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Twin–twin transfusion syndrome: a frequently missed diagnosis with important consequences

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KEYWORDS: fetal surgery; fetoscopy; laser; misdiagnosis; monochorionic twin; TTTS; twin–twin transfusion

ABSTRACT

Objective *To evaluate the incidence and consequences of 'misdiagnosed' cases of twin–twin transfusion syndrome (TTTS).*

Methods *Chorionicity and referral diagnoses were reviewed in pregnant women with monochorionic twin pregnancies complicated by TTTS treated with fetoscopic laser ablation. 'Misdiagnosed' cases, defined as failure to correctly identify chorionicity and/or to diagnose TTTS prior to referral, were compared with cases in whom chorionicity and TTTS were diagnosed correctly. TTTS stage, gestational age at referral, overall survival, fetal and perinatal mortality, gestational age at delivery, operating time and maternal complications were compared.*

Results *Failure to identify monochorionicity and/or TTTS was observed in 33% (107/323) of referrals to our center. Compared with cases in whom chorionicity and TTTS were correctly diagnosed, misdiagnosed patients were referred at a more advanced stage of disease (Stage IV TTTS: 16.8%* vs *7.9%, P = 0.014) and later in pregnancy (gestational age at laser: 20.9 weeks* vs *20.1 weeks, P = 0.018). They also delivered more prematurely (30.3 weeks' gestation* vs *31.5 weeks' gestation, P = 0.04) and fetal and neonatal mortality were higher (neonatal death within 7 days: 19.6%* vs *6.0%, P < 0.001). When the diagnosis was incorrect, major maternal complications and intensive care unit admissions were increased.*

Conclusions *Poor recognition of chorionicity in the first trimester of pregnancy might lead to inadequate ultrasound follow up (failure to assess every 2 weeks) and patient education. Early accurate recognition of both chorionicity and TTTS, with timely referral to a fetal therapy center, are key to ensuring optimal maternal and fetal outcomes.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Twin–twin transfusion syndrome (TTTS) is a serious complication affecting approximately 15% of monochorionic (MC) twin pregnancies[1] as a result of unbalanced placental vascular anastomoses. The diagnosis relies on, first, the accurate determination of chorionicity at 11–14 weeks and, second, demonstration of polyuric polyhydramnios in a recipient twin and oliguric oligohydramnios in a donor[2]. Close ultrasound monitoring of MC pregnancies every 2 weeks and patient education facilitate timely diagnosis and therapy of TTTS[3–7]. TTTS staging is based on the presence (Stage I) or absence (Stage II) of bladder filling in the donor, Doppler abnormalities in one or both fetuses (Stage III) and the development of hydrops (Stage IV)[1,2]. If TTTS goes unrecognized, perinatal loss is > 90%, with a high risk of neurologic impairment in survivors and severe maternal complications, including 'mirror' syndrome. Fetoscopic laser ablation of placental anastomoses enables both twins to survive in 60–70% of cases and at least one twin survives in 80–90% of cases[8]. As such, early recognition of this disease and referral of patients for therapy is mandatory.

Based on population estimates (400 000 deliveries per year[9]) and the incidence of MC pregnancies (1/330 live births[10,11]), approximately 240 TTTS cases would be expected each year in Canada, only 40% of which reach a fetoscopy center. In this study, we evaluate the incidence and consequences of 'misdiagnosed' TTTS.

METHODS

We performed a retrospective chart review of chorionicity ascertainment and referral diagnoses in 323 consecutive pregnancies with TTTS, treated with fetoscopic laser ablation of placental anastomoses at Mount Sinai Hospital, Toronto, from January 1998 to April 2012. Failure to identify monochorionicity and/or to diagnose TTTS on ultrasound scans before referral were considered

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as 'misdiagnosed' cases. Patient demographics, TTTS stage, peri-operative characteristics, complications and maternal and neonatal outcomes of 'misdiagnosed' TTTS cases were compared with cases in which chorionicity and TTTS were correctly diagnosed. Our Research Ethics Board approved this study (MSH REB #12-0190-C).

