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Intertwin Membrane Perforation and Umbilical Cord Entanglement after Laser Surgery for Twin-Twin Transfusion Syndrome: Prevalence, Risk Factors, and Outcome

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Mini-Summary

What does this study add to current knowledge?

- The rate of intertwin membrane perforation after laser surgery for twin-twin transfusion syndrome is 16%. Iatrogenic monoamniotic twins were born at a lower gestational age, leading to more severe cerebral injury. In only 20% of iatrogenic monoamniotic twins, cord entanglement was observed and it was not associated with adverse outcome.

What are the main clinical implications?

- The rate of cerebral injury related to the lower gestational age at birth in iatrogenic monoamniotic twins demands a critical review of the management of these pregnancies. An early elective caesarean section as performed in spontaneous monoamniotic twins to prevent cord entanglement should be weighed against the risks of premature birth.

Keywords

Twin-twin transfusion syndrome · Fetoscopic laser surgery · Iatrogenic monoamniotic twin pregnancy · Intertwin membrane perforation · Cord entanglement

Abstract

Introduction: Perforation of the intertwin membrane can occur as a complication of fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS). Data on the occurrence and the risk of subsequent cord entanglement are limited. The objective of this study was to assess the prevalence, risk

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factors and outcome of intertwin membrane perforation, and cord entanglement after laser surgery for TTTS. ***Methods:*** In this multicenter retrospective study, we included all TTTS pregnancies treated with laser surgery in two fetal therapy centers, Shanghai (China) and Leiden (the Netherlands) between 2002 and 2020. We evaluated the occurrence of intertwin membrane perforation and cord entanglement after laser, based on routine fortnightly ultrasound examination and investigated the risk factors and the association with adverse short- and long-term outcomes. ***Results:*** Perforation of the intertwin membrane occurred in 118 (16%) of the 761 TTTS pregnancies treated with laser surgery and was followed by cord entanglement in 21% (25/118). Perforation of the intertwin membrane was associated with higher laser power settings, 45.8 Watt versus 42.2 Watt ($p = 0.029$) and a second fetal surgery procedure 17% versus 6% ($p < 0.001$). The group with intertwin membrane perforation had a higher rate of caesarean section (77% vs. 31%, $p < 0.001$) and a lower gestational age at birth (30.7 vs. 33.3 weeks of gestation, $p < 0.001$) compared to the group with an intact intertwin membrane. Severe cerebral injury occurred more often in the group with intertwin membrane perforation, 9% (17/185) versus 5% (42/930), respectively ($p = 0.019$). Neurodevelopmental outcome at 2 years of age was similar between the groups with and without perforation of the intertwin membrane and between the subgroups with and without cord entanglement. ***Conclusion:*** Perforation of the intertwin membrane after laser occurred in 16% of TTTS cases treated with laser and led to cord entanglement in at least 1 in 5 cases. Intertwin membrane perforation was associated with a lower gestational age at birth and a higher rate of severe cerebral injury in surviving neonates.

Introduction

Twin-twin transfusion syndrome (TTTS) complicates 10–15% of all monochorionic-diamniotic twin gestations and is caused by an unbalanced intertwin blood flow through placental anastomoses [1, 2]. Fetoscopic laser photocoagulation of the vascular anastomoses is the only causal treatment for TTTS and results in major improvements of outcome with perinatal survival rates ranging from 70 to 90% [3, 4]. Although very effective, fetoscopic laser surgery can be associated with a number of complications [5–8]. One important complication is rupture of the intertwin amniotic membranes, creating an iatrogenic monoamniotic twin (iMAT) pregnancy. Data on the occurrence of iMAT after fetoscopic laser surgery are scarce and reported rates vary greatly from 1.3% to 20% [6, 9, 10, 11].

One of the main risks of monoamnionicity is umbilical cord entanglement. In *spontaneous* monoamniotic twin pregnancies, umbilical cord entanglement occurs in almost all pregnancies and is the leading cause of fetal mortality [12–15]. Inpatient or outpatient fetal monitoring is often advised, starting as early as 26 weeks' gestation. An elective caesarean section is then often performed around 32–34 weeks' gestation to avoid further risks due to cord entanglement. Whether these management strategies in *spontaneous* monoamniotic twin pregnancies are also necessary for *iatrogenic* monoamniotic pregnancies is not known, as the prevalence, risk factors and outcome in iMAT with or without cord entanglement remain to be elucidated. More data are necessary for the development of scientifically based clinical management strategies for these pregnancies.

Our primary aim was to evaluate the prevalence of perforation of the intertwin membrane and subsequent cord entanglement after fetoscopic laser therapy for TTTS. Our secondary aims were to evaluate risk factors for iMAT and cord entanglement and the association with adverse short- and long-term outcomes.

