ORIGINAL ARTICLE

Fetoscopic laser photocoagulation in the management of twin-twin transfusion syndrome: local experience from Hong Kong

X Yang 楊 昕
TY Leung 梁德楊
Warwick D Ngan Kee 顏 傑
M Chen 陳 敏
LW Chan 陳連偉
TK Lau 劉子建

Objective To review the perinatal outcome of monochorionic twin pregnancies treated by fetoscopic laser coagulation for twin-twin transfusion syndrome.

Design Retrospective study.

Setting A university teaching hospital in Hong Kong.

Patients Thirty consecutive cases of fetoscopic laser coagulation of placental anastomoses for twin-twin transfusion syndrome performed in a single centre.

Main outcome measures Operative complications and perinatal survival rates.

Results The median gestational age at initial presentation, laser photocoagulation, and delivery were 22 (range, 16-27) weeks, 23 (18-28) weeks, and 32 (21-37) weeks, respectively. To improve the visualisation, in three cases amnio-exchange was undertaken; the procedure was abandoned in two due to poor visualisation. The overall fetal survival rate, the double infant survival rate, and survival rate for at least one twin were 72% (43/60), 60% (18/30), and 83% (25/30), respectively. The most common peri-operative complication was bleeding from the uterine wall into the amniotic cavity, which affected three (10%) patients.

Conclusions Our results of fetoscopic laser surgery for twin-twin transfusion syndrome were similar to those in specialised centres in other countries.

Introduction

Monochorionic (MC) twin pregnancies are the result of splitting of fertilised ova after the third day of fertilisation, which occurs in about two thirds of all monozygotic twins.[1] Monochorionic twins are very high risk pregnancies, and the associated perinatal mortality and morbidity are 3- to 10-fold higher than those in dichorionic twins.[2] Twin-twin transfusion syndrome (TTTS) is one of the most serious obstetric complications specific to MC twinning, occurring in about 10 to 20% of MC twin pregnancies.[3] It is now clear that TTTS is the result of a chronic imbalanced unidirectional blood flow from one twin to the other, through placental arterio-venous anastomoses between the two fetal circulations sharing the same placental mass (Figs 1a and 2a).[4] Such anastomoses are present to some degree in virtually all MC placentae.[4] The donor twin becomes progressively hypovolaemic, and develops anaemia, growth restriction, oliguria and severe oligohydramnios. In TTTS, the recipient twin becomes hypervolaemic and develops progressive cardiac failure and polyhydramnios. Further deterioration may result in in-utero death of both twins. In addition, polyhydramnios could be severe, leading to preterm rupture of membranes, preterm labour, and extreme preterm delivery. If left untreated, the perinatal mortality of affected pregnancies exceeds 80%.[2]

Close monitoring by antenatal ultrasound examinations enables early detection of TTTS in the mid-trimester. The earliest signs are discordance in liquor volume between the two gestational sacs, one with oligohydramnios and the other with polyhydramnios (Quintero stage I).[5] In stage II disease, the donor twin has severe oligohydramnios with non-visualisation of the fetal bladder. In more severe cases, there will be Doppler blood flow abnormalities (stage III), fetal hydrops (stage IV), and eventually fetal demise (stage V).

If one of the fetuses dies in utero, there will be sudden exsanguinations from the remaining fetus to the dead fetus through the vascular communication, resulting in either death or cerebral damage to the remaining fetus.

Key words
Fetofetal transfusion; Fetoscopy; Laser coagulation; Pregnancy outcome; Twins, monozygotic

Hong Kong Med J 2010;16:275-81

Prenatal Diagnostic Centre, Guangzhou Obstetrics and Neonatal Hospital, Guangzhou, Guangdong, PR China
X Yang, MD
The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong:
Department of Obstetrics and Gynaecology
TY Leung, MD, FRCOG
M Chen, PhD
LW Chan, MB, ChB, MRCOG
TK Lau, MD, FRCOG
Department of Anaesthesia and Intensive Care
WD Ngan Kee, MD, FANZCA

