment. We suggest institutions to focus on long-term pediatric neurodevelopmental outcomes. Follow-up into childhood is indispensable to determine outcome in terms of motor, cognitive and behavioral development.[66]

Fetoscopic laser treatment is often hindered by technical difficulties such as reduced visibility due to stained amniotic fluid or poor accessibility of some anastomoses due to placenta location or the position of fetal parts on the vascular equator.[67] Possibly, such limitations may affect the outcome results of the treatment. Technological innovations may aid us to overcome these limitations and help us improve our outcomes. Remarkably, technological innovations in instrumentation and equipment, common in in the field of laparoscopic surgery, appeared to be virtually absent in the fetoscopic treatment of TTTS. The equipment used 25 years ago is almost identical to what we use today. A lack of interest from commercial companies paired with complicated licensing issues for use in pregnancy may play a role.

ACKNOWLEDGEMENT

This research is supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organisation for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs.

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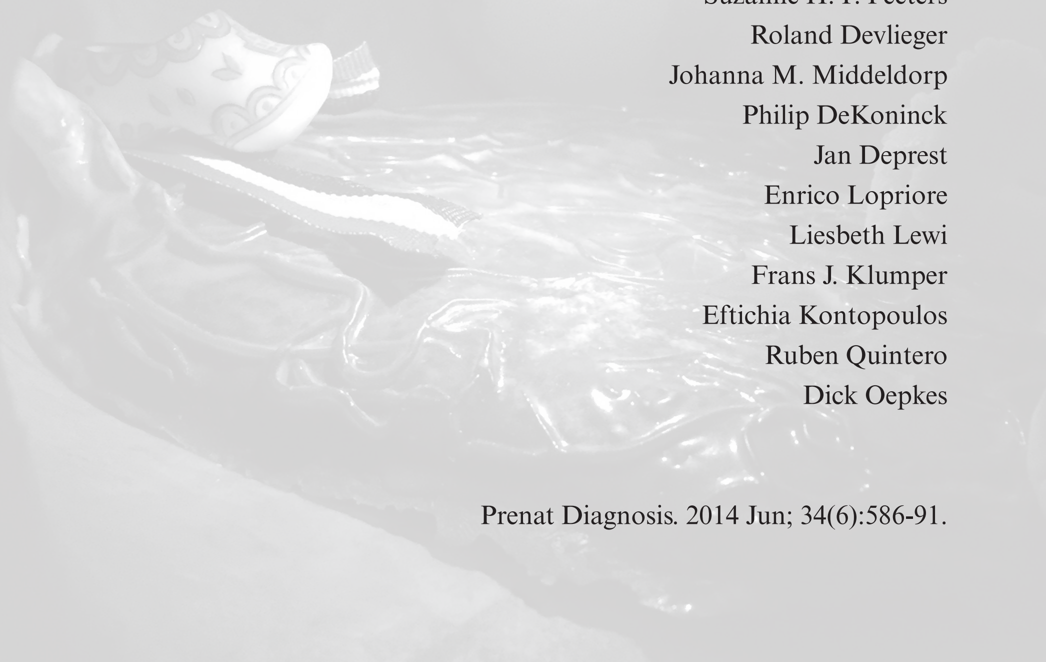
Part III

Challenging monochorionic pregnancies

Chapter 4

Fetal surgery in complicated monoamniotic pregnancies: case series and systematic review of the literature



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Prenat Diagnosis. 2014 Jun; 34(6):586-91.

ABSTRACT

Objective. This study aimed to analyze perinatal outcome in monoamniotic (MA) pregnancies that underwent antenatal surgical interventions for fetal complications.

Methods. Review of all MA pregnancies treated with antenatal surgical interventions in three fetal treatment centers between 2000 and 2013. Indications were twin–twin transfusion syndrome, twin reversed arterial perfusion sequence, discordant anomalies, or elective reduction. We analyzed associations between indication, type of intervention, perinatal survival, and gestational age (GA) at birth and compared our results with a systematic review of the literature.

Results. Fifty-eight MA pregnancies were included. Median GA at treatment was 18.0 weeks (range: 13.1–33.0). Procedures included cord coagulation plus transection (n= 42), cord coagulation without transection (n = 7), laser coagulation of placental anastomoses (n = 7), and one case each with interstitial laser and radiofrequency ablation. Median GA at birth was 34 weeks (range 16.0–41.0), and 75% (53/71) of fetuses intended to survive indeed survived. Literature review included 20 articles, reporting on a total of 45 cases of surgically treated MA pregnancies, showing similar outcome results.

Conclusion. We present the largest series concerning surgical interventions in complicated MA pregnancies. Despite being rare in experienced hands, a 75% survival is achieved. Collaboration between centers, data sharing, and benchmarking may further improve outcome.

INTRODUCTION

Monoamniotic (MA) twins account for approximately 1% of all monozygotic conceptions[1–3] and are the result of late splitting of the developing embryo, 8 to 9 days after fertilization. The perinatal loss rate in MA twins varies from 8% to as high as 42%.[4–6] High perinatal loss rates have been attributed mainly to umbilical cord entanglement, intertwin transfusion syndromes (including twin reversed arterial perfusion), discordant fetal abnormalities or growth, and preterm birth.[1,7,8]

Compared with complicated monochorionic–diamniotic cases, MA pregnancies carry additional risks, which should be taken into account when considering invasive interventions.[9,10] The most important factors being the presence of cord entanglement and the high incidence of proximate cord insertions.[11] So far, only a few small studies have specifically reported on treatment and clinical outcome in MA pregnancies requiring fetal surgical procedures during pregnancy, and all concerned only a single type of intervention.[12,13] Anecdotally, outcome in terms of survival and rate of prematurity appear disappointing.[13,14]

Fetal interventions performed in MA pregnancies mainly consist of laser coagulation of vascular anastomoses, selective feticide via interstitial laser, radiofrequency ablation (RFA), injection of vascular sclerosants, fetoscopic ligation, and umbilical cord occlusion. Cord transection has been proposed to improve the outcome of MA pregnancies by reducing the risk of fetal demise due to cord entanglement after cord occlusion.[14]

Specific series on technical details of these fetal interventions in relation to outcome are lacking. Therefore, we aimed to review relevant aspects of fetal surgical interventions in complicated MA pregnancies and to compare our experience with data obtained by a systematic review of the literature.

METHODS

Study population

All consecutive cases of fetal surgery in MA pregnancies performed at three major fetal treatment centers, the Leiden University Medical Center (The Netherlands), the University Hospitals, KU Leuven (Belgium), and the Jackson Fetal Therapy Institute, Miami (United States), between January 2002 and December 2012 were included in this retrospective study. All three fetal surgical centers have extensive experience in fetoscopic interventions. Chorionicity and amnionicity were established by ultrasound in the first trimester of pregnancy. Detailed sonographic examination was performed in all fetuses at the treatment centers and continued on a weekly or biweekly basis. Indications for surgery included the following: twin reversed arterial perfusion sequence (TRAP), twin-to-twin transfusion syndrome (TTTS), MA pair discordant for fetal anomaly, or elective selective reduction on request of parents. Triplet pregnancies, consisting of a singleton and an MA twin pair requiring an antenatal surgical intervention, were also included in analyses. TTTS was diagnosed by the recognition of absent bladder filling in donor and/or polyuria in recipient and/or abnormal umbilical Doppler flows or signs of progressive TTTS. Iatrogenic MA pregnancies after fetal surgery in monochorionic diamniotic (MCDA) twin with (un)intentional perforation of the intertwin membrane that required additional antenatal intervention were also included in analyses.

Fetoscopic procedures

In MA pregnancies affected by TTTS, fetoscopic laser coagulation of the vascular equator was considered treatment of choice. The fetoscopic procedure was performed using (2 or 3.3 mm) fetoscope (Storz, Vianen, the Netherlands, or Richard Wolf Inc., Vernon Hills, IL, USA), for percutaneous introduction through a 3.3 or 3.8 mm shaft into the amniotic sac. Coagulation of the anastomoses was performed using a diode laser (Diomed Limited, Cambridge, UK) or ND: YAG laser (Dornier Medizin Technik, Germering, Germany) with an output of 15 to 70 W. In cases with discordant fetal anomalies or elective reduction on the parents' request, selective feticide was performed using the following techniques: Fetoscopic laser was used for coagulation and transection to cut the umbilical cord of the affected fetus; although in cases with hydropic cord or such advanced gestational age (GA, >18 weeks) where laser was expected to fail, bipolar coagulation of the umbilical cord was performed using either a disposable 3-mm forceps (Everest Medical Maple Grove, MN) or reusable 2.4-mm or 3-mm forceps (Karl Storz, Vianen). A portion of the umbilical cord was grasped under ultrasound guidance and occluded or ligated and transected with the laser fiber (400–600 μm), set in the cutting mode (40 W). Some operators used additional fetoscopic verification of the coagulation. Technical details on the procedure were also described in detail in previous publications.[14–16] Radiofrequency ablation and interstitial laser were only used in cases with TRAP at an early GA. The procedure used to arrest the flow toward the acardiac twin was performed by using a laser fiber through an 18G needle (Cook Medical, Limmerick, Ireland) or by a 17G radiofrequency needle (Cooltip RF ablation system; Valleylab, Boulder, CO, or Starburst SDE RFA Device, AngioDynamics Netherlands BV).

Operative technical data, including difficulties such as inability to transect the umbilical cord and suboptimal visualization due to bleeding, were recorded in all cases. After the procedure, patients remained in the hospital for 12 to 48 h. Ultrasound examination was performed within 24 h after surgery and then on a weekly or biweekly basis. After an initial follow-up in our centers, patients were often referred back to their local fetal-medicine specialist for further follow-up. Intact MA twins were planned to be delivered by elective cesarean, after steroid administration, at 32 to 34 weeks of gestation. Elective admission was preferred at 26–28 weeks to allow daily fetal monitoring. Pregnancies with one remaining viable fetus were managed as singletons, at the discretion of the local obstetrician. After delivery, macroscopic examination of the placenta was performed to confirm the diagnosis of monoamnionicity.

Information regarding postsurgical complications and perinatal outcome was retrieved prospectively in all cases from referring physicians and patients, and written medical reports were available in most cases. Complications including vaginal blood loss, hypotension, bleeding from uterine vessels, pre-labor premature rupture of membranes (PPROM), and maternal fever were recorded. Primary outcome variables were perinatal survival rate, defined as survival up to discharge from neonatal unit and GA at delivery. Secondary outcomes included technical complications during procedure, PPROM before 32 weeks of gestation and birth weight.

Systematic review of literature

Publications between 2000 and March 2013 reporting data on interventions and perinatal outcome in MA pregnancies were reviewed. An electronic literature search using MEDLINE, EMBASE, and Cochrane database was performed to find all relevant articles reporting perinatal outcome and fetal interventions in MA twin pregnancies, using the following keywords 'Twins, Monozygotic' OR 'Monoamnionicity' OR 'monochorionic' OR 'monochorionicity' AND 'Fetal Therapies' OR 'Obstetric Surgical Procedures' OR 'Electrocoagulation' OR 'electrocautery' OR 'thermocoagulation' OR 'diathermy' OR 'coagulation' OR 'coagulations' OR 'Laser Therapy' OR 'laser' OR 'Pregnancy Reduction, Multifetal' OR 'pregnancy reduction' OR 'selective fetal termination' OR 'fetal reduction' OR 'Selective feticide' OR 'Umbilical Cord/surgery' OR 'occlusion' OR 'transection' OR 'surgical' OR 'Ligation' OR 'ligation' OR 'photocoagulation'. No language restrictions were applied. We accepted original articles, short communications, letters to the editor, and case reports. In addition, a search was performed from the reference list of all identified articles. When needed, we contacted authors for additional, unpublished information. Articles were included irrespective to their primary objective.

We included all reported cases of MA twin pregnancies assessed by first-trimester ultrasound or iatrogenic MA due to perforation of the intertwine membrane during fetal surgery (confirmed during surgery or ultrasound and after delivery) in MCDA pregnancies with a second intervention in the MA sac. Exclusion criteria were as follows: termination of pregnancy <12 weeks gestation, pseudomonoamniotic cases, conjoined twins, and medical amnioreduction (using sulindac or indometacin). Two of the authors (S. P. and J. M.) initially screened all the titles and abstracts of papers, identified by the review search strategy, for relevance. Only studies that were obviously irrelevant were excluded at this stage. All other studies were assessed on the basis of their full text for inclusion versus exclusion by two reviewers independently (S. P. and J. M.) using the aforementioned criteria. Data extracted from each article included indication for intervention and type of intervention. Primary outcomes were similar to our case series: perinatal survival rate, defined as survival up to discharge from neonatal unit, and GA at delivery. Secondary outcomes included birth weight and PPROM before 32 weeks gestation. Statistical analysis was performed with SPSS version 21.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.).

RESULTS

During the study period, 58 complicated MA pregnancies were treated with antenatal surgical interventions (15 in Leuven, 25 in Leiden, and 18 in Miami, respectively). Fifty-one cases (88%) were true MA pairs and seven cases (12%) were iatrogenic MA pregnancies due to unintentional septostomy in a MCDA pregnancy after a fetoscopic procedure for TTTS. Seven triplets, including an MA twin pair requiring antenatal surgical intervention, were included in this study. The main indications for surgery were discordancy for a severe fetal anomaly (N = 23, 40%), TRAP-sequence (N = 13, 22%), and TTTS (N = 16, 28%). In two cases (3%) TTTS occurred in combination with a severe fetal anomaly in one of the twins. In one case complicated with selective intrauterine growth restriction resulting in fetal demise, a cord transection was performed to prevent cord related accidents. In three cases (5%), selective reduction of one of the viable MA twins was performed for elective reasons to prevent cord accidents. A summary of indications for fetal intervention in MA pregnancies included in this study and review of literature is displayed in Table 1.

Characteristics	Current study n/total (%)	Literature n/total (%)
Monoamnioticity		
True MA	50/58 (88)	45/45 (100)
Iatrogenic MA after laser surgery	7/58 (12)	
Triplets	7/58 (12)	1/45 (2)
Indication for intervention		
TRAP	13/58 (22)	17/45 (38)
TTTS	16/58 (28)	4/45 (9)
TAPS		1/45 (2)
Discordancy for fetal anomaly	23/58 (40)	14/45 (31)
TTTS combined with discordant anomaly	2/58 (3)	1/45 (2)
Severe sIUGR	1/58 (2)	7/45 (16)
Elective to prevent cord accidents	3/58 (5)	1/45 (2)
Technical details		
Gestational age at intervention in weeks (median, range)	18.0 (13.1–33.0)	20.0 (12.0–33.0)
Fetoscopic laser coagulation of equator	7/58 (12)	1/45 (2)
Cord occlusion	7/58 (12)	4/45 (9)
Cord occlusion + transection	42/58 (72)	21/45 (48)
RFA	1/58 (2)	6/45 (13)
Interstitial laser	1/58 (2)	7/45 (15)
Alcohol injection		2/45 (4)
Serial amniodrainage		3/45 (7)
Cord ligation		1/45 (2)

MA, monoamniotic; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome; sIUGR, selective intrauterine growth restriction; RFA, radiofrequency ablation; TAPS, twin anemia polycythemia sequence.

Table 1 Characteristics and technical details

In almost all twin cases, there was a single intended survivor (due to for example congenital anomalies), except for seven cases of MCMA twins affected by TTTS, in which the aim was to save both twins. Of seven triplet pregnancies, one case of TTTS included three intended survivors, four triplets contained two intended survivors, and two triplets included a single intended survivor (one case with double TRAP and one case of selective reduction of both MA twins). Giving the characteristics of these pregnancies, the total number of intended survivors in this series adds up to 71.

In 42 cases, cord transection was attempted, and this was successful in 38/42 (90%). Cord occlusion alone was carried out in 7/58 (12%), and fetoscopic laser coagulation of the equator was performed in 7/58 (12%). In our series, only two cases of MA pregnancies complicated by TRAP were treated with RFA and interstitial laser therapy, respectively.

Postoperative PPROM before 32 weeks of gestation occurred in 16/58 cases (28%). Median (range) GA at treatment was 18.0 (13.1–33.0) weeks. Surgery was performed under local (N = 30, 52%), regional (N = 12, 21%), or general (N = 16, 27%) anesthesia using an ultrasound-guided single port procedure, except for one case where a second port was necessary for access. Introduction was performed percutaneously, except for one case in which the combined open laparoscopy and fetoscopy for completely anterior placenta procedure was used.17 The procedure was uncomplicated in 43/58 (74%) cases with a median duration of 60 min (range 20–142 min). Technical difficulties included decreased visibility due to bleeding or blurred amniotic fluid (N = 7, 12%), severe cord entanglement preventing successful procedure (N = 3, 5%), and inability to perform complete coagulation of the vascular equator (N = 4, 7%). This series included one case in which fetoscopic laser coagulation of the vascular anastomoses was performed, with intraoperative demise of the donor then followed by cord transection. In another case operated at 16 weeks of gestation because of a severe congenital anomaly in one twin, the wrong cord was sectioned because of severe entanglement limiting visibility.

Furthermore, the procedure was complicated by perioperative rupture of membranes, and the parents decided to terminate the pregnancy.

In this study, 55/71 (77%) of fetuses were live-born, and 18/71 (23%) pregnancies were complicated by intrauterine fetal demise. Two of the 55 live-born babies died in the neonatal period (4%). Therefore, perinatal survival in this series was 53/71 (75%). Median GA at delivery was 34.0 weeks (range 16.0–41.0 weeks). The median birth weight of live-born children was 2475 g (range: 745–4044 g). In none of the cases, maternal morbidity occurred. Details on pregnancy outcomes are summarized in Table 2. This study includes a few cases that were previously published.[14,15,18–21]

	Current study n/total (%)	Literature n/total (%)
No. of pregnancies/no of fetuses (incl. TRAP)	58/123	49/91
No. of triplet pregnancies	7	1
No. of intended survivors	71	49
Perinatal survival at 28 days	55/71 (77)	41/49 (84)
IUFD	17/71 (23)	8/49 (16)
NND	2/55 (4)	4/41 (10)
Gestational age at birth in weeks (median, range)	34.0 (16.0–41.0)	33.5 (13.0–39.0)
Birth weight in grams* (median, range)	2475 (745–4044)	1890 (648–3050)
PPROM < 32 weeks	16/58 (28)	9/45 (20)
Preterm birth between 24 and 32 weeks	17/58 (29)	14/45 (29)

*Live births.

TRAP, twin reversed arterial perfusion; IUFD, intrauterine fetal demise; NND, neonatal death within 28 days after birth; PPROM, preterm prelabor rupture of membranes.

Table 2 Pregnancy outcomes

Systematic review of the literature

Combination of the four search strategies revealed 820 references in MEDLINE, 964 in EMBASE, 647 references in ISI Web of Science, and none in the Cochrane library. A manual search revealed no additional studies for consideration. In total, after removal of duplicates, 32 relevant published reports were screened. Figure 1 provides a flow diagram with the number of studies screened, assessed for eligibility, and included for review according to our search strategies. Unfortunately, 12 articles failed to discuss amnionicity or included cases without surgical interventions. Because unpublished information could not be obtained, these cases were excluded from this study. To obtain the full range of research to date, we accepted case series (n= 5) and case reports (n = 13) as well. A total of 20 articles met the inclusion criteria, and we identified 50 cases of MA pregnancies that underwent surgical interventions.[4,7,13,22–38]

Baseline characteristics of the study population and indications for surgery are summarized in Table 1 and clinical outcome in Table 2. Combination of our data and review of literature showed perinatal survival rates (of intended survivors) of 78% (25/32) in 20 cases of TTTS, 77% (24/31) in 30 cases of TRAP, 72% (28/39) in 37 cases of twins discordant for anomalies, 63% (5/8) in eight cases of IUGR, and 80% (4/5) in four cases in which selective reduction was performed only to prevent cord accidents. We pooled the data from the MA pregnancies treated with selective feticide (n = 74), and we compared cases that underwent umbilical cord occlusion without transection with cases in which the cord was successfully transected after occlusion. Survival and GA at birth tend to increase after transection compared with cases having intact cords. Perinatal survival of 56/64 (88%) and median GA at birth of 36 weeks was reached after transection of the cords compared with 9/15 (60%) and 28 weeks after cord coagulation alone. Analysis of these pregnancies outcomes is shown in Table 3.

Figure 1 Flow with number of studies screened, assessed for eligibility, and included for review with exclusion criteria according to our search strategies.

Pregnancy outcomes in cases of selective feticide n=74	Successful transection n/total (%)	Selective feticide with intact cords n/total (%)
No. of pregnancies	60	14
No. of triplet pregnancies	5	2
No. of intended survivors	64	15
Perinatal survival at 28 days	56/64 (88)	9/15 (60)
IUFD	8/64 (12)	6/15 (40)
NND	3/56 (5)	2/9 (22)
Gestational age at birth in weeks (median, range)	36.0 (16.0–40.0)	28.0 (16.0–41.0)
Birth weight in grams* (median, range)	2775 (796–4044)	2150 (745–3325)
PPROM < 32 weeks	16/60 (27)	4/14 (29)
Preterm birth between 24 and 32 weeks	8/60 (13)	4/14 (29)

*Live births.
IUFD, intrauterine fetal demise; NND, neonatal death within 28 days after birth; PPROM, preterm prelabor rupture of membranes

Table 3 Pooled data on pregnancy outcome intact versus transected cords

DISCUSSION

This paper reports on the largest series to date of antenatal surgical procedures in complicated MA pregnancies. Combining our data with the published literature, we can conclude that these complex procedures in this rare and highly complicated group of pregnancies, performed in highly specialized fetal treatment centers, can lead to good outcome in the majority of cases.

In case of a single intended survivor, our results suggest improved pregnancy outcomes in cases treated with cord transection. Diversity in indication and intervention makes it difficult to arrive at a consensus for an optimal strategy regarding fetal surgery in MA pregnancies. Individualization of cases is critical when determining the timing and type of intervention. Operator's experience, preferences, and pregnancy details – such as an anterior placenta, a triplet pregnancy, or signs of TTTS – may all influence options and choices.

A few other studies reported on surgical interventions in MA pregnancies. If anomalies affect only one twin, selective feticide is frequently offered as an intervention. The option of cord occlusion and transection in MA twin discordant for fetal anomalies to prevent fetal demise due to cord accidents was already proposed by Middeldorp et al.[14] and Quintero et al.[18] Valsky et al. showed that cord occlusion and transection in MA twins resulted in similar perinatal outcomes compared with those of diamniotic discordant twins treated with cord occlusion.[13] Perinatal outcome after selective feticide was also reported by van den Bos et al.[19] Preterm birth and adverse perinatal outcome appeared to occur more frequently with use of the fetoscopic laser coagulation compared with bipolar cord coagulation. However, authors stated that their population was inhomogeneous and therefore difficult to compare, and these results may be influenced by the GA at which the procedure is performed – before 18 weeks versus after 18 weeks gestation.

Although often performed with technical success, surgical procedures in MA pregnancies can be technically challenging. Especially, cord entanglement can be hazardous during fetoscopic interventions. Multiple loops of entanglement make identification of the correct cord difficult. Although rare, accidental coagulation of the wrong cord does occur, as presented in our series and previously reported.[30]

Another dilemma is the management of MA pregnancies diagnosed with TRAP. In addition to the threatened compromise of the pump twin, the risk of cord pathology seems to justify surgical intervention. Our data combined with literature data showed 30 cases treated using several surgical approaches, but predominantly cord coagulation and transection, with perinatal survival rates of 77%. Previously published series of a combination of MA and diamniotic TRAP pregnancies undergoing prophylactic surgery at 16–18 weeks showed survival rates from 74% up to 90%.[15,39,40]

Analysis of published studies over the last 20 years reported a lower but non-negligible incidence of TTTS in MA twins (6%), compared with MCDA pregnancies (10–15%).[9] This is most likely due to the protective effect of arterio–arterial placental anastomoses.[8,41,42]

The combined outcome from our series and the literature shows that perinatal survival using fetoscopic laser in MA twins with TTTS is 78%, similar to recent outcomes in MCDA twins.43 In addition, a case of twin anemia polycythemia sequence (TAPS) in an MA pregnancy was successfully treated with laser coagulation by Diehl et al.[33]

A remarkable discordance in the prevalence of TTTS (28% vs 9%) and selective intrauterine growth restriction (2% vs 16%) in MA twins could be noted when comparing the results of current study with previously published literature. This effect may be due to the matter how diagnoses were made. In addition, these numbers may reflect some degree of referral and publication bias.

Our study does have some limitations. Reports on MA pregnancies mainly consist of case reports or small case series; therefore, conclusions drawn from the literature are limited. Amnionicity is underreported in literature, perhaps under documented, especially in earlier years. Even though authors were personally approached to gain more data, the number of cases that could be included for this paper was limited. Because our centers are acknowledged as regional or national tertiary institutions for complex fetoscopic interventions, cases may reflect some degree of referral bias, and this may influence pregnancy outcomes. Our data should be interpreted with care due to the retrospective nature of this study, the relative small number of cases in each subgroup, and varying GAs at diagnosis and interventions.

In summary, all surgical interventions in MA twins, despite being minimally invasive techniques, carry a high risk of complications and require highly skilled operators. Survival and short-term morbidity were similar to rates reported in MCDA pregnancies. However, as in other areas of fetal intervention, there is a growing awareness that it is also essential to evaluate long-term outcome in survivors. The limited numbers and variety in pathology make prospective comparative studies, let alone randomized trials, extremely difficult to perform within a reasonable timeframe. To improve outcomes in these rare, high-risk pregnancies, international collaboration, sharing data on techniques and protocols, benchmarking, and setting standards for indications and interventions are more achievable and still very valuable goals.

ACKNOWLEDGEMENTS

We would like to acknowledge Dr. C. A. M. van der Hoorn-van Velthoven, medical information services coordinator, for assistance with the literature search.

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Chapter 5

Iatrogenic perforation of the intertwin membranes after laser surgery for twin-twin transfusion syndrome

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Ultrasound Obstet Gynecol. 2014 Nov;44(5):550-6.

ABSTRACT

Objective To evaluate management and outcome of iatrogenic monoamniotic twins (iMAT) compared with twins with intact intertwin dividing membranes after laser surgery for twin-to-twin transfusion syndrome (TTTS).

Methods This was a retrospective analysis of twins with and without iatrogenic rupture of the intertwin membranes that had been treated for TTTS with laser surgery at our center between 2004 and 2012. Primary outcomes were perinatal survival and severe neonatal morbidity. Secondary outcomes were mode of delivery, gestational age at birth and cord entanglement.

Results In total, 338 pregnancies were included. In 67/338 (20%) pregnancies, iMAT was suspected antenatally. In 47 of these 67 (70%), a preterm Cesarean section was performed for monoamnionicity. Perinatal survival was 108/134 (81%) vs 396/542 (73%) in twins with intact intertwin membranes (P=0.13). Mean gestational age at birth in iMAT was 31 completed weeks, compared to 33 weeks in twins with intact membranes (P<0.01). At birth, cord entanglement was present in 8/67 (12%) iMAT pregnancies. Severe neonatal morbidity was assessed in 106/110 (96%) in iMAT cases and 392/416 (94%) in controls. The incidence of severe neonatal morbidity was 28/106 (26%) in iMAT vs 72/392 (18%) in controls (P=0.25). Severe cerebral injury was significantly increased in the iMAT group as compared with controls, at 16/106 (15%) vs 18/392 (5%) (P<0.01).

