

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intrauterine laser ablation of placental vessels for the treatment of twin to twin transfusion syndrome

Twin to twin transfusion syndrome occurs when unborn identical twins have different sacs in the womb but share the same placenta. This may result in blood flow from one twin to the other through connections between blood vessels in the shared placenta. The volume of fluid around the twins can also become uneven. This procedure uses laser to separate the shared blood vessels in the placenta.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2006

Procedure name

- Other procedure terms used include: Selective laser ablation, fetoscopic laser ablation, endoscopic laser ablation.
- Other indicatio terms used include: Feto-Fetal Transfusion Syndrome, Twin Oligohydramnios-Polyhydramnios Sequence

Specialty societies

- British Maternal and Fetal Medicine Society
- Royal College of Obstetricians and Gynaecologists

Description

Indications:

Approximately 70% of monozygotic twins are monochorionic/diamniotic (one placenta with two amniotic sacs). Twin to twin transfusion syndrome (TTTS) affects approximately 15% of monochorionic/diamniotic pregnancies and historically has perinatal mortality of up to 80% if untreated¹. TTTS results

from shunting between the circulations of unborn twins through abnormal communications (anastomoses) in vessels of the shared placenta. Blood is transfused from the donor twin, whose growth becomes restricted and who develops oligohydramnios or anhydramnios (low or absent amniotic fluid), to the recipient, who develops circulatory overload, cardiac compromise and polyhydramnios (too much amniotic fluid). The combination of polyhydramnios in the recipient and oligo/anhydramnios in the donor squashes the donor twin against the wall of the uterus. This is referred to as a 'stuck twin'. The general disturbance of circulation and perfusion in both twins is associated with high morbidity and mortality. Morbidity among survivors includes cardiac, renal and serious neurological impairment, such as cerebral palsy. It is estimated that around 15% of survivors will have long-term neurological sequelae ².

A staging system for TTTS has been developed by Quintero et al ³ that considers a sequence of progressive sonographic features from early (stage I) to late stage disease, ultimately ending in the demise of either fetus (stage V). Generally the earlier in gestation TTTS presents, the worse the prognosis.

Current treatment and alternatives

The options for managing TTTS include expectant medical management, amniodrainage, septostomy, laser ablation and selective fetal termination using techniques such as umbilical cord occlusion. In some cases the treatment aim is to enable one twin to survive as the chances for both surviving are extremely poor. Some women may choose to terminate the pregnancy because of the high risk of perinatal morbidity and mortality in both twins.

Expectant management will only be appropriate in a few mild cases because of the high perinatal mortality and morbidity. Amniodrainage is a long-established procedure which aims to reduce amniotic fluid volume in the recipient polyhydramniotic twin and to prevent extremely preterm delivery. It does not treat the underlying pathophysiological cause (i.e. abnormal communications between vessels in the shared placental) nor allow the amniotic fluid volume to normalise around the donor twins.

What the procedure involves

The procedure is performed under local anaesthesia (with maternal sedation). Under ultrasound guidance, a cannula and stylet needle is advanced through the maternal abdomen, uterine wall into the amniotic sac of the recipient twin. The needle is removed and a fetoscope with a thin fiber to carry the laser energy is then inserted through the cannula. The fetoscope is used to look at the blood vessels on the surface of the placenta. Vessels that are found to communicate between the twins are then coagulated using the laser. At the completion of the surgery, excess amniotic fluid in the recipient twin's sac is also removed to achieve a normal volume.

Laser ablation can be undertaken both as a non-selective and as a selective technique. In the non-selective technique, laser is used to coagulate all vessels crossing the intertwin membrane. This may mean that some vessels that are not associated with TTTS are ablated potentially resulting in a higher

mortality of the donor twin. In contrast, the more recently developed selective approach only ablates specific connections (e.g. arterio-arterial and veno-venous), sparing the remaining vessels.

Efficacy

The evidence on efficacy is based on two systematic reviews, two controlled trials (one randomised controlled, one non-randomised) and three case series.

Survival

A systematic review ⁴, included ten studies assessing laser ablation (both non-selective and selective) for treatment of TTTS. Overall perinatal survival ranged from 61% (87/142) to 70% (210/300), with survival rates for at least one twin ranging from 61% (11/18) - 83% (79/95). The systematic review included the single one randomised controlled trial of selective laser ablation versus amniodrainage. This study found that compared with the amniodrainage group, those treated with laser had a greater likelihood of at least one twin surviving to 28 days (76% (55/72) vs. 56% 36/70 $p=0.002$). This difference was also maintained to 6 months of age ($p=0.01$) ⁵. Similar results were also reported in two non-randomised controlled trials.

Neurological impairment

Post-natal neurological sequelae were reported in eight of the ten studies included in the systematic review ⁴. The incidence of neurological morbidity ranged from 1.2% (1/87) to 7.6% (2/26) among fetuses born alive. Two additional case series specifically evaluating long term neurological sequelae reported major neurological abnormalities in 6% (10/167) and 11% (10/89%) of twins treated with laser and followed up to a median post-natal follow-up of 22 and 38 months respectively. Results from three studies comparing laser and amniodrainage (one randomised and two non-randomised controlled trials) found that neurological morbidity was reduced following laser compared with amniodrainage.

Specialist Advisors

The Specialist Advisors commented there are some uncertainties around the whether the procedure improves long-term neurodevelopmental outcome, and the degree of selectivity required when performing laser ablation. They also expressed uncertainty as to what is the best treatment for early stage TTTS.

Safety:

The evidence on efficacy is based on two systematic reviews, two controlled trials (one randomised controlled, one non-randomised) and two case series.