Correspondence to: Prof TK Lau
Email: tzekinlau@cuhk.edu.hk

胎兒鏡下激光凝固胎盤血管術治療單絨毛膜雙胎：香港經驗交流

目的 回顧研究胎兒鏡下激光凝固胎盤血管術治療雙胎輸血綜合症（TTTS）病例出生結果。

設計 回顧研究。

安排 香港一所教學醫院。

患者 就診於一所產前診斷中心的30宗接受胎兒鏡下激光凝固胎盤血管術治療的TTTS病例。

主要結果測量 術後併發症發生率及新生兒存活率。

結果 30例接受激光治療的病例中，就診孕齡、激光治療及出生孕齡中位數分別為22（16-27）周、23（18-28）周及32（21-37）周。其中3例為了改善手術視野而進行羊水交換。2例由於手術視野差而放棄治療。胎兒整體存活率、雙胎存活率及單胎存活率分別為72%（43/60）、60%（18/30）和83%（25/30）。本研究中最常見的圍手術期併發症為穿刺點宮腔內出血，共3例（10%）。

結論 本中心的胎兒鏡激光治療術治療TTTS病例結果與其他國家專科治療中心相若。

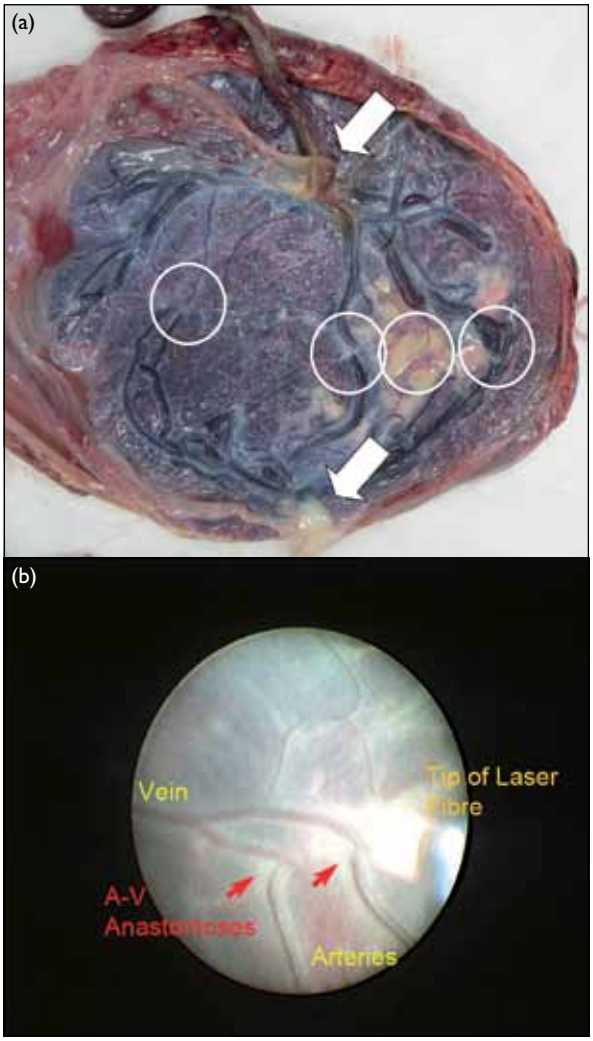

FIG 1. (a) A placenta from a monochorionic twin pregnancy after delivery at 34 weeks of gestation. Arrows indicate the umbilical cord insertions. Circles indicate arterio-venous (A-V) vascular communications between the vascular territories of the two fetuses. (b) Pre-laser fetoscopic view of the A-V anastomoses on the placental surface of a monochorionic diamniotic twins pregnancy undergoing laser photocoagulation for twin-twin transfusion syndrome. Arrows indicate the A-V anastomoses

Traditional treatment by repeated amnioreduction is a simple procedure and is effective in preventing polyhydramnios-related preterm delivery, but is only able to prolong these pregnancies to a median gestation of 29 weeks.[6,7] On the other hand, although fetoscopic laser photocoagulation of placental vascular anastomoses is technically more challenging, it directly addresses the underlying placental vascular pathology. Laser therapy aims at dividing the two fetal circulations into independent functioning units by blocking the communicating vessels, thereby stopping inter-twin transfusion (Figs 1b and 2b). Previous studies have shown that compared with repeated amnioreduction, laser treatment results in lower perinatal mortality, longer gestational age at delivery, and less long-term neurological impairment.[7-9]

In 2002, we performed the first fetoscopic laser coagulation for TTTS in Hong Kong.[10] The aim of the current study was to review the perioperative complications and perinatal outcomes of the initial 30 consecutive cases of fetoscopic laser coagulation for TTTS in a fetal medicine centre in Hong Kong.