Conclusions Iatrogenic rupture of intertwin membranes was suspected in 20% of pregnancies treated with laser therapy for TTTS and was associated with a lower gestational age at birth and increased neonatal morbidity.

INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is a serious complication of monochorionic twin gestations, with a high risk of perinatal morbidity and mortality. Fetoscopic laser photocoagulation of the vascular anastomoses is the preferred treatment, with an overall survival of up to 74%.[1] As it is an invasive procedure, perioperative complications of laser surgery itself increase the risk of adverse outcome.[2] One of these complications is unintentional perforation of the intertwin dividing membranes, thereby creating an iatrogenic monoamniotic twin (iMAT) pregnancy.

Rupture of intertwin membranes can occur as a consequence of perforation of the donor's collapsed membrane at the trocar insertion site, which may be invisible on ultrasound. Another mechanism for perforating the membranes is by coagulation of vascular anastomoses through the membrane, which is sometimes unavoidable. iMAT is reported to occur in 1.3–8.7% of cases and is associated with preterm prelabor rupture of membranes (PPROM), premature delivery, pseudo-amniotic band syndrome and complications due to cord entanglement, as seen in spontaneous monoamniotic twins.[2–4] There have been only a few reports on iMAT as a complication of invasive procedures.[2–4] Clinical implications of iMAT and optimal management strategies in these pregnancies have not been established. Since perforation is not always detected during or directly after surgery, this diagnosis can be easily missed, unless specific attention is given to its features during follow-up examinations.

If iMAT is suspected, pregnancies are often more closely monitored, hospitalization after viability is considered and a preterm, elective Cesarean section is scheduled between 32 and 34 weeks' gestation to prevent cord accidents. Uncomplicated monochorionic twin pregnancies after laser surgery are often allowed to continue to around 36 weeks. We therefore hypothesized that iMAT could be associated with a lower gestational age at birth as compared with twins with intact intertwin membranes after laser treatment, with concomitant adverse effects on neonatal morbidity.[5]

The aim of this study was to investigate the incidence of iMAT after laser surgery for TTTS and compare management and perinatal outcomes of suspected iMAT cases with those of twins with intact intertwin membranes.

METHODS

At Leiden University Medical Center, the Dutch national tertiary referral center for invasive fetal therapy, fetoscopic laser surgery has been the preferred treatment modality for all pregnancies complicated by TTTS Quintero stage II or higher, and for selected cases with Quintero stage I with symptomatic polyhydramnios, since August 2000. Chorionicity and amnionicity are established by sonographic examination in the first trimester of pregnancy. The diagnostic (established) criteria for TTTS are defined according to the Eurofoetus protocols.[6]

In this study fetoscopic surgery was performed by one of four specialized surgeons after written consent of the patient had been obtained. All procedures were performed through a single percutaneous port in the recipient sac, except for a few cases with completely anterior placenta, in which introduction of the shaft in the posterior uterine wall was assisted by open-entry laparoscopy under general anesthesia, a technique that was used until 2009.[7]

Fetoscopic procedures were performed using a 1.3-mm or 2.0-mm semi-rigid or rigid fetoscope or a 1.0-mm embryoscope (Storz, Vianen, The Netherlands), introduced through operative fetoscopic sheaths and trocars with maximum external diameters of 8 or 10 French, depending on placental location and gestational age. If necessary, Ringer's lactate warmed to body temperature was infused to improve distention or visualization. Coagulation of the anastomoses was performed using a diode laser (Diomed Limited, Cambridge, UK) or Nd:YAG laser (Dornier Medizin Technik, Germering, Germany). The technique used for the laser procedure was adapted over the years; selective sequential laser was performed from 2006. The 'Solomon technique' (coagulation of the complete vascular equator after selective sequential laser) was introduced in March 2008. A subset of the patients (n=141) included in this study also participated in the Solomon trial.[1] At the end of the procedure, amniotic fluid was drained until the deepest amniotic fluid pocket was<6 cm on ultrasound examination.

Complications and technical difficulties such as (un)intentional perforation of the intertwin membranes, significant intra-amniotic bleeding or incomplete procedure were documented directly after surgery. Ultrasound examination was performed within 24 h after surgery to detect early iMAT and then at least biweekly at our center by highly specialized sonographers or by shared care with referring centers. A standardized ultrasound follow-up protocol was used from 2004 for all patients treated with laser therapy, including specific assessment of the intertwin membranes as a standard element of care.

Perforation of the intertwin membranes was diagnosed either by direct observation of a gradual filling of the donor sac at the time of the fetoscopic procedure or during the follow-up ultrasound examination (on the first postoperative day, or later) if increased amniotic fluid was noted in the donor sac in conjunction with free-floating intertwin membrane and a non-cycling donor bladder and/or entanglement of the cords was suspected.[8]

After delivery, the presence of cord entanglement was noted, and macroscopic examination of the placenta and membranes was performed to confirm the diagnosis of monoamnionicity.

For this study we performed a retrospective analysis of prospectively collected data on perinatal outcome and management of all pregnancies with TTTS treated at our center. Data on obstetric and neonatal outcomes were derived from medical charts. In cases in which the delivery did not take place at our center, data were provided by outcome reports from the referring obstetricians and pediatricians.

Since iatrogenic rupture of the membranes was underreported in the first years after the start of laser therapy, we included only cases from 2004 (after we started using a standardized follow-up protocol) until 2012, to exclude reporting bias. We included all monochorionic twin pregnancies complicated by TTTS treated with fetoscopic laser coagulation, not clinically in labor at the time of the procedure. Triplet pregnancies, twins with one or more major congenital anomalies or chromosomal abnormalities, sonographic evidence of perforation of intertwin membranes prior to laser therapy and spontaneous monoamniotic pregnancies were excluded from this study. None of the pregnancies was excluded from analysis once the fetoscope had been introduced into the amniotic cavity, even if laser coagulation was not possible.

Primary outcomes were perinatal survival at 4 weeks of age and severe neonatal morbidity. Secondary outcomes included PPROM, gestational age at birth, birth weight and the need to perform a re-intervention. Severe neonatal morbidity was defined as the presence of at least one of the following: respiratory distress syndrome (requiring medical ventilation and surfactant), patent ductus arteriosus (requiring medical therapy or surgical closure), right ventricular outflow tract obstruction, renal failure, necrotizing enterocolitis ≥Grade 2, amniotic band syndrome, ischemic limb injury or severe cerebral injury. Severe cerebral injury included at least one of the following: intraventricular hemorrhage ≥Grade III, cystic periventricular leukomalacia ≥Grade II, ventricular dilatation above 2 SDs (including posthemorrhagic ventricular dilatation), intraparenchymal echodensities, porencephalic or parenchymal cysts, arterial infarction, congenital brain malformation or other severe cerebral lesions associated with adverse neurological outcome.[9]

Statistical analysis

Patients were categorized into one of two groups: pregnancies in which perforation of the intertwin membranes was antenatally suspected (iMAT) and pregnancies with intact intertwin membranes. Intentional perforation of the intertwin membranes was applied only in a few exceptional cases, however all cases with intentional or unintentional membrane perforation were included in the analysis. Continuous variables were reported as median (range) or mean (SD); group differences were compared using the Mann–Whitney *U*-test or independent Student's *t*-test. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate. All analyses per fetus or neonate were performed using the generalized estimated equation module to account for the effect that observations between cotwins are not independent. Statistical analysis was performed with SPSS version 21.0 (SPSS IBM, New York, NY, USA), and $P<0.05$ was considered to be statistically significant.

RESULTS

Laser coagulation was performed in 338 pregnancies fulfilling the inclusion criteria. iMAT was suspected antenatally in 67/338 (20%) cases; in 39/67 (58%), this was within 24 h after surgery. No significant differences in perioperative variables (i.e. maternal age, severity of TTTS, location of placenta, introduction technique, laser technique or fetoscopy time) were detected, except for mean gestational age at surgery, which was 21 weeks in iMAT and 20 weeks in cases with intact membranes ($P<0.01$). Detection of iMAT was not associated with laser surgery performed after 26 weeks' gestation; 4/67 (6%) *vs* 14/271 (5%) ($P=0.76$). Visibility was reduced by significant intra-amniotic bleeding in 9% of procedures, a similar percentage in both groups.

Characteristic	iMAT (n=67)	Intact membranes (n= 271)	P value
Maternal age (years, mean (range))	30 (20–41)	31 (19–42)	0.28
Placental location			0.24
Anterior	34 (51)	116 (43)	
Posterior	33 (49)	155 (57)	
Quintero stage			0.32
I	3 (4)	25 (9)	
II	17 (25)	88 (32)	
III	44 (66)	146 (54)	
IV	3 (4)	12 (4)	
Introduction technique			0.16
Percutaneous	59 (88)	254 (94)	
Mini-laparotomy	—	2 (1)	
Combined open laparotomy for anterior placenta	8 (12)	15 (6)	
Laser technique			0.31
Selective	53 (79)	198 (73)	
Solomon	14 (21)	73 (27)	
GA at laser (weeks, mean (range))	21 + 0 (15 + 3 to 29 + 5)	19 + 6 (13 + 3 to 29 + 1)	< 0.01
Laparoscopy time (min, median (range))	30 (5–100)	29 (8–113)	0.29
Significant intra-amniotic bleeding during procedure	6 (9)	20 (7)	0.73
Re-intervention necessary	12 (18)	19 (7)	< 0.01
Indication for re-intervention			0.79
Recurrence/reversal	8/12 (67)	10/19 (53)	
TAPS	2/12 (17)	5/19 (26)	
Severe cerebral injury	1/12 (8)	1/19 (5)	
Other	1/12 (8)	3/19 (16)	
Type of re-intervention			0.78
Laser	3/12 (25)	3/19 (16)	
Amniodrainage	2/12 (17)	4/19 (21)	
IUT	3/12 (25)	5/19 (26)	
Selective feticide	3/12 (25)	7/19 (37)	
Laser + IUT	1/12 (8)	—	

Data given as *n* (%) unless indicated.
GA, gestational age; TAPS, twin anemia–polycythemia sequence; IUT, intrauterine transfusion.

Table 1 Baseline characteristics of 338 pregnancies treated for twin-to-twin transfusion syndrome, according to whether laser surgery perforated the intertwin membrane (iatrogenic monoamniotic twin (iMAT)) or not

Overall perinatal survival rate in this cohort was 504/676 (75%), with a mean gestational age at birth of 31+6 (range, 24+0 to 41+2) weeks. Perinatal survival at 4 weeks was not significantly different between the groups: 108/134 (81%) in iMAT cases *vs* 396/542 (73%) in cases with intact membranes (*P*=0.13). Fetal demise occurred in 24/134 (18%) in the iMAT group and 126/542 (23%) in the group with intact membranes (*P*=0.27). In the iMAT group, there was one case of double fetal demise, which occurred at 25 weeks' gestation, in which cord entanglement was the most likely cause of death. In the control group none of the cases of fetal demise was related to cord entanglement. Neonatal death was observed in 2/110 (2%) and 20/416 (5%) in the iMAT group and the intact-membranes group, respectively (*P*=0.17). Details of pregnancy outcomes per group are summarized in Table 2.

In the iMAT group, PPROM before 32 weeks' gestation occurred more frequently; 32/67 (48%) *vs* 74/271 (27%), although the difference did not reach statistical significance (*P*=0.15).

Pregnancies complicated by iMAT had a significantly higher rate of preterm birth before 32 weeks of 39/67 (58%), compared with 101/271 (37%) in pregnancies with intact membranes (*P*<0.01). Accordingly, the birth weight of liveborn children was significantly lower in the iMAT group (1524 (range, 607–2765) g) than in the intact-membranes group (1936 (range, 585–4190) g; *P*<0.01). Iatrogenic preterm delivery before 32 weeks in cases of iMAT occurred in 10/67 (15%), compared with 22/67 (33%) cases with spontaneous preterm delivery and seven cases of immature delivery or double fetal demise. Additionally, in 16 cases, iatrogenic preterm delivery was induced between 32 and 35 weeks' gestation because of iMAT.

Twenty-eight of the 526 (5%) liveborn neonates were lost to follow-up and excluded from the analysis of morbidity. Severe neonatal morbidity was assessed in 106/110 (96%) iMAT cases and 392/416 (94%) controls. Severe neonatal morbidity was more frequently observed in the iMAT group than in the twins with intact membranes (28/106 (26%) *vs* 72/392 (18%), respectively), but the difference was not statistically significant (*P*=0.25). Severe cerebral injury was significantly more common in the iMAT group (16/106 (15%) *vs* 18/392 (5%); *P*<0.01), as well as the occurrence of respiratory distress syndrome (RDS) (23/106 (22%) *vs* 43/392 (11%); *P*=0.05) and necrotizing enterocolitis (5/106 (5%) *vs* 1/392 (0.3%); *P*=0.01). Amniotic band syndrome was diagnosed in four cases, all within the group with intact intertwin dividing membranes.

Outcome	iMAT (n=67)	Intact membranes (n= 271)	P value
Perinatal survival (at 28 days)*	108/134 (81)	396/542 (73)	0.13
IUFD*	24/134 (18)	126/542 (23)	0.27
Double IUFD	7/67 (10)	28/271 (10)	
NND*	2/110 (2)	20/416 (5)	0.17
PPROM < 32 weeks	32/67 (48)	74/271 (27)	0.15
Preterm birth < 32 weeks	39/67 (58)	101/271 (37)	< 0.01
Mode of delivery†			< 0.01
Vaginal	20/67 (30)	197/262 (75)	
Cesarean section	47/67 (70)	62/262 (24)	
1st vaginal, 2nd Cesarean section	—	3/262 (1)	
GA at birth (weeks)‡	31 + 0 (26 + 0 to 36 + 5)	33 + 4 (24 + 0 to 41 + 2)	< 0.01
Birth weight (g)*, ‡	1524 (607–2765)	1936 (585–4190)	< 0.01
Severe neonatal morbidity*, §, ¶	28/106 (26)	72/392 (18)	0.25
Severe cerebral injury*, ¶, **	16/106 (15)	18/392 (5)	< 0.01
RDS*	23/106 (22)	43/392 (11)	0.05
PDA*	5/106 (5)	7/392 (2)	0.18
RVOTO*	1/106 (1)	3/392 (1)	0.87
Renal failure*	1/106 (1)	2/392 (1)	0.63
NEC*	5/106 (5)	1/392 (0.3)	0.01
Amniotic band syndrome††	—	4/392 (1)	0.50
Ischemic limb injury††	—	2/392 (1)	0.14
Only comfort care because of severe prematurity††	—	9/392 (2)	0.84

Data given as *n* /*N* (%) or mean (range).

* Measured per fetus using the generalized estimated equation module.

† Mode of delivery was unknown in 9/271 cases in the intact-membranes group.

‡ Live births.

§ Severe neonatal morbidity includes at least one of the following: respiratory distress syndrome (RDS) (requiring medical ventilation and surfactant), patent ductus arteriosus (PDA) (requiring medical therapy or surgical closure), right ventricular outflow tract obstruction (RVOTO), renal failure, necrotizing enterocolitis (NEC) ≥ Grade 2, amniotic band syndrome, ischemic limb injury or severe cerebral injury.

¶ Denominator is number of liveborn neonates (excluding those lost to follow-up).

** Severe cerebral injury includes at least one of the following: intraventricular hemorrhage ≥ Grade III, cystic periventricular leukomalacia ≥ Grade II, ventricular dilatation (including posthemorrhagic ventricular dilatation) above 2 SD, intraparenchymal echodensities, porencephalic or parenchymal cysts, arterial infarction, congenital brain malformation or other severe cerebral lesions associated with adverse neurological outcome.

†† Measured using the method of Firth.20 GA, gestational age; IUFD, intrauterine fetal demise; NND, neonatal death within 28 days after birth; PPROM, preterm prelabor rupture of membranes.

Table 2 Outcomes of 338 pregnancies treated for twin-to-twin transfusion syndrome, according to whether laser surgery perforated the intertwin membrane (iatrogenic monoamniotic twin (iMAT)) or not

Details of pregnancies in which iMAT was suspected are summarized in Table 3. In 29/67 (43%) of cases the operator was already aware of perforation during the procedure. In 39/67 (58%) iMAT was observed at the first ultrasound scan within 1 day after the procedure. If iMAT was suspected at a later stage of pregnancy (28/67 (42%)), this occurred after a mean of 28 (range, 5–68) days after the procedure. Fetal monitoring was offered in cases with suspected iMAT in 28/67 (42%), starting at a mean gestational age of 28+2 weeks. Monoamnionicity could be confirmed postnatally in 38/67 (57%) cases with suspected iMAT. Medical charts did not provide information on (mono) amnionicity at birth in 29/67 (43%). After birth, cord entanglement was observed in 8/67 (12%) iMAT cases. In none of the cases without antenatal evidence of iMAT was cord entanglement observed after birth.

Patients delivered by Cesarean section in 47/67 (70%) cases. Eight twins with suspected iMAT and two survivors delivered vaginally, because perforation of the intertwin membranes was not communicated to the referring specialist or very early spontaneous delivery occurred (<30 weeks).

Parameter	Value
Operator aware of perforation during procedure	29/67 (43)
Time from procedure to detection	
< 1 day	39/67 (58)
> 1 day	28/67 (42)
Days if detection > 1 day	28 (5–68)
Fetal monitoring	28/67 (42)
Outpatient clinic > once/week	3/28 (11)
Hospitalization	25/28 (89)
GA at start of fetal monitoring(weeks)	28 + 2 (22 + 0 to 33 + 3)
Mode of delivery	
Elective Cesarean section	39/67 (58)
Emergency Cesarean section	8/67 (12)
Vaginal delivery in case of twosurvivors	8/50 (16)
MA confirmed at birth	38/67 (57)
Cord entanglement	
Confirmed at birth	8/67 (12)
No entanglement	23/67 (34)
Unknown	28/67 (42)
Single IUFD directly after laser not related	8/67 (12)

Data given as *n*/*N* (%) or mean (range). GA, gestational age; IUFD, intrauterine fetal demise; MA, monoamnionicity.

Table 3 Details of pregnancies in which iatrogenic monoamniotic twins (iMAT) were suspected (*n* = 67)

DISCUSSION

In this study, antenatal suspected iMAT was found in 20% of TTTS pregnancies treated with laser therapy. Patients with iMAT were more likely to deliver prematurely than were patients with twins with intact membranes, and this was associated with increased neonatal morbidity.

Fetal surgeons need to be aware of this common and clinically relevant complication, and take the utmost care to prevent it from happening. Once iMAT occurs, close monitoring and adaptation of management are required.

A lower incidence than we observed, 7.2%, was described in a prospective cohort study by Cruz-Martinez *et al.*[4] Habli *et al.*[3] reported a rate of occurrence of iMAT of 1.3% (2/152) in a single-center retrospective study. Chmait *et al.*[2] found an incidence of 8.7% with a significant association with preterm birth<32 weeks. All authors mention the importance of careful routine evaluation of the intertwin membranes at every follow-up ultrasound examination.

Previous studies have indicated that unintentional perforation due to intrauterine interventions, such as amniodrainage, may give a false impression of improvement in TTTS.[10,11] This study supports the idea that septostomy as a primary treatment for TTTS is not to be advised, and should be avoided owing to the subsequent surgical challenges that it creates if an operative laser procedure later becomes necessary.[11–13]

An association of iMAT with the risk of pseudoamniotic band syndrome and PPROM was found in previous studies but could not be confirmed in this one despite the higher reported incidence of iMAT.[4,14] Only four cases of amniotic band syndrome were detected in our cohort but, surprisingly, they were only found in the group with intact intertwin membranes. Free-floating fibrous strings of the membranes could increase the risk of pseudo-amniotic band syndrome, but at present the true etiology of this complication has yet to be established. Although, before starting a procedure, the insertion site is carefully chosen, in some cases perforation of the membrane is unavoidable while entering the amniotic cavity. Even more common is the need to coagulate anastomoses on the other side of the membrane, thereby occasionally creating a defect. In some cases the defect in the membranes seems small at first, but can lead to complete rupture of the intertwin membrane.[4] However, using the laser to coagulate anastomoses through the membranes does not necessarily mean the membranes will be perforated. Amniotic fluid and the absorbing capacities of vessels and blood, together with the wavelength of the laser used, have an influence on absorption of the laser energy and its capacity to effect coagulation.[15] These effects allow the surgeon to coagulate the vessels without damaging the membranes.

Signs of iMAT should be actively sought after laser surgery for TTTS, since awareness of this complication may influence obstetric management. Accurate evaluation of the intertwin membranes, especially after a laser procedure, may be challenging. Chorioamniotic separation, remnants of ruptured membranes, amniotic bands, intrauterine synechia or placental interposition may give the false impression of an 'uncomplicated' diamniotic twin pregnancy.[14] Although when perforation occurs it is likely that it happens during the intervention, in our study this was noticed at the time of the surgery or within 1 day after the procedure in only 58% of cases. Close attention to the intertwin membranes is advised during all follow-up ultrasound examinations in these twins. It is important to realize the pitfalls in the diagnosis of amnionicity.[16]
Re-interventions after laser therapy were performed more frequently in cases of iMAT. We therefore hypothesize that iMAT can serve as an indicator for technically difficult procedures. This was also recently advocated by Chmait *et al.*[2] If perforation occurs during surgery, the leakage of fluid behind the membranes often reduces visibility and makes coagulation of the complete vascular equator in that area challenging. Residual anastomoses after incomplete coagulation are the most common cause of severe complications such as recurrence of TTTS or TAPS, and should be prevented.[17]

We found that pregnancies complicated by iMAT are more likely to deliver prematurely, a finding that is in agreement with those of previous studies.[2,4] In this study, monoamnionicity was confirmed at birth in 58% of cases and cord entanglement could be detected in 12%. Possible explanations for this increased risk are the intensive fetal surveillance and preterm elective Cesarean sections that are carried out in this group in order to prevent cord accidents. Since cord entanglement could be confirmed in 12% of iMAT cases after birth, while observed in almost all true monoamniotic twin pregnancies, the increased risk of adverse perinatal outcome in iMAT pregnancies may not only be related to cord entanglement or monoamnionicity itself. It is likely that other factors such as a technically difficult procedure, need for re-intervention and aggressive perinatal management play a role.
An important difference in severe neonatal morbidity in this study was related to the occurrence of RDS and severe cerebral injury. In iMAT cases 23/106 (22%) neonates suffered from RDS compared with 43/392 (11%) in the control group (P=0.05). The criteria for a diagnosis of RDS in this study were restricted to the most severe form of respiratory failure (requiring mechanical ventilation and surfactant). Severe RDS is associated with an increased risk of chronic lung disease and a concomitant increase in rates of adverse long-term outcomes.[18,19]

A limitation of this study is its retrospective design. Despite extensive follow-up according to antenatal care protocols and prospective data collection with specific attention to perforation of the intertwin membranes during the Solomon trial[1], in this study monoamnionicity was confirmed at birth in 40/67 (60%) and not reported in 27/67 (40%) of cases. Therefore, the percentage of true iatrogenic monoamniotic pregnancies after laser treatment is estimated to be at least 12%, but is likely to be higher. Furthermore, some cases with iMAT might have been missed, thereby the rate of iMAT would even be underestimated. While short-term neonatal morbidity could be assessed in 97% of cases, long-term follow-up was not available for this cohort. These endpoints will be a focus of future investigations.

In conclusion, rupture of the intertwin membranes after invasive antenatal interventions is associated with an increased rate of preterm birth, low birth weight and neonatal morbidity. Prospective studies should focus on prevention, detection and optimal management strategies to reduce these risks.

ACKNOWLEDGMENTS

We would like to acknowledge Lia Wijnberger, MD, PhD, for assistance with obtaining the preliminary data. We thank Robert Jan Meerman for support with data management.

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Chapter 6

Monochorionic triplets complicated by fetofetal transfusion syndrome: A case series and review of the literature

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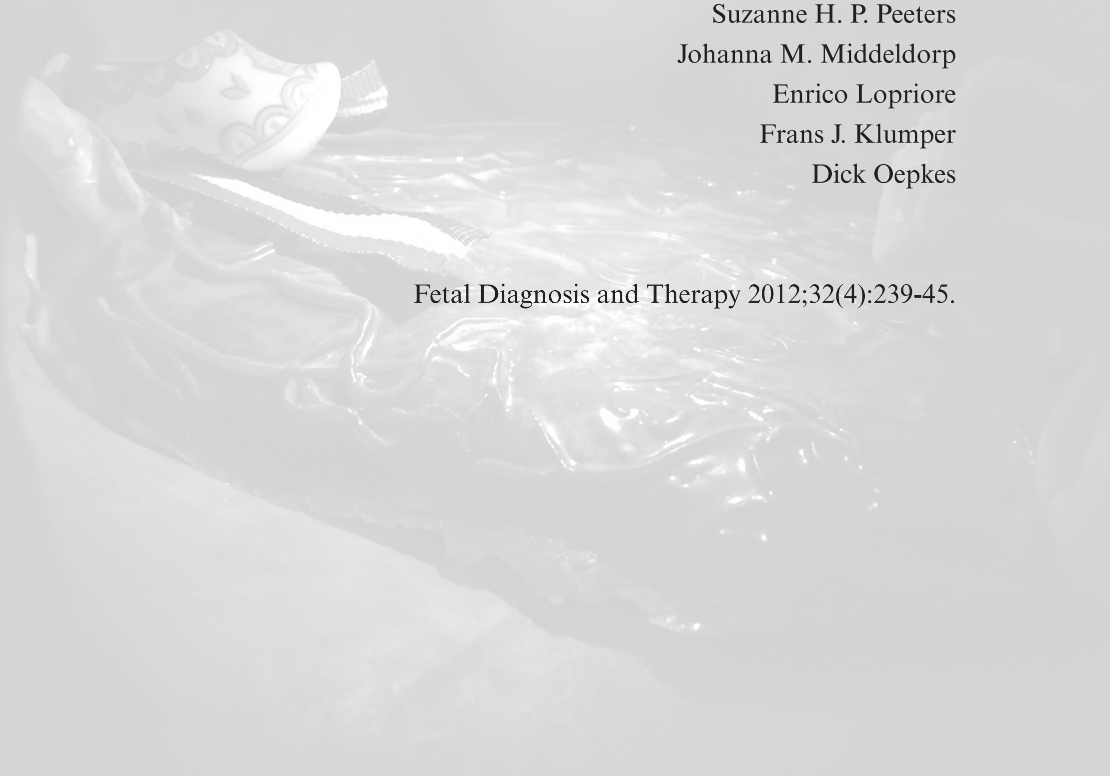
Fetal Diagnosis and Therapy 2012;32(4):239-45.



ABSTRACT

Objective To compare perinatal outcome in monochorionic (MC) triplets with twin-to-twin transfusion syndrome (TTTS) versus dichorionic (DC) triplets with TTTS.

Study Design Retrospective analysis of all triplets with TTTS treated at our center and all cases reported in the literature between 1990 and 2010. Survival and gestational age at birth of MC and DC triplets were compared and stratified by type of intervention. We excluded triplets with one or more fetal deaths <16 weeks' gestation and those with one or more fetuses with congenital anomalies.

