Technical aspects of laser surgery for TTTS

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Citation

Akkermans, J. (2017, June 22). *Technical aspects of laser surgery for TTTS*. Retrieved from https://hdl.handle.net/1887/49723

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Title: Technical aspects of laser surgery for TTTS
Issue Date: 2017-06-22

TECHNICAL ASPECTS OF LASER SURGERY FOR TTTS

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ISBN:	978-90-826920-0-6
Cover and layout:	Joost Akkermans
Illustrations:	Amanda Gautier, www.gautierillustration.com

The research described in this thesis was performed at the Department of Obstetrics of the Leiden University Medical Center, the Netherlands. This research is supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organisation for Scientific Research (NWO) and partly funded by the Ministry of Economic Affairs (project number 12711).

The publication of this thesis was financially supported by: STW, Afdeling Verloskunde LUMC, Afdeling Neonatologie LUMC, Walaeus bibliotheek.

TECHNICAL ASPECTS OF LASER SURGERY FOR TTTS

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 donderdag 22 juni 2017
klokke 16:15 uur.

door

Joost Akkermans

geboren te Steenbergen
in 1982

Promotiecommissie

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CONTENTS

PART TWO: CURRENT PRACTICE

PART THREE: TECHNIQUE AND TECHNOLOGY

PART FOUR: TRAINING AND EVALUATION

PART FIVE: SUMMARY AND DISCUSSION

PART SIX: APPENDICES

PART ONE

General Introduction

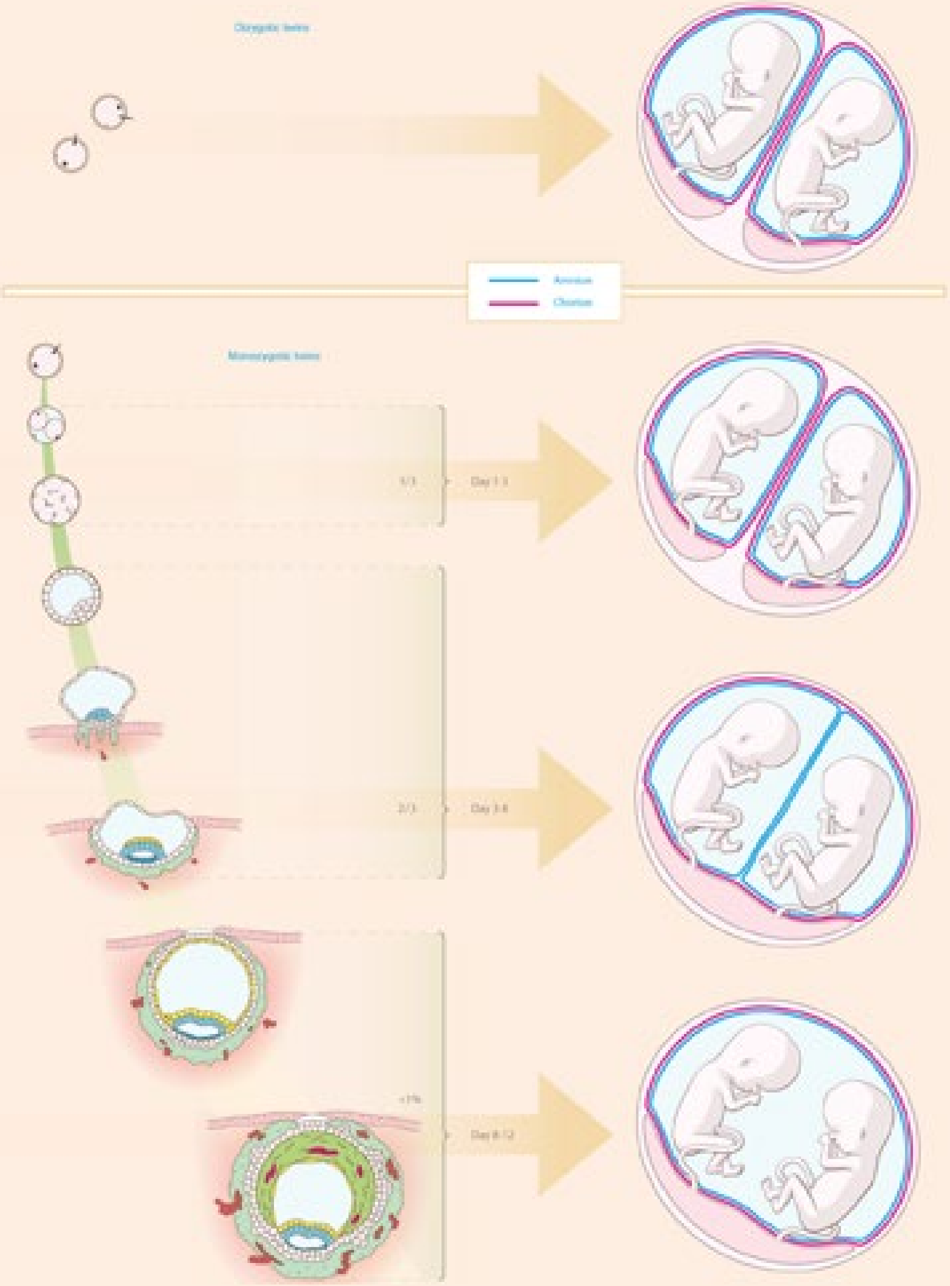


Figure 1 Overview of distribution and developement of different tyes of twin gestations.

Twin pregnancies occur in approximately 2% of all pregnancies in the Netherlands.[1] As shown in figure 1, two-third of these pregnancies result in dizygotic- or non-identical twins and one-third result in monozygotic- or identical twins. Dizygotic twins develop from two fertilized eggs and generally have their own placenta and membranes and are thus always dichorionic. Monozygotic twin pregnancies develop from one fertilized egg and chorionicity and amnionicity depend on the moment of division into two embryos. When division occurs within three days after fertilization, the pregnancy will develop into dichorionic twins. This group accounts for approximately 33% of monozygotic twin pregnancies. In about 77% of all monozygotic twins, division takes place between 3 and 8 days after fertilization which leads to a monochorionic (MC) diamniotic twin pregnancy. These pregnancies are characterized by two fetuses with their own amniotic sac, sharing one placenta and chorionic sac. A small group of monozygotic twins, less than 1%, divide after 8 days and develop into monochorionic monoamniotic (MA) twins, sharing both the placenta, chorionic- and amniotic sac.

Figure 2 Photo of a monochorionic twin placenta showing different types of anastomoses. AA = arterio-arterial anstomoses, AV = arterio-venous anastomoses.

Compared to singleton pregnancies, twin pregnancies have a higher risk of developing complications. The risk of adverse pregnancy outcome in monochorionic twins is twice as high as dichorionic twins and even four times as high as singleton pregnancies. A perinatal mortality rate of approximately 11% has been reported.[2, 3] This increased risk is attributed to the presence of a shared blood circulation. The monochorionic twin placenta, shared by both twins, is characterized by superficial vascular anastomoses.[3] These are direct connections of blood vessels from both fetuses (figure 2). Three types of placental anastomoses can be distinguished, artery-to-vein (AV), artery-to-artery (AA) and vein-to-vein (VV). Direction of flow over an anastomosis is dependent on the pressure gradient. When an artery (high pressure) is connected to a vein (lower pressure), blood will flow in the direction of the vein. With AA or VV anastomoses, the flow can be bidirectional. In most monochorionic twin pregnancies the net flow from one fetus to the other is balanced but in about 10%, at some point during gestation, an imbalance occurs leading to twin-twin transfusion syndrome (TTTS).

TTTS

Imbalanced blood flow over one or more anastomoses, in time, leads to hypovolemia with subsequent oligohydramnios in the donor twin, and hypervolemia with polyhydramnios in the recipient twin (figure 3). TTTS is detected on ultrasound scans based on the twin

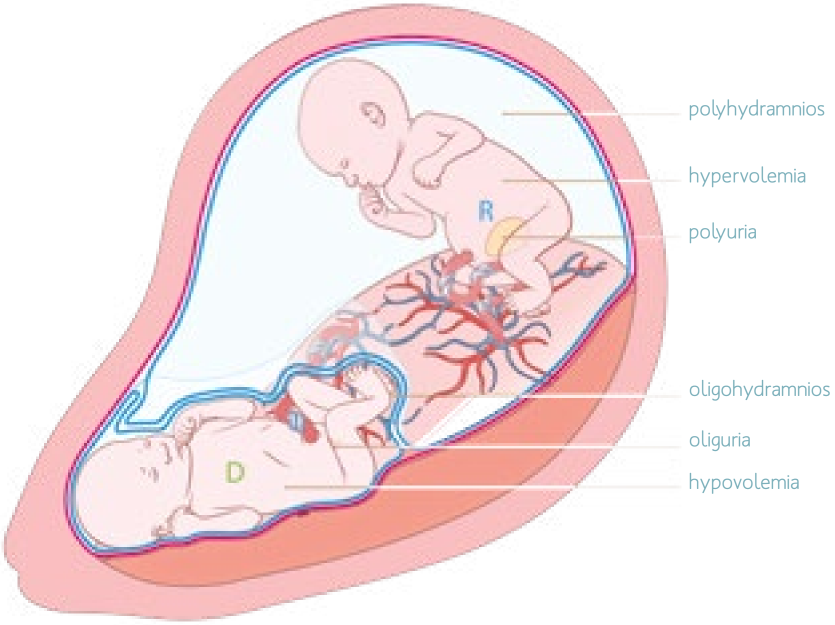
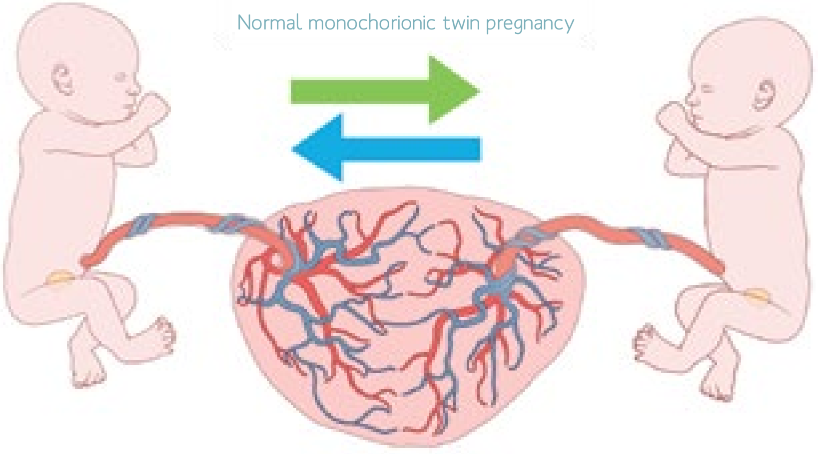
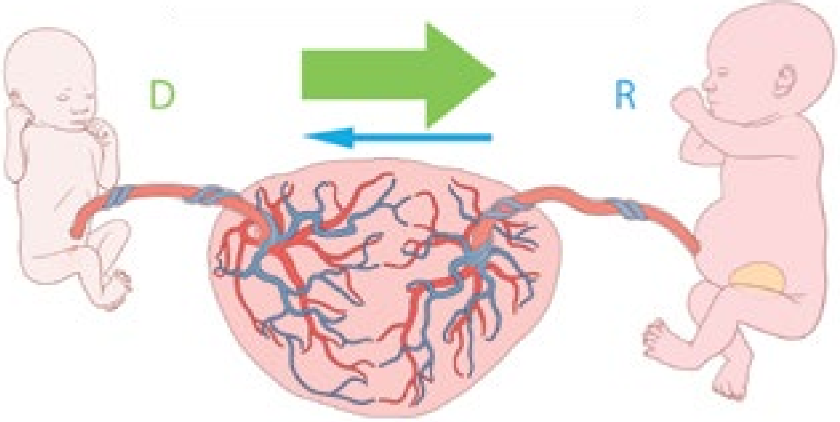


Figure 3a Schematic drawing of a TTTS complicated monochorionic twin pregnancy describing the diagnostic features. R represents the recipient twin, D is the donor twin.



Normal monochorionic twin pregnancy



Twin-twin transfusion syndrome complicated pregnancy

Figure 3b Schematic drawing of a normal monochorionic twin pregnancy and a TTTS complicated pregnancy. The arrows represent the amount of flow over the anastomoses. R represents the recipient twin, D is the donor twin.

oligo-polyhydramnios sequence. Further ultrasound staging of the disease is based on identification of the donor bladder, abnormal flow in the umbilical artery, fetal hydrops and single fetal demise. Adverse perinatal outcome in TTTS is mainly attributed to intrauterine death due to heart failure, and premature birth due to rupture of membranes or cervical shortening. Untreated TTTS is associated with a perinatal mortality rate between 80% and 100%.[4] In the Netherlands, approximately 775 monochorionic twin pregnancies are seen yearly. With an incidence of about 10%, each year on average 77 cases of TTTS need treatment.[1] Until two and a half decades ago symptomatic treatment by (serial) amniodrainage, where amniotic fluid is drained from the amniotic sac of the recipient, decreasing pressure and maternal discomfort, was the only option. In 1990, doctor De Lia was the first to describe fetoscopic laser surgery as a causal treatment strategy for TTTS. [5]

LASER SURGERY

Fetoscopic laser surgery is considered the 'gold standard' for treating TTTS. The rationale of this procedure is to divide both fetal circulations by occluding all vascular anastomoses on the placental surface. This is done by introducing a small endoscope, usually with a diameter

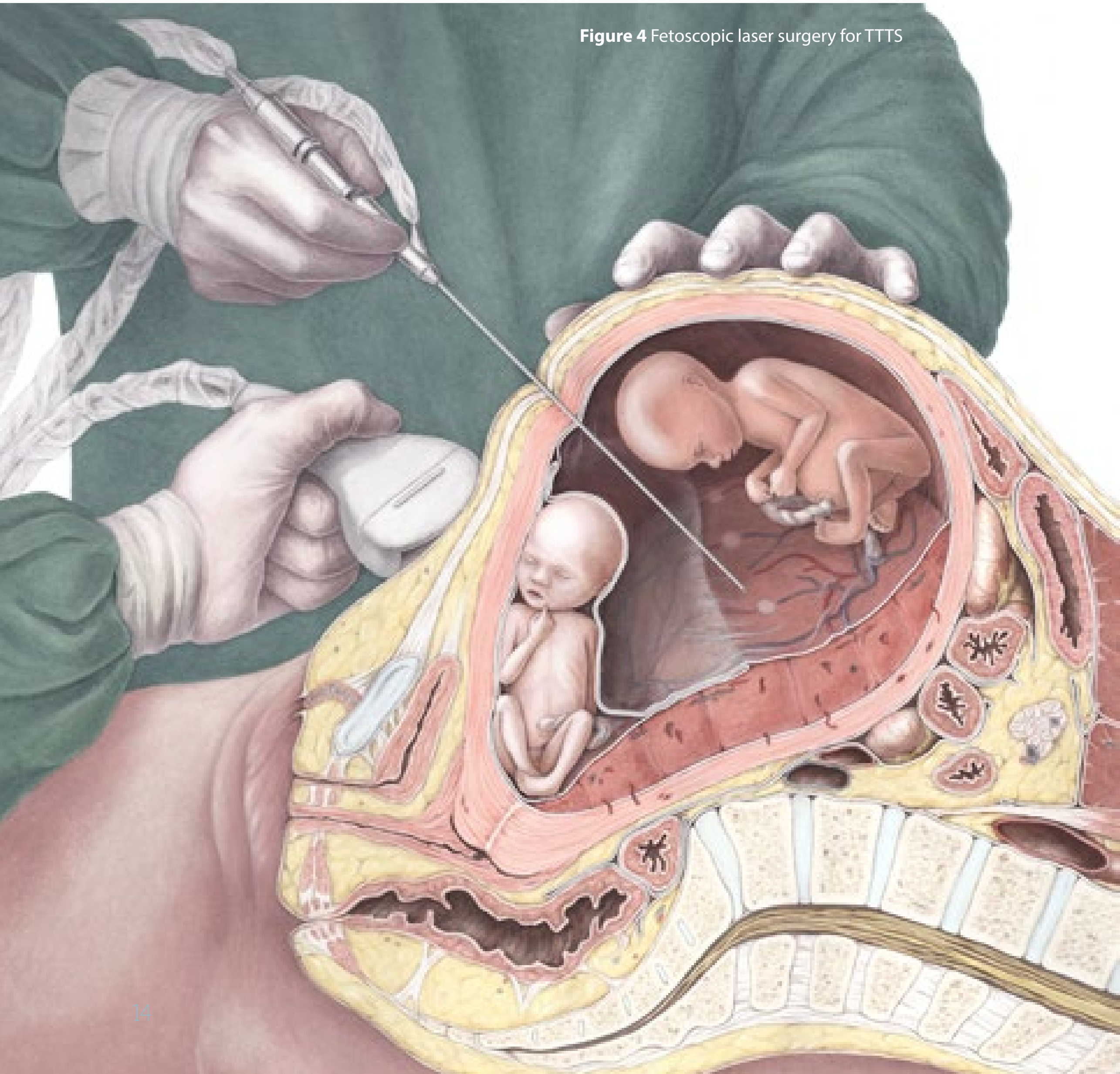


Figure 4 Fetoscopic laser surgery for TTTS

of 3-4mm, through the maternal abdominal- and uterine wall into the amniotic sac of the recipient twin (figure 4). With this endoscope the vascular equator (the line that divides the placenta at the point where all anastomoses meet) is identified and all anastomoses are first selectively coagulated with a high powered medical laser. Subsequently, a line is drawn from one placenta margin to the other along the vascular equator connecting all coagulated anastomoses making sure even the smallest anastomoses are lasered.[6] Finally, excessive amniotic fluid is drained from the recipient amniotic sac by amniodrainage until a deepest vertical pool of 6-7cm is achieved. In general, the procedure is performed under local anesthesia with sedation of the mother.

Compared to (serial) amnioreduction fetoscopic laser surgery improved perinatal survival of both fetuses from 26% up to 65% and survival of at least one fetus from 51% up to 88%.[7, 8] However still, of all surviving children, 6-18% show neurodevelopmental complications and 4-16% show signs of cerebral injury.[9, 10] It is evident that still room for improvement in outcome exists. Gaining better insight in all steps and technical aspects of the procedure might help bringing outcomes to an even higher level.

TECHNICAL ASPECTS

Different types of endoscopes are used for laser surgery for TTTS. Semi rigid fiberscopes (1-2.2mm) with a remote eye-piece, through an operating sheath with a working channel that allows for a 400-600µm laser fiber are mainly used. Currently 3.3mm endoscopes with integrated fiber optic and two working channels are gaining popularity (figure 5). Scopes or working channels are available straight or curved, curved scopes allow for increased maneuverability and better access to the anastomoses in case of anterior placenta position.[11]

Figure 5 Karl Storz Miniature Straight Forward telescope 0° 11506AAK and the Miniature Curved Forward Telescope 0° 11508AAK. Both with a 4 Fr. and a 3 Fr. working chanel.

Laser types that are used for fetoscopic laser surgery for TTTS are mainly Nd:YAG (neodymium-doped ytrium aluminium garnet; Nd:Y3Al5O12) with a 1064nm wavelength or a 940nm wavelength diode laser. Both laser types have similar absorption characteristics for hemoglobin and water (figure 6) that make them ideal for coagulation of blood vessels and highly perfused tissue. Both are continuously emitting laser systems with a power range of up to 80-100 Watt. The optical penetration depth of the photons emitted by the diode laser is substantially lower than that of the Nd:YAG laser.[12] Another laser type that is sometimes used is potassium titanyl phosphate ($KTiOPO_4$) or KTP laser with a wavelength 532nm. Laser power is one of the variables that can be adjusted by the operator and determines the amount of energy in Joule that is delivered per second. A certain amount of focused laser energy is needed for successful coagulation of a vessel. This amount is highly dependent on the diameter of the vessel, the flow in the vessel and the distance between the laser tip and the vessel wall. Another factor that is thought to significantly impact the energy needed for coagulation is the angle at which the laser fiber is aimed at the vessel.[13] Although the vessel is bulging up from the placental surface, a perpendicular approach is desirable.

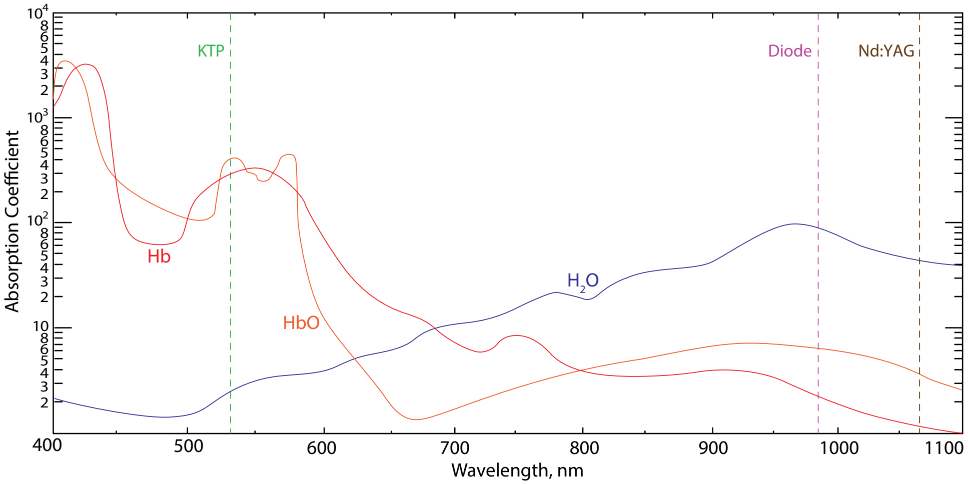


Figure 6 Absorption coefficients of water (H_2O), hemoglobin (Hb) and oxygenated hemoglobin (HbO) for different laser wavelengths and types (KTP, Nd:YAG and Diode)

Over the years' different laser techniques have been described and used. The rationale for the selective laser technique[14], now adopted by most fetal treatment centers, is 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, as was commonly done in the early years. Sequential selective laser[15] is an adaptation of this technique whereby anastomoses are coagulated in a specific order. The theoretical aim is to obliterate the anastomoses in a sequence that allows, at least partly, an inter-operative correction of the hypoperfusion of the donor and hyperperfusion of the recipient.[16] Recently an international multi-center randomized controlled trial showed that an adaptation of the selective technique, called the Solomon technique, lead to a significant reduction of recurrence of TTTS and post laser twin anemia polycythemia sequence (TAPS).[6] With this technique, in addition to selectively coagulating all anastomoses, a line is drawn with the laser from one placenta margin to the other connecting all laser spots.

LEARNING NEW TECHNIQUES

Training a new generation of fetal therapists for laser surgery for TTTS is challenging, even in large centers the annual number of procedures is low and gaining supervised hands-on experience is difficult. For centers starting up a laser program this problem is even bigger since, most often, a local experienced mentor is lacking and surgeons in training need to travel to an established center in order to get some experience. Therefore, we set out to develop a standardized training program for fetoscopic laser surgery on a high fidelity fetoscopy simulator model and an evidence based procedure specific evaluation tool.

OUTLINE OF THIS THESIS

Technical aspects of laser surgery for Twin-Twin Transfusion Syndrome. Fetoscopic laser surgery is currently considered the best treatment strategy for TTTS and is gaining popularity worldwide. It has evident advantages over alternative treatments such as serial amniodrainage.[7] Although perinatal outcome has advanced significantly, still room for improvement exists. In this thesis we evaluate current practice and investigate different techniques and technical aspects of the procedure and its impact on perinatal outcome. Furthermore, we propose a standardized tool that will aid training the next generation of fetal therapists performing laser surgery for TTTS.

PART 1 - GENERAL INTRODUCTION

PART 2 - CURRENT PRACTICE

Chapter 1: A systematic review of perinatal survival after laser surgery for TTTS over a 25-year period, comparing outcomes of the early years to the current practice.

Chapter 2: A survey amongst 64 established fetal therapy centers worldwide performing laser surgery for TTTS. Analyzing differences in approach, technique and equipment.

PART 3 - TECHNIQUE AND TECHNOLOGY

Chapter 3: A systematic review and meta-analysis evaluating efficacy of the sequential laser technique for TTTS compared to the standard selective laser technique.

Chapter 4: This study investigates risk factors for extensive post-partum placental damage after laser surgery for TTTS and its impact on different outcome measures.

Chapter 5: An experimental study using an ex-vivo perfused human placenta model to evaluate the impact of different laser power settings and firing angle on coagulation efficiency in laser treatment for TTTS.

PART 4 - TRAINING AND EVALUATION

Chapter 6: A Delphi consensus study among established fetal therapists to identify the essential steps of laser surgery for TTTS. The consensus outcome was used to develop an evidence based evaluation tool for fetal surgeons.

Chapter 7: A study assessing inter-observer reliability and construct validity of the procedure specific evaluation tool described in chapter 7.

Chapter 8: A pilot randomized trial evaluating the effect of standardized training for fetoscopic laser surgery using the previously described evaluation tool

PART 5 – SUMMARY AND DISCUSSION

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

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PART TWO

Current Practice

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PUBLISHED IN: FETAL DIAGNOSIS AND THERAPY 2015; 38: 241-253

Chapter 1

Twenty-Five Years of Fetoscopic Laser Coagulation in Twin-Twin Transfusion Syndrome: A Systematic Review

ABSTRACT

Objective

The aim of this study was to assess the perinatal outcome of pregnancies with twin-twin transfusion syndrome (TTTS) treated with laser therapy over the past 25 years, and in relation to different techniques used in this time period.

Methods

A systematic review of studies reporting on perinatal outcome according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines was conducted. The MEDLINE, Embase and Cochrane Library databases were systematically searched. Comparisons were made in respect to time period and laser technique.

Results

In total, 34 studies reporting on 3,868 monochorionic twin pregnancies were included. The 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 introduction of laser therapy for TTTS more than two decades ago, perinatal survival improved significantly. Improved outcome is probably associated with several factors, including evolution of the laser technique, learning curve effect, better referral and improved early neonatal care.

INTRODUCTION

Monochorionic 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. [3] proposed fetoscopic laser coagulation of the placental vessels in 1990, 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 (GA) 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 ranging 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 inter-twin membrane was abandoned because it led to unnecessary placental loss [10]. In 1998, Quintero et al. [11] introduced the selective laser coagulation technique. 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.

Author and year	N	Inclusion period	Type of study	Dual survival (%)	GA at birth	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)	
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)	

Author and year	N	Inclusion period	Type of study	Dual survival (%)	GA at birth	Comments
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 multi-center 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 multi-center 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. GA= gestational age. Figures for GA at birth are mean ± SD. NA = Not assessed; RCT = randomized controlled trial.

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 on the impact of the above-mentioned changes in laser treatment strategies on the outcome results. We systematically reviewed all published series since the introduction of laser treatment of TTTS with respect to survival, GA at birth and procedural or postoperative complications in relation to the time and the laser technique used.

METHODS

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 literature review was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [14], and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] where applicable.

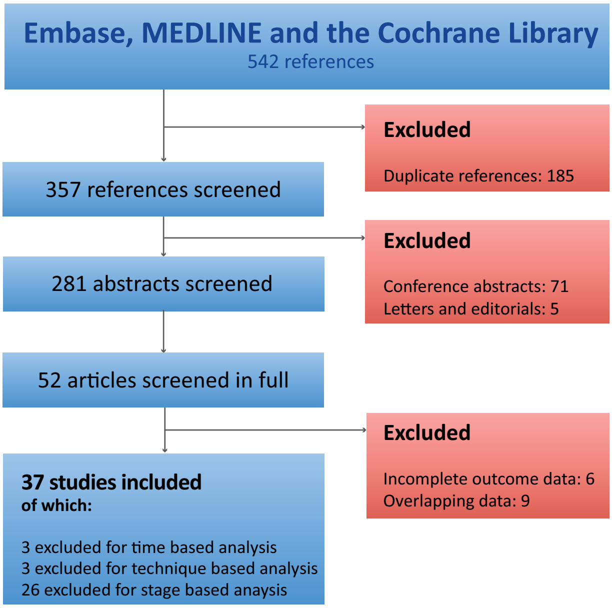


Figure 1 Flow chart of study selection according to the MOOSE guideline.

