NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous fetal balloon valvuloplasty for pulmonary atresia with intact ventricular septum (PAIVS).

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 September 2005

Procedure name

Percutaneous fetal pulmonary balloon valvuloplasty

Specialty societies

- Paediatric Intensive Care Society
- British Paediatric Cardiac Association
- Royal College of Obstetricians and Gynaecologists
- British Maternal and Foetal Medicine Society
- British Association of Perinatal Medicine (advice requested not yet received)
- Society of Clinical Perfusionists (advice requested not yet received)

Description

Indications:

Congenital heart defects are the most common type of birth defects and include critical pulmonary stenosis and pulmonary atresia with intact ventricular septum (PAIVS).

Mild pulmonary stenosis is rarely diagnosed in utero. However, the more severe lesion of pulmonary atresia with intact ventricular septum (PAIVS) has a high mortality and morbidity and can leading to hypoplastic right heart syndrome (HRHS). It is associated with underdevelopment of the tricuspid value and the right ventricle but relatively normal growth of the pulmonary vessels and vascular bed, the persistence of a good interatrial communication (patent foramen ovale) protects the lungs from the high right sided pressure.

Diagnosis can be made at the routine screening ultrasound performed at about 20 weeks of pregnancy when a dilated right atrium, thickened right ventricle and an immobile pulmonary valve are visualised. Tricuspid valve dysplasia is present in about 70% of cases. Many fetuses diagnosed with PAIVS will survive until birth, and treatment is possible. However the presence of tricuspid regurgitation and a dilated rather than a muscular right ventricle in utero carries a poor prognosis; these fetuses tend to develop pericardial effusions or hydrops and die in utero therefore some parents may choose to terminate the pregnancy. Neonatal mortality is much lower than for severe aortic stenosis with or without hypoplastic left heart syndrome; although about half will have only a uni-ventricular heart this is a morphologically left sided ventricle and the pulmonary vessels and vascular bed tend to develop relatively normally, about 85% are alive at 5 years. Death can occur in the newborn period from right ventricular dysfunction and myocardial disease.

Current treatment and alternatives

The majority of congenital heart defects can be treated surgery after birth with good outcomes. In these cases in-utero intervention would be unnecessary. For other defects staged surgical palliation is the only option[2].

For babies born with mild pulmonary stenosis postnatal balloon valvuloplasty is the preferred option. For babies born with more severe pulmonary disease and PAIVS a prostaglandin infusion is started immediately after birth to keep the Ductus Arteriosus open and investigation undertaken to establish the severity of HLHS. A staged approached to treatment is undertaken with postnatal balloon valvuloplasty the initial preferred option to encourage remodelling and growth of the right ventricle. Further balloon valvuloplasty is often required with later valve replacement. If balloon valvuloplasty is unsuccessful then the radiofrequency valvotomy is performed while keeping the Ductus Arteriosus open. If this fails, the next stage is a modified Blalock-Taussig shunt; this a palliative procedure where a shunt is created to allow blood to pass from the aorta to the pulmonary artery by either placing a Gore-Tex systemic to pulmonary shunt between the left subclavian artery and left pulmonary artery or by dividing the left subclavian artery and connecting it to the left pulmonary artery).

The final surgical option is the Fontan procedure, which creates a univenticular heart, is required when right ventricular function is poor, or the outflow tract cannot be opened up or when other abnormalities co-exist in the right heart. A right ventricular bypass is created by using one of two methods (baffle or Gore-Tex conduit), the superior and inferior vena cava are connected to the pulmonary artery thereby ensuring blood returning from the body flows directly to the lungs.

What the procedure involves:

The aim of the fetal pulmonary balloon valvuloplasty is to reduce pulmonary stenosis and encourage the development of ventricular muscle while in-utero to allow a greater chance of success with surgery interventions preformed after birth along with the preservation of a biventricular heart.

Fetal pulmonary valvuloplasty may be considered where there is expected high postnatal mortality or morbidity and progressively worsening disease in the fetus. Improvements in fetal imaging have assisted with this identification.

The procedure is performed at 21-32 weeks' gestation under local anaesthesia (with maternal sedation) and ultrasound guidance. A cannula and style needle is advanced through the maternal abdomen, uterine wall and fetal chest wall into the right ventricular infundibulum of the fetus. A guidewire is then inserted through the

needle and across the pulmonary valve. A balloon catheter is inserted and inflated to dilate the stenotic valve. The balloon catheter and needle are then withdrawn.