Results MC triplets were affected by TTTS in a total of 27 cases, and overall survival was 51% (38/75 fetuses) compared to 105 DC triplets with a survival of 76% (220/291 fetuses) ($p < 0.05$). Mean gestational age at birth in MC triplets was 28 weeks, compared to 31 weeks in DC triplets ($p < 0.05$). Perinatal survival of at least one fetus in MC triplet and DC triplet pregnancies was 70% (19/27) and 91% (96/105) ($p < 0.05$). In DC triplets, survival after laser therapy was significantly improved compared to expectant management, amniodrainage or selective feticide ($p < 0.05$).

Conclusion MC triplets with TTTS are at a considerably higher risk for perinatal mortality and preterm birth than DC triplets. The optimal strategy to manage MC triplets with TTTS, including the role of selective feticide and laser therapy of all anastomoses, is still to be established.

INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is a serious complication of monochorionic (MC) twin gestations and is the result of an unbalanced exchange of blood due to vascular anastomoses that connect the circulations. If untreated, this condition is associated with high perinatal mortality and morbidity rates. Survival is improved with fetoscopic laser coagulation of the placental anastomoses.[1] TTTS is not only seen in MC twins, but can also occur in MC and dichorionic (DC) triplet gestations.

Spontaneous triplets occur in about 1 in 7,000 deliveries, but incidences have increased over the past decades, mainly because of assisted reproductive technologies.[2] Depending on the type of placentation, triplet pregnancies can be trichorionic triplets (i.e. 3 fetuses with separate placentas and amniotic cavities), DC triplets (i.e. monochorionic twins and a singleton with a separate placenta) and MC triplets (i.e. 3 fetuses with one shared placenta and three amniotic cavities). Only a few cases of MC (triamniotic) triplets have been reported, with estimated incidences of 1–1.6 in 100,000 deliveries.[3,4] Since trichorionic triplets have no placental vascular anastomoses, TTTS may only occur in MC and DC triplets. The incidence of TTTS in MC twins is approximately 9% of all cases[5], and this is probably similar for DC triplets. However, the incidence of TTTS in MC triplets, in which all 3 fetuses shared a common circulation, is not well known.

Management options and survival of triplets with TTTS are frequently discussed in the literature.[2,6-9] Because an MC twin pair can also be part of any other high-order multiple pregnancy, survival rates of MC triplets are often confused with DC triplets, with one pair of MC twins affected by TTTS and one singleton. The prognosis of TTTS for MC triplets is considered to be different from that for DC triplets and has been reported to be severe, with higher rates of mortality and preterm birth, despite interventions.[7, 10] However, the literature on triplets and higher-order multiple births with TTTS consists mainly of case reports and small series, most of which fail to discuss placentation.[3,11-19]

In this study, we aim to compare the perinatal outcomes of all the MC and DC triplets with TTTS treated at our center and reported in the literature in the last two decades.

METHODS

At the Leiden University Medical Center (LUMC), the national tertiary referral center for invasive fetal therapy, fetoscopic laser surgery has been the preferred treatment modality for all pregnancies complicated by TTTS Quintero stage II or higher, and for selected cases with Quintero stage I with symptomatic polyhydramnios since August 2000.[20]

Cases in LUMC

We performed a retrospective analysis of prospectively collected data on perinatal outcome and management of all MC and DC triplet pregnancies with TTTS treated at our center. An MC triplet pregnancy was diagnosed when the 3 fetuses shared the same MC placenta, and a DC triplet pregnancy was determined when 2 fetuses shared one MC placenta, whereas the third fetus had an independent single placenta.

Detailed sonograpic examination was performed in all fetuses at the referral center and continued on a weekly or biweekly basis at our center. Chorionicity and amnioniticy were established by sonographic examination in the first trimester of pregnancy. The diagnostic (established) criteria for TTTS in triplets were similar to that for twins. Details on sonographic criteria and details on procedures for fetoscopic laser surgery and umbilical-cord coagulation have been described previously.[20] Once the diagnosis of TTTS was established, parents were counseled regarding the outcome and offered the options of expectant treatment, termination of the whole pregnancy, serial amniodrainage, selective termination of (one of) the MC twins in cases of DC triplets, or one of the fetuses in the case of lethal prognosis or fetoscopic coagulation of the communicating vascular anastomoses. After written informed consent was obtained from the parents, the procedure was performed by one of the four operators, specialized in fetoscopic surgery, as previously reported[20], using a fetoscope (2 mm; Storz, Vianen, the Netherlands) for percutanous introduction through a 3.3-millimeter shaft into the amniotic sac of the recipient(s). Coagulation of the anastomoses or umbilical cord was performed using a diode laser (Diomed Limited, Cambridge, UK) or Nd:YAG laser (Dornier Medizin Technik, Germering, Germany) with an output of 15–70 W. If there were two recipients in MC triplets, the fetoscope was introduced into both cavities via two different uterine entries, but if there were two donors, only the vascular anastomoses between the recipient and both donor fetuses were coagulated.

After the procedure, patients remained in the hospital for 12–48 h. Complications including vaginal blood loss, hypotension, bleeding from uterine vessels, prelabor premature rupture of membranes (PPROM) and maternal fever were recorded. Ultrasound examination was performed within 24 h after surgery and then on a weekly or biweekly basis. The data on obstetric and neonatal outcomes were derived from medical charts. In cases where the delivery did not take place in our center, data were provided by outcome reports from the referring obstetricians and pediatricians.

Meta-analysis of cases reported in the literature

An electronic literature search using MEDLINE, EMBASE and the Cochrane Database was performed to find all relevant articles reporting perinatal outcome and management in MC and DC triplet pregnancies with TTTS. A search in PubMed was performed to find relevant articles reporting outcomes of MC and DC triplet pregnancies complicated by TTTS using the following keywords 'fetofetal transfusion' AND 'triplet', 'survival rate', 'monochorionic' AND 'laser therapy' OR 'intervention'. No language restrictions were applied. We accepted original articles, short communications, letters to the editor and case reports. In addition, a search was performed from the reference list of all identified articles. When needed, we contacted authors for additional, unpublished information. Articles were included irrespective of their primary objective. We included all reported cases of MC and DC triplet pregnancies assessed by 1st-trimester ultrasound and complicated by TTTS. TTTS was diagnosed with standard criteria (polyhydramnios >8 cm in the recipient(s) sac(s) and oligohydramnios <2 cm in the donor sac). Exclusion criteria were one or more fetal deaths <16 weeks' gestation and pregnancies with 1 or more fetuses with congenital anomalies. Cases in which artificial termination of the whole pregnancy was performed were not included.

Two of the authors (S.H.P.P. and D.O.) initially screened all the titles and abstracts of papers, identified by the review search strategy, for their relevance. Only studies that were obviously irrelevant were excluded at this stage; they independently assessed all other studies independently (on the basis of their full text) for inclusion or exclusion, using the above criteria. Discrepancies were to be resolved by discussion with a third reviewer, but this proved unnecessary.

Data extracted from each article included survival, gestational age at birth, intervention, and, if reported, long-term perinatal outcomes in donors and recipients. A p value ≤ 0.05 was considered to indicate statistical significance. A χ^2 test and an independent Student t test were used to compare survival and gestational age between triplets. Statistical analysis was performed with SPSS version 18.0 (SPSS, Inc., Chicago, Ill., USA).

RESULTS

Cases in LUMC

During the 10-year study period from 2000 to 2010, 10 fetoscopic procedures in 2 MC and 8 DC triplet pregnancies were performed in our center. All triplet pregnancies were triamniotic.

A total number of 340 laser surgeries were performed for all twin and triplet pregnancies affected by TTTS during this 10-year period. Details on gestational age at procedure, type of intervention and outcome in triplet pregnancies are described in table 1.

Fetoscopic laser coagulation was performed in 9 cases, including 1 case of MC triplets with percutaneous entry into two amniotic sacs. In 1 case of MC triplets, umbilical cord coagulation with selective reduction of the recipient was carried out. The procedure was performed at a median gestational age of 18 weeks (range 14–26 weeks). Three cases were classified as Quintero stage II and 7 cases Quintero stage III. Fetal demise occurred in 9 of 30 fetuses (30%) (including 2 cases of selective feticide) and neonatal demise in 1 neonate (3%). Overall perinatal survival was 70% (20/30). In the DC triplets, perinatal survival of both children involved in the monochorionic twin pair was 50% (4/8). Median gestational age at delivery was 31 weeks' gestation (range 21–36 weeks). Median birth weight in live-born neonates was 1,661 g (range 845–2,780 g).

A procedure-related complication occurred in 1 case (table 1, case No. 3) where laser coagulation of a DC triplet was performed. During uterine entry, an umbilical artery of the donor was perforated and massive bleeding occurred, with the result of intrauterine fetal demise of the donor. The recipient twin and the singleton were born at 34 weeks' gestation. No maternal complications occurred.

In one of the DC triplets (table 1, case No. 7) treated with laser surgery at 20 weeks' gestation, intrauterine fetal demise of the donor was assessed at 22 weeks. PPROM occurred at 27 weeks' gestation and corticosteroids, antibiotics and atosiban were administered to prevent preterm labor. Nevertheless, the patient went into spontaneous labor at 29 weeks and 6 days. The MC twin in this pregnancy was delivered at 30 weeks' gestation, including the stillborn donor, but the recipient died 4 days after birth due to intracranial hemorrhage grade IIb and sepsis due to group B streptococcus. The delivery of the third child took place on the same day and it was alive and well at discharge.

In 1 case of DC triplets (table 1, case No. 9) fetoscopic laser coagulation was performed with intentional perforation of the intertwin membrane because of the presence of vascular anastomoses in the other amniotic cavity, thereby creating a monoamniotic twin and one singleton. Unfortunately MRI scans that were performed during follow-up of the pregnancy showed severe brain damage with ventriculomegaly and ischemic lesions of the former recipient. A reintervention was performed and selective feticide of the recipient twin was carried out. The donor and the singleton were born healthy at 35 weeks' gestational age.

From 1990 to 2010, 22 articles met the inclusion criteria and we identified 25 MC and 97 DC triplet pregnancies with TTTS.[2,3,6-19,21-25] Quintero stage, in the reported cases including the cases in this study, was stage I in 7% (2/27) stage II in 15% (4/27), stage III in 45% (12/27) and stage IV in 33% (9/27) of the MC triplets. In the DC triplets, Quintero stage I was classified in 2% (2/105), stage II in 23% (24/105), stage III in 68% (72/105) and stage IV in 7% (7/105).

Survival rates of all triplet pregnancies complicated by TTTS reported in the literature (including the cases in our center) – classified according to chorionicity – are presented in table 2. Perinatal survival of at least 1 fetus in MC and DC triplet pregnancies was 70% (19/27) and 91% (96/105), respectively ($p = 0.004$). Overall perinatal survival of MC and DC triplets was 51% (38/75) and 76% (220/291), respectively ($p = 0.018$). Median gestational age at delivery was 28 weeks (range 18–40 weeks) for the MC triplets, compared to 31 weeks (range 20–39 weeks) in the DC triplets ($p = 0.016$). In DC triplets, survival after laser therapy was significantly improved compared to expectant management, amniodrainage or selective feticide ($p = 0.007$). Neonatal death within 4 weeks after birth occurred in 8% (6/75) of MC cases and in 8% (24/291) of DC cases (p = NS). In 1 case of MC triplets, a neonate died on the 75th day after birth.

Case	Chorionicity	Intervention	Quintero stage	Placenta location	GA at diagnosis (wks)	GA at intervention (wks)	GA at birth (wks)	Fetuses	Outcome	Birth weight	Follow up
1	MC	selective fetocide	3	ant	17	22	22	donor	stillbirth at 22+3 wks	330 g	
								recipient	select fetocide at 22 wks*	340 g	
								asymptomatic	stillbirth at 22+3 wks	430 g	
2	DC	laser	2	post	17	17	30	donor	Live birth at 30+4 wks	1180 g	Alive and well
								recipient	Live birth at 30+4 wks	1490 g	Alive and well
								dichorionic	Live birth at 30+4 wks	1455 g	Alive and well
3	DC	laser	2	post	14	17	34	donor	IUFD at 17 wks	50 g	Due to damage chorial vessel during intervention
								recipient	Live birth at 34+3 wks	845 g	Alive and well
								dichorionic	Live birth at 34+3 wks	1120 g	Alive and well
4	DC	laser	3	post	25	25	30	donor	Live birth at 30 wks	1180 g	Alive and well
								recipient	Live birth at 30 wks	1350 g	Alive and well
								dichorionic	Live birth at 30 wks	1195 g	Alive and well
5	DC	laser	3	ant	16	16	28	donor	IUFD 18 wks		
								recipient	Live birth at 28+4 wks	1050 g	Alive and well
								dichorionic	Live birth at 28+4 wks	1130 g	Alive and well
6	DC	laser	3	post	18	19	36	donor	Live birth at 35+6 wks	2300 g	Alive and well
								recipient	Live birth at 35+6 wks	2600 g	Severe congenital cardiac disorder
								dichorionic	Live birth at 35+6 wks	2780 g	Alive and well
7	DC	laser	3	ant	12	20	30	donor	IUFD 22 wks		
								recipient	Live birth at 29+6 wks	1440 g	Neonatal death 4 days intracranial hemorrhage and sepsis**
								dichorionic	Live birth at 29+6 wks	1600 g	Alive and well

8	DC	laser	2	post	15	15	32	donor	Live birth at 32+4 wks	1950 g	Alive and well
								recipient	Live birth at 32+4 wks	1743 g	Alive and well
								dichorionic	Live birth at 32+4 wks	2030 g	Alive and well
9	DC	laser	2	ant	15	15	35	donor	Live birth at 35+1 wks	2310 g	Alive and well
		reintervention						recipient	selective feticide at 21 wks ***		
		selective fetocide						dichorionic	Live birth at 35+1 wks	2435 g	Alive and well
10	MC	laser	3	post	14	15	30	donor	IUFD at 22 wks		
								recipient	IUFD at 16 wks		
								donor	Live birth at 30+5 wks	1640 g	Alive and well

MC: monochorionic, DC: dichorionic, IUFD: intra uterine fetal demise, ant: anterior placenta, post: posterior placenta

* Laser coagulation impossible due to decreased visibility because of bleeding in uterine wall converted to selective fetocide

** PPROM occurred at GA 27 weeks.

*** Iatrogenic monoamnioticity. Severe hypoperfusion damage was diagnosed after laser procedure.

Table 1. Our center experience: pregnancy outcome after endoscopic laser coagulation and selective feticide in triplet pregnancies complicated by TTTS

6

Intervention	Survival (fetuses) MC triplets	n	DC triplets	n	GA at birth wks (range) MC triplets	DC triplets
Laser	26/48 (54%)	16	184/237 (78%)	79	28 (18-34)	31 (20-36)
Selective feticide	1/6 (17%)	2	11/24 (46%)	8	31 (22-40)	32 (25-37)
Amniodrainage	4/9 (44%)	3	20/39 (51%)	13	26 (23-27)	29 (24-39)
Expectant	7/18 (39%)	6	5/15 (33%)	5	28 (23-35)	26 (23-29)
Total	38/81 (47%)	27	220/315 (70%)	105	28 (18-40)	31 (20-39)

Table 2. Survival rates and gestational age at birth of MC and DC triplet pregnancies according to type of intervention

Figures 1 and 2 demonstrate the difference between a triplet pregnancy with an MC placenta with vascular anastomoses and a DC placenta of an MC twin (and one singleton) complicated by TTTS and treated with laser coagulation.

Figure 1. Placenta of MC triplets with vascular anastomoses.

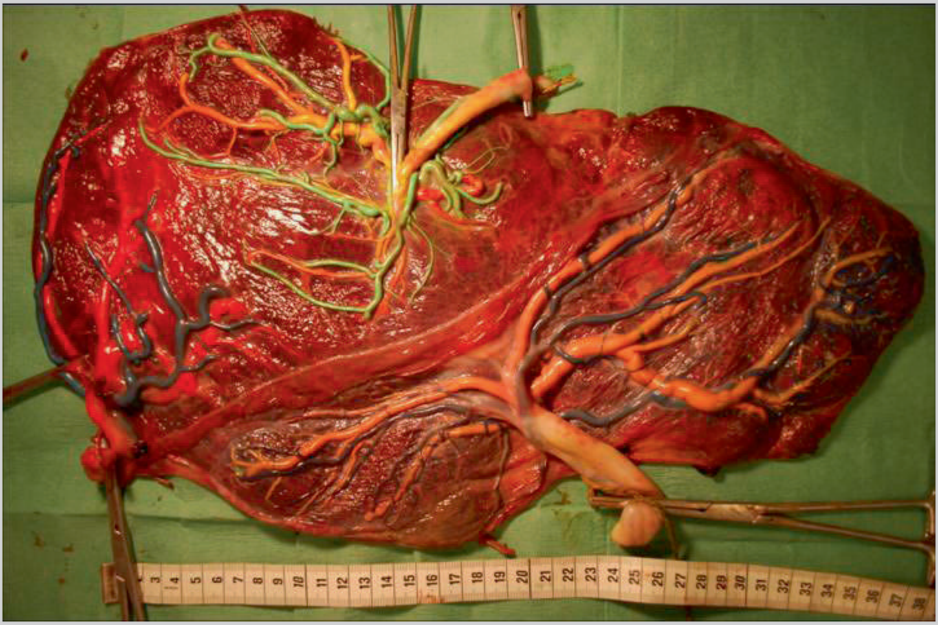


Figure 2. Placenta of DC triplet with MC twin complicated by TTTS and treated with laser surgery and one singleton. As is common in dichorionic placentas, the placenta of the singleton is fused together with the monochorionic twin placenta. The thick intertwin membrane indicates dichorionicity.

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DISCUSSION

This study shows that perinatal morbidity and mortality in MC triplets with TTTS is higher than in DC triplets. Of the 81 fetuses involved in fetofetofetal transfusion, only 38 (51%) survived. In addition, median gestational age at delivery in MC triplet pregnancies is significantly shorter than in DC triplets (28 vs. 31 weeks' gestation). This outcome could be due to the technical difficulties of interventions in MC triplets because all three circulations are connected, therefore making fetoscopic treatment much more challenging.

The data in this study also demonstrate that fetoscopic laser coagulation of communicating vascular anastomoses in DC triplet pregnancies complicated by TTTS is a feasible treatment option with increasing survival rates and more advanced gestational age at birth. Perinatal survival rates of at least one survivor (91%) appear comparable to MC twins (around 90%).[26,27] Although treatment appears to be associated with an improved perinatal outcome for DC triplets, survival rates are still limited for MC triplets.

Various therapeutic measures have been proposed for triplets with TTTS. Amnioreduction, to decrease the pressure of the amniotic cavity with polyhydramnios, is not a permanent solution and is associated with a high risk of mortality and morbidity to the cotriplets due to the presence of vascular anastomoses in the case of intrauterine fetal demise. Serial amnioreduction is therefore considered, at best, a temporary treatment and does not correct the underlying problem.

Fetoscopic laser coagulation is the only causative treatment option because, provided that all anastomoses can be visualized on the chorionic surface, this operation will separate the fetal circulations.[28] This technique potentially avoids perinatal mortality and the high morbidity rate attributed to vascular accidents mainly after intrauterine death of one of the multiplets.[7] Loss of cotyledons following laser ablation could either cause or exacerbate placental insufficiency in the normal triplets; however, according to Chmait et al.[29], twin weight discordance and donor fetus intrauterine growth restriction appear to improve after laser therapy. In DC triplet pregnancies with severe TTTS, the technique for fetoscopic laser coagulation is the same as in MC twins with this condition. Comparable to Sepulveda et al.[7], survival rates appear similar to that of MC twins when a successful procedure was performed. Conversely, in MC triplet pregnancies the outcome was poor. In 6 cases of MC [3,6,9,11,15,22] and 5 cases of DC [6,23,24] triplets complicated by TTTS, only 12/33 (36%) survived with expectant management. Although based on small numbers, these results strongly suggest that laser coagulation is preferable to expectant management or amniodrainage.[17] Five successful cases of MC triplet gestations (with 3 survivors) treated with laser coagulation were reported (including the cases in our study),[2,7-10,21] but 11 other cases were not successful.

Most likely, this is due to the technical difficulties of the fetoscopic treatment because of the identification and coagulation of vascular anastomoses between all 3 fetuses. To reach the appropriate location of the interfetal communicating vessels, it is necessary to have two uterine entries with the fetoscope into two different sacs. In addition, complete ablation of the intercommunications can be technically impossible to achieve because of placental location, the presence of multiple fetal parts that hamper visualization of the placental anastomoses and oligohydramnios in the sac of the donor. Incomplete separation could result in the intrauterine death or severe morbidity of the remaining fetus(es) after the procedure, because of retrograde hemorrhage of the live fetuses into the dead placental tissue.

Selective feticide of the affected triplets [i.e. the MC pair in a DC triplet or a compromised triplet(s)] offers the potential advantages of interrupting the circulatory imbalance with a single procedure and provides a maximal placental volume for the remaining fetus.

Umbilical cord coagulation has proven beneficial in conditions such as twin-reversed arterial perfusion or MC twins discordant for a major anomaly, with survival of 78% of co-twins and an excellent long-term outcome; therefore, it may also be used in triplets with these kinds of conditions.[30] Furthermore, some parents could consider selective reduction of 1 or more healthy fetuses, to improve the survival and long-term follow-up of the remaining children.

Care should be taken when interpreting these results due to the limited data on perinatal outcome in triplets with TTTS, particularly MC triplets. Only 27 cases of MC triplet pregnancies with TTTS have been reported in the literature. The actual number of MC and DC triplets with TTTS may be higher due to underreporting/publication bias. Several cases in which the pregnancy was terminated or fetal demise occurred spontaneously have probably not been reported. Irrespective of zygocity, triplets are high-risk pregnancies due to the high incidence of preterm delivery, intrauterine growth restriction and congenital anomalies.[31] Only 1 case of fetofetal transfusion syndrome in MC quadruplets has ever been reported. Laser ablation of vascular anastomoses between one donor and two recipients was carried out at 20 weeks' gestation and fetal demise of one quadruplet occurred shortly after procedure. Delivery occurred at 25 weeks after the recurrence of TTTS. Only the sole survivor, not affected by transfusion, was born alive.[32]

In conclusion, this case series and review of the literature demonstrates that, although technically more challenging, fetoscopic surgery is feasible in triplets. In cases of MC triplets where fetoscopic laser coagulation is technically impossible, parents should be counseled on the increased likelihood of unfavorable outcome. However, the rarity of these conditions, the required operator and prenatal diagnostic skills, the variety of management options and the requirement of in-depth counseling of patients currently limit the availability of such interventions to referral centers for fetal medicine. Further experience will be required in order to evaluate the risks and efficacy of this therapy in triplet cases.

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Part IV

Model for training laser therapy

Chapter 7

Identification of essential steps in laser procedure for twin-twin transfusion syndrome using the Delphi methodology: SILICONE study

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Ultrasound Obstet Gynecol. 2014 Dec 11.

ABSTRACT

Objective. To determine, by expert consensus, the essential substeps of fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome (TTTS) that could be used to create an authority-based curriculum for training in this procedure among fetal medicine specialists.

Methods. A Delphi survey was conducted among an international panel of experts ($n = 98$) in FLS. Experts rated the substeps of FLS on a five-point Likert-type scale to indicate whether they considered them to be essential, and were able to comment on each substep, using a dedicated online platform accessed by the invited tertiary care facilities that specialize in fetal therapy. Responses were returned to the panel until consensus was reached (Cronbach's $\alpha \geq 0.80$). All substeps that were rated ≥4 by 80% of the experts were included in the evaluation instrument.

Results. After the first iteration of the Delphi procedure, a response rate of 74% (73/98) was reached, and in the second and third iterations response rates of 90% (66/73) and 81% (59/73) were reached, respectively. Among a total of 81 substeps rated in the first round, 21 substeps had to be re-rated in the second round. Finally, from the initial list of substeps, 55 were agreed by experts to be essential. In the third round, the 18 categorized substeps were ranked in order of importance, with 'coagulation of all anastomoses that cross the equator' and 'determination of fetoscope insertion site' as the most important.

Conclusions. A total of 55 substeps of FLS for TTTS were defined by a panel of experts to be essential in the procedure. This list is the first authority-based evidence to be used in the development of a final training model for future fetal surgeons.

INTRODUCTION

A randomized trial, published in 2004, established fetoscopic laser surgery (FLS) as the best treatment modality for twin–twin transfusion syndrome (TTTS).[1] With an incidence of 10% in monochorionic twin pregnancies, TTTS is rare and treatment is offered in a limited number of specialized maternal–fetal medicine (MFM) expert centers around the world.[2] With the economic growth of developing countries and the identification of new potential indications for FLS, such as twin anemia–polycythemia sequence and selective fetal growth restriction, the expectation is that, in the future, a greater number of FLS procedures will be performed. Objective assessment of technical performance is essential for such complex procedures. In order to maintain optimal performance and quality of care, increasing attention is being given to the teaching, training, retention of skills and quality control of FLS. Even large fetal treatment centers have limited numbers of TTTS cases,[3] therefore the teaching and training of this procedure are challenging. Currently, standardized surgical training programs for FLS are unavailable. As surgical errors and suboptimal technique are also yet to be defined, teachers often base their training on personal experience and individual preference. Learning technical skills from an experienced mentor will probably continue to play a significant role in future training. However, there is an increasing need for a standardized tool to train and evaluate trainees. Similar issues have been raised in other invasive obstetric procedures and surgical areas, such as endoscopy.[4,5]

An essential first step towards the creation of a training curriculum is to determine the items that need to be assessed, preferably by using quality indicators.[6] These indicators can be derived from the outcomes of studies, historical data and expert opinions. The elements need to be measurable, so they can be used in the assessment of trainees during their learning process, to monitor performance and maintain quality control. Authority-based indicators for FLS can be obtained using the Delphi method for international expert consensus. The Delphi methodology is an internationally-accepted tool that allows a group of individuals to achieve consensus on a complex problem effectively, by structuring the group communication process.[7,8]

The aim of this study was to achieve expert consensus regarding the substeps that are considered to be essential in performing FLS for TTTS, which can be used as a framework for standardized training. Furthermore, we aimed to create an instrument that could be used to evaluate a surgeon's technical performance during FLS, both in a high-fidelity simulator training model and in real-life situations, and serve as a means for quality control.

METHODS

Study design

This study is part of the SILICONE project (SImulator for Laser therapy and Identification of Critical steps of Operation: New Education program), conducted with the aim of developing a standardized training program for FLS in cases of TTTS. In the first part of the project, we intended to develop an evaluation instrument based on the essential steps of treatment. In the second part of the project, not included in this study, the instrument will be validated and used to evaluate a training session that uses a SILICONE simulator.

