NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous laser therapy for fetal tumours

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 October 2005.

Procedure names

- Percutaneous laser therapy, photocoagulation or ablation for fetal tumours.
- Intrafetal interstitial laser therapy, photocoagulation or ablation for fetal tumours.

Specialty societies

- British Maternal and Foetal Medicine Society.
- Royal College of Obstetricians and Gynaecologists.

Description

Indications

This overview has only considered the following types of fetal tumours: sacrococcygeal teratomas, cervical teratomas, cystic hygromas and congenital cystic adenomatoid malformations (CCAM). Other types of fetal tumours did not form part of this overview.

Sacrococcygeal teratomas, cervical teratomas, cystic hygromas and CCAM are usually benign tumours, although teratomas may also be malignant. These tumours can become very large and highly vascularised, causing stress on the heart of the fetus. This can lead to the development of non-immune hydrops fetalis (in utero heart failure), and may be complicated by polyhydramnios (excessive accumulation of amniotic fluid) for teratomas and CCAM, or oligohydramnios (too little amniotic fluid) for cystic hygromas. Fetal mortality is high and a poor prognosis is associated with

non-immune hydrops fetalis, placentomegaly, cardiomegaly, large tumour size and high tumour growth rate. Obstetric complications include preterm labour and dystocia.

Teratomas are germ cell tumours that contain a variety of tissues derived from the three main embryonic germ cell layers: ectoderm, mesoderm, and endoderm. Sacrococcygeal teratoma is the most common type of fetal teratoma, which occurs as a mass in the base of the spine (coccyx). These tumours appear solid, or partly solid and partly cystic, and may be associated with abnormalities of other body systems. Cervical teratoma occurs as a mass in the neck of the fetus. These tumours usually contain calcifications and appear partly solid and partly cystic. They often surround vital structures, such as the oesophagus, thyroid and trachea, which may cause airway obstruction at the time of birth. Upper airway obstruction is the main cause of neonatal death.

Cystic hygroma is a developmental abnormality of the lymphatic system and appears as a mass with multiple cysts. It can occur anywhere in the body, but is found most frequently in the neck. Airway obstruction is the main complication of cystic hygromas in the neck. Cystic hygromas are often associated with other malformations and chromosomal abnormalities, particularly Turner's syndrome. Fetal prognosis is usually poor, especially in the context of associated chromosomal abnormalities, or in the presence of non-immune hydrops fetalis and/or bilateral pleural effusions.

Congenital cystic adenomatoid malformation (CCAM) is a developmental abnormality of the lung and appears as a solid or cystic mass of lung tissue with proliferation of bronchial structures. CCAM lesions are usually unilateral and involve only one lobe, although two or more lobes may be affected. Large, bulky tumours can cause mediastinal shift, prevent normal pulmonary growth, and compress the oesophagus, leading to complications of non-immune hydrops fetalis, pulmonary hypoplasia and polyhydramnios. Mortality of untreated fetuses with CCAM and non-immune hydrops fetalis is high.

Current treatment and alternatives

Conventional options in managing pregnancies with fetal tumours such as sacrococcygeal or cervical teratoma, cystic hygroma and CCAM include:

- termination of the pregnancy which may happen later in pregnancy if fetal compromise becomes severe;
- continuation of the pregnancy without intervention to let nature take its course; or
- elective early caesarean delivery of the fetus if significant problems develop. The prognosis is poor even when the fetus is approaching term.

Following birth, the extent of the tumour is assessed and surgery is the mainstay of treatment with the aim of removing the tumour completely to avoid local recurrence. This, however, may not be possible if vital structures are intimately involved with the tumour. Additional surgery may be required for removal of residual tumour, and neck masses may require further surgery for reconstruction of the trachea or other neck structures that were distorted by the tumour. The prognosis of neonates who undergo successful surgery is generally good, and long-term follow-up is usually needed for possible recurrence of tumours later in life. Medical treatment is reserved for recurrent or unresectable tumours and includes injection of sclerosing agents and/or steroids.