Methods

All TTTS pregnancies treated with fetoscopic laser surgery at the Leiden University Medical Center (LUMC, the Netherlands) and the Shanghai First Maternity and Infant Hospital (SFMIH, China) between January 2002 and January 2020 were eligible for this study. The LUMC is the Dutch national referral center for fetal therapy and the SFMIH is one of the major fetal therapy centers in China. The LUMC (the Netherlands) started with fetoscopic laser surgery in August 2000, whereas the SFMIH (China) started with fetoscopy later on in 2011. We therefore included TTTS cases from the SFMIH treated between January 2011 and January 2020. We excluded spontaneous monoamniotic twins, TTTS cases with perforation of the intertwin membrane *prior* to laser surgery and cases where follow-up information after laser therapy was incomplete. The Research Ethics Board of both participating centers approved the study protocol of this retrospective study (G20.015 and 2018yxy27).

TTTS was defined by the diagnostic criteria provided in the Eurofetus protocols and classified according to the internationally agreed staging system [16, 17]. Fetoscopic laser surgery was performed by well-trained fetal surgeons. The operation procedure has been described in detail previously [6, 18]. In the Netherlands, the selective technique was exclusively performed from 2002 to 2007. From 2008 to 2012, the Solomon trial was conducted in which both techniques were used. From 2012 onward, the Solomon technique is standard care. In the SFMIH, the selective technique was performed from 2011 to 2015, whereafter the

Solomon technique became standard treatment. A subset of patients (n = 142) included in this study also participated in the Solomon trial [3] and a subset of LUMC patients (n = 338) has been previously reported by Peeters et al. [6].

Sonographic examinations were performed within 24 h after surgery and subsequently at least fortnightly until the end of the pregnancy with the aim to monitor fetal condition and to detect complications such as perforation in the intertwin membrane and the occurrence of cord entanglement. Technical difficulties and complications, including unintentional perforation of the intertwin membranes, were reported directly after surgery. A standardized ultrasound protocol that includes specific assessment of the intertwin membranes was used. Perforation of the intertwin membranes was defined according to previously reported definitions [19]. We diagnosed iMAT when either filling of the amniotic sac of the donor was observed intraoperative or directly after surgery or when free-floating intertwin membranes or cord entanglement was detected during follow-up.

Chorionicity and amnionicity were determined in the first trimester of pregnancy by ultrasound examination. After delivery, macroscopic examination of the placenta and membranes was performed and presence of umbilical cord entanglement was recorded. All available placentas were routinely injected with colored dye according to our previously published protocol and analyzed using ImageJ software (version 1.51) [20–22]. Umbilical cord insertion was considered velamentous when it was located directly in the membranes. Insertions located less than 1 cm from the placental edge were labelled as marginal and insertions more than 1 cm from the placental edge as central [23].

Data on obstetric and neonatal outcomes were derived from medical records. In cases in which delivery took place in another Dutch hospital, data were retrieved from referring obstetricians and pediatricians. Due to geographical differences, patients treated in SFMIH were only included when delivered in the same hospital.

The following variables were collected: TTTS stage, placental location (anterior or posterior), gestational age at laser, laser technique, duration of fetoscopy, used energy, maximum power setting, a second fetal surgery procedure, location of the cord insertions, gestational age at birth, mode of delivery, birth weight, sex, fetal demise and neonatal mortality, and severe neonatal morbidity.

A second fetal surgery was defined as a second fetoscopic laser surgery procedure or an amniotic fluid drainage, intrauterine transfusion, umbilical cord occlusion, or a intracardiac potassium chloride injection. Severe neonatal morbidity was defined as one of the following: respiratory distress syndrome needing treatment with surfactant, patent ductus arteriosus requiring medical treatment or surgical closure, necrotizing enterocolitis grade ≥2, severe anemia requiring a blood transfusion on the first day after birth, severe polycythemia requiring a partial exchange transfusion on the first day after birth or severe cerebral injury. Severe cerebral injury was defined as the presence of cystic periventricular leukomalacia grade ≥2, intraventricular hemorrhage grade ≥3, ventricular dilatation greater than the 97th percentile, porencephalic or parenchymal cysts, arterial or venous infarction or other severe cerebral lesions associated with adverse neurological outcome on neonatal ultrasound.