The Delphi methodology was used to achieve expert consensus on which substeps of FLS performed for TTTS are essential. The Delphi methodology is, in essence, a series of sequential questionnaires or 'rounds', followed by controlled feedback, that seeks to gain the most reproducible consensus among a panel of experts.[9] Consensus occurs because the views of the participants converge through a process of informed decision-making.[8] The Delphi method was first developed by the Research ANd Development (RAND) Corporation, a non-profit global policy think-tank, formed in 1950 to offer research and analysis to the USA armed forces.[10-12] It is an anonymous process in which ideas are expressed to the participants in the form of a questionnaire. In repeated rounds, respondents are questioned individually, with self-administered surveys. In each subsequent round, the results of the previous round are provided, thus enabling the range of answers to converge towards a consensus. An overview of the study design is presented in Figure 1.

A panel of experts in FLS was presented with a list of substeps of the procedure and asked to rate each substep, using a Likert scale from 1 (strongly disagree) to 5 (strongly agree), with the level at which they believed the step should be included in an evaluation tool. In addition, all participants were encouraged to clarify their ratings in a comments box. Each round started with a new questionnaire consisting of a list of these substeps. The participation of the FLS experts was not disclosed to the other experts (quasi-anonymity). The total response rate was based on the number of fully completed surveys. We identified an initial list of possible substeps of FLS during the first iteration of the survey from three sources: expert opinion, textbooks on fetal therapy and published peer-reviewed literature. Each substep of FLS that was identified from any of these three sources was included in the survey. Before the first iteration of the study, an international pilot panel meeting took place that consisted of senior FLS experts from several large international centers, with extensive experience in fetoscopic surgery. They assessed the survey for comprehensiveness and integrity. After taking into account their comments, invitations to participate in the survey were sent out.

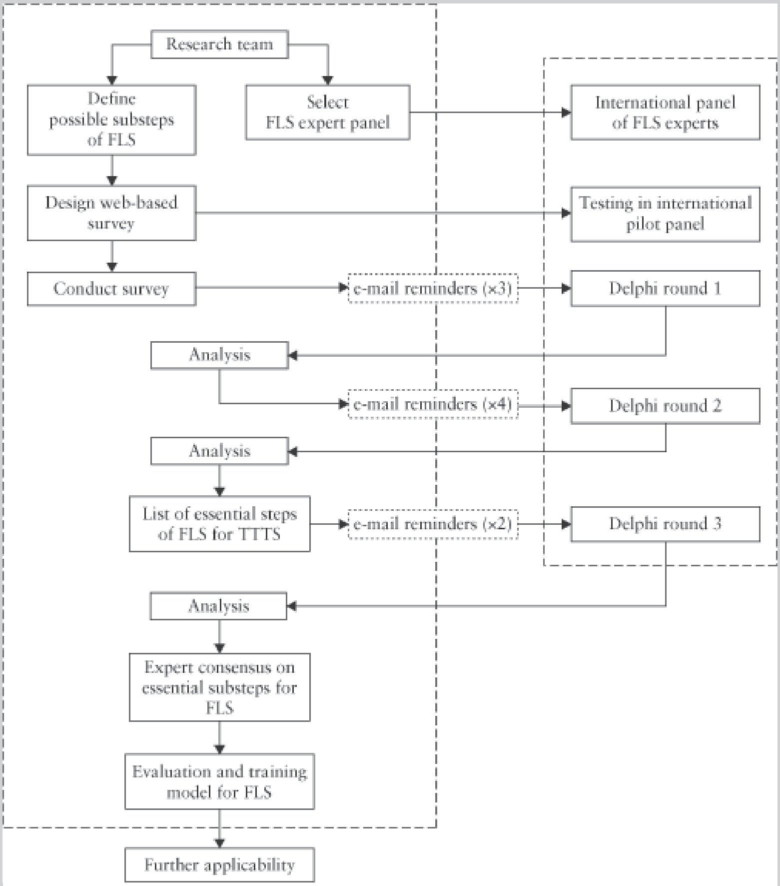

Figure 1. Overview of study design to achieve expert consensus on substeps of fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome (TTTS) that are essential to the procedure.

Selection of experts

All FLS experts included in the study were selected through membership lists of MFM organizations (Society for Maternal-Fetal Medicine (SMFM), Eurofoetus, USFetus, North American Fetal Therapy Network (NAFTnet), International Fetal Medicine and Surgery Society (IFMSS), International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), World Association of Perinatal Medicine (WAPM), The American Congress of Obstetricians and Gynecologists (ACOG), North American

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Society of Obstetrics Medicine (NASOM) and Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)). We defined an expert as someone who currently performs FLS for TTTS. Furthermore, all experts were identified as leaders in the field of fetal therapy as evidenced by their role as opinion leaders within their MFM organizations and supported by their track record of publications in peer-reviewed literature. The expert panel was selected specifically to represent a wide geographic area including Australia, Asia, Canada, Europe, South America and the USA. We invited 98 individuals from 23 different countries to participate. The size of Delphi panels can vary widely and there is disagreement about what constitutes an appropriate panel size. Panel size in Delphi studies is considered to be researcher- and situation-specific. For this study, we aimed to contact the entire international community of MFM specialists who had extensive experience with FLS.

Surveys

Delphi round 1

At the start of the first round, an e-mail was sent to all FLS experts that included: the invitation, background, short instructions and the link to the first survey. Later, for each round, multiple reminders were sent out to non-responders. The first survey consisted of two parts: in Part I (Appendix S1), the participants were asked to rate each possible substep of FLS for TTTS; in Part II, the experience and surgical practices of the survey respondent and of their center were obtained. The estimated time to complete Round 1 was 15 min.

The first round of data was analyzed and results were pooled. Two of the authors (M.W. and S.P.) independently categorized the comments on the basis of the presence of essential elements. For each substep we ascertained if the essential element of the comment consisted of an addition or a substitution to the substep. A third author (J.A.) assessed the categorized comments and the revised substeps independently for clarification and to make sure all further areas were explored. Figure 2 shows how the comments were incorporated into the second round of the survey.

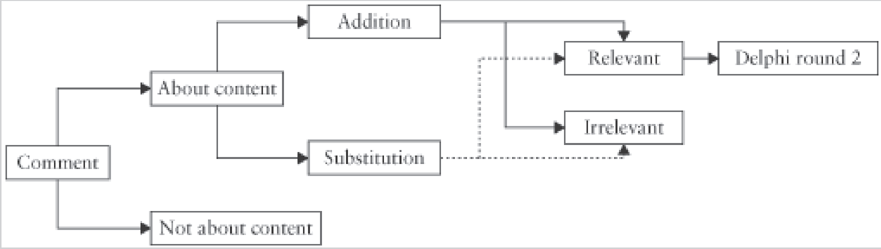

Figure 2. Method of incorporating survey respondents' comments for development of second round of Delphi survey.

Delphi round 2

In the second round, the results of the first round were made available to the FLS experts (Appendix S2).

The second Delphi round was sent out 1 month after the first, to optimize the response rate and ensure that participants remained interested in the process. In accordance with the Delphi method, participants were asked to re-rate substeps for which no consensus had been achieved. In this round, some of the substeps were altered on the basis of the feedback of the FLS experts from the first round. The substeps for which consensus had been achieved in the first round could not be re-rated in the second questionnaire, but were available for review.

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Delphi round 3

Based on the results from the first two rounds, a list of all essential substeps of FLS for TTTS was defined. In order to use this final list for evaluation and training with the SILICONE simulator, a third round of the Delphi procedure was carried out to determine the appropriate distribution of importance of the steps. For the purpose of Part 2 of the SILICONE project, only the substeps that could be simulated were included in this round. The included substeps were categorized into 18 items, and those categorized within the domains 'diagnostic procedure', 'presurgical management' and 'follow-up ultrasound examination' were excluded. All respondents rated the level of importance of the 18 categorized substeps on a Likert scale of 0–10, with respect to each other. With this order of importance, we were able to give a certain value to each separate substep, and we incorporated this into the evaluation tool.

Statistical analysis

For this study, the concept of consensus was predefined as a condition of homogeneity or consistency within the opinions of the FLS experts. There are no established criteria for determining consensus using a Delphi methodology.[6,12]

Cronbach's α was chosen as the statistical index for quantifying the reliability of a summation of entities, in this case the view of the experts in FLS. In this study, an α-value of 0.80 defined an acceptable and high level of consensus.[6,13]

Rate of agreement

To ascertain whether consensus was reached for each substep separately, the rate of agreement (RoA) was used. The RoA is defined as:

$$\text{RoA (\%)} = \frac{\text{(strongly) agree } (n) - \text{(strongly) disagree } (n)}{\text{(strongly) agree } (n) + \text{(strongly) disagree } (n) + \text{indifferent } (n)} \times 100\%$$

Scaled responses to the categorical items (strongly disagree to strongly agree) were analyzed as percentages (Appendix S2). Feedback to the panel of experts included providing the Cronbach's α score of the previous round, percentages and means of the answers to all items and the RoA for each item separately. After reaching a consensus (Cronbach's $\alpha \geq 0.80$), only the substeps with an RoA of 80% or higher were included in the final evaluation tool. Substeps with an RoA of less than 20% were not reassessed and were removed from the evaluation tool.

In the second round of the Delphi procedure, the substeps with $20\% < \text{RoA} < 80\%$ were re-rated. After the final round, only items with an $\text{RoA} \geq 80\%$ were included in the final evaluation tool. The other substeps were excluded from the list.

Data were collected using our online survey tool, www.deltafetus.nl, and analyzed using SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY, USA).

The study was performed by the Departments of Obstetrics and Pediatrics at the Leiden University Medical Center, Leiden, The Netherlands, in association with Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; Jackson Fetal Therapy Institute, Miami, FL, USA; University of Southern California, Keck School of Medicine, Los Angeles, CA, USA; Liverpool Hospital, Liverpool, Australia; and the University Hospitals KU, Leuven, Belgium. The data were collected between February 2014 and July 2014.

RESULTS

In the first round, a response rate of 74% (73/98) was reached. Table 1 presents a summary of characteristics of the FLS experts. The majority of the participants (77%; 56/73) worked at university hospitals. Most of the responding experts were MFM specialists, a minority (7%; 5/73) were pediatric surgeons. All the experts also performed other antenatal procedures besides FLS for TTTS. Almost all had more than 5 years' experience performing FLS, except for two who had been performing the procedure for only 2 and 4 years, respectively. The mean length of experience with FLS of the participating experts was 10.2 years. The most frequently mentioned teaching centers for FLS were King's College Hospital, London, UK ($n = 15$); University Hospitals KU Leuven, Belgium ($n = 15$); University Hospital Center Paris - Hôpital Necker-Enfants Malades, Paris, France ($n = 10$); and Jackson Fetal Therapy Institute, Miami, FL, USA ($n = 7$).

In the subsequent rounds of the survey, the response rate was 90% (66/73) for round 2 and 81% (59/73) for round 3.

Substeps

After the first round of the Delphi procedure, a Cronbach's α score of 0.911 was reached, and consensus was attained, on 52 of the 81 substeps (Figure 3). In the second round (Appendix S2), the 28 substeps for which no consensus was reached were merged and rephrased into 21 substeps, because, according to most FLS experts, these substeps were not well formulated. One clearly inappropriate substep, 'mark recipient with laser spot on left upper leg', was purposely incorporated into the first survey round as a check for validity. This item was excluded after the first round. After the second round, consensus was reached on another four substeps (RoA ≥ 80%). One substep was removed from the final list owing to duplication. Table 2 shows the list of substeps that were included in the evaluation end tool.

Experts	n/N (%)
Type of hospital	
university hospital	56/73 (77%)
private hospital/tertiary care facility	11/73 (15%)
public hospital	5/73 (7%)
other	1/73 (1%)
Medical specialty	
obstetrics and gynecology	6/73 (8%)
pediatric surgery	5/73 (7%)
Maternal Fetal Medicine (MFM)	62/73 (85%)
Antenatal invasive procedures	
amniocentesis	69/73 (95%)
chorionic villus sampling	59/73 (81%)
intrauterine transfusion	64/73 (88%)
fetal shunt placement	62/73 (85%)
bipolar cord occlusion	50/73 (68%)
open fetal surgery	16/73 (22%)
Experience	
years currently working as MFM specialist (mean; range)	17.3 (5.0 - 36.0)
years performing FLS for TTTS (mean; range)	10.2 (2.0 - 25.0)
Number of lasers performed annually	
<10	12/73 (16%)
10-25	27/73 (37%)
25-50	18/73 (25%)
50-100	12/73 (16%)
>100	4/73 (5%)
Centers	**n/N (%)**
Number of lasers performed annually	
<10	11/73 (15%)
10-25	23/73 (32%)
25-50	18/73 (25%)
50-100	18/73 (25%)
>100	3/73 (4%)
Experience	
years laser performed at center (mean; range)	10.5 (1.0 - 25.0)
no. of surgeons performing laser (median; range)	2 (1 - 5)
no. of trainees (median; range)	1 (0 - 9)

Table 1. Experience and surgical practice and center characteristics of the 73 experts in fetoscopic laser surgery (FLS) who responded to the survey.
MFM: maternal fetal medicine FLS: fetoscopic laser surgery TTTS: twin-to-twin transfusion syndrome

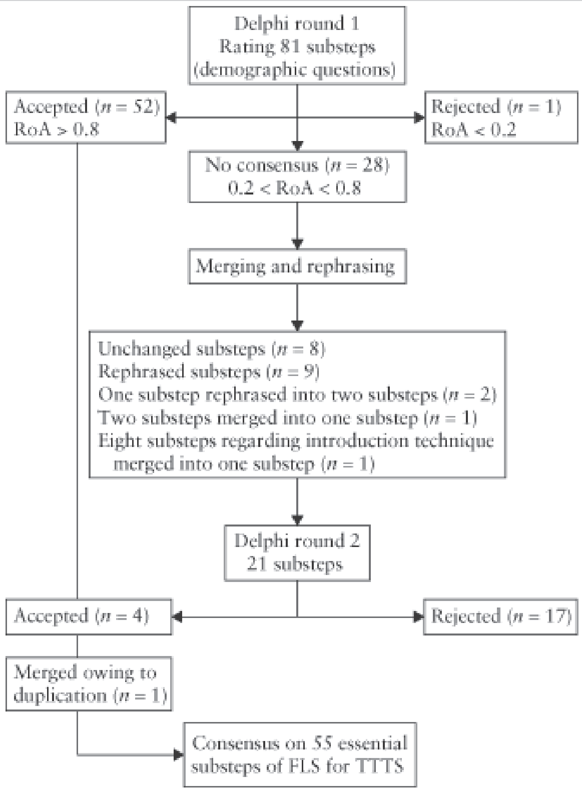

Figure 3. Flowchart of the selection of substeps determined by expert consensus to be essential in fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome to be included in an evaluation instrument. RoA, rate of agreement.

Some substeps were considered more important than others. 'Coagulation of all vascular anastomoses that cross the vascular equator' and 'determine site of insertion of fetoscope' were items that were considered as most important during FLS. Table 3 shows a list of the 18 most important substeps that can be used for training and evaluation in order of importance.

No.	Domain and substeps
1.	**Diagnostic procedure**
1.1	Make sure advanced ultrasound scan is performed to exclude fetal anomalies
1.2	Confirmation of monochorionicity, diagnosis, Quintero stage of TTTS
1.3	Consider cervical length measurement
1.4	Consider risk of complications (cervix shortening, fetal deterioration etc)
1.5	Determine whether laser is best treatment option (and consider alternatives)
1.6	Determine whether laser procedure should be performed as soon as possible or expectant management can be an option
1.7	Obtain full informed consent
2.	**Pre-surgical management**
2.1	Blood group and Rhesus typing should be known, respect local protocols concerning Rh-D prophylactics
2.2	Prescribe all procedure-related medications (tocolytics, antibiotics etc)
2.3	Determine and arrange type of anesthesia
3.	**Preparation in operating room**
3.1	Knowledge of technical equipment (ultrasound, scopy tower, laser, instruments)
3.2	Positioning of screens, assistants and lights
3.3	Determine laser modus and power settings
3.4	Positioning of patient
4.	**Ultrasound examination (together with sonographer)**
4.1	Identification of both fetuses, presentation and position
4.2	Visualize placenta localization, umbilical cord insertions
4.3	Assess deepest pockets of amniotic fluid
4.4	Determine expected position of vascular equator
4.5	Determine site of insertion of fetoscope
4.6	Choose type of introduction (set) and type of fetoscope
5.	**Sterile procedure and anesthesia**
5.1	Surgical briefing (time out) about (complete) procedure to fetal therapy team
5.2	Aseptic procedure for surgeon, scrub nurse and sonographer
5.3	Monitoring maternal condition (during complete procedure)
5.4	Placement of sterile covers over patient and instruments
6.	**Positioning and connection of instruments (pre-insertion)**
6.1	Connection of fetoscope (orientation, focus and white balance)
6.2	Connection of laser fiber to laser machine, insertion of fiber in fetoscope
7.	**Insertion**
7.1	Performance of all manipulations under ultrasound visualization
7.2	In case of local anesthesia: administer anesthetic to skin and peritoneum
7.3	Make adequate-size skin incision with surgical knife
7.4	Correct use of (Seldinger or trocar) technique for insertion
7.5	Awareness of location of maternal uterine vessels and intestines, and placental edge during insertion
7.6	Insertion of shaft/scope

8.	**Orientation**
8.1	Assess visibility (optional: score visibility)
8.2	Determine need for amniotic exchange
8.3	Confirm position of placenta, fetuses and cord insertions
8.4	Identification of intertwin dividing membrane (and use for reference)
8.5	Mapping of placental surface and vascular equator
9.	**Laser coagulation**
9.1	Coagulation of all vascular anastomoses that cross the vascular equator
9.2	Prevent the unnecessary sacrifice of placental tissue
10.	**Assessment during procedure**
10.1	Prevent unnecessary delay during procedure
10.2	Check for complications(e.g. bleeding, rupture intertwin membranes
10.3	Identify and record number and type of anastomoses coagulated
11.	**Amniodrainage**
11.1	Controlled drainage of polyhydramnios
11.2	Assess adequate drainage (ultrasound guided) until pre-defined level to decrease uterine distention and promote patient comfort
12.	**Closure**
12.1	Closing skin incision (suture or suture free adhesive product)
13.	**Direct post-operative management**
13.1	Inform patient, partner/family and referring specialist
13.2	Administration (surgical report, fetal therapy database)
13.3	Instructions for monitoring of maternal and fetal condition
14.	**Follow up ultrasound examination**
14.1	Knowledge of follow-up until delivery of (un)complicated monochorionic pregnancies
14.2	Assessment of fetal condition including bladder filling, deepest vertical pockets and Doppler flows
14.3	Knowledge of MCA-PSV measurement to detect post-laser TAPS
14.4	Signs of iatrogenic perforation of the intertwin membrane
14.5	Signs of amnion-chorionic separation
14.6	Record which fetus is former donor and recipient, respectively
14.7	Knowledge of signs and options with regards to iatrogenic PPROM

Table 2. The 55 essential substeps of fetoscopic laser surgery (FLS), performed in cases of twin–twin transfusion syndrome (TTTS), to be included in an evaluation and training instrument.
FLS: fetoscopic laser surgery TTTS: twin-to-twin transfusion syndrome PPROM: preterm premature rupture of membranes, MCA-PSV: middle cerebral artery peak systolic velocity, TAPS: twin anemia polycythemia sequence.

1	Coagulation of all vascular anastomoses that cross the vascular equator
2	Determine site of insertion of fetoscope
3	Ultrasound identification of placenta, fetuses, umbilical cord insertions and expected vascular equator
4	Mapping of placental surface and vascular equator
5	Identification of intertwin dividing membrane (and use for reference)
6	Prevent the unnecessary sacrifice of placental tissue
7	Confirm position of placenta, fetuses and cord insertions
8	Choose and prepare type of introduction (set) and type of fetoscope
9	Connection of fetoscope and laser equipment (including white balance and orientation of the scope)
10	Prevent unnecessary delay during procedure
11	Controlled amniodrainage until pre-defined level (to decrease uterine distention and promote patient comfort)
12	Placement of sterile covers over patient and instruments
13	In case of local anesthesia: administer anesthetic to skin and/or peritoneum
14	Identify and record number and type of anastomoses coagulated
15	Performance of all manipulations under ultrasound visualization
16	Make adequate-size skin incision with surgical knife
17	Assess visibility (optional: score visibility)
18	Closing skin incision (suture, or suture free adhesive product)

Table 3. The 18 substeps of fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome, determined to be essential by expert consensus, in order of importance.

DISCUSSION

We achieved an international expert consensus on the technical approach and identification of the essential steps of FLS for TTTS. We produced a list of 55 substeps that are deemed to be essential during FLS. All items were ranked in order of importance, with 'coagulation of all vascular anastomoses that cross the vascular equator', 'determination of site of insertion of fetoscope' and 'ultrasound identification of placenta, fetuses, umbilical cord insertions and expected vascular equator' as the most important substeps. This list can be used as a reference guide to improve the standardization of training in fetoscopic techniques.

A large number of FLS experts participated in our Delphi procedure; 74% of all FLS experts worldwide took part in the first round. We were pleasantly surprised by how involved and interested the international group of FLS experts was. The high Cronbach's α score – 0.911 – after the first round of the Delphi procedure confirms homogeneity within the panel of experts.

In 1988, Julian De Lia first performed laser therapy as treatment for severe TTTS.[14] Over the last two decades, the procedure has undergone many changes. The era in which a handful of pioneers performed and personally adjusted fetoscopic laser surgery in their own centers has now moved into a time in which there is a need for a more standardized approach, enabling the training of many next-generation fetal surgeons worldwide with comparable quality of work. The curriculum suggested here, based on expert consensus, provides the best available basis for such a training program.

Specific operative situations may require deviation from the recommended standard technique. Therefore, strict adherence to the teaching instrument developed may not always be desirable. We suggest that these guidelines should be used primarily as an instrument for training.

Similar research has not been performed previously in fetal therapy. However, in other surgical fields the Delphi methodology has been used to create an authority-based curriculum for evaluation and training.[5,6] As such, the Delphi methodology has been an effective method of achieving expert consensus in the first phase of developing a training model for laparoscopic surgery.[6,15]

In this study, FLS items were ranked to determine their order of importance. In the eyes of an expert, some substeps are a natural part of the procedure and are performed automatically, however, for a novice, attention to these substeps is vitally important. By assigning value to the specific elements, we were able to emphasize certain substeps in the list of objectives to attain during training.

The Delphi methodology can be used to develop a curriculum that reflects international consensus as opposed to simply local expertise. Studies employing Delphi make use of individuals who are presumed to have the best knowledge of the topic being investigated. Usually, consensus is only achieved among experts after protracted discussions. The Delphi method does not require the panel to meet, and thus largely avoids these discussions. Also, experts from different geographic locations can be recruited,[11] as in this study, which recruited a large panel from 23 different countries. In the Delphi methodology, participants have access to the group's responses, and may change their views in line with what others are saying.[16] Providing a summary of opinions ensures that consensus is reached quickly, by two, or at most three, rounds.[8] The web-based design speeds up the process, improves feasibility and lowers associated costs. In addition, the anonymous nature ensures that outcomes are not influenced inappropriately by a single dominant group member and allows the opportunity to re-evaluate one's own 'answers'.[11]

It is important to note that the existence of a consensus does not mean that the correct answer, opinion or judgment has been found,[16] however, by using an expert panel, an acceptable accuracy is created. A potential limitation of the methodology is that the significance of each step, in terms of outcome, is not addressed. Although consensus was reached for a specific substep, this study does not provide information on whether this substep is associated with better or worse outcomes when performed.

One of the substeps that did not meet our consensus criteria concerned the laser technique used. In a recent multicenter randomized controlled trial, the Solomon laser technique (complete dichorionization of the vascular equator) was shown to reduce postoperative fetal morbidity in severe TTTS.[17] Although this study provides the highest level of evidence, which might imply that all centers should adopt this new technique, not all experts considered this step to be essential in an evaluation instrument for future fetal surgeons. Moreover, steps such as 'check for limb abnormalities of recipient' and 'determine placental sharing' were considered to be time-consuming rather than contributory, and therefore were not included.

Another limitation is that it is lengthy and quite time-consuming for the facilitator and the participant to take part in a Delphi procedure, compared to a single-round survey. Even though each round took only 5–15 min to complete, not all panel members maintained interest and responded in the second and third rounds of our survey, which is probably related to the relatively time-consuming process and the fact that it was a web-based questionnaire that participants can ignore or avoid more easily.

In summary, attention must be paid to the evaluation and training of fetal surgeons, to maintain a high standard of clinical performance. This study provides a first step towards an authority-based training curriculum and an evaluation tool for FLS performed in cases of TTTS. Further research should focus on the applicability of the instrument in simulator training as well as in real-life situations.

ACKNOWLEDGEMENTS

We thank the members of the expert panel for providing their expertise to the consensus process. These members include Dr S. Al Shenaifi, Dr F. Audibert, Dr A. Baschat, Dr M. Belfort, Dr W. A. Block Jr, Dr R. N. Brown, Dr E. Carreras, Dr D. Challis, Dr Y. L. Chang, Prof. T. M. Crombleholme, Dr J. E. De Lia, Dr J. Dickinson, Dr A. Edwards, Dr S. Ek, Dr R. Favre, Dr B. Feltis, Prof. N. Fisk, Dr A. Gagnon, Dr D. Gallot, Prof. E. Gratacos, Dr S. Haeri, Dr C. R. Harman, Prof. K. Hecher, Dr J. Hyett, Dr R. P. Japaraj, Dr A. Johnson, Dr M. Johnson, Dr N. Khalek, Prof. M. Kilby, Dr M. M. Lanna, Dr H. Lee, Dr S. Lipitz, Dr F. Luks, Dr D. Lynch-Salamon, Prof. F. Malone, Dr R. Miller, Dr K. Moise Jr, Dr J. Moldenhauer, Dr F. Molina, Dr T. Murakoshi, Dr C. Pennell, Dr T. Pressey, Dr J. N. Robinson, Dr M. A. Rustico, Dr G. Ryan, Dr R. de Sá, Dr H. Sago, Dr W. Sepulveda, Dr L. Simpson, Dr P. Stone, Dr K. Sundberg, Prof. D. Surbek, Prof. M. Tchirikov, Prof. B. Thilaganathan, Dr M. Vlastos, Dr M. Walker, Dr T. Wataganara, Dr

C. P. Weiner, Prof. A. Welsh, Dr R. Wimalasundera, Dr M. Yamamoto, Prof. Y. Zhao and Dr R. Zimmermann.
This research is supported by the Dutch Technology Foundation STW, which is part of The Netherlands Organization for Scientific Research (NWO), and is partly funded by the Ministry of Economic Affairs.

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Chapter 8

Operative competence in fetoscopic laser surgery for TTTS: a procedure-specific evaluation

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In press. Ultrasound Obst Gyn 2015

ABSTRACT

Objective. Fetoscopic laser surgery for twin-twin transfusion syndrome is a procedure for which no objective tools exist to assess technical skills. To ensure that future fetal surgeons reach competence prior to performing the procedure unsupervised, we developed a performance assessment tool. The aim of this study was to validate this assessment tool for reliability and construct validity.

Methods. A procedure-specific evaluation instrument containing all essential steps of the fetoscopic laser procedure was created using Delphi methodology. Eleven experts and 13 novices from three Fetal Medicine centers performed the procedure on the same simulator. Two independent observers assessed each surgery using the instrument (maximum score: 52). Inter-observer reliability was assessed using Spearman correlation. We compared performance of novices and experts to assess construct validity.