Fetuses with large neck masses (cervical teratomas or cystic hygromas) and upper airway obstruction require immediate assessment at birth and may require emergency tracheotomy at delivery. The “EXIT” procedure where an airway is surgically established during caesarean section delivery while the fetus is still attached to and sustained by the placenta is rarely an option in the UK.

Percutaneous laser therapy is reserved for fetuses who develop signs of cardiac comprise (including non-immune hydrops) or severe airway obstruction before delivery. Once these develop, even if the fetus survives to be delivered at term, survival is poor. If delivered prematurely, most will die. Other percutaneous techniques may include radiofrequency ablation and thermocoagulation with monopolar diathermy. Open fetal surgery remains experimental and is not an available treatment option in the UK.

What the procedure involves

Percutaneous laser therapy for fetal tumours is performed under maternal local anaesthesia and light sedation by inserting a needle into the uterine cavity through the mother's abdomen under ultrasonographic guidance. An analgesic is then injected subcutaneously or intramuscularly into the fetus before advancing the needle to the site of the fetal tumour (such as the sacral area for sacrococcygeal teratoma or the chest for CCAM). Colour-Doppler imaging is used to guide placement of the needle. A laser fibre is passed through the needle lumen and laser energy is then delivered in pulses causing coagulation of blood vessels within the tumour. If necessary, laser therapy may be repeated in a further session, usually one or more weeks later. During the procedure, cystic components of tumours may be aspirated.

Efficacy

The efficacy and safety of the procedure are based on reports for only 3 fetuses: 2 with CCAM and 1 with sacrococcygeal teratoma. Both the efficacy and safety of the procedure reported for these fetuses are described below.

In a case series of 67 fetuses that were diagnosed with cystic lung abnormalities, one fetus was treated by percutaneous laser therapy[1]. The fetus received 2 treatments of percutaneous laser therapy at 19 weeks’ and 31 weeks’ gestation. Reductions in non-immune hydrops, mediastinal shift, ascites and in the blood flow within the tumour were reported following the first treatment. The neonate was delivered at 38 weeks’ gestation with surgical excision of the tumour performed after birth. Neonatal death due to sepsis-related complications was reported 4 days after birth.

In a case report of a fetus with CCAM[2], the fetus received 2 treatments of percutaneous laser therapy: the first treatment at 23 weeks’ and 2 days’ gestation followed by a second treatment one week later. Both treatments had to be terminated early due to the occurrence of fetal bradycardia. Reduction in tumour size was reported following the first treatment. Worsening of non-immune hydrops was reported 4 days after the first treatment. No outcomes were reported following the second treatment except that the fetal heart tracing was normal. Three days following the second treatment (at a scheduled visit), fetal death in utero was diagnosed.

In a case report of a fetus with sacrococcygeal teratoma[3], the fetus received 2 treatments of percutaneous laser therapy. The first treatment was performed at about 20 weeks’ gestation, while the timing for the second treatment was not specified. Increase in tumour size was reported following the first treatment, while a similar

tumour size as compared with that prior to treatment was reported following the second treatment. Moderate increase in tumour size occurred during the remainder of the pregnancy. Bleeding, possibly within the cystic area, occurred following the first treatment and required intrauterine blood transfusion. Drainage of blood from the cystic area and drainage of amniotic fluid were performed during the second treatment. The neonate was delivered by elective caesarean section at 37 weeks' gestation with surgical excision of the tumour performed after birth. The neonate was reported to be healthy and developing normally at 8 months of age.

The Specialist Advisors stated that there is uncertainty about the effectiveness of the procedure. Key efficacy outcomes include decrease in the vascularity of the fetal tumour leading to potential shrinkage of the tumour in utero and decrease in cardiac failure in the fetus.

Safety

The safety of the procedure has been described in the efficacy section above.

The Specialist Advisors stated that theoretical risks to the fetus include failure of the treatment (continued growth of the tumour with progressive fetal compromise and hydrops), and fetal death (for example, due to pre-term birth or due to haemorrhage secondary to laser ablation, exsanguination and tissue oedema leading to hydrops). There are also uncertainties about the harmful effects of the procedure on other anatomical areas. The theoretical risks to the mother include pre-term labour following the procedure and laser burn if the needle is not sited correctly.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous laser therapy for fetal tumours. Searches were conducted via the following databases, covering the period from their commencement to October 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. If 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	Fetuses with sacrococcygeal teratomas, cervical teratomas, cystic hygromas or congenital cystic adenomatoid malformations.
Intervention/test	Percutaneous laser therapy.
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 the use of percutaneous laser therapy in only 3 fetuses, 2 with CCAM and 1 with sacrococcygeal teratoma. No studies were found on the use of percutaneous laser therapy for cervical teratoma or cystic hygroma.

