The Impact of Entry Technique and Access Diameter on Prelabour Rupture of Membranes Following Primary Fetoscopic Laser Treatment for Twin–Twin Transfusion Syndrome

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Key Words

Fetal endoscopic surgery · Fetal therapy · Laser therapy · Membrane · Monochorionic twin · Premature rupture of membrane · Preterm delivery · Twin pregnancy · Twin-twin transfusion syndrome

Abstract

Objective: To evaluate the impact of entry method and access diameter at fetoscopic surgery for twin–twin transfusion syndrome in twin pregnancies with at least one survivor. The outcomes evaluated were prelabour rupture of membranes (PROM) and birth <4 weeks, preterm birth (PTB) <28 weeks, and latency to birth. **Methods:** A retrospective analysis of prospectively collected data of consecutive laser procedures from 6 centers was performed. Three entry methods (sheath + trocar; cannula + trocar; cannula + Seldinger) and 6 access diameters (2.3, 3.0, 3.3, 3.5, 3.8, 4.0 mm) were used. Exclusion criteria were subsequent invasive interventions, termination of pregnancy or double fetal death after laser. Multivariate analysis was performed to determine

risk factors for the study outcomes. **Results:** Six hundred seventy three fetoscopic laser cases were analyzed. The use of different entry methods and access diameters did not affect PROM or birth <4 weeks, or latency from laser to birth. Access diameter was associated with PTB <28 weeks. Cervical length was associated with PROM and birth <4 weeks, and latency from laser to birth. **Conclusion:** Instrument choice at fetoscopic laser procedures did not affect outcomes <4 weeks. Access diameter may affect the likelihood for PTB <28 weeks. Cervical length is critically associated with obstetrical outcomes following laser surgery.

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Introduction

Twin to twin transfusion syndrome (TTTS) affects up to 9% of monochorionic diamniotic (MCDA) twin pregnancies [1]. It is readily diagnosed by ultrasound using internationally accepted criteria for discordant amniotic fluid volume [2–4]. Although the pathophysiology is not

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Fig. 1. Instruments used for different uterine entry methods. Sheath + trocar: photo of a fetoscopic sheath, loaded with stabbing trocar used for 'direct' entry (a) and fetoscope, laser fiber and deflecting mechanism (b); cannula + trocar: artistic impression of

rigid cannula loaded with a pyramidal trocar (c); cannula + Seldinger: artistic impression of flexible cannula loaded with conical dilator over guide wire, with a pyramidal trocar drawn alongside, which may be loaded for cannula + trocar entry (d).

completely understood [2], fetoscopic laser ablation of placental vascular anastomoses combined with amniodrainage effectively separates the 2 fetal circulations and corrects the polyhydramnios, the factors linked inextricably to poor pregnancy outcome. Compared with no treatment or amniodrainage, fetoscopic laser surgery reduces the rate of preterm birth (PTB) and increases the likelihood of survival without neurologic morbidity [3–5].

Since the first report [6] of fetoscopic laser surgery in 1990, many different entry techniques, instruments and access diameters have been described for this procedure [7]. Any refinements in instrumentation and technique have been made to improve efficacy and reduce compli-

cations [8]. Fetoscopic surgery may be performed percutaneously [4, 9] or through mini-laparotomy [10, 11]. Methods to enter the gestational sac based on ultrasound guidance (fig. 1) include direct entry with a fetoscope using an individually shaped stabbing sharp pyramidal trocar within the sheath of the fetoscope (sheath + trocar) [8] or entry with a cannula to create a working entry port (referred to as cannula) for passage of the fetoscope or other instruments [3, 10–12]. This cannula can be inserted in 1 of 2 ways. The Seldinger technique, also used for vascular access, involves needle-and-guidewire insertion over which a dilator and cannula are passed (cannula + Seldinger) [10, 11]. Alternatively, the cannula is inserted

directly with a trocar, similar to laparoscopic entry (cannula + trocar) [12]. Access outer diameters for fetoscopic surgery reportedly range from 2.3 mm (7 French) to 4.0 mm (12 French) [7].