Methods

This was a retrospective review of the initial 30 consecutive cases of laser coagulation for TTTS performed in our unit between January 2002 and March 2008. Cases of laser coagulation for other indications, such as selective fetal growth restriction or discordant fetal anomalies, were excluded. The diagnosis and staging of TTTS was according to established standards.[5] Measurement of cervical length was not routinely performed. In general, laser therapy was offered only to mothers with TTTS having at least Quintero stage II before 26 weeks of gestation. All procedures in this series were performed on an in-patient basis by a single operator. Patients were usually admitted on the day of surgery, and discharged on the following day. After the procedure, all the patients were given an oral tocolytic (nifedipine GITS, 60 mg) daily for 3 weeks and monitored weekly by ultrasound scans for evidence of resolution, persistence or recurrence of TTTS based on fetal viability, liquor volume, and Doppler study of the fetal vessels. Fetal growth parameters

were assessed by ultrasound every 2 weeks. The frequency of monitoring was reduced when the treatment was considered to be successful and there was no evidence of recurrence. The operative details, peri- and post-operative complications, and pregnancy outcome were reviewed.

The overall survival rate was given by the number of surviving fetuses divided by the total number (60) of fetuses. The double survival rate was the proportion of pregnancies in which both fetuses survived. The one-twin survival rate was the proportion of pregnancies in which one or both fetuses survived.

Protocol of fetoscopic laser photocoagulation

All operations were performed in the operating theatre. General anaesthesia was used in the initial 19 cases, and spinal anaesthesia in the subsequent 11 cases. All patients were fasted for 8 hours or more before the operation. Prophylactic antibiotics (amoxicillin and clavulanic acid 1.2 g) were given at induction of anaesthesia. Tocolytic treatment in the form of nifedipine GITS 60 mg was given on the morning of the operation, but this practice was stopped after 19 cases. An ultrasound examination was performed immediately before starting the operation to confirm fetal viability, the location of the placenta, and to determine a site of entry for the fetoscope. In choosing the site of insertion, we always used ultrasound to avoid big vessels and areas with excessive vascular flow. The typical instrument used included a 2-mm fetoscope with detached eye-piece from Karl Storz (Tuttlingen, Germany) and a diode laser with a 600 μm laser fibre (Medlilas D; Dornier MedTech, Munich, Germany). A single 2.7-mm cannula allowed the passage of both the fetoscope and laser fibre in one single port. Under direct ultrasound guidance, the cannula was introduced transabdominally into the amniotic cavity after making a small abdominal incision. The site of entry primarily depended on the location of placenta and cord insertion. Once inside the amniotic cavity, a systematic fetoscopic examination was performed to identify the placental chorionic plate and to determine the number and nature of all anastomoses. In case of an anterior placenta, the site of insertion was carefully chosen, and external manipulation and pressure were used to change the shape and orientation of the placenta to bring it to a better orientation. If amnio-infusion or amnio-exchange was deemed necessary, warm normal saline solution was used. All types of anastomoses between the two vascular territories were coagulated with the diode laser at 30 to 60 W, with the laser fibre tip at a distance of about 1 cm from the vessels. At the end of the procedure, amniotic fluid was drained through the cannula to restore normal liquor volume in the recipient's gestational sac. The abdominal wound was closed with sterile strips; sutures were not used. Fetal viability was confirmed by ultrasound at the end of operation.