No other studies that were considered to be relevant to the procedure were found at the time of the literature search.

Existing reviews on this procedure

There were no systematic reviews identified on this procedure at the time of the literature search.

Related NICE guidance

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

Interventional procedures:

None applicable

Technology appraisals:

None applicable

Clinical guidelines:

None applicable

Public health:

None applicable

Table 2 Summary of key efficacy and safety findings on percutaneous laser therapy for fetal tumours

Abbreviations used: CCAM, congenital cystic adenomatoid malformation

Study details	Key efficacy findings	Key safety findings	Comments
Davenport M et al (2004)[1] Retrospective case series (includes 1 fetus treated with percutaneous laser therapy) Diagnosed from Jan 1995 to July 2001 UK 67 fetuses with cystic lung abnormality (includes CCAM, pulmonary sequestration, or hybrid of both) Median fetal age at diagnosis = 21 (range 19–28) weeks gestation Antenatal intervention was attempted in 4 fetuses with severe hydrops and marked mediastinal shift. • n = 1 Percutaneous laser therapy for a female fetus with unilateral microcystic lesions • n = 3 Thoraco-amniotic shunts for fetuses with unilateral macrocystic lesions Cyst size was described as macrocystic (≥ 5 mm) or microcystic (< 5 mm) Follow-up of the fetus that was treated by percutaneous laser therapy was until death (4 days after birth) Disclosure of interest: not specified	The outcomes for only the antenatal interventions are reported below. **Percutaneous laser therapy (n = 1)** First procedure at 19 weeks' gestation: • Immediate reduction in blood flow within the lesion after the procedure • Reduction in ascites over the following weeks • Resolution of hydrops • Reduction of mediastinal shift Second procedure at 31 weeks' gestation: • No outcomes reported. Birth at 38 weeks' gestation: • Thoracotomy at 6 hours after birth with excision of a large multicystic lesion surrounding a necrotic cavity Neonate at 4 days after birth: • death due to sepsis-related complications **Thoraco-amniotic shunt (n = 3)** All 3 fetuses had a reduction in cyst size, mediastinal shift, and resolution of hydrops.	See key efficacy findings for the fetus having percutaneous laser therapy. **Fetal outcome for the entire cohort:** • 64 born alive (2 died in post-natal period, including the fetus having interstitial laser therapy) • 2 intrauterine deaths (both severe microcystic lesions) • 1 pregnancy termination.	The study reviews the outcomes of fetuses diagnosed with cystic lung disease in a large tertiary referral fetal medicine unit in the UK. Only 4 out of 67 (6%) fetuses were treated antenatally, of which 1 fetus (1.5%) was treated by percutaneous laser therapy. Reporting of safety and efficacy outcomes was limited and did not include tumour size. The authors concluded that "antenatally diagnosed cystic lung disease has an excellent prognosis in the absence of signs of fetal distress".