All TTTS survivors treated with fetoscopic laser coagulation and born in the Netherlands were routinely assessed at 2 years of age by a team of pediatricians, psychologists, and physical therapists to assess the presence of severe neurodevelopmental impairment (NDI), except for children born between 2006 and 2007 (due to organizational reasons). Severe NDI was defined as at least one of the following: Bayley-III-NL cognitive and/or motor scores <70, CP GFMCS ≥ grade 3, blindness or severe visual impairment, and/or severe hearing impairment requiring amplification. Mild NDI was defined as CP grade 1 or 2, cognitive and/or motor test scores <85, mild visual and/or hearing impairment.

Statistical Analyses

Continues variables were reported as mean (SD) or median (range) or median (interquartile range [IQR]), and group differences were analyzed using the Mann-Whitney U test or independent Student's t test, as appropriate. χ^2 test or Fisher's exact test was used to analyze proportions. Trend analysis was performed to determine the rate of iMAT over the years. Risk factor analyses were performed using logistic regression models with iMAT or cord entanglement as primary outcome. The following potential risk factors for iMAT were included in the analysis: TTTS stage, placental location, laser technique, duration of fetoscopy, gestational age at laser, used laser energy, maximum laser power, and the occurrence of a second fetal surgery procedure. The following potential risk factors for cord entanglement were included in the analysis: sex, TTTS stage, placental location, laser technique, duration of fetoscopy, gestational age at laser, and the location of cord insertions.

Neonatal and long-term outcome data were analyzed using a generalized estimating equation to correct for the relation between twins. All analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). A p value of <0.05 was considered significant.

Results

In the Netherlands, 752 women with TTTS pregnancies treated with laser were eligible for this study. In Shanghai, 217 TTTS pregnancies were treated in SFMIH between 2011 and 2019, of which 90 were monitored and delivered in their hospital after the laser surgery. We excluded 81 TTTS cases (9.6%, 81/842) due to incomplete data (LUMC, n = 48 [6.4%]; SFMIH, n = 33 [36.7%]) (Fig. 1). During the study period, perforation of the intertwin membrane occurred in 16% (118/761) of cases. In 38% (45/118), perforation of the intertwin membrane was detected during surgery or at ultrasound examination 1 day after the procedure.

Iatrogenic Monoamniotic Twin

Clinical characteristics and risk factor analysis in TTTS pregnancies with and without iMAT are depicted in Table 1. In the group of pregnancies with iMAT, median gestational age at laser surgery was 20.4 (IQR 18.0–23.3) weeks compared to 19.8 (IQR 17.7–22.1) weeks in the group without iMAT (p = 0.050). Maximum laser power was higher in iMAT pregnancies;