Results. Inter-observer reliability was high ($r=0.974$, $p<0.001$). Checklist scores for experts and novices were significantly different: median score for novices was 28/52 (54%) while for experts 42/52 (81%) ($p<0.001$). Procedure time and fetoscopy time were significantly shorter ($p<0.001$) for experts. Residual anastomoses were found in 1/11 (9%) procedures performed by experts and in 9/14 (64%) performed by novices ($p=0.006$). Multivariate analysis showed that the checklist score independently from age and gender predicted competence.

Conclusions. The procedure-specific assessment tool for fetoscopic laser surgery shows a good inter-observer reliability and discriminates experts from novices. This instrument may therefore be a useful tool in the training curriculum for starting fetal surgeons. Further intervention studies with reassessment before and after training may increase the construct validity of the tool.

INTRODUCTION

Fetoscopic laser therapy is the preferred treatment modality for twin-twin transfusion syndrome (TTTS),[1-3] but is only offered in a few highly specialized Fetal Medicine centers around the world.[4] Although fetoscopic laser surgery is a complex procedure that has been in use for more than two decades, standardized surgical training programs for fetoscopic interventions are nonexistent and performance is often authority based, i.e. on personal experience, belief and individual preferences. Also, the learning curve is ill-defined, and varies between 21 to 75 cases (based different survival outcome measures such as minimal double survival rates of 54% or at least one survivor in 70% of cases) to acquire the necessary skills.[5-8] Therefore, there is a need for a reliable assessment tool of technical performance. Such a tool would be useful to monitor progress, provide constant feedback along the learning curve, to serve as an instrument for (re-)certification and offer standardized training.

We previously reported on a list of steps judged essential to the laser procedure based on the Delphi methods.[9] These steps were consensus based by a sample of international experts, making the final tool representative of international, rather than local practice. The aim of this prospective cohort study was to assess reliability and validity of this instrument in the context of simulated operating room performance. We hypothesized that, based on the systematic manner in which this tool was created; we would obtain an acceptable level of inter-observer reliability and that the instrument would discriminate the performance of experts from that of novices.

METHODS

Participants and study design

This study is part of the SILICONE project (**SI**mulator for **L**aser therapy and **I**dentification of **C**ritical steps of **O**peration: **N**ew **E**ducation program), conducted to develop a standardized training program for fetoscopic laser surgery for TTTS. In the first part of the project we determined the essential steps of treatment to develop an assessment instrument.[9] In the current part of the project, this instrument was validated using a silicone simulator involving the complete laser procedure.

This study was conducted in three Fetal Medicine centers: Leiden University Medical Center (the Netherlands), University Hospitals KU Leuven (Belgium) and Karolinska Institutet, Stockholm (Sweden) from September 2014 until December 2014. We recruited

24 volunteers with special interest in fetal therapy to participate in the study. All participants completed a questionnaire to establish baseline demographic characteristics and previous experience in fetoscopic surgery to measure potential confounding factors that affect performance. Participants were stratified into 3 groups with regard to the level of previous experience; expert or novice or intermediate.

An expert was defined as a physician who currently practices fetoscopic laser surgery for TTTS and has performed at least 25 fetoscopic laser procedures independently.[8] Novices included fetal medicine specialists without practical fetal therapy experience OR obstetricians attending a fellowship in perinatology OR senior residents with special interest in perinatology and minimal invasive therapy. All novices were experienced sonographers and had appropriate knowledge of TTTS and its treatment options, but had never performed a fetoscopic laser procedure and had little or no previous experience with other ultrasound-guided invasive procedures (amniocentesis, chorionic villus sampling and/or intrauterine transfusion). Participants with an intermediate level of experience (e.g. performed between 1-25 fetoscopic laser procedures) were excluded.

Assessment

All participants (irrespective of the level of expertise) performed a similar assignment on the simulator. The scenario involved a patient of 17 weeks' gestation with stage 3 TTTS referred for laser therapy. The assignment included the complete fetoscopic laser procedure; starting from the moment the operation room is entered, until the surgery was finished and direct post-operative management was ordered. Three different items were scored: 'time', 'checklist with essential steps of procedure' and 'complete identification of vascular equator'.

All participants were evaluated by 2 independent observers (S.P. and J.A.), using the assessment instrument created by the Delphi consensus.[9] This list of essential steps was modified into a checklist adjusted to the simulated scenario. A detailed description of the instrument is available in the appendix. Each item was awarded 1 point if it was done properly (range 0-52). Procedure time, defined as 'the moment the surgeon enters the operating room until the moment that direct post-operative management is ordered' and fetoscopy time, defined as 'the moment the fetoscope is introduced for the first time until final removal' were recorded. A map of the placental architecture was used by the assessors to mark the coagulated anastomoses.

Simulated scenario

To explain the task, all participants were shown a standardized multimedia presentation outlining the background and aim of the study, as well as the performance metrics (time, missed essential steps and complete coagulation of the vascular equator). Finally, the context of the scenario (including patient characteristics, findings of diagnostic procedure and pre-surgical management) was presented.

Simulator characteristics

The simulator used for this study has previously been described[10] (Francis LeBouthillier, Surgical touch, Toronto, Canada), but was modified with a highly realistic silicone copy of a 17 week monochorionic twin placenta and twin fetuses (R. Bakker, Manimalworks, Rotterdam, The Netherlands). The silicone topping on the model mimics the abdominal wall. Inside there is a mimic of a uterus, which contains water and the placenta. The individual layers of the abdominal wall, the uterus and placenta have sonographic and compliance properties that mimic the clinical situation. The model allows an operator to practice ultrasound examination of a monochorionic pregnancy, required to select the best site for introduction of the instruments. The model also provides a realistic intrauterine environment, optimal to practice manual dexterity skills and to train navigation along the placental surface. Moreover, the addition of a "stuck" donor twin on the placenta simulates the inability to oversee the complete vascular equator. The addition of a "free-floating" recipient simulates a realistic complex situation of floating fetal extremities and umbilical cord in the recipients' sac. All necessary instruments (i.e. fetoscope, introduction set, endoscopy tower etc.) were used from the local Fetal Medicine center so that participants perform their tasks in a setting that was identical to what would be their clinical environment. Figure 1 shows a participant performing the procedure on the simulator model.

Figure 1 Participant performing procedure on simulator for fetoscopic laser surgery

Statistical analysis

Demographics, procedure- and fetoscopy time, checklist score and presence of residual anastomoses were compared between experts and novices. Due to the small sample size and non-normality of the data, the Mann Whitney U test was used to test for differences between groups for the continuous variables. To test for differences between groups on non-ordinal categorical outcomes, such as presence or absence of experience, Fisher's exact test was used.

Spearman correlation coefficient was used to measure the inter-observer reliability. A correlation of 0.9 or higher was considered to be indicative of an excellent agreement.

We used a multivariate regression analysis to determine independent predictors for the construct validity of the instrument. Construct validity refers to the degree to which any measurement approach or instrument succeeds in describing or quantifying what it is designed to measure. Moreover, to evaluate the accuracy with which scores on a given instrument can classify groups that are already known to differ on a criterion measure

(i.e. experts and novices). In other words, if experts are the ones with the construct (surgical skills) and the novices are the ones without the construct; construct validity determines whether the instrument identifies the presence or absences of the construct (surgical skills).
A two-sided p-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed with IBM. SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0 Armonk, New York: IBM Corp.) Since no patients were involved, no formal ethical approval and written informed consent was needed for this study.

RESULTS

In this study, 24 fetoscopic simulated laser surgeries were analyzed. They were performed by 11 (46%) experts and 13 (54%) novices. Eleven participants were male, 13 were female. Although 4/13 (31%) of the novices in the study had previous limited experience with invasive obstetric procedures (e.g. amniocentesis, chorionic villus sampling, intrauterine transfusion etc.) none had previously performed the fetoscopic laser procedure for TTTS. In the group of experts, 5/11 (45%) had performed >100 procedures with a median of 10 procedures (range 8-20) annually. The demographics of the participants are shown in table 1.

Overall median procedure time was 40 minutes (range: 26-50 minutes). Experts were able to complete the procedure in 32 minutes, versus 43 minutes (p=0.003) by novices. Fetoscopy time was also significantly different between the groups. Median fetoscopy time for all participants was 17 minutes, (range: 10-27 minutes): 11 minutes for experts versus 20 minutes for novices (p<0.001). Residual anastomoses were found in 10/25 (40%) procedures, 1/11 (9%) performed by experts and in 9/14 (64%) performed by novices (p=0.005).

Demographics	Expert n/N (%)	Novices n/N (%)	p value
Gender			
Male	8/11 (73)	3/13 (23)	0.015
Female	3/11 (27)	10/13 (77)	
Age			
(median in years, range)	52 (35-59)	32 (28-42)	<0.001
Experience with invasive obstetric procedures			
Has experience with invasive obst. procedures	11/11 (100)	4/13 (31)	0.001
years (median, range)	15 (7-23)	3 (1-8)	0.003
Type of invasive obstetric procedures			
Amniocentesis	11/11 (100)	3/13 (23)	
Chorionic villus sampling	11/11 (100)	3/13 (23)	
Intrauterine transfusion	8/11 (73)	1/13 (8)	
Fetal shunt placement	8/11 (73)	0	
Bipolar cord occlusion	11/11 (100)	0	
Open fetal surgery	4/11 (36)	0	
Other	4/11 (36)	0	
No. of FLS attended (incl. assisting or watching procedure)			
None	0	2/13 (15)	0.001
< 10 procedures	0	7/13 (54)	
10-25 procedures	0	0	
25-50 procedures	1/11 (9)	2/13 (15)	
50-100 procedures	1/11 (9)	0	
>100 procedures	9/11 (82)	2/13 (15)	
Experience with simulator training			
Never	2/11 (18)	1/13 (8)	0.447
A few times	4/11 (36)	8/13 (62)	
Regularly	5/11 (46)	4/13 (30)	

Table 1 Demographics of study participants

Reliability

The overall inter-observer reliability of the two raters' total scores (J.A. and S.P.) for the fetoscopic laser procedure was excellent (r_s): 0.974 *(* p<0.001) (Figure 2).

Agreement was less but still strong in the domains concerning 'direct post-operative management' (r_s: 0.722; p<0.001) and 'assessment during procedure' (r_s: 0.789; p<0.001) as displayed in table 2. The inter-observer variability did not significantly change over time (data not shown).

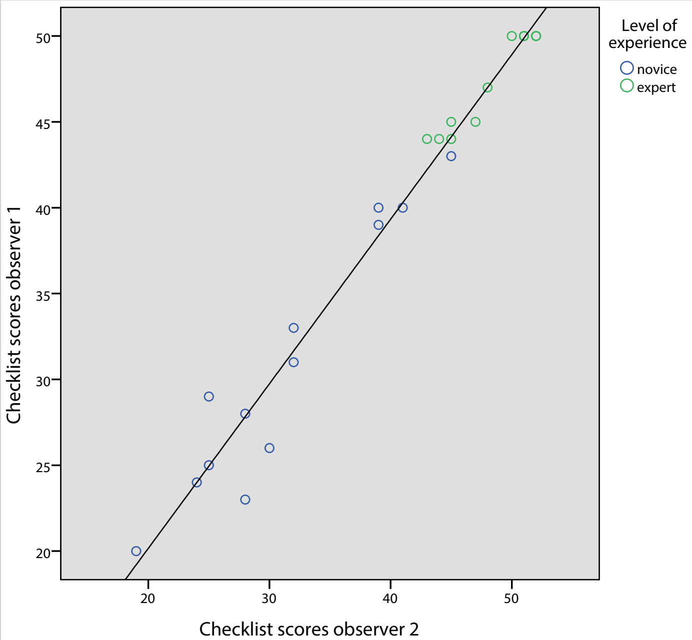

Figure 2 Correlation of checklist scores of the two observers

	Domain	No. of steps	R_s	p value
A	Preparation in operating room	7	0.956	<0.001
B	Ultrasound examination (together with sonographer)	7	0.862	<0.001
C	Pre-operative preparations	7	0.943	<0.001
D	Positioning and connection of instruments (pre-insertion)	6	0.977	<0.001
E	Insertion	5	0.947	<0.001
F	Orientation	8	0.857	<0.001
G	Laser coagulation	4	0.862	<0.001
H	Assessment during procedure	3	0.789	<0.001
I	Amniodrainage	2	1.000	<0.001
J	Closure	1	0.845	<0.001
K	Direct post-operative management	2	0.722	<0.001
	Overall	52	0.974	<0.001

Table 2 Inter-observer reliability by domain
R_s : Spearman correlation coefficient

Construct validity

Rater 1's median score for novices on the assessment tool was 29/52 (56%) (range: 20-43), compared to an median expert score of 47/52 (90%) (range: 44-50) ($p<0.001$). Rater 2's median novice score similarly demonstrated statistically significant differences between novice and expert performance [30/52 (58%) (range: 19-45) versus 48/52 (92%) (range: 43-52)] ($p<0.001$).

The overall median checklist scores (combining the scores of the two raters) were 28/52 (54%) 20-44) in novices versus 42/52 (81%) (44-51) in experts ($p<0.001$) and were significantly associated with the presence of residual anastomoses as demonstrated in figure 3 ($p=0.002$). Sensitivity-specificity analysis showed an area under the curve of 0.861. Multivariate analyses showed that age (b_1: 0.203; $p= 0.351$) and gender (b_1: 0.088; $p=0.539$) of participants were not significantly associated with checklist scores and level of experience.

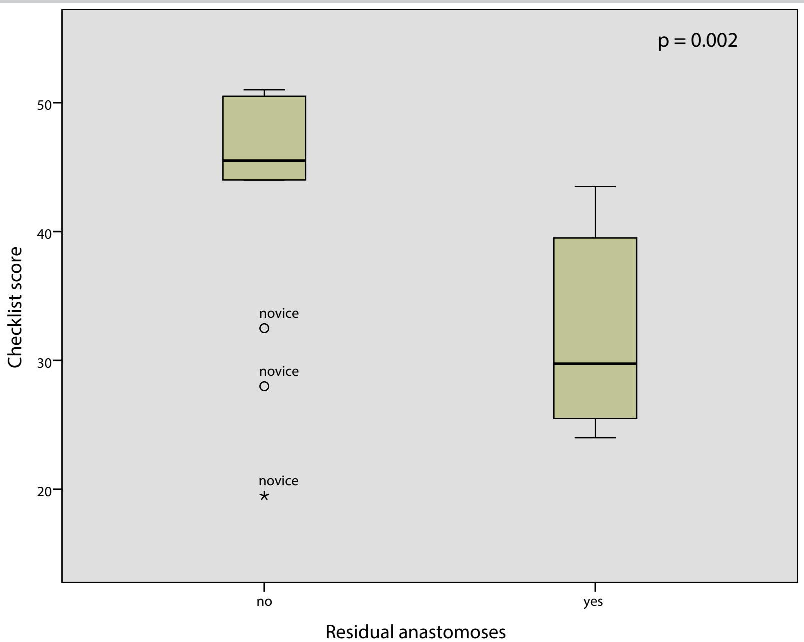

Figure 3 Checklist score and presence of residual anastomoses

DISCUSSION

This study assessed the inter-observer reliability and construct validity of a procedure-specific evaluation tool for fetoscopic laser surgery of TTTS, created using the Delphi methodology.[9] Our instrument effectively distinguished performance of experts and novices with an acceptable level of inter-observer reliability.

Any discussion of evaluation or assessment must address issues of validity and reliability. The instrument will only be useful to educators or surgeons as a measure of competence when it does measure the construct that it intends to measure (validity) and when the results that are obtained are consistent and therefore meaningful (reliability). Inter-observer reliability refers to a degree to which difference in score on the tool reflects a difference in quality of performance rather than a difference between the raters. A high level of inter-observer reliability allows evaluation of skills by different observers and will be minimally affected by the variability of the rater.[11]
Till today, trainees in fetal surgery are educated according to the “master–apprentice” principle. Direct observation by experts alone may not be a reliable method of assessment and may lead to recall bias due to the retrospective nature of the evaluation. Use of fixed criteria such as a validated checklist by observing experts can address these concerns.[12,13] Additionally, task-specific checklists provide trainees with detailed methods on how to perform the procedure and enable formative feedback and deliberate practice. To achieve standardization and wide implementation, an assessment tool must be reflective of practice among many institutions; therefore we included participants from three major Fetal Medicine centers.

Validation of assessment tools for training has been done frequently in other medical areas,[14-17] but never in the field of fetal therapy. Observation of surgical skills without structured criteria has poor reliability and will result in a low level of agreement among the raters.[18] The values for inter-observer reliability in this study indicate that our evaluation tool reaches the cut-off of 0.8 deemed acceptable for assessment.[11]

The purpose of this study was to validate the evaluation tool for surgeon’s technical performance using a highly realistic simulator. Objective feedback to fetal surgeons on their performance based on highly reliable assessment tools could also be of great value for ongoing assessment and lifelong learning. Developing similar assessment tools for other invasive obstetric procedures will make it possible to teach and evaluate procedures using disseminated learning materials. Since we want to make the curriculum competency based, it is also important to define expert benchmark levels of proficiency for the final curriculum.

Procedure-specific checklists have been shown to be less reliable and less construct valid than global rating scales[19] However, a global assessment scale can make an instrument indistinctly and have an apparent precision, since items are rated on scales (e.g. 1-10) instead of 'achieved' or 'failed'. For feedback purposes it is sufficient to know at a glance which elements need improvement (instead of adding values to the assessed items).

Procedure time and fetoscopy time were significantly lower in the expert group compared to novices. This may be explained by the often interrupted flow of thoughts when performing a procedure for the first time. Surgical steps need to be carried out consciously for novices, as opposed to automatically for experts, making a procedure-specific tool even more valuable for training purposes and combines efficacy (closing all anastomoses) with safety (avoid complications).

A limitation of this study is that a few items identified through the prior Delphi consensus could not be analyzed during the simulator experiments since they take place in the diagnostic and pre-operative phase of the procedure. These steps include: "diagnostic procedure" (e.g. ultrasound examination at out-patient clinic confirming diagnosis and determine treatment options), "pre-surgical management" (e.g. prescription of procedure related medication etc.) and "follow-up ultrasound examination". Therefore the construct validity and reliability measurement of this tool does not include these particular steps.

Due to nature of the procedure, we were unable to assess the validity of the instrument in surgery on real patients; therefore the simulator was used. Even though the simulator was regarded highly realistic, clinical features such as 'tissue reaction after firing the laser' and 'complications such as bleeding' could not be simulated. On the other hand, assessment using a simulator model can also be advantageous, since the lack of standardization in real patients makes consistent assessment of technical skills difficult. Advantages of the simulator model include the fact that tasks can be presented consistently to many trainees, who can operate independently, objective assessment by more than one faculty member is possible and there is no intrusion on operating room time, which has financial and ethical advantages.[20]

For this study, participants were assessed live in the operating room, therefore observers were able to oversee all steps, in contrast to only fetoscopic view or single camera position. This allowed us to evaluate the complete procedure, including all its facets such

as sterility and handling of the instruments. Unfortunately, this element of our study prevented blinding the raters for the level of experience.
The construct validity of the instrument could be further assessed with a study with a pre- and post-training design. Correlation with a learning curve would further support its validity. Future studies should focus on the development and validation of a training curriculum aimed at improving the operative and technical skills of trainees in fetal therapy. Finally, additional studies should be performed to assess how well instructors can evaluate clinical skills when observing surgeons working with real patients and how to implement this into clinical practice.

ACKNOWLEDGEMENTS

We would like to thank all the participants from the MFM centers who generously shared their time, experience and materials for the purpose of this project.
This research is supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organisation for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs.

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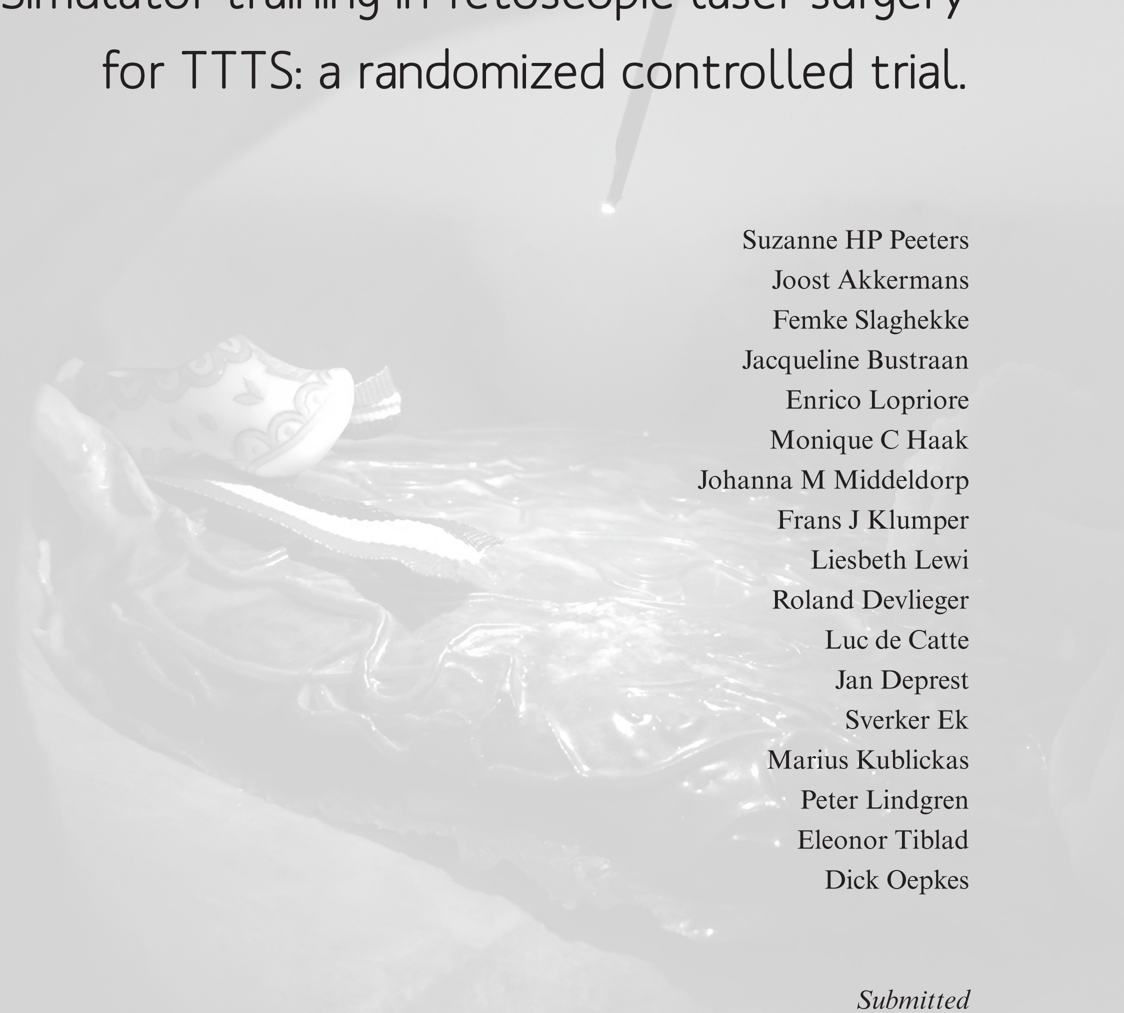
APPENDIX

No.	Domain and substeps	Score
A	Preparation in operating room	7
1	Ultrasound correct settings	
2	Endoscopy tower settings	
3	Positioning of screens	
4	Adjusting lights	
5	Correct laser modus	
6	Correct power settings	
7	Positioning of patient	
B	Ultrasound examination (together with sonographer)	7
8	Identification of donor	
9	Identification of recipient	
10	Identification localization placenta	
11	Identification cord insertions	
12	Assess deepest pockets	
13	Determine expected position equator	
14	Determine insertion site fetoscope	
C	Pre-operative preparations	7
15	Surgical briefing (time out) about (complete) procedure to fetal therapy team	
16	Aseptic procedure for surgeon, scrub nurse and sonographer	
17	Mention maternal condition	
18	All instrumentation remains sterile	
19	All is sufficiently covered	
20	Pre-insertion connection scope - shaft	
21	Pre-insertion connection light cable	
D	Positioning and connection of instruments (pre-insertion)	6
22	Choose fetoscope	
23	Fetoscope: orientation	
24	Fetoscope: focus	
25	Fetoscope: white balance	
26	Connection of laser fiber	
27	Correct loading of laser fiber in fetoscope	
E	Insertion	5
28	Preparation of introduction method	
29	Performance of all manipulations under ultrasound visualization	
30	Correct administration of local anesthetic	
31	Make adequate-size skin incision with surgical knife	
32	Awareness of location of maternal uterine vessels and intestines, and placental edge during insertion	
F	Orientation	8
33	Assess visibility (optional: score visibility)	
34	Determine need for amniotic exchange	
35	Fetoscopic view of placenta	
36	Fetoscopic view of donor	
37	Fetoscopic view of cord insertion recipient	

38	Identification of placental edges	
39	Difference between artery and vene	
40	Find (part of) vascular equator	
G	Laser coagulation	4
41	Coagulation of all vascular anastomoses that cross the vascular equator	
42	Laser fiber correct position in fetoscope	
43	Laser fiber correct distance from vessel during coagulation	
44	Prevent the unnecessary sacrifice of placental tissue	
H	Assessment during procedure	3
45	Prevent unnecessary delay during procedure	
46	Check for complications(e.g. bleeding, rupture intertwin membranes)	
47	Identify and record number and type of anastomoses coagulated	
I	Amniodrainage	2
48	Controlled drainage of polyhydramnios	
49	Assess adequate drainage (ultrasound guided) until pre-defined level	
J	Closure	1
50	Closing skin incision (suture or suture free adhesive product)	
K	Direct post-operative management	2
51	Inform patient, partner/family and referring specialist	
52	Instructions for monitoring of maternal and fetal condition	

Appendix 1 Evaluation instrument

8



Chapter 9

Simulator training in fetoscopic laser surgery for TTTS: a randomized controlled trial.

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ABSTRACT

Objective: To evaluate the effect of a newly developed training curriculum on performance of fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS) using an advanced high-fidelity simulator model.

Methods: Ten novices were randomized to receive verbal instructions and skills training using the simulator (study group, n=5) or no training (control group, n=5). Both groups were evaluated with a pre-training test and post-training test. Assessment was performed by two independent observers and compromised a 52-item checklist for surgical performance (SP score), measurement of procedure time and number of anastomoses missed. Face validity, educational value and user friendliness of the simulator were assessed using a questionnaire. Eleven experts from three fetal therapy centers set the benchmark level of performance.

Results: Both groups showed an improvement in SP score compared to the pre-training test. The simulator-trained group significantly outperformed the control group with a median SP score of 28 (52%) in the pre-test and 46 (88%) in the post-test versus 25 (48%) and 36 (69%) (p=0.008). Procedure time decreased 11 min in the study group versus 1 min in the control group; to 32 min versus 38 min, respectively (p=0.69). The number of missed anastomoses was not different between the groups (1 versus none). Feedback provided by the participants indicated that training on the simulator was perceived as a useful educational activity.

Conclusion: Proficiency-based simulator training improves performance on surgical performance score for fetoscopic laser therapy. Practice on a simulator is recommended before trainees carry out laser therapy for TTTS in pregnant women.