Abbreviations used: CCAM, congenital cystic adenomatoid malformation

Study details	Key efficacy findings	Key safety findings	Comments
Bruner JP et al (2000)[2] Case report USA One male fetus with CCAM III lesion in the left fetal hemithorax Mother: • 30 year-old Caucasian woman, gravida 3, P1011 Fetus before treatment at 23 weeks' gestation: • growing CCAM III lesion • no other congenital anomalies • normal male karyotype • presence of mediastinal shift, non-immune hydrops and polyhydramnios Follow-up until fetal death (at 25 weeks' gestation) Disclosure of interest: not specified	The procedure aimed to debulk the CCAM III lesion and relieve the developing hydrops. **First procedure at 23 weeks' and 2 days' gestation:** Laser energy was delivered to about 15% of the calculated tumour mass. Three days after the procedure: • tumour size was smaller (dimensions were not reported) • volume of the unaffected lung was subjectively larger **Second procedure at 24 weeks' and 2 days' gestation:** Laser energy was delivered to the remainder of the tumour mass. • tumour size was not reported	**First procedure at 23 weeks' and 2 days' gestation:** After 52 minutes of the procedure: • fetal bradycardia occurred and the procedure was terminated early Three days after the procedure: • worsening hydrops **Second procedure at 24 weeks' and 2 days' gestation:** After 73 minutes of the procedure: • fetal bradycardia occurred and the procedure was terminated early • fetal heart tracing was normal Three days after the procedure (scheduled visit): • fetal death diagnosed **Post-partum (5 days after second procedure)** • 1050g stillborn male infant delivered following induced labour • Mother's postpartum course was uneventful **Infant findings** • CCAM III occupied the entire upper lobe of the left lung confirmed by autopsy • Haemorrhage and necrosis of the tumour resulting from the laser therapy; tumour margins appeared unaffected as expected • No laser injury found outside the tumour • Myocardial necrosis present, determined not to be a result of laser injury	Percutaneous laser therapy was offered as an alternative after pregnancy termination or open fetal resection were declined. Reporting of safety and efficacy outcomes was limited. The authors suggested that fetuses with CCAM complicated by non-immune hydrops are already too compromised by their advanced disease state to recover from the acute changes (for example oedema) associated with percutaneous laser therapy. The authors also suggested that fetuses with CCAM treated by percutaneous laser therapy may benefit from earlier intervention. However, uncertainty of the diagnosis and incomplete understanding of the natural course of the disease make therapy before the onset of fetal hydrops unjustifiable. They therefore conclude that, at present, percutaneous laser debulking of CCAM is unlikely to be successful.

Abbreviations used: CCAM, congenital cystic adenomatoid malformation

Study details	Key efficacy findings	Key safety findings	Comments
Hecher K et al (1996)[3] Case report Germany One fetus with sacrococcygeal teratoma (with a solid and cystic component) Mother: 32 years old (gravida 4 , para 4) Fetus before treatment at 20 weeks' gestation: • Tumour size = 6 x 4 cm • Polyhydramnios with deepest vertical pool of amniotic fluid measuring 7 cm Follow-up: up to 8 months after birth Disclosure of interest: not specified	**After first procedure** Between 20 to 23 weeks gestation: • fetal condition remained stable Between 23 to 26 weeks gestation: • tumour size increased to 10 x 6 cm • polyhydramnios with deepest vertical pool of amniotic fluid measuring 9.5 cm • hyperechogenic netlike pattern suggestive of intraluminal bleeding within cystic area At cordocentesis (time not specified): • haemoglobin 6g/dL requiring intrauterine blood transfusion **At second procedure** (time not specified) with drainage of blood from cystic area and drainage of amniotic fluid. **After second procedure** (time not specified): • tumour size =7 x 4 cm • during the remainder of the pregnancy tumour size increased moderately and there was no further bleeding **Birth at 37 weeks' gestation:** • delivery by elective caesarean section • girl weighing 3500g • neonate underwent surgical treatment on same day – tumour size = 11 x 9 cm **At 8 months after birth:** • neonate healthy and developing normally	See key efficacy findings	The report describes a case of fetal sacrococcygeal tumour treated antenatally by percutaneous laser therapy and after delivery by surgery. Apart from tumour size, reporting of safety and efficacy outcomes was limited.

Validity and generalisability of the studies

- This overview considered only the following types of fetal tumours: sacrococcygeal teratomas, cervical teratomas, cystic hygromas and congenital cystic adenomatoid malformations (CCAM). No studies on the use of percutaneous laser therapy were found in fetuses with cervical teratoma or cystic hygroma at the time of the literature search.
- The overview is based on only 3 case reports with limited safety and efficacy data on the use of percutaneous laser therapy in CCAM (2 fetuses) and sacrococcygeal teratoma (1 fetus).
- One case report came from the UK.