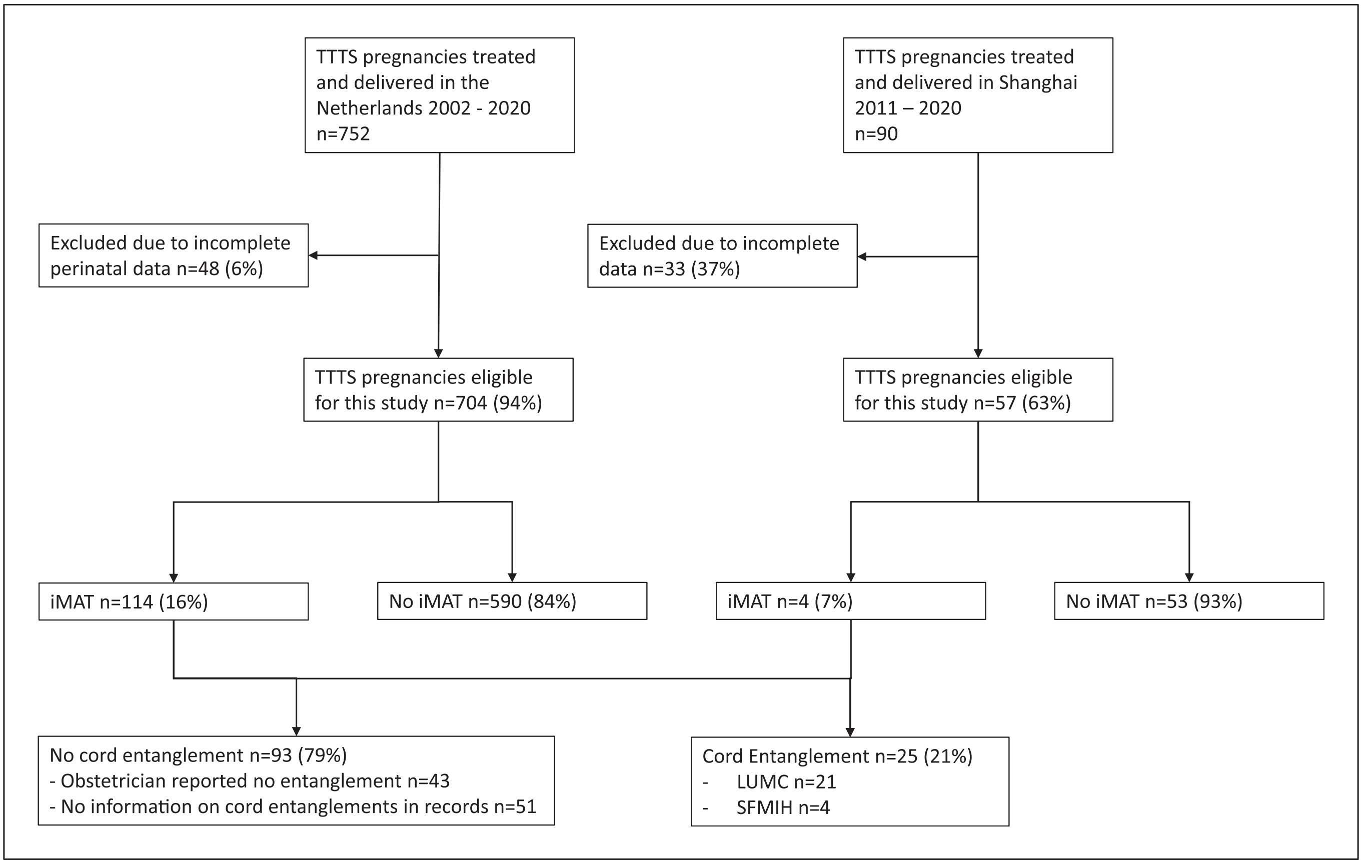

Fig. 1. Flowchart depicting the derivation of our population.

45.8 ± 14.5 Watt compared to 42.2 ± 13.6 Watt in the no iMAT group ($p = 0.024$). iMAT occurred more frequently in TTTS cases requiring a second consecutive fetal surgery procedure, 17% (20/118) versus 6% (36/643) in the group without iMAT ($p < 0.001$). Second fetal surgeries included laser surgery ($N = 11$), amniondrainage ($N = 10$), intrauterine transfusions ($N = 15$), umbilical cord coagulations ($N = 14$), intracardiac kaliumchloride injections ($N = 2$), amnionpatch ($N = 1$), and laser surgery followed by intrauterine transfusions ($N = 2$).

Gestational age at birth in TTTS pregnancies with and without iMAT was 30.7 weeks (IQR 28.4–32.9) and 33.3 weeks (IQR 29.7–35.9) ($p < 0.001$), respectively (Table 3). Perinatal survival rates were similar between pregnancies with and without iMAT. iMAT pregnancies without fetal demise were hospitalized in 53% of cases at a mean of 28 + 5 weeks of gestation (±21 days) for fetal monitoring and an elective caesarean section was scheduled between 32 and 34 weeks' gestation. In 20% (24/118) spontaneous delivery occurred before 28 weeks of gestation. Severe neonatal morbidity was similar in the groups with and without iMAT, but severe cerebral injury occurred more often in the iMAT group, 9% (17/185) versus 5% (42/930), respectively ($p = 0.019$). When corrected for gestational age at birth the association between iMAT and severe cerebral injury was not significant ($p = 0.342$). Neurodevelopmental outcome at 2 years of age was available for 125 iMAT survivors and 617 TTTS survivors without a ruptured intertwin membrane (Table 3). Lost-to-follow-up rate in children born in the Netherlands of at least 2 years of age was 22% (36/161) in iMAT survivors and 27% (234/851) in the group without iMAT. Severe NDI in the iMAT and no iMAT group was detected in 8% (10/125) and 6% (35/617), respectively ($p = 0.507$). In Figure 2, the rate of iMAT is reported over the years.

Umbilical Cord Entanglement

Umbilical cord entanglement was detected in 21% (25/118) of cases in the iMAT group (Table 2). An example of an iMAT placenta with cord entanglement is shown in Figure 3. Cord entanglement was detected on ultrasound

Table 1. Clinical characteristics of 761 pregnancies with twin-twin transfusion syndrome (TTTS) treated with laser therapy, with and without an intertwin membrane perforation (iMAT)