The most common maternal complication following laser surgery was premature rupture of the membranes. In a case series evaluating perioperative complications following laser ablation, premature rupture of the membranes occurred in 28% of women (49/175), with 43% (21/49) occurring within 3 weeks of the procedure. Placental abruption and pregnancy loss (miscarriage) was also reported, occurring in 2% (3/175) and 7% (12/175) of women respectively. In the randomised controlled trial, premature rupture of the membranes within 28 days of the procedure occurred equally in the two groups (9%). Placental abruption occurred in one women in the laser group 1% (1/69) and two women in the amniodrainage group 2% (3/68). Pregnancy loss within seven days after the procedure was reported in 8% (12/69) women in the laser group and 2% (3/68) in the amniodrainage group $p=0.1$. Other complications reported in the studies included amniotic fluid leakage and vaginal bleeding. Only one study ($n=101$) reported recurrence of TTTS (14%) following the procedure.

Specialist Advisors

The Specialist Advisors listed potential complications as premature rupture of the membranes, infection (chorioamnitis), pregnancy loss, iatrogenic donor intrauterine death and sometimes recipient intrauterine death, persistent disease, and reverse transfusion. The Specialist Advisors also noted that there was a risk of maternal death, however this risk has been reduced with improvements in technique

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intrauterine laser ablation. Searches were conducted via the following databases, covering the period from their commencement to 25th November 2005: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1. Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Pregnant women with twin to twin transfusion syndrome
Intervention/test	Laser ablation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on nine publications, including two systematic reviews^{4 6} together reporting on a total of 10 studies of laser ablation for TTTS. Two of the comparative studies^{5 7} extracted in Table 2 have been described in the systematic reviews, an additional five studies have also been extracted including two studies specifically looking at longer term neurological outcomes following laser ablation^{8 9}.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) have been listed in Appendix A.

Existing reviews on this procedure

A Cochrane review has been published on interventions for the treatment of twin-twin transfusion syndrome¹⁰. However at the time of publication no randomised controlled trials had been published on the treatment of TTTS. The review is currently being updated.

Two other reviews have been published on treatments for twin to twin transfusion syndrome^{11 12}. Both are referenced in Table 2, one of these reviews only includes comparative studies⁶ whereas the second includes both controlled and non-controlled studies⁴.

Related NICE Guidance:

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional Procedures:

Amnioreduction using septostomy with or without amniodrainage for the treatment of twin-to-twin transfusion syndrome (Guidance in development:).

Technology Appraisals:, None relevant

Clinical Guidelines: None relevant

Public Health: None relevant

Table 2. Summary of key efficacy and safety findings on intrauterine laser ablation of placental vessels for the treatment of TTTS