INTRODUCTION

Twin–twin transfusion syndrome (TTTS) is a serious complication affecting approximately 10% of monochorionic (MC) twin pregnancies.[1] Treatment is offered in specialized fetal therapy centers around the world.[2] Fetoscopic laser surgery enables both twins to survive in 60–70% of cases, and at least one twin survives in 80–90%.[3] Only a few studies have been performed to gain more insight in the learning curves and pitfalls of this complex procedure.[4-8]

In the coming years, we anticipate an increasing number of fetal surgeons to start training for fetoscopic laser surgery. With the economic growth in developing countries, and increasing knowledge of this treatment option through internet information, the interest of both patients and doctors in fetoscopic laser surgery will continue to grow. In addition, the next generation of fetal surgeons will gradually start to take over practice from the pioneers in the established centers. Therefore, attention is gradually shifting from pregnancy outcomes per center towards appropriate training and exposure of surgeons to a sufficient number of procedures. This will secure proper skills and satisfactory results. To support this process, an evidence-based training curriculum and continuous process of reporting and monitoring of outcomes is highly valuable.

Since fetoscopic procedures are performed on an infrequent basis, a surgeon-in-training is forced to a lengthy and expensive stay in a (often distant) fetal therapy center to accumulate at least some hands-on experience. Even large centers have limited numbers of cases, therefore teaching and training this procedure is challenging. A growing need for alternative methods to train surgical skills through simulation has been recognized.[4,5,9] Several attempts have been made to develop simulators for invasive fetal procedures with various levels of physical resemblance and functional task alignment.[9-13] Most reported simulators were used for teaching in absence of well-planned and comprehensive training curricula.

A procedure-specific simulator for fetoscopic laser surgery has not yet been developed before and standardized surgical training programs are nonexistent. Therefore, the aim of this study was to demonstrate face and construct validity of a highly realistic simulator and training for fetoscopic laser surgery for TTTS.

METHODS

Study design

For this study we recruited volunteers with special interest in fetal therapy and no practical experience with the fetoscopic laser procedure (novices), and all currently active fetal therapy experts in three Fetal Medicine centers: Leiden University Medical Center (the Netherlands), University Hospitals KU Leuven (Belgium) and Karolinska University Hospital, Stockholm (Sweden) from September 2014 until December 2014. All participants completed a questionnaire to establish baseline demographic characteristics, previous experience in surgical/obstetrical skills in order to exclude potential confounding factors that may affect performance. Participants were eligible to take part in this study if they were: fetal medicine specialists without practical fetal therapy experience OR obstetrician/gynecologists attending a fellowship perinatology OR senior OBGYN residents with special interest in perinatology and/or minimal invasive therapy; AND had a high level of skills in diagnostic ultrasound, appropriate knowledge of TTTS and its treatment options, but little or no previous experience with other ultrasound-guided invasive procedures (amniocentesis, chorionic villus sampling, cordocentesis and/or intrauterine transfusion).
A training curriculum using a simulator for fetoscopic laser surgery was generated based on a previously developed evaluation instrument.[5] We conducted a non-blinded randomized controlled trial using a parallel study design. For randomization, we used a block randomization list (non-stratified, with the same block lengths), generated by www.random.org sequentially. Novices were randomly assigned to either the training group (study group) or the no-training group (control group). Because of the nature of the intervention, blinding for randomization allocation was not possible. Lack of data regarding training for fetoscopic laser surgery prevented a formal sample size calculation. Giving the rarity of the procedure and the estimation that in the coming years two eligible trainees per fetal center will be trained, a sample size of 12 was chosen for this study. A pre-test/post-test research design was used to evaluate the effect of simulator-based training on surgical performance. Performance was assessed with an assignment involving the complete fetoscopic laser procedure, comparing the two groups before and after training. A flowchart of participant enrolment is shown in figure 1.

All currently practicing experts (n=11) from the three MFM centers were asked to complete the same assignment to define a benchmark level. An "expert" was defined as an individual who is currently practicing fetoscopic laser surgery for TTTS and has independently performed >25 fetoscopic laser procedures.[4] Baseline characteristics of all study participants are listed in table 1.

Demographics	Experts n/11 (%)	Novices (no training) n/5 (%)	Novices (training) n/5 (%)	p value
Gender				
Male	8/11 (73)	2/5 (40)	0	0.44
Female	3/11 (27)	3/5 (60)	5/5 (100)	
Age				
(median in years, range)	52 (35-59)	30 (30-34)	34 (30-37)	0.15
Experience with invasive obstetric procedures				
Has experience with invasive obstetric procedures	11/11 (100)	0/5 (0)	2/5 (40)	0.44
Years of experience (median, range)	15 (7-23)	0	2 (1-2)	
Type of invasive obstetric procedures				
Amniocentesis	11/11 (100)	0	2/5 (40)	
Chorionic villus sampling	11/11 (100)	0	2/5 (40)	
Intrauterine transfusion	8/11 (73)	0	0	
Fetal shunt placement	8/11 (73)	0	0	
Bipolar cord occlusion	11/11 (100)	0	0	
Open fetal surgery	4/11 (36)	0	0	
Other	4/11 (36)	0	1/5 (20)	
No. of FLS attended (incl. assisting or watching procedure)				
None	0	2/5 (40)	0	0.28
< 10 procedures	0	2/5 (40)	4/5 (80)	
10-25 procedures	0	1/5 (20)	0	
25-50 procedures	1/11 (9)	0	0	
50-100 procedures	1/11 (9)	0	1/5 (20)	
>100 procedures	9/11 (82)	0	0	
Experience with simulator training				
Never	2/11 (18)	1/5 (20)	0	1.00
A few times	4/11 (36)	2/5 (40)	3/5 (60)	
Regularly	5/11 (46)	2/5 (40)	2/5 (40)	

FLS: fetoscopic laser surgery

Table 1. Demographics of study participants

Simulator characteristics

An advanced simulator (Francis LeBouthillier, Surgical Touch, Toronto, Canada) that was previously used for the training of amniocentesis [11] was modified. A monochorionic twin placenta model and realistic models of twin fetuses were inserted. (R. Bakker, Manimalworks, Rotterdam, The Netherlands). Placenta and fetuses had a size comparable to 17 weeks of gestation. The silicone interface at the top of the model

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mimicked the abdominal wall. The simulator contained water and had appropriate sonographic properties. The model allowed an operator to perform ultrasound examination of the monochorionic pregnancy and to select the site for introduction of the instruments. The model provided a realistic intrauterine environment, optimal to practice manual dexterity skills and to train navigation along the placental surface. The "stuck" donor twin was positioned on the placenta. The addition of a "free-floating" recipient simulated the floating fetal extremities and umbilical cord in the recipients' sac. Besides the simulator model, all standard equipment (i.e. fetoscope, introduction set, ultrasound machine, endoscopy tower etc.) clinically used in the participating fetal therapy centers was used to perform the assignment.

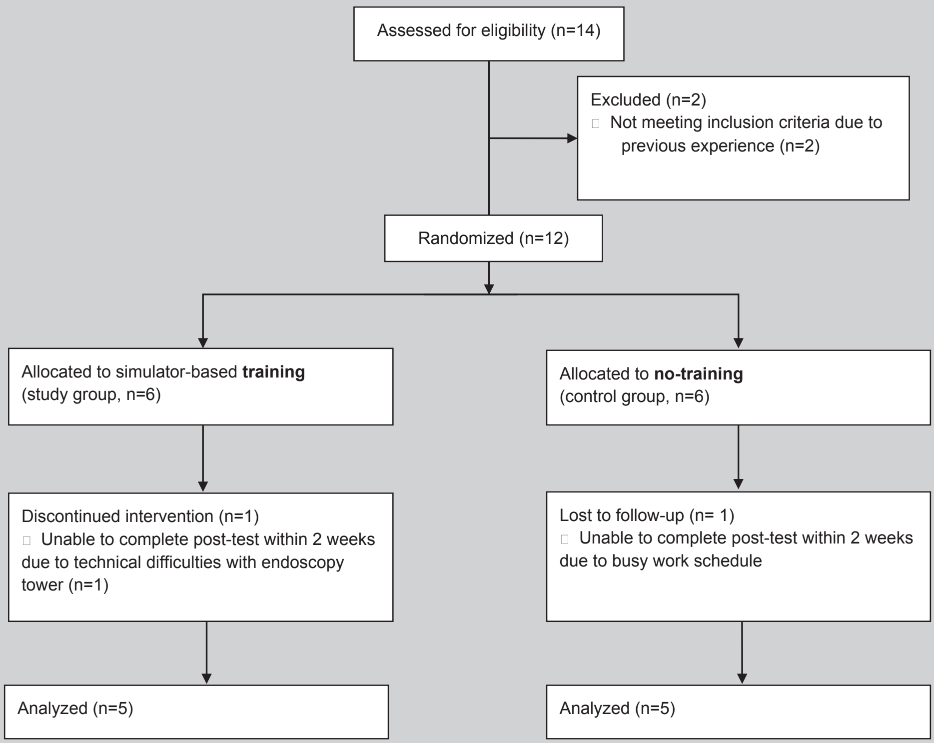


Figure 1 Flowchart of the study showing participant enrolment, randomization, allocation of interventions and follow-up.

Evaluation and training

Participants and experts were evaluated by 2 independent observers (S.P. and J.A.), using the evaluation instrument created by the Delphi consensus.[5] The list of essential steps was modified into a surgical performance score (SP score) adjusted to the simulated scenario. This 52–item list consisted of 'achieved' and 'failed' items in 11 domains pertaining specifically to the fetoscopic laser procedure for TTTS. (Appendix 1) Each item was awarded 1 point if it was done properly (range 0-52). Procedure time, defined as 'the moment the surgeon enters the operating room until the moment that direct post-operative management is ordered' and fetoscopy time, defined as 'the moment the trocar was introduced until final removal' was recorded. A map of the placental architecture was used by the observers to mark the coagulated anastomoses (total n=8). Since there was no international consensus on the Solomon technique[3] at the time of development of the checklist, participants were instructed to coagulate all vascular anastomoses (that connected the circulation of the donor and the recipient twin) one by one; referred to as the 'selective laser technique'.

The structured fetoscopic laser surgery skills training and evaluation consisted of five phases:

Phase 1: Introduction

Each participant was familiarized with the simulator by a member of the study team (SP or JA).

All participants were shown a standardized multimedia presentation outlining the background and aim of the study to explain the task; including the assessed performance metrics. Finally, the context of the scenario was presented. No assistance was provided during completion of the assignment unless the participant was unable to proceed with the procedure. In that case (for example: 'switch on the laser') the item was appointed but scored as 'failed'.

Phase 2: Pre-training test

All subjects in the study participated in a pre-training test to assess baseline competency and technical skills in fetoscopic surgery. The participants performed an assignment in the simulator, including the complete fetoscopic laser procedure for a patient of 17 weeks' gestation with stage 3 TTTS; starting from the moment the operation room is entered, until the surgery was finished and direct post-operative management was ordered.

Phase 3: Training

After the pre-training test, novices who were randomized to the training curriculum were trained in a 1 day session by a fetal therapy expert who was not involved in the evaluation process. The curriculum comprised two components: a theoretical part and practical session. The procedure-specific instrument served as a framework for curricular development. An instructor script and multimedia presentation including step-by-step actions and decisions required to perform the fetoscopic laser surgery, were developed by DO, RD and SP.

The theoretical part of the training consisted of a multimedia presentation outlining the indication for surgery, relevant anatomy, control of the instruments including the fetoscope, and a video demonstration of the simulated steps. The purpose of this session was to allow participants to understand the flow of the procedure and to conceptualize how to plan and execute the fetoscopic laser surgery.

The training continued with a practical session using the simulator with three subsequent practice rounds. In round 1, an attending fetal expert showed how to perform the procedure step-by-step, in round 2 the trainee performed the procedure under supervision of the expert provided with direct verbal feedback. In the last round, the complete procedure was performed by the trainee and evaluated directly afterwards with the expert.

The participants that were allocated to the control group did not receive feedback with regard to their performances. They were also not involved in the training sessions.

Phase 4: Post-training test

Within 2 weeks after the training, all novices (study group and control group) performed a post-training test, evaluated by the same independent observers (J.A. and S.P.). The post-training test included a different assignment (regarding the location of the placenta and the fetuses), but was performed on the same simulator.

Phase 5: User experience evaluation

Participants completed a survey to collect qualitative data regarding participant perceptions of the value of the simulation and training. Face and content validities were assessed concerning participants' opinions about realism (9 items), usefulness (5 items), and overall opinion about the simulator (3 items). All items were scored on an ordinal 10-point Likert scale (1 = not at all realistic/useful and 10 = very realistic/useful).

Statistical analysis

Demographics, SP score, procedure time, fetoscopy time and presence of residual anastomoses, of both pre-training and post-training tests, were compared for the groups. For the SP score, a higher score is better; therefore an improvement is reflected by a positive pre- and post-test difference. For procedure time and fetoscopy time, improvement was calculated as pre-training test minus post-training test value.

Due to the small sample size and non-normal distribution of the data, the Mann Whitney U test was used to test for differences between groups for the continuous variables. To test for differences between groups on non-ordinal categorical outcomes, Fisher exact test was used. For ordinal outcome such as a Likert agreement scale the χ^2 test was used. Spearman correlation coefficient was used to measure the inter-observer reliability. A correlation of 0.9 or higher was considered to be indicative of an excellent agreement. A p value ≤ 0.05 was considered statistical significant. Statistical analysis was performed with IBM SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

Participant enrolment, randomization and follow-up are illustrated in figure 1. Within the three participating centers 12 volunteers were included in the trial and randomized. One participant was lost to follow up, another was not able to complete the test due to technical difficulties, therefore we were able to analyze the results of 10 participants (study group n=5 and control group n=5).

The randomized study group (with training) and control group (without training) were well balanced for baseline characteristics (Table 1). Analysis revealed no differences between the groups regarding prior knowledge of the procedure or experience with other obstetric invasive procedures or simulators. In the expert group, 9/11 (82%) of participants had attended > 100 laser procedures and 5/11 (45%) had performed >100 procedures themselves. A median of 10 procedures per expert (range 8-20) was performed annually.

Experts

The expert benchmark level was set with a median SP score of 44/52 (85%) (range: 44-51), a procedure time of 32 minutes (range: 26-46 minutes) and fetoscopy time of 11 minutes (range: 10-18 minutes). One expert missed a small AV anastomosis at the margin of the placenta (1/11, 9%). In table 2 results of performance of all participants are shown.

	Expert (benchmark) n=11	*range*	Novices (study group) n=5	*range*	Novices (control group) n=5	*range*	p value
SP score (max 52)							
pre-training test	48 (92%)	(44-51)	28 (52%)	(27-41)	25 (48%)	20-44	0.55
post-training test			46 (88%)	(43-51)	36 (69%)	30-41	<0.01
difference			plus 18		plus 11		
Procedure time (minutes)							
pre-training test	33	(26-46)	44	40-50	39	33-45	0.06
post-training test			33	29-44	38	27-49	0.69
difference			minus 11		minus 1		
Fetoscopy time (minutes)							
pre-training test	12	(10-18)	22	18-25	18	16-20	0.06
post-training test			14	(10-20)	14	(11-24)	0.69
difference			minus 8		minus 4		
Missed anastomoses							
pre-training test	1/11 (9%)		4/5 (80%)		2/5 (40%)		0.52
post-training test			1/5 (20%)		0 (0%)		1.00

SP score: surgical performance score

Table 2. Performance of experts and study participants

Pre-training test

The median SP score for the study group was 28/52, 54% (range: 27-41) versus 25/52, 48% (range: 27-41) in the control group (p=0.55). Median procedure time in the study group was 44 minutes (range: 40-50 minutes) versus 39 minutes (range: 33-45 minutes) in the control group (p=0.06). Fetoscopy time was 22 minutes (range: 18-25 minutes) in the study group versus 18 minutes (range: 16-20 minutes) in the control group (p=0.06). In the study group 4/5 (80%) participants did not coagulate all anastomoses versus 2/5 (40%) in the control group (p=0.52). In the study group 3 participants missed 2 out of 8 anastomoses and 1 participant 1 out of 8 anastomoses, all located on the placenta margin. In the control group one participant missed 3 anastomoses in the center of the placenta and one participant 2 anastomoses on the placenta margin.

Post-training test

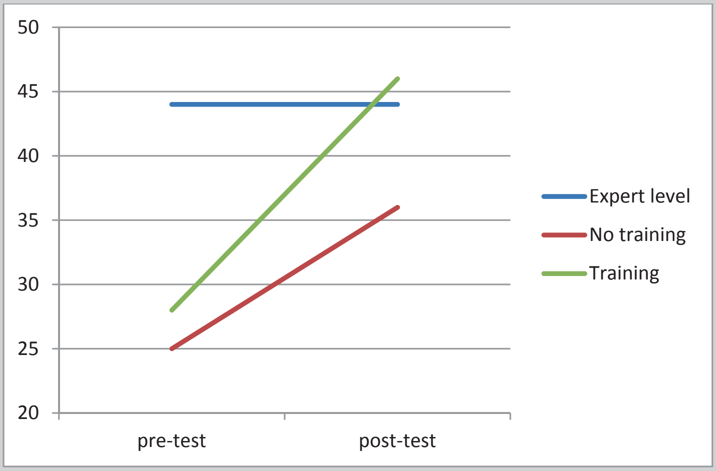
Novices in both groups showed an improvement in SP scores and performed the procedure in less time compared to the pre-training tests. The study group outperformed the control group after the training session significantly with median SP scores 46/52 88% (range 43-51) versus 36/52 69% (range 30-41) (p=0.008).

Median procedure time decreased 11 minutes in the study group versus 1 minute in the control group, to 32 minutes (range: 29-44 minutes) and 38 minutes (range: 27-49) respectively. Median fetoscopy time improved to 14 minutes in both groups; study group range: 10-20 minutes, control group range: 11-24 minutes ($p=0.69$). In the post-training test one participant (1/5 (20%)) in the study group missed 1 (out of 8 anastomoses) located on the placenta margin versus none in the control group ($p=1.00$).
Figure 2 shows the performance of both groups in the pre-training test and post-training test on SP scores, procedure time and fetoscopy time plotted against the expert benchmark level.

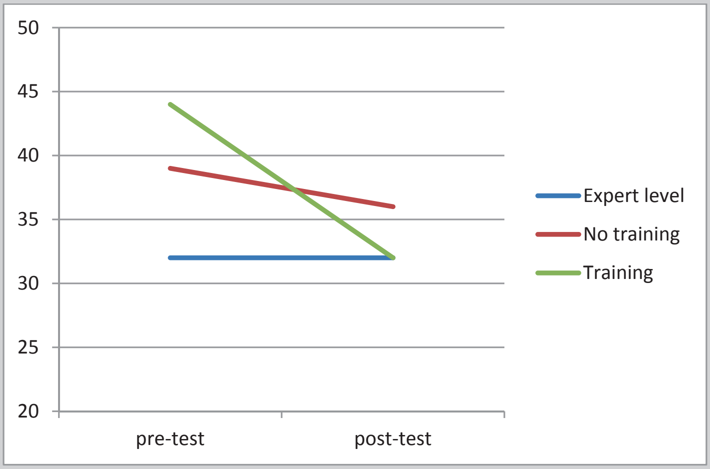
Figure 3 shows that experts felt that the simulator was very useful in training to identify the vascular equator and to practice the complete laser procedure. (score of 9 on Likert scale 1-10) All experts stated that training with the simulator provided good preparation before starting to operate on real patients. Except for the sonographic properties, the simulator was judged highly realistic.

The overall inter-observer reliability of the two raters' total scores (J.A. and S.P.) for the fetoscopic laser procedure was excellent (Spearman correlation coefficient: 0.984 $p<0.001$).

Checklist score (52-items) medians per group



Procedure time in minutes



Fetoscopy time in minutes.

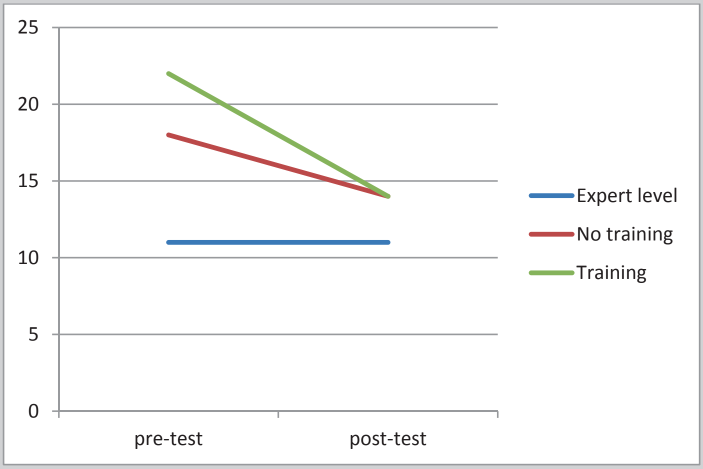


Figure 2 Performance of both groups in the pre-test and post-test on checklist scores, procedure time and fetoscopy time plotted against the expert benchmark level.

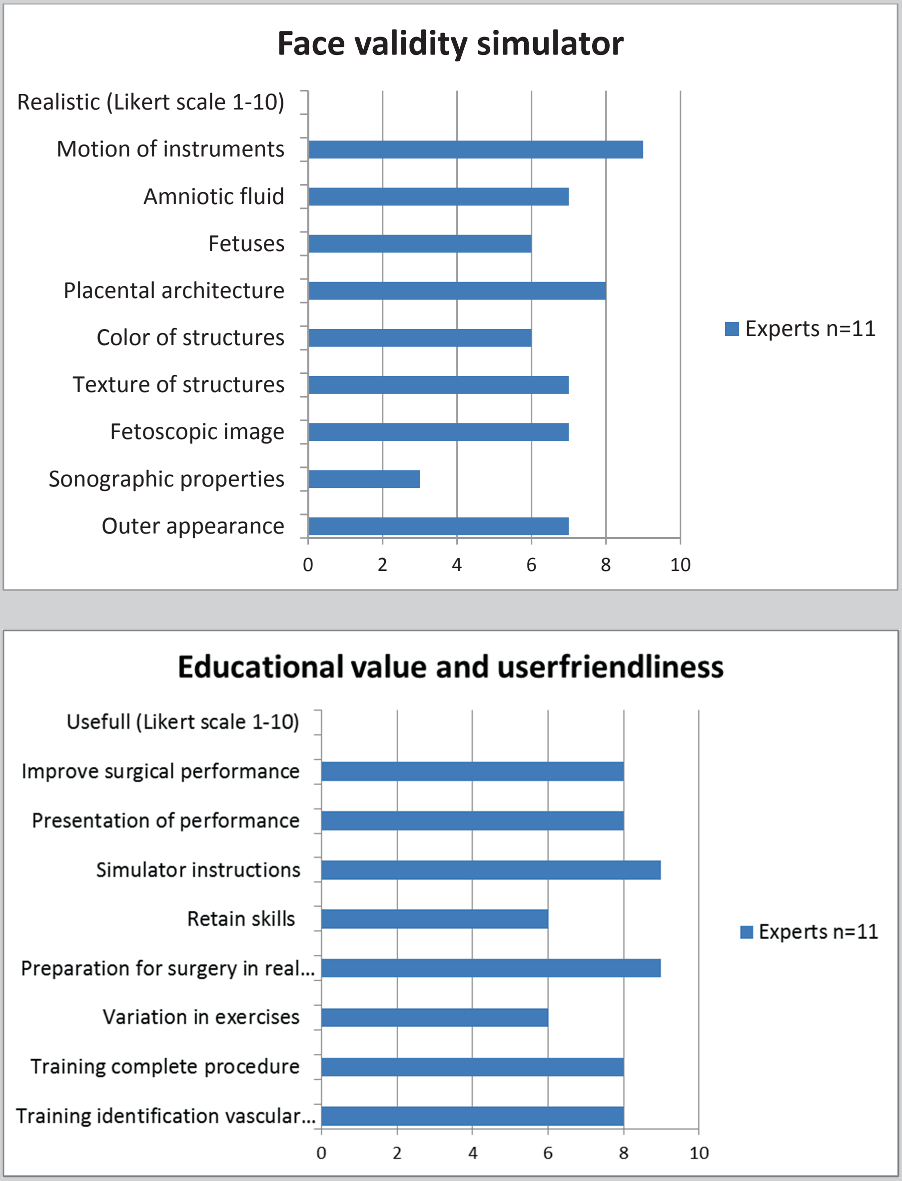


Figure 3 Expert responsens to questionnaire regarding: face validity, educational value and user friendliness of the simulator.

DISCUSSION

This study shows that training in a lifelike environment significantly increases performance for fetoscopic laser surgery in a standardized simulator model. The effect of the training was evaluated using a surgical performance score designed specifically for the evaluation of performance of therapists performing this procedure. In this study we found no difference in time taken or the presence of missed anastomoses between the groups. We defined expert benchmark levels for the curriculum to make it proficiency based. Feedback provided by the participants indicated that simulator training was perceived as a useful educational activity.

Fetoscopic laser surgery is a rarely performed, invasive procedure that is associated with a relatively high rate of fetal loss. The outcomes are shown to be operator and experience dependent.[4,8] Since the number of procedures per center is limited, organizing appropriate training and providing sufficient exposure is difficult.[2] To date, a standardized training curriculum is lacking. The main advantage of our simulator is that it enables to train fetal surgeons and trainees to gain experience in laser surgery without jeopardizing patient safety. In addition, it is readily available and allows training the entire procedure; including instrumentation set-up, which could be beneficial for a smooth workflow.

In other surgical fields, simulation based ex-vivo training has already been successfully integrated into different levels of education.[14-16] Several attempts have been made in the last years to develop simulators for invasive obstetrical procedures.[11,12,17,18] Most of these simulators are designed primarily to assess performance during critical parts of a procedure, rather than a complete operation. In this study we used a highly realistic simulator with the aim that the operators would treat the model like a real patient. There is evidence that physical resemblance can be reduced with minimal loss of educational effectiveness, provided there is appropriate correspondence between the functional aspects of the simulator and the applied context.[19] However, the choice of physical resemblance for the maximal training effectiveness depends on a number of factors, including the context within the simulator is used, kind of task that is trained, level of learning involved, abilities and capabilities of the trainee, difficulty of the task and effect of various instructional features.[20]
Most reported simulations are used for teaching in absence of well-planned and comprehensive curricula. A structured curriculum is designed with a logical sequence of learning objectives and associated activities.[21] The combination of our surgical

performance score and simulator appeared useful for training novice fetal surgeons. In addition, the set-up can be used to assess performance of practicing surgeons. Furthermore, it is an ideal environment to test new equipment or new techniques for experienced surgeons in a safe environment.[22]

Another objective of this study was to set a performance standard for the laser surgery assignment by using the parameters of the experts' performance. We expected no differences in these parameters since they had already achieved proficiency as demonstrated by other simulation studies[23], therefore experts performed the task only once. This performance standard can be used for training purposes and also for assessment or even certification in order to enhance patient safety. Performance was quite consistent as expressed by the small ranges in scores and procedure time.