Literature Search

An initial literature search on survival after laser coagulation for TTTS was conducted in MEDLINE, Embase and the Cochrane Library using the PubMed and OVID search engines without restriction on the language or type of publication. Key words and free text searches were performed with combinations of the following key words: 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. Akkermans and S.H.P. Peeters). Disagreement on the 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 [5] or the Quintero criteria [16] 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 GA at birth. Other important parameters were complications, such as PPROM, GA 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 GA 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.

Statistical Analysis

Continuous variables were reported as median (range) or mean ± standard deviation (SD); for synthesis of data, medians (range) were recalculated as means ± SD using the method described by Hozo et al. [17].

For comparing survival outcomes of different techniques, a cumulative survival rate was calculated and the 95% confidence intervals (CIs) were estimated using binomial distribution. The survival rates were pooled using the DerSimonian and Laird random-effects models with heterogeneity estimated from the Mantel-Haenszel model. The results of multiple groups were compared using analysis of variance (ANOVA) statistics. Results of categorical variables were compared using Fisher's exact test or χ^2 test, as appropriate. Student's t test was used to compare normally distributed values between two groups. The Mann-Whitney U test was used to compare non-parametric variables. A p value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS (IBM SPSS Statistics 20 for Windows; IBM, New York, N.Y., 2011) and MS Excel (Microsoft Excel 2010; Microsoft, Redmond, Wash., 2010). This 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 PRISMA 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, 18- 48]. Twelve studies [5, 49-59] presented data overlapping other series, of which one presented data relevant for the technique-based analysis [58].

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, 18-20, 22-26, 28, 30, 32], 18 retrospective single-center cohort studies [27, 29, 31, 33- 44, 46, 47, 59], 2 prospective multicenter cohort studies [21, 58] and 3 retrospective multicenter cohort studies [45, 48, 55]. The studies were from the United States, Belgium, Australia, Canada, Spain, Poland, Italy, Taiwan, Germany, The Netherlands, Denmark, the United Kingdom, France, Japan, Mexico, Brazil, China and Chile. The primary outcomes - perinatal survival of at least one or both twins and GA at birth - were well defined in all included studies.

There were three non-English language articles [34, 35, 40]. The language skills of the authors and co-workers (Chinese) were sufficient to analyze these articles.Three authors described their series in two separate cohorts in order to display their learning curve [20, 39, 42]. Eight studies compared different (adaptations of) laser techniques [12, 13, 20, 21, 30, 46, 48, 58]. Baud et al. [47] compared the 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.

For the overlapping series of Nakata et al. [58] and Murakoshi et al. [41], we used the latter for the time-based analysis and the former for the technique-based analysis. For the study of Liu et al. [40] it was unclear what technique was used and therefore it was excluded in the technique-based analysis.

Primary Outcome

A total of 3,868 women with a monochorionic 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 2-6).

The mean GA at the time of surgery was 20.9 ± 1.9 weeks. Combining all series, the mean perinatal survival of both twins, one twin and at least one twin was 52 ± 14.8%, 29 ± 10.5% and 81 ± 8.3%, respectively. The overall survival of fetuses was 5,348/7,736 (69.1%). Figure 2a displays a forest plot with double twin survival rates in all included studies subdivided into time groups based on their study period, and the difference between the time periods. Figure 2b displays the forest plot of single twin survival rates. For both twins survival rates significantly increased from 31% (1990-1995) to 62% (2011-2014) ($p < 0.001$), and survival rates for at least one twin significantly increased from 70% (1990-1995) to 88% (2011-2014) ($p = 0.009$). No significant change in survival of one twin was seen between 1990 and 1995 (39%) and between 2011 and 2014 (26%) ($p = 0.09$). The overall mean GA at birth of all series was 32.4 ± 1.3 weeks. GA at birth did not change in time for the included series ($p = 0.226$).

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, 20, 21, 30, 46, 48, 58]. These groups were analyzed separately, resulting in 41 subgroups describing survival results for different laser techniques. The non-selective laser technique was used in five series [10, 18-21], 28 series used the selective laser technique [12, 20-39, 42, 43, 45-48, 58], the selective sequential technique was used in five series [12, 13, 30, 41, 44], and three series used the Solomon technique [13, 46, 48].

Figure 3a shows a forest plot with the individual studies and the inter-study heterogeneity per technique as well as the subgroup difference and heterogeneity between the subgroups for double twin survival. Figure 3b shows a forest plot with the results for single twin survival. Survival of both twins improved significantly ($p = 0.0001$) over the course of the introduction of new or modified techniques to the detriment of survival of only one twin ($p = 0.01$). Overall a gradual improvement in survival of at least one twin was seen for the newer techniques ($p = 0.004$).

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, 27, 29, 31, 32, 35, 36, 38, 39, 42, 46, 47].

DISCUSSION

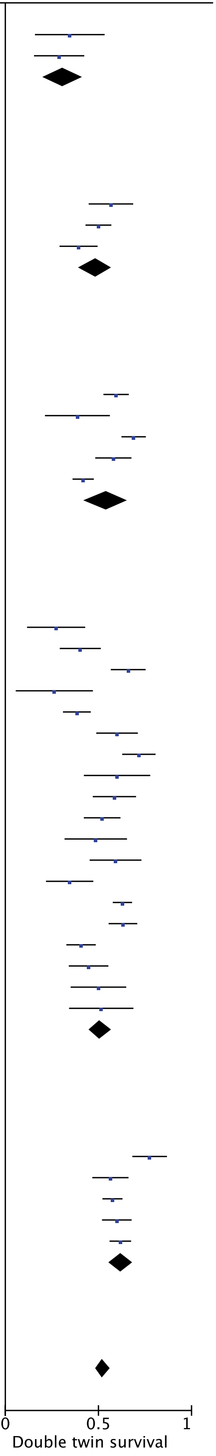
In this review of all published series reporting on outcomes after fetoscopic laser treatment for TTTS, we found a significant improvement in survival of both twins and at least one twin over the past 25 years. This study also shows a significant improvement in survival of both twins with the more recently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

The shown improvement in survival is likely multifactorial and potentially affected by different forms of bias. There are several important 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

2a

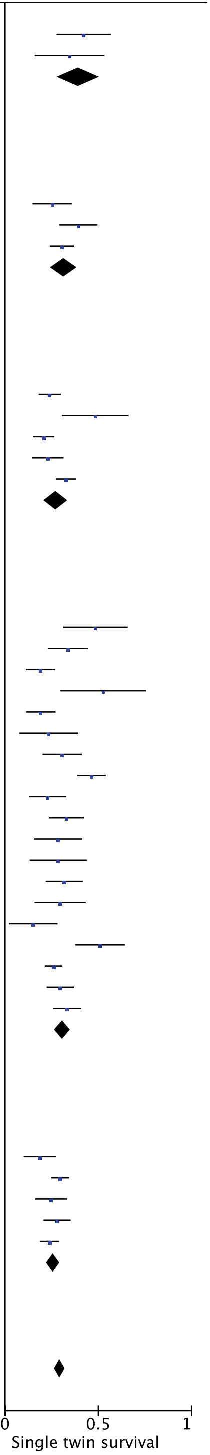
Study or Subgroup	Events	Total	Weight	Survival Rate [95% CI]
Time group 1 (1990-1995)				
De Lia 1995	9	26	2.1%	0.35 [0.16, 0.53]
Ville 1995	13	45	2.7%	0.29 [0.15, 0.42]
Subtotal (95% CI)		**71**	**4.8%**	**0.31 [0.20, 0.42]**
Total events	22			
Heterogeneity: I^2 = 0%				
Time group 2 (1996-2000)				
De Lia 1999	38	67	2.8%	0.57 [0.45, 0.69]
Hecher 2000	100	200	3.4%	0.50 [0.43, 0.57]
Quintero 2000	35	89	3.0%	0.39 [0.29, 0.50]
Subtotal (95% CI)		**356**	**9.3%**	**0.48 [0.40, 0.57]**
Total events	173			
Heterogeneity: I^2 = 61%				
Time group 3 (2001-2005)				
Huber 2006	119	200	3.4%	0.59 [0.53, 0.66]
Gray 2006	12	31	2.2%	0.39 [0.21, 0.56]
Quintero 2007	133	193	3.4%	0.69 [0.62, 0.75]
Middeldorp 2007	58	100	3.1%	0.58 [0.48, 0.68]
Stirneman 2008	120	287	3.5%	0.42 [0.36, 0.48]
Subtotal (95% CI)		**811**	**15.7%**	**0.54 [0.42, 0.66]**
Total events	442			
Heterogeneity: I^2 = 91%				
Time group 4 (2006-2010)				
Sepulveda 2007	9	33	2.4%	0.27 [0.12, 0.43]
Ierullo 2007	31	77	3.0%	0.40 [0.29, 0.51]
Cincotta 2009	66	100	3.1%	0.66 [0.57, 0.75]
Ruano 2009	5	19	1.9%	0.26 [0.06, 0.47]
Morris 2010	63	164	3.3%	0.38 [0.31, 0.46]
Meriki 2010	45	75	2.9%	0.60 [0.49, 0.71]
Chmait 2010	71	99	3.2%	0.72 [0.63, 0.81]
Yang 2010	18	30	2.2%	0.60 [0.42, 0.78]
Lombardo 2011	41	70	2.9%	0.59 [0.47, 0.70]
Weingertner 2011	52	100	3.1%	0.52 [0.42, 0.62]
Hernandez-Andrade 2011	17	35	2.3%	0.49 [0.32, 0.65]
Delabaere 2011	29	49	2.6%	0.59 [0.45, 0.73]
Sundberg 2012	19	55	2.8%	0.35 [0.22, 0.47]
Valsky 2012	210	334	3.6%	0.63 [0.58, 0.68]
Murakoshi 2012	96	152	3.3%	0.63 [0.55, 0.71]
Rustico 2012	61	150	3.3%	0.41 [0.33, 0.49]
Swiatkowska-Freund 2012	38	85	3.0%	0.45 [0.34, 0.55]
Chang 2012	22	44	2.5%	0.50 [0.35, 0.65]
Liu 2012	17	33	2.2%	0.52 [0.34, 0.69]
Subtotal (95% CI)		**1704**	**53.7%**	**0.51 [0.45, 0.57]**
Total events	910			
Heterogeneity: I^2 = 83%				
Time group 5 (2011-2014)				
Tchirikov 2011	62	80	3.2%	0.78 [0.68, 0.87]
Ruano 2013	57	102	3.1%	0.56 [0.47, 0.66]
Baud 2013	187	325	3.5%	0.58 [0.52, 0.63]
Baschat 2013	88	147	3.3%	0.60 [0.52, 0.68]
Slaghekke 2014	168	272	3.5%	0.62 [0.56, 0.68]
Subtotal (95% CI)		**926**	**16.6%**	**0.62 [0.56, 0.69]**
Total events	562			
Heterogeneity: I^2 = 73%				
Total (95% CI)		**3868**	**100.0%**	**0.52 [0.48, 0.56]**
Total events	2109			
Heterogeneity: I^2 = 84%				

Test for subgroup differences: $Chi^2 = 25.42$, df = 4 ($P < 0.0001$), $I^2 = 84.3\%$



2b

Study or Subgroup	Events	Total	Weight	Survival Rate [95% CI]
Time group 1 (1990-1995)				
Ville 1995	19	45	2.0%	0.42 [0.28, 0.57]
De Lia 1995	9	26	1.4%	0.35 [0.16, 0.53]
Subtotal (95% CI)		**71**	**3.4%**	**0.39 [0.28, 0.51]**
Total events	28			
Heterogeneity: I^2 = 0%				
Time group 2 (1996-2000)				
De Lia 1999	17	67	2.8%	0.25 [0.15, 0.36]
Quintero 2000	35	89	2.9%	0.39 [0.29, 0.50]
Hecher 2000	61	200	3.9%	0.30 [0.24, 0.37]
Subtotal (95% CI)		**356**	**9.5%**	**0.32 [0.25, 0.39]**
Total events	113			
Heterogeneity: I^2 = 45%				
Time group 3 (2001-2005)				
Huber 2006	48	200	4.0%	0.24 [0.18, 0.30]
Gray 2006	15	31	1.5%	0.48 [0.31, 0.66]
Quintero 2007	40	193	4.0%	0.21 [0.15, 0.26]
Middeldorp 2007	23	100	3.3%	0.23 [0.15, 0.31]
Stirneman 2008	94	287	4.1%	0.33 [0.27, 0.38]
Subtotal (95% CI)		**811**	**17.0%**	**0.27 [0.21, 0.34]**
Total events	220			
Heterogeneity: I^2 = 75%				
Time group 4 (2006-2010)				
Sepulveda 2007	16	33	1.6%	0.48 [0.31, 0.66]
Ierullo 2007	26	77	2.8%	0.34 [0.23, 0.44]
Cincotta 2009	19	100	3.5%	0.19 [0.11, 0.27]
Ruano 2009	10	19	1.1%	0.53 [0.30, 0.76]
Chmait 2010	19	99	3.5%	0.19 [0.11, 0.27]
Yang 2010	7	30	1.8%	0.23 [0.08, 0.39]
Meriki 2010	23	75	2.8%	0.31 [0.20, 0.41]
Morris 2010	76	164	3.5%	0.46 [0.39, 0.54]
Lombardo 2011	16	70	2.9%	0.23 [0.13, 0.33]
Weingertner 2011	33	100	3.1%	0.33 [0.24, 0.42]
Delabaere 2011	14	49	2.3%	0.29 [0.16, 0.41]
Hernandez-Andrade 2011	10	35	1.9%	0.29 [0.13, 0.44]
Swiatkowska-Freund 2012	27	85	2.9%	0.32 [0.22, 0.42]
Chang 2012	13	44	2.1%	0.30 [0.16, 0.43]
Liu 2012	5	33	2.3%	0.15 [0.02, 0.28]
Sundberg 2012	28	55	2.2%	0.51 [0.38, 0.64]
Valsky 2012	87	334	4.3%	0.26 [0.21, 0.31]
Murakoshi 2012	45	152	3.6%	0.30 [0.22, 0.37]
Rustico 2012	50	150	3.5%	0.33 [0.26, 0.41]
Subtotal (95% CI)		**1704**	**51.5%**	**0.31 [0.26, 0.35]**
Total events	524			
Heterogeneity: I^2 = 71%				
Time group 5 (2011-2014)				
Tchirikov 2011	15	80	3.2%	0.19 [0.10, 0.27]
Baud 2013	96	325	4.2%	0.30 [0.25, 0.35]
Ruano 2013	25	102	3.3%	0.25 [0.16, 0.33]
Baschat 2013	41	147	3.6%	0.28 [0.21, 0.35]
Slaghekke 2014	65	272	4.2%	0.24 [0.19, 0.29]
Subtotal (95% CI)		**926**	**18.6%**	**0.26 [0.22, 0.29]**
Total events	242			
Heterogeneity: I^2 = 29%				
Total (95% CI)		**3868**	**100.0%**	**0.29 [0.27, 0.32]**
Total events	1127			
Heterogeneity: I^2 = 67%				
Test for subgroup differences: Chi^2 = 7.92, df = 4 (P = 0.09), I^2 = 49.5%				



this true effect is to perform a randomized controlled trial adequately powered for perinatal survival.

Previous two pages figure 2 a Forest plot showing double twin survival rates over 25 years of laser therapy for TTTS subdivided into 5-year time periods. **b** Forest plot showing single twin survival rates over 25 years of laser therapy for TTTS subdivided into 5-year time periods.

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 [57].

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 a 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 maternal-fetal medicine centers has been advocated. With the most recent survival rates as a benchmark, (real-time) monitoring and quality control are essential to prevent a more widespread use of this technique, at least temporarily, from leading to less favorable 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 [60].

With this study we hope to set a benchmark level which established and starting centers can compare their individual results with. Regular structural reflection on one's 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 to publish their series in order to keep updating the benchmark for other centers [61].

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 into the important complications of laser treatment, it is crucial 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.

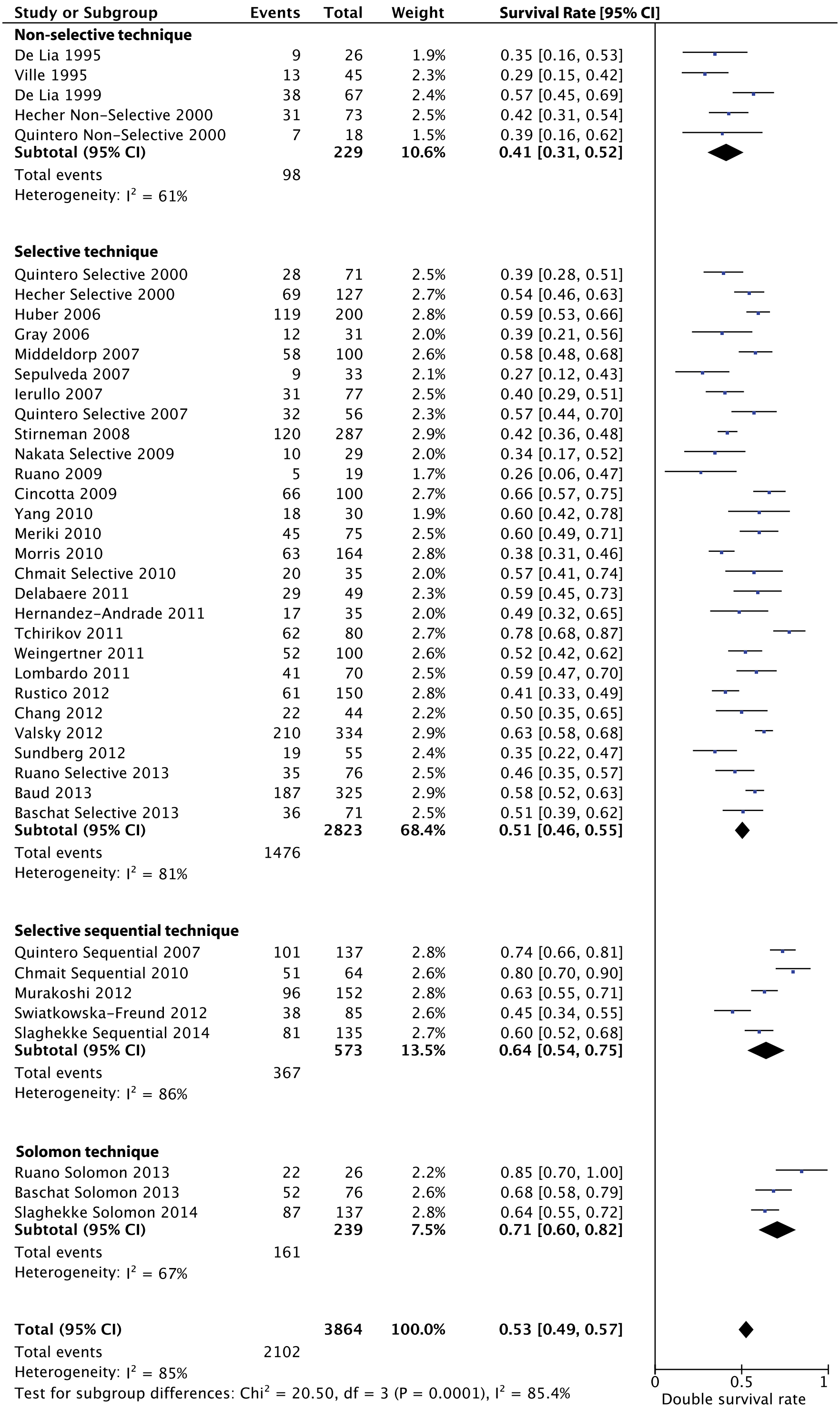
This study has some important limitations. Our findings could be influenced by publication bias. Centers that are still in their learning curve, or otherwise have less favorable results, might be hesitant to publish their series when they underperform compared to the published series of established centers. Also, the data may reflect selection bias. Less experienced centers may only treat less difficult cases and refer difficult cases to experienced centers, resulting in better survival in their centers and decreased survival in the latter.

The past decades have also shown significant improvements regarding (early) neonatal care resulting in overall better outcomes after preterm birth [62-64]. 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. The value of meta-analysis is highly dependent on the quality of the included studies. Most of the introduced techniques and adaptations have not been evaluated in randomized controlled trials. Comparison of survival outcomes of different

3a



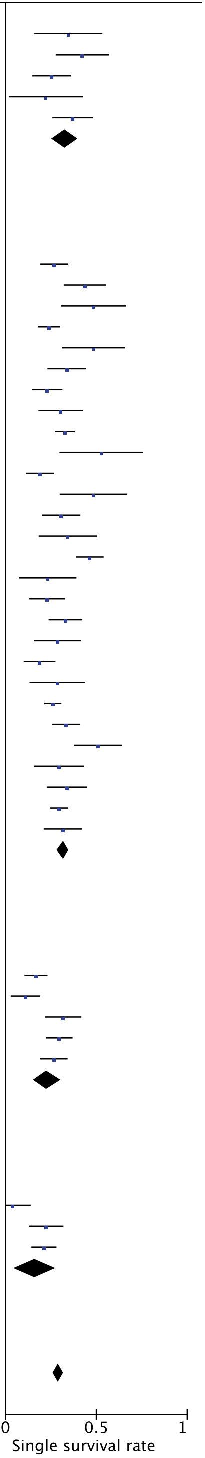
Study or Subgroup	Events	Total	Weight	Survival Rate [95% CI]
Non-selective technique				
De Lia 1995	9	26	1.9%	0.35 [0.16, 0.53]
Ville 1995	13	45	2.3%	0.29 [0.15, 0.42]
De Lia 1999	38	67	2.4%	0.57 [0.45, 0.69]
Hecher Non-Selective 2000	31	73	2.5%	0.42 [0.31, 0.54]
Quintero Non-Selective 2000	7	18	1.5%	0.39 [0.16, 0.62]
Subtotal (95% CI)		**229**	**10.6%**	**0.41 [0.31, 0.52]**
Total events	98			
Heterogeneity: I^2 = 61%				
Selective technique				
Quintero Selective 2000	28	71	2.5%	0.39 [0.28, 0.51]
Hecher Selective 2000	69	127	2.7%	0.54 [0.46, 0.63]
Huber 2006	119	200	2.8%	0.59 [0.53, 0.66]
Gray 2006	12	31	2.0%	0.39 [0.21, 0.56]
Middeldorp 2007	58	100	2.6%	0.58 [0.48, 0.68]
Sepulveda 2007	9	33	2.1%	0.27 [0.12, 0.43]
Ierullo 2007	31	77	2.5%	0.40 [0.29, 0.51]
Quintero Selective 2007	32	56	2.3%	0.57 [0.44, 0.70]
Stirneman 2008	120	287	2.9%	0.42 [0.36, 0.48]
Nakata Selective 2009	10	29	2.0%	0.34 [0.17, 0.52]
Ruano 2009	5	19	1.7%	0.26 [0.06, 0.47]
Cincotta 2009	66	100	2.7%	0.66 [0.57, 0.75]
Yang 2010	18	30	1.9%	0.60 [0.42, 0.78]
Meriki 2010	45	75	2.5%	0.60 [0.49, 0.71]
Morris 2010	63	164	2.8%	0.38 [0.31, 0.46]
Chmait Selective 2010	20	35	2.0%	0.57 [0.41, 0.74]
Delabaere 2011	29	49	2.3%	0.59 [0.45, 0.73]
Hernandez-Andrade 2011	17	35	2.0%	0.49 [0.32, 0.65]
Tchirikov 2011	62	80	2.7%	0.78 [0.68, 0.87]
Weingertner 2011	52	100	2.6%	0.52 [0.42, 0.62]
Lombardo 2011	41	70	2.5%	0.59 [0.47, 0.70]
Rustico 2012	61	150	2.8%	0.41 [0.33, 0.49]
Chang 2012	22	44	2.2%	0.50 [0.35, 0.65]
Valsky 2012	210	334	2.9%	0.63 [0.58, 0.68]
Sundberg 2012	19	55	2.4%	0.35 [0.22, 0.47]
Ruano Selective 2013	35	76	2.5%	0.46 [0.35, 0.57]
Baud 2013	187	325	2.9%	0.58 [0.52, 0.63]
Baschat Selective 2013	36	71	2.5%	0.51 [0.39, 0.62]
Subtotal (95% CI)		**2823**	**68.4%**	**0.51 [0.46, 0.55]**
Total events	1476			
Heterogeneity: I^2 = 81%				
Selective sequential technique				
Quintero Sequential 2007	101	137	2.8%	0.74 [0.66, 0.81]
Chmait Sequential 2010	51	64	2.6%	0.80 [0.70, 0.90]
Murakoshi 2012	96	152	2.8%	0.63 [0.55, 0.71]
Swiatkowska-Freund 2012	38	85	2.6%	0.45 [0.34, 0.55]
Slaghekke Sequential 2014	81	135	2.7%	0.60 [0.52, 0.68]
Subtotal (95% CI)		**573**	**13.5%**	**0.64 [0.54, 0.75]**
Total events	367			
Heterogeneity: I^2 = 86%				
Solomon technique				
Ruano Solomon 2013	22	26	2.2%	0.85 [0.70, 1.00]
Baschat Solomon 2013	52	76	2.6%	0.68 [0.58, 0.79]
Slaghekke Solomon 2014	87	137	2.8%	0.64 [0.55, 0.72]
Subtotal (95% CI)		**239**	**7.5%**	**0.71 [0.60, 0.82]**
Total events	161			
Heterogeneity: I^2 = 67%				
Total (95% CI)		**3864**	**100.0%**	**0.53 [0.49, 0.57]**
Total events	2102			
Heterogeneity: I^2 = 85%				

Test for subgroup differences: Chi^2 = 20.50, df = 3 (P = 0.0001), I^2 = 85.4%

3b

Study or Subgroup	Events	Total	Weight	Survival Rate [95% CI]
Non-selective technique				
De Lia 1995	9	26	1.5%	0.35 [0.16, 0.53]
Ville 1995	19	45	1.9%	0.42 [0.28, 0.57]
De Lia 1999	17	67	2.5%	0.25 [0.15, 0.36]
Quintero Non-Selective 2000	4	18	1.3%	0.22 [0.02, 0.43]
Hecher Non-Selective 2000	27	73	2.4%	0.37 [0.26, 0.48]
Subtotal (95% CI)		**229**	**9.6%**	**0.33 [0.25, 0.40]**
Total events	76			
Heterogeneity: $I^2 = 22\%$				
Selective technique				
Hecher Selective 2000	34	127	2.9%	0.27 [0.19, 0.35]
Quintero Selective 2000	31	71	2.3%	0.44 [0.32, 0.55]
Gray 2006	15	31	1.6%	0.48 [0.31, 0.66]
Huber 2006	48	200	3.2%	0.24 [0.18, 0.30]
Sepulveda 2007	16	33	1.6%	0.48 [0.31, 0.66]
Ierullo 2007	26	77	2.5%	0.34 [0.23, 0.44]
Middeldorp 2007	23	100	2.8%	0.23 [0.15, 0.31]
Quintero Selective 2007	17	56	2.2%	0.30 [0.18, 0.43]
Stirneman 2008	94	287	3.3%	0.33 [0.27, 0.38]
Ruano 2009	10	19	1.1%	0.53 [0.30, 0.76]
Cincotta 2009	19	100	2.9%	0.19 [0.11, 0.27]
Nakata Selective 2009	14	29	1.5%	0.48 [0.30, 0.67]
Meriki 2010	23	75	2.5%	0.31 [0.20, 0.41]
Chmait Selective 2010	12	35	1.8%	0.34 [0.18, 0.50]
Morris 2010	76	164	2.9%	0.46 [0.39, 0.54]
Yang 2010	7	30	1.8%	0.23 [0.08, 0.39]
Lombardo 2011	16	70	2.6%	0.23 [0.13, 0.33]
Weingertner 2011	33	100	2.7%	0.33 [0.24, 0.42]
Delabaere 2011	14	49	2.1%	0.29 [0.16, 0.41]
Tchirikov 2011	15	80	2.8%	0.19 [0.10, 0.27]
Hernandez-Andrade 2011	10	35	1.8%	0.29 [0.13, 0.44]
Valsky 2012	87	334	3.4%	0.26 [0.21, 0.31]
Rustico 2012	50	150	3.0%	0.33 [0.26, 0.41]
Sundberg 2012	28	55	2.1%	0.51 [0.38, 0.64]
Chang 2012	13	44	2.0%	0.30 [0.16, 0.43]
Baschat Selective 2013	24	71	2.4%	0.34 [0.23, 0.45]
Baud 2013	96	325	3.3%	0.30 [0.25, 0.35]
Ruano Selective 2013	24	76	2.5%	0.32 [0.21, 0.42]
Subtotal (95% CI)		**2823**	**67.6%**	**0.32 [0.29, 0.35]**
Total events	875			
Heterogeneity: $I^2 = 66\%$				
Selective sequential technique				
Quintero Sequential 2007	23	137	3.1%	0.17 [0.10, 0.23]
Chmait Sequential 2010	7	64	2.9%	0.11 [0.03, 0.19]
Swiatkowska-Freund 2012	27	85	2.6%	0.32 [0.22, 0.42]
Murakoshi 2012	45	152	3.0%	0.30 [0.22, 0.37]
Slaghekke Sequential 2014	36	135	3.0%	0.27 [0.19, 0.34]
Subtotal (95% CI)		**573**	**14.5%**	**0.23 [0.15, 0.31]**
Total events	138			
Heterogeneity: $I^2 = 80\%$				
Solomon technique				
Ruano Solomon 2013	1	26	2.6%	0.04 [0.00, 0.14]
Baschat Solomon 2013	17	76	2.6%	0.22 [0.13, 0.32]
Slaghekke Solomon 2014	29	137	3.1%	0.21 [0.14, 0.28]
Subtotal (95% CI)		**239**	**8.3%**	**0.16 [0.05, 0.27]**
Total events	47			
Heterogeneity: $I^2 = 80\%$				
Total (95% CI)		**3864**	**100.0%**	**0.29 [0.26, 0.32]**
Total events	1136			
Heterogeneity: $I^2 = 74\%$				

Test for subgroup differences: $Chi^2 = 10.57$, df = 3 (P = 0.01), $I^2 = 71.6\%$



techniques based on data from non-comparative observational studies is potentially hampered by high interstudy heterogeneity, as found in this study. Due to the nature of the data, statistical correction is impossible. Interpretation of the results should be done with caution and can only be used to generate hypotheses.