Abbreviations used: TTTS – twin to twin transfusion syndrome, GA – gestational age, IUFD – intrauterine fetal death, RR- relative risk, PROM – premature rupture of the membranes, OR – Odds ratio, Overall survival – total number of live births/total number of possible live births (fetuses); Two survivors – both the donor and recipient twin from one pregnancy																																																																								
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Robyr et al (2005) et al ⁴ and Fox et al ⁶ Review 10 included studies (including 3 comparative studies) Literature search dates ⁴: not stated Inclusion criteria for studies : not stated Literature search dates ⁶: until 2004 Inclusion criteria for studies: comparative studies		Outcomes measured:		Complications: Major maternal morbidity ⁴ (as defined by authors)	Two reviews have recently been published on treatment for TTTS. The results of both reviews have been incorporated here, however the majority of results are from the review by Robyr et al ⁴. This review has included studies on laser ablation regardless of study design, however the review metholody has not been described at all (for example literature sarch dates) and review is primarily a narrative one with no additional analysis. The second review ⁶ has only included only comparative studies. The review methodology is well described and the authors have sought to undertaken some analysis. Studies in bold fonts are comparative studies (amniodrainage versus laser) however only the study by Senat paper is randomised (see below) Number of cases refers to number of pregnancies - number of fetuses will be double the number of cases.																																																																			
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Senat et al (2004)⁵ France (EUROFOETUS) Randomised controlled trial Study period: January 1999 – March 2002 142 pregnant women - 72 in the laser group (144 fetuses) - 70 in the amniodrainage group (140 fetuses) Population: Women were recruited from six countries (France, Netherlands, US, Belgium, Italy and Switzerland) <table><tr><td></td><td>Laser</td><td>Amnio-reduction</td></tr><tr><td>Age</td><td>31.8 yrs</td><td>31.5 yrs</td></tr><tr><td>Gestational age</td><td>20.6</td><td>20.9</td></tr><tr><td>Placenta</td><td></td><td></td></tr><tr><td>Anterior</td><td>30</td><td>40</td></tr><tr><td>Posterior</td><td>42</td><td>30</td></tr><tr><td>Staging*</td><td></td><td></td></tr><tr><td>Stage1</td><td>6</td><td>5</td></tr><tr><td>Stage2</td><td>31</td><td>31</td></tr><tr><td>Stage 3</td><td>34</td><td>33</td></tr><tr><td>Stage 4</td><td>1</td><td>1</td></tr></table> *Quintero et al.³ Indications: Women presenting between 15-26 weeks gestation with TTTS i.e. recipient twin presented with polyuric polyhydramnios and the donor twin presented with oliguric oligohydramnios. Technique: Selective laser ablation			Laser	Amnio-reduction	Age	31.8 yrs	31.5 yrs	Gestational age	20.6	20.9	Placenta			Anterior	30	40	Posterior	42	30	Staging*			Stage1	6	5	Stage2	31	31	Stage 3	34	33	Stage 4	1	1	Outcomes measured: survival, gestational age at delivery <table><tr><td></td><td>Laser</td><td>Amniodrainage</td></tr><tr><td>Survival (up to 28 days)</td><td>n=72</td><td>n=70</td></tr><tr><td>0 Survivors</td><td>17 (24%)</td><td>34 (49%)</td></tr><tr><td>1 Survivors</td><td>29 (40%)</td><td>18 (26%)</td></tr><tr><td>2 survivors</td><td>26 (36%)</td><td>18 (26%)</td></tr><tr><td>At least 1 survivor</td><td>55 (76%)</td><td>36 (51%)</td></tr><tr><td>Stage 1 or 2</td><td>32 (86%)</td><td>21 (58%)</td></tr><tr><td>Stage 3 or 4</td><td>23 (66%)</td><td>15 (44%)</td></tr><tr><td>GA at delivery</td><td></td><td></td></tr><tr><td>Median</td><td>33.3 weeks</td><td>29 weeks</td></tr><tr><td colspan="3">GA at delivery – no of pregnancies</td></tr><tr><td><24 weeks</td><td>12 (17%)</td><td>8 (11%)</td></tr><tr><td>24 – 27 weeks</td><td>9 (12%)</td><td>22 (31%)</td></tr><tr><td>28 – 31 weeks</td><td>9 (12%)</td><td>18 (26%)</td></tr><tr><td>32 – 33 weeks</td><td>9 (12%)</td><td>7 (10%)</td></tr><tr><td>34 – 35 weeks</td><td>17 (24%)</td><td>11 (16%)</td></tr><tr><td>> 36 weeks</td><td>16 (22%)</td><td>4 (6%)</td></tr><tr><td>Cesarean section</td><td>57%</td><td>69%</td></tr></table>			Laser	Amniodrainage	Survival (up to 28 days)	n=72	n=70	0 Survivors	17 (24%)	34 (49%)	1 Survivors	29 (40%)	18 (26%)	2 survivors	26 (36%)	18 (26%)	At least 1 survivor	55 (76%)	36 (51%)	Stage 1 or 2	32 (86%)	21 (58%)	Stage 3 or 4	23 (66%)	15 (44%)	GA at delivery			Median	33.3 weeks	29 weeks	GA at delivery – no of pregnancies			<24 weeks	12 (17%)	8 (11%)	24 – 27 weeks	9 (12%)	22 (31%)	28 – 31 weeks	9 (12%)	18 (26%)	32 – 33 weeks	9 (12%)	7 (10%)	34 – 35 weeks	17 (24%)	11 (16%)	> 36 weeks	16 (22%)	4 (6%)	Cesarean section	57%	69%	Complications: No significant differences between the groups. <i>Laser group: n=69</i> 2 women (3%) intraabdominal leakage of amniotic fluid 1 woman (1%) placental abruption 8 women (12%) pregnancy loss within 7 days after the procedure 4 women (6%) premature rupture of membranes within 7 days after the initial procedure 6 women (9%) premature rupture of membranes within 28 days after the initial procedure 16 fetuses (12%) intrauterine death within 7 days after the procedure <i>Amniodrainage group: n=68</i> 0 women intraabdominal leakage of amniotic fluid 2 women (3%) placental abruption 2 women (3%) pregnancy loss within 7 days after the procedure 1 woman (1%) premature rupture of membranes within 7 days after the initial procedure 6 women (9%) premature rupture of membranes within 28 days after the initial procedure 9 fetuses (7%) intrauterine death within 7 days after the procedure		This study is included in the systematic review⁴. The trial was stopped early because of the high rate of neurologic sequelae in those survivors treated by amniodrainage. Allocation to treatment was done using a random sequence of numbers. Groups for comparable except for location of placenta. There were more anterior insertions in the amniodrainage group. In both groups the majority of fetuses were Stage 2 or 3. Laser coagulation was performed at 3 centres, amniodrainage was performed by experienced operators at these 17 centres. Perinatal management was not standardised but the level of the care should, have been similar across the centres. Outcomes were assessed by a neonatologist who was blinded to the treatment. Five women did not undergo the procedure (3 in the laser group; 2 in the amniodrainage group). Six women in the amniodrainage group subsequently underwent
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Perinatal and Infant Outcomes <table><tr><td></td><td>Laser</td><td>Amniodrainage</td></tr><tr><td></td><td>n=144</td><td>n=140</td></tr><tr><td>All deaths</td><td>63 (44%)</td><td>86 (61%)</td></tr><tr><td>RR (95% CI) 0.71 (0.55 – 0.92) p=0.01</td><td></td><td></td></tr><tr><td>Donor</td><td>33 (46%)</td><td>42 (60%)</td></tr><tr><td>RR (95% CI) 0.76 (0.56 – 1.05) p=0.09</td><td></td><td></td></tr><tr><td>Recipient</td><td>30 (42%)</td><td>44 (63%)</td></tr><tr><td>RR (95% CI) 0.66 (0.48 – 0.92) p=0.01</td><td></td><td></td></tr><tr><td>Neonatal or</td><td>12 (8%)</td><td>41 (29%)</td></tr></table>			Laser	Amniodrainage		n=144	n=140	All deaths	63 (44%)	86 (61%)	RR (95% CI) 0.71 (0.55 – 0.92) p=0.01			Donor	33 (46%)	42 (60%)	RR (95% CI) 0.76 (0.56 – 1.05) p=0.09			Recipient	30 (42%)	44 (63%)	RR (95% CI) 0.66 (0.48 – 0.92) p=0.01			Neonatal or	12 (8%)	41 (29%)																																																																	
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Study Details		Key efficacy findings		Key safety findings	Comments																					
Mean follow-up: 6 months Disclosure of interest: Supported by a biology, medicine and development contact		infant death			laser after 2-6 repeat amniodrainage sessions. Authors report that fetuses in Stage 1 or 2 had better outcomes than those with higher stages in both treatment groups. Neurological outcomes were not measured by a valid means.																					
		Intraventricular haemorrhage																								
		RR (95% CI) 0.24 (0.05 – 1.11) p=0.10																								
		Donor	2/72 (3%)			2/70 (3%)																				
		RR (95% CI) 0.97 (0.14 – 6.71) p=1.0																								
		Recipient	0/72			6/70 (9%)																				
		Cystic periventricular leukomalacia																								
		RR (95% CI) 0.39 (0.18 – 0.86) p=0.02																								
		Donor	2/72 (3%)			5/70 (7%)																				
		RR (95% CI) 0.24 (0.05 – 1.11) p=0.27																								
		Recipient	6/72 (8%)			15/70 (21%)																				
		RR (95% CI) 0.39 (0.16 – 0.94) p=0.03																								
		Alive without major neurological complications																								
			75 (52%)			44 (31%)																				
		RR (95% CI) 1.66 (1.17 – 2.34) p=0.003																								
		Donor	36 (50%)			25 (36%)																				
		RR (95% CI) 1.40 (0.95 – 2.07) p=0.09																								
		Recipient	39 (54%)			19 (27%)																				
		RR (95% CI) 2.00 (1.29 – 3.09) p=0.001																								
Quintero et al (2003) ⁷ US, Australia Non randomised controlled trial (cohort) Study period: not stated 173 pregnant women - 95 in the laser group - 78 in the amniodrainage group Population: Three centres with experience of > 10 patients with TTTS Mean age: not stated. Gestational age at the time of treatment; laser median 20.7 weeks (range 16.7 – 25.6 weeks);		Outcomes measured: <table><thead><tr><th></th><th>Laser n=95 (190 fetuses)</th><th>Amnio n=78 (156 fetuses)</th></tr></thead><tbody><tr><td>Gestational age at delivery (median) p=0.005</td><td>32 weeks</td><td>29 weeks</td></tr><tr><td>Overall fetal survival p=0.21</td><td>122/190 (64.2%)</td><td>90/156 (57.7%)</td></tr><tr><td>No survivors</td><td>16 (17.7%)</td><td>26 (33.3%)</td></tr><tr><td>One survivor</td><td>36 (38.1%)</td><td>14 (17.9%)</td></tr><tr><td>Two survivors</td><td>43 (44.3%)</td><td>38 (48.7%)</td></tr><tr><td>At least one survivor</td><td>79 (83.2%)</td><td>52 (66.7%)</td></tr></tbody></table>			Laser n=95 (190 fetuses)	Amnio n=78 (156 fetuses)	Gestational age at delivery (median) p=0.005	32 weeks	29 weeks	Overall fetal survival p=0.21	122/190 (64.2%)	90/156 (57.7%)	No survivors	16 (17.7%)	26 (33.3%)	One survivor	36 (38.1%)	14 (17.9%)	Two survivors	43 (44.3%)	38 (48.7%)	At least one survivor	79 (83.2%)	52 (66.7%)	Complications: not specified.	This study is included in the systematic review ⁴ Allocation to treatment: authors note that patients were informed all treatment alternatives. However in Australia laser was not available during the study period (possible selection bias) Pregnancy outcomes was defined as neonatal survival of at least one twin. Purpose of this study was to
	Laser n=95 (190 fetuses)	Amnio n=78 (156 fetuses)																								
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Study Details			Key efficacy findings			Key safety findings	Comments													
amniodrainage 21.6 weeks (range 15.9 -26.7 weeks) p=0.03			<table><tr><td>p=0.12</td><td></td><td></td></tr><tr><td>Miscarriage/2 fetuses</td><td>8/16 (8.4%)</td><td>8/16 (10.3%)</td></tr><tr><td>Neurological morbidity (at least one fetus) p<.001</td><td>4/95 (4.2%)</td><td>19/78 (24.4%)</td></tr><tr><td>Intact neurological survival p<.001</td><td>75/95 (78.9%)</td><td>40/78 (51.3%)</td></tr></table>			p=0.12			Miscarriage/2 fetuses	8/16 (8.4%)	8/16 (10.3%)	Neurological morbidity (at least one fetus) p<.001	4/95 (4.2%)	19/78 (24.4%)	Intact neurological survival p<.001	75/95 (78.9%)	40/78 (51.3%)			compare the outcomes of patients treated with either laser or amniocentesis according to disease severity (stage). The purpose of this review is not to comment upon staging hence much of this information has not be extracted. Authors note that there as so significant differences in the distribution of patients by stage.
p=0.12																				
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Stage 4	11 (11.3%)	17 (21.8%)																		
Indications: Women presenting between < 27 weeks gestation with TTTS i.e. recipient twin presented with polyuric polyhydramnios and the donor twin presented with oliguric oligohydramnios.			Staging and outcomes: Authors concluded that there appears to be a relationship between perinatal morbidity and mortality rates and state in serial amniocentesis but not in regards to laser ablation (outcomes are relatively unformed).																	
Technique: Selective laser ablation																				
Mean follow-up: 6 months																				
Disclosure of interest: Supported by a biology, medicine and development contact																				