Fetal positioning is critical in determining the success of the procedure.

Efficacy:

Fetus
There is limited published evidence on this procedure. The total number of reported cases in the published literature is less than 10 and these cases are highly selected. The largest series reports on the outcomes of 5 fetuses following fetal pulmonary vavlvuloplasty. Technical success was achieved in three cases with some reported improvements in fetal hemodynamics. All three survived to have further postnatal surgery and are alive at 2, 3 and 4.5 years respectively. The two technical failures were both delivered, with one going on to have further surgery, however both died in the newborn period. Conclusions are difficult to draw given the small number of cases and the heterogeneity of disease.

Mother
None of the studies specifically reported on maternal outcomes.

Specialist Advisors
The Specialist Advisors noted the lack of data on this procedure and the difficulty in basing efficacy on survival when cases are rare and carefully selected. Specialist Advisors also noted that selection criteria are not yet clear.

Safety:

Fetus
The evidence on safety is based on a small number of cases. In one study of two fetuses both had pericardial effusions that resolved spontaneously. There was also one instance of transient pericardial effusions in a study of five fetuses.

Mother
None of the studies specifically reported on maternal outcomes.

Specialist Advisors
The Specialist Advisors listed fetal death, bleeding, bradycardia, pericardial effusion and balloon rupture as potential complications. They also noted that there was a risk of premature labour and possible maternal morbidity associated with the use of anaesthesia.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous fetal pulmonary valvuloplasty. Searches were conducted via the following databases, covering the period from their commencement to September 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 excluded unless they were thought to add substantively to the published evidence base
Patient	Fetuses with pulmonary atresia or pulmonary stenosis
Intervention/test	In utero balloon valvuloplasty
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

There were few published studies on this procedure. This overview is based on four studies, including three full text papers and one abstract.

No other clinical studies were identified.

Existing reviews on this procedure

There were no published reviews identified 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 guidance listed below.

Interventional Procedures:

Published:

IPG067 Balloon dilatation of pulmonary valve stenosis
IPG075 Balloon angioplasty of pulmonary vein stenosis in infancy
IPG076 Balloon dilatation with or without stenting for pulmonary artery or non-valve right ventricular outflow tract obstruction in children
IPG 077 Balloon dilation of systemic to pulmonary arterial shunts in children
IPG 095 Radiofrequency valvotomy for pulmonary atresia

IPG 078 Balloon valvuloplasty for aortic valve stenosis

In development:

322 Fetal aortic valvuloplasty

Technology Appraisals:

None relevant

Guideline Development

None relevant

Public Health

None relevant

Table 2 Summary of key efficacy and safety findings on percutaneous fetal pulmonary balloon valvuloplasty

Abbreviations used: PAIVS - pulmonary atresia with intact ventricular septum, RV – right ventricle, AS – aortic stenosis