Previous two pages figure 3 a Forest plot showing double twin survival rates subdivided by the laser technique used. **b** Forest plot showing single twin survival rates subdivided by the laser technique used.

The 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 81- 88% of pregnancies and survival of both twins in 52-54% of pregnancies. The median GA at delivery in these series was 32.4 weeks. Nevertheless, we believe that 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 [65].

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 [66]. 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 the field of laparoscopic surgery, appear 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 was supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organization for Scientific Research (NWO), which is partly funded by the Ministry of Economic Affairs.

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PUBLISHED IN: ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 2015; 45(2): 168-74

Chapter 2

A Worldwide Survey of Laser Surgery for Twin-Twin Transfusion Syndrome

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.

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).

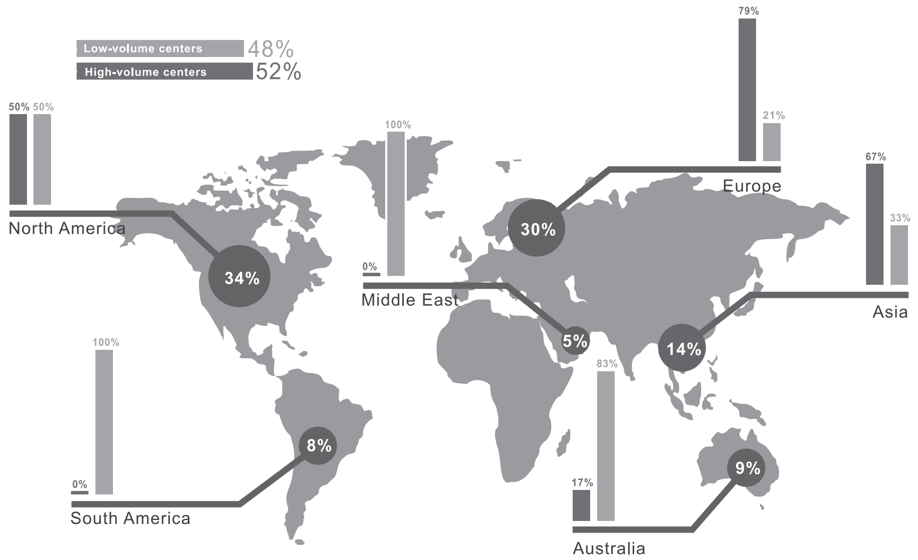

Figure 1 Geographical location of respondents and corresponding distribution of low-volume (n = 31, 48%) (▨) vs high-volume (n = 33, 52%) (■) fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

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.

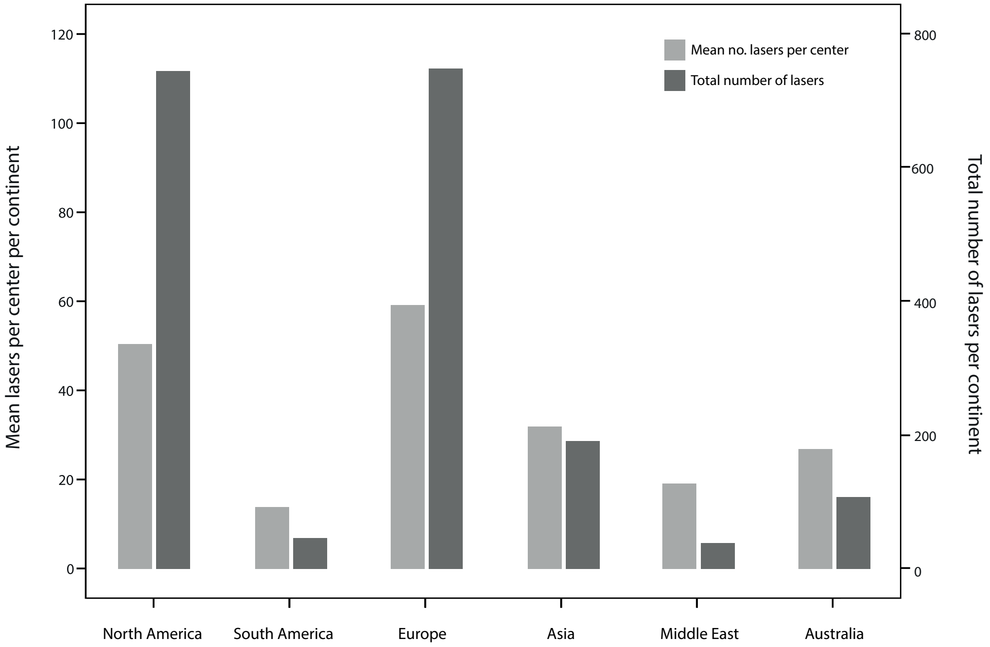

Figure 2 Total number of reported annual laser procedures (▨) according to geographical area and corresponding mean number of procedures per center (■) in fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

Table 1 describes the demographics of the respondents. No significant differences in geographic distribution existed between responders and non-responders. 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

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)

Table 1 Demographic characteristics of study population of 76 fetal therapy specialists. Data are given as *n* (%), median interquartile range or mean ± SD.

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.

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).

Characteristic	All (n = 64)	Type of center		P
		High-volume (n = 33)*	Low-volume (n = 31)†	
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

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

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.

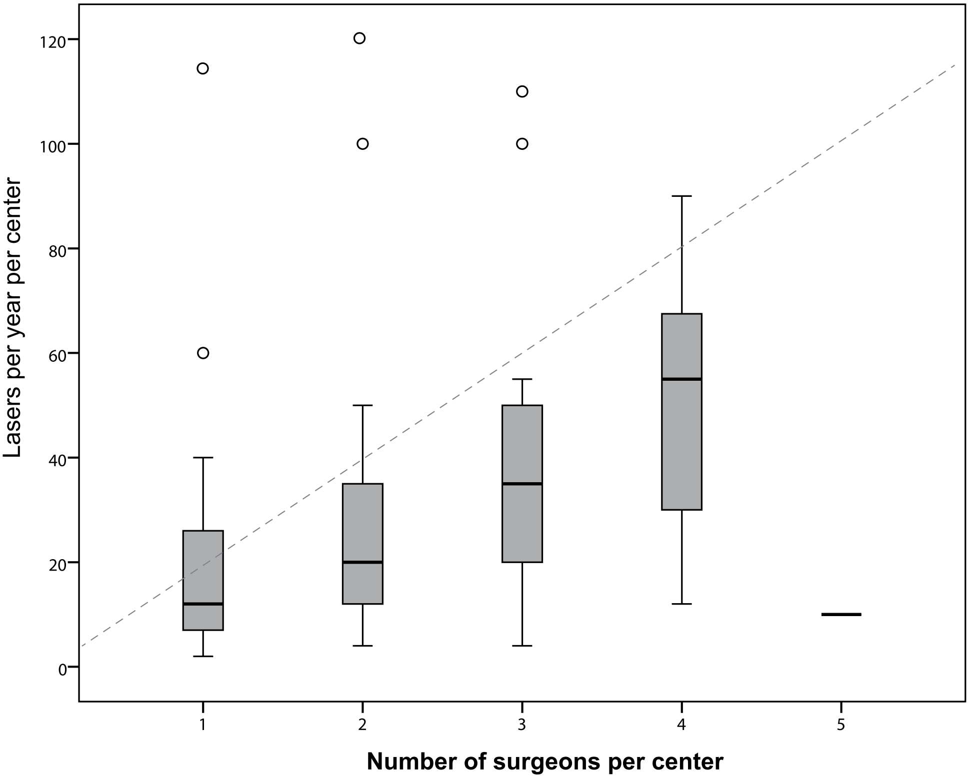

Figure 3 Box-and-whisker plots of number of surgeons per fetal therapy center according to number of procedures performed annually in centers offering laser treatment for twin–twin transfusion syndrome. Boxes represent median and interquartile range, whiskers are range excluding outliers and circles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

Therapist and center section	Options
Gender	• Male • Female
Age	• < 35 years • 36-45 years • 46-55 years • > 56 years
What is your medical specialty?	• Obstetrics/Gynaecology • Pediatric Surgery • Other, please specify below
Years of practice in OB/Gyn or Pediatric Surgery after residency or training period.	• 1-5 years • 6-10 years • > 10 years
Which best describes your current center?	• University hospital • Private hospital tertiary care facility • Private practice referral center • Other
Geographical location of your center?	• North America • South America • Europe • Asia • Australia
How many TTTS cases does your center see yearly?	• 0-20 cases • 21-60 cases • 61-100 cases • > 100 cases
How many laser procedures are annually performed at your center?	• 0-20 procedures • 21-60 procedures • 61-100 procedures • > 100 procedures
How many fetal surgeons perform laser therapy in your center?	• 1 • 2 • 3 • 4 • 5 • > 5
How many years have you been performing ultrasound guided invasive obstetric procedures? (intra uterine transfusion, chorionic villus sampling, amniocentesis)	• 1-5 years • 6-10 years • > 10 years
How many years have you been performing laser therapy for TTTS?	• 1-5 years • 6-10 years • > 10 years
How many laser procedures do you perform annually?	• < 10 procedures • 11-20 procedures • 21-40 procedures • 41-60 procedures • > 60 procedures
Do you perform other interventions in twin pregnancies (IUT, RFA, cord coagulation, etc)? If yes, please specify.	• Yes • No
Where is the laser procedure performed at your center?	• Dedicated fetal surgery room • General operating room • Other, please specify below

Appendix S1 Therapist and center section

Techniques section	Options
What is your cerclage policy in case of laser treatment?	• Never • Only with a cervical length 15-25mm • Only in case of dilatation • Always • Other, please specify below
What is the preferred type of anaesthesia used during the procedure?	• General anaesthesia • Regional anaesthesia (epidural/spinal) • Local anaesthesia with sedation • Local anaesthesia without sedation • Other, please specify below
What is the preferred entry type used for the fetoscope?	• Percutaneous via trocar insertion • Percutaneous via Seldinger technique • Mini laparotomy • Other, please specify below
What is the preferred laser technique used in case of posterior placenta position?	• Selective laser coagulation of placental vessels • Selective sequential laser coagulation of placental vessels • Solomon technique with sequential laser coagulation • Solomon technique • Other, please specify below
What is the preferred laser technique used in case of anterior placenta position?	• Selective laser coagulation of placental vessels • Selective sequential laser coagulation of placental vessels • Solomon technique with sequential laser coagulation • Solomon technique • Other, please specify below
In case of amnioreduction during laser procedure, how much amniotic fluid is drained?	• Until SDP $\leq$ 8 cm • Until SDP $\leq$ 6 cm • Until SDP $\leq$ 4 cm • Other, please specify below
Is post-partum placental color dye injection standard procedure in your center in order to detect residual anastomoses?	• Yes • No

Appendix S2 Techniques section

Instrumentation section	Options
What type and diameter of endoscope is used under 16 weeks gestation?	
What type and diameter of operating sheat / trocar is used under 16 weeks gestation?	
What type and diameter of endoscope is used after 16 weeks gestation in case of posterior placenta?	
What type and diameter of operating sheat / trocar is used after 16 weeks gestation in case of posterior placenta?	
What type and diameter of endoscope is used after 16 weeks gestation in case of anterior placenta?	
What type and diameter of operating sheat / trocar is used after 16 weeks gestation in case of anterior placenta?	
What type of laser is used at your center? (multiple selection possible)	• Nd:YAG laser • Diode laser • Other, please specify below
Is there a cervical length below which you will NOT offer/perform laser for TTTS? If Yes, please specify this cervical length.	• • No • Yes
Is there a BMI level above which you will NOT offer/perform laser for TTTS? If Yes, please specify this BMI value.	• • No • Yes
Will you offer / perform laser for TTTS if an amnioreduction has been done previously?	• • No • Yes
Will you offer/ perform laser for TTTS in Triplets?	• • No • Yes
Excluding PPROM and active labour. Are there any other criteria which will exclude a patient from being offered laser at your centre? If yes, please specify.	• • No • Yes
Will you offer selective TOP via cord occlusion as an alternative to laser for TTTS?	• • No • Yes
Will you offer laser in cases of severe MC growth discordance (in absence of diagnostics of TTTS)?	• • No • Yes
For an anterior placenta, what is the upper limit at which you will offer/ perform laser for TTTS? Specify: wks/days	…weeks …days
For a posterior placenta, what is the upper limit at which you will offer/ perform laser for TTTS? Specify: wks/days	…weeks …days
For an anterior placenta, what is the lower limit at which you will offer/ perform laser for TTTS? Specify: wks/days	…weeks …days
For a posterior placenta, what is the lower limit at which you will offer/ perform laser for TTTS? Specify: wks/days	…weeks …days

Appendix S3 Instrumentation section

PART THREE

Technique and Technology

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Chapter 3

Is the Sequential Laser Technique for Twin-to-Twin Transfusion Syndrome Truly Superior to the Standard Selective Technique? A Meta-Analysis

ABSTRACT

Background and Objective

To investigate the efficacy of sequential laser coagulation in the treatment of twin-twin transfusion syndrome (TTTS).

Data Sources

MEDLINE, EMBASE and the Cochrane Library were systematically searched for comparative studies on the efficacy of sequential versus standard selective laser coagulation for TTTS. The primary outcome measure in these studies was survival of at least one twin, both twins and fetal demise.

Results

Three cohort studies comparing the selective laser treatment technique (n = 120) versus the sequential technique (n = 224) in 344 monochorionic twin pregnancies were included. Mean survival of at least one twin was 88% in the selective group versus 92% ($p = 0.22$) in the sequential group. Mean survival of both twins was lower in the selective group (52%) than in the sequential group (75%) ($p = 0.002$). Donor fetal demise decreased from 34% in the selective to 10% in the sequential group ($p < 0.01$), and recipient fetal demise decreased from 16 to 7% ($p = 0.02$).

Conclusion

Limited evidence suggests improved double neonatal survival as well as decreased donor and recipient fetal demise with the use of the sequential technique. However, these results are based on small non-randomized studies with evident forms of bias and methodological limitations. A randomized controlled trial to assess the efficacy of sequential laser technique is therefore required.

INTRODUCTION

Laser surgery is the accepted treatment of choice for twin-twin transfusion syndrome (TTTS). However, results are still far from satisfactory, with mortality rates varying from 20 to 48% [1] and significant neurodevelopmental problems in 6-18% of surviving children [2, 3]. Important complications include iatrogenic preterm premature rupture of membranes [4] resulting in preterm delivery, twin anemia-polycythemia sequence [5] and recurrence or reversal of TTTS [6].

Since the first publications on fetoscopic laser surgery by De Lia et al. [7] in 1990, several technical and surgical modifications have been described. In 1998, Quintero et al. [8] introduced the selective laser coagulation technique and in 2007 they proposed the sequential selective laser coagulation technique [9]. The rationale for selective laser, now adopted by most fetal treatment centers, is 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 as was commonly done in the early years. Sequential selective laser is an adaptation of this technique whereby anastomoses are coagulated in a specific order. The theoretical benefit 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 occlusion of the arteriovenous anastomoses from recipient to donor and finally occlusion of the arterioarterial (AA) and the venovenous (VV) anastomoses, if present.

According to Quintero et al. [9], this sequential strategy improves the rate of double survival. However, the quality of evidence to support this finding is limited and well-controlled trials are lacking. 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. In order to assess the potential benefit of this technique, we performed a meta-analysis based on the published studies comparing the sequential selective with the (standard) selective technique.

DATA SOURCES

Prior to the meta-analysis, we created a detailed protocol that included the search strategies, inclusion and exclusion criteria, outcome parameters, and methods of statistical analysis. This meta-analysis of selective versus sequential laser in TTTS was performed according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [10], and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11].

Literature Search

An initial literature search on studies comparing selective laser versus sequential laser was conducted in MEDLINE, EMBASE and the Cochrane Library using PubMed and OVID search engines without restriction on the language of publication. Key words and free text searches were performed with combinations of the following key words: twin-to-twin transfusion syndrome, TTTS, fetofetal transfusion, laser, 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.

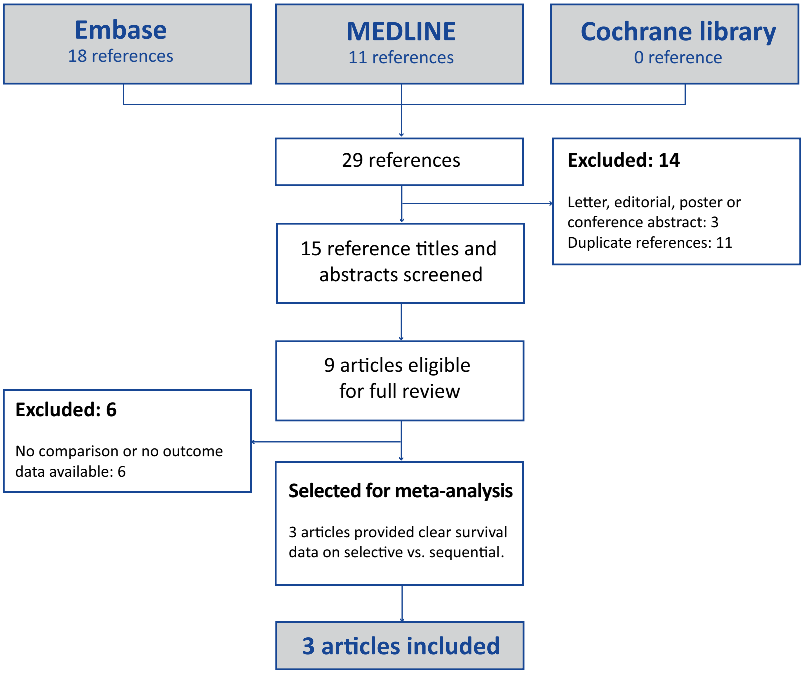


Figure 1 Flow diagram according to the PRISMA statement.

Inclusion and Exclusion Criteria

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

Selection and Data Extraction

Studies presenting data on twin pregnancies with confirmed monochorionicity by first-trimester ultrasound, affected by TTTS according to either the Eurofetus criteria [12] or the criteria described by Quintero et al. [13], treated with either selective or selective sequential fetoscopic laser coagulation of vascular anastomoses were included.

Studies were selected when presenting the number of patients treated, inclusion dates, laser technique used, survival rate of both twins, survival rate of one twin and overall survival defined as alive at 28 days after birth. Other important parameters were donor fetal demise, recipient fetal demise, gestational age at surgery and at birth and operative characteristics such as placenta localization and operating time. Studies that presented incomplete data were excluded.

Primary and Secondary Outcomes

Series were primarily analyzed for differences in survival of at least one twin, of both twins, and recipient or donor fetal demise with respect to treatment allocation. Furthermore, analyses were performed on operating time, gestational age at laser and at birth.

Series	Year	Method	n	Period	2 survivors	1 survivor	At least 1 survivor	Mean GA at birth	NOQAS
Quintero et al.	2007	sequential	137	2003 - 2005	101 (74%)	23 (17%)	91%	33.7 (4.4)	5
		selective	56		32 (57%)	17 (30%)	87%	33.6 (4.3)	
Nakata et al.	2009	sequential	23	2002 - 2006	15 (65%)	8 (35%)	100%	32.2 (4.1)	6
		selective	29		10 (34%)	14 (48%)	82%	31.8 (4.2)	
Chmait et al.	2010	sequential	64	2006 - 2008	51 (80%)	7 (11%)	91%	32.8 (4.7)	5
		selective	35		20 (57%)	12 (34%)	91%	31.6 (4.3)	

Table 1 Characteristics of studies comparing sequential versus selective laser therapy. GA = Gestational age (in weeks). Data are presented as n (percentage) and mean (standard deviation).

Quality Assessment and Statistical Analysis

All selected observational studies were assessed for the level of evidence provided according to criteria proposed by the Newcastle-Ottawa Quality Assessment Scale (NOQAS) [14]. We assessed the studies for methodological quality and appropriateness for inclusion without consideration of results. The studies were not assessed blindly. The review authors (J.A., S.H.P.) knew the authors' names, institutions and the sources of publication. We resolved disagreement by discussion until consensus was reached.

A meta-analysis was performed using Review Manager (RevMan) 5.2 Version 5.0 (The Nordic Cochrane Centre/The Cochrane Collaboration, Copenhagen 2008). Continuous variables were reported as the median (range) or mean (SD), and for synthesis of data, medians (range) were recalculated as mean (SD) using the method described by Hozo et al. [15]. Continuous data are presented as mean differences (MD) using inverse variance statistics with 95% confidence intervals (CI). For dichotomous data, we presented results as summary risk ratio (RR) with 95% CI.

In order to estimate the overall effect, the fixedand random-effect models were used (significance set at p = 0.05). The I2 statistic was used to assess statistical heterogeneity. An I2 value <25% was considered as low heterogeneity and an I2 value >50% as high heterogeneity. In case of low heterogeneity the fixed-effects model was used.

Statistical analysis was performed using SPSS (IBM SPSS Statistics 20 for Windows; IBM, New York 2011) and MS Excel (Microsoft Excel 2010; Microsoft, Redmond 2010). Being a literature review, no approval from our ethics committee was required 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 [11] with the total number of citations retrieved by the search strategy and the number included in the meta-analysis. A total of three studies clearly compared selective with sequential laser technique [9, 16, 17]. These three studies were pooled for meta-analysis of survival. Two excluded studies described sequential laser as the technique used in a proportion of their cohort but did not provide separate survival data [18, 19]. One of the excluded studies described a cohort of patients primarily treated with sequential laser surgery [20] but did not compare this with a selective laser cohort.

Study Characteristics

None of the studies enrolled were randomized controlled trials (RCTs). The three included studies were prospective cohort studies comparing the standard selective technique to the sequential technique [9, 16, 17]. A total of 344 women were included; the study sample size ranged from 52 to 193 pregnancies. The studies were conducted in the USA and Japan. The primary outcomes, neonatal survival of at least one or both twins as well as fetal demise were well defined in all included studies.

Quintero et al. [9] prospectively compared the selective technique with the sequential technique by using the latter as intended surgery technique in all cases. All cases where the sequence could not be met due to technical limitations or cases that were treated out-of-sequence were classified as standard selective.

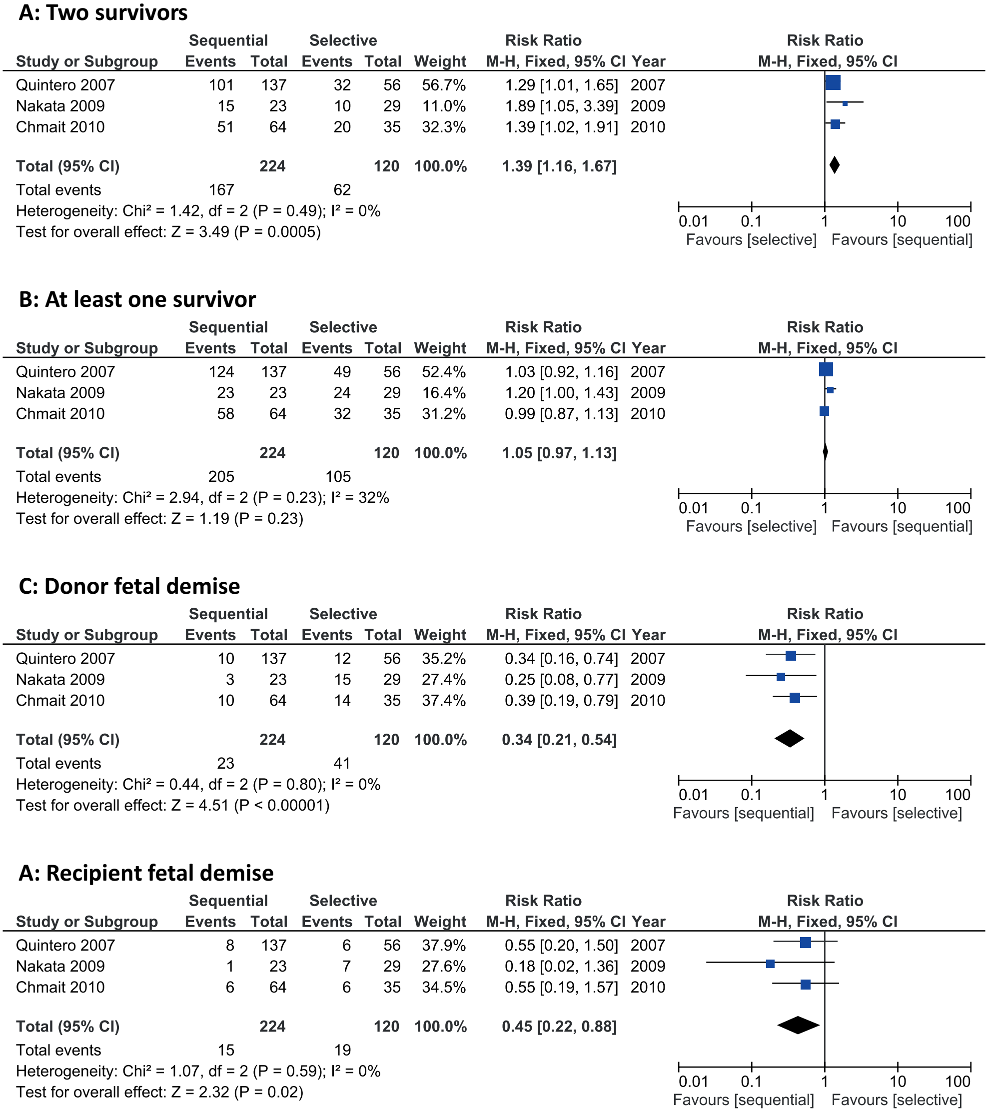
Nakata et al. [17] prospectively compared selective versus sequential technique in a subgroup of TTTS cases complicated with absent or reversed end-diastolic flow in the umbilical artery. If the sequence of coagulation was not consistent with the defined sequence, the procedure was categorized as the standard selective laser group. If the sequence of coagulation was not recorded completely because of the difficulty of identification of blood flow direction or lack of recording, the procedure was also categorized as selective.