Specialist Advisors' opinions

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

Mr A Cameron, Prof N Fisk, Mr T Overton, Prof S Robson

- The procedure is definitely novel and of uncertain safety and efficacy.
- This is a novel procedure done in extremely rare circumstances where there is a substantial and heightened risk of fetal death and there is no established alternative. It will therefore not be performed regularly even in large tertiary fetal medicine procedures.
- Percutaneous laser therapy and all methods of reducing vascularity of tumours in the fetus are highly experimental. Although such therapy is only contemplated when the fetus is in heart failure (hydrops), there is little positive data to support its use.
- There are no randomised trials comparing percutaneous laser treatment with other forms of treatment. Published experience will be in the form of isolated case reports or small series.
- The aim of the procedure is to completely destroy the blood supply to the tumour and it is uncertain how effective the treatment is in achieving this. Failure to do this will need to be assessed following delivery using other imaging modalities.
- There are uncertainties about which cases should be considered for the procedure and what power of laser setting to use.
- There are uncertainties about the fetal morbidity and mortality from the procedure and the risk of the procedure causing premature labour.
- There is some concern that the procedure is not as efficacious as radiofrequency ablation as an alternative.
- There is concern that the resultant tissue oedema from the laser therapy would worsen fetal hydrops, the usual indication for such an approach. This also applies to radiofrequency ablation and chemosclerosants.
- The operator should be trained in maternal fetal medicine and have a high level of expertise in fetal in-utero needling procedures, ultrasound guided procedures and use of laser for other fetal interventions (e.g. laser ablation of placental anastomoses.

Issues for consideration by IPAC

There is an open registry funded by the European Commission that aims to collect data on all experience with fetoscopic procedures worldwide. This is available at www.eurofoetus.org/index.htm.

References

1. Davenport M, Warne SA, Cacciaguerra S et al. (2004) Current outcome of antenally diagnosed cystic lung disease. *Journal of Pediatric Surgery* 39(4): 549–56.
2. Bruner JP, Jarnagin BK, Reinisch L. (2000) Percutaneous laser ablation of fetal congenital cystic adenomatoid malformation: too little, too late? *Fetal Diagnosis and Therapy* 15: 359–63.
3. Hecher K, Hackeloer B-J. (1996) Intrauterine endoscopic laser surgery for fetal sacrococcygeal teratoma. *Lancet* 347: 470.

Appendix A: Additional papers on percutaneous laser therapy for fetal tumours not included in summary table 2

No other studies considered potentially relevant to the overview were found in the literature search.

Appendix B: Related published NICE guidance for percutaneous laser therapy for fetal tumours

Guidance programme	Recommendation
Interventional procedures	None applicable
Technology appraisals	None applicable
Clinical guidelines	None applicable
Public health	None applicable

Appendix C: Literature search for percutaneous laser therapy for fetal tumours

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	The Cochrane Library 2005, Issue 4	28/10/2005
CRD		28/10/2005
Embase	1980 to 2005 Week 43	25/10/2005
Medline	1966 to October Week 2 2005	25/10/2005
PreMedline	October 27, 2005	28/10/2005
CINAHL	1982 to October Week 3 2005	25/10/2005
British Library Inside Conferences (limited to current year only)		28/10/2005
National Research Register	2005 Issue 4	28/10/2005
Controlled Trials Registry		28/10/2005

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

1. exp laser surgery/
2. (laser$ adj3 (interstitial or ablat$ or coagulation or photocoagulation or surg$ or thermocoagulation or thermotherap$ or hyperthermia)).tw.
3. 1 or 2
4. hemangioma/
5. chorioangioma.tw.
6. exp fetal diseases/
7. (tumor$ or tumour$ or lesion$ or cancer$ or neoplasm$).tw.
8. exp arteriovenous malformations/
9. (vascular adj3 malformation$).tw.
10. (vascular adj3 (hemangioma$ or haemangioma$)).tw.
11. teratoma/
12. teratoma$.tw.
13. lymphangioma, cystic/
14. hygroma.tw.
15. "Cystic Adenomatoid Malformation of Lung, Congenital"/
16. ccam.tw.
17. or/4-16
18. 3 and 17
19. Fetus/
20. (fet$2 or foet$2 or intrafet$).tw.
21. 19 or 20
22. 18 and 21