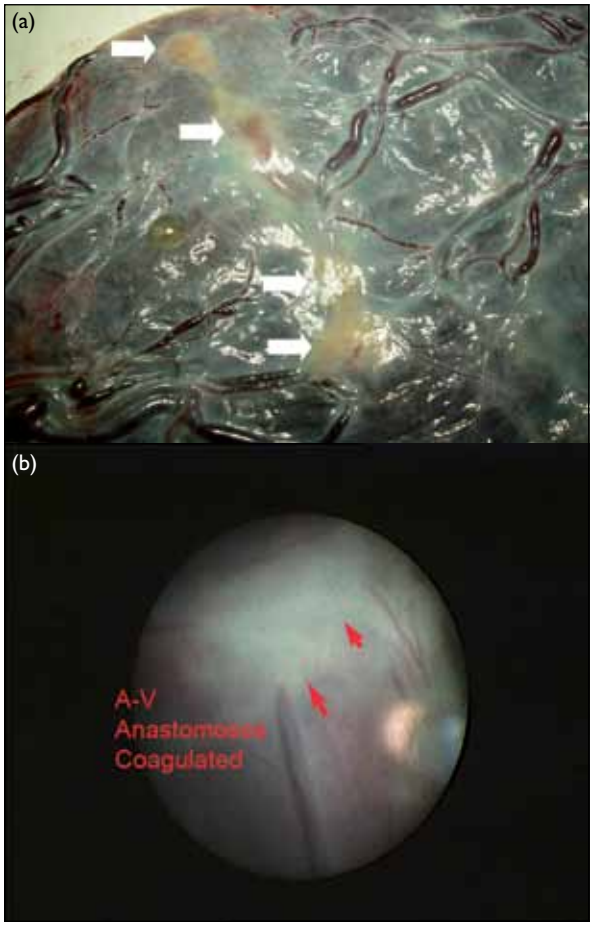

FIG 2. (a) A placenta from a monochorionic twin pregnancy complicated by twin-twin transfusion syndrome (TTTS) after delivery at 35 weeks of gestation. Endoscopic laser photocoagulation was performed at 21 weeks of gestation. Arrows indicate areas of tissue necrosis as a result of the laser therapy, which effectively divided the single placental mass into two independent fetal circulations. (b) Post-laser fetoscopic view of the arterio-venous anastomoses on the placental surface of a monochorionic diamniotic twins pregnancy undergoing laser photocoagulation for TTTS. Arrows indicate that the anastomoses were coagulated

A video of fetoscopic laser photocoagulation for twin-twin transfusion syndrome is available at <www.hkmj.org>.

Results

A total of 30 patients were reviewed, of which 15 were Hong Kong inhabitants, 13 were from mainland China, one from Malaysia, and one from Thailand. Cases were referred from other regions or countries because this operation was not available there. Amnioreduction was performed in one case in China, before referral to our centre. In this series, there was no significant maternal morbidity.

The median gestational age at presentation was 22 (range, 16-27) weeks, and the median gestational

TABLE 1. Perinatal outcomes of the 30 twin pregnancies treated with fetoscopic laser ablation for twin-twin transfusion syndrome

Perinatal outcome	No. (%) or median (range)
Overall survivor (per fetus)	43/60 (72%)
Double survivor (per pregnancy)	18/30 (60%)
Only one survivor (per pregnancy)	7/30 (23%)
At least one survivor (per pregnancy)	25/30 (83%)
Gestational age at delivery (weeks)	
<24	1/30 (3%)
24-28	5/30 (17%)
28-32	8/30 (27%)
32-37	16/30 (53%)
Procedure-delivery interval (weeks)	10 (0-18)
Birth weight (g)	
Larger twin	1817 (495-2450)
Smaller twin	1150 (245-2350)

age at laser photocoagulation was 23 (range, 18-28) weeks. At the time of the operation, the severity of TTTS was as follows: one case was at Quintero stage I (3%), 10 at stage II (33%), 12 at stage III (40%), and 7 at stage IV (23%). Laser therapy was performed in the patient with stage I disease because of severe polyhydramnios with the deepest vertical pocket being 12.3 cm. In two cases from mainland China, laser therapy was performed beyond 26 weeks of gestation (at 27 and 28 weeks). Both entailed severe fetal cardiac dysfunction and features of fetal hydrops. These parents also indicated that they would have the pregnancy termination in China, if laser therapy was not to be performed.