Intuitively, these technical aspects of fetoscopy may affect the rates of prelabour rupture of membranes (PROM), pregnancy loss and PTB. To date, the evaluation of entry method and access diameters on obstetric outcomes has been limited, as it requires large data sets and contributions from multiple centers [5, 13, 14]. The purpose of the study was to evaluate the impact of choice of entry instrument at fetoscopic laser surgery for TTTS in twin pregnancies with at least one survivor at birth. Specifically, the entry method and access diameter were analyzed against other factors considered to influence the timing of PROM and birth following the laser procedure.

Materials and Methods

This was a multicenter retrospective analysis of prospectively collected data on consecutive fetoscopic laser procedures for mid-gestational TTTS in MCDA twin pregnancies with intact membranes. The centers participating in this study were identified because they use different entry methods and access diameters: Mater Mothers' Hospital (Brisbane, Australia); University Hospitals Leuven (Leuven, Belgium); Alpert Medical School of Brown University (Providence, R.I., USA); University Medical Center Hamburg-Eppendorf (Hamburg, Germany); King Edward Memorial Hospital (Perth, Australia); and Necker Hospital (Paris, France). Each center provided data for all consecutive laser cases performed before January 1, 2008. The study was approved by the human research ethics committees at each participating center. Data were provided in a purpose-designed standardized spreadsheet containing the following variables: the fetal treatment center, maternal characteristics (age, parity, miscarriage history), TTTS disease characteristics (before laser: prior amnioreduction; at the time of laser: cervical length; disease stage according to the Quintero classification (I–IV); deepest vertical pocket (cm); placental location (anterior/posterior); gestational age (GA; weeks); placement of cervical cerclage), procedural characteristics (anesthetic technique; uterine entry method (sheath + trocar; cannula + trocar; cannula + Seldinger); access diameter (mm); number of ports used; amniotic fluid volume drained (ml); occurrence of perioperative intra-amniotic bleeding), post-laser characteristics (occurrence of, and GA at diagnosis of single or double in utero fetal death [IUFD]), and obstetrical outcomes (occurrence of, and GA at PROM; GA at birth). From the data, the latency to PROM (interval from procedure to PROM) or to birth (interval from procedure to birth) were calculated. PROM was defined as the loss of amniotic fluid per vagina prior to labour onset or delivery, confirmed clinically by visualization of amniotic fluid and/or nitrazine positive test.

Outcome measures for analysis included the occurrence of PROM and birth <4 weeks of the procedure, PTB <28 weeks, and latency to birth. We restricted our study to twins, cases that did not

have postoperative double IUFD, and cases that did not undergo subsequent invasive procedures, because these factors would have directly influenced the studied obstetric outcomes.

Statistical Analysis

Variables were tested for normal distribution using D'Agostino and Pearson omnibus normality testing, and data are reported using appropriate descriptive statistics (n (%); mean $\pm$ SD; or median with interquartile range [IQR]). Bivariate analysis was initially performed to determine appropriate variables (from the maternal, TTTS disease, procedural and post-laser characteristics) for the multivariate analysis of each study outcome. Variables to be included had a p value less than 0.20 on the bivariate analysis. The number of variables used in a multivariate analysis was restricted by the number of outcome events (i.e. 1 variable per 10 events) [15]. The number of cases and centers included in a multivariate analysis were determined by the variables used; to be included, all data for the relevant variables to be used in the analysis had to be available. Mixed-effects multivariate linear or logistic regression analyses were then undertaken to analyse the effect of the entry method and access diameter on study outcomes after adjusting for included variables.

The fetoscopic center was included as a random effect in the multivariate model. An interaction term between the entry method and access diameter was included in the initial analyses; however, as it was not significant, the results are not reported.

In the analysis of PROM, IUFD was included as a variable only if the GA at diagnosis was documented before PROM. In the analysis of birth outcomes, PROM and IUFD were included as variables only if the GA at PROM or IUFD were documented before the birth. Cases with missing data on GA at birth were considered lost to follow-up.

Results are reported as a coefficient (for continuous outcomes – latency to birth) or adjusted OR (for categorical outcomes) with associated 95% CI. Cannula + trocar was used as the reference for entry method; 3.0 mm was used as the reference for access diameter. A p value <0.05 was considered clinically significant. Analyses were performed using StataSE (version 10.1; College Station, Tex., USA).