Chmait et al. [16] attempted a sequential laser technique in all patients. The group of patients categorized as having had selective laser failed the sequential process at some point during surgery for technical reasons. Each case was categorized as having had sequential versus selective treatment directly after surgery.

All three studies used the Quintero criteria for the diagnosis of TTTS defined as the presence of polyhydramnios (maximum vertical pocket of ≥8 cm) and oligohydramnios (maximum vertical pocket of ≤2 cm). The mean gestational age at time of surgery was 20.6 weeks (SD 2.3). Two of the included studies [9, 16] used the sequential technique as proposed by Quintero et al. Nakata et al. [17] used a modification of this technique in which AA and VV anastomoses were occluded first.

Quality of Included Studies

The risk of bias in the observational studies was evaluated using the NOQAS (table 1). In the study by Chmait et al. [16] there were important baseline differences between the compared groups with significantly earlier gestational age at surgery ($p < 0.05$), less anterior placentae ($p = 0.03$) and shorter operating time ($p = 0.01$) in the sequential laser group. This problem was also seen in the publication of Quintero et al. [9] with less anterior placentae ($p < 0.01$), less arteriovenous anastomoses ($p < 0.01$) and a shorter operating time ($p < 0.01$) in the sequential laser group.



A: Two survivors

Study or Subgroup	Sequential Events	Sequential Total	Selective Events	Selective Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Quintero 2007	101	137	32	56	56.7%	1.29 [1.01, 1.65]	2007
Nakata 2009	15	23	10	29	11.0%	1.89 [1.05, 3.39]	2009
Chmait 2010	51	64	20	35	32.3%	1.39 [1.02, 1.91]	2010
Total (95% CI)		**224**		**120**	**100.0%**	**1.39 [1.16, 1.67]**	
Total events	167		62				

Heterogeneity: Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)

B: At least one survivor

Study or Subgroup	Sequential Events	Sequential Total	Selective Events	Selective Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Quintero 2007	124	137	49	56	52.4%	1.03 [0.92, 1.16]	2007
Nakata 2009	23	23	24	29	16.4%	1.20 [1.00, 1.43]	2009
Chmait 2010	58	64	32	35	31.2%	0.99 [0.87, 1.13]	2010
Total (95% CI)		**224**		**120**	**100.0%**	**1.05 [0.97, 1.13]**	
Total events	205		105				

Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.19 (P = 0.23)

C: Donor fetal demise

Study or Subgroup	Sequential Events	Sequential Total	Selective Events	Selective Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Quintero 2007	10	137	12	56	35.2%	0.34 [0.16, 0.74]	2007
Nakata 2009	3	23	15	29	27.4%	0.25 [0.08, 0.77]	2009
Chmait 2010	10	64	14	35	37.4%	0.39 [0.19, 0.79]	2010
Total (95% CI)		**224**		**120**	**100.0%**	**0.34 [0.21, 0.54]**	
Total events	23		41				

Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.51 (P < 0.00001)

A: Recipient fetal demise

Study or Subgroup	Sequential Events	Sequential Total	Selective Events	Selective Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Quintero 2007	8	137	6	56	37.9%	0.55 [0.20, 1.50]	2007
Nakata 2009	1	23	7	29	27.6%	0.18 [0.02, 1.36]	2009
Chmait 2010	6	64	6	35	34.5%	0.55 [0.19, 1.57]	2010
Total (95% CI)		**224**		**120**	**100.0%**	**0.45 [0.22, 0.88]**	
Total events	15		19				

Heterogeneity: Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

Figure 2 Comparison of selective versus sequential laser technique, main outcomes. Effects displayed as RR using Mantel-Haenszel (M-H) statistics.

Synthesis of Results

Survival

Pooling the data of the 344 cases in the included studies, we found an increased neonatal survival of both twins from 52% (n = 62/120) after use of the selective technique to 75% (n = 162/224) using the sequential technique; with an RR of 1.39; 95% CI 1.16-1.67; p < 0.01 (fig. 2a). No significant difference between the two techniques was observed for survival of at least one twin: 88% (n = 105/120) for the selective technique versus 92% (n = 205/224) for the sequential technique; RR 1.05; 95% CI 0.97-1.13; p = 0.23 (fig. 2b).

Fetal Demise

Donor demise decreased from 34% (n = 41/120) in the selective to 10% (n = 23/224) in the sequential group with an RR 0.34; 95% CI 0.21-0.54; p < 0.01 (fig. 2c). Recipient demise decreased from 16% (n = 19/120) to 7% (n = 15/224) after sequential treatment with an RR of 0.45; 95% CI 0.22-0.88; p = 0.02 (fig. 2d).

Secondary Outcomes

Meta-analysis of secondary outcomes is shown in figure 3. Mean gestational age at surgery and at birth was 21.3 (2.4) and 32.3 (4.3) weeks in the selective group versus 20.6 (2.2) and 32.9 (4.4) weeks in the sequential group. There was a significant difference in gestational age at surgery (MD -0.68; 95% CI -1.24 to -0.13; p = 0.02) between selective and sequential treatment but no difference in gestational age at birth (MD 0.47; 95% CI -0.51 to 1.44; p = 0.35). Median operating time was 60.4 min (range 47.0-90.1) in the selective group and 45.4 min (range 38.0-75.2) in the sequential group. A significant difference in mean operating time was found between the two groups (MD -12.16; 95% CI -18.22 to -6.10; p < 0.01).

Sensitivity Analysis

The findings were similar whether fixedor randomeffects models were used.

DISCUSSION

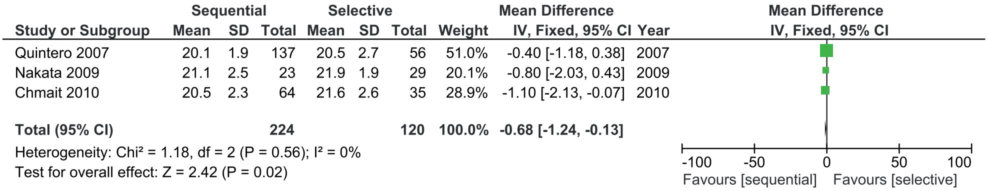
Our meta-analysis systematically summarizes the available evidence on outcomes of MC twin pregnancies complicated by TTTS undergoing either standard selective or sequential laser treatment. Unfortunately, to date, no RCTs have been published on this subject.

Primary Outcomes

Data from three prospective cohort studies [9, 16, 17] suggest that the sequential technique is beneficial over the standard selective technique with respect to dual survival and single fetal demise of donor or recipient. No significant difference was seen in survival of at least one fetus.

The theory behind the sequential laser technique is based on the concept of an intraoperative retrograde transfusion leading to hemodynamic stabilization or at least improvement of both twins. This could especially aid the severely hypovolemic donor resulting in less donor demise. However, concomitant acute volume depletion in the recipient twin might lead to higher recipient demise. The results from this meta-analysis show significant lower donor and recipient demise, which confirms the first hypothesis and appears to reject the latter.

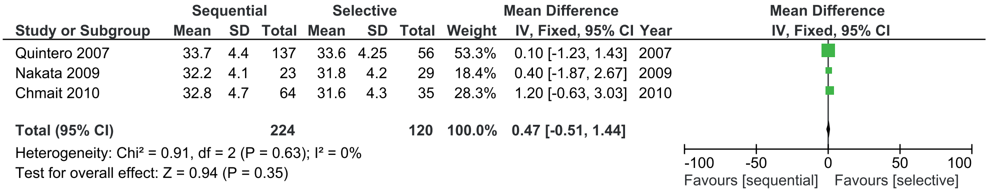
A: Gestational age at laser



	Sequential			Selective				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
Quintero 2007	20.1	1.9	137	20.5	2.7	56	51.0%	-0.40 [-1.18, 0.38]	2007	
Nakata 2009	21.1	2.5	23	21.9	1.9	29	20.1%	-0.80 [-2.03, 0.43]	2009	
Chmait 2010	20.5	2.3	64	21.6	2.6	35	28.9%	-1.10 [-2.13, -0.07]	2010	
Total (95% CI)			**224**			**120**	**100.0%**	**-0.68 [-1.24, -0.13]**		

Heterogeneity: Chi² = 1.18, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

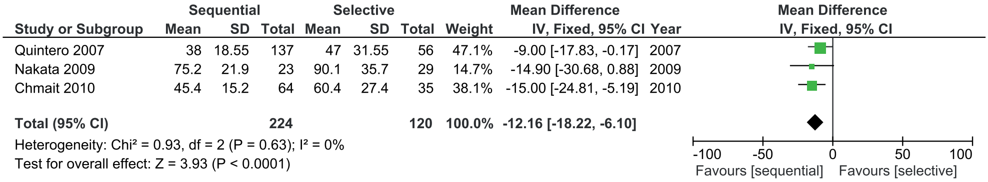
B: Gestational age at birth



	Sequential			Selective				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
Quintero 2007	33.7	4.4	137	33.6	4.25	56	53.3%	0.10 [-1.23, 1.43]	2007	
Nakata 2009	32.2	4.1	23	31.8	4.2	29	18.4%	0.40 [-1.87, 2.67]	2009	
Chmait 2010	32.8	4.7	64	31.6	4.3	35	28.3%	1.20 [-0.63, 3.03]	2010	
Total (95% CI)			**224**			**120**	**100.0%**	**0.47 [-0.51, 1.44]**		

Heterogeneity: Chi² = 0.91, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)

C: Operating time



	Sequential			Selective				Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year	IV, Fixed, 95% CI
Quintero 2007	38	18.55	137	47	31.55	56	47.1%	-9.00 [-17.83, -0.17]	2007	
Nakata 2009	75.2	21.9	23	90.1	35.7	29	14.7%	-14.90 [-30.68, 0.88]	2009	
Chmait 2010	45.4	15.2	64	60.4	27.4	35	38.1%	-15.00 [-24.81, -5.19]	2010	
Total (95% CI)			**224**			**120**	**100.0%**	**-12.16 [-18.22, -6.10]**		

Heterogeneity: Chi² = 0.93, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.93 (P < 0.0001)

Figure 3 Comparison of selective versus sequential laser technique, secondary outcomes. Effects displayed as MD using inverse variance (IV) statistics.

However, there were considerable differences in baseline characteristics between the two groups, hampering comparability. The study design used in the three studies is prone to selection bias based on the difficulty of the procedure which is shown by a significantly higher proportion of anterior placentae and longer operating time in the selective subgroup. Furthermore, Nakata et al. [17] described a method that is slightly different from the sequential laser technique described by Quintero et al. [9]. Instead of coagulating the arteriovenous anastomoses first, Nakata et al. [17] started with the AA and VV anastomoses. Although the underlying theory is the same, with this adaptation the theoretical protective function of AA anastomoses is omitted [21]. In their study, design allocation was dependent on the physician performing the procedure. Additionally, all cases where a full sequential technique could not be achieved or was not well recorded were categorized as standard selective. Furthermore, they only included TTTS cases with absent or reversed end-diastolic flow in the umbilical artery. Due to the above-mentioned forms of bias in the included studies, we believe that with the present available evidence, a clear benefit of sequential laser over standard selective is still lacking.

Secondary Outcomes

We found significant differences in gestational age at laser treatment which shows one of the important baseline differences due to the non-randomized nature of the studies. There was no significant difference in gestational age at birth, an important factor with respect to neonatal morbidity [22]. Another significant difference was seen in operating time. This parameter is largely influenced by the complexity of the procedure. We anticipated a longer operating time in the sequential group due to the more advanced form of placental mapping needed for this technique. In contrast, operating time was significantly lower in the sequential group, which could be explained by the above-mentioned methodology in the included studies where more difficult cases or unsuccessful sequential procedures were coded as selective procedures.

Evidence-Based Medicine

The sequential technique, where arteriovenous connections from donor to recipient are coagulated first, has gradually been adopted by an increasing number of centers. Although the rationale for this technique sounds solid, proper evidence for clinically relevant benefit is still lacking. Mathematical simulation by van Gemert et al. [23] supports the concept of sequential selective laser surgery. Nevertheless, the authors raise an important concern that the diameter of the anastomoses is an essential factor in defining the ideal sequence and that it might not always be beneficial to coagulate all arteriovenous anastomoses from donor to recipient first.

The ideal study design to assess the benefits of this technique would be randomization, with intention-totreat analysis, between sequential and standard selective laser coagulation of vascular anastomoses in TTTS. In 2010, Chmait et al. [16] mentioned that a multicenter randomized trial was in the making.

Due to the upsurge in fetal therapy centers providing laser therapy for TTTS resulting in more patients being treated, the importance of a solid evidence-based approach is essential. To date only three RCTs on laser therapy have been published. In 2004, Senat et al. [12] published an RCT comparing serial amnioreduction to fetoscopic laser ablation of placental vessels for the treatment of TTTS. This trial was stopped at the second interim analysis due to a significantly higher survival rate in the laser arm. In 2007, Crombleholme et al.

[24] published data on an RCT also comparing amnioreduction to laser treatment. This trial was halted by request of the investigators due to reluctance of referring clinicians to refer to centers only offering laser treatment through randomization as part of a trial. At the same time a statistical trend in adverse outcome affecting the recipient twin in the laser treatment arm was detected that ratified the decision.

In 2014, the Solomon trial [25] was published; five European fetal therapy centers including ours randomized 274 pregnancies with TTTS to receive either the standard selective (sequential) laser coagulation or the 'Solomon' method whereby following, either selective or sequential, coagulation of the anastomoses, a line was drawn with the laser across the placenta connecting the laser spots. The new technique was found, in an intention-to-treat analysis, to significantly reduce the incidence of twin anemia-polycythemia sequence and recurrence of TTTS [25]. A study with a similar design, and likely similar numbers of patients and centers, could provide more solid evidence for a benefit of the sequential technique. Whether such an effort and associated costs are considered worthwhile is open for discussion. With a theoretical and in some studies possible benefit of sequential laser and a thus far apparent lack of disadvantages, adopting this strategy without further studies could be acceptable. However, we would urge the use of a strict, prospective quality monitoring and audit system to enable reconsideration in case of an unexpected rise of adverse events.

Limitations

The clinical relevance of these results must be interpreted with caution. No RCTs were available. Most of the included studies were prospective cohort studies with designs at risk for several types of bias, as outlined above. The only option to address such limitations is to be very careful not to draw too optimistic conclusions from the meta-analysis.

Conclusion

The results of our meta-analysis show that there may be a true increased double survival rate and a decrease in the fetal demise of donor or recipient in pregnancies where the sequential technique was actually used compared to pregnancies treated with selective laser surgery. However, since the included studies comparing selective and sequential techniques were limited in number, and prone to several forms of bias, a possible benefit of sequential laser is still unproven.

ACKNOWLEDGEMENTS

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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PUBLISHED IN: PLACENTA 2017; 52; 71-76

Chapter 4

What is the Impact of Placental Tissue Damage after Laser Surgery for Twin-Twin Transfusion Syndrome? A Secondary Analysis of the Solomon Trial

ABSTRACT

Background

The introduction of the Solomon technique for the treatment of twin-twin transfusion syndrome (TTTS) increased placental exposure to laser energy. This study aims to identify the impact of power and energy used in laser treatment on placental tissue and pregnancy outcome.

Methods

Pictures of all dye-injected placentas since the start of the Solomon trial were analyzed. Placental damage was scored using a grading system including visual scar depth and affected proportion of the vascular equator. Parameters analyzed included laser power and total energy, gestational age (GA) at laser, GA at birth, laser-to-delivery interval and preterm premature rupture of membranes (PPROM).

Results

We included 122 cases in the analysis. More placental damage occurred more often in the Solomon group (42%) compared to the selective group (15%) ($p<0.001$). In multivariate analysis, more placental damage was associated with higher laser energy (regression coefficient B 0.002) but not with higher power setting (regression coefficient B -0.442). More damage was associated with earlier GA at birth (regression coefficient B -0.167), higher incidence of PPROM <32 weeks (regression coefficient B 0.003) and a shorter laser-to-delivery interval (regression coefficient B -0.168).

Conclusions

Placental damage is positively associated with more laser energy but negatively associated with higher power setting. More placental damage was associated with a lower GA at birth, shorter laser-to-delivery interval and higher PPROM rate. Whether these results should lead to a change in surgical technique requires more research, both further ex-vivo experiments on human placentas and clinical studies.

INTRODUCTION

Monochorionic (MC) twin pregnancies are high-risk pregnancies, often (10%) complicated by twin-twin transfusion syndrome (TTTS). Untreated, this condition is associated with approximately 90% perinatal mortality and severe morbidity.[1-3] Survival rates increase significantly after treatment with fetoscopic laser therapy up to 88% for at least one twin and 62% for survival of both twins, in experienced centers.[4]

In 2008, the Solomon technique was introduced as an adaptation of the selective fetoscopic laser coagulation technique for the treatment of TTTS complicated MC pregnancies. [5] The rationale behind the Solomon technique is to eliminate even the smallest anastomoses by coagulating a line between the visible anastomoses, thereby avoiding residual anastomoses leading to recurrence of TTTS or occurrence of post-laser twin anemia polycythemia sequence (TAPS). We concluded that the Solomon technique significantly reduces the incidences of recurrent TTTS and post-laser TAPS.[5]

A possible drawback of the Solomon technique is a larger surface area of the placenta being exposed to laser energy, compared to the selective laser coagulation technique (Figure 1). Animal studies suggest that superficial coagulation, in time, may lead to functional loss of the entire underlying cotyledon.[6] Little research has been conducted on the impact of laser energy and laser power setting (wattage) on the human placental tissue. Emery et al. described the effect of Solomon laser treatment after pathological analysis on a human placenta. They concluded that solomonization leads to devitalization of the chorionic plate with shallow devitalization of the underlying villi. [7]

A worldwide expert survey showed significant variation in laser power settings between centers.[8] Furthermore, it showed that the Solomon technique is gaining popularity. We therefore consider it important to investigate the impact of laser power and laser energy on placental tissue. Laser power is defined as the output wattage of the laser device that can be set by the operator. The total amount of laser energy (joule) used during a procedure is calculated automatically by the laser device and is the result of laser power and the laser time. This study aims to identify the impact of the level of laser power and the amount of energy used in laser treatment on placental tissue and pregnancy outcome.

METHODS

Data source

For this study, all cases from the Leiden University Medical Center included in the Solomon Trial[5] were used, as well as all cases treated in our national referral center after the Solomon study was concluded.

All subjects treated between 2008 and 2014 at the Leiden University Center during the Solomon trial were eligible for this study. 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 the analyses we extracted data on laser treatment specifics (including laser power, laser time and total energy usage), clinical outcome parameters and postpartum color-dye injected placenta pictures. Details on the color-dye procedure were previously reported [9].

Inclusion and exclusion criteria

All cases with an available placenta picture after selective or Solomon laser were included. Exclusion criteria were: missing documentation on both total energy and laser power setting, missing scale on the picture, single fetal demise and re-intervention laser therapy after the initial laser procedure. Cases with single fetal demise were excluded because placental maceration hampers color-dye injection. Cases with a re-intervention laser procedure were excluded because the visible damage could not be directly linked to either one of the laser procedures. Pictures from cases with a laser-to-delivery interval under seven days were excluded from grading, because these pictures showed no or little scarring.

Scoring placental tissue damage

In the absence of a validated scoring system for placental tissue damage, we developed one (Table 1) based on validated scar scales.[10, 11] The amount of damage of each grade was measured in millimeters length and expressed as percentages of the total lasered line in Solomon cases, or lasered sections in selective cases of the placenta. In pictures that had a missing scale but showed an umbilical cord clamp, the clamp was used to gauge the scale. Measurements were performed using ImageJ 1.47v software (ImageJ, National Institutes of Health, Bethesda, Maryland, USA). Placental tissue damage was defined as the summed up value of grade 2 and 3 tissue damage. These two categories most likely cover the damage that is considered to be more severe than intended with laser coagulation. Two observers (SdV and JA) assessed all pictures independently and blinded from outcome, patient and procedural parameters. Inter-observer variability was assessed calculating the intraclass correlation coefficient. In cases with an inter-observer scoring difference of >5% of the tissue damage score, the case was discussed by the observers until consensus was achieved. We used the mean value of the tissue damage scores of both observers combined for analyses.

Analysis

The influence of laser power and laser energy on placental tissue damage was analyzed. Further analyses were conducted to determine the relation of placental tissue damage, laser power and laser energy to various outcome parameters. These included gestational age (GA) at birth, laser-to-delivery interval and preterm prelabor rupture of membranes (PPROM) before 32 weeks' gestation.

Statistical analysis

Analyses were conducted using SPSS Statistics (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Analysis for risk factors, visual placental tissue damage, laser power and laser energy, influencing either the gestational age at birth, laser-to-delivery interval and PPROM under 32 weeks gestation was conducted using univariate and multivariate regression methods. Normality of all variables was asessed prior to moddeling. The potential risk factors for each of the three outcomes were studied in a univariate linear regression model. The multivariate regression model included all factors that showed significant association in the univariate analysis. Results are expressed as regression coefficients (B) with 95% confidence intervals (95%C.I.). Numerical variables with a normal distribution were expressed in mean (SD) and variables with a skewed distribution were expressed in median (range). A p-value of <0.05 was considered statistically significant.

RESULTS

Selected Cases

A total of 159 placenta pictures, documented after selective (n=44 (28%)) or Solomon (n=115 (72%)) laser coagulation, were available for this study. Included selective laser cases were treated between March 2008 - June 2012 and included Solomon cases between January 2008 - January 2014. Four cases were excluded because of single fetal demise with partial placental maceration, and three because a second laser procedure was performed. No pictures of double demise cases were available. Data on both laser power setting and total energy was missing in 17 cases, all in the Solomon group. Another 10 cases were excluded due to missing scale or inadequate quality of the picture. Finally, three pictures were excluded from grading because of a laser-to-delivery interval within 7 days. These cases were lasered at 25+3, 22+0 and 25+5 weeks GA and could not be scored due to insufficient visual placental scarring. In total, 122 placenta pictures were included in this study, 44 (36%) after selective laser and 78 (64%) after Solomon laser.

Category	Definition	**Selective Technique** median % (range)	**Solomon Technique** median % (range)	P-value
Grade 0	No visible signs of laser coagulation	70,1 (13-94)	3,4 (0-89)	<0.001
Grade 1	Membranes intact, white/brownish	15,1 (0-58)	46,2 (0-98)	<0.001
Grade 2	Membranes perforated, red	4,6 (0-31)	19,0 (0-87)	<0.001
Grade 3	Underlying tissue damaged, irregular surface	7,5 (0-59)	13,0 (0-100)	0.021
Grade 2+3	Grade 2 and 3 combined	15,1 (0-59)	41,8 (0-100)	<0.001

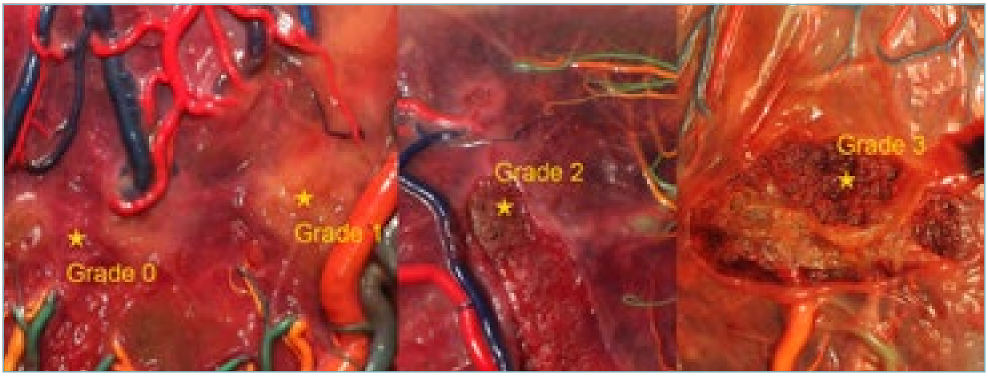

Table 1 Placental damage grading system with median damage scored per category and technique. Proportion expressed in percentages of total vascular equator. Mann-Whitney U test. The numbers in the pictures correspond with the damage grading category

Case Characteristics

The mean GA at laser was 20 (±3) weeks and mean GA at birth was 32 (±5) weeks (Table 2). Seven cases were lasered after 26 weeks' gestation, with a maximum GA at laser of 28+4 weeks. The placenta was localized posterior in 57% of the cases. Most lasers were performed for TTTS with Quintero stage 3 (49%). One of the cases involved a dichorionic triplet pregnancy, with a monochorionic component. Two placentas were lasered for the treatment of TAPS. The Nd:YAG laser (Dornier Fibertom 5100) was replaced by a diode laser (Dornier Medilas D Multibeam) in May 2013 due to regular replacement of equipment. Thirteen of the 78 Solomon cases in this study were lasered using the diode laser, generally with lower power levels compared to the Nd:YAG laser, in sub analyses laser type had no effect on the outcome of this study. All case characteristics and procedural parameters are shown in Table 2.

	All cases n=122	Selective Technique n=44	Solomon Technique n=78	P-value
Case Characteristics				
Quintero stage				
Stage 1	15 (12)	7 (16)	8 (10)	0.762
Stage 2	38 (31)	12 (27)	26 (33)	
Stage 3	60 (49)	23 (52)	37 (47)	
Stage 4	6 (5)	2 (5)	4 (5)	
Placenta localization				
Anterior	48 (39)	17 (39)	31 (40)	0.375
Posterior	69 (57)	27 (61)	42 (54)	
Lateral	4 (3)	0 (0)	4 (5)	
Anterior and posterior	1 (1)	0 (0)	1 (1)	
Laser type				
YAG	109 (89)	44 (100)	65 (83)	0.004*
Diode	13 (11)	NA	13 (17)	
GA at laser	142 (±22)	141 (±20)	143 (±23)	0.633
GA at birth	229 (±23)	228 (±26)	229 (±21)	0.775
Pregnancy prolongation	86 (±30)	87 (±29)	86 (±31)	0.900
Procedural Parameters				
Fetoscopy time (min)	28 (±11)	23 (±9)	30 (±11)	0.004
Maximum power setting (watt)	53 (±15)	55 (±12)	53 (±16)	0.477
YAG	55 (±14)	55 (±12)	56 (±15)	0.665
Diode	36 (±14)	NA	36 (±14)	NA
Total laser energy (joule)	5668 (673-32300)	2704 (673-20500)	7171 (797-32300)	<0.001*
YAG	5998 (673-32300)	2704 (673-20500)	8070 (2285-32300)	<0.001*
Diode	4175 (797-14924)	NA	4175 (797-14924)	NA
Amount anastomoses	6 (2-23)	6 (2-19)	6 (2-23)	0.841

Table 2 Baseline characteristics All categorical values are expressed as N(%). All numerical values are expressed as mean (SD) or median (range). GA laser, GA birth and Pregnancy prolongation are reported in number of days. Pregnancy prolongation is defined as the number of days of pregnancy prolongation after laser therapy until the delivery.

Grading

The 122 pictures were scored using the tissue damage grading system. The mean proportion of damage, expressed as the percentage of the total vascular equator for each grade is shown in Table 1 for both selective and Solomon cases. Placental tissue damage was found more frequently in the Solomon group (42%) compared to the selective group (15%) (p<0.001). Inter observer variability in defining grade 2 and 3 damage was good with an intraclass correlation of 0.997 (95%CI 0.995-0.998). In 5 cases we found an inter-observer grading difference of >5%, these cases were discussed by both observers blinded from procedural and outcome parameters until consensus was reached.

Variable	Univariate analysis B (95% CI)	SE	P	Multivariate analysis B (95% CI)	SE	P
Laser power	-0,256 (-0,596 - -0,070)	0,166	**0,022**	-0,442 (-0,833 - -0,050)	0,198	**0,027**
Laser energy	0,001 (0,000 - 0,002)	0,000	**<0,01**	0,002 (0,001 - 0,003)	0,000	**<0,01**
GA at laser	-0,106 (-0,335 - 0,123)	0,116	0,361	-0,072 (-0,327 - 0,183)	0,129	0,577

Table 3 Analysis of factors contributing to grade 2 and 3 damage. Values are regression coefficient B (95%CI, standard error (SE) and P.