The most common intra-operative complication was bleeding from the uterine wall into the amniotic cavity at the site of entry of the fetoscope, which occurred in three (10%) of the cases. Amnio-exchange was performed in two cases to regain visualisation for the laser procedure. Amnio-exchange was performed in another case, because turbidity of the amniotic fluid interfered with visualisation.

The laser procedure was abandoned before completion in two (7%) of the cases because of poor visualisation; both had bleeding from the uterine wound.

During the operation, the median energy used was 6439 J (range, 1104-27 794 J). The median amount of amnioreduction was 1750 mL (range, 600-5400 mL).

Perinatal outcomes and delivery details are summarised in Table 1. The median interval between laser treatment and delivery was 10 (range, 0-18) weeks. The overall fetal survival rate was 72% (43/60). There was at least one surviving infant in 83% (25/30) of the treated pregnancies. The double-infant survival rate was 60% (18/30). The median gestational age at delivery was 32 (range, 21-37) weeks.

Table 2 shows that the survival rate was lower among patients from mainland China than elsewhere, although the difference did not reach statistical significance; for at least one twin surviving, the rates were 69% vs 94%, respectively (P=0.153). Similarly, those with stage IV disease had significantly lower overall survival rates than the others (43% vs 80%; P=0.008). There were no significant differences or observable trends in survival with respect to the gestational age at laser treatment or the location of placenta.

Subjects from mainland China were seen at a more advanced gestational age than the Hong Kong citizens; the median gestational age at the time of laser treatment being 24 and 20 weeks, respectively (P=0.003). The percentage with stage IV disease was also significantly higher in mainland Chinese patients; 54% (7 cases) vs 0%, respectively (P=0.013).

Table 3 shows the clinical details associated with pregnancies that suffered any fetal loss. There were five with double fetal losses, including three due to spontaneous abortion/preterm labour within 4 weeks of the operation. In two cases there was a single intra-uterine death (IUD) and the patient opted for termination of the remaining pregnancy. There were seven cases of single fetal losses, including three IUDs, and four neonatal deaths. In the three cases of

TABLE 2. Effect of maternal and pregnancy characteristics on perinatal outcomes after laser therapy for twin-twin transfusion syndrome

Characteristic	No. of subjects	Overall % that survived	% With at least one survivor
Overall	30	72	83
Citizenship			
Hong Kong	15	77	93
Mainland China	13	62	69
Malaysia	1	100	100
Thailand	1	100	100
Disease stage at laser			
I	1	100	100
II	10	90	90
III	12	71	92
IV	7	43	57
Gestation at laser (weeks)			
<20	10	65	80
20-24	16	78	88
≥25	4	63	75
Placental site			
Anterior	13	65	77
Posterior	14	75	86
Left lateral	2	100	100
Fundal	1	50	100

TABLE 3. Details of perinatal losses after laser therapy for twin-twin transfusion syndrome*

Case No.	Patient	Details	Outcome
Double fetal losses			
Case 1	Local resident	Stage II disease	Spontaneous abortion 2 weeks after laser at 21 weeks of gestation
Case 2	Mainland China	Stage IV disease	Spontaneous abortion 3 weeks after laser at 26 weeks of gestation
Case 3	Mainland China	Stage IV disease with very severe cardiac dysfunction of the recipient twin	IUD of donor twin 2 days after laser; decided to have TOP in China 6 weeks after laser at 25 weeks of gestation, when there was no significant improvement in cardiac function of the recipient twin
Case 4	Mainland China	Stage IV disease	IUD of donor twin 3 days after laser; decided to have TOP in China within 1 week of laser at 26 weeks of gestation
Case 5	Mainland China	Stage II disease	Spontaneous preterm labour 4 weeks after laser at 28 weeks in China; both baby had NND after delivery
Single fetal loss			
Case 1	Local resident	IUD of smaller twin 3 weeks after laser	Normal development of the remaining twin, delivered at 35 weeks of gestation
Case 2	Local resident	IUD of smaller twin 12 weeks after laser	Normal development of the remaining twin, delivered at 32 weeks of gestation
Case 3	Local resident	SROM 2 weeks after laser at 27 weeks followed by preterm labour	NND of one fetus and the other survived
Case 4	Local resident	Laser abandoned due to persistent bleeding at insertion site	Couple decided to continue with pregnancy; spontaneous preterm delivery 7 weeks later at 27 weeks of gestation; NND of one fetus and the other survived
Case 5	Local resident	Successful laser; delivered at 35 weeks for significant maternal proteinuria	The original donor twin was found to have oesophageal atresia with tracheoesophageal fistula which was surgically repaired; however, the baby developed sudden cardiac arrest and died 2 days after operation; the other baby was normal
Case 6	Mainland China	IUD of smaller twin 1 day after laser	Normal further development of the remaining twin, delivered at 36 weeks of gestation
Case 7	Mainland China	Atypical case of TTTS. The larger fetus had oligohydramnios while the smaller fetus had polyhydramnios; no significant deterioration or improvement after laser; delivered at 31 weeks for reduced fetal movement	Larger twin had NND because of severe persistent pulmonary hypertension; smaller twin was confirmed to have Hirschsprung's disease