Results

Table 1 describes the technique for the fetoscopic laser procedure at each center. Three different uterine entry methods and 6 access diameters were used. Each center used perioperative tocolytics and antibiotics. One center did not perform fetoscopic laser procedures when the cervix measured less than 20 mm or had a cerclage in situ; 3 centers did not routinely perform laser for cases presenting at stage 1 TTTS.

Exclusions and Missing Values

Of the 867 cases submitted, 194 were excluded from analysis: double IUFD ($n = 54$); terminations ($n = 5$); additional invasive procedures prior to PROM ($n = 66$);

Table 1. Technical details of the 673 fetoscopic laser ablations at each of the contributing centers

Technical detail	Specific	%	Center					
			1	2	3	4	5	6
Number of laser cases, n (%)			101 (15.0)	191 (28.4)	33 (4.9)	176 (26.2)	27 (4.0)	145 (21.5)
Anesthesia	General	10.8	X	X	X		X	
	Local	60.2	X			X	X	X
	Regional	29.0		X				
Abdominal wall Technique	Mini laparotomy	4.9			X			
	Percutaneous	95.1	X	X		X	X	X
Uterine entry method	Cannula + Seldinger	26.4			X			X
	Cannula + trocar	47.4	X	X			X	
	Sheath + trocar	26.2				X		
Access diameter	2.3 mm	1.8		X				
	3.0 mm	14.9				X		
	3.3 mm	51.0		X			X	X
	3.5 mm	6.8	X					
	3.8 mm	20.6	X			X	X	
	4.0 mm	4.9			X			

Table 2. Summary of timing of prelabour rupture of membranes (PROM) and preterm birth

	Total cases, n (%)	PROM onset	Cases, n (%)			
			PROM, %	PTB		
				<4 weeks	<24 weeks ^b	<28 weeks ^c
PROM	174 (25.9)			36 (22.4)	25 (14.4)	52 (29.9)
		<4 weeks	54 (32.0)	36 (66.7)	24 (44.4)	39 (72.2)
		<24 weeks ^{a, b}	40 (23.7)	28 (70.0)	25 (62.5)	30 (75.0)
		<28 weeks ^{a, c}	79 (46.7)	36 (45.6)	25 (31.6)	52 (65.8)
No PROM	499 (74.1)			39 (7.8)	16 (3.2)	58 (11.6)

^a Gestational age at PROM not known in 5 cases (2.9%); ^b 84 (12.5%) fetoscopic cases performed from 24 + 0 weeks; ^c 2 (0.3%) fetoscopic cases performed from 28 + 0 weeks.

cases lost to follow-up (n = 69), because of missing data on GA at birth. They were equally distributed across participating centers. This resulted in 673 cases for analysis. Two centers did not provide data systematically for all variables requested; other data were randomly missing.

Surgery

The mean GA at laser for the 673 cases analyzed was 20.9 ± 2.3 weeks, with 27 (4.0%) cases performed before 17 weeks and 84 (12.5%) cases beyond 24 weeks (including 2 at 28 weeks). Table 2 summarizes the timing of PROM and birth outcomes for the entire group.

Short Term (<4 Weeks) Occurrence of PROM and/or Birth

PROM <4 weeks following laser occurred in 54 (8.0%) cases. The entry method and access diameter were not associated with PROM <4 weeks; only cervical length at laser was (table 3a). Birth <4 weeks occurred in 75 (11.1%) cases. PROM preceded delivery in 48.0% (36/75) of these cases. The entry method and access diameter were not associated with birth <4 weeks. Cervical length and GA at laser, as well as the occurrence of PROM, were associated with birth <4 weeks.

Obstetric Outcomes – PROM and/or PTB

PROM occurred in 174 (25.9%) cases. The GA at PROM was documented in 169 of these cases, allowing calculation of latency. The median interval from procedure to PROM was 51 (IQR 18–73) days, coinciding with a mean GA at PROM being 28.1 ± 4.8 weeks. PROM <4 weeks following laser accounted for 32.0% (54/169) of these cases. The entry method, but not the access diameter, was associated with the occurrence of PROM after the procedure. Cervical length was not associated with the occurrence of PROM on bivariate analysis ($p = 0.618$).

The mean GA at birth was 32.0 ± 4.3 weeks, with a median interval from laser to birth of 83 (IQR 55–104) days. PTB <28 weeks occurred in 16.4% (110/671) of cases. PROM preceded birth <28 weeks in 47.3% (52/110) of cases. Access diameter, but not the entry method, was associated with PTB <28 weeks; cervical length and PROM were also associated with PTB <28 weeks.