	iMAT group (*n* = 118)	no iMAT group (*n* = 643)	OR 95% CI	*p* value
Placenta location				
Anterior	54 (46)	248 (39)	1.34 (0.90–1.99)	0.146
Posterior	61 (52)	380 (59)	0.74 (0.50–1.09)	0.130
Lateral	3 (3)	15 (2)		
TTTS stage				
I	12 (10)	89 (14)	0.64 (0.33–1.24)	0.185
II	37 (31)	221 (34)	0.91 (0.60–1.38)	0.648
III	65 (55)	302 (47)	1.39 (0.93–2.05)	0.106
IV	4 (3)	31 (5)	0.69 (0.24–2.00)	0.497
Laser technique				
Selective	56 (47)	254 (40)[a]	0.73 (0.49–1.08)	0.113
Solomon	62 (53)	387 (60)		
GA at laser, weeks	20.4 (18.0–23.3)	19.7 (17.7–22.1)	1.06 (1.00–1.12)	**0.050**
Duration of fetoscopy, min	30 (20–40)[b]	29 (21–39)[c]	1.00 (0.99–1.02)	0.707
Laser energy, kJ	5.7 (2.6–9.1)[d]	4.6 (2.7–7.7)[e]	1.01 (0.98–1.03)	0.516
Maximum laser power, Watt	45.8±14.5[f]	42.2±13.6[g]	1.02 (1.00–1.03)	**0.024**
Second fetal surgery procedure	20 (17)	36 (6)	3.44 (1.91–6.19)	<**0.001**

Data are given as *n* (%) or mean ± standard deviation or median (interquartile range). TTTS, twin-to-twin transfusion syndrome; iMAT, iatrogenic monoamniotic twin; OR, odds ratio; CI, confidence interval; GA, gestational age. [a]Data missing for 2 cases. [b]Data missing for 32 cases. [c]Data missing for 129 cases. [d]Data missing for 31 cases. [e]Data missing for 177 cases. [f]Data missing for 29 cases. [g]Data missing for 110 cases.

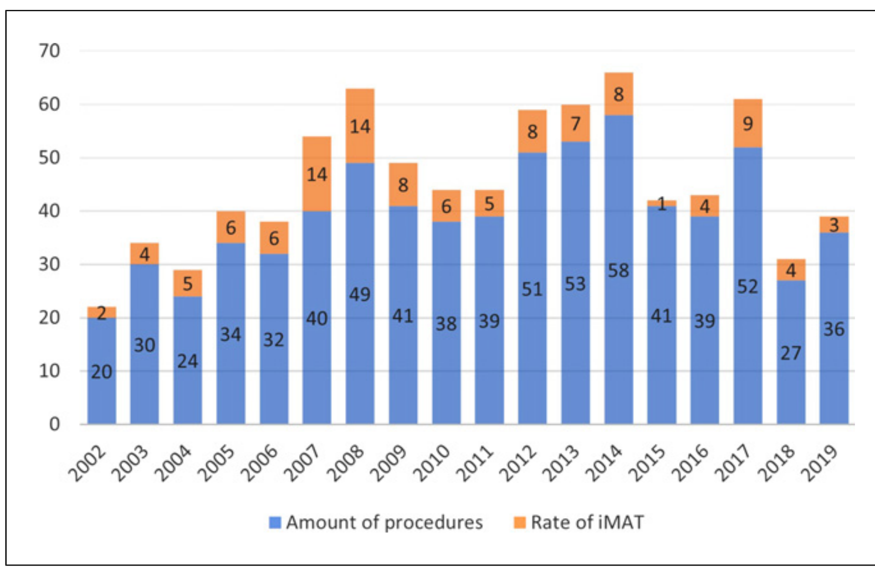

Fig. 2. Rate of iMAT over the years.

examinations in 84% (21/25) of cases. In 4 cases, cord entanglement was not mentioned in the ultrasound records but detected at placenta evaluation. Cord entanglement was the most likely cause of death in two pregnancies, where the cord of the earlier demised twin circled the cord of the larger twin leading to a second fetal demise at 25 and 28 weeks of gestation. We found a significant association between cord entanglement and TTTS stage 1 and with the use of Solomon technique. Perinatal mortality, severe neonatal morbidity, and severe NDI at 2 years of age were similar in iMAT pregnancies with and without cord entanglement (Table 3).