TTTS was diagnosed using standard ultrasound criteria[2,12] including oligohydramnios (deepest vertical pool < 2 cm) in the donor and polyhydramnios (deepest vertical pool > 8 cm before 20 weeks or > 10 cm after 20 weeks) in the recipient twin. Staging was performed according Quintero *et al.*[12].

Selective laser ablation of placental anastomoses was performed as previously described[13–15]. The majority of procedures were carried out under intravenous sedation (remifentanyl, with or without propofol) and local maternal anesthesia (xylocaine). A 2-mm 0° fetoscope and 3.7-mm (11 F) operating sheath (Karl Storz GmbH, Tüttlingen, Germany) and a 600-μ Nd:YAG laser fiber (Surgical Laser Technologies Inc, Montgomeryville, PA, USA) were introduced through a 12-F operating sheath (Cook, Medical Inc., Bloomington, IN, USA), which had been inserted directly using a trochar under continuous ultrasound guidance. For visualization of anterior placentae, 30° or 70° fetoscopes and a curved operating sheath were used. Intertwin placental vascular anastomoses were ablated selectively along the vascular equator. Amnioinfusion was used as necessary and amnioreduction was performed to leave the deepest amniotic fluid pool in the normal range at the end of the procedure. Prophylactic antibiotics (intravenous cefazolin) and tocolytics (indomethacin given rectally and nifedipine given orally) were administered routinely.

After laser procedures, patients were kept overnight in hospital and discharged the following day. They were either followed at Mount Sinai or referred back to their local regional perinatal center for follow up. Details regarding pregnancy and neonatal outcomes were prospectively collected and obtained from hospital records, patients and/or referring physicians.

Categorical variables were compared between cases with a correct and 'missed' diagnosis using Pearson's chi-square test (or Fisher's exact test, as indicated). For continuous variables, median values were compared using the Wilcoxon–Mann–Whitney test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with Stata software (version 12; Stata Corporation, College Station, TX, USA).

RESULTS

Details of 'misdiagnosed' cases are shown in Table 1. Among 323 consecutive patients requiring laser for TTTS, 107 (33.1%) were referred with either an incorrect diagnosis of chorionicity ($n = 95$, 88.8% of 'misdiagnosed' cases) and/or a diagnosis other than TTTS ($n = 23$, 21.5% of 'misdiagnosed' cases).

In 37 (11.5%) patients, chorionicity was not mentioned on any ultrasound report. An early ultrasound was not carried out in 19 of these cases and was performed, but did not assess chorionicity, in the other 18.

Table 1 Details of 'misdiagnosed' cases among 323 patients requiring laser for twin–twin transfusion syndrome (TTTS)

Incorrect diagnosis of:	n (%)
Chorionicity	95 (29.4)
Chorionicity not mentioned	37 (11.5)
Monoamniotic	46 (14.2)
Dichorionic	12 (3.7)
TTTS	23 (7.1)
Growth anomaly	5 (1.5)
Polyhydramnios	5 (1.5)
Oligo-/anhydramnios	3 (0.9)
Cardiomegaly	3 (0.9)
Hydrops	2 (0.6)
Lower urinary tract obstruction	2 (0.6)
Other	3 (0.9)
Both chorionicity and TTTS	11 (3.4)
Either chorionicity or TTTS	107 (33.1)

Table 2 shows pregnancy and intraoperative characteristics, complications and neonatal outcomes for correctly and incorrectly diagnosed cases. Maternal age, parity and year of laser were similar between groups. Compared with cases with a correct diagnosis, 'misdiagnosed' TTTS patients were referred later ($P = 0.018$), and at a more advanced stage (Stage IV TTTS in 16.8% of 'misdiagnosed' cases *vs* 7.9% of cases with a correct diagnosis, $P = 0.014$, or Stage III or more in 72.0% of 'misdiagnosed' cases *vs* 59.3% of cases with a correct diagnosis, $P = 0.019$). Laser duration was significantly longer in the 'misdiagnosed' group ($P = 0.04$). There were no differences in terms of deepest vertical pocket (12.2 cm *vs* 11.8 cm, $P = 0.232$) and volume of amniodrainage (1655 mL *vs* 1555 mL, $P = 0.619$). Survival was lower in 'misdiagnosed' cases ($P = 0.068$), albeit not significantly so. Preterm delivery was more common ($P = 0.022$), birth weight was lower ($P = 0.01$ for the donor and $P = 0.04$ for the recipient) and neonatal deaths were 14% higher ($P < 0.001$). Although statistically non-significant, severe maternal complications doubled when chorionicity or TTTS were incorrectly diagnosed ($P = 0.109$).