The latency to birth was analyzed as a continuous outcome (table 3b). The entry method and access diameter were not associated with latency to birth. Factors associated with this outcome were cervical length, GA at laser, and the occurrence of PROM.

Upon analysis including cervical length as a categorical variable (<20 vs. ≥ 20 mm), allowing data from all centers to be used, additional associations only for PTB <28 weeks and latency to birth were identified. The entry method was associated additionally with PTB <28 weeks, and access diameter with latency to birth.

Sub-group analysis was performed on data from 2 centers that used different access diameters but no other technical differences when doing the procedure. In one center using the fetoscopic sheath + trocar entry method, a 3.8 mm diameter is used for anterior placenta cases instead of the 3.0 mm diameter used for other placental locations. Another center using the trocar + cannula method had an equipment change from 3.5 to 3.8 mm during the course of the study. There was no effect of diameter

on PROM outcomes, birth <4 weeks and PTB <28 weeks. Diameter did, however, adversely influence latency to birth and the GA at birth on bivariate analysis (table 4). Two other centers used different access diameters but small numbers precluded analysis.

Discussion

Fetoscopic laser surgery combined with amniodrainage is the optimal management for TTTS, as it allows direct treatment of the underlying pathophysiology [3, 4]. Few studies have evaluated the factors associated with PROM and PTB following fetoscopic laser [5, 9, 13, 14, 16–20]. No prior study has attempted to compare outcomes against different invasive fetoscopic techniques, which may contribute to complication rates. To evaluate the entry methods and access diameters commonly used at fetoscopic laser surgery for TTTS against key obstetric adverse outcome measures, we performed a study across 6 centers that were using different fetoscopic techniques.

The fetoscopic procedures evaluated in this study differed with respect to the anesthesia used and how the surgery was performed [3, 8, 10–12]. One center performed fetoscopy through mini-laparotomy; percutaneous access was used at all other centers. Four centers used different access diameters over the study period. One center used the smallest access diameter fetoscope available for cases before 17 weeks; 1 center changed their instrumentation for anterior placental locations [8]; 2 centers had an equipment change to a different access diameter. In addition, differences in case selection exist between centers. For instance, the cut off for polyhydramnios defining TTTS in the Australia [12] and the United States [11, 20] is 8 cm, whereas in Europe [3, 8, 10] from 20 weeks it is 10 cm. One center excluded cases with a short cervix, a known predictor of poor outcome [13, 14].

There are a number of theoretical and technical aspects to be considered when a uterine fetoscopic entry method is chosen. We first described [10] the use of the Seldinger technique and some claim that it is the entry method that allows the most controlled access to the uterine cavity [21]. This technique involves the initial insertion of a small gauge (16–20 G) needle into the amniotic cavity, followed by the insertion of a round-tipped guide wire, over which a dilator and cannula are passed. Advancing this conical dilator may stretch the myometrium and chorioamniotic membranes to the definitive access diameter more gradually than the insertion of a sharp tro-

Table 3.**a** Multivariate analysis for short-term outcomes, outcomes related to PROM and preterm birth <28 weeks