Table 2. Risk factor analysis for cord entanglement (CE) in 118 iMAT pregnancies

	iMAT group with CE (*N* = 25)	iMAT group without CE (*N* = 93)	OR (95% CI)	*p* value
Female	10 (40)	54 (58)	0.53 (0.21–1.31)	0.170
TTTS stage				
1	5 (20)	6 (7)	3.63 (1.01–13.07)	**0.049**
2	7 (28)	31 (33)	0.78 (0.29–2.05)	0.613
3	13 (52)	52 (56)	0.85 (0.35–2.07)	0.727
4	0	4 (4)		
Placental location anterior	10 (40)	44 (47)	0.874 (0.30–1.82)	0.516
Laser technique				
Selective	6 (24)	50 (54)		
Solomon	19 (76)	43 (46)	3.68 (1.35–10.05)	**0.011**
Duration of the fetoscopy, min	28 (20–35)	30 (20–45)	0.98 (0.94–1.01)	0.185
GA at laser, weeks	20.2 (18.1–23.0)	20.4 (17.6–23.4)	0.97 (0.85–1.10)	0.596
Interval septostomy to birth, days	47.2±26.5[a]	51.3±33.4[b]	1.00 (0.99–1.02)	0.660
Cord insertion type				
Central – central	10 (50)[a]	21 (29)[b]	2.43 (0.88–6.69)	0.086
Central – marginal/velamentous	7 (35)	40 (56)	0.43 (0.15–1.21)	0.109
Marginal/velamentous – marginal/velamentous	3 (15)	11 (15)	0.98 (0.25–2.45)	0.976

Data presented as *n* (%) or median (interquartile range). OR, odds ratio; CI, confidence interval; iMAT, iatrogenic monoamniotic twin; CE, cord entanglement; CI, confidence interval; TTTS, twin-twin transfusion syndrome; GA, gestational age. [a]5 placentas were lost. [b]11 placentas were lost.

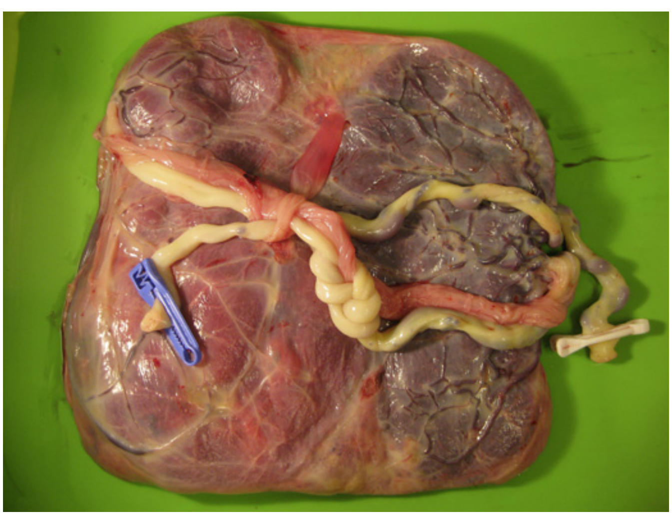

Fig. 3. Iatrogenic monoamniotic twin (iMAT) placenta with umbilical cord entanglement. A caesarean section was performed at 30 1/7 weeks of gestation. Of note, the intertwin membrane was also entangled between the two cords.

Discussion

This large cohort study on iatrogenic rupture of the intertwin membranes after laser shows a prevalence of 16% with a subsequent cord entanglement of only 21%. Rupture of the intertwin membrane was associated with a higher maximum power setting at laser surgery and repeated fetoscopic procedures.

Previous studies often reported a lower rate of iMAT after laser surgery, ranging from 1.3% to 9.0% [9–11]. However, most of these studies were either small or assessment of iMAT was not performed routinely, which could have led to underreporting. In contrast, the current study was performed in a very large consecutive cohort and the assessment of the intertwin membrane was part of the standardized protocol in which a sonography was performed within 24 h after surgery and subsequently at least fortnightly until the end of the pregnancy. The iMAT rate in this study was comparable to the 20% rate previously reported by our research group in a subset of these patients ($n = 338$) [6]. The relatively higher iMAT rate demonstrated in this study emphasizes the importance of careful routine assessment of the intertwin membranes during sonographic follow-up to detect cord entanglement.

In this study, a second fetal surgery procedure was associated with the rupture of the intertwin membrane. This could be expected as a second procedure damages the amniotic membranes twice and thereby increases the risk of rupture. We also found an association with higher laser power settings. A possible explanation

Table 3. Short- and long-term outcome in TTTS cases with and without iMAT and with and without cord entanglement

	iMAT group	no iMAT group	*p* value	iMAT with CE	iMAT without CE	*p* value
	N = 118 pregnancies	*N* = 643 pregnancies		*N* = 25 pregnancies	*N* = 93 pregnancies	
	N = 236 children	*N* = 1,289 children		*N* = 50 children	*N* = 186 children	
GA at birth, weeks	30.7 (28.4–32.9)	33.3 (29.7–35.9)	<**0.001**	30.1 (28.3–32.8)	30.7 (28.6–33.0)	0.875
Birth weight, g[a]	1,558 (1,144–1,959)	1,960 (1,490–2,425)[b]	<**0.001**	1,395 (1,005–1,851)	1,550 (1,136–1,932)	0.239
Delivery by caesarean section	88 (75)	203 (32)[c]	<**0.001**	21 (84)	67 (72)	0.230
Perinatal survival, >28 days	194 (82)	980 (76)		41 (82)	153 (82)	
No survival	10 (8)	81 (13)	0.212	2 (8)	8 (9)	0.924
Single survivor	22 (19)	145 (23)	0.512	5 (20)	17 (18)	0.845
Double survival	86 (73)	417 (65)	0.092	18 (72)	68 (73)	0.911
Severe neonatal morbidity	57 (33)	174 (26)	0.143	16 (52)[d]	41 (29)[e]	0.084
Severe cerebral injury	17 (9)[f]	42 (5)[g]	**0.019**	5 (15)	12 (8)	0.243
Severe NDI	10 (8)[h]	35 (6)[j]	0.507	2 (7)[e]	8 (8)[k]	0.906
Mild-moderate NDI	15 (12)	107 (17)	0.217	6 (22)[e]	9 (9)[k]	0.129