Associations with placental damage

Analysis of factors associated with grade 2 and 3 placental tissue damage is shown in Table 3. Since gestational age at laser was strongly correlated with laser power (Pearson correlation 0.468; p<0.001), laser energy (Spearman correlation 0.297; p<0.001) and the laser-to-delivery interval (Spearman correlation -0.635; p<0.001), multivariate analyses were performed. Multivariate analysis showed that laser energy (p<0.01) was positively associated and that laser power (p=0.027) was negatively associated with more placental damage (grade 2 and 3 damage combined). The amount of grade 2 and 3 placental damage negatively affected the GA at birth as shown in Table 4 (p=0.020). Table 4 also shows that less grade 2 and 3 placental damage (p=0.020) and a lower GA at laser (p<0.01) were both associated with a longer laser-to-delivery interval in multivariate analysis. This finding was the same for PPROM <32 weeks' gestation. More grade 2 and 3 damage (p=0.031) and a lower GA at laser (p=0.028) were associated with a higher rate of early PPROM as shown in Table 4.

DISCUSSION

Main findings

In this study, we evaluated the impact of gestational age of laser, laser power, laser total energy and post-partum visual placental damage after laser treatment for TTTS on pregnancy outcome. Visual tissue damage appeared to be a significant risk factor for a higher incidence of PPROM under 32 weeks' gestation and a shorter laser-to-delivery interval and a lower GA at birth. Cases with more extensively damaged placentas more often developed PPROM and had a lower GA at birth compared to cases with less placental tissue damage. Anterior placenta localization did not lead to use of more laser energy or more placental tissue damage. More laser energy used during the procedure was associated with more extensive placental damage, whereas a higher power setting was found to lead to less damage. Furthermore, we found a significant correlation between GA at laser with laser power and laser energy used.

Variable	Univariate analysis B (95% CI)	SE	P	Multivariate analysis B (95% CI)	SE	P
Factors associated with gestational age at birth						
Laser power	0,045 (-0,233 - 0,323)	0,140	0,750	-0,021 (-0,362 - 0,319)	0,172	0,901
Laser energy	0,000 (-0,001 - 0,001)	0,000	0,821	0,000 (-0,001 - 0,001)	0,000	0,944
Grade 2 and 3 damage	-0,163 (-0,296 - -0,029)	0,067	**0,017**	-0,167 (-0,307 - -0,026)	0,071	**0,020**
GA at laser	0,093 (-0,098 - 0,283)	0,096	0,338	0,063 (-0,158 - 0,284)	0,111	0,563
Factors associated with the laser-to-delivery interval						
Laser power	-0,646 (-0,997 - -0,296)	0,177	**<0,01**	-0,036 (-0,388 - 0,315)	0,177	0,838
Laser energy	-0,001 (-0,002 - 0,000)	0,000	0,244	0,00 (-0,001 - 0,001)	0,000	0,871
Grade 2 and 3 damage	-0,137 (-0,314 - -0,041)	0,090	0,130	-0,168 (-0,306 - -0,026)	0,071	**0,020**
GA at laser	-0,907 (-1,098 - -0,717)	0,096	**<0,01**	-0,937 (-1,161 - -0,713)	0,113	**<0,01**
Factors contributing to PPROM before 32 weeks' gestation						
Laser power	0,010 (-0,016 - 0.036)	0,010	0,450	0,032 (-0,003 - 0,067)	0,018	0,073
Laser energy	0,000 (0,000 - 0,000)	0,000	0,457	0,000 (0,000 - 0,000)	0,000	0,711
Grade 2 and 3 damage	0,015 (0,001 - 0,028)	0,007	**0,030**	0,016 (0,001 - 0,030)	0,007	**0,031**
GA at laser	-0,016 (-0,036 - 0,003)	0,010	**0,049**	-0,026 (-0,05 - -0,003)	0,012	**0,029**

Table 4 Analysis of factors associated with different outcomes. Values are regression coefficient B (95%CI, standard error (SE) and P.

Interpretation

The correlation of GA at laser with laser power, and total energy is most likely explained by the fact that the superficial placental vessels increase in diameter over time, and concurrently the fetal blood volume increases during pregnancy. [12] Larger vascular diameter requires more energy to achieve successful coagulation of the vessel and a higher power setting delivers this energy more rapidly. The significant association between laser power and laser-to-delivery interval in the univariate linear regression model is explained by the strong correlation of both variables with GA at laser. Higher laser power settings are used in cases with more advanced GA and these cases are associated with shorter pregnancy prolongation than cases with laser therapy at earlier GA.

With the results of this study, we speculate that higher total energy use in laser treatment for TTTS leads to significantly more placental tissue damage. Higher laser power showed the opposite effect. We hypothesize that, with a higher power setting, energy transfer is more effective and takes shorter time and less energy than with a lower wattage. In addition, the energy is less dispersed than in a low power setting and thus leads to less collateral damage.

This study is the first to systematically evaluate and score placental damage in relation to laser power, time and total energy. Previous studies showed a relation between laser power setting and tissue damage in tissues other than placenta. Kirschbaum et al.[13] showed a significant positive correlation between laser power output and the mean cutting depth in paracardiac lung lobes of pigs. Likewise, an ex-vivo experiment on kidney models by Khoder et al. [14] showed a nearly linear increase of ablation depth with increasing laser power output. These studies were performed in an experimental setting and used interstitial laser techniques. In contrast to the laser therapy for TTTS, interstitial laser treatment is used for direct tissue destruction. Hence, tissue damage could be analyzed more precise because the effect is directly visible after treatment. With the interstitial laser technique, the transfer of energy to the tissue is direct, whereas in laser therapy for TTTS the distance between the tip of the laser fiber to the placenta highly impacts effective energy transfer.[14]

Firing distance and angle are thought to be important factors influencing effective energy transfer to the tissue. These factors are difficult to control and hard to measure in vivo. Khoder et al. [14] showed a significant reduction in ablation depth with increasing tissue distance in experimental setting. A higher power setting is necessary in order to achieve tissue ablation because laser energy is lost in the distance between the laser fiber and tissue. The true influence of firing angle is unclear. Theoretically, because the vessels are localized on the placental surface, a wide range of angles should lead to comparable energy transmission onto the vessel. Future studies should provide more knowledge about the optimal distance and angle for laser therapies.

The optimal laser power setting for laser coagulation of placental vessels is unknown.

A wide range of laser power setting and technique is used worldwide.[8] It is also unclear whether coagulating with a high laser power setting for a short time span would lead to different results than coagulating longer with a lower laser power. It is plausible that various settings lead to different tissue effects. Branisteau et al. addressed the effect of laser coagulation on placental tissue using an in-vivo ovine placenta model. Results showed that the tissue effects, in time, spread beyond the surface and induces complete functional elimination of the involved cotyledon.[6] The results of this study might imply that the operator should strive towards superficial coagulation of the placental tissue in order to obtain complete cotyledon elimination while avoiding the risk of complications as PPROM or early delivery.

In order to decrease the amount of energy used during a Solomon procedure for treating TTTS one could lower the laser power setting during coagulation between true anastomoses. More research on human placentas is necessary in order to confirm this, the results of this study, and to determine the optimal laser power setting.

Limitations

An important limitation in this study is the case selection of treated pregnancies with two live born children. This prevents us from drawing conclusions about the strong outcome measure of survival. Furthermore, documentation on laser power included only the maximum used setting. In most of the cases this is the predominant setting used during a procedure, however, in some cases the results might be influenced because the maximum setting was used for only a short time span.

Another limitation of this type of study is the retrospective nature, based on placenta pictures and not live tissue preventing us to use other anticipated important factors as number, type and caliber of anastomoses and placental weight. Finally, a wide range of pregnancy prolongation after laser was present in our sample. Scar tissue develops in time and therefore it is possible that cases with a short prolongation are graded differently than ones with a longer prolongation, even though perhaps the same scarring would have developed within more time.

Conclusion

We found a significant association between laser power and total energy used during laser treatment for TTTS and postpartum placental tissue damage. More energy leads to more damage whereas a higher power setting leads to less damage. In this study, greater tissue damage was associated with a lower GA at birth, a higher PPROM rate under 32 weeks' gestation and a shorter laser-to delivery interval. These early results of our research into detailed technical aspects of fetoscopic laser surgery should be interpreted with caution, we do not recommend changes in practice at this time. We do believe more in-depth analysis of all details of fetoscopic surgery may ultimately lead to improvements in outcome.

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 5

Impact of Laser Power and Firing Angle on Coagulation Efficiency in Laser Treatment for Twin-Twin Transfusion Syndrome? An Ex-Vivo Placenta Study

ABSTRACT

Introduction

To assess the impact of laser power and firing angle on coagulation efficiency for closing placental anastomoses in the treatment of twin-twin transfusion syndrome (TTTS).

Methods

We used an ex-vivo blood-perfused human placenta model to compare time to complete coagulation using 30W versus 50W of Nd:YAG laser power, and using a 90° versus a 45° firing angle. Placentas were perfused with pig blood at 5mL/min. Differences were analyzed using an independent samples T-test, Mann-Whitney U test and Chi-square test where appropriate.

Results

Coagulation took less time and energy using 50W(n=53) compared to 30W(n=52); 11s vs. 22s, p<0.001, and 557J vs. 659J, p=0.007. Perpendicular coagulation (n=53) took less time and energy compared to a 45°-degree angle(n=21); 11s vs. 17s, p=0.004 and 557J vs. 871J, p=0.004. Bleeding complicated 2(3%) measurements in the 50W group, 5(10%) in the 30W and 3(14%) in the 45° group.

Discussion

In a highly controlled model, a 50W laser power setting was more energy efficient than 30W in coagulating a placental vein. A more perpendicular laser firing angle resulted in more efficient coagulation. Furthermore, bleeding due to vessel wall disruption occurred more often with lower power and a more tangential approach.

INTRODUCTION

Fetoscopic laser surgery (FLS) is currently the best treatment modality for twin-twin transfusion syndrome (TTTS). De Lia et al. first proposed fetoscopic laser surgery in 1990.[1] In 2004 a randomized trial showed FLS to be superior to serial amnioreduction[2] and since then FLS has been widely adopted as the 'first-choice' treatment for TTTS.

Different types of laser and power settings have been used for this procedure. Most centers now use either a Neodymium-doped Yttrium Aluminum Garnet (Nd:YAG) laser with a 1064nm wavelength or a diode laser with a 940nm wavelength and power setting between 20 and 80 watts.[3] Both laser systems are continuously emitting laser systems with similar absorption properties. However, the optical penetration depth of the photons emitted by the diode laser is substantially lower than that of the Nd:YAG laser.[4]

In 2014 Slaghekke et al. showed that the Solomon technique, laser coagulation of the total vascular equator from one placenta margin to the other, was superior to the selective technique where only visible anastomoses are coagulated, in respect to recurrence of TTTS and incidence of post-laser twin-anemia-polycythemia sequence (TAPS).[5] With the Solomon technique, a larger surface area of the placenta is exposed to laser energy (time x power) and, in total, more energy is used during a procedure.

Laser firing angle is believed to be of importance for successful efficient coagulation.[6] The more perpendicular the laser fiber is pointed at the vessel, the faster coagulation is achieved. This is one of the reasons that choosing the optimal introduction site for the fetoscope is found to be one of the most important steps in the procedure.[7] However, the actual impact of a tangential approach has never been evaluated.

We hypothesized that faster, more efficient laser coagulation of placental vascular anastomoses would increase the safety and improve outcome in the treatment of TTTS. This study is a first step in proving this hypothesis, aiming to analyze the impact of laser power and firing angle on coagulation efficiency.

METHODS

Study design

This ex-vivo experimental human placenta study was conducted at the Department of Fetal Therapy of the Leiden University Medical Center between March 2015 and July 2015. After informed consent, term placentas from women with uncomplicated vaginal deliveries were obtained. Placentas were rinsed and stored at room temperature in a sodium chloride 0.9% solution directly after delivery. All experiments took place within 8 hours after delivery of the placenta.

Three groups of measurements were performed comparing laser power setting and laser firing angle. Group 1 consisted of measurements perpendicular to the vein with a power setting of 50 Watt. Group 2 consisted of measurement perpendicular to the vein with a 30-watt power setting and the third group of measurements was performed at a 45^o angle to the vein with a 50-watt power setting. All placentas were randomly assigned to each group.

Laser system

A Medilas Fibertom 5100 Nd:YAG laser (Dornier MedTech Europe Gmbh, Weßling, Germany) with a 1064nm wavelength was used for all experiments. A 600µm bare-tip laser fiber was used which was replaced after every 25 measurements. The laser was serviced and calibrated before the study was started.

Tissue preparation

All placentas were screened for eligible veins with a diameter of approximately 1.5 – 2.0mm, relatively straight and without branches over a 2cm length. These vessels were dissected on both ends and cannulated with a 1.4mm plastic cannula. The cannulas were kept in place with a surgical stich. The placenta samples were casted in a 2% agar solution (Sigma-Aldrich Chemie B.V., Zwijndrecht, The Netherlands) filled 12cm petri dish with the maternal side downward with a layer of agar preventing the placenta to touch the bottom of the petri dish. The adhesive character of the agar solution prevented leakage from minor defects of the basal plate. A high-definition photograph was taken of each cannulated vessel. All vessel diameters were measured using ImageJ 1.47v software (ImageJ, National Institutes of Health, Bethesda, Maryland, USA).

Experimental set-up

A diagram of the experimental set-up are shown in Figure 1. The placenta samples were

placed in a sodium chloride 0.9% bath, kept at a steady 37ºC temperature. The cannulated vein was connected to the circulation system that consisted of a calibrated syringe pump (Fresenius-Kabi Pilot C, Zeist, The Netherlands) with ± 2% flow rate accuracy, connected to a P10EZ-1 pressure sensor (Becton Dickinson Medical, Franklin Lakes, USA) and a flow sensor (Transonic clamp-on 2pxl flow sensor with a Transonic TS410 amplifier).
The laser fiber was kept in place by a system that allowed for easy and accurate adjustment, and was pointed either perpendicular or at a 45º angle at the vein. The distance between the laser fiber tip and the vein was kept at 4.0mm for each experiment.

Fresh heparinized (5.000 IU/L) pig blood with a 37ºC temperature was used to circulate the placental vein. Flow rate was set at 5ml/min. The entire circulation was checked for leaks before each experiment.

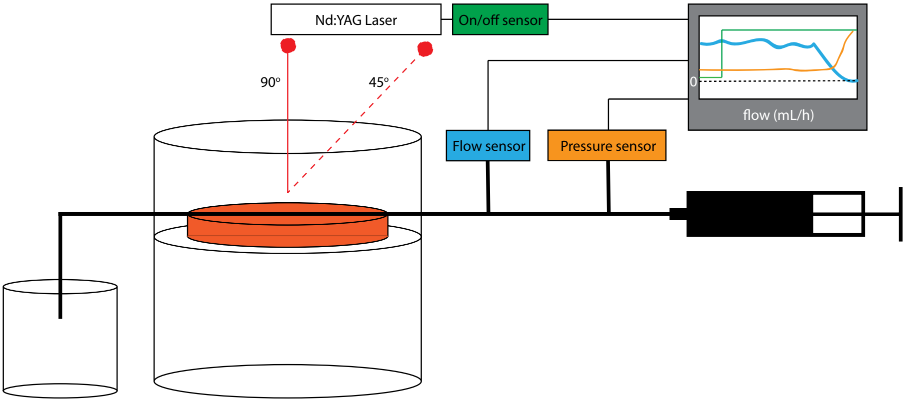

Figure 1 Diagram of the experimental set-up.

A computer program continuously measured the flow and the pressure in the circulation and the modus of the laser system (on/off). Results of these measurements were plotted on a screen in real-time. Measurements started when the laser was activated and continued until successful coagulation of the vein was achieved. Successful coagulation was defined by a drop of the flow speed below 2.5mL/min without recovery. The noise on the flow sensor signal combined with the already low flow prevented us from using a flow of 0mL/min to define stagnation of flow. Time was automatically measured between activation of the laser and stagnation of flow. Concurrently, the total energy used in each experiment was calculated based on the power setting.

Statistical analysis

Comparisons were made between group 1 and group 2, and between group 1 and group 3, with respect to time and energy used for successful coagulation defined as cessation of flow. Cases that were complicated by vessel wall disruption and bleeding were omitted from the analyses. Analyses were conducted using SPSS Statistics (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Normally distributed data were expressed as mean ± standard deviation (SD) and compared using an independent samples T-test. Skewed data were expressed as median with range and were compared using a Mann-Whitney U test. For comparison of categorical data, a Chi-square test was used. A p-value of <0.05 was considered statistically significant.

RESULTS

Out of 37 fresh human placentas, a total of 126 viable samples were retrieved. A total of 126 measurements were conducted, successful coagulation was achieved in 116 samples. All results and comparisons between groups are shown in Table 1. Figure 2 shows a sample before and during successful coagulation.

Group 1

In total 53 measurements were performed perpendicular to the vein with a 50 Watt laser power setting. In two samples (3%), bleeding occurred during coagulation of which in one case successful coagulation was achieved. 51 cases were eligible for analysis. Mean vessel diameter was 1.60 (SD 0.14) millimeter. Median time needed for cessation of flow in the vein was 11.1 seconds ranging from 1.4 to 32.8, which lead to a median energy used of 557 Joule ranging from 72 to 1639.

Group 2

Fifty-two measurements were performed perpendicular to the vein at 30 Watt power. Five cases (10%) were complicated by bleeding and in two cases successful coagulation could not be achieved. 47 cases were analyzed. Mean vessel diameter in this group was 1.6 (SD 0.12) millimeter. Median coagulation time was 22.0 seconds ranging from 8.5 to 314.4. Median energy used for coagulation was 659 Joule and ranged from 254 to 9431.

Group 3

At a 45° angle using 50 Watts laser power, 21 measurements were performed. Three samples (14%) were complicated by vessel wall disruption and in none of these successful coagulation could be accomplished. Mean vessel diameter was 1.65 (SD 0.12) millimeter and median time for coagulation was 17.4 seconds ranging from 2.6 to 78.1 leading to a median total energy used of 871 Joule, ranging from 132 to 3906.

Coagulation took significantly less time and energy using 50W laser compared to 30W (11.1 vs. 21.0s, p<0.001 and 556 vs. 659 Joule, p=0.007). Perpendicular coagulation took significantly less time and energy compared to a 45°-degree angle (11.1s vs. 17.4s, p=0.004 and 556 vs. 871 Joule, p=0.004). Vessel diameter did not differ between 50W and 30W samples (1.6 vs. 1.6 p=0.347) or between 90° and 45° samples (1.6 vs. 1.6mm p=0.223).

	Group 1 n=53	Group 2 n=52	Group 3 n=21	P-value	P-value
	50 watt 90°	30 watt 90°	50 watt 45°	1 vs 2	1 vs 3
Laser duration (seconds)	11.13 (1.43 - 32.77)	21.98 (8.49 - 314.39)	17.42 (2.64 - 78.13)	<0.001*	0.004*
Laser energy used (Joule)	556.50 (71.50 - 1638.50)	659.40 (254.70 - 9431.70)	871.25 (132.00 - 3906.50)	0.007*	0.004*
Diameter of vein (mm)	1.61 ±0.14	1.63 ±0.12	1.65 ±0.12	0.347	0.223
Complications, bleeding	2 (3%)	5 (10%)	3 (14%)	0.116**	0.104**

Table 1 Analysis of laser duration and total energy for each group. Values expressed as median (range), mean ±SD or as n(%). * Mann-Whitney U test used. ** Chi-square test used. All cases where bleeding occurred were excluded in the analyses.

DISCUSSION

This is the first study reporting on an ex-vivo perfused human placenta model to evaluate laser coagulation efficiency of different power settings for obliterating superficial placental vessels. To date, despite more than 25 years of laser surgery for TTTS, the ideal power setting for coagulation of anastomosis is unknown. Different strategies are being used, e.g. lower power setting at early gestational age at treatment or power setting dependent on size of the anastomosis.[3]

In this study we found that a higher power setting was associated with more efficient coagulation, shown by a shorter coagulation time and less energy used. In addition, we found that the firing angle significantly impacts the coagulation efficiency. A 45° angle almost doubles the amount of energy and time needed for successful coagulation compared to a perpendicular approach. With currently used equipment, optimization of the angle of approach can only be achieved by careful selection of the site of entry of the fetoscope. Innovations in instrument design may be needed to optimize the efficiency of laser coagulation in difficult cases with anterior placenta or suboptimal position of the donor.

Bleeding due to vessel wall disruption, although rare, occurred slightly more often with lower power settings and with a more tangential laser angle. We hypothesize that a low power setting used for a longer period of time causes more endothelium damage[8] and without swift occlusion of the vessel by coagulated blood, this might increase the risk of vessel wall disruption and bleeding.

Recently, Zhao et al. showed that, after a laser procedure, more chorioamnionitis and funisitis is seen compared to non-lasered monochorionic (MC) twin pregnancies. [9] A possible explanation for this finding is the iatrogenic placental tissue necrosis caused by laser coagulation that may induce a maternal inflammatory response. In their study, a trend was seen towards more chorioamnionitis with higher energy use ($p=0.06$). A previous study looked at the impact of laser coagulation on the ovine placenta with respect to local, collateral and peripheral damage at different time points after treatment.[10] This study showed that the tissue effect, especially collateral and peripheral, increases over time. Superficial vessel coagulation induced complete functional elimination of the involved cotyledon caused either by direct tissue damage and/or from arrest of cotyledonary flow, leading to ischemic necrosis. In this study, the impact of the amount of energy delivered and the relation to the tissue damage was not reported. A study evaluating different Nd:YAG power settings for the cutting and coagulation of pulmonary parenchyma with interstitial laser found that reducing the exposure time reduces local tissue coagulation even when the laser power output was increased.[11] Combining our results with previous research suggests that efficiency in the use of laser energy for laser treatment of TTTS might be beneficial and that a higher power setting and a perpendicular approach are more energy efficient, and safer, in attaining successful coagulation.

Although the highly realistic ex-vivo human placenta model we used eliminated many confounding factors, some limitations exist. The most important limitations of the model are the flow rate and the resistance of the circulation. It is difficult to accurately measure and control flow at flow rates below 5 milliliters per minute in a model. Not much is known about single anastomotic blood flow rates. Two studies reporting on anastomotic blood flow showed very different results, between 11.6mL/min with intra-amniotic Doppler measurements[12] and 5.6mL/24h based on calculation on decreasing hemoglobin levels between intrauterine transfusion and birth[13]. The first one being highly unlikely due to the fact that the amount of flow exceeds the total blood volume of a mid-gestation fetus. Currently no reliable technique exists to assess single anastomotic blood flow. The higher flow rate used in this model, compared to true TTTS anastomotic flow, leads to longer coagulation time due to the heat sink phenomenon, constant dissipation of laser energy caused by blood flow from the coagulation site. Also, higher flow rate may result in higher pressure buildup during coagulation leading to a higher incidence of vessel wall disruption compared to in vivo coagulation of anastomoses in TTTS. Furthermore, the model uses pig blood instead of human blood, although this is similar to human in respect to size of red blood cells, red blood cell life span and hemoglobin content and structure.[14] These limitations cause that time and energy results may not exactly correspond to reality. However, the use of the model ensures that all measurements are performed under constant conditions. We do not expect that the limitations mentioned to have influenced the effect we showed. Future studies using the model will focus on using diode laser and multiple power settings to identify the optimal power setting for different types and size anastomoses.

Conclusion

This study demonstrates that, in a highly controlled, though realistic, environment, a 50 Watt laser power setting is more efficient in coagulating a placental vein in respect to time and total energy needed compared to a 30 Watt laser power setting. In addition, we showed that the firing angle of the laser has a great impact on coagulation efficiency. The more perpendicular the approach the more efficient coagulation is achieved.

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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PART FOUR

Training and Evaluation

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PUBLISHED IN: ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 2015; 45; 439-446

Chapter 6

Identification of Essential Steps in Laser Procedure for Twin-Twin Transfusion Syndrome Using the Delphi Methodology: SILICONE study

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.

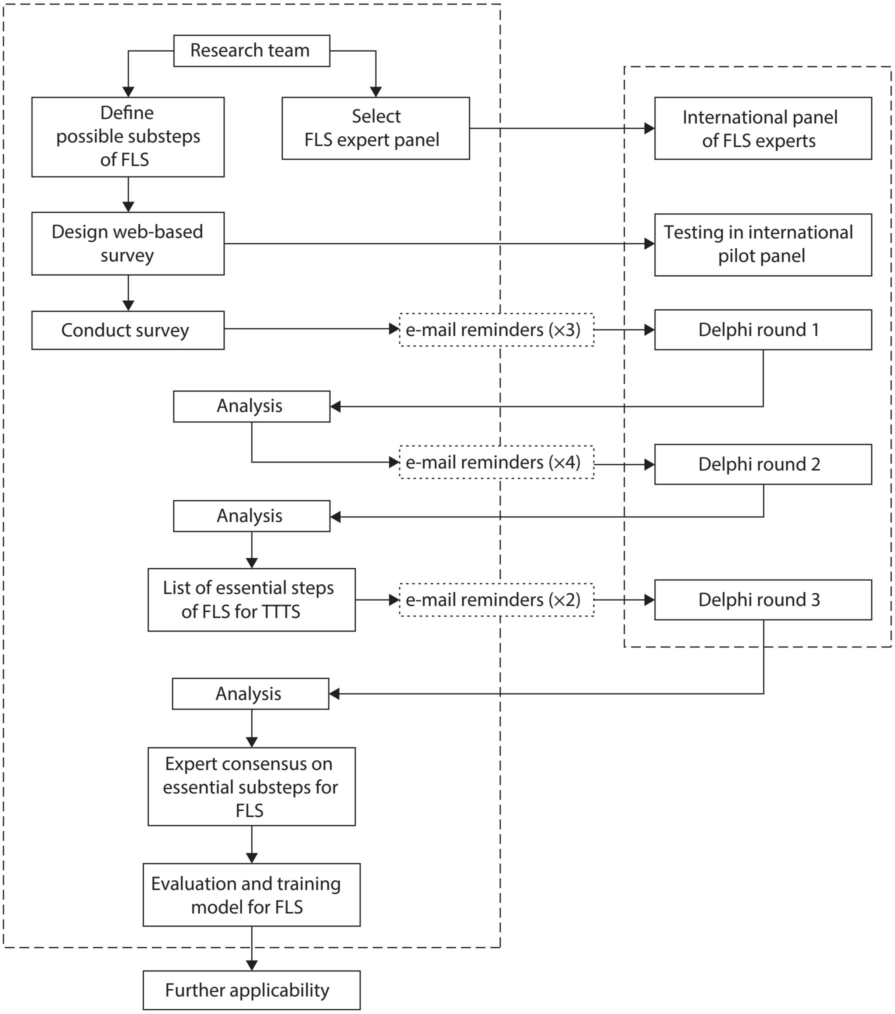

Figure 1. Overview of study design to achieve expert consensus on substeps of fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome (TTTS) that are essential to the procedure.

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 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.

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.

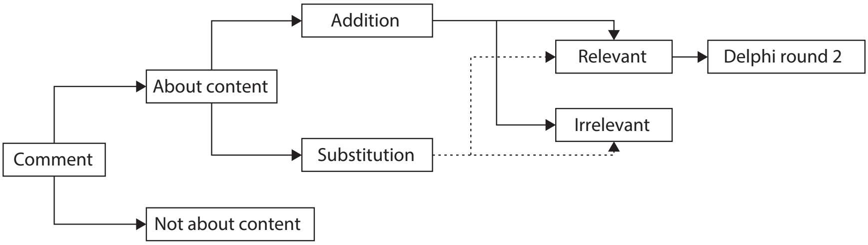

Figure 2. Method of incorporating survey respondents' comments for development of second round of Delphi survey.

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:

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

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.

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.

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

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

No.	Domain and substeps
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.

	Substeps
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.

