National Institute for Health and Care Excellence
IP322/2 / Percutaneous balloon valvuloplasty for fetal critical aortic stenosis
IPAC date: 8 March 2018

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Specialist Adviser	**1**	Dear Sir / Madam, I was one of the specialist advisers with respect to this document for consultation. I assume it is fine for such advisers to comment. If not, please do not include my comments. I note the recommendations: 1.1 Current evidence on the safety and efficacy of percutaneous balloon valvuloplasty for fetal aortic stenosis is limited in quantity and the results are inconsistent. Therefore, this procedure should only be used in the context of research. 1.2 NICE encourages the peer-reviewed publication of all further research. Further research could be in the form of controlled trials, analysis of registry data or other observational studies. It should address patient selection, timing of the intervention and the natural history of the disease.	Thank you for your comment. The consultee agrees with main recommendation.

			My interpretation of the recommendations is that such procedures might be undertaken with institutional approval and only if part of a structured study such as a RCT or with contribution of data to an International registry. Currently, contribution to an international registry is the only possibility as there are no international RCTs in operation. The two international registries (IFCIR and AEPC) are both active in publication of data. In my opinion, assuming my interpretation is correct, I would fully support these recommendations as fair and balanced. Yours sincerely, [redacted] [redacted]	
2	Consultee 2 NHS Professional	**Title**	Percutaneous balloon valvuloplasty for fetal critical aortic stenosis	Thank you for your comment. The committee decided to change the title to percutaneous balloon valvuloplasty for fetal critical aortic stenosis.
3	Consultee 2 NHS Professional	**1.1**	Safety aspects are well described in previous papers eg Moon-Grady et al http://dx.doi.org/10.1016/j.jacc.2015.05.037 They quote a risk of peri-procedural fetal death of 17%. The Boston Children's Hospital data is more difficult to ascertain the	Thank you for your comment. The Moon-Grady (2015) paper is included in the main extraction table (Table 2) in the overview. The fetal death rate for aortic valvuloplasty reported in this paper is 12% (10/86).

			procedural fetal demise given that they report 77 of 100 cases performed. In the recent review they report a peri-procedural fetal mortality of 11%. (Freud, Curr Opin Pediatr 2016, 28:156 – 162 DOI:10.1097/MOP.0000000000000331) No adverse effects on the mother have been reported to date.	The Freud (2016) paper is a review paper. Therefore, it has not been included in the overview. The Freud (2014) paper is included in Table 2 and the fetal death rate of 11% is reported in the overview. We have also reported that no maternal complications were reported in the case series of 100, 123 and 12 fetuses and in the international fetal cardiac intervention registry of 86 fetuses with aortic stenosis.
4	Consultee 2 NHS Professional	**1.1**	Efficacy is inconsistent, I agree and thus robust data collection is required with each case of intervention performed to assess efficacy. Furthermore a new UK Nationwide study to provide the natural history of fetal aortic stenosis needs to be undertaken given that there is improved prenatal screening compared to the era of previous data from Simpson, 1997. This could easily be facilitated via the National Fetal Cardiology Group.	Thank you for your comment. The consultee agrees that the evidence on efficacy is inconsistent. Section 3.5 of the guidance has been changed as follows: *''There is uncertainty about the natural progression of fetal aortic stenosis and about who may benefit from the procedure, so a study about the natural history of fetal aortic stenosis would be useful.''*
5	Consultee 2 NHS Professional	**2.2**	This is usually referred to as critical aortic stenosis rather than severe in the literature and consideration should be given to keep a consistent terminology.	Thank you for your comment. The committee decided to change the word ''severe'' to ''critical'' in the guidance.
6	Consultee 2 NHS Professional	**2.4**	*'' At birth, most babies with severe aortic stenosis will not be able to have biventricular heart repair ''*	Thank you for your comment. The consultee refers to the following paper *Natural history of 107 cases of fetal aortic stenosis from a European multicenter*

			The recent data from Gardiner et al does not suggest this and perhaps the wording needs to reflect this. The Gardiner data does have its limitations and there are certainly methodological issues.	*retrospective study.* from Gardiner et al. (2016) which says: *''Among the 107 ongoing pregnancies there were eight spontaneous fetal deaths and 99 livebirths. Five were lost to follow-up, five had comfort care and four had mild aortic stenosis not requiring intervention. There was intention-to-treat in these 85 newborns but five died prior to surgery, before circulation could be determined, and thus 80 underwent postnatal procedures with 44 BV,29 UV and seven BV-to-UV circulatory outcomes*.'' Section 2.4 of the guidance has been changed as follows: *''At birth, some babies with critical aortic stenosis will not be able to have biventricular heart repair and about 50% of babies will die during the first year of life despite surgical treatment. This prognosis can lead parents to ask for a termination of pregnancy*.''
7	Consultee 2 NHS Professional	**2.6**	The phrasing here needs to demonstrate that HLHS is not a curable condition. It is a condition that if no treatment was offered the baby would die within a few days. However, a high risk surgical strategy is possible which allows the child to survive, but this does not correct the circulation, it gives the child the potential to survive. The surgical strategy for HLHS results in a single ventricle ("half a heart") circulation. The medium term outcome is significantly impaired.	Thank you for your comment. Section 2.6 of the guidance has been changed as follows: '' *Staged reconstruction to create a single ventricle circulation can improve survival for babies with HLHS. This takes multiple operations over several years and involves complex high-risk open-heart surgery*.''

8	Consultee 2 NHS Professional	**2.8**	*‘’development of pulmonary vascular hypertension’’*: This is not a cited aim of the procedure. In utero perforation of the atrial septum would be regarded to prevent development of pulmonary hypertension.	Thank you for your comment. Section 2.8 of the guidance has been changed as follows: ‘’ *The aim of fetal aortic balloon valvuloplasty is to prevent progressive damage to the ventricle. This may allow postnatal surgical intervention to have more chance of success*.’’
9	Consultee 2 NHS Professional	**2.9**	maternal sedation is not routinely required for these procedures	Thank you for your comment. Section 2.9 of the guidance has been changed as follows: ‘’ *Fetal aortic balloon valvuloplasty is done at 21 to 32 weeks’ gestation. Under maternal local anaesthesia (with or without sedation), a needle is inserted through the mother's abdominal wall into the uterine cavity with ultrasound guidance. Analgesia is injected into the fetus before advancing the needle through the fetal chest wall into the left ventricle. A guidewire is inserted through the needle and across the aortic valve. A balloon catheter is then inserted and inflated to dilate the stenotic valve. The catheter and needle are then withdrawn*.’’
10	Consultee 2 NHS Professional	**3.2**	*The consultee highlighted the words ‘’long-term survival and quality of life’’ in the text.* Intertwinned with this long term outcome is the development of pulmonary hypertension in those with a biventricular circulation. An assessment of this was not clearly accurately	Thank you for your comment. Section 3.2 of the guidance has been changed as follows: ‘’ *The specialist advisers and the committee considered the key efficacy outcomes to be: fetal survival to delivery, achieving a biventricular*

			ascertained in the natural history study from Gardiner et al. Thus a child may have a biventricular circulation but at the expense of pulmonary hypertension, for which the outcome is poor.	*circulation, the need for subsequent complex cardiac surgical procedures, long-term survival and quality of life*.''

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