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Study Details	Key efficacy findings	Key safety findings	Comments																																																												
Lopriore et al (2005)²⁰ Netherlands Non-randomised controlled trial (purpose of this overview considered a case series) Study period: June 2002 – December 2004 166 infants - 76 TTTS infants - 90 non-TTTS infants Population: 40 TTTS pregnancies treated with laser and delivered at the study centre. Mean gestational age at treatment was 19.9 weeks. Mean gestational age at birth: 32.6 weeks Mean stage: Stage II Lost to follow-up: 4 twins intrauterine fetal death No-TTTS group: 46 monochorionic pregnancies delivered at the study centre. Mean gestational age at birth: 33.6 weeks. Lost to follow-up: 2 twins intrauterine fetal death Indications: Consecutive cases of monochorionic twins. Technique: unclear whether non selective or selective laser ablation Mean follow-up: unclear Disclosure of interest: none specified	Outcomes measured: Authors write that during the study period 85 women with TTTS pregnancies were treated with laser (not all were delivered at the same centre). - Laser ablation resulted in at least 1 survivor in 82% (70/85) pregnancies. - Intrauterine fetal demise occurred in 25% (42/170) fetuses. - Neonatal death occurred in 7% (9/128) of live-born infants. - Overall perinatal survival rate was 70% (119/170) Neonatal mortality and morbidity rates <table><tr><th></th><th>Laser forTTTS</th><th>No-TTTS</th></tr><tr><td></td><td>n=76</td><td>n=90</td></tr><tr><td>Neonatal death</td><td>6 (8%)</td><td>3 (3%)</td></tr><tr><td>Adverse neonatal outcome</td><td>20 (26%)</td><td>12 (13%)</td></tr><tr><td>Severe cerebral lesions</td><td>10 (14%)</td><td>5 (6%)</td></tr><tr><td>Small for gestational age</td><td>19 (25%)</td><td>17 (19%)</td></tr><tr><td>Respiratory distress syndrome</td><td>26 (34%)</td><td>19 (21%)</td></tr><tr><td>Chronic lung disease</td><td>5 (7%)</td><td>4 (4%)</td></tr><tr><td>Patent ductus arteriosus</td><td>5 (7%)</td><td>4 (4%)</td></tr><tr><td>Necrotizing enterocolitis</td><td>2 (3%)</td><td>2 (2%)</td></tr><tr><td>Hypotension at birth</td><td>11 (14%)</td><td>9 (10%)</td></tr><tr><td>Hydrops</td><td>1 (1%)</td><td>1 (1%)</td></tr><tr><td>Anemia at birth</td><td>13 (17%)</td><td>4 (5%)</td></tr><tr><td>Polycythemia-hyperviscosity</td><td>4 (5%)</td><td>1 (1%)</td></tr></table>		Laser forTTTS	No-TTTS		n=76	n=90	Neonatal death	6 (8%)	3 (3%)	Adverse neonatal outcome	20 (26%)	12 (13%)	Severe cerebral lesions	10 (14%)	5 (6%)	Small for gestational age	19 (25%)	17 (19%)	Respiratory distress syndrome	26 (34%)	19 (21%)	Chronic lung disease	5 (7%)	4 (4%)	Patent ductus arteriosus	5 (7%)	4 (4%)	Necrotizing enterocolitis	2 (3%)	2 (2%)	Hypotension at birth	11 (14%)	9 (10%)	Hydrops	1 (1%)	1 (1%)	Anemia at birth	13 (17%)	4 (5%)	Polycythemia-hyperviscosity	4 (5%)	1 (1%)	Complications: Also see efficacy section <table><tr><td></td><td>Donor</td><td>Recipient</td></tr><tr><td>Anemia at birth</td><td>8 (21%)</td><td>4 (11%)</td></tr><tr><td>Polycythemia-hyperviscosity</td><td>4 (11%)</td><td>0 (0%)</td></tr><tr><td>Severe cerebral lesions</td><td>4 (11%)</td><td>6 (16%)</td></tr><tr><td>Neonatal death</td><td>2 (5%)</td><td>4 (11%)</td></tr><tr><td>Adverse neonatal outcomes</td><td>8 (21%)</td><td>12 (32%)</td></tr></table> Authors make note of two TTTS pregnancies that were complicated: - one pregnancy had incomplete laser treatment - second pregnancy resulted in preterm premature rupture of the membranes (PROM).		Donor	Recipient	Anemia at birth	8 (21%)	4 (11%)	Polycythemia-hyperviscosity	4 (11%)	0 (0%)	Severe cerebral lesions	4 (11%)	6 (16%)	Neonatal death	2 (5%)	4 (11%)	Adverse neonatal outcomes	8 (21%)	12 (32%)	Comments on comparator group: Prognosis of untreated TTTS is extremely poor - however monochorionic twins without TTTS are still at a higher risk for complications since they share a common placenta – however outcomes will be better than those with TTTS. Authors have defined adverse neonatal outcome as neonatal death or severe cerebral lesions or one a major neonatal disorder. Authors undertook power calculations – noted that a group of 69 infants would be required to demonstrate a 15% difference in adverse neonatal outcome (power of 80%). The primary aim of the paper is not to provide comparative information on TTTS vs no TTTS but to describe outcomes after laser ablation. Authors have been more inclusive in their definition of severe cerebral lesions than in other studies such as⁵.
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IP Overview: Intrauterine laser ablation of placental vessels for the treatment of TTTS Page 11 of 23																																																															