Outcome measure	Raw data, n (%)	Variables used in model	Cases in model, n (%)	Logistic regression analysis		
				characteristic	OR (95% CI)	p value
<i>Short term outcomes</i>						
PROM ^a <4 weeks	54/673 (8.0)	Cervical length (mm); access diameter; entry method; deepest vertical pocket; placental location	491 (73.0)	Cervical length, mm	0.97 (0.94–0.997)	0.031
Birth <4 weeks	75/673 (11.1)	Cervical length (mm); access diameter; entry method; quintero stage; deepest vertical pocket; gestational age at laser; PROM	492 (73.1)	Cervical length, mm	0.94 (0.92–0.97)	<0.001
				Gestational age at laser	1.17 (1.01–1.36)	0.036
				PROM	4.32 (2.26–8.24)	0.000
<i>Obstetrical outcomes</i>						
PROM documented before birth	174/673 (25.9)	Access diameter; entry method; quintero stage; placental location	668 (99.3)	Entry method		
				Cannula + trocar	1	
				Sheath + trocar	0.43 (0.20–0.90)	0.025
				Cannula + Seldinger	0.52 (0.31–0.89)	0.017
PTB <28 weeks ^c	110/638 (16.3)	Cervical length (mm); access diameter; entry method; anesthetic technique; placental location; PROM <28 weeks; deepest vertical pocket; fetal death	489 (72.7)	Cervical length (mm)	0.95 (0.93–0.98)	0.001
				PROM	25.0 (12.5–49.7)	<0.001
				Access diameter		
				2.3 mm	23.1 (1.3–421.9)	0.034
				3.0mm	1	
				3.3 mm	5.0 (0.7–37.0)	0.112
				3.5 mm	0.7 (0.1–6.2)	0.743
3.8 mm	2.3 (0.5–9.9)	0.278				
PTB <28 weeks ^c (all centers) ^d	110/671 (16.3)	Cervical length (categorical); access diameter; entry method; anesthetic technique; placental location; PROM <28 weeks; deepest vertical pocket; fetal death	515 (76.5)	Cervical length (categorical)	0.19 (0.08–0.46)	<0.001
				PROM	23.6 (12.0–46.5)	<0.001
				Access diameter		
				2.3 mm	21.6 (1.1–407.0)	0.040
				3.0 mm	1	
				3.3 mm	5.4 (0.8–37.7)	0.086
				3.5 mm	0.9 (0.1–8.1)	0.958
				3.8 mm	2.4 (0.6–10.1)	0.229
				4 mm	46.7 (3.0–717.9)	0.006
				Entry method		
				Cannula + trocar	1	
				Sheath + trocar	0.93 (0.27–3.26)	0.911
Cannula + Seldinger	0.23 (0.06–0.91)	0.037				

^a Gestational age at PROM reported in 169 (97.1%) cases; ^b latency to PROM could not be analysed as a continuous variable for the 169 cases; ^c 671 (99.7%) cases performed before 28 weeks; ^d for analysis of data from all 6 centers used, cervical length was categorized as < or ≥20 mm.

Table 3. (continued)**b** Multivariate analysis of latency to birth

Outcome measure	Raw data, n (%)	Variables used in model	Cases in model, n (%)	Linear regression analysis		
				characteristic	coefficient of regression (95% CI)	p value
Birth Latency to birth	640 (95.1)	Cervical length (mm); cerclage; access diameter; entry method; deepest vertical pocket; volume drained; gestational age at laser; placenta location; PROM	397 (62.0)	Cervical length (mm)	16.6 (2.9 to 30.4)	0.018
				Gestational age at laser	-7.5 (-8.7 to -6.2)	<0.001
				PROM	-24.0 (-30.3 to -17.7)	<0.001
Birth Latency to birth (all centers) ^a	673 (100)	Cervical length (categorical); access diameter; entry method; deepest vertical pocket; gestational age at laser; placental location; PROM	517 (76.8)	Cervical length (categorical)	17.0 (7.8 to 26.2)	<0.001
				Gestational age at laser	-7.2 (-8.3 to -6.1)	<0.001
				PROM	-26.2 (-31.8 to -20.7)	<0.001
				Diameter		
				2.3 mm	-9.5 (-37.7 to 18.6)	0.507
				3.0 mm	1	
				3.3 mm	0.1 (-14.4 to 14.7)	0.987
				3.5 mm	5.2 (-10.8 to 21.2)	0.525
				3.8 mm	-3.7 (-15.3 to 7.9)	0.534
				4.0 mm	-19.6 (-39.1 to -0.2)	0.048

^a For analysis of data from all 6 centers used, cervical length was categorized as <20 or ≥20 mm. Raw data of latency to birth (days) for each access diameter -2.3 mm: 124.5 days; 3.0 mm: 96 days; 3.3 mm: 84 days; 3.5 mm: 74 days; 3.8 mm: 75 days; 4.9 mm: 72 days.