Study Details	Key efficacy and safety findings	Comments
Tulzer and Gardniner (2005) [3] UK Case series (style of five case reports) 5 fetuses - Case 1 pulmonary valve atresia in a 26 week fetus (later changed to critical pulmonary stenosis) - Intervention: perforation and dilation. - Case 2 pulmonary valve atresia in a 29 week fetus - Intervention: perforation and dilation. - Case 3 pulmonary valve atresia in a 22 week fetus - Intervention: perforation and dilation (procedure performed twice) - Case 4 pulmonary valve atresia in a 20 week fetus (placenta bleeding) - Intervention: planned but was not performed - Case 5 critical pulmonary stenosis in a 26 week fetus - Intervention: Right ventricle was puncture two times but a wire was not ale to be passed through the pulmonary valve – procedure was aborted.	Case 1 In utero changes: Right ventricle inflow became biphasic, velocity across the pulmonary valve initially decreased and increased again. However the diameter of the pulmonary valve increased steadily. Outcome: Baby was delivered at 38 weeks, postnatal balloon valvuloplasty was performed to eliminate the residual high gradient at the pulmonary value and a modified Blalock Taussig shunt was placed. Eight months later the shunt was removed. At the age of 4.5 years the patients is asymptomatic without mediation and RV size and function are within normal limits. Case 2 In utero changes: Right ventricle inflow became biphasic, velocity across the tricuspid valve initially decreased and increased again. Pericardial effusion occurred on withdrawal of the balloon (resolved in 1 hour). Outcome: Baby was delivered by elective caesarean at 35 weeks weighing 2.45kgs. There was no flow across the pulmonary valve which measured 7.5mm and the tricuspid valve measured 12mm. Radiofrequency perforation of the pulmonary value and dilation were performed with a modified Blalock-Taussig shunt a week later. At four years the child has a biventricular circulation with a closed shunt but required pulmonary valve replacement at 2 years of age. Case 3: In utero changes: Decrease in right ventricular pressure, valvar atresia recurred. Outcome: Baby was delivered spontaneously at term but although there had been good right ventricular growth this had not ensured tricuspid value growth (diameter 3.7 mm). This baby received an arterial shunt and has undergone a one and a half ventricle repair and is well at 3 years. Case 4: In utero changes: no intervention Outcome: Baby was delivered by emergency caesarean. Treatment was withdrawn because of a cerebral haemorrhage diagnosed 3 days postnatally. Case 5: In utero changes: dilation was not carried out. Outcome: Baby delivered at 32 weeks weighing 2100g and was dysmorphic with bilateral coanal atresia and oesophageal atresia. Further operations were performed on day 2 and 4 of life. At 3 weeks open valvotomy and placement of a modified right Blalco Tausiig shunt was performed, however the newborn died.	Unpublished paper (submitted for publication at the time of writing). Selected cases. Intervention was performed in fetuses with a gestational age of less than 34 weeks.

Abbreviations used: PAIVS - pulmonary atresia with intact ventricular septum, RV – right ventricle, AS – aortic stenosis		
Study Details	**Key efficacy and safety findings**	**Comments**
Tulzer et al (2002) [4] and Arzt (2003) [5] UK 2 fetuses pulmonary stenosis or atresia with intract septum - fetus A had pulmonary atresia at 28 weeks gestation with imminent hydrops [5] - fetus B had critical pulmonary stenosis at 30 weeks gestation with imminent hydrops Mean follow-up: 12 months Disclosure of interest: None declared.	Authors report: Both fetuses had pericardial effusions that resolved spontaneously. Doppler studies showed successful perforation of both pulmonary valves with immediate improvement in the function of the right ventricle that was sustained for up to 12 weeks before restenosis of the valve prompted delivery. Both babies delivered in good condition Baby A at 38 weeks (+3 days) Weighing 2640g with a length of 48cm and Apgar scores of 9, 10 and 10 at 1, 5 and 10 minutes. Baby B at 35 weeks (+3 days) Both children, now aged 18 months and 12 months, have biventricular circulation.	Further details of fetus A are given in a later paper [5] The mother of fetus A was given a general anesthesis and local anaesthesia was given to fetus B. Authors note the rationale for intervention: Both had impending congensitive heart failure with signs of imminent hydrops Both had favourable cardiac anatomy: membranous atresia of the pulmonary valve with reasonable sized main and branch pulmonary arteries.
Huhta et al (2004) [1] USA Case report Fetus A was diagnosed with PAVIS in addition to critically severe aortic valve stenosis - diagnosed at 32 weeks.	Fetus A – intervention was attempted however the valve could not be accessed and the fetus died.	Review paper - includes details of one case with valvuloplasty was attempted. Two other fetuses were identified that could have had in-utero procedures however both parents declined and the fetuses died in utero.

Abbreviations used: PAIVS - pulmonary atresia with intact ventricular septum, RV – right ventricle, AS – aortic stenosis

Study Details	Key efficacy and safety findings	Comments
Gardiner (2005) [6] UK Case series 6 fetuses (7 procedures) - 4 pulmonary atresisa with intract ventricular septum (PAIVS) - 3 critical aortic stenosis (AS) Mean age: 21-30 weeks gestation Follow-up: maximum 5 yeras Disclosure of interest: not stated.	Six procedures were technically successful. Three with hydrops (I PAVIS 2 AS) showed resolution and improved circulatory indices. All had good forward flow after procedure but restenosis occurred in 4 (2PAVIS and 2AS), requiring a second procedure in one PAIVS with a large coronary fistula. One PAIVS procedure was stopped at uterine puncture due to placental haemorrhage One PAIVS has a biventricular circulation at 5 years following valvuloplasty, the other a Fontan.	Abstract Includes fetuses with either pulmonary atresia or aortic stenosis Limited information

Validity and generalisability of the studies

- There is limited published evidence on this procedure, with the total number of cases in the published literature less than 10.
- Most of the experience in this procedure would seem to be from two centres.
- The procedure is undertaken in severe and highly selected cases.
- Given that cases are rare it is unlikely that there will be a substantial body of published evidence in the near future.
- Despite cases being highly selected there is still substantial variation in terms of presenting disease.
- Most of studies include a discussion on the need to better define selection criteria to determine those cases that would benefit most from the procedure.