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Study Details	Key efficacy findings	Key safety findings	Comments
Yamamoto (2005) ²¹ France Case series Study period: November 1999 – April 2004 175 pregnant women Population: Women with TTTS. Gestational age at treatment was 20 weeks. Of all pregnancies: • 17 (9.7%) stage 1 • 84 (48%) stage 2 • 66 (37.5%) stage 3 • 8 (4%) stage 4 Indications: Women presenting between <26 weeks gestation with severe TTTS i.e. recipient twin presented with polyuric polyhydramnios and the donor twin presented with oliguric oligohydramnios. Technique: Selective approach was used. Nonselective ablation was only performed if there was difficulty with the visualisation of the vessels. Mean follow-up: 6 months Disclosure of interest: none specified.	Outcomes measured: survival Forty-seven (27%) pregnancies resulted in no survivors, 67 (38%) pregnancies resulted in one survivor 61 (35%) pregnancies resulted in two survivors Survival rates at 6 months of at least 1, 1 and 2 babies were 71%, 38% and 35%.	Complications 13 women amniotic fluid leakage in to the peritoneal cavity was observed in the immediate postoperative period. All 13 women had pain and discomfort – controlled by medication 49 women experienced PROM events: - 7% occurred within 1 week - 5% between 8-21 days - 17% between after 3 weeks 4 women had chorioamnionitis (all after PROM) 7 women developed vaginal bleeding 12 women had a miscarriage (after PROM in 8 cases) 3 women experienced placental abruption resulting in one of each: - emergency caesarean - miscarriage - preterm labour (4 weeks after laser)	Retrospective analysis. The article includes 72 pregnant women already reported in the EUROFOETUS trial ⁵. Prior to laser ablation 5 women had experienced vaginal bleeding and 13 women had amniodrainage had performed. No fetuses survived when PROM occurred before 24 weeks. Authors note that it is difficult to make conclusions about the role of laser ablation in the development of PROM when the interval between the procedure and PROM > 3 weeks. As with the EUROFETUS trial paediatric follow-up was not standardised across the centres involved in this report.