Table 4. Bivariate analysis of the impact of access diameter within an entry method

	Entry method: cannula + trocar			Entry method: sheath + trocar		
	3.5 mm	3.8 mm	p value	3.0 mm	3.8 mm	p value
Number	46	55		100	76	
Characteristics						
Gestational age at laser (weeks) ^a	22.1±2.6	21.6±2.4	0.336	20.6±2.3	20.8±1.8	0.557
PROM outcome						
<4 weeks ^b	4 (8.7)	9 (16.4)	0.372	4 (4.0)	4 (5.2)	0.728
Birth						
Gestational age at birth (weeks) ^a	32.7±3.8	30.6±4.3	0.012	33.4±4.1	32.3±4.1	0.075
<4 weeks ^b	5 (10.9)	8 (14.5)	0.767	7 (7.0)	5 (6.6)	1.0
<28 weeks ^b	5/45 ^d (11.1)	13 (23.6)	0.123	8 (8.0)	12 (15.8)	0.149
Latency - laser to birth (days) ^c	74 (50-106)	67 (41-90)	0.105	96 (70-111)	84 (67-105)	0.048

Data are reported as mean ± SD, n (%) or median (range). ^a t test; ^b Fisher's exact test; ^c Mann-Whitney U test; ^d one case treated after 28 weeks.

car within a cannula or fetoscopic sheath. The use of a cannula has another theoretical advantage over direct entry with the fetoscopic sheath, as this can limit friction and irritation on the uterus and chorioamnion when the fetoscope moves back and forth during the operation.

The use of a smaller access diameter instrument would be intuitively beneficial, as it causes lesser damage to the chorioamniotic membranes. Therefore, the use of different fetoscopic instruments and entry methods may directly influence the rates of chorioamnion separation;

this has been reported as a risk factor for PROM after laser surgery (as well as the risk for PROM in general) [16]. To the authors' knowledge, there are no published reports to reveal information on how the use of different fetoscopic techniques impacts the ability of clinicians to complete fetoscopic laser procedures. Bleeding complications at fetoscopy were rare in our study (data not shown), and/or may be reported unreliably. Therefore, the impact of bleeding could not be assessed.

Fetoscopic laser ablation is a relatively common procedure with a wide variability in technique. So far, no association has been reported between the technique at fetoscopy and short-term obstetrical outcomes. In order to evaluate the impact of technique, critical clinical outcomes must be chosen. As for any surgery, reporting short-term outcomes (i.e. <4 weeks from surgery) is often used to analyse the direct impact of the surgery [3, 12]. We also evaluated latency from the laser procedure. PROM or birth <24 weeks' gestation were the outcomes reported in a review by Yamamoto and Ville [5]. They found PROM complicated between 1 and 13% of cases and the rate of pregnancy loss <24 weeks was reported to be between 6.8 and 23%. Outcomes related to PROM were only reported by 53% (9/17) of the case series of fetoscopic laser surgery in that review. Beck et al. [19] reported considerable heterogeneity in the reporting of PROM rates following placental laser ablation for TTTS cases. A recent retrospective study of PROM before the onset of labour from a single center reported on rates within 1 (5.4%) and 4 (10.9%) weeks, and before 34 weeks (18.5%) [20]. PROM is the most common iatrogenic complication following fetoscopic laser treatment for TTTS [9]. The overall rate of PROM reported in our study (25.9%) is consistent with the range of PROM outcomes reported recently from a single-center series using different fetoscopic instrumentation [16, 17, 20–24]. Cervical length, and not the fetoscopic technique, was demonstrated in our large multicenter study to be associated with PROM <4 weeks. It is not possible to distinguish if the occurrence of PROM following fetoscopic surgery is primarily iatrogenic and procedure related, or if it is a consequence of the primary disease process with multiple pregnancy and/or the additional development of polyhydramnios [3, 25–27]. Twin pregnancies are known to have higher rates of spontaneous PROM compared with singleton pregnancies [25] and the occurrence of PROM in multiple pregnancies is considered to reflect factors unique to multiple pregnancies rather than infection [26]. Two retrospective studies evaluating spontaneous PROM in twin pregnancies reported the mean GA at PROM to

be 30.1 ± 4.3 weeks and 31.3 ± 3.8 weeks, respectively [25, 27].

Unlike PROM, the occurrence of PTB in multiple pregnancies, including following fetoscopic laser, has been investigated far more rigorously [4, 5, 28, 29]. In this study, just under half of births <4 weeks and PTB <28 weeks were reported in association with PROM. This implies that either the PROM is under-reported or the consequences of fetoscopic surgery are more complex and dynamic than simply perforation of the myometrium and chorioamnion [5]. In singleton pregnancies at high risk of PTB, Odibo, Talucci and Berghella reported different factors associated with PROM <35 weeks, as compared with PTB <35 weeks [30].

