Chapter 2

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

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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 $P \leq 0.05$ 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).

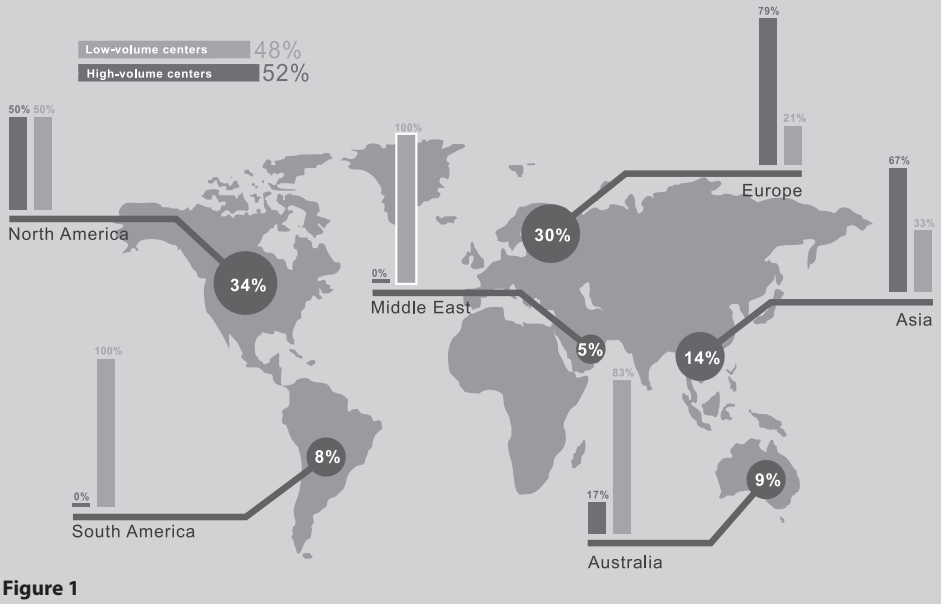

Figure 1
Geographical location of respondents and corresponding distribution of low-volume (n=31, 48%) ( ) vs high-volume (n=33, 52%) ( ) fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

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

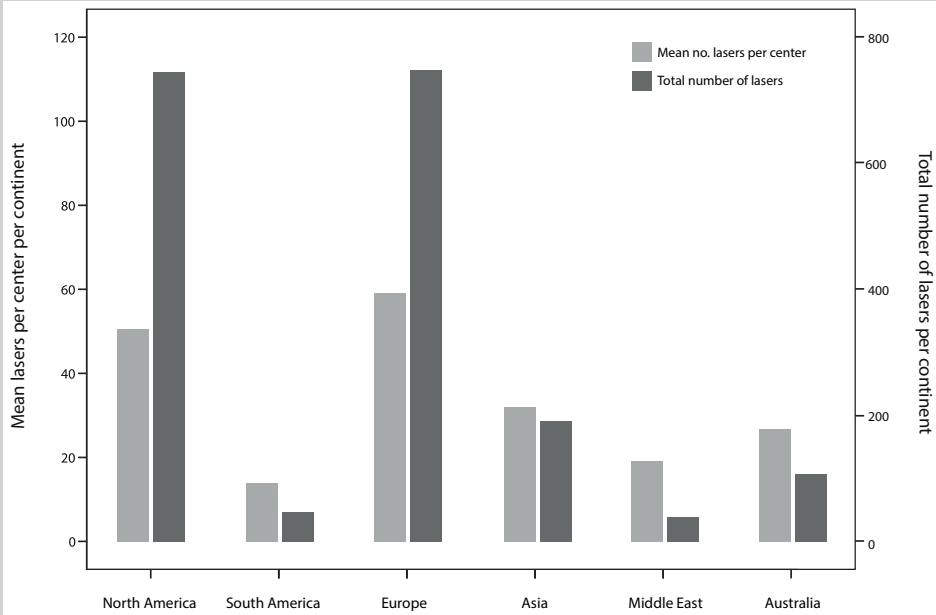

Figure 2
Total number of reported annual laser procedures ( ) according to geographical area and corresponding mean number of procedures per center ( ) in fetal therapy centers offering laser treatment for twin–twin transfusion syndrome.

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

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

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

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

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

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

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

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

Characteristic	All (*n* = 64)	Type of center		*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

Data are given as *n* (%).

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

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

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

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

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

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

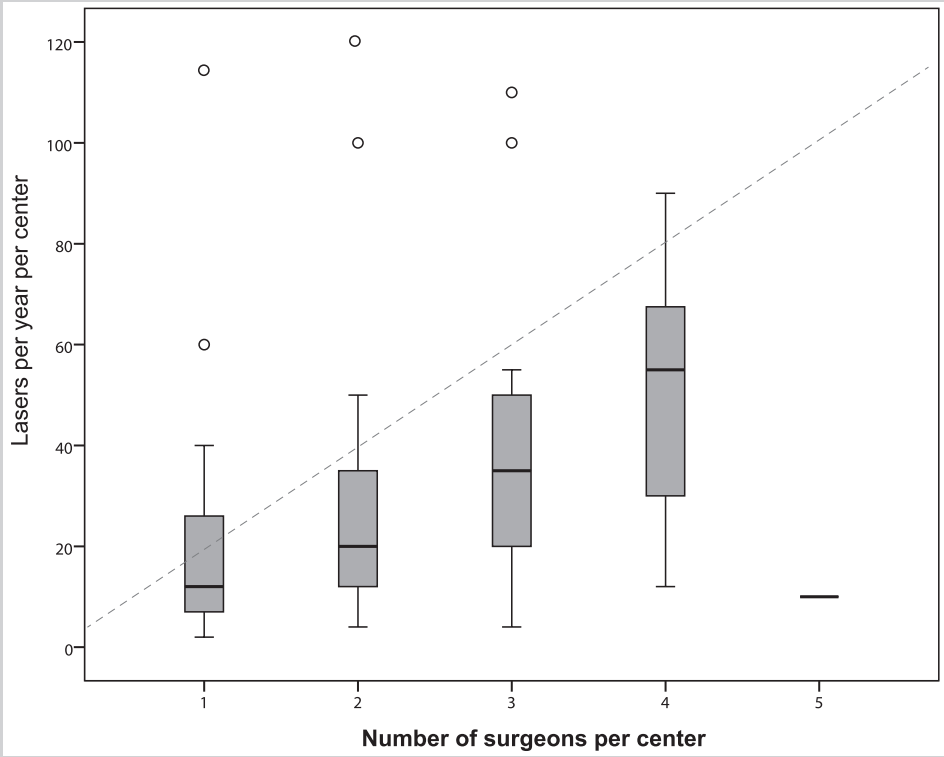

Figure 3
Box-and-whisker plots of number of surgeons per fetal therapy center according to number of procedures performed annually in centers offering laser treatment for twin–twin transfusion syndrome. Boxes represent median and interquartile range, whiskers are range excluding outliers and circles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

DISCUSSION

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

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

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

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

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

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

In 55% of fetal medicine centers selective termination is available as an option, but it is

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

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

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

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

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

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