Abbreviations used: TTTS – twin to twin transfusion syndrome, GA – gestational age, IUFD – intrauterine fetal death, RR- relative risk, PROM – premature rupture of the membranes, OR – Odds ratio, Overall survival – total number of live births/total number of possible live births (fetuses); Two survivors – both the donor and recipient twin from one pregnancy			
Study Details	Key efficacy findings	Key safety findings	Comments
Robyr et al (2006)²² France/Belgium Case series Non randomised controlled trial Study period: June 2002 – April 2004 101 women (from original population of 151) Population: Twin survivors 7 days after laser ablation. Staging: not stated; gestational age at delivery: not stated for entire group Indications: Consecutive cases of monochorionic twins. Technique: Selective laser ablation Mean follow-up: 1 month Disclosure of interest: none specified	Outcomes measured: survival There were 101/151 cases (67%) with two survivors more than 7 days after surgery. In the surviving cases 41 patients (41%) had an uneventful pregnancy with delivery of 2 live born infants more than 32 weeks gestation. Neonatal survival rates of at least 1 or both twins were 88% and 66%. There was no surviving infant in 13 cases (13%). The procedure has reportedly failed in 28 pregnancies.	Complications: n=101 7 patients single IUFD 17 cases (17%) had premature rupture of the membranes (PROM) before 32 weeks Failed surgery group n=28 14 cases (14%) had recurrence of TTTS 13 cases (13%) showed isolated marked discordant haemoglobin levels 1 case of double IUFD	Purpose of the paper was to look at late complications in those infants surviving > 7 days. Possible overlap of patients in already published studies as cases came from two referral centres. To be included in the study both twins needed to be alive at > 7 days.

Abbreviations used: TTTS – twin to twin transfusion syndrome, GA – gestational age, IUFD – intrauterine fetal death, RR- relative risk, PROM – premature rupture of the membranes, OR – Odds ratio, Overall survival – total number of live births/total number of possible live births (fetuses); Two survivors – both the donor and recipient twin from one pregnancy								
Study Details		Key efficacy findings			Key safety findings	Comments		
Banek et al (2003) ⁸ Germany		Outcomes measured:			Complications: not the aim of the paper	Survival rate and obstetric outcomes of the pregnancies have been reported in Hecher paper.		
Case series		Neurological and developmental outcomes.						
Study period: January 1995 – May 1997			No	Group 1			Group2	Group3
		All	89	69 (78%)			10 (11%)	10 (11%)
		Recipients	51	40 (78%)			6 (12%)	5 (10%)
		Donors	38	29 (76%)			4 (11%)	5 (13%)
		Live born as twins	65	53 (81%)			7 (11%)	5 (8%)
89 infants Population: 31 pairs of twins, 3 children born as twins with postnatal death of the co-twin, 17 recipients with IUFD of the donor twin, and 7 donor twins with IUFD of the recipient twin. Median gestational age: 22 months.		Live born singleton twin	24	16 (67%)	3 (12%)	5 (21%)		
Indications: Surviving infants of intrauterine laser ablation performed > 25 weeks for the treatment of TTTS.Median follow-up: 22 months. Range: 14-44 months		Authors note that the number of very premature infants who were born before 32 weeks were significantly higher in groups 2 and 3.				Outcome measures used: Griffiths' Developmental Test Scale (German version), 14 children were tested by the Snijders-Oomen-Non-Verbal-Intelligence Test (SOT).		
Disclosure of interest: None specified.						Outcomes were classified as: Group 1 – normal physical and neurological examination Group 2 – minor neurological abnormalities (e.g.strabismus, mildly delayed motor speech development) Group 3 – major neurological abnormalities (cerebral palsy, hemiparesis, spastic quadriplegia)		
						Unclear when outcomes were measured		

Abbreviations used: TTTS – twin to twin transfusion syndrome, GA – gestational age, IUFD – intrauterine fetal death, RR- relative risk, PROM – premature rupture of the membranes, OR – Odds ratio, Overall survival – total number of live births/total number of possible live births (fetuses); Two survivors – both the donor and recipient twin from one pregnancy					
Study Details	Key efficacy findings			Key safety findings	Comments
Graef et al (2001) ⁹	Outcomes measured: Neurological and developmental outcomes (as measured by the Griffiths' Developmental Test Scale and the SOT)			Complications: not aim of the paper	Survival rate and obstetric outcomes has previously been reported ¹⁶
Germany					
Case series	Neurological and developmental outcomes.				
Study period: June 1997 – September 1999		No	Group 1	Group2	Group3
167 infants (127 pregnancies)	All	167	145 (86.6%)	12 (7.2%)	10 (6%)
	Recipients	90	75 (83.3%)	8 (8.9%)	7 (7.8%)
	Donors	77	70 (90.9%)	4 (5.2%)	3 (3.9%)
	Live born as twins	136	119 (87.5%)	11 (8.1%)	6 (4.4%)
Population: 90 infants were former recipients and 77 were former donors.	Live born singleton twin	31	26 (83.9%)	1 (3.2%)	4 (12.9%)
Indications: Surviving infants of intrauterine laser ablation performed for the treatment of severe TTTS.					
Median follow-up: 38 (range: 14 months - 53 months)	Authors note that there was no difference in outcome between donor or recipient twins (p=0.349) nor between infants who were born as twins or singletons (p=0.154).				
Technique: Selective laser ablation	The number of very premature infants who were born before 32 weeks of gestation was significantly higher in groups II (p<0.001) and group III compared with group I.				
Disclosure of interest: Cost of travel for families was provided by grants from Milupa.	Characteristics and neurological diagnosis in infants with abnormal follow-up (Group III)				
	6 infants spastic tetraparesis 3 infants right hemiparesis 1 infant ventriculomeglia and multicystic encephalomalacia				Outcome measures used: Griffiths' Developmental Test Scale (German version) in 40 infants, Snijders-Oomen-Non-Verbal-Intelligence Test (SOT) in 112 infants. In 15 infants no standardised test could be accomplished. Outcomes were classified as: Group I – normal physical and neurological examination Group 2 – minor neurological abnormalities (e.g.strabismus, mildly delayed motor speech development) Group 3 – major neurological abnormalities (cerebral palsy, hemiparesis, spastic quadriplegia)