Table 3 provides details on 17 (5.3%) patients who experienced severe maternal complications. Nine developed pulmonary edema. All but one case of 'mirror' syndrome occurred in patients with Stage III or Stage IV TTTS. Seven required a blood transfusion and five were admitted to the intensive care unit (ICU). There were no maternal deaths.

DISCUSSION

In Canada, only about 40% of 240 expected TTTS cases are actually referred to a fetoscopy center[10,11]. The outcome for the remainder of cases is unknown, but it is highly likely that these are either not recognized or are recognized too late to allow adequate therapy. In referrals to our center, chorionicity and/or TTTS were incorrectly diagnosed in one third of cases. These patients were referred later, and at a more advanced stage of disease, resulting in worse maternal and neonatal outcomes.

Table 2 Characteristics, complications and neonatal outcomes for 323 monochorionic twin pregnancies with twin–twin transfusion syndrome (TTTS) treated with fetoscopic laser ablation, according to whether diagnosis of chorionicity and/or TTTS was made before (correct diagnosis) or after (misdiagnosis) referral

Variable	*Correct diagnosis (n = 216)*	*Misdiagnosis (n = 107)*	P
Maternal age (years)	31 ± 5	30 ± 5	0.138
Nulliparous	43.1	35.5	0.228
Any comorbidity*	12.5	12.2	1.000
Interval from referral US to laser (days)	1.6 ± 0.2	1.8 ± 0.2	0.183
Year of laser			0.226
1998–2003	59.7	40.3	
2004–2006	73.8	26.2	
2007–2009	62.8	37.2	
2010–2012	70.7	29.3	
TTTS stage			0.037
Stage I	4.6	2.8	
Stage II	36.1	25.2	
Stage III	51.4	55.1	
Stage IV	7.9	16.8	
Amniotic fluid DVP (cm)	12.2 ± 3.8	11.8 ± 2.9	0.232
Amniodrainage†(mL)	1655 ± 118	1555 ± 154	0.619
GA at laser (weeks)	20.1 ± 0.2	20.9 ± 0.3	0.018
Duration of surgery (min)	55 ± 2	62 ± 3	0.04
Cerclage	8.3	9.4	0.834
Anterior placenta	46.3	37.4	0.15
PPROM < 7 days after fetoscopy	7.4	10.3	0.398
Delivery < 7 days after fetoscopy	8.3	10.3	0.54
Major maternal complication‡	3.7	8.4	0.109
GA at delivery (weeks)	31.5 ± 0.3	30.3 ± 0.5	0.04
Preterm labor			
< 32 weeks	44.4	57.9	0.022
< 28 weeks	22.2	33.6	0.031
Neonatal survival and outcome			
Dual survival	61.1	50.5	0.068
Donor survival	70.4	61.7	0.131
Recipient survival	78.2	75.7	0.672
Donor weight at delivery (g)	1451 ± 55	1218 ± 78	0.01
Recipient weight at delivery (g)	1714 ± 53	1550 ± 76	0.04
NND < 7 days after birth	6.0	19.6	< 0.001
NND < 28 days after birth	6.5	20.6	< 0.001

Values are given as mean ± SD or %. *For example, asthma, hypertension, diabetes, thyroid disorder, blood disorder, inflammatory bowel syndrome. †Difference between amnioinfusion and amniodrainage performed during fetoscopy. ‡Details in Table 3. DPV, deepest vertical pocket; GA, gestational age; NND, neonatal death; PPROM, preterm prelabor rupture of membranes; TTTS, twin–twin transfusion syndrome; US, ultrasound.