* IUD denotes intra-uterine death, NND neonatal death, SROM spontaneous rupture of membranes, TOP termination of pregnancy, and TTTS twin-twin transfusion syndrome

single IUD, the TTTS resolved after treatment, IUD of the smaller twin having occurred probably as a consequence of inadequate placental function after the separation of placental anastomoses. One of the neonatal deaths was due to undiagnosed congenital anomalies unrelated to laser.

Discussion

In this local series of 30 mothers with TTTS treated by fetoscopic laser, we achieved an overall survival rate of 72%, which was comparable to those in other published reports.[7,9,11] In our series, there was no obvious relationship between outcome and increasing experience with the operation. We believe that our good outcomes were due to a combination of a carefully planned programme, carefully planned treatment for each patient, close communication with world experts, and careful pre- and post-operative assessment, monitoring, and interventions. A single operator was chosen because of his expertise rather than seniority. He was a competent endoscopic surgeon involved in the early development of gynaecological endoscopy in Hong Kong. He also had extensive prior experience in obstetric ultrasound, as well as ultrasound-guided invasive diagnostic and therapeutic procedures. Although all laser procedures were performed by a single operator, the success and smooth conduct of all operations required the close collaboration and support of the anaesthetists, and nurse specialists, assisted by other fetal medicine specialists.

Our results showed a significantly worse perinatal outcome in those with stage IV disease, consistent with the previous publication from Quintero et al.[5] For different stages of TTTS, the double perinatal survival rate decreased from 90% at stage II to 29% at stage IV. For at least one survival, it was from 92 to 57%, and for overall survival, the decrease was from 90 to 43%. Therefore, it is important for those who care for women with monochorionic twin pregnancies to monitor them closely, at least once

every 2 weeks between 16 and 26 weeks of gestation. This should enable detection and treatment of TTTS at an earlier stage, and thus offer a higher chance of perinatal survival.

Although an anteriorly located placenta is technically more challenging, there are many manoeuvres that can be used to overcome the problem. In general, a carefully chosen insertion site for the fetoscope and external manipulation of the uterine shape and position were most useful. In this series, we were able to achieve a similar survival rate irrespective of the placental site.

Laser therapy does not treat the fetal condition directly, rather, it only destroys the underlying pathology, allowing time for the sick fetus to recover. Even after successful laser therapy, there may be transient deterioration of the fetal condition. It may take a few weeks before liquor volume is normalised in the two fetuses, and severe cardiac dysfunction may take even longer to recover. Therefore, both doctors and parents should not expect an immediate improvement after the treatment.

The most common intra-operative complication was bleeding from the uterine wall into the amniotic cavity (3 cases, 10%); in two cases this resulted in abandonment of the procedure. In choosing the site of insertion of the fetoscope, we always used ultrasound guidance to avoid large vessels or areas with excessive vascular flow. However, even with such careful planning, three cases were complicated by uterine bleeding. Although the exact reason was not known, we suspected that it was due to our very effective preoperative tocolysis or related to general anaesthesia. After we stopped using preoperative tocolytics and general anaesthesia, such complications ceased.