Validity and generalisability of the studies

- Twin-to-twin transfusion syndrome is a rare condition.
- Only a few centres in the world undertake and publish results on this procedure. Therefore it is likely that there is some overlap in terms of patients in the published papers
- Conversely amniodrainage can be carried out in non-specialised centres. Differences in selection of fetuses and operator / centre characteristics may in principle account for at least some of the difference between the procedures.
- The one randomised controlled trial on this procedure was stopped early because of the high rate of neurologic sequelae in those survivors treated by amniodrainage.
- One of the criticisms of the randomised controlled trial is that there were relatively few cases of fetuses with Stage III and IV disease as this is the group thought to be most appropriate for laser. There are still some uncertainties around the influence of disease severity (staging) in terms of treatment outcomes. There has been some suggestion that while staging may be a factor that influences outcomes for amniodrainage procedures it may not have an impact when treating with laser ⁷.
- The technique has evolved from a non-selective approach to a selective approach. This change in practice occurred around the year 2000.
- In general length of follow-up was poorly reported, with few studies clearly defining at what point outcomes were measured (such as perinatal survival).
- Long term (at least 5 years) follow-up is needed to assess neurological outcomes.

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Professor Mark Kilby and Professor N Fisk

- The appropriate clinical comparator for early stage disease (Stage I and II) is amniodrainage and/or conservative management. The appropriate comparator for advanced stage III/IV disease would now be ultrasound-guided bipolar cord occlusion for selective termination.
- Optimal therapy for early stage (I/II) disease remains controversial

- Uncertainties around the efficacy of this procedure include whether the procedure improves long-term neurodevelopmental outcome, how to treat the completely anterior placenta and the degree of selectivity required.
- Live birth rate associated with treatment by fetoscopic laser ablation are not significantly different from amniodrainage but long term neurologic morbidity appears to be significantly lesser in fetuses treated by laser (>5%) compared to amniodrainage (20%).
- Further long term research is needed – however long term follow up studies demonstrate a persistent handicap rate associated with severe TTTS whatever treatment utilised.
- Specialised skills are need to perform this procedure and training is very important

Issues for consideration by IPAC

A recent trial conducted by the US-based National Institutes of Health (NIH) comparing aggressive amniodrainage with selective fetoscopic laser photocoagulation for advanced stage TTTS disease was stopped due to poor recruitment. It was thought that the availability of fetoscopic laser treatment in multiple centers outside the trial, reluctance to submit to randomization, and the impression among lay public and obstetricians alike that fetoscopic laser therapy may be superior contributed to poor recruitment.

While entry into the trial was closed after 42 patients were randomized, follow-up of all patients treated in the trial will continue until neurodevelopment assessment at 18 to 22 months.

There has been a suggestion that radiofrequency energy could also be used to perform this procedure.

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Appendix A: Additional papers on intrauterine laser ablation not included in summary Table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non inclusion in Table 2
Cavicchioni O, Yamamoto M, Robyr R et al. (2006) Intrauterine fetal demise following laser treatment in twin-to-twin transfusion syndrome. BJOG: an International Journal of Obstetrics & Gynaecology 113: 590-594.	45 cases with fetal demise of one or both twins from a series of 120 cases of TTTS treated by laser	IUFD of one or both twins occurred in 45 of 120 (38%) cases of severe TTTS treated by laser.	Specific outcome
De Lia JE, Kuhlmann RS, and Lopez KP. (1999) Treating previable twin-twin transfusion syndrome with fetoscopic laser surgery: outcomes following the learning curve. Journal of Perinatal Medicine 27: 61-67.	N=74	Overall survival rate of 69%.	Study included in the systematic review in Table 2
Gardiner HM, Taylor MJ, Karatza A et al. (15-4-2003) Twin-twin transfusion syndrome: the influence of intrauterine laser photocoagulation on arterial distensibility in childhood. Circulation 107: 1906-1911.	N=27	Vascular programming is evident in monozygotic twins with intertwin transfusion and is altered but not abolished by intrauterine therapy to resemble that seen in dichorionic twins	Specific outcome
Gratacos E, Van Schoubroeck D, Carreras E et al. (2002) Impact of laser coagulation in severe twin-twin transfusion syndrome on fetal Doppler indices and venous blood flow volume. Ultrasound in Obstetrics & Gynecology 20: 125-130.	N=32	Laser results in the reversions of the disturbances associated with TTTS.	Specific outcome
Gratacos E, Van Schoubroeck D, Carreras E et al. (2002) Transient hydropic signs in the donor fetus after fetoscopic laser coagulation in severe twin-twin transfusion syndrome: incidence and clinical relevance. Ultrasound in Obstetrics & Gynecology 19: 449-453.	N=40	Transient hydropic signs may develop in a proportion of donor fetus after laser treatment.	Specific outcome
Hecher K, Diehl W, Ziklignig L et al. (2000) Endoscopic laser coagulation of placental anastomoses in 200 pregnancies with severe mid-trimester twin-to-twin transfusion syndrome. European Journal of Obstetrics, Gynecology, & Reproductive Biology 92: 135-139.	N=200 Two groups of patients - earlier non selective and later (selective)	Overall survival of non selective 61% to 68% in selective group.	Overlap of patients already included in Table 2