Possible reasons for these 'misdiagnosed' cases include: poor recognition of chorionicity in early pregnancy (11–14 weeks); suboptimal knowledge amongst health-care providers and patients regarding MC twin complications; inadequate ultrasound follow-up of MC pregnancies; failure to recognize the urgency of TTTS, with subsequent delay in referral; and perhaps suboptimal access to specialized obstetric ultrasound in more remote areas of Canada.

Recently, Gandhi *et al.* showed that 23% of referrals for suspected TTTS were not confirmed[16]. Of the patients confirmed with TTTS, two-thirds of the referrals had advanced-stage disease (Stages III–V), whereas only approximately one-third presented with Stage I and Stage II disease. The authors concluded that early referral would allow for potential laser treatment in a timely manner with the potential for improved dual twin survival and a decreased risk of neurodevelopmental delay.

Our findings underline the importance of (i) correctly identifying chorionicity at the 11–14-week scan and (ii) following all MC pregnancies with ultrasound every 2 weeks, looking specifically for any evidence of TTTS[4–7]. Had this practice been followed, we suggest that it may potentially have avoided fetal and neonatal deaths, as well as maternal admissions to the ICU. Moreover, early referral could have enabled more timely therapy, thus potentially decreasing neurologic morbidity, which in some studies was higher in more advanced TTTS stages[17,18]. Correct diagnosis and timely therapy also lead to more advanced gestational age at delivery, thus improving neurologic outcomes[19].

To our knowledge, this is the first study evaluating both fetal and maternal consequences of 'misdiagnosed' chorionicity and/or TTTS. Strengths included the comprehensive, clinically meaningful nature of the outcomes chosen, the rigorous review of all referrals to our hospital and a large sample size.

The main limitation of our study was its retrospective design (although infant outcomes and pregnancy complications were gathered prospectively as part of our quality insurance program). Moreover, our data were only derived from pregnancies that underwent fetoscopic laser ablation. This might underestimate the true rate of 'misdiagnosed' patients, as true 'missed' cases of TTTS,

Table 3 Severe maternal complications experienced in 17 monochorionic twin pregnancies with twin–twin transfusion syndrome (TTTS) treated with fetoscopic laser ablation, according to whether diagnosis of chorionicity and/or TTTS was made before (correct diagnosis) or after (misdiagnosis) referral

Diagnosis	*MA (years)*	*GA (weeks)*		*TTTS stage**	*Blood transfusion*	*Pulmonary edema*	*ICU admission*	*Comments*	*Neonatal survival*
		At laser	*At birth*						
Correct diagnosis	29	21	21	III R	+	+	+	'Mirror' syndrome	—
	29	18	20	III R + D	+	–	–	Major bleeding from uterine incision, mini-laparotomy	—
	27	24	25	III R + D	–	–	+	Abruption immediately post-procedure, DIC	D
	33	24	36	IV		+		'Mirror' syndrome	R + D
	35	19	36	III D	+	–	–	Intraperitoneal bleeding, laparoscopic procedure converted to laparotomy, suspicion of bowel injury not confirmed	R + D
	34	24	26	II	–	+	+	'Mirror' syndrome	—
	30	26	27	III R	–	–	–	Abruption immediately post-procedure	R + D
	27	22	25	III D	–	+	–	Hemorrhage from placental vessel followed by severe RDS. Suspicion of amniotic fluid embolism	R
Misdiagnosis	22	23	23	IV	–	+	–	'Mirror' syndrome	—
	29	25	25	III R	–	–	+	Abruption immediately post-procedure, DIC	R
	35	23	33	IV	–	+	+	'Mirror' syndrome	R + D
	31	25	26	III R + D	+	+	–	Ascites, 'mirror' syndrome, abruption	R
	30	18	23	III R	+	–	–	Heavy vaginal bleeding	—
	34	17	28	II	+	–	–	Heavy vaginal bleeding, abruption	R + D
	32	21	26	IV	–	+	–	'Mirror' syndrome	R
	27	23	35	III D	–	+	–	Cardiac failure	R
	30	16	33	III R	+	–	–	Heavy vaginal bleeding	R + D