There was no case of ruptured membranes, but one instance of abortion within the first week post-procedure. There were three cases with double fetal losses due to abortion or preterm delivery between 2 and 4 weeks following the procedure, signifying that after the laser procedure pregnancies are still at higher risk of preterm labour. A recent report suggested that at the time of laser therapy, a short cervix was associated with a higher risk of postoperative abortion or preterm labour, in which case it may be preventable by combining cervical cerclage with laser.[12] However, cervical cerclage is an invasive procedure, which may itself precipitate preterm labour. Management of these cases therefore needs to be individualised. In two cases (both from mainland China), pregnancy termination was performed after a single IUD, resulting in double fetal losses. It is unknown whether the remaining fetuses would have survived had pregnancy termination not been performed.

In this series, single IUD occurred in five cases (including the two in which the pregnancies were subsequently terminated). If a single IUD occurs after successful laser therapy, it is usually due to unequal placental sharing, which cannot be changed by the laser procedure. By dividing the communicating vessel, each fetus has to rely on the function of its own share of placental mass, which may not be enough for some fetuses. However, if the laser procedure successfully divides all vascular communications, death of one fetus should no longer affect the haemodynamics of the remaining twin. The latter should then progress normally, as evidenced by the three cases in our series in which the pregnancy was allowed to continue.

It is obvious that after laser therapy, all pregnancies remained high risk because of the various potential post-procedure complications. Such cases are therefore best managed by maternal fetal medicine specialists; the operation itself is only one part of the overall management of TTTS.

Being a retrospective descriptive study, we were not able to compare the outcome of TTTS cases treated by laser versus other methods. Our study, however, clearly demonstrated that outcomes in our series were comparable to those reported internationally. However, we did not assess long-term neurological and developmental outcomes.

In conclusion, TTTS can be effectively treated by laser therapy with minimal maternal complications. Favourable overall outcomes require careful monitoring before and after the procedure. Because of the highly variable clinical course in these pregnancies, patient counselling is very important. We recommend these pregnancies be managed in specialised referral centres.

References

1. Nikkels PG, Hack KE, van Gemert MJ. Pathology of twin placentas with special attention to monochorionic twin placentas. J Clin Pathol 2008;61:1247-53.
2. El Kateb A, Ville Y. Update on twin-to-twin transfusion syndrome. Best Pract Res Clin Obstet Gynaecol 2008;22:63-75.
3. Harkness UF, Crombleholme TM. Twin-twin transfusion syndrome: where do we go from here? Semin Perinatol 2005;29:296-304.
4. Denbow ML, Cox P, Taylor M, Hammal DM, Fisk NM. Placental angioarchitecture in monochorionic twin pregnancies: relationship to fetal growth, fetofetal transfusion syndrome, and pregnancy outcome. Am J Obstet Gynecol 2000;182:417-26.
5. Quintero RA, Dickinson JE, Morales WJ, et al. Stage-based treatment of twin-twin transfusion syndrome. Am J Obstet

Gynecol 2003;188:1333-40.
6. Mari G, Roberts A, Detti L, et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. Am J Obstet Gynecol 2001;185:708-15.
7. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med 2004;351:136-44.
8. Lenclen R, Ciarlo G, Paupe A, Bussieres L, Ville Y. Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin-to-twin transfusion syndrome: comparison with dichorionic twins. Am J Obstet Gynecol 2009;201:291.e1-5.
9. Rossi AC, D'Addario V. Laser therapy and serial amnioreduction as treatment for twin-twin transfusion syndrome: a metaanalysis and review of literature. Am J Obstet Gynecol 2008;198:147-52.
10. Lau TK, Leung TY, Fung TY, Leung TN. Treatment of twin-twin transfusion syndrome by fetoscopic laser photocoagulation. Chin Med J (Engl) 2004;117:1431-4.
11. Middeldorp JM, Sueters M, Lopriore E, et al. Fetoscopic laser surgery in 100 pregnancies with severe twin-to-twin transfusion syndrome in the Netherlands. Fetal Diagn Ther 2007;22:190-4.
12. Salomon LJ, Nasr B, Nizard J, et al. Emergency cerclage in cases of twin-to-twin transfusion syndrome with a short cervix at the time of surgery and relationship to perinatal outcome. Prenat Diagn 2008;28:1256-61.