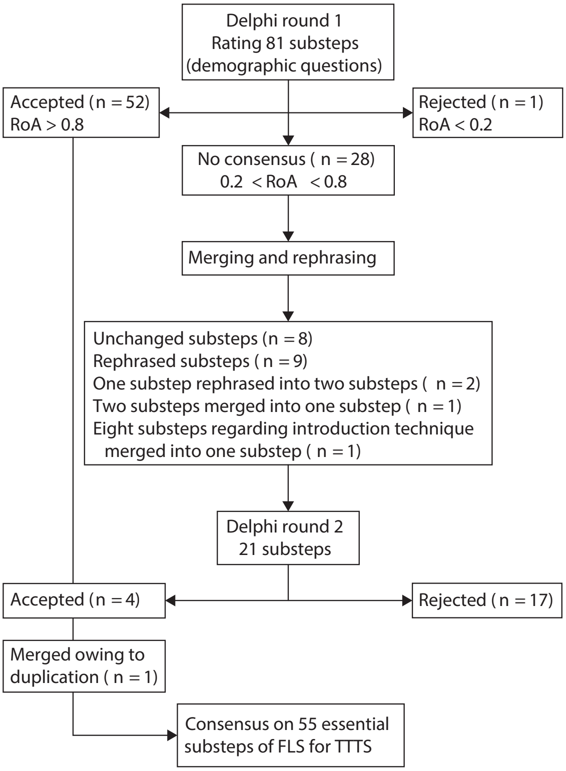

Figure 3. Flowchart of the selection of substeps determined by expert consensus to be essential in fetoscopic laser surgery (FLS) for twin–twin transfusion syndrome to be included in an evaluation instrument. RoA, rate of agreement.

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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APPENDICES

No.	Domain and substeps	Mean	RoA
1.	Diagnostic procedure		
1.1	Make sure advanced ultrasound scan is performed to exclude fetal anomalies	4.71	91.8
1.2	Confirmation of monochorionicity, diagnosis, Quintero stage of TTTS	4.89	97.3
1.3	Endovaginal ultrasound examination for cervical length measurement	4.38	75.3
1.4	Consider risk of complications (cervix shortening, fetal deterioration etc)	4.70	94.5
1.5	Consider relevant maternal factors (i.e. BMI) and medical history	4.08	72.6
1.6	Determine whether laser is best treatment option (and consider alternatives)	4.63	93.2
1.7	Determine whether laser procedure should be performed as soon as possible or expectant management can be an option	4.62	97.3
1.8	Obtain full informed consent	4.85	95.9
2.	Pre-surgical management		
2.1	Consider need for anti-D prophylaxis to minimize sensitization	4.21	71.2
2.2	Prescribe all procedure-related medications (tocolytics, antibiotics etc)	4.55	87.7
2.3	Arrange maternal (and depending on gestational age; fetal) monitoring	4.29	79.5
2.4	Determine and arrange type of anesthesia	4.51	84.9
3.	Preparation in operating room		
3.1	Knowledge of technical equipment (ultrasound, scopy tower, laser, instruments)	4.86	97.3
3.2	Positioning of screens. assistants and lights	4.66	95.9
3.3	Determine laser modus and power settings	4.70	93.2
3.4	Positioning of patient	4.81	97.3
4.	Ultrasound examination (together with sonographer)		
4.1	Identification of both fetuses, presentation and position	4.78	95.9
4.2	Visualize placenta localization, umbilical cord insertions	4.90	98.6
4.3	Assess deepest pockets of amniotic fluid	4.47	80.8
4.4	Determine expected position of vascular equator	4.71	94.5
4.5	Determine site of insertion of fetoscope	4.95	98.6
4.6	Choose type of introduction (set) and type of fetoscope	4.67	90.4
5.	Sterile procedure and anesthesia		
5.1	Surgical briefing (time out) about (complete) procedure to fetal therapy team	4.48	90.4
5.2	Aseptic procedure for surgeon. scrub nurse and sonographer	4.78	93.2
5.3	Monitoring maternal condition (during complete procedure)	4.60	90.4
5.4	Placement of sterile covers over patient and instruments	4.68	93.2
6.	Positioning and connection of instruments (pre-insertion)		
6.1	Connection of fetoscope (orientation, focus and white balance)	4.79	98.6
6.2	Connection of laser fiber to laser machine, insertion of fiber in fetoscope	4.68	91.8
6.3	Connect amnio-infusion and/or cooling system to fetoscope	4.26	79.5
7.	Insertion		
7.1	Performance of all manipulations under ultrasound visualization	4.44	80.8
7.2	Avoid damage to maternal bowel, blood vessels and placental edge	4.89	97.3
7.3	Administration of local anesthesia skin - peritoneum	4.19	75.3
7.4	Make adequate-size skin incision with surgical knife	4.59	91.8
7.5	Correct use of (Seldinger or trocar) technique for insertion	4.63	86.3
7.6	Drain 10-20 cc amniotic fluid for prenatal testing	3.92	56.2
7.7	Determine need for pre-surgical amnio-infusion	4.18	71.2

No.	Domain and substeps	Mean	RoA
7.8	Insertion of shaft/scope	4.64	91.8
	Use of Seldinger technique		
7.8.1.1	Awareness of location maternal uterine vessels and intestines	3.81	76.7
7.8.1.2	Insert needle percutaneously in the uterine cavity	3.67	71.2
7.8.1.3	Introduction of soft J-tipped guide wire through the needle	3.64	69.9
7.8.1.4	Removal of needle	3.62	68.5
7.8.1.5	Introduction of cannula loaded with dilator over the guide wire	3.64	69.9
7.8.1.6	Insert shaft with scope percutaneously in the uterine cavity	3.60	67.1
	Use of direct insertion		
7.8.2.1	Awareness of location maternal uterine vessels and intestines	4.36	86.3
7.8.2.2	Insert shaft with scope percutaneously in the uterine cavity	4.21	79.5
8.	Orientation		
8.1	Assess visibility (optional: score visibility)	4.21	80.8
8.2	Determine need for amniotic exchange	4.18	82.2
8.3	Confirm position of placenta, fetuses and cord insertions	4.68	90.4
8.4	Identification of intertwin dividing membrane (and use for reference)	4.70	97.3
8.5	Mapping of placental surface and vascular equator	4.75	95.9
8.6	In case of using separate scope to map equator. change scope	2.73	31.5
9.	Laser coagulation		
9.1	Use of selective laser technique (only coagulation of anastomoses)	4.45	83.6
9.1.1	In case of selective laser technique: use sequential technique	3.54	32.9
9.2	Use of Solomon technique	3.54	35.6
9.2.1	In case of Solomon technique: use sequential technique	3.26	41.1
9.3	Prevent the unnecessary sacrifice of placental tissue	4.42	83.6
10.	Assessment during procedure		
10.1	Prevent unnecessary delay during procedure	4.40	91.8
10.2	Check for complications (e.g. bleeding, rupture intertwin membranes)	4.48	91.8
10.3	Check fetal condition regularly	4.05	68.5
10.4	Identify and record number and type of anastomoses coagulated	4.29	82.2
10.5	While finishing procedure check for amniotic leakage in maternal abdomen	3.82	54.8
10.6	Check for amnion-chorion dehiscence	4.00	67.1
10.7	Determine placental sharing	3.48	34.2
10.8	Check limb abnormalities recipient	3.42	28.8
10.9	Mark recipient with laser spot on left upper leg	1.23	-94.5
11.	Amniodrainage		
11.1	Controlled drainage of polyhydramnios	4.53	95.9
11.2	Assess adequate drainage (ultrasound guided) until pre-defined level to decrease uterine distention and promote patient comfort	4.36	87.7
12.	Closure		
12.1	Closing skin incision (suture or Steri-strip)	4.19	79.5
13.	Direct post-operative management		
13.1	Inform patient. partner/family and referring specialist	4.71	93.2
13.2	Administration (surgical report, fetal therapy database)	4.59	90.4
13.3	Instructions for monitoring of maternal and fetal condition	4.73	98.6
13.4	Inform patient of peritoneal irritation due to leakage of amniotic fluid	4.07	72.6
13.5	Consider administration of postoperative tocolytics	4.15	76.7

No.	Domain and substeps	Mean	RoA
14.	Follow up ultrasound examination		
14.1	Knowledge of follow-up until delivery of (un)complicated monochorionic pregnancies	4.67	94.5
14.2	Assessment of fetal condition including bladder filling. deepest vertical pockets and doppler flows	4.78	98.6
14.3	Knowledge of MCA-PSV measurement to detect post-laser TAPS	4.73	93.2
14.4	Signs of iatrogenic perforation of the intertwin membrane	4.48	90.4
14.5	Signs of amnion-chorionic separation	4.41	90.4
14.6	Record which fetus is former donor and recipient. respectively	4.64	97.3
14.7	Order follow up cervical length measurement	3.89	56.2
14.8	Knowledge of signs and options with regards to iatrogenic PPROM	4.52	90.4

Appendix 1. Round 1 of Delphi survey: Summary of initial substeps and results of ratings. If RoA > 80 (Rate of Agreement coefficient) the substep was included in the evaluation instrument. Mean: mean scores of panel ratings on 5-point Likert scale. BMI: Body Mass Index. Rh-D: Rhesus-D. CS: cesarean section. TTTS: Twin-Twin Transfusion Syndrome. TAPS: Twin Anemia Polycythemia Sequence. sIUGR: selective Intrauterine Growth Restriction. MCA-PSV: Middle cerebral artery- peak systolic velocity measurement. PPROM: preterm premature rupture of membranes..

No.	Rounds	Domain and substeps	Mean	RoA
1.		Diagnostic procedure		
1.3	Round 1	Endovaginal ultrasound examination for cervical length measurement	4.38	75
	Comments	The panel mentioned no clear evidence exists on the use of endovaginal versus abdominal ultrasound. the consequences of a short cervix and the right timing of the endovaginal measurement.		
	Action Round 1	Rephrased		
1.3	Round 2	Consider cervical length measurement	4.68	88
	Action Round 2	Item included		
1.5	Round 1	Consider relevant maternal factors (i.e. BMI) and medical history	4.08	73
	Comments	This item was considered to generic. It was separated into two items.		
	Action Round 1	Rephrased		
1.5.1	Round 2	Consider maternal factors as possible exclusion criteria for laser therapy according to centers protocol. (i.e. maternal condition mandating delivery)	4.18	74
	Action Round 2	Item deleted		
1.5.2	Round 2	Consider relevant maternal factors (that may influence surgery and post-operative management (i.e. maternal BMI))	4.20	77
	Action Round 2	Item deleted		
2.		Pre-surgical management		
2.1	Round 1	Consider need for anti-D prophylaxis to minimize sensitization	4.21	71
	Comments	According to textual suggestions by respondents that blood group and Rhesus typing should be known this item was adjusted.		
	Action Round 1	Rephrased		
2.1	Round 2	Blood group and Rhesus typing should be known; with respect local protocols concerning Rh-D prophylactics	4.83	95
	Action Round 2	Item included		

No.	Rounds	Domain and substeps	Mean	RoA
2.3	Round 1	Arrange maternal (and depending on gestational age; fetal) monitoring	4.29	79
	Comments	The panel noted fetal monitoring often is irrelevant at GA of laser. The panel also noted that the decision for laser as preferred management has been made (instead of emergency CS in cases with advanced gestational age). Statement was considered confusing regarding timing of maternal monitoring.		
	Action Round 1	Included comments for consideration, rephrased and partly deleted substep		
2.3	Round 2	Consider pre-operative maternal monitoring	4.03	65
	Action Round 2	Item deleted		
3.		Preparation in operating room		
	Round 1	Consensus on all items		
4.		Ultrasound examination (together with sonographer)		
	Round 1	Consensus on all items		
5.		Sterile procedure and anesthesia		
	Round 1	Consensus on all items		
6.		Positioning and connection of instruments (pre-insertion)		
6.3	Round 1	Connect amnio-infusion and/or cooling system to fetoscope	4.26	79
	Comments	The words "cooling system" were considered confusing by the panel; therefore a textual change was made.		
	Action Round 1	Rephrased		
6.3	Round 2	Connect amnio-infusion and/or flushing system to fetoscope	4.15	71
	Action Round 2	Item deleted		
7.		Insertion		
7.3	Round 1	Administration of local anesthesia skin - peritoneum	4.19	75
	Comments	Panel responded: In case regional of general anesthesia is used, local anesthesia is not administered.		
	Action Round 1	Rephrased		
	Round 2	In case of local anesthesia: administer anesthetic to skin and peritoneum	4.65	92
	Action Round 2	Item included		
7.6	Round 1	Drain 10-20 cc amniotic fluid for prenatal testing	3.92	56
	Comments	The panel members noted differences in timing (beginning or end of procedure). and that this item is not always applicable due to the consent of the parents and/or gestational age of pregnancy.		
	Action Round 1	Included comments for consideration. panel asked to re-rate substep		
	Round 2	Drain 10-20 cc amniotic fluid for prenatal testing	4.00	56
	Action Round 2	Item deleted		
7.7	Round 1	Determine need for pre-surgical amnio-infusion	4.18	71
	Comments	Comments of the panel mentioned this item is rarely necessary in TTTS (originally in protocol in cases of TAPS or sIUGR). Also some doubt on the timing was mentioned: with needle of Seldinger inside or with trocar.		
	Action Round 1	Included comments for consideration, panel asked to re-rate substep		
	Round 2	Determine need for pre-surgical amnio-infusion	3.91	59

No.	Rounds	Domain and substeps	Mean	RoA
	Action Round 2	Item deleted		
7.8	Round 1	Insertion using Seldinger technique		
7.8.1.1		Awareness of location maternal uterine vessels and intestines	3.81	77
7.8.1.2		Insert needle percutaneously in the uterine cavity	3.67	71
7.8.1.3		Introduction of soft J-tipped guide wire through the needle	3.64	70
7.8.1.4		Removal of needle	3.62	69
7.8.1.5		Introduction of cannula. loaded with dilator over the guide wire	3.64	70
7.8.1.6		Insert shaft with scope percutaneously in the uterine cavity	3.60	67
		Direct insertion		
7.8.2.2		Insert shaft with scope percutaneously in the uterine cavity	4.21	79
7.9	Comments	Panel members did not reach consensus on the insertion technique. Comments included that "Awareness of location of maternal uterine vessels and intestines during insertion" was considered relevant by respondents, though not in relation to insertion technique (e.g. Seldinger or direct).		
	Action Round 1	We rephrased the item regardless of the technique used.		
	Round 2	Awareness of location of maternal uterine vessels and intestines during insertion	4.7	94
	Action Round 2	Items on type of introduction rejected. "awareness of location maternal uterine vessels and intestines during insertion" merged with other item on this topic.		
8.		Orientation		
8.6	Round 1	In case of using separate scope to map equator, change scope	2.73	32
	Comments	Most panel members responded they do not use a separate scope for mapping		
	Action Round 1	Included comments for consideration. panel asked to re-rate substep		
8.6	Round 2	In case of using separate scope to map equator, change scope	2.47	9
	Action Round 2	Item deleted		
9.		Laser coagulation		
9.1.1	Round 1	Use of selective laser technique (only coagulation of anastomoses)	4.45	84
9.2		In case of selective laser technique: use sequential technique	3.54	33
9.2.1		Use of Solomon technique	3.54	36
		In case of Solomon technique: use sequential technique	3.26	41
	Comments	Responses of the panel with respect to laser technique included comments on technique that was used locally, and the benefits of the different techniques in detail. The panel mentioned there is little evidence for the sequential laser technique, and that use of this technique should not prolong the scopy time. The panel commented that there is level 1 evidence for use of the Solomon technique and perhaps dichorionization could be preferred terminology.		
	Action Round 1	We rephrased the items, included comments and asked to re-rate these items		
9.1	Round 2	Coagulation of all vascular anastomoses that cross the vascular equator	4.44	79
	Action Round 2	Item merged with "use of selective laser technique (only coagulation of anastomoses)"		
9.2.1	Round 2	Use sequential technique	3.29	30

No.	Rounds	Domain and substeps	Mean	RoA
	Action Round 2	Item deleted		
9.2.2	Round 2	Use of Solomon technique (complete dichorionization)	3.89	62
	Action Round 2	Item deleted		
10.		Assessment during procedure		
10.3	Round 1	Check fetal condition regularly	4.05	69
	Comments	Responses of panel included: Assessment of fetal condition must not prolong the procedure, you cannot stop halfway the procedure, only applicable in viable time period. not much you can do in case of deterioration		
	Action Round 1	Included comments for consideration. re-rate substep		
	Round 2	Check fetal condition regularly	3.74	56
	Action Round 2	Item deleted		
10.5	Round 1	While finishing procedure check for amniotic leakage in maternal abdomen	3.82	55
	Comments	Comments on this item included: this is not a predictor of outcome, no treatment options are available, may occur after finishing procedure.		
	Action Round 1	Included comments for consideration, panel asked to re-rate substep		
	Round 2	While finishing procedure check for amniotic leakage in maternal abdomen	3.24	23
	Action Round 2	Item deleted		
10.6	Round 1	Check for amnion-chorion dehiscence	4.00	67
	Comments	The panel mentioned this item is also displayed in follow up ultrasound and that no treatment option is available		
	Action Round 1	Included comments for consideration panel asked to re-rate substep		
	Round 2	Check for amnion-chorion dehiscence	3.85	61
	Action Round 2	Item deleted		
10.7	Round 1	Determine placental sharing	3.48	34
	Comments	The panel noted no standardized assessment exists for this item: it is considered a rough estimation and it has questionable value for treatment management		
	Action Round 1	Included comments for consideration, panel asked to re-rate substep		
	Round 2	Determine placental sharing	3.09	11
	Action Round 2	Item deleted		
10.8	Round 1	Check limb abnormalities recipient	3.42	29
	Comments	The panel mentioned it is better to check this (pre-op or follow up) with ultrasound, that it prolongs scopy time, that no direct clinical implications exist and that it will not provide any information on the donor		
	Action Round 1	Included comments for consideration, panel asked to re-rate substep		
	Round 2	Check limb abnormalities recipient	3.02	-2
	Action Round 2	Item deleted		
10.9	Round 1	Mark recipient with laser spot on left upper leg	1.23	-95
	Comments	This item was incorporated on purpose in the first survey round as a check for validity.		

No.	Rounds	Domain and substeps	Mean	RoA
	Action Round 1	Panel members were informed about this check. Item was excluded from subsequent rounds.		
11.		Amniodrainage		
	Round 1	Consensus on all items		
12.		Closure		
12.1	Round 1	Closing skin incision (suture or Steri-strip)	4.19	79
	Comments	Panel included comments on steri-strip equivalents. considers this basic surgical care.		
	Action Round 1	Rephrased		
	Round 2	Closing skin incision (suture or suture free adhesive product)	4.39	82
	Action Round 2	Item included		
13.		Direct post-operative management		
13.4	Round 1	Inform patient of peritoneal irritation due to leakage of amniotic fluid	4.07	73
	Comments	The panel noted this already has been mentioned at 13.1. (post-operative information to the patient. family and referring specialist). Not every complication should be displayed as a separate item.		
	Action Round 1	Included comments for consideration, panel asked to re-rate substep		
	Round 2	Inform patient of peritoneal irritation due to leakage of amniotic fluid	3.74	61
	Action Round 2	Item deleted		
13.5	Round 1	Consider administration of postoperative tocolytics	4.15	77
	Comments	Comments included: depending on gestational age, clinical signs and according to local protocol. Therefore this step was edited.		
	Action Round 1	Rephrased		
	Round 2	Consider administration of postoperative tocolytics (based on local protocol or clinical signs.)	4.18	74
	Action Round 2	Item deleted		
14.		Follow up ultrasound examination		
14.7	Round 1	Order follow up cervical length measurement	3.89	56
	Comments	The panel noted no evidence or therapeutic implications exist and that it should not be performed without clinical signs.		
	Action Round 1	Rephrased		
	Round 2	Order follow up cervical length measurement when indicated	4.02	65
	Action Round 2	Item deleted		

Appendix 2. Summary of the evaluation and selection process of substeps in round 2 of the Delphi survey. If RoA > 80 (Rate of Agreement coefficient). the substep was included in the evaluation instrument.
Mean: mean scores of panel ratings on 5-point Likert scale. BMI: Body Mass Index. Rh-D: Rhesus-D. CS: cesarean section. TTTS: Twin-Twin Transfusion Syndrome. TAPS: Twin Anemia Polycythemia Sequence. sIUGR: selective Intrauterine Growth Restriction

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PUBLISHED IN: ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 2016; 47; 350-355

Chapter 7

Operator Competence in Fetoscopic Laser Surgery for Twin-Twin Transfusion Syndrome: Validation of a Procedure-Specific Evaluation Tool

ABSTRACT

Objectives

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

We made use of a procedure-specific evaluation instrument containing all essential steps of the fetoscopic laser procedure, which was previously 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). Interobserver reliability was assessed using Spearman correlation. We compared the performance of novices and experts to assess construct validity.

Results

The interobserver reliability was high (Rs = 0.974, P < 0.001). Checklist scores for experts and novices were significantly different; the median score for novices was 28/52 (54%), whereas that for experts was 47.5/52 (91%) (P < 0.001). The 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 9/13 (69%) procedures performed by novices (P = 0.005). Multivariable analysis showed that the checklist score, independent of age and gender, predicted competence.

Conclusions

The procedure-specific assessment tool for fetoscopic laser surgery shows good interobserver reliability and discriminates experts from novices. This instrument may therefore be a useful tool in the training curriculum for 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 non-existent and performance is often authority based, i.e. based on personal experience, belief and individual preferences. Also, the learning curve is ill-defined, and varies between 21 and 75 cases (based on 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 for technical performance. Such a tool would be useful to monitor progress, provide constant feedback along the learning curve, 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 the 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 interobserver 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 (SImulator for Laser therapy and Identification of Critical steps of Operation: New Education 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 instrument9. In the current part of the project, this instrument was validated using a silicone simulator involving the complete laser procedure. The Medical Ethics committee of the Leiden University Medical Center declared that no formal ethical approval or written informed consent was needed for this study.

Figure 1 Participant performing procedure on simulator for fetoscopic laser surgery

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 to December 2014. We recruited 24 volunteers with special interest in fetal therapy to participate in the study. All participants completed a questionnaire to establish the baseline demographic characteristics and previous experience in fetoscopic surgery to measure potential confounding factors that affect performance. Participants were stratified into three groups with regard to the level of previous experience: expert, 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, obstetricians attending a fellowship in perinatology or senior residents with a 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). Practicing fetal surgeons who were still on their learning curve (e.g. having performed 1-25 fetoscopic laser procedures) were considered intermediates and were excluded. For secondary analyses, experts were categorized into two groups: intermediate expert level (having performed < 50 procedures) and senior expert level (having performed > 50 procedures).

Assessment

All participants (irrespective of the level of expertise) performed a similar assignment on the simulator. The scenario involved a patient of 17weeks' gestation with Stage III TTTS referred for laser therapy. The assignment included the complete fetoscopic laser procedure, starting from the moment that the operation room was entered, until the surgery was finished and direct postoperative 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 two independent observers (S.H.P.P. and J.A.), using the assessment instrument created by the Delphi consensus9. This list of essential steps was modified into a checklist adjusted to the simulated scenario. A detailed description of the instrument is available in Appendix S1. Each item was awarded 1 point if it was performed properly (range, 0-52). The procedure time, defined as 'the moment the surgeon enters the operating room until the moment that direct postoperative 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.

Scenario and simulator characteristics

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 presurgical management) was presented.

The simulator used for this study has been described previously10 (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, being required to select the best site for introduction of the instruments. The model also provides a realistic intrauterine environment, optimal for the practice of 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.

Demographics	Expert n=11	Novices n=13	p value
Gender			
Male	8 (73)	3 (23)	0.015
Female	3 (27)	10 (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 (100)	4 (31)	0.001
years (median, range)	15 (7-23)	3 (1-8)	0.003
Type of invasive obstetric procedures			
Amniocentesis	11 (100)	3 (23)	
Chorionic villus sampling	11 (100)	3 (23)	
Intrauterine transfusion	8 (73)	1 (8)	
Fetal shunt placement	8 (73)	0	
Bipolar cord occlusion	11 (100)	0	
Open fetal surgery	4 (36)	0	
Other	4 (36)	0	
No. of FLS attended *			
None	0	2 (15)	0.001
< 10 procedures	0	7 (54)	
10-25 procedures	0	0	
25-50 procedures	1 (9)	2 (15)	
50-100 procedures	1 (9)	0	
>100 procedures	9 (82)	2 (15)	
Experience with simulator training			
Never	2 (18)	1 (8)	0.447
A few times	4 (36)	8 (62)	
Regularly	5 (46)	4 (30)	

Table 1 Demographic characteristics of study participants: 11 experts and 13 novices using a fetoscopic laser simulator. Data are given as n (%) or median (range). *Including assisting or watching procedure. FLS, fetoscopic laser surgery; No., number.

The addition of a 'free-floating' recipient simulates a realistic complex situation of floating fetal extremities and umbilical cord in the recipient's sac. All necessary instruments (i.e. fetoscope, introduction set, endoscopy tower, etc.) were from the local fetal medicine center so that participants performed their tasks in a setting that was identical to their clinical environment. Figure 1 shows a participant performing the procedure on the simulator model.

Statistical analysis

The 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. Fisher's exact test was used to test for differences between groups on non-ordinal categorical outcomes, such as the presence or absence of experience. Spearman's correlation coefficient was used to measure the interobserver reliability. A correlation of 0.9 or higher was considered to be indicative of excellent agreement.

In order to assess the construct validity of the instrument, we used multivariable logistic regression analysis to determine whether any independent predictors other than checklist score were associated with experience level (i.e. expert vs novice). 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, it reflects 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 those with the construct (surgical skills) and novices are those without the construct; construct validity determines whether the instrument identifies the presence or absence of the construct (surgical skills).

A two-sided $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed with SPSS version 21.0 (SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA). As 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 and 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.

	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 Interobserver reliability, according to domain of the evaluation instrument for fetoscopic laser surgery for twin–twin transfusion syndrome. R_s : Spearman correlation coefficient.

The overall median procedure time was 40 min (range, 26 - 50 min). Experts were able to complete the procedure in 32 min vs 43 min by novices (P = 0.003). The fetoscopy time was also significantly different between the groups. The median fetoscopy time for all participants was 17 min (range, 10 - 27 min), 11 min for experts vs 20 min for novices (P < 0.001). Residual anastomoses were found in 10/25 (40%) procedures, 1/11 (9%) performed by experts and 9/13 (69%) performed by novices (P = 0.005).

Secondary analyses were performed with regard to the level of expertise in the expert group comparing the results for intermediate and senior experts. The procedure time and fetoscopy time were not significantly different between the groups (32 vs 31min, P=0.776 and 12 vs 11 min, P = 0.376), and neither was the surgical performance score (45/52 (87%) vs 49/52 (94%), P = 0.630).

Reliability

The overall interobserver reliability of the two (J.A. and S.H.P.P.) total scores for the fetoscopic laser procedure was excellent (Rs = 0.974; P < 0.001) (Figure 2). Agreement was less but was still strong in the domains concerning 'direct postoperative management' (Rs = 0.722; P < 0.001) and 'assessment during procedure' (Rs = 0.789; P < 0.001) as displayed in Table 2. Agreement for the two raters remained high amongst intermediate experts (Rs = 0.866) and senior experts (Rs = 0.938). The interobserver variability did not significantly change over time (data not shown).

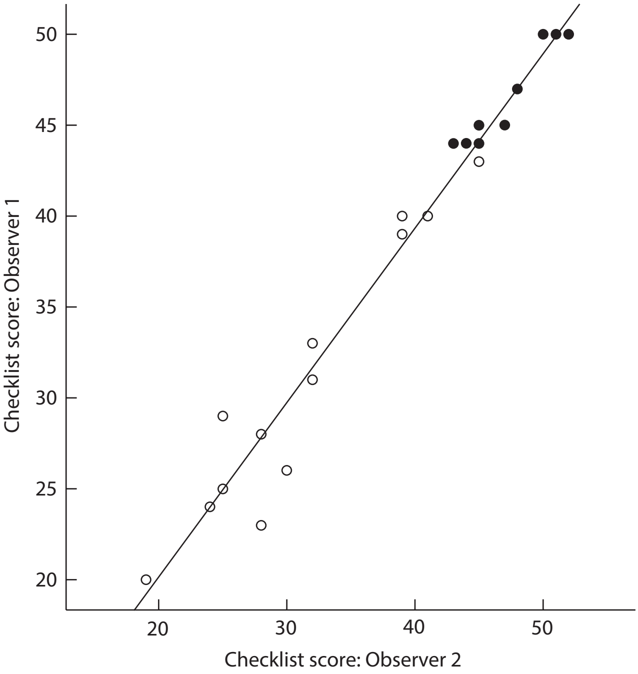

Figure 2 Scatterplot showing correlation between checklist scores of the two observers using fetoscopic laser simulator, according to level of experience: novice (o) or expert (•). Scores for experts were overlapping in two cases.