Herberg U, Gross W, Bartmann P et al. (2006) Long term cardiac follow up of severe twin to twin transfusion syndrome after intrauterine laser coagulation. Heart Vol. 92: 100.	N=89 survivors	Greater increase of cardiac events in recipients	Specific outcome.
Moreira Sa RA, Salomon LJ, Takahashi Y et al. (2005) Analysis of fetal growth after laser therapy in twin-to-twin transfusion syndrome. Journal of Ultrasound in Medicine Vol. 24: 1220.	N=98	The fetal growth pattern in TTTS can change after laser treatment.	Specific outcome
Pedreira DA, Acacio GL, Drummond CL et al. (2005) Laser for the treatment of twin to twin transfusion syndrome. Acta Cirurgica Brasileira 20: 478-481.	N=5 FU = 18 months	Total survival rate was 50% (5/10)	Small preliminary case series
Quintero RA, Bornick PW, Allen MH et al. (2001) Selective laser photocoagulation of communicating vessels in severe twin-twin transfusion syndrome in women with an anterior placenta. Obstetrics & Gynecology 97: 477-481.	N=35	Laser can be performed in women with anterior placentas	Studies by Quintero included in Table 2 -this study specifically looks at women with anterior placentas
Quintero RA, Bornick PW, Morales WJ et al. (2001) Selective photocoagulation of communicating vessels in the treatment of monochorionic twins with selective growth retardation.[see comment]. American Journal of Obstetrics & Gynecology 185: 689-696.	N=11	Survival of at least one fetus 72.3%	Studies by Quintero included in Table 2
Quintero RA, Comas C, Bornick PW et al. (2000) Selective versus non-selective laser photocoagulation of placental vessels in twin-to-twin transfusion syndrome. Ultrasound in Obstetrics & Gynecology 16: 230-236.	N=18 non selective N=74 selective	Survival of at least one infant was 61% in non selective group compared to 83% in selective group.	Studies by Quintero included in Table 2 - this study specifically compares the non selective to selective approach
Santiago JC, Ramos-Corp, and Castillo MJ. (2006) Endoscopic laser surgery after therapeutic amniocentesis in the treatment of severe twin-twin transfusion syndrome. International Journal of Gynaecology & Obstetrics 92: 262-263.	N=16	Overall survival for those given amniodrainage prior to laser was 72%.	Limited information, small study – look at influence of amniodrainage prior to laser
Sutcliffe AG, Sebire NJ, Pigott AJ et al. (2001) Outcome for children born after in utero laser ablation therapy for severe twin-to-twin transfusion syndrome. BJOG: an International Journal of Obstetrics & Gynaecology 108: 1246-1250.	N=24	The overall cerebral palsy rate was 9%: 0% in the singleton survivors group and 13.3% in the twin survivors group	Similar studies reported in Table 2
Ville Y, Hecher K, Gagnon A et al. (1998) Endoscopic laser coagulation in the management of severe twin-to-twin transfusion syndrome. British Journal of Obstetrics & Gynaecology 105: 446-453.	N=132	Overall survival was 55%, at least one survivor in 73%	Study included in the systematic review in Table 2
Zikulnig L, Hecher K, Bregenzner T et al. (1999) Prognostic factors in severe twin-twin transfusion syndrome treated by endoscopic laser surgery. Ultrasound in Obstetrics & Gynecology 14: 380-387.	N=121	The overall survival rate was 64% (156/242).	Earlier study looking at non selective technique.

Appendix B: Related published NICE guidance for intrauterine laser ablation for the treatment of TTTS

Guidance	Recommendation
Interventional Procedures	Guidance in development: Amnioreduction using septostomy with or without amniodrainage for the treatment of twin to twin transfusion syndrome
Technology Appraisals	None relevant
Clinical Guidelines	None relevant
Public Health	None relevant

Appendix C: Literature search for intrauterine laser ablation for the treatment of TTTS

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	2005 Issue 4	25/11/2005
CRD	October 2005	25/11/2005
Embase	1980 to 2005 Week 47	25/11/2005
Medline	1966 to November Week 1 2005	25/11/2005
Premedline	November 23, 2005	25/11/2005
CINAHL	1982 to November Week 3 2005	25/11/2005
British Library Inside Conferences (limited to current year only)	1993 to date	25/11/2005
National Research Register	2005 Issue 4	25/11/2005
Controlled Trials Registry	N/A	25/11/2005

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases

- 1 laser coagulat\$.tw.
- 2 laser surg\$.tw.
- 3 laser ablat\$.tw.
- 4 laser photocoagulat\$.tw.
- 5 laser therap\$.tw.
- 6 fetoscop\$.tw.
- 7 foetoscop\$.tw.
- 8 Laser Coagulation/
- 9 FETOSCOPY/
- 10 or/1-9
- 11 twin-twin transfusion\$.tw.
- 12 twin to twin transfusion\$.tw.
- 13 TTTS.tw.
- 14 Fetofetal Transfusion/
- 15 foeto-foetal transfusion\$.tw.
- 16 or/11-15
- 17 10 and 16
- 18 Animals/
- 19 Humans/
- 20 18 not (18 and 19)
- 21 17 not 20