*R (recipient) and D (donor) indicate which fetus had abnormal Doppler ultrasound. +, present; –, absent; DIC, disseminated intravascular coagulation; GA, gestational age; ICU, intensive care unit; MA, maternal age; RDS, respiratory distress syndrome.

ending in premature labor or perinatal mortality, would be unaccounted for. Indeed, the denominator for the rate of 'missed' monochorionicity should consist of all liveborn and stillborn MC pregnancies, not only those referred for therapy, while the denominator for the rate of 'missed' TTTS should consist of all liveborn and stillborn infants with TTTS. Among them, we also acknowledge Stage I cases that do not progress and are associated with favorable perinatal outcomes[1,20].

It should also be acknowledged that the frequency of sonographic examinations performed by referring providers was not documented consistently. However, our clinical experience confirms that a 'misdiagnosed' patient referred with TTTS usually also did not undergo close monitoring of the pregnancy with fortnightly ultrasound examinations and patient education.

Guidelines for the management of MC twin pregnancies were published by the Royal College of Obstetricians and Gynaecologists in 2008[5], the Collège National des Gynécologues et Obstétriciens Français in 2009[4] and the Royal Australian and New Zealand College in 2011[7]. In Canada, guidelines for 'Ultrasound in Twin Pregnancies' were published in 2011[6]. We hope to witness their impact in the near future. These guidelines all call for the early establishment of chorionicity on first-trimester ultrasound in multiple gestations, along with fortnightly ultrasound monitoring of all MC twin gestations. Indeed, about one in four MC diamniotic twins will experience some form of pregnancy complication[2], including TTTS (10–15%), selective growth restriction (10–15%) or twin anemia–polycythemia sequence (TAPS, 5%). Our study reinforces the need to follow these guidelines.

During the last few years, extensive efforts have been carried out to better inform healthcare professionals caring for twins. Different websites are dedicated both to parents and to professionals[21]. Over the last 16 years, we have also put great effort into organizing regular local, regional and national Continuing Medical Education (CME) meetings at which the diagnostic criteria for TTTS are extensively discussed and early referral is encouraged. This CME activity has been largely directed at members of the obstetric and medical imaging communities. In our study, the rate of correct diagnosis was only 59.7% in the time period 1998–2003, and then increased to 73.8% in 2004–2006. Despite this initial improvement, the rate of correct diagnosis dropped to 62.8% in 2007–2009 and was 70.7% in 2010–2012 ($P = 0.226$). Despite a steady increase in the number of cases that have been appropriately diagnosed and referred, there is still much room for improvement.

In several cases that have come to our unit, the referral has been prompted by the patient, having done her own research online – this emphasizes the importance of educational online resources for patients. We have

recently developed such a resource. We know that this problem with diagnosis and referral is not unique to our region, and, although difficult to find specific figures in the literature, this has been confirmed by colleagues from leading fetal therapy units in several other countries.

We strongly endorse the importance of accurately documenting chorionicity in all multiple pregnancies and of raising the awareness of the potential complications of MC twin pregnancies, specifically TTTS, TAPS and placental growth discordance. This is best done through proper ultrasound training, continuing medical education and ongoing audit of practice. All healthcare providers looking after multiple gestations must strive to ensure that chorionicity is correctly diagnosed, ideally at 11–14 weeks. Patients with MC twins should be educated about the symptoms of TTTS (e.g. a sudden increase in abdominal circumference) and fortnightly ultrasound examinations should be performed to detect oligo- and polyhydramnios, differences in bladder sizes and the cardiac changes typical of TTTS[3,14,22,23]. Healthcare professionals caring for twins must be aware of the diagnostic criteria for TTTS and refer patients to a fetoscopy center once this disease is suspected.

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