The process of skills acquisition may demonstrate individual differences between trainees depending on cognitive capacity, perceptual speed, and psychomotor abilities.[24] Setting a certain number of procedures performed on simulator or actual patients to form an option for fetoscopic proficiency may cause bias. Furthermore, initial improvement in performance cannot be retained without regular repetition.[25] Therefore simulators provide a useful tool for the attainment and maintenance of trainees' surgical skills and for immediate or late assessment of their proficiency in those skills. However, a validation study of the simulator is always important to determine its capacities for training and objective assessment of the surgeons' performance with different levels of experience.
The current enthusiasm for validation of training and assessment tools and strategies is relatively new in the fetal therapy community. Before implementing a simulator in training curricula, it should be evaluated whether it trains what it is supposed to train, also known as its construct validity. In the design of a curriculum to train surgical skills, specification of the training objectives, including identification of the procedural steps and analysis of pitfalls, is essential.

Some limitations were notable in this study. While groups were not significantly different in gender demographics and previous technical skills training, the small number of participants makes it difficult to classify the groups as fully equivalent. In our study, participants were not matched according to demographics and technical capabilities. We emphasize that not only 'number of procedures attended', 'experience with other invasive obstetric procedures' and 'simulation training', but also sonographic experience, minimally invasive skills, and intrinsic qualities (such as spatial awareness) are of major importance when selecting a cohort for training fetoscopic laser surgery. It is important to note that future fetoscopic surgeons in training are not compatible to a general population of residents.

Before training, we noticed a shorter procedure and fetoscopy time in the control group. We emphasize this illustrates that differences in baseline characteristics are probably related to many other factors than represented in our questionnaire. Therefore our results should be interpreted with care. Even though a greater number of participants in the study may have provided further evidence of significant differences in outcomes and increased study power, this would not reflect reality.

This simulator training can be an effective tool for improvement of technical skills under a safe learning environment before performing fetoscopic laser surgery in the operating room.

Certainly, future studies would be required to establish reliability and implementation of such a training in a more expanded setting. Research should be focused on validation of the curriculum to make sure that trainees that go through this curricular training process, actually perform better in the operating room with more technical proficiency. Above all, monitoring of quality of care is of utmost importance.

ACKNOWLEDGEMENTS

We would like to thank all the participants from the fetal therapy centers who generously shared their time, experience and materials for the purpose of this project.

This research is supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organization for Scientific Research (NWO), and which is partly funded by the Ministry of Economic Affairs.

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APPENDIX

No.	Domain and substeps	Score
A	Preparation in operating room	7
1	Ultrasound correct settings	
2	Endoscopy tower settings	
3	Positioning of screens	
4	Adjusting lights	
5	Correct laser modus	
6	Correct power settings	
7	Positioning of patient	
B	Ultrasound examination (together with sonographer)	7
8	Identification of donor	
9	Identification of recipient	
10	Identification localization placenta	
11	Identification cord insertions	
12	Assess deepest pockets	
13	Determine expected position equator	
14	Determine insertion site fetoscope	
C	Pre-operative preparations	7
15	Surgical briefing (time out) about (complete) procedure to fetal therapy team	
16	Aseptic procedure for surgeon, scrub nurse and sonographer	
17	Mention maternal condition	
18	All instrumentation remains sterile	
19	All is sufficiently covered	
20	Pre-insertion connection scope - shaft	
21	Pre-insertion connection light cable	
D	Positioning and connection of instruments (pre-insertion)	6
22	Choose fetoscope	
23	Fetoscope: orientation	
24	Fetoscope: focus	
25	Fetoscope: white balance	
26	Connection of laser fiber	
27	Correct loading of laser fiber in fetoscope	
E	Insertion	5
28	Preparation of introduction method	
29	Performance of all manipulations under ultrasound visualization	
30	Correct administration of local anesthetic	
31	Make adequate-size skin incision with surgical knife	
32	Awareness of location of maternal uterine vessels and intestines, and placental edge during insertion	
F	Orientation	8
33	Assess visibility (optional: score visibility)	
34	Determine need for amniotic exchange	
35	Fetoscopic view of placenta	
36	Fetoscopic view of donor	

37	Fetoscopic view of cord insertion recipient	
38	Identification of placental edges	
39	Difference between artery and vene	
40	Find (part of) vascular equator	
G	Laser coagulation	4
41	Coagulation of all vascular anastomoses that cross the vascular equator	
42	Laser fiber correct position in fetoscope	
43	Laser fiber correct distance from vessel during coagulation	
44	Prevent the unnecessary sacrifice of placental tissue	
H	Assessment during procedure	3
45	Prevent unnecessary delay during procedure	
46	Check for complications(e.g. bleeding, rupture intertwin membranes)	
47	Identify and record number and type of anastomoses coagulated	
I	Amniodrainage	2
48	Controlled drainage of polyhydramnios	
49	Assess adequate drainage (ultrasound guided) until pre-defined level	
J	Closure	1
50	Closing skin incision (suture or suture free adhesive product)	
K	Direct post-operative management	2
51	Inform patient, partner/family and referring specialist	
52	Instructions for monitoring of maternal and fetal condition	

Appendix 1. Surgical performance score

Part V

Summary

Nederlandse samenvatting

SUMMARY

Learning curve and current practice

The concept of a "learning curve" is being used increasingly in surgical training and education to denote the process of gaining knowledge and improving skills. An often arising question in all types of surgery is the actual number of procedures an individual operator has to perform to achieve and maintain satisfactory outcome results. This is even truer for complex and rare interventions, such as fetoscopic surgery. Fetoscopic surgery is a surgical technique that is used to treat fetus(es) that are still inside the pregnant uterus. The most commonly performed procedure is laser surgery for twin-twin transfusion syndrome.

Twin-twin transfusion syndrome (TTTS) is one of the most common major complications of monochorionic (MC) twin pregnancies and carries a high risk of perinatal mortality and morbidity. Fetoscopic laser coagulation is the treatment of choice offered in approximately 100 specialized centers around the world. TTTS is rare and fetoscopic laser treatment is complex. With an increasing number of centers offering this procedure there is concern that, at least temporarily, less favorable outcomes will be seen because of limited experience in new centers and learning curve effects.

In **chapter 1** of this thesis we used the cumulative sum analysis to assess the learning curves and monitor ongoing performance of four operators performing fetoscopic laser therapy. This study shows an increase in survival rates with growing operator experience. The number of procedures required to reach an adequate level of performance ranged between 26 and 35 surgeries. The minimal individual variation in learning profiles that we found may be explained by the "group" learning effect, by influence of general expertise and exchange of experience.
Fetoscopic laser surgery was first performed in a few centers in the United States and Europe. These pioneer centers have made several modifications to the technique, making it difficult to compare results between centers. In **chapter 2** we conducted an international survey and took an important first step in the process of developing evidence-based international guidelines, by evaluating differences between international fetal centers in their treatment of TTTS. Considerable variations were found in patient characteristics, instrumentation and techniques, which appeared to be, at least partially, related to the volume of patients treated and geographical circumstances of the centers.

In **chapter 3** we reviewed the early years of practice compared to current practice. Since the first publications on fetoscopic laser surgery, survival rates have increased from 35% survival of both twins to 65%, with a consistent mean gestational age of 32 weeks. The evolution of the laser technique is likely to have significantly impacted this. Learning curve effects and improved early neonatal care may be other attributing factors. Even though we showed a significant increase in neonatal survival in 25 years, results are still far from optimal. We see challenges in improving the treatment of TTTS to increase survival of both twins and in prolonging pregnancies beyond 34 weeks of gestation.

Challenges in monochorionic pregnancies

Some MC pregnancies are more challenging than others. Fetoscopic laser surgery may then either not be considered as the first treatment of choice or may fail due to technical limitations in identifying anastomoses. Identification of those challenging subgroups is important to determine the best management options.

In **chapter 4** we focused on antenatal surgical interventions in monoamniotic (MA) pregnancies. Compared with complicated diamniotic cases, MA pregnancies carry additional risks. We studied MA pregnancies complicated by TTTS, twin reversed arterial perfusion, discordant anomalies, or request for reduction. We investigated relevant technical aspects of several fetal surgical interventions in complicated MA pregnancies and compared our experience with data obtained by a systematic review of the literature. We concluded that these complex procedures in this rare and highly complicated group of pregnancies, can lead to good outcome in the majority of cases, when performed in highly specialized fetal treatment centers. In case of a single intended survivor, our results suggest improved pregnancy outcomes in cases treated with cord transection (e.g. cutting the cord of the affected twin to prevent entanglement). Considering the rarity and complexity of these pregnancies, it remains crucial to individualize each case when determining the timing and type of intervention.
As it is an invasive procedure, perioperative complications of laser surgery itself increase the risk of adverse outcome. One of these complications is unintentional perforation of the intertwin dividing membranes, thereby creating an iatrogenic monoamniotic twin (iMAT) pregnancy. If iMAT is suspected, pregnancies are often more closely monitored, hospitalization after viability is considered and a preterm, elective Cesarean section is scheduled between 32 and 34 weeks' gestation to prevent complications related to cord entanglement.

In **chapter 5** we investigated the incidence of iMAT after laser surgery for TTTS and compared management and perinatal outcomes of suspected iMAT cases with those of twins with intact intertwin membranes. Patients with iMAT were more likely to deliver prematurely, and this was associated with increased neonatal morbidity. Moreover, iMAT may serve as an indicator for technically difficult procedures.

Another group in which laser therapy can be more difficult includes triplet pregnancies. Because a MC twin pair can be part of any other high-order multiple pregnancy, survival rates of MC triplets are often confused with dichorionic (DC) triplets, with one pair of MC twins affected by TTTS and one singleton. This situation is different to MC triplets that share a single placenta with three fetuses and therefore all three, instead of two fetuses, are connected by vascular anastomoses.

In **chapter 6** we compared the perinatal outcomes of all MC and DC triplets with TTTS treated at our center and reported in the literature in the last two decades. Perinatal morbidity and mortality in MC triplets with TTTS was higher and gestational age at birth earlier than in DC triplets. The data demonstrate that fetoscopic laser coagulation in DC triplet pregnancies complicated by TTTS is a feasible treatment option with increasing survival rates and more advanced gestational age at birth.

Model for training laser therapy Knowing that laser therapy is a complex procedure and there is an increased need for training, the final part of this thesis is dedicated to development of a training curriculum for this procedure. The SILICONE project: **SI**mulator for **L**aser therapy and **I**dentification of **C**ritical steps of **O**peration: **N**ew **E**ducation program; consists of three parts:

Part 1: Development of an evaluation instrument for fetoscopic laser surgery.

Part 2: Validation of this instrument.

Part 3: Validation of a training curriculum based on the instrument.

A first essential step towards a training curriculum was determining the applicable items to assess. In **chapter 7** we used the Delphi methodology to achieve expert consensus regarding the substeps that are considered essential in performing laser surgery for TTTS. The majority of fetal surgery experts participated. We produced a list of substeps deemed essential. Items were ranked in order of importance. This study provides a first step towards an authority-based training curriculum and evaluation tool for laser surgery for TTTS.

In the second part of the project we assessed the reliability and construct validity of the evaluation instrument in the context of fetoscopic operating room performance.

(**chapter 8**) We developed a silicone simulator for laser therapy and asked experts and novices to perform the laser procedure on the simulator. The assignment was evaluated by two independent observers using the evaluation instrument. An acceptable level of inter observer reliability was demonstrated. The instrument effectively distinguished between performance of experts and novices.

In order to evaluate whether simulator training could be attributable to gain and retain skills in fetal therapy, in the third part of the project we performed a prospective randomized controlled trial and assessed a comprehensive training curriculum (based on the essential steps defined in part 1) for fetoscopic laser surgery. (**chapter 9**) Novices who participated in the curriculum showed better performances during an ex vivo assignment on the high fidelity simulator for laser therapy for TTTS, compared to novice without training. Using the same simulator, expert benchmark levels for proficiency were set.

NEDERLANDSE SAMENVATTING

Dit proefschrift beschrijft de behandeling van ongeboren kinderen door een kijkoperatie in de baarmoeder; dit noemt men foetoscopische chirurgie. Het tweeling transfusie syndroom, een zeldzame ziekte bij ééneiige tweelingen, is één van de aandoeningen waarvoor deze operatie nodig is. Deze zeldzame ingreep wordt op dit moment uitgevoerd in slechts honderd gespecialiseerde centra wereldwijd, maar zal komende jaren in steeds meer centra worden verricht. Dit proefschrift richt zich daarom op de kwaliteit en het aanleren van deze operatie.

Tweelingen

Ongeveer twee op de honderd zwangerschappen betreft een tweeling. Er bestaan twee soorten tweelingen: een- en twee-eiige. Twee-eiige tweelingen ontstaan na de bevruchting van twee eicellen. Bij twee-eiige tweelingen heeft ieder kind een eigen placenta (moederkoek) en een eigen vruchtzak. Dit wordt een "dichoriale" tweeling genoemd.

Een-eiige tweelingen ontstaan na de bevruchting van één eicel, waarna splitsing in twee embryo's plaatsvindt. Een-eiige tweelingen zijn genetisch identiek. Van de eeneiige tweelingen heeft 30% ook een eigen placenta en vruchtzak (en is dus dichoriaal). Echter de meerderheid (70%) van de eeneiige tweelingen deelt een placenta, waarbij ieder kind een eigen vruchtzak heeft. Dit wordt "monochoriaal (MC) diamniotische" tweeling genoemd. Bij 1% van de eeneiige tweelingen delen de kinderen zowel de placenta als de vruchtzak. Dit heet "monochoriaal monoamniotisch" (MA). Het moment van splitsing na de bevruchting bepaalt of de kinderen placenta en vruchtzak gemeenschappelijk hebben. Vroege splitsing (binnen 3 dagen na bevruchting) leidt tot een dichoriale tweeling, latere splitsing (tussen dag 3 en 9) leidt tot MC diamniotische tweeling en splitsing na dag 9 leidt tot een MA tweeling.

Tweelingen hebben een hogere kans op complicaties dan eenlingen. MC tweelingen hebben op hun beurt weer een hoger risico dan dichoriale tweelingen. Dit verschil wordt met name veroorzaakt door vaatverbindingen op de gemeenschappelijke placenta. Deze vaatverbindingen zijn aanwezig bij vrijwel alle MC tweelingen. Via deze vaatverbindingen zijn de bloedsomlopen van beide kinderen aan elkaar verbonden en kan gedurende elk moment tijdens de zwangerschap en bevalling bloeduitwisseling plaatsvinden.

Bij negen van de tien MC tweelingen stroomt even veel bloed van het ene kind naar het andere als andersom. Hiermee is de bloedstroom in balans en ontstaan er meestal geen problemen. Als de bloedstroom tussen beide kinderen echter niet in balans is, ontstaan er complicaties zoals het tweeling transfusie syndroom (TTS).

Tweeling tranfusie syndroom

Bij TTS stroomt meer bloed door de vaatverbindingen van het ene kind (de "donor") naar de ander (de "recipiënt" of "ontvanger"), dan omgekeerd. Bij de donor ontstaat hierdoor een tekort aan bloed, waardoor hij eerst minder en later helemaal niet meer plast (doordat de nieren al het vocht dat er nog is vasthouden) en daardoor uiteindelijk geen vruchtwater meer heeft. Het vlies van zijn vruchtzak zit dan strak om hem heen. De ontvanger krijgt juist te veel bloed en gaat hij steeds meer plassen. Hij krijgt daardoor te veel vruchtwater in zijn vruchtzak. De grootte van de baarmoeder neemt door dat vele vruchtwater in korte tijd fors toe, waardoor er een grote kans is op vroegtijdige weeën, het breken van de vliezen en vroegtijdige geboorte. Beide kinderen worden in korte tijd ernstig ziek.

Als TTS niet wordt behandeld dan is de sterfte 80-100%. De beste behandeling voor TTS is foetoscopische laser behandeling waarbij de vaatverbindingen tussen de kinderen worden dicht gebrand. Bij deze behandeling wordt tijdens de zwangerschap (via de buik van de moeder) in de baarmoeder een klein instrument met een camera (de foetoscoop) ingebracht waarmee de vaatbindingen kunnen worden opgespoord en één voor één dicht gebrand met laserlicht. Na een succesvolle behandeling zijn de twee bloedsomlopen volledig van elkaar gescheiden.

TTS is zeldzaam en foetoscopische laserbehandeling is complex. Wereldwijd wordt op dit moment de foetoscopische laser behandeling aangeboden in ongeveer 100 gespecialiseerde centra. Het Leids Universitair Medisch Centrum (LUMC) is het nationaal verwijscentrum voor invasieve foetale therapie (chirugische behandelingen van ongeboren kinderen) in Nederland. Sinds 2000 wordt hier de laserbehandeling uitgevoerd. Jaarlijks worden in Leiden 50-70 gevallen van TTS behandeld.

Dit proefschrift richt zich op het in kaart brengen van de laser behandeling voor TTS. In het eerste deel beschrijven we hoe op dit moment de laser behandeling wordt uitgevoerd, hoeveel kinderen overleven na deze behandeling en hoeveel ingrepen een beginnende operateur moet doen voordat de kwaliteit van zorg gelijk is aan die van een ervaren operateur (leercurve).

In het tweede deel beschrijven we een aantal groepen zwangerschappen met TTS waarbij de laser behandeling technisch lastig is, te weten MA zwangerschappen en drielingen.

In het derde deel van dit proefschrift hebben we ons gericht op het ontwikkelen van een gestandaardiseerde training voor deze ingreep en hebben deze getest op een simulator.

Leercurve en huidige stand van zaken

Recent gepubliceerde studies over TTS laten ondanks de vooruitgang op gebied van de foetale therapie nog steeds een relatief hoog sterftepercentage en vroeggeboortes zien. De publicaties over de resultaten van de laserchirurgie komen vooral van de grote, meest ervaren centra. Het is aannemelijk dat in kleinere of meer recent geopende centra de resultaten minder succesvol zijn. Met de verbeterde economische situatie in een aantal niet-westerse landen zoals China, Brazilie en India zal het aantal centra dat deze ingreep aanbiedt toenemen. Door deze ontwikkelingen is er vraag naar training, evaluatie van leercurven, mentoring en andere vormen van ondersteuning van nieuwe centra.

Een veel gestelde vraag binnen het vakgebied is: Wat is het gewenste aantal procedures dat een individuele operator moet verrichten om de huidige resultaten van de ervaren centra te bereiken en behouden?

In **hoofdstuk 1** van dit proefschrift hebben we de leercurve van de laserbehandeling voor TTS onderzocht. Voor dit onderzoek hebben we de resultaten van vier operateurs geanalyseerd. Deze studie toont een stijging van de overlevingskansen van de kinderen naarmate de operateur meer ervaring heeft. Het aantal procedures dat nodig is om minimaal in 36% van de ingrepen overleving van twee kinderen te bereiken varieerde tussen de 26 en 35 operaties. We vonden slechts minimale variatie in leerprofiel tussen de verschillende operateurs. Dit kan mogelijk verklaard worden doordat men de procedure als groep heeft geleerd en betrokkenen hun ervaringen en kennis regelmatig uitwisselden.

Foetoscopische laser behandeling werd 25 jaar geleden voor het eerst uitgevoerd in enkele centra in de Verenigde Staten en Europa. Deze pioniercentra hebben onafhankelijk van elkaar diverse wijzigingen aangebracht in de techniek, waardoor het moeilijk is om de resultaten tussen de centra te vergelijken. In **hoofdstuk 2** hebben we een internationaal vragenlijst onderzoek uitgevoerd om de verschillen in behandelingen tussen centra in kaart te brengen. Dit onderzoek vormt een belangrijke eerste stap in het ontwikkelen van internationale evidence-based richtlijnen voor deze behandeling. Aanzienlijke verschillen werden gevonden in de karakteristieken van patienten die in aanmerking kwamen voor een behandeling, de gebruikte instrumenten en techniek van de behandeling. Deze verschillen bleken gerelateerd aan het aantal patiënten dat per centrum jaarlijks werd behandeld en geografische omstandigheden van de centra.

In **hoofdstuk 3** geven we een overzicht van de zwangerschapsuitkomsten na laserbehandeling in 25 jaar tijd. Sinds de eerste publicaties over de laser behandeling is de kans op overleving voor beide kinderen significant gestegen van 35% tot 65%, met een constante gemiddelde zwangerschapsduur van 32 weken. Aanpassingen van de lasertechniek hebben deze resultaten waarschijnlijk aanzienlijk beïnvloed. Daarnaast spelen leercurve-effecten en verbeterde vroege neonatale zorg een rol. Dit onderzoek geeft een goed overzicht van de resultaten na behandeling als benchmark voor startende centra.

Gecompliceerde monochoriale zwangerschappen

Sommige MC zwangerschappen zijn gecompliceerder dan andere. Het kan hierbij gaan om monochoriale monoamniotische (MA) zwangerschappen, zwangerschappen waarbij tijdens de behandeling extra complicaties optreden of drielingen waarbij TTS ontstaat. Het is van belang deze subgroepen te herkennen omdat de laserbehandeling in die gevallen technisch lastig kan zijn, of niet als eerste keus behandeling overwogen zou moeten worden.

MA zwangerschappen hebben een nog hoger risico op vroeggeboorte en sterfte dan MC diamniotische zwangerschappen. Een groot deel van de problemen van MA zwangerschappen wordt veroorzaakt doordat de kinderen in één vruchtzak zitten waardoor verstrengeling en knopen in de navelstrengen kunnen ontstaan. Omdat MA zwangerschappen weinig voorkomen, zijn er maar weinig onderzoeken gepubliceerd over de uitkomst van deze zwangerschappen met bovendien wisselende gegevens over overleving, complicaties en het nut en mogelijkheid van een behandeling tijdens de zwangerschap. In **hoofdstuk 4** bestudeerden wij de uitkomsten van MA zwangerschappen die in aanmerking kwamen voor een operatie voor de geboorte. Redenen voor operaties waren TTS, andere aandoeningen gerelateerd aan gemeenschappelijke vaatverbindingen, ernstige aangeboren afwijkingen bij één van de twee kinderen of het verzoek tot "selectieve reductie" om risico's voor het andere kind te verminderen. In deze studie beschreven wij de mogelijke behandelopties en zwangerschapsuitkomst. Wij concludeerden dat mits de gecompliceerde procedures worden uitgevoerd in gespecialiseerde foetale behandelingscentra, deze kunnen leiden tot goede zwangerschapsuitkomsten. Wanneer de behandeling erop gericht is om één kind te laten overleven (omdat de andere afwijkingen heeft die niet met het leven verenigbaar zijn) dan blijkt het helemaal doornemen van de navelstreng (in plaats van alleen maar afsluiten van de navelstreng van het aangedane kind) de beste behandeloptie. Hiermee zou verstrengeling kunnen worden voorkomen.

Laserbehandeling is een invasieve procedure die als zodanig ook de nodige risico's met zich meebrengt. Eén van deze risico's is onbedoelde perforatie van de vliezen (het tussenschot) tussen de twee kinderen. De kinderen, die eerst ieder in hun eigen vruchtzak zaten, komen als gevolg van deze complicatie in één vruchtzak te zitten. Hierbij zouden dezelfde problemen kunnen optreden als bij kinderen die in aanleg al in dezelfde vruchtzak zitten (MA tweelingen).

Als het vermoeden bestaat van een performatie van het tussenschot wordt de zwangerschap intensiever gecontroleerd, en wordt, wanneer de kinderen de levensvatbare grens hebben bereikt, de moeder soms opgenomen in het ziekenhuis om de conditie van de kinderen te kunnen monitoren. Vervolgens wordt een geplande keizersnede afgesproken bij een zwangerschapsduur van 32-34 weken om problemen ten gevolge van de verstrengeling te voorkomen.

In **hoofdstuk 5** wordt gerapporteerd over hoe vaak perforatie van het tussenschot voorkomt na laserbehandeling voor TTS en vergeleken we het beleid en de zwangerschapsuitkomsten van de groep met deze complicatie met de tweelingen die een intact tussenschot hadden. In 20% van de behandelde zwangerschappen werd het tussenschot geperforeerd. Patienten waarbij na de operatie het vermoeden was op een perforatie van het tussenschot bevielen eerder dan wanneer dat niet zo was. Dit was geassocieerd met een laag geboortegewicht en een hogere kans op neonatale problemen, zoals hersenschade. Daarnaast vonden we dat perforatie van het tussenschot eerder optrad wanneer de ingreep technisch lastig was.

Een andere groep waarbij de laserbehandeling moeilijker kan zijn betreft de drielingen. Bij de meeste drielingen heeft elk kind een eigen placenta en eigen vruchtzak. Er zijn dan geen vaatverbindingen en de bloedsomlopen zijn niet aan elkaar verbonden. Wanneer er sprake is van een drielingzwangerschap waarbij twee of drie kinderen één placenta delen, kan TTS optreden. Vaak is het zo dat de drieling bestaat uit een tweeling, met een gedeelde placenta en een afzonderlijk kind met een eigen placenta en vruchtzak.

("dichoriale drieling") Hierbij zijn alleen de bloedsomlopen van de tweeling met elkaar verbonden. In zeldzame gevallen delen de drie kinderen samen één placenta en zijn de bloedsomlopen van alle drie de kinderen met elkaar verbonden ("monochoriale drieling").

In **hoofdstuk 6** analyseerden we de zwangerschapsuitkomsten van dichoriale en monochoriale drielingen met TTS in de laatste twee decennia. De kans op sterfte en complicaties na geboorte was significant hoger bij monochoriale drielingen vergeleken met dichoriale drielingen. Monochoriale drielingen werden ook veel eerder geboren. Wij toonden aan dat de resultaten van dichoriale drielingen niet veel verschilt van de tweelingen, mist de behandeling wordt uitgevoerd door ervaren operateurs. Voor dichoriale drielingen met TTS is laser een goede behandeling.

Training van laser behandeling

Laserbehandeling voor TTS is een zeldzame en complexe ingreep waarvoor geen gestandardiseerde opleiding bestaat. Om deze reden is het laatste deel van dit proefschrift gewijd aan de ontwikkeling van een training curriculum voor deze procedure. Dit onderdeel kreeg de naam SILICONE (SImulator for Laser therapy and Identification of Critical steps of Operation: New Education program) en bestond uit drie delen:
Deel 1: Ontwikkeling van een evaluatie-instrument en definieren van de kritieke stappen van de foetoscopische laser behandeling.
Deel 2: Validatie van dit instrument met behulp van een siliconen simulator.
Deel 3: Validatie van een trainingscurriculum op basis van het instrument.

Een eerste stap op weg naar een opleidingscurriculum was het bepalen van de verschillende onderdelen die zouden moeten worden geleerd en beoordeeld. In **hoofdstuk 7** wordt gebruik gemaakt van de Delphi-methodiek om expert consensus te bereiken over de stappen die essentieel zijn bij het uitvoeren van laser behandeling voor TTS. Voor deze studie vroegen we de meerderheid van de foetale chirurgen wereldwijd om via een anonieme vragenlijst te beoordelen welke stappen naar hun mening essentieel zijn en deze te voorzien van commentaar. De antwoorden van de experts werden net zo lang aan de respondenten teruggespeeld tot iedereen het eens was. Het eindproduct was een lijst van de deelstappen die essentieel worden geacht voor de behandeling. Daarna werden deze stappen gerangschikt in volgorde van belangrijkheid. Hiermee werd een evaluatieinstrument opgesteld dat gebruikt kan worden om een operateur te kunnen beoordelen die de laserbehandeling uitvoert.