Construct validity

Observer 1's median score for novices on the assessment tool was 29/52 (56%) (range, 20 - 43) compared with a median expert score of 47/52 (90%) (range, 44 - 50) (P < 0.001). Observer 2's median novice score similarly demonstrated statistically significant differences between novice and expert performance (30/52 (58%) (range, 19 - 45) vs 48/52 (92%) (range, 43 - 52)) (P < 0.001).

The overall median checklist scores (combining the scores by taking the average of the two observers) were 28/52 (54%) (range, 20 - 44) in novices vs 47.5/52 (91%) (range, 44 - 51) in experts (P < 0.001) and scores were also significantly associated with the presence of residual anastomoses as demonstrated in Figure3 (P=0.002). Receiver-operating characteristics analysis showed an area under the curve of 0.861 for the use of checklist score to identify experience level. Multivariable analyses showed that the age (b1 = 0.203;

P = 0.351) and gender (b1 = 0.088; P = 0.539) of participants were not significantly associated with level of experience given the checklist score.

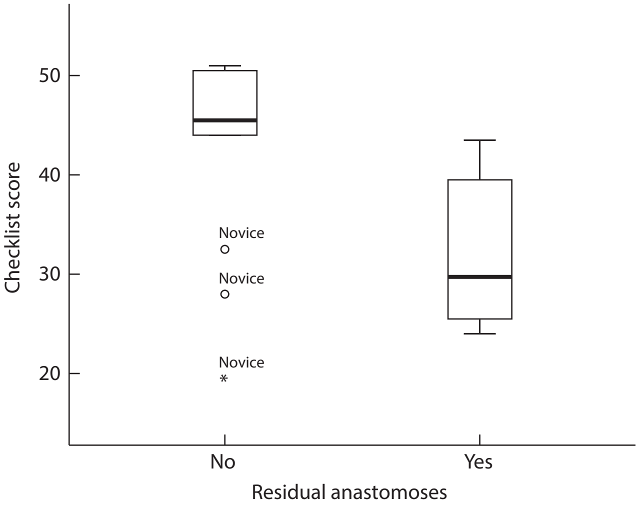

Figure 3 Boxplots of checklist score according to presence or absence of residual anastomoses in 11 experts and 13 novices using a fetoscopic laser simulator (P = 0.002). Boxes with internal lines represent median and interquartile range, whiskers are range, and outliers are plotted.

DISCUSSION

This study assessed the interobserver 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 the performance of experts and novices with an acceptable level of interobserver 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). Interobserver reliability refers to the degree to which a difference in score on the tool reflects a difference in quality of performance rather than a difference between the raters. A high level of interobserver reliability allows the evaluation of skills by different observers and will be minimally affected by the variability of the rater11.

Trainees in fetal surgery have to date been 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; we therefore included participants from three major fetal medicine centers.

The validation of assessment tools for training has been performed frequently in other medical areas[14-17] , but never in the field of fetal therapy. The 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 interobserver 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 a 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. As 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 indistinct despite having an apparent precision, as 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).

The procedure time and fetoscopy time were significantly lower in the expert group compared with 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 that combines efficacy (closing all anastomoses) with safety (avoiding complications) even more valuable for training purposes.

A limitation of this study is that a few items identified through the prior Delphi consensus could not be analyzed during the simulator experiments as they take place in the diagnostic and preoperative phase of the procedure. These steps include: 'diagnostic procedure' (e.g.

ultrasound examination at outpatient clinic confirming the diagnosis and determining treatment options), 'presurgical management' (e.g. prescription of procedure-related medication, etc.) and 'follow-up ultrasound examination'. Therefore, our assessment of the construct validity and reliability of this tool does not include these particular steps.

Due to the nature of the procedure, we were unable to assess the validity of the instrument in surgery on real patients and therefore the simulator was used. Although the simulator is regarded as highly realistic, clinical features such as 'tissue reaction after firing the laser' and 'complications such as bleeding' could not be simulated. However, assessment using a simulator model can also be advantageous, as the lack of standardization in real patients makes the 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].

Quite often, even experienced operators work as a team, and the effect of the collective experience of such a team may be greater than the sum of its individual parts. This effect is difficult to quantify and was not measured in this study. For this study, participants were assessed live in the operating room and 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 of 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 pretraining and post-training design. Correlation of the score with the progress of inexperienced operators along 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 of the participants from the maternal fetal medicine centers who generously shared their time, experience and materials for the purpose of this project. This research was 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	

No.	Domain and substeps	Score
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

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ENRICO LOPRIORE
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FRANS J. KLUMPER
LIESBETH LEWI
ROLAND DEVLIEGER
LUC DE CATTE
JAN DEPREST
SVERKER EK
MARIUS KUBLICKAS
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ELEONOR TIBLAD
DICK OEPKES

PUBLISHED IN: ULTRASOUND IN OBSTETRICS AND GYNECOLOGY 2015; 46; 319-326

Chapter 8

Simulator Training in Fetoscopic Laser Surgery for Twin-Twin Transfusion Syndrome: A Pilot Randomized Controlled Trial

ABSTRACT

Objective

To evaluate the effect of a newly developed training curriculum on the 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 either skills training using the simulator (study group; n = 5) or no training (control group; n = 5). Both groups were evaluated with a pre-training and post-training test on the simulator. Performance was assessed by two independent observers and comprised a 52-item checklist for surgical performance (SP) score, measurement of procedure time and number of anastomoses missed. Eleven experts set the benchmark level of performance. Face validity and educational value of the simulator were assessed using a questionnaire.

Results

Both groups showed an improvement in SP score at the post-training test compared with the pre-training test. The simulator-trained group significantly outperformed the control group, with a median SP score of 28 (54%) in the pre-test and 46 (88%) in the post-test vs 25 (48%) and 36 (69%), respectively (P = 0.008). Procedure time decreased by 11 min (from 44 to 33 min) in the study group vs 1 min (from 39 to 38 min) in the control group (P=0.69). There was no significant difference in the number of missed anastomoses at the post-training test between the two groups (1 vs 0). Subsequent feedback provided by the participants indicated that training on the simulator was perceived as a useful educational activity.

Conclusions

Proficiency-based simulator training improves performance, indicated by SP score, for fetoscopic laser therapy. Despite the small sample size of this study, 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 twin pregnancies[1]. Treatment is offered at 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 in 80-90%[3], but few studies have been performed to gain more insight into the learning curves and pitfalls of this complex procedure[4-8].

We anticipate that in the coming years an increasing number of fetal surgeons will begin training in fetoscopic laser surgery. With the economic growth in developing countries, and increasing knowledge of this treatment option through better access to online 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 take over practice from the pioneers in the established centers. Therefore, focus is gradually shifting from pregnancy outcomes per center towards appropriate training and exposure of surgeons to a sufficient number of procedures. This will ensure proper skills and satisfactory results. To support this process, an evidence-based training curriculum and a continuous process of reporting and monitoring of outcomes are highly desirable.

Since fetoscopic procedures are performed on an infrequent basis, a surgeon-in-training is required to undergo a lengthy and expensive stay in an (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 in this procedure are 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] , but most simulators that have been reported on have been used for teaching in the absence of well-planned and comprehensive training curricula.

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

METHODS

For the study we recruited volunteers with a special interest in fetal therapy and no practical experience with the fetoscopic laser procedure (novices), from a population of currently active fetal therapy experts in three maternal-fetal medicine centers: Leiden University Medical Center (The Netherlands), University Hospitals KU Leuven (Belgium) and Karolinska University Hospital, Stockholm (Sweden), from September to December 2014. All participants completed a questionnaire to establish baseline demographic characteristics and previous experience in surgical/obstetrical skills to exclude potential confounding factors that might have affected performance. Volunteers, hereafter referred to as 'novices', were eligible if they were a fetal medicine specialist without practical fetal therapy experience or an obstetrician/ gynecologist currently undergoing a perinatology fellowship or a senior obstetrics/gynecology resident with a special interest in perinatology and/or minimally invasive therapy. In addition, the participant was required to have high levels of skill 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 an evaluation instrument developed previously[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 sequentially by www.random.org (School of Computer Science and Statistics, Trinity College, Dublin, Ireland). Novices were assigned randomly to either the training group (study group) or the no-training group (control group). Owing to the nature of the intervention, blinding for randomized allocation was not possible. Lack of data regarding training for fetoscopic laser surgery prevented a formal sample size calculation. Given 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 the study. A pre-test/post-test research design was used to evaluate the effect of simulator-based training on surgical performance. Performance was assessed by an assignment involving the complete fetoscopic laser procedure, comparing the two groups' performance before and after training.

All currently practicing experts from the three maternal-fetal medicine centers (n=11) were asked to complete the same assignment to define a benchmark level. An 'expert' was defined as an individual who was currently practicing fetoscopic laser surgery for TTTS and had independently performed more than 25 fetoscopic laser procedures[4]. Baseline characteristics of all study participants are listed in Table 1.

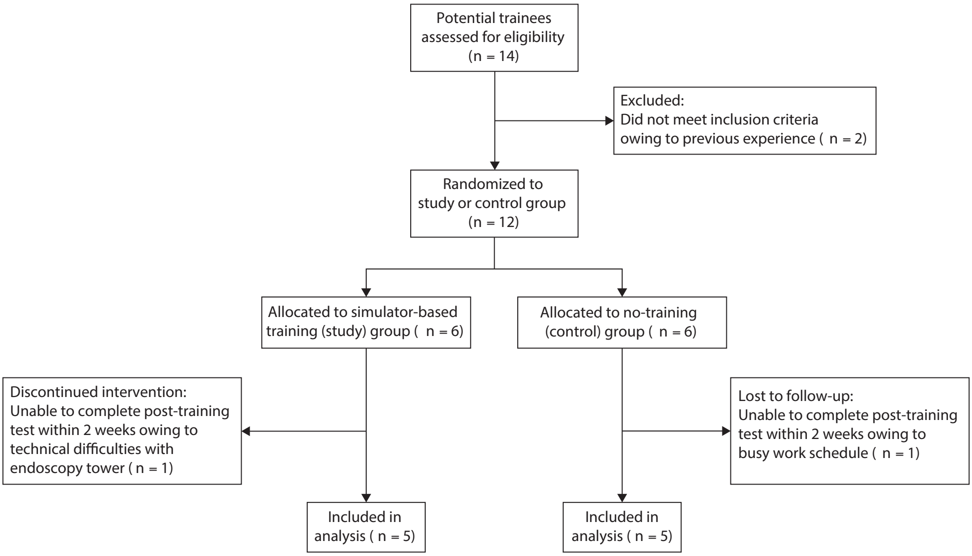

Figure 1 Flowchart of the study showing participant enrolment, randomization, allocation of interventions and follow-up.

An advanced simulator (Francis LeBouthillier, Surgical Touch, Toronto, Canada) that had previously been used in training for amniocentesis[11] was modified. A monochorionic twin placenta model and realistic models of twin fetuses (R. Bakker, Manimalworks, Rotterdam, The Netherlands) were inserted. Placenta and fetuses had a size compatible with that of a monochorionic twin pregnancy of 17 weeks' gestation. The silicone interface at the top of the model imitated 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, optimized for practicing manual dexterity skills and training navigation along the placental surface. The 'stuck' donor twin was positioned on the placenta. The addition of a 'free-floating' recipient twin simulated the floating fetal extremities and umbilical cord in the recipient's sac. Apart from the simulator model, all standard equipment (i.e. fetoscope, introduction set, ultrasound machine, endoscopy tower) used clinically in the participating fetal therapy centers was used to perform the assignment.

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

Table 1. Demographic characteristics of study participants with expert level of experience and those with no practical experience with fetoscopic laser surgery (FLS) who did or did not receive simulator training. Data are given as n (%) or median (range). *Characteristics of novices with vs those without training. †Watched procedure only.

Novices and experts were evaluated by two 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 (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 (Table S1). Each item was awarded 1 point if it was completed properly, providing a range of final SP scores of 0-52. Duration of the procedure, defined as the moment the surgeon entered the operating room until the moment that direct postoperative management was ordered, and duration of fetoscopy, defined as the moment the trocar was introduced until final removal, were recorded. A map of the placental architecture was used by the observers to mark the coagulated anastomoses (a total of eight). Since there was no international consensus on the Solomon technique at the time of development of the checklist[3], participants were instructed to coagulate all vascular anastomoses that connected the circulations of the donor and the recipient twin one by one - the 'selective laser technique'.

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

Phase 1: Introduction (experts, novices (study group), novices (control group))

Each participant was familiarized with the simulator by a member of the study team (S.P. or J.A.). 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 noted but scored as 'failed'.

Phase 2: Pre-training test (experts, novices (study group), novices (control group))

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 on the simulator, including the complete fetoscopic laser procedure for a patient of 17 weeks' gestation with Stage III TTTS, assessed from the moment the operating room was entered until the surgery was finished and direct postoperative management was ordered.

Phase 3: Training (novices (study group))

After the pre-training test, novices who were randomized to the training curriculum received a 1-day training session from a fetal therapy expert who was not involved in the evaluation process. The curriculum comprised two components: a theoretical part and a practical session. The procedure-specific instruments provided a framework for curriculum development. An instructor script and multimedia presentation, including step-by-step actions and decisions required to perform the fetoscopic laser surgery, were developed by D.O., R.D. and S.P. 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 novices 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 in three subsequent practice rounds. In round 1, an attending fetal therapy expert demonstrated how to perform the procedure step-by-step; in round 2, the trainee performed the procedure under the supervision of the expert, who provided direct verbal feedback. In the last round, the complete procedure was performed by the trainee and evaluated directly afterwards with the expert. The novices that were allocated to the control group did not receive feedback with regard to their performance and were not involved in the training sessions.

Phase 4: Post-training test (novices (study group), novices (control group))

Within 2 weeks after the training of the study group, 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 with regard to the location of the placenta and the fetuses, but was performed on the same simulator.

Phase 5: User experience evaluation (experts, novices (study group), novices (control group))

Participants completed a survey to collect qualitative data regarding their perceptions of the value of the simulation and training. Face validity was assessed by the experts in the context of participants' opinions about realism (nine items). Educational value as well as usefulness (five items), and overall opinion about the simulator (three items) were assessed by experts and novices. All items were scored on an ordinal 10-point Likert scale, where 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 between the groups. For the SP score, a higher score signifies better performance, therefore improvement was reflected by a positive difference in pre- and post-test performance. For duration of the procedure and fetoscopy, improvement was calculated from pre-training test value minus post-training test value.

Owing 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 continuous variables. To test for differences between groups on non-ordinal categorical outcomes, Fisher's exact test was used. For ordinal outcomes, such as a Likert agreement scale, the χ^2 test was used. Spearman's correlation coefficient (r) was used to measure interobserver reliability. A correlation of r ≥ 0.9 was considered to be indicative of an excellent agreement, and $P \leq 0.05$ was considered to be statistically significant. Statistical analysis was performed with IBM SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp., Armonk, NY, USA).

RESULTS

Participant enrollment, randomization and follow-up are illustrated in Figure1. Within the three participating centers, 12 volunteers were included in the trial and subsequently randomized to the two groups. One participant was lost to follow-up and another was unable to complete the test owing to technical difficulties, therefore the results of 10 participants (study group, n = 5 and control group, n = 5) were included in the analysis.

The randomized study group with training and the 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%) participants had attended more than 100 laser procedures and 5/11 (45%) had performed more than 100 procedures themselves. A median of 10 (range, 8-20) procedures per expert were performed annually.

The expert benchmark level was set with a median SP score of 48/52 (92%) (range, 44-51), a procedure duration of 33 (range, 26 - 46) min and fetoscopy duration of 12 (range, 10 - 18) min. One (9%) expert missed a small arteriovenous anastomosis at the margin of the placenta. Results of the performance of all participants are shown in Table 2.

For the pre-training test, the median SP score for the study group was 28/52 (54%) (range, 27 - 41) vs 25/52 (48%) (range, 20 - 44) in the control group (P = 0.55). Median procedure time in the study group was 44 (range, 40 - 50) min vs 39 (range, 33 - 45) min in the control group (P=0.06). The duration of fetoscopy was 22 (range, 18-25) min in the study group vs 18 (range, 16 - 20) min in the control group (P = 0.06). In the study group, 4/5 (80%) novices did not coagulate all anastomoses compared with 2/5 (40%) in the control group (P = 0.52). In the study group, three participants missed 2/8 anastomoses and one missed 1/8 anastomoses, all located on the placental margin. In the control group, one participant missed 3/8 anastomoses in the center of the placenta and one missed 2/8 anastomoses on the placental margin.

	Expert (benchmark)		Novices (study group)		Novices (control group)		p value
	n=11	range	n=5	range	n=5	range	*
SP score †							
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	0.008
difference			+18		+ 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			- 11		- 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			- 8		- 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

Table 2. Performance of experts in fetoscopic laser surgery and novices who received simulator training or no training, assessed before and after training. SP score: surgical performance score. Data are given as median (range), median (range) (%) or n/N (%). *Performance of novices with vs those without simulator training. †Maximum surgical performance score = 52.

For the post-training test, novices in both groups showed an improvement in SP score and performed the procedure in less time than they did in the pre-training tests. The study group significantly outperformed the control group after the training session, with median SP scores of 46/52 (88%) (range, 43 - 51) vs 36/52 (69%) (range, 30 - 41) (P = 0.008). Median procedure time decreased by 11min in the study group compared to only 1 min in the control group, to 33 (range, 29 - 44) min and 38 (range, 27 - 49) min, respectively. Median fetoscopy time improved to 14 min in both groups; study group range, 10 - 20 min, control group range, 11 - 24 min (P = 0.69). In the post-training test, one participant (20%) in the study group missed 1/8 anastomoses located on the placental margin compared with no participants in the control group (P = 1.00). Figure 2 shows SP scores and procedure and fetoscopy durations for both groups in the pre- and post-training tests, plotted against the expert benchmark level.

Figure 3 shows that both experts and novices felt that the simulator was useful for training to identify the vascular equator and to practice the complete laser procedure (score of at least 8 on a 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 on all aspects.

The overall interobserver reliability of the two raters' total scores (J.A. and S.P.) for the fetoscopic laser procedure was excellent ($r = 0.984$, $P < 0.001$).

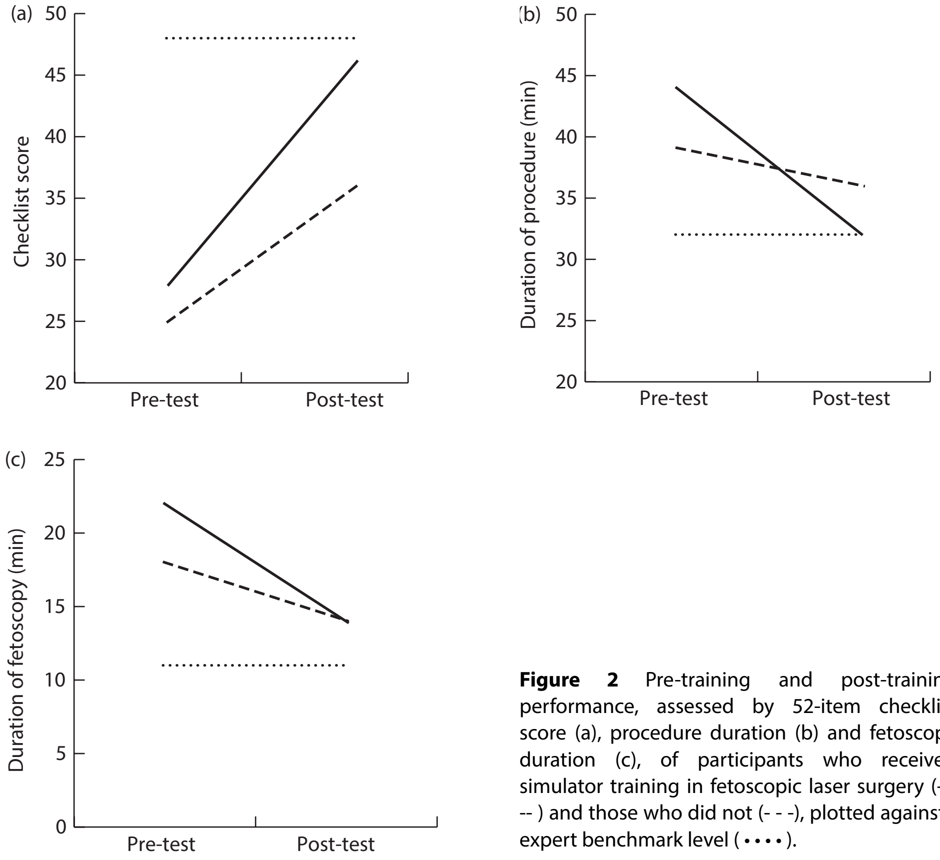

Figure 2 Pre-training and post-training performance, assessed by 52-item checklist score (a), procedure duration (b) and fetoscopy duration (c), of participants who received simulator training in fetoscopic laser surgery (-----) and those who did not (- - -), plotted against (expert benchmark level (••••).

DISCUSSION

This study shows that training in a life-like environment significantly improves the performance of fetoscopic laser surgery in a standardized simulator model. The effect of the training was evaluated using an SP score designed specifically to evaluate the performance of therapists carrying out this procedure. In this study we found no difference in the duration of the procedure 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 associated with a relatively high rate of fetal loss. Outcomes have been shown to be dependent on the operator and their experience[4,8]. Since the number of procedures undertaken per center is limited, organizing appropriate training and providing sufficient exposure are difficult[2]. To date, a standardized training curriculum is lacking. The main advantage of our simulator is that it enables the training of fetal surgeons and trainees, to gain experience in laser surgery without jeopardizing patient safety. In addition, it is readily available and allows training in the entire procedure, including instrumentation set-up, which may be beneficial for a smooth workflow.

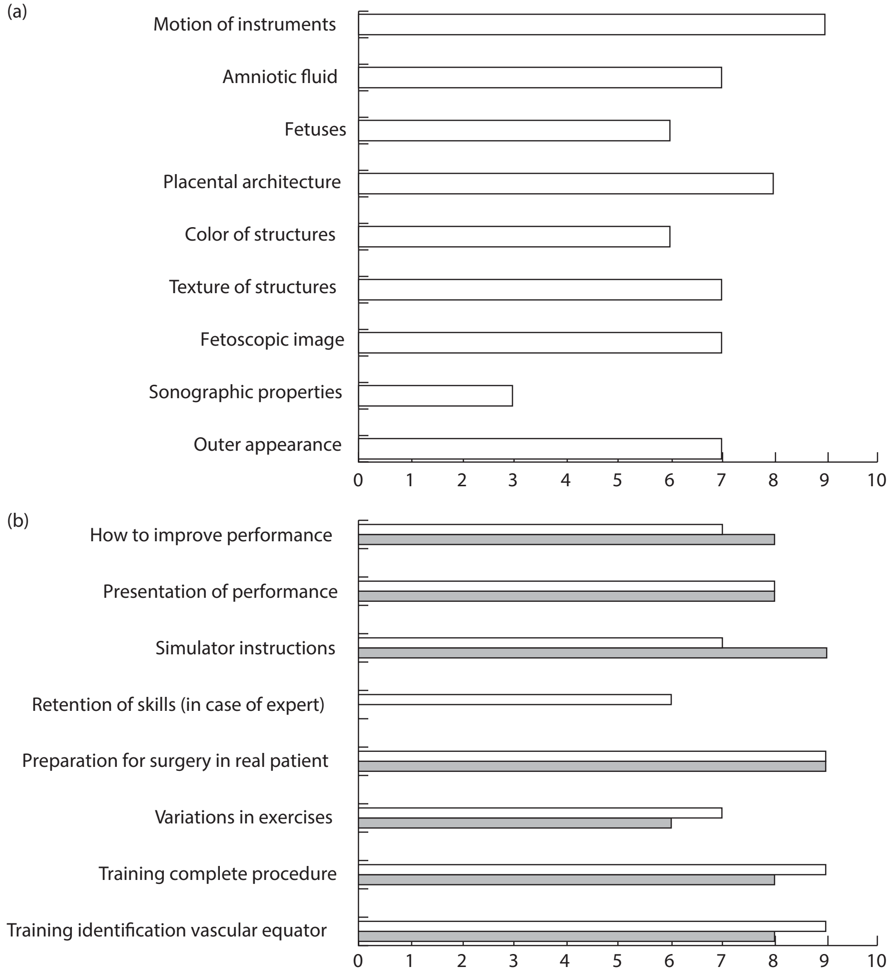

Figure 4 Responses to questionnaire regarding face validity (a) and educational value and user friendliness (b) of simulator according to experts (, n = 11) and novices (, n = 10) in fetoscopic laser surgery.

In other surgical fields, simulation based ex-vivo training has already been integrated successfully into different levels of education[14-16]. Several attempts have been made in recent years to develop simulators for invasive obstetric procedures[11,12,17,18] . Most of these simulators are designed primarily to assess performance during critical stages 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 that there is appropriate correspondence between the functional aspects of the simulator and the real-life situation[19]. However, the choice of physical resemblance for maximal training effectiveness depends on a number of factors, including the context within which the simulator is used, the sort of task that is being taught, the level of learning involved, the abilities and capabilities of the trainee, the difficulty of the task and the effect of various instructional features[20].

Most reported simulators are used for teaching in the 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 SP score and simulator appears to be useful for training novice fetal surgeons. In addition, the set-up can be used to assess the performance of practicing surgeons. Furthermore, it is ideal for testing new equipment or new techniques by 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 the experts performed the task once only. This performance standard can be used for training purposes and also for assessment or even certification in order to enhance patient safety. Performance was fairly consistent, as expressed by the small ranges in SP scores and procedure times.

The process of skill acquisition may reveal individual differences between trainees depending on cognitive capacity, perceptual speed and psychomotor abilities[24]. Setting a certain number of procedures performed on a simulator or actual patients to determine 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 important for determining 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 the use of a simulator in a training program, it should be ascertained whether it is actually teaching what it is supposed to be also known as its construct validity. In the design of a curriculum to teach surgical skills, specification of the training objectives, including identification of the procedural steps and analysis of pitfalls, is essential.

Some limitations of this study should be noted. The small sample size limits the strength of our conclusions. 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 in fetoscopic laser surgery. The general population of residents in obstetrics and gynecology is not representative of the small group of future fetoscopic surgeons-in-training.

Before training, we noticed shorter durations of the overall procedure and the fetoscopy itself in the control group. We emphasize that 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 caution. Even though a greater number of participants in the study may have provided further evidence of significant differences in outcomes and increased the power of the study, this would not reflect the clinical situation.

Such simulator training can be an effective tool for the improvement of technical skills in a safe learning environment before performing fetoscopic laser surgery in the operating room. Future studies are needed to establish reliability and implementation of such training in a wider setting. Research should be focused on validation of the curriculum to make sure that trainees who go through this curricular training process actually perform better in the operating room with greater 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 was supported by the Dutch Technology Foundation STW, which is part of the Netherlands Organization for Scientific Research (NWO), and was partly funded by the Ministry of Economic Affairs. The Medical Ethics committee of the Leiden University Medical Center declares that no formal ethical approval and written informed consent were needed for the study.

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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	

No.	Domain and substeps	Score
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 FIVE

Summary and Discussion

Summary and General Discussion

SUMMARY

This thesis consists of a series of studies on technical and procedural aspects of laser surgery for the treatment of twin-twin transfusion syndrome (TTTS), a causal treatment modality first described by De Lia et al. in 1990.[1] TTTS is caused by unbalanced blood flow across placental vascular communications between both twins called anastomoses.[2] The aim of the treatment is to close of all anastomoses in order to separate both fetal circulations. In part one, we give a general introduction to the subject and its challenges. Part two consists of studies evaluating current practice with the aim to identify potential areas of improvement. Part three deals with several techniques, the impact of laser energy and placental damage and, it introduces a model to investigate different technical parameters of the laser procedure. Finally, in part four, we discuss the development of a standardized training model for fetoscopic laser surgery.