Specialist advisors' opinions

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

Dr H Gardiner, Mr D Howe, Professor M Kilby, Professor S Robson, Professor C Rodeck, Dr G Sharland, Professor PW Soothill, Dr O Stumper, Mr S Walkinshaw, Dr C Wren and Professor M Whittle.

- Comparator would be to wait until after birth to undertaken intervention
- This is a procedure that is rarely performed in the UK or worldwide.
- The procedure is usually felt to be indicated in fetuses with severe fetal pulmonary valve stenosis which is through to be likely to progress to pulmonary atresia with a hypoplastic right heart. Assessing whether a case would have evolved into hypoplastic right heart without intervention is almost impossible retrospectively.
- Criteria for case selection need to be developed and benefits assessed more formally –as being able to do the procedure does not mean that it is indicated
- The procedure should be performed in a specialised fetal medicine unit with high quality imaging, trained midwives and the ability to deliver the baby urgently if required.
- There is a learning curve associated with this procedure.

Issues for consideration by IPAC

There is a voluntary European database on fetal cardiac interventions held by two members of the Fetal Working Group of the Association of European Paediatric Cardiologists.

There is greater controversy regarding the place of fetal intervention in fetus with pulmonary stenosis as many cardiologist feel the postnatal outcome is sufficiently good to obviate the need for fetal intervention [7].

References

1 Huhta J, Quintero RA, Suh E et al. (2004) Advances in fetal cardiac intervention. *Current Opinion in Pediatrics* 16: 487-493.

2 Tworetzky W and Marshall AC. (2003) Balloon valvuloplasty for congenital heart disease in the fetus. *Clinics in Perinatology.Vol.30(3)()(pp 541-550), 2003.* 541-550.

3 Tulzer G and Gardiner HM. (2005) Cardiac Interventions in the Fetus II: potential for right sided lesions (submitted for publication) .

4 Tulzer G, Arzt W, Franklin RCG et al. (16-11-2002) Fetal pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. *Lancet* 2002 Nov 16; 360: 1567-1568.

5 Arzt W, Tulzer G, Aigner M et al. (2003) Invasive intrauterine treatment of pulmonary atresia/intact ventricular septum with heart failure. *Ultrasound in Obstetrics & Gynecology.Vol.21(2)()(pp 186-188), 2003.Date of Publication: 01 FEB 2003.* 186-188.

6 Gardiner HM. (2005) Percutaneous fetal valvuloplasty: four years experience. *Presentation AHA Dallas November 2005*

7 Gardiner HM and Kumar S. (2005) Fetal cardiac interventions. *Clinical Obstetrics and Gynecology* 48, 4 (published on-line):

Appendix A: Additional papers on percutaneous fetal pulmonary valvuloplasty

No additional literature was identified at the time of the literature search.

Appendix B: Related NICE guidance for percutaneous fetal pulmonary balloon valvuoplasty

Programme	Recommendation
Interventional Procedures	**IPG067 Balloon dilatation of pulmonary valve stenosis** Recommendation: 1.1 Current evidence on the safety and efficacy of balloon dilatation of pulmonary valve stenosis appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 Balloon dilatation of pulmonary valve stenosis should only be performed in a specialist unit where paediatric cardiac surgery is available. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). Other Comments: This procedure has become established practice on the basis of clinical experience. There is very limited research evidence published. Most of the data relates to neonates and children, but the procedure can also be performed in adults. **IPG075 Balloon angioplasty of pulmonary vein stenosis in infancy** Recommendation: 1.1 Current evidence on the safety and efficacy of balloon angioplasty of pulmonary vein stenosis in infants does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. The available evidence suggests that the procedure is not efficacious. However, there are no special concerns about the safety of the procedure, especially in the context of very ill infants for whom it is used. 1.2 Clinicians wishing to undertake balloon angioplasty of pulmonary vein stenosis in infants should take the following