Data are given as *n* (%) or median (range). iMAT, iatrogenic monoamniotic twin; GA, gestational age. [a]IUFD was excluded. [b]Data are missing for 11 cases. [c]Data missing for 6 cases. [d]Data missing for 8 cases. [e]Data are missing for 14 cases. [f]Data missing for 9 cases. [g]Data missing for 45 cases. [h]Data missing for 69 cases. [j]Data missing for 358 cases. [k]Data are missing for 56 cases.

could be that higher laser power is associated with a more difficult procedure. The difficulty of the procedure may be a confounder that influences both the perforation of the intertwin membrane and maximum power settings. Contributing to this theory is the higher amount of anterior located placentas in the iMAT group, 46% (54/118) compared to 39% (248/643). The approach of an anterior located placenta is considered to be more difficult. The fetoscope can be tangential to the placental surface, causing the surgeon to use a higher power setting. In addition, during the introduction of the fetoscope, it may be more difficult to avoid damage to the intertwin membrane as the places to enter the recipients sac are limited. To our knowledge, there are no previous studies reporting a relation between higher laser power settings and complications after laser therapy. One study reported an association between lower power settings and placental damage [24]. The same study described an association between placental tissue damage and higher energy use. The authors speculated that the usage of a higher power setting for a short time is more efficient, leads to lower energy use, and is therefore negatively associated with collateral damage. In accordance with this theory, Mort et al. [25] reported an association between high laser energy use above 13.8 kJ (75th percentile) and delivery prior to 32 weeks. Of note, the median energy use in our cohort was much lower (4.8 kJ, IQR 2.7–7.9). No association between laser energy and iMAT was detected in this study or in a previous study by Brock et al. [26]. Future studies should include laser power settings and used laser energy to determine if there is a true association between laser power, total amount of energy used, and damage to the intertwin membrane.

We found that gestational age at birth was significantly lower and caesarean delivery rates were higher in iMAT. This is consistent with the results of the meta-analysis of Nassr et al. [27]. In both our centers, patients with iMAT are often hospitalized from 28 weeks of gestation for fetal monitoring and an elective caesarean section is planned at 32–34 weeks of gestation. Therefore, a likely explanation for this finding is that the intensive fetal monitoring in the iMAT cases results in preterm delivery. This is probably motivated by the risk of fetal demise due to cord entanglement in monoamniotic pregnancies. Importantly, severe cerebral injury occurred significantly more often in the iMAT group and was associated with the premature delivery. Finding the right balance between continuation of the pregnancy with the risk of cord accidents and preterm delivery with the accompanying complications of prematurity remains a challenge for perinatologists.

Despite the increased risk of severe cerebral injury in the iMAT group, the risk of long-term NDI was not significantly higher. The lack of association could partly be due to the high lost-to-follow-up rate and lack of power.

In this study, cord entanglement occurred in 21% of iMAT pregnancies. This is comparable to the rate of 17% described in a previous study [28]. Cord entanglement was associated with the Solomon laser technique. As the Solomon technique is performed in more recent years, the higher rates of cord entanglement might also be explained by improvement of the sonographic follow-up examinations and accurate reporting of cord entanglement in patient records. Detailed descriptions of delivery and placental examination were more often lacking in the older patient records. The true rate of cord entanglement is therefore possibly higher than the rate reported in this study. In addition, we found an association between TTTS stage 1 and cord entanglement. This result should be interpreted with caution as the low numbers hamper a valid risk assessment. Cord entanglement was diagnosed in the antenatal period during the routine ultrasound in 84% of cases. In the other 16%, cord entanglement was not reported in ultrasound records, either because the reporting was inaccurate or chorion amnion separation and lack of amniotic fluid after PPROM impaired visualization in these cases.