Current practice

In **chapter 1** we describe a systematic review of the literature on outcome after laser surgery since inception of this technique. Our study showed that treatment of TTTS yielded a fair improvement in perinatal survival with the introduction of laser surgery. The 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 81-88% of pregnancies and survival of both twins in 52-54% of pregnancies. The median gestational age (GA) at delivery in these series was 32.4 weeks. We note that, 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.

A survey amongst fetal therapy centers worldwide is discussed in **chapter 2**. In this chapter, 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. Furthermore, 63% of fetal therapists and 48% of centers perform less than 20 procedures per annum. The ideal number of procedures that should be performed

to maintain high-quality results is difficult to determine[3], studies have investigated the relationship between hospital volume data and postoperative outcomes.High-volume institutions tend to have better outcomes for high-risk procedures.[4, 5]

Laser techniques

Over the years different (adaptations of) laser techniques have been proposed. The selective laser technique is currently the standard approach. Recent adaptations of this technique include the selective sequential technique and the Solomon technique. Unfortunately, only the Solomon technique has been evaluated in a randomized controlled trial.[6] The sequential selective laser technique[7], where anastomoses are closed in a specific sequence to allow for inter-procedural transfusion of blood volume from recipient to the donor twin has only been evaluated in relatively small non-randomized series. In **chapter 3** we performed a meta-analysis in order to assess the potential benefit of this technique over the standard selective laser technique. Limited evidence suggests improved double neonatal survival as well as decreased donor and recipient fetal demise with the use of the sequential technique. However, these results are based on small non-randomized studies with evident forms of bias and methodological limitations.

The damaged placenta

Through post-delivery color dye injection of the placentas that have been treated with fetoscopic laser surgery we found different degrees of placental laceration at the laser site. Hence, we set out to evaluate the impact of this placental damage on pregnancy outcome and identify possible causal factors of this damage. In **chapter 4** we developed a scoring system for placental damage and found a higher amount of laser energy used during a procedure this to be positively associated with more extensive damage. On the other hand, higher laser output power (Wattage) setting was negatively associated with placental damage. Thus, more energy lead to more damage and a higher power setting lead to less damage. We hypothesize that, with a higher power setting, energy transfer is more effective and takes shorter time and less energy than with a lower wattage. In addition, the energy is less dispersed than in a low power setting and thus leads to less collateral damage. Furthermore, more placental damage was associated with a lower GA at birth, shorter laser-to-delivery interval and higher PPROM rate.

Placenta laser model

When a new technique or instrument is invented, one should first test this in a lab setting or animal model. In TTTS this is challenging since a good animal model is lacking, the only animal known to have TTTS is the nine-banded armadillo[8]. In **chapter 5** we describe an ex-vivo perfused human placenta model for evaluation of laser surgery for TTTS. This model allows for standardized evaluation of different laser parameters and techniques. In the study, the model was used to evaluate coagulation efficiency with different laser power settings and firing angles. We demonstrated that, in a highly controlled, though realistic, environment, a 50 Watt laser power setting was more efficient in coagulating a placental vein in respect to time and total energy needed compared to a 30 Watt laser power setting. In addition, we showed that the firing angle of the laser had a great impact on coagulation efficiency. The more perpendicular the approach the more efficient coagulation is achieved. Bleeding due to vessel wall disruption, although rare, occurred slightly more often with lower power settings and with a more tangential laser angle. We hypothesize that a low power setting used for a longer period of time causes more endothelium damage[9] and without swift occlusion of the vessel by coagulated blood, this might increase the risk of vessel wall disruption and bleeding.

Laser training model

Laser surgery for TTTS is a technical skill that takes extensive training to achieve and maintain. In the final part of this thesis we developed and validated a training and evaluation tool for fetoscopic laser surgery that can aid to maintain a high standard of clinical performance.

In **chapter 6** we present an international expert consensus on the technical approach and identification of the essential steps of fetoscopic laser surgery for TTTS. By means of a Delphi consensus method including a broad list of internationally renowned specialists in fetal therapy, we produced a list of 55 essential sub-steps. This study provided a first step towards an authority-based procedure-specific evaluation tool for fetoscopic laser surgery for the treatment of TTTS. In order to determine the reliability and construct validity of the evaluation tool developed in **chapter 6**, we assessed the inter-observer reliability and construct validity of this tool in **chapter 7**. We developed a realistic simulator setting for fetoscopic laser surgery and used the tool to score expert and novice fetal surgeons performing the complete procedure. The study showed that the instrument effectively distinguished the performance of experts and novices with an acceptable level of inter-observer reliability. Finally, in **chapter 8** we evaluated whether fetal therapists in training could benefit from simulator based training based on the evaluation tool as developed in **chapter 6**. We performed a pilot randomized trial assigning novices to either simulator training or no training. The study showed that training in a life-like environment significantly improves the performance of fetoscopic laser surgery in a standardized simulator model. No differences in duration of the procedure or presence of missed anastomoses between the groups were seen. An expert benchmark levels for the curriculum was defined to make it proficiency based. Feedback provided by the participants indicated that simulator training was perceived as a useful educational activity.

GENERAL DISCUSSION

The introduction of fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS) as a treatment option, 25 years ago, led to a major improvement in perinatal outcome. With this, a causal treatment became available. Not only did this treatment prolong pregnancy, it also improved perinatal outcome[10] and long term neurodevelopmental outcome[11] of the affected twin pairs.

In this thesis, we have focused on different aspects of the treatment process. We evaluated inter center differences in program setup and treatment strategies, and the improvement of outcome over the past decades in respect to different techniques. Furthermore, we investigated some technical aspects of the procedure in a newly developed life-like model.

Evaluation of current practice shows that there still is room for improvement. Although a big step ahead was made with fetoscopic laser surgery, since then no big improvement in perinatal outcome was achieved. In about 80-90% at least one twin survives and in about 50-60% both twins survive. In order to further improve outcome of TTTS complicated pregnancies worldwide this thesis touches on several subjects that could aid fetal therapist in optimizing their treatment strategy.

Center volume and operator proficiency

Even though limited evidence concerning the ideal number of procedures that should be performed to maintain high-quality level of care exists[3], several studies have investigated the relationship between volume data and outcomes in other fields of surgery. Better outcomes have been reported in high-volume institutions for high-risk procedures[4, 5, 12]. This is in line with findings from learning-curve and monitoring studies. These show that a number of approximately 20 to 30 procedures per year is required to maintain a requisite skill level[3, 13]. To optimize surgical outcomes, concentration of care for this highly specialized procedure has been advocated.[14] Although, in case of TTTS 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] Centralization of the treatment of monochorionic twin pregnancies in expert centers is preferable but largely depend on the regional referral system. Therefore, such expert centers not only have a responsibility in the care for the patient, but should also educate referring institutions in early detection and referral of TTTS complicated pregnancies.

Evidence based evaluation of new techniques

In modern medicine an evidence based approach is crucial, new techniques and technology should be tested in proper (animal) studies that lead to a good level of evidence before adoption to clinical practice. As fetal therapy is a young, and rapidly developing subspecialty, new ideas are often tried out and evaluated in small series. For instance, as shown in chapter 2 and 3, the sequential laser technique has been adopted by a significant number of therapists while the evidence proving this technique to be beneficial is wafer-thin. Unfortunately, only few attempts have been made in performing randomized controlled trials, and to date, only one trial was completed.[6]

The sequential laser technique, as described in chapter 3, is based on the following theory. By first coagulating anastomoses that flow towards the recipient and finally the ones that flow towards the donor some transfusion of blood from the recipient back to the donor occurs, which is thought to benefit the donor. While the actual volumetric blood flow over an arteriovenous anastomosis is difficult to assess, studies suggest this to be in the order of 5mL/24h.[16] The duration of a laser procedure from entering the womb until removing the scope ranges between 10-20 minutes on average, as shown in chapter 8. In 15 minutes, a transfusion of approximately 0.05mL will occur over one anastomosis. Based on this finding, one could suspect the effect of a sequential approach to be clinically insignificant. The only way to properly investigate such a technical adaptations is performing a proper randomized trial assigning participants to either selective or selective sequential laser technique.

Primum non nocere: Laser damage and coagulation efficiency

As with many forms of surgery, also with laser surgery for TTTS some 'harm' is unavoidable or even desired. When using laser energy in a precarious situation as a pregnancy it is important to be aware of the risks and disadvantages. In chapter 4 we evaluated placental damage after laser therapy and showed that the extent of this damage is correlated with PPROM and gestational age at delivery. Branisteau et al. showed that by coagulating an anastomosis the functionality of the underlying cotyledon is compromised[17]. In contrast with these findings Emery et al show that the impact of the laser energy remains largely limited to the chorionic plate. We found the amount of damage to be related with the amount of energy used. This finding is in line with the trend seen by a recent study by Zhao et al., where total laser energy seemed to be associated with chorioamnionitis. This study showed that, after a laser procedure, more chorioamnionitis and funisitis is seen compared to non-lasered monochorionic (MC) twin pregnancies.[18] A possible explanation for these findings could be that, due to necrosis of the lasered tissue, cytokine-release and other inflammatory responses occur that have an impact on PPROM and term of delivery. Most importantly the success of the laser treatment is defined by the completeness of the procedure; close all vessels off but do as little harm as possible.

A better understanding of the impact of what we do could help us improve outcome. The ex-vivo perfused human placenta model described in this thesis showed the difference in coagulation efficiency between two different power settings. We learnt that 80 Watts is more efficient than 50 Watts. Nevertheless, the optimal setting still has to be investigated and is likely highly dependent on the circumstances such as vessel type, diameter, flow and amniotic fluid characteristics.

Training before trying, evaluation after doing

Currently, in western countries, fetoscopy is readily available in contrast to a large part of the world where this treatment modality is still inaccessible. It is a matter of time when centers in these areas start performing laser therapy for TTTS. We anticipate a significant increase in fetal therapists, and with this in mind we developed a validated simulator-based training curriculum for fetoscopic laser surgery. Randomized trials in the field of general surgery literature have shown that simulation-based training leads to detectable benefits for trainees in clinical settings.[19, 20]

Fetoscopy simulator courses are ideally organized by expert centers, nevertheless startup centers should invest in obtaining a simulator themselves in order to keep training and improve their skill. When starting a fetoscopy center it is of utmost importance to introduce a good quality control system and to evaluate short, and long-term outcome. Centers should not hesitate to publish their early series, even if the results are poor. Most of the published series are from high volume, high experience centers. It is important to note that these numbers are not a good benchmark for startup centers. A startup center benchmark is needed for quality control and evaluation of center learning curve. Therefore, it is important to follow up participants and persuade them to publish early results in order to create this benchmark.

Conclusions

This thesis describes a, newly developed, ex-vivo human placenta model mimicking the intrauterine conditions of feto-placental circulation. The model allows for experiments to take place in a highly-controlled setting and can be used to study laser coagulation as presented in this thesis in chapter 5. It can be of great scientific value when it comes to testing new instruments and (laser) techniques.

Chapter 4 of this thesis suggests that it is important to use as little energy (Joule) as possible during laser surgery for TTTS. Efficient coagulation, using less energy, decreases the extent of placental damage, reduces the incidence of PPROM and extends the pregnancy duration. In Chapter 5 we showed that the use of a higher power setting (Wattage) and a perpendicular approach leads to more efficient coagulation, and could be a good strategy.

Furthermore, we developed and validated a highly realistic training model that can aid current, and future fetal therapists to improve their skill level and keep it up to par. While fetoscopy is gaining popularity worldwide it is of utmost importance that the new generation of fetal therapists receive high level training.

Future perspectives

We believe that significant improvement opportunities prevail regarding perinatal outcome after laser surgery for TTTS 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 preventing short-term neonatal morbidity should not be the only goals. The ultimate goal should be 'disease-free survival' of both twins, and focus on reducing the rate of long-term neurodevelopmental impairment.

Our developed ex-vivo human placenta model can be used to further investigate different parameters of laser surgery and optimize the treatment strategy. Future experiments could include defining the ideal laser power setting in different situations. Also, experiments comparing different types of laser, different vessel diameters and types combined with histological studies[21] will increase our knowledge on the actual effect of laser energy efficiency and collateral tissue damage. The impact of the amount of energy and placental damage, as investigated in chapter 4, and its association with PPROM and preterm delivery needs to be explored further. With a prospective study focused on energy use, histologic findings and pregnancy outcomes we hope to be able to shed more light on this subject.

Although, some development was seen in the field of fetoscopic instruments mainly focusing on decreasing scope diameter and improving image quality, we think the next step is developing smart instruments. Instruments that can measure vessel diameter and assess successful coagulation could potentially positively impact coagulation efficiency. Furthermore, instruments that can better reach difficult areas of the placenta or look and coagulate at an angle could also improve the outcome after laser surgery for TTTS.

The anticipated increase of the availability of fetoscopic laser surgery worldwide will lead to an upsurge of small volume centers offering this form of treatment. In order to gain a proficient level of skill and expertise we think it is important that a regular training program is available and that quality assessment, either by cusum analysis[3] or by regular publication of series, is part of the procedure. Another tool that may aid these start-up centers in gaining expertise is telementoring. With a telementoring program a starting, or low-volume center can be supervised by an expert center, especially in complicated cases. Telementoring can be achieved at low cost wit standard AV equipment and a broadband internet connection.[22]

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Nederlandse Samenvatting

Dit proefschrift bestaat uit een reeks van studies over technische en procedurele aspecten van de laserchirurgie voor de behandeling van tweeling transfusie syndroom (TTS), een causale behandel modaliteit, voor het eerst beschreven door De Lia et al. in 1990.[1] TTS wordt veroorzaakt door onevenwichtige bloedstroom over communicerende vaten tussen beide tweelingen (anastomosen) op het placentaoppervlak.[2] Het doel van de behandeling is het sluiten van alle anastomosen om zo beide foetale circulaties te scheiden. In het eerste deel geven we een algemene inleiding over het onderwerp en de uitdagingen. Het tweede deel bestaat uit studies waarin huidige praktijk wordt geëvalueerd met als doel mogelijke gebieden te identificeren waar verbeteringen kunnen worden aangebracht. Deel drie belicht verscheidene technieken, het effect van laser energie en placenta beschadiging, en introduceert een model om verschillende technische parameters van de laserbehandeling te onderzoeken. Ten slotte, in het vierde deel, bespreken we de ontwikkeling van een gestandaardiseerd trainingsmodel voor foetoscopische laserchirurgie.

De huidige praktijk

In hoofdstuk 1 beschrijven we een systematisch overzicht van de literatuur over uitkomst na laserchirurgie sinds de introductie van deze techniek. De studie toonde aan dat behandeling van TTS een behoorlijke verbetering in perinatale overleving doormaakte met de introductie van laserchirurgie. De evaluatie toont een significante toename in de perinatale overleving sindsdien. Combineren van alle gepubliceerde series, als benchmark, toont een perinatale overleving van 'ten minste één' tweeling na laserbehandeling van in 81- 88% van de zwangerschappen en overleving van beide tweelingen in 52-54% van de zwangerschappen. De mediane zwangerschapsduur bij geboorte in deze serie was 32,4 weken. Evaluatie van technische of andere aanpassingen van chirurgische technieken met behulp van historische controles wordt beperkt door invloed van verschillende factoren zoals een toename van de ervaring na verloop van tijd, het leercurve-effect en verbeterde neonatale zorg.

Een enquête onder de foetale therapie centra wereldwijd wordt besproken in hoofdstuk 2. In dit hoofdstuk tonen we aanzienlijke verschillen in patiëntkarakteristieken, instrumenten en technieken tussen de centra aan. Ten minste gedeeltelijk, kunnen die verschillen worden toegeschreven aan het aantal patiënten en de geografische omstandigheden van de centra. Over de hele wereld worden verschillende criteria voor de lasertherapie gebruikt onder gevestigde foetale geneeskunde centra. Met name zijn er verschillen in beperkingen van zwangerschapsduur en cervixlengte waarbij lasertherapie wordt aangeboden. Verschillen in selectie van patiënten, verwijzing en behandelopties kunnen significante invloed hebben op de perinatale uitkomst. Bovendien, voert ongeveer 63% van foetale therapeuten en 48% van de centra minder dan 20 operaties per jaar uit. Ook al is er beperkt bewijs met betrekking tot het ideale aantal operaties dat moeten worden uitgevoerd om een goed vaardigheidsniveau en hoge kwaliteit zorg te behouden [3], toch hebben vele studies de relatie tussen ziekenhuis volume en postoperatieve chirurgische resultaten onderzocht in andere gebieden van geneeskunde. Betere resultaten zijn gerapporteerd in hoog-volume instellingen voor hoog-risico procedures. [4, 5]

Lasertechnieken

Door de jaren zijn verschillende (aanpassingen van) lasertechnieken voorgesteld. Helaas is alleen de Solomon-techniek geëvalueerd in een gerandomiseerde gecontroleerde trial. [6] Een andere recente techniek is de sequentiële selectieve lasertechniek [7], waarbij anastomosen in een bepaalde volgorde worden gesloten waardoor er inter-procedurele transfusie van bloedvolume van de ontvanger naar de donor tweeling kan plaatsvinden. In hoofdstuk 3 voerden we een meta-analyse uit om de mogelijke voordelen van deze techniek evalueren ten opzichte van de standaard selectieve lasertechniek. Enige aanwijzingen voor verbeterde neonatale overleving van beide kinderen en verminderde donor en ontvanger intra uteriene sterfte werd gezien bij de sequentiële techniek. Echter, deze resultaten berusten op kleine, niet-gerandomiseerde studies met duidelijke vormen van bias en methodologische beperkingen.

De beschadigde placenta

Bij injectie studies van placenta's behandeld met laserchirurgie zagen wij verschillende gradaties van placenta schade ter plaatse van de laserbehandeling. Vandaar dat we de invloed van deze placenta schade op de zwangerschap uitkomst hebben onderzocht en geëvalueerd wat de mogelijke oorzakelijke factoren van deze schade zijn. In hoofdstuk 4 ontwikkelden we een gradatie systeem voor placenta schade en toonden we aan dat placentaire schade een positieve associatie heeft met de hoeveelheid laserenergie die tijdens een procedure wordt gebruikt. Anderzijds, werd deze schade negatief geassocieerd met de laser vermogen instelling. Dus meer energie leidt tot meer schade en een hoger laser vermogen leidt tot minder schade. Onze hypothese is, dat met een hoger vermogen de energie-overdracht efficiënter is en dat het minder tijd en energie kost om een vat te coaguleren dan met een lager vermogen. Bovendien, leidt de grotere hoeveelheid benodigde energie bij een laagvermogen mogelijk tot het optreden van meer collaterale schade. Verder werd uitgebreidere placenta schade geassocieerd met een lager zwangerschapsduur bij de geboorte, kortere laser-geboorte interval en hogere incidentie van PPROM onder 32 weken. Een recente studie door Zhao et al. toonde aan dat, na een laserbehandeling, meer chorioamnionitis en funisitis wordt gezien in vergelijking met niet-gelaserde monochoriale (MC) tweelingzwangerschappen. [8] Een mogelijke verklaring hiervoor is de iatrogene placenta weefselnecrose veroorzaakt door lasercoagulatie dat een maternale ontstekingsreactie kan induceren.

Placenta laser model

Wanneer een nieuwe techniek of instrument wordt ontwikkeld, moet men dit eerst testen in een laboratoriumomgeving of een diermodel. In TTS blijkt dit een uitdaging, een goed diermodel is niet voorhanden. Het enige dier waarvan bekend is dat TTS voorkomt is het negenbandgordeldier[9]. In hoofdstuk 5 beschrijven we een ex-vivo geperfundeerd menselijke placenta model voor de evaluatie van laserchirurgie voor TTS. Dit model maakt gestandaardiseerde evaluatie van verschillende laser parameters en technieken mogelijk. In de studie werd het model gebruikt om coagulatie efficiëntie van verschillende laservermogen instellingen en aanvuur hoeken te evalueren. We hebben aangetoond dat, in een zeer gecontroleerde maar realistische opstelling, een 50 Watt laservermogen efficiënter een placentaire vene coaguleert met betrekking tot duur en totale energie vergeleken met een 30 Watt laservermogen. Bovendien toonden we aan dat de aanvuurhoek van de laser een grote invloed op de coagulatie efficiëntie heeft. Met een loodrechte aanvuurhoek, wordt efficiëntere coagulatie bereikt dan met een meer tangentiële hoek. Bloeding door het barsten van de vaatwand, hoewel zeldzaam, deed zich iets vaker met een lager vermogen en met een meer tangentiële laser hoek. Onze hypothese is dat bij een laag vermogen-instelling door de langere duur en langzamere energieoverdracht meer endotheel schade optreedt [10] en dat zonder snelle afsluiting van het vat door gestold bloed, dit het risico op een vaatwand ruptuur kan vergroten.

NL

Laser training model

Laserchirurgie voor TTS is een technische vaardigheid waarvoor een gedegen opleiding nodig is om een adequaat niveau te bereiken en te handhaven. In het laatste deel van dit proefschrift hebben wij een training en evaluatie-instrument voor foetoscopische laserchirurgie ontwikkeld en gevalideerd. Dit instrument kan helpen sneller een betere vaardigheid voor de laserchirurgie te ontwikkelen en te behouden.

In hoofdstuk 6 presenteren we een internationale expert consensus over de technische aanpak en de identificatie van de essentiële stappen van foetoscopische laserbehandeling voor TTS. Door middel van een Delphi consensus methode met medewerking van een uitgebreide lijst van internationaal gerenommeerde specialisten in foetale therapie, hebben we een lijst met 55 essentiële sub-stappen geproduceerd. Dit onderzoek leverde een eerste stap naar een op autoriteit-gebaseerd procedure-specifiek evaluatie-instrument voor foetoscopische laserchirurgie voor de behandeling van TTS. Om de betrouwbaarheid en de geldigheid van het evaluatie-instrument uit hoofdstuk 6 te onderzoeken hebben we de inter-observer betrouwbaarheid en validiteit van dit instrument beoordeeld in hoofdstuk 7. We ontwikkelden een realistisch simulator model voor foetoscopische laserchirurgie en gebruikten het evaluatie-instrument om deskundige en beginnende foetale chirurgen tijdens het uitvoeren van de volledige laser procedure te scoren. De studie toonde aan dat het instrument effectief was in het onderscheiden van de prestaties van experts en beginners met een aanvaardbaar niveau van inter-observer betrouwbaarheid. Tenslotte werd in hoofdstuk 8 onderzocht of foetaal therapeuten in opleiding kunnen profiteren van simulator training op basis van de evaluatie-instrument ontwikkeld in hoofdstuk 6. We voerden een pilot gerandomiseerde trial uit waar beginners werden gerandomiseerd voor ofwel simulator training of geen training. De studie toonde aan dat de training op het simulatormodel in een realistische omgeving de prestaties van foetoscopische laserchirurgie aanzienlijk verbeterde. Er werd geen verschil in duur van de procedure of aanwezigheid van gemiste anastomosen tussen de groepen waargenomen. Een expert referentieniveau voor het curriculum werd gedefinieerd door observatie van ervaren foetaal therapeuten. Feedback van de deelnemers gaf aan dat simulator training werd gezien als een bruikbare educatieve activiteit.

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PART SIX

Appendices

PUBLICATIONS
CURRICULUM VITAE
DANKWOORD
LIST OF ABBREVIATIONS

AP

PUBLICATIONS

1. **J. Akkermans**, M. Diepeveen, W. Ganzevoort, G.A. van Montfrans, B.E. Westerhof, H. Wolf, Continuous Non-Invasive Blood Pressure Monitoring, a Validation Study of Nexfin in a Pregnant Population, Hypertension in Pregnancy 28(2) (2009) 230-242.

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CURRICULUM VITAE

Joost Akkermans was born on February 9, 1982, at home in De Heen, a small village in the south of the Netherlands. Early on in life he developed an entrepreneurial mind. At an age of 17 he started a business providing internet services for business clients. After graduating from RK. Gymnasium Juvenaat in 2002 he first studied Law at Leiden University. One year later he started his medicine study at the University of Amsterdam. As a medical student, he started conducting research in the field of pregnancy hypertension and pre-eclampsia.

After obtaining his medical degree (cum laude) from the University of Amsterdam in 2011 he first worked as a research physician at the BC Women's Hospital of the University of British Columbia in Vancouver, Canada. Back in the Netherlands he continued his scientific endeavors combined with clinical work as a physician at the department of obstetrics and gynecology of the OLVG hospital in Amsterdam.

In 2013 he came in contact with prof. dr. Dick Oepkes who offered him an STW (Dutch Technology Foundation) PhD scholarship to evaluate, develop and improve techniques for laser surgery for twin-twin transfusion syndrome. This led to numerous publications, presentations at international conferences, training sessions and finally, this thesis.

He started his residency in Obstetrics and Gynecology in 2015 at the HagaZiekenhuis in The Hague and continued this residency at the Leiden University Medical Center where he now works.

Joost currently resides with his wife Carolien and two children, Guus and Keet in Middelie, a small village in North-Holland.

DANKWOORD

Promoveren is een mooie ervaring, mooi omdat je het kunt delen met anderen. Het is een wandeling waarbij je soms langs een tropisch strand wandelt en op een ander moment een berg beklimt... en daar dan van afdondert. Gelukkig zijn er op die momenten belangrijke mensen die je steunen. Voor hen dit dankwoord.

Eline, dank dat je me met Dick in contact bracht. Dick, ik wandelde binnen met een rugzakje promotie ervaring maar jij hebt me promoveren doen ervaren. Jouw kijk op de zaken is inspirerend, prikkelend en uitdagend. Je bent altijd bereikbaar en bereid om een idee een kans te geven. Ik kan me werkelijk geen betere promotor toewensen.

Enrico, de meest ingewikkelde projecten of artikelen weet jij altijd vlot te stroomlijnen. Daarbij werkt jouw wetenschappelijke enthousiasme aanstekelijk.

Annemieke, jouw deur staat altijd open op de moeilijke momenten kan ik altijd voor een luisterend oor of een goed advies terecht. Daarnaast altijd even scherp wanneer je een stuk redigeert.

Dank aan het gehele foetale therapie team in het LUMC voor alle steun, data en inspiratie. Met name Frans, jouw combinatie van handigheid en ICT kennis is een voorbeeld voor mij.

Dear colleagues of the Universities of Leuven, Karolinska and the Mt. Sinai hospital in Toronto, thank you for your collaboration. I am looking forward to our future collaboration.

Ivanka en Gladys, de jaren op K6 kan ik me niet voorstellen zonder jullie. Altijd staan jullie klaar om te helpen, vragen is vaak niet nodig. Dank daarvoor!

Alle collega-onderzoekers, promoveren doe je niet alleen. Ook de onderzoeksdagen, cursussen en zeilwedstrijden helpen mee aan een gebalanceerde promotie. Opleiders, gynaecologen, verloskundigen en verpleegkundigen van het HagaZiekenhuis en LUMC dank voor jullie interesse, motiverende woorden en opleidingsmomenten die jullie mij blijven bieden.

Mijn paranimfen, Suzanne en Femke. Waar moet ik beginnen, op een klein kamertje op K6. Synergie lijkt het juiste woord. In een relatief korte tijd hebben we veel bereikt. Veel

wetenschappelijke projecten hebben we bedacht en uitgevoerd, trainingen gegeven over de hele wereld en mooie reisjes gemaakt. Bedankt voor al deze, en toekomstige momenten.

Geert-Jan, mijn sparringpartner sinds jaren, wat heb ik jou verveeld de afgelopen jaren met verhalen en vragen over wetenschap en geneeskunde. Nooit heb je de indruk gewekt het vervelend te vinden.

Papa, Mama, Jeroen en Robbert jullie staan aan de basis van wie ik nu ben. Jullie steun, vertrouwen en interesse heeft mij dit pad doen bewandelen.

Lieve Carolien zonder jou was het überhaupt niet gelukt. Jij inspireert mij, maakt me aan het lachen en stuurt mij op de momenten dat ik sturing nodig heb. Dank voor jouw oeverloze steun.

Guus en Keet dank voor jullie…

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