In het tweede deel van het project (**hoofdstuk 8**) onderzochten we de betrouwbaarheid en validiteit van het instrument bij het meten van prestaties tijdens het doen van de laserbehandeling. Hiervoor ontwikkelden we een siliconen simulator waarin levensecht de laserbehandeling voor TTS kon worden nagebootst. We vroegen vrijwillers een laserprocedure uit te voeren op de simulator. Deze vrijwillers waren experts en beginners en zij kregen dezelfde opdracht. De opdracht werd beoordeeld door twee onafhankelijke waarnemers met behulp van het evaluatieinstrument. De scores van de waarnemers kwamen goed overeen zodat een goede inter-beoordelaar betrouwbaarheid is aangetoond. Daarnaast maakte het evaluatie-instrument effectief onderscheid tussen prestaties van experts en beginners.

In het laatste onderdeel van het project (**hoofdstuk 9**) analyseerden we of trainen aan de hand van de lijst met stappen op de simulator zou leiden tot betere prestaties. Opnieuw maakte we gebruik van vrijwilligers die allen een opdracht uitvoerden op de simulator. Alle deelnemers kregen dezelfde opdracht met gelijke instructie (pre-test). Experts voerden de opdracht één keer uit om het expert-niveau te bepalen. Alle beginners voerden de opdracht twee keer uit. Voor dit onderzoek stelden we ad random twee groepen samen: een groep met beginners die voorafgaand aan de tweede opdracht een training zou krijgen en een groep dit geen training kreeg.

De beginners die hadden geloot voor de training, kregen een training onder leiding van een expert gebaseerd op het instrument uit hoofdstuk 7. Zij mochten ook oefenen op de simulator. De andere groep kreeg geen training. Alle beginners voerden daarna nog een opdracht uit op de simulator (post-test). De prestaties werden door twee onafhankelijke waarnemers beoordeeld. De getrainde beginners presteerden significant beter dan de ongetrainde beginners en benaderden het niveau van de experts na het uitvoeren van de tweede opdracht. Deze studie toont aan dat trainen van operateurs aan de hand van een lijst met essentiele stappen en een simulator leidt tot een significante verbetering van de resultaten van de laserbehandeling.

Part VI

General discussion

GENERAL DISCUSSION

The past two decades have led to significant advances in the fields of prenatal diagnosis and fetal intervention. The rationale behind fetal interventions is to improve fetal, neonatal and long-term outcomes. However, advances in fetal therapy also raise ethical issues. These concerns involve maternal autonomy and autonomous decision-making, concepts of innovation versus research and organizational aspects in the development of fetal care centers. Priority is the safety of both pregnant women and her fetuses. It is impossible to treat the fetus without going through the pregnant women (either physically or pharmacologically); therefore any fetal intervention has implications for the pregnant women's health.

Antenatal interventions have been offered for a variety of fetal diseases, many of which would be lethal without treatment. Nowadays, fetal surgery is standard of care for highly selected indications, such as TTTS, TAPS and TRAP. Availability of this technique is limited to approximately 100 specialized centers. Starting off with pioneers' "with their backs against the wall" attempts to prevent fetal demise, the efficacy of fetal surgery has now been validated for selected indications by well-designed, randomized controlled trials. [1, 2].

The primary problems continue to be accurately identifying which fetuses will almost certainly die or become severely injured without intervention, but still will have the capacity to recover with relatively normal function if fetal surgery is performed, and to minimize the risk for preterm delivery after fetal intervention.[3] The goal of fetal surgery is clear: to improve chances of survival and the long-term health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities.

Volume issues

In this thesis we focused on treatment for TTTS, as it is currently one of the most performed fetoscopic interventions. In chapter 2 we identified that 63% of fetal therapists and 52% of centers perform < 20 procedures per year. Even though there is limited evidence concerning the ideal number of procedures that should be performed to maintain high quality results (chapter 1), many studies have investigated the relationship between hospital volume data and post-operative surgical outcomes in other fields of surgery. Better outcomes have been reported in high volume institutions for high-risk procedures.[4-6] "Learning curve" and monitoring studies on fetoscopic surgery show that approximately 20-30 procedures per year (per operator) are needed to reach and maintain a requisite skill level.[7] However, for intrauterine transfusion these numbers are higher (34-49 procedures).[8]

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One of the limitations in these studies is that the effect on an individual learning curve by first assisting a senior operator was not measured. Also not included in the analysis was the extent of the operators' experience with obstetric ultrasound, invasive fetal diagnostic and other therapeutic procedures, and endoscopy prior to starting laser therapy.

Some other considerations have to be taken into account when assessing a learning curve: Case selection, or case-mix, by either treating predominantly high-risk or low-risk cases during the learning phase, will influence learning curve results. Moreover, when operating in a low volume center or center with multiple fetal surgeons, equal division of the number of procedures performed by each operator annually should be pursued in case of rare procedures such as laser surgery in TTTS.

The learning curves in our series represented the improvement of both the operators, from experience and practice, and the performance of the entire team at managing pregnancies with TTTS. Teamwork, multidisciplinary discussion with colleagues from the neonatology department (including international audits)[9], stimulation, controllability, and continuity may be beneficial factors. Another most helpful tool, in our view, was the systematic evaluation of each treated placenta through careful placental injection of colored dye.[10]

Quality control and monitoring

To optimize surgical outcomes and to decrease medical error, we propose the implementation of a continuous audit system, allowing timely feedback at each center (chapter 1). When a limited number of surgeries are performed annually, lower volume centers will be at risk of late recognition of substandard care or the incidence of complications. Aside from medical-legal aspects arising from the public's interest and willingness to invest in healthcare, we found that doctors themselves are increasingly interested in development and maintenance of expertise. The objective measurement and understanding of surgical expertise acquisition is, not surprisingly, at the forefront of surgical education programs.

To fully assess the perinatal outcomes related to the expanding number of centers performing fetoscopic laser therapy reporting and monitoring is necessary. Each center should at least report short- and long-term maternal and pediatric outcomes and the results of placental injection. Furthermore, centers performing fetal therapy should have multidisciplinary teams that evaluate the care being offered and discuss difficult cases. Regular structural reflection on ones' own practice is essential to prevent late detection of suboptimal performance. If less favorable outcomes are noticed, a quality

cycle including further education, supervision of practice and improvement of learning environment should be initiated. As stated in chapter 3, we encourage starting up centers, as well as established centers to share their performance for peer review and publish their series.
A suggestion for monitoring of performance could be implementation of a central registry. Expert centers should establish criteria for certification and periodic rectification, and review the certification process. This should include criteria to be considered competent to perform laser surgery as well as the optimal volume of cases. We believe patients and referring colleagues are entitled to obtain knowledge of at least center performance for any operative procedure, including fetoscopic surgery. Practically, in case of a period of deviating or disappointing outcomes, real-time assessment using for example CUSUM methodology should be standard practice. Awareness of underperformance alone may already improve outcomes.

Access and centralization

Balancing offering geographical access while maintaining sufficient quantity of cases is challenging. (Chapter 2). Concentration of care for this highly specialized procedure has been advocated.[11, 12] On the other hand, geographical circumstances may justify the need for low volume centers, since timely referral and treatment is associated with improved dual twin survival and decreased neurodevelopmental delay.[13]
Centers offering fetal therapy should be geographically distributed throughout a country (or province, or continent) to improve access. Patients should be allowed to receive care at the institution of their choice even when this institution is located abroad, provided that care is given without unnecessary loss of time, or unrealistic burden on health care expenses when provided by public money. Close links and ongoing education to community providers and referral centers is essential to ensure timely referral.

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New fetal therapy centers

The expertise and services required to be considered a fetal center appropriately equipped to perform prenatal surgical interventions (such as fetoscopic laser therapy), involves a tremendous institutional commitment.[14] This should include: an experienced fetal care team, (with fetal surgeons, dedicated sonographers and specialized nurses), available for urgent referrals every day of the year, a level III neonatal intensive care unit, a labor and delivery unit capable of caring for perioperative complications and obstetric emergencies with around the clock availability of MFM specialist/obstetricians. Logically, neonatologists should be involved, because they will typically be the primary physicians managing the care of the neonate and dealing with the medical consequences of the antenatal intervention. Moreover, it should be an institutional commitment to track long-term pediatric neurodevelopmental outcomes. Follow-up into childhood is indispensable to determine outcome in terms of motor, cognitive and behavioral development.[15] Additionally, a center should have the capability, manpower and laboratory to perform placental injection studies to evaluate treatment.

Postoperative and delivery care may be provided at an outside perinatal center or referring secondary or tertiary care center acting in close liaison to the fetal therapy center that performed the intervention. The resources should be similar to the resources provided at the fetal therapy center in order to maintain uniform care for ongoing outcome evaluation. This includes regular of weekly contact with the fetal team coordinator with (bi) weekly review by the MFM obstetrician. The fetal therapy team must provide the opportunity of around the clock immediate contact and advice for caregivers outside the perinatal center.

It is essential to have an established functional cohesive multidisciplinary team with the individual members of the team exhibiting and maintaining a level of expertise in their respective fields. To ensure quality and safety, it is paramount that this fetal surgery team operates together with some regularity. Centers developing new fetal therapy programs must receive guidance and training from experienced centers. This should include mentoring on the process of evaluation, performing the actual procedure and perioperative and post-operative care. The optimal definition for a fetal therapy center has yet to be established. Preferably however, national professional bodies such as Boards of Obstetricians & Gynecologists should have guidelines describing optimal care for pregnancies complicated by fetal anomalies potentially treatable before birth.

Challenges for fetal surgeons

Despite the increasing number of studies that have been published the last decade increasing our knowledge, MC pregnancies complicated by TTTS still pose challenging problems. Some pregnancies are even more complicated than others.

We studied antenatal surgical interventions in spontaneous MA in chapter 4. When anomalies affect only one twin, selective feticide is frequently offered as an intervention. In case of a single intended survivor, our results suggest improved pregnancy outcomes in cases treated with cord transection. Although often performed with technical success, surgical procedures in MA pregnancies can be technically challenging. Especially, cord entanglement can be hazardous during fetoscopic interventions. Multiple loops of entanglement make identification of the correct cord difficult. Although rare, accidental coagulation of the wrong cord does occur, as presented in our series and previously reported.[16]

In summary, all surgical interventions in MA twins, despite being minimally invasive techniques, carry a high risk of complications and require highly skilled operators. To improve outcomes in these rare, high-risk pregnancies, international collaboration, sharing data on techniques and protocols, benchmarking, and setting standards for indications and interventions are achievable and still very valuable goals.

Perforation of the intertwin membrane during the laser procedure, creating an iMAT pregnancy, is a common complication, which is associated with preterm birth (chapter 5). Possible explanations for this increased risk are the intensive fetal surveillance and preterm elective Cesarean sections that are carried out in this group in order to prevent cord accidents.

Recent evidence suggests that cord entanglement and monoamnionicity in themselves (after excluding congenital abnormalities) are not associated with increased perinatal mortality or morbidity[17, 18]. Moreover, iMAT differs from spontaneous amnionicity in many respects: in our series, cord entanglement was observed in only 12% of iMAT cases after birth, while it is observed almost universally in spontaneous MA pregnancies. The placental angioarchitecture of these two groups is also quite different.[19, 20] It is likely that not only cord entanglement or monoamnionicity itself, but also technical difficulties of the laser procedure and aggressive perinatal management influence perinatal outcome in iMAT pregnancies.

Another challenging group includes the triplet pregnancies complicated by TTTS (chapter 6).

In MC triplet pregnancies the outcome was poor. Most likely, this is due to the technical difficulties of the fetoscopic treatment because of the identification and coagulation of vascular anastomoses between all 3 fetuses. Care should be taken when interpreting these results due to the limited data on perinatal outcome in triplets with TTTS, particularly MC triplets. Only 27 cases of MC triplet pregnancies with TTTS have been reported in the literature. The actual number of MC and DC triplets with TTTS may be higher due to underreporting/publication bias. Several cases in which the pregnancy was terminated or fetal demise occurred spontaneously have probably not been reported. Irrespective of zygosity, triplets are high-risk pregnancies due to the high incidence of preterm delivery, intrauterine growth restriction and congenital anomalies.[21]

However, the rarity of these conditions, the required operator and prenatal diagnostic skills, the variety of management options and the requirement of in-depth counseling of patients currently limit the availability of such interventions to referral centers for fetal medicine.

Training fetal therapy

There is a need to train and educate the next generation of fetal surgeons. Expert fetal centers need a solid program in order to prepare their trainees to take over practice. Moreover, it is expected that new centers that start to perform fetal therapy will exhibit a learning curve and require guidance in learning the procedure. To ensure that the level of expertise is maintained, an evidence-based training curriculum and continuous process of reporting and monitoring of outcomes would be highly valuable.

In the absence of standardized protocols for fetal therapy, the content of the training curriculum developed in this thesis was created with international (authority based) consensus (chapter 7). It is important to note that the existence of a consensus does not mean that the correct answer, opinion or judgement has been found.[22] However, according to our expert panel, an acceptable accuracy is created. A potential limitation of the methodology is that no significance to each step in terms of outcome could be addressed. Although consensus was reached on specific substeps of the procedure, this study does not provide information whether this correctly executing a certain substep is associated with better or worse outcomes in those that perform it.

Besides evidence on how to perform the procedure, experience with performing the procedure itself is essential. The rapid pace of innovation in surgical procedures, combined with new technologies, the need to enhance patient safety and limited operating room resources illustrate the need for simulator training.

Simulator training

Simulators provide a useful tool for the attainment and maintenance of trainees' surgical skills and for immediate or late assessment of their proficiency in those skills (Chapter 8). The process of skills acquisition may demonstrate individual differences between trainees depending on cognitive capacity, perceptual speed, and psychomotor abilities.[23] Setting a certain number of procedures performed on a simulator or actual patients to form an option for fetoscopic proficiency may cause bias. Furthermore, initial improvement in performance cannot be retained without regular repetition.[24]

Perhaps more important than the simulation equipment itself, is the creation of the simulation program or curriculum. As with any curriculum development, the educator must determine several factors to create a simulation program that will be useful.

Simulation is simply one aspect of the larger educational program, not the focus of the program.[25]

Implementation of training

Despite all positive effects of simulation in fetoscopic surgical training, there are various practical limitations to implementing simulation training programs. The most obvious obstacle is the need for instructors with available time to teach those learning on simulators (internationally). The expenses currently incurred in obtaining a simulator model adequate for fetoscopic surgical training may also be challenging for individuals of MFM centers, especially in developing countries.

In addition, validation of simulator-based fetoscopy training is required by correlating the actual surgical experience with the performance on the simulator. A significant amount of important work has been done to validate simulators as viable systems for teaching technical skills outside the operating room. The next step is to integrate simulation training into a comprehensive curriculum (Chapter 9). Randomized controlled trials from the general surgery literature have proven that simulation-based training leads to detectable benefits for learners in clinical settings.[26, 27]

International collaboration

Fetal therapy centers have developed through a variety of multi-disciplinary collaborative relationships among pediatric surgery, maternal-fetal medicine and radiology (sub) specialists. They exist within established obstetric departments of (academic) centers or freestanding centers. Cooperation between fetal therapy centers should be encouraged to establish collaborative research networks (such as www.tapsregistry.org) and training curricula.

Since fetal therapy concerns rare diseases and procedures, the establishment of centers of excellence for those procedures that are both rare and technically challenging may help to improve maternal and fetal outcome.[28]

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FUTURE PERSPECTIVES

Telementoring

Supervised training is essential for safe and effective development of surgical skills. Fetoscopic procedures are performed on an infrequent basis, therefore there is a need for prolonged and expensive stay in distant fetal therapy centers to accumulate hands-on experience.

We believe that a potential new strategy, involving telementoring, could enhance the rate of trainees' supervision, making training safer. Moreover, telementoring could be used to support real "competency based" training, guiding trainees from competence under supervision to competence for unsupervised procedures in a controlled environment.

Telementoring could also be used for intraoperative consultations between colleagues and to deliver new skills to remote units without the need for the mentor to be physically present or for the surgeons to travel and attend courses in distant locations. Similarly, telementoring could be an inexpensive and efficient system to accredit specialists for advanced techniques.

Finally, versatile telementoring systems could be used as a teaching aid for groups of trainees and students gathered outside the OR (e.g. in a lecture room), thus reducing the number of observers in the room, often competing for a narrow surgical field like fetal therapy. If this technique is combined with the use of a simulator, this would allow future fetal surgeons to train new techniques at a desired moment, with guidance of a fetal expert without jeopardizing patients safety.

Technical innovations

Since relatively new, often described as 'experimental', some fetal interventions are performed within research protocols. It is important to distinguish which fetal interventions are standard or evidence based therapy and which are innovative or experimental. Especially in this field, surgeons encounter blurring boundaries between scientific research and therapeutic medicine. Although innovative practice is associated with the rapidly developing technologies used in fetal intervention, this raises concerns about the protection of pregnant women and their fetuses from the risks of unproven therapies.[14] On the other hand without these innovations fetal therapy would not even exist. Once feasibility and potential benefit have been identified; innovations should be subjected to systematic formal research as soon as feasible.

Fetoscopic surgery, as all endoscopic surgeries, has shown rapid development in recent decades, including advances in quality of imaging instruments and surgical techniques.

The fetoscope is used as a diagnostic tool to expand vision by magnifying objects inside the uterus, displaying the images on a 2D monitor. Diagnostic accuracy depends on optical resolution of the scope and the physiological ability of the operators' brain for perception. During surgery the fetoscope is moved to cover the wide area inside the uterine cavity creating a flowing image. All information produced by the endoscope, i.e. motion, color and shape, is integrated to create a spatial color map in the brain of the operator that cannot be produced in a still picture. In other words, an entire three-dimensional image is created in the mind of the surgeon that cannot be shared objectively; this may result in imprecise identification of location and size of the placental vessels after fetoscopic observation. Also, each endoscope generally has a blind spot.

In fetoscopic surgery, magnified vision enables visualization of the fine architecture of the placenta and fetuses. At the same time, the surgeon encounters several challenges due to the limitations of this technique; including incorrect accommodation of the surgeons hand and vision, loss of 3D information, and narrow field of view. These associated problems could be reduced by the use of a high dynamic range camera, computer and new software to enhance imaging. In other words, showing the operator an augmented overview of the placental surface and the vascular equator to enhance efficient en complete coagulation of the anastomoses. Optimizing the operation conditions by improving imaging will undoubtedly benefit the outcomes. Computer-based image processing of fetoscopic video images adds new functionality to conventional fetoscopy, following the development of new surgical devices, laser techniques and approaches and biological knowledge.

As a surgeon, on has a unique and best view on the operating field. No trainee will experience that same look and feel before being in charge on his own. Imagine the benefits of seeing through the surgeon's eyes at that moment. Today, the implementation of a small camera, a screen and audio capability in a spectacles' frame (Google Glass, Google Inc, Mountain View, CA) is able to do that and more. The concept of using Google glass consultation while performing an operation has recently been proven.[29]

In addition to communication with others, interaction with live information adds value to technical devices such as these glasses. Imagine the possibilities: patient charts, monitoring data, pre-operative diagnostic information, equipment warning signs or augmented reality overlays, can be presented without having to turn away from the patient. Operating under the watchful eye of a world's expert, either walking you through the procedure or as a second opinion will come within everyone's reach. The sky is the limit…

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Part VII

Abbreviations

Publications

Curriculum Vitae

Dankwoord

LIST OF ABBREVIATIONS

AA-anastomosis	Arterio-arterial anastomosis
AV-anastomosis	Arterio-venous anastomosis
CLD	Chronic Lung Disease
COLFAP	Combined Laparoscopy and Fetoscopy in cases with completely Anterior Placenta
cPVL	Cystic Periventricular Leukomalacia
CUSUM	Cumulative Sum analysis
DC	Dichorionic
DVP	Deepest Vertical Pocket
FLS	Fetoscopic Laser Surgery
GA	Gestational Age
iMAT	Iatrogenic Monoamniotic Twins
IUFD	Intrauterine Fetal Demise
IUT	Intra Uterine Transfusion
LC-CUSUM	Learning Curve Cumulative Sum analysis
LUMC	Leiden University Medical Center
MA	Monoamniotic
MC	Monochorionic
MFM	Maternal Fetal Medicine
NEC	Necrotizing enterocolitis
NND	Neonatal Death
PDA	Patent ductus arteriosus
PPROM	Preterm Premature Rupture Of Membranes
RA	Residual Anastomosis
RDS	Respiratory Distress Syndrome
RFA	Radiofrequency Ablation
ROP	Retinopathy of prematurity
RVOTO	Right Ventricular Outflow Tract Obstruction
SILICONE	SImulator for Laser therapy and Identification of Critical steps of Operation: New Education program
sIUGR	selective Intrauterine Growth restriction
TAPS	Twin Anemia Polycythemia Sequence
TRAP	Twin Reversed Arterial Perfusion
TTTS	Twin-Twin Transfusion Syndrome

TTS	Tweeling-Transfusie syndroom
VA-anastomosis	Veno-arterial anastomosis
VV-anastomosis	Veno-venous anastomosis

PUBLICATIONS

1. Peeters SHP, Akkermans J, Westra M, Lopriore E, Middeldorp JM, Klumper FJ, Lewi L, Devlieger R, Deprest J, Kontopolous EV, Quintero R, Chmait RH, Smoleniec JS, Otano L, Oepkes D. Identification of essential steps in laser procedure for twin-to-twin transfusion syndrome using the delphi methodology: silicone study. Ultrasound Obstet Gynecol 2014 Dec 11.
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CURRICULUM VITAE

Suzanne Peeters was born on 7 January 1985 in Dordrecht. She graduated from the Johan de Witt Gymnasium, Dordrecht in 2003. After her graduation she moved to Leiden to study at the Medical Faculty of the University of Leiden. As a student, she conducted field research for the Female Cancer Programme in Jakarta, Indonesia (Prof. Dr. A.A.W. Peters) in 2007. Here she assisted her first delivery. During a scientific internship at het division of Fetal medicine (prof. Dr. D. Oepkes), Department of Obstetrics at the Leiden University Medical Center (LUMC), her fascination for monochorionic twins and twin-twin transfusion syndrome was aroused. This project on learning curves in fetoscopic surgery was the foundation for her scientific career. In 2008 Suzanne commenced her internships in the Netherlands and Suriname, which made her even more enthusiastic to become a medical professional.

In 2010, she obtained her medical degree (cum laude) and started working as a physician (ANIOS) at the department of Obstetrics and Gynecology of the HagaZiekenhuis, Den Haag. Five months later, she started her residency in Obstetrics and Gynecology at the same department (Mentor: Dr. B.W.J. Hellebrekers), during which she continued writing this thesis.

She continued her residency at the LUMC (Mentor: Prof. Dr. J.M.M. van Lith) and she was given the opportunity to work as full time researcher for 1,5 years to finish her PhD. During her studies she was supervised by prof. Dr. D. Oepkes, Dr. J.M. Middeldorp from the department of Obstetrics and Dr. E. Lopriore from the department of Neonatology. Her research on teaching and quality control of fetoscopic surgery was presented at national and international meetings and resulted in a team procedure training program for laser therapy and this thesis. She hosted two pilot training sessions for medical professionals in South Africa and Sweden. In February 2015 she continued her residency training at the LUMC.

Suzanne lives together with Elmer and their son Thijmen (2014) in Rotterdam.

DANKWOORD

Onderzoek doe je nooit alleen! Er zijn veel mensen die hebben bijgedragen aan de totstandkoming van dit proefschrift. Graag wil ik een aantal personen in het bijzonder bedanken:

Dick, dank voor je inspirerende begeleiding en visie, dankzij jou werden de meest ambitieuze ideeën al snel omgezet in realistische wetenschappelijke projecten. Je deur stond altijd open en je leerde me hoe je je staande houdt in de internationale onderzoekswereld.
Enrico, dank voor je oneindige enthousiasme, kritische blik, onvoorstelbare reactietijd en leerzame commentaar: het is een eer om met jou onderzoek te mogen doen.
Annemieke, dank voor je opbouwende feedback, heldere inzichten en je emotionele ondersteuning. Je bent echt een voorbeeld hoe ik me als gynaecoloog hoop te ontwikkelen.

Dank aan het foetale therapie team, in het bijzonder Frans, voor jou is geen ingreep te ingewikkeld, en Jennie; met goede herinneringen aan onze bijzondere reis naar Zuid-Afrika.
Dear colleagues of the Universities of Leuven and Karolinska, thank you for the collaboration and the promising start of our consortium.

Lieve Ivanka en Gladys, het zal nu weer een stuk stiller zijn op K6, dank voor alles dat jullie (ongemerkt) uit handen hebben genomen. Promoveren zonder jullie hulp lijkt onmogelijk.

Collega-onderzoekers, bedankt voor de gezellige en leerzame tijd samen. Ondanks dat we op verschillende afdelingen werken, zijn we toch heel veel met hetzelfde bezig.
Opleiders, gynaecologen, verloskundigen en verpleegkundigen van het HagaZiekenhuis en LUMC dank voor jullie interesse, gezelligheid, motiverende woorden en opleidingsmomenten.

Veel dank naar alle zwangere vrouwen en kinderen die deelnamen aan de verschillende studies in dit proefschrift. Mijn dank gaat uit naar alle vrijwilligers van het SILICONE project, die zelfs aansluitend aan drukke nachtdiensten nog laseroperaties wilden simuleren.

Dank aan Stephan, Rens en Jenny voor het ontwerpen van de cover van dit proefschrift.

Mijn vrienden en vriendinnen, in het bijzonder mijn oudste vriendinnetjes Sofie, Han en Fem, de meiden van HW4c en Wieveskunne, dank voor de goede balans tussen werk en ontspanning. Joan en An, nu zit ik niet als paranimf achterin in het bankje, wat hebben jullie de lat hoog gelegd, mede dankzij jullie heb ik een superleuke onderzoekstijd gehad, bedankt!

Natuurlijk mijn paranimfen; Fem en Joost, zonder jullie was het nooit gelukt; in vele opzichten. In ons 'vruchtbare' kamertje op K6 zijn de grootste wetenschappelijke ideeën geboren en werkelijkheid geworden. Ik ben supertrots dat jullie vandaag naast mij staan. Dank voor jullie steun en vriendschap.

Tot slot wil ik mijn familie bedanken:

Lieve Bernd; Bro, je bent een topper, zonder jouw ICT hulp en marketing kennis lag hier nu geen boekje. Lieve Renee, Muriel en Idwer, een leukere schoonfamilie kan ik niet wensen.
Lieve opa en oma, ik ben heel blij en trots dat jullie deze promotie mogen meemaken en dat jullie ondanks hoge leeftijd alle publicaties en congressen hebben kunnen volgen via de e-mail.

Lieve Papa en Esther, Mama en Arie, Loes en Sjoerd, dank voor jullie onuitputtelijke vertrouwen, interesse en steun en dat jullie altijd voor ons klaar staan.

Lieve El, één plus één is drie, je bent mijn kanjer, grootste supporter en criticus. Met jou en onze kleine aap Thijmen is het leven een feest.