We expected an increased risk of entanglement when both umbilical cords were inserted centrally. Presumably, a shorter distance between cord insertions could result in higher risk of cord entanglement. However, no significant association was detected.

Cord entanglement occurred in only 1 in 5 of the iMAT pregnancies, 3% of all TTTS pregnancies. The lack of cord entanglement in 4 out of 5 *iatrogenic* monoamniotic twin pregnancies mandates a different approach for this group than the management of *spontaneous* monoamniotic twin pregnancies. The strict treatment strategies of early hospitalization, extensive monitoring and an elective preterm delivery may be more harmful than beneficial. Monoamniotic twins in this study were born earlier in gestation and the rate of severe cerebral injury associated with prematurity was higher. Although in this study the rates of mild-moderate and severe long-term NDI were comparable between TTTS survivors with and without iMAT, extreme or very preterm delivery is associated with high mortality and morbidity rates and poorer long-term neurodevelopmental outcomes [29, 30]. The lack of adverse outcome in twins with cord entanglement may be attributed to the strict management strategies of early and extensive monitoring and the elective preterm caesarean section, or cord entanglement poses a smaller threat than obstetricians fear. Some studies in spontaneous monoamniotic gestations demonstrate that monoamnionicity and cord entanglement in themselves are not associated with increased perinatal morbidity and mortality [31–35]. The results of this study warrant a debate on the best management strategies in iMAT pregnancies. We propose a more personalized approach to each monoamniotic twin pregnancy depending on the gestational age at intertwin membrane rupture and the presence of cord entanglement on sonographic follow-up.

Strengths and Limitations

An important limitation of this study was its retrospective nature. Detailed descriptions of the umbilical cords after delivery were often lacking, possibly leading to an underreporting of cord entanglement. In 36% (42/118) of patient records, the obstetrician reported that no cord entanglement was observed after delivery. In 42% (51/118), an observation of the umbilical cords was not specifically reported. Therefore, we expect the true rate of cord entanglement may lie between 21% (25/118) and 37% (25/67). In addition, not all placentas were available for examination after delivery, and follow-up data on morbidity and long-term outcome were only available for part of the group. Another limitation is that around 10% of TTTS cases were excluded due to incomplete data, of which 1/3 of cases from SFMIH. Whether this could have led to an under- or overestimation of our findings is not clear. Finally, although this is the largest study investigating iMAT after laser surgery treatment for TTTS, the absolute number of cases with cord entanglement was still relatively low, hampering a valid risk factor analysis. Consequently, the absence of a significant association in these analyses could (partly) be ascribed to a lack of power. Larger prospective studies with standardized screening protocols and systematic reports of iMAT and cord entanglement are needed to determine rates and consequences of intertwin membrane perforation and cord entanglement. More information of rates and consequences can provide a validated base for management strategies of these complicated pregnancies. A strength of this study is the use of a standardized sonography protocol during follow-up that included specific assessment of the intertwin membranes and placental examination after the delivery. In addition, a large cohort of TTTS survivors with and without a ruptured intertwin membrane was evaluated at the age of 2 years. Follow-up of this high-risk group is of utmost importance to improve treatment strategies, to refine counselling, and to offer timely support in children with neurodevelopmental difficulties [36].

Conclusion

This study demonstrates that the intertwin membrane may rupture in 16% of TTTS pregnancies after laser surgery and may be followed by umbilical cord entanglement in 21% of cases. The occurrence of iMAT was associated with lower gestational age at birth and higher rates of severe cerebral injury but not with increased risk of perinatal mortality or adverse long-term outcome. This is a large retrospective study comprising 18 years of consequently heterogenous and incomplete data. Nevertheless, the results of this study warrant critical evaluation of the current clinical management guidelines involving iMAT pregnancies with or without cord entanglement. Larger multicenter studies are necessary to improve the knowledge and management of iMAT pregnancies.

Statement of Ethics

This research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Research Ethics Board of both participating centers, the Medical Ethics Committee of Leiden-the Hague-Delft, the Netherlands (registration number G20.015), and the Ethics Committee of Tongji University, China (REB registration numbers 2018yxy27) approved the study protocol of this retrospective study. Due to the retrospective and anonymous data collection, the Ethics Committee exempted this study from obtaining written parental consent.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Patricia J. C. Knijnenburg, Femke Slaghekke, Chinar Rahmattulla, Y. Ge, Irene M. Scholl, Jeanine M.M. van Klink, Monique C. Haak, Johanna M. Middeldorp, Luming Sun, and Enrico Lopriore have contributed to designing the study, writing of the manuscript, and/or collection and interpretation of the data. All authors have revised the manuscript critically.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the privacy of research participants. Further inquiries can be directed to the corresponding author.

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