GA at birth is an obvious, clinically relevant outcome to study; low GA at birth is consistently reported as a critical determinant of adverse neurologic outcome in MCDA twins [31–33]. PROM unsurprisingly was associated with all birth outcomes. Cervical length at the time of laser was confirmed in this study as an independent predictor for birth outcomes [13, 14]. Of the 6 centers contributing data, 1 center specified that patients with a cervical length <20 mm were not offered laser surgery. Given this information, analysis was performed separately with cervical length as a continuous variable and as a categorical variable (<20 or ≥ 20 mm). The independent association of cervical length remained, irrespective of the variable type used in the analysis. Cervical length was associated independently with PROM <4 weeks, birth <4 weeks and latency from procedure to birth.

We report an association between access diameter and PTB <28 weeks. Additional independent predictors of birth <28 weeks were cervical length and PROM. The GA at laser may have accounted for the association between the smallest access diameter (2.3 mm) and PTB <28 weeks. All cases using a diameter of 2.3 mm were performed before 17 weeks. GA at laser was not included as a variable in the multivariable analysis because it was not demonstrated as a significant confounder on bivariate analysis. An inverse relationship was demonstrated for GA at laser and the outcomes of latency to birth and birth <4 weeks. The use of the smallest access diameter did not affect the latency to birth. GA at laser was not associated with any PROM outcomes.

In addition, the use of the largest diameter (4 mm) was found associated with a shorter latency to birth and PTB <28 weeks, when cervical length was included as a categorical variable and all cases were evaluated. Only in this context, were access diameter and entry method both demonstrated as additional independent predictors of an evaluated outcome – PTB <28 weeks.

Our analysis suggests that any apparent linear association between access diameter and birth outcomes on bivariate analysis (tables 3b and 4) may be lost on multivariate analysis. This suggests that other clinical confounders are more significant in determining obstetric outcomes. Alternatively, any demonstrated association between the 2.3 and 4 mm access diameters and birth outcomes may be related to chance, given the small case numbers. The impact of performing fetoscopic laser surgery through mini-laparotomy, as opposed to percutaneously, could not be evaluated given the colinearity with the 4 mm access diameter. One could speculate that it was not the 4 mm access diameter that was the associated factor but rather the mini-laparotomy. Interestingly, a systematic review of minimally invasive fetal surgery, including case series of fetoscopic laser procedures, reported that combined stepwise multivariate analysis of pool data identified the maximum diameter of the instrument used at uterine entry as a factor associated with PROM, GA at birth and fetal survival [19].

It is challenging to account for any impact of access diameter or entry method on outcomes remote from the surgery date. Intuitively, it would be simpler to account for access diameter having an impact on PROM outcomes, but none was shown. A multivariate analysis can only adjust for specified confounders and identify case characteristics associated with the outcome in the studied population.

Operator experience and learning curve were not evaluated in the regression analyses, and may have contributed to any differences associated with different fetoscopic

techniques [34]. Fetoscopic center was included as a random effect in our statistical model to account for potential differences between centers. The duration of surgery was not included as a variable, given no consensus definition between the centers, thereby reflecting inappropriate standardized collection of this potentially important variable. Absorbable gelatin sponges have been developed to 'plug' the chorioamnion at removal of the fetoscopic instruments to reduce the incidence of PROM, though without any proven benefit so far [17, 18]. The utility of a sealant at closure to prevent PROM cannot be evaluated in this study.

In conclusion, it was found that the choice of instrument at fetoscopic laser procedures did not affect outcomes within <4 weeks. Access diameters may affect the likelihood for PTB <28 weeks and reduce the latency to birth. Cervical length is a critical independent characteristic of twin pregnancies with TTTS undergoing fetoscopic laser surgery.

Acknowledgments

The authors acknowledge the contribution by clinicians, midwives and research fellows to this study, who cannot be listed as authors, but without whom this study would not have been possible. J.E.D. is a clinical researcher funded by the Fonds voor Wetenschappelijk Onderzoek Vlaanderen (FWO; 1801207N).

Disclosure Statement

The authors have no financial interests to disclose.

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