Programme	Recommendation
	actions: • Inform the clinical governance leads in their Trusts. • Ensure that the parents of patients understand that the limited available evidence indicates a lack of efficacy. Parents should be given clear written information. Use of the Institute's *Information for the Public* is recommended. • Audit and review clinical outcomes of all patients having balloon angioplasty of pulmonary vein stenosis in infancy. 1.3 This procedure should only be offered to gravely ill infants with a very poor prognosis and in the setting of a specialist paediatric cardiology unit. 1.4 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). 1.5 1.5 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence. **IPG076 Balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children** Recommendation: 1.1 Current evidence on the safety and efficacy of balloon dilatation with or without stenting for pulmonary artery or non-valvar right ventricular outflow tract obstruction in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should only be undertaken in specialist paediatric cardiology units. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). Other comments:

Programme	Recommendation
	Fewer data were available on the use of the technique for non-valvar right ventricular outflow tract obstruction than for pulmonary artery or branch pulmonary artery obstruction. **IPG 077 Balloon dilation of systemic to pulmonary arterial shunts in children** Recommendation: 1.1 Current evidence on the safety and efficacy of balloon dilatation of systemic to pulmonary arterial shunts in children appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 The procedure should only be undertaken in specialist paediatric cardiology units. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). **IPG 095Radiofrequency valvotomy for pulmonary atresia** Recommendation: 1.1 Current evidence on the safety and efficacy of radiofrequency valvotomy for pulmonary atresia with intact interventricular septum is limited due to the rarity of the condition, but appears adequate to support the use of the procedure for the treatment of seriously ill neonates, provided that normal arrangements are in place for consent, audit and clinical governance. 1.2 Radiofrequency valvotomy for pulmonary atresia with intact interventricular septum should be performed in carefully selected patients in specialist centres with paediatric cardiac surgery facilities. 1.3 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk). Other comments: In making its recommendations, the Advisory Committee was influenced by the specialist advice that the procedure is established

Programme	Recommendation
	treatment for severely ill neonates who may otherwise die. **IPG 078 Balloon valvuloplasty for aortic valve stenosis** Recommendation: 1.1 Current evidence on the safety and efficacy of balloon valvuloplasty for aortic valve stenosis in adults and children appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. 1.2 In adults, the procedure should only be used to treat patients who are unsuitable for surgery, as the efficacy is usually shortlived. 1.3 In infants and children, the procedure should be undertaken in specialist paediatric cardiology units. 1.4 The Department of Health runs the UK Central Cardiac Audit Database (UKCCAD) and clinicians are encouraged to enter all patients onto this database (www.ccad.org.uk).
Technology Appraisals	None relevant
Clinical Guidelines	None relevant
Public Health	None relevant

Appendix C: Literature search for percutaneous fetal pulmonary balloon valvuloplasty

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	The Cochrane Library 2005, Issue 3	19/09/2005
CRD		21/09/2005
Embase	1980 to 2005 Week 37	19/09/2005
Medline	1966 to September Week 1 2005	19/09/2005
Premedline	September 15, 2005	19/09/2005
CINAHL	1982 to September Week 2 2005	19/09/2005
British Library Inside Conferences (limited to current year only)		21/09/2005
National Research Register		21/09/2005
Controlled Trials Registry		21/09/2005

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

Search strategy used in Medline

1. valvuloplast$.tw.
2. valvoplast$.tw.
3. valvotom$.tw.
4. exp balloon dilatation/
5. (balloon adj3 (dilation or dilatation)).tw.
6. ptpv.tw.
7. or/1-6
8. pulmonary valve/
9. pulmonary atresia/
10. pulmonary valve stenosis/
11. pulmon$.tw.
12. heart defects, congenital/
13. (congenital adj3 (cardiac or cardiovascular or heart$) adj3 (disease$ or defect$)).tw.

14. aortic valve/
15. aortic valve stenosis/
16. aortic$.tw.
17. or/8-16
18. 7 and 17
19. fetus/
20. fetal heart/
21. fetal diseases/
22. (fet$2 or foet$2).tw.
23. or/19-22
24. 18 and 23
25. animal/ not human/
26. 24 not 25