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Fetal cardiac interventions: Rationale, risk and benefit

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SUMMARY

Fetal congenital heart disease may progress during pregnancy and may lead to irreversible myocardial or pulmonary damage. The rationale of fetal intracardiac interventions is to change fetal hemodynamics, prevent secondary damage and improve long-term outcome at an acceptable risk for mother and fetus. This review focuses on the current experience about patient selection, risks and benefits of this technique.

1. Introduction

Numerous studies have been published documenting the natural history of congenital heart defects in utero and the potential of prenatal progression.[1,2] A well-functioning biventricular heart may develop into a univentricular heart, or it may acquire myocardial damage, which can lead to congestive heart failure (CHF), arrhythmias, hydrops and intrauterine death. Pulmonary development may be also affected.

It would therefore seem logical that a fetal intracardiac intervention at the right time and in the right patient should be able to improve or even normalize hemodynamics and should be able to prevent secondary damage to the fetal heart and lungs. CHF, arrhythmias or hydrops could be improved or reversed, and fetal death prevented.

A group in London made the very first attempts with fetal intracardiac interventions in 1991 by dilating a stenotic aortic valve.[3] Following this initial experience several other centers around the world have tried the same procedure. Their experience in 12 third trimester fetuses was published in 2000.[4] Out of seven technically successful procedures only one patient had prolonged survived. At that time all procedures were performed in fetuses with a predicted 100% mortality to ensure survival. Today, with the achievements of pediatric cardiac surgery, pediatric cardiac intensive care and pediatric cardiology, fetal and postnatal survival is no longer the main issue, but the improvement of morbidity and long-term outcome. This review focuses on three different intracardiac interventions: (i) critical valvar aortic stenosis (CAS); (ii) critical valvar pulmonary stenosis or pulmonary atresia with intact septum; (iii) closed or severely restrictive foramen ovale in fetuses with critical left heart obstructive lesions, e.g. hypoplastic left heart syndrome.

2. Rationale for intervention

2.1. Critical valvar aortic stenosis

A valvar aortic stenosis significantly alters hemodynamics. The fetal circulation and the fetal heart can respond in different ways depending on the time of development, rate of progression and severity. If aortic stenosis is only mild, develops late in gestation and progresses slowly, sufficient left ventricular (LV) systolic function is maintained until birth and these patients are good candidates for postnatal interventional therapy, with good long-term outcome. So there is no need to expose them to the risk of a prenatal intracardiac intervention. However, if significant aortic stenosis is already present in the first or early second trimester fetus, deleterious effects on the fetal heart and lung can be expected. At least four different kinds of pathophysiology can develop.

2.1.1. Early LV hypoplasia due to impaired LV growth

In the first or early second trimester these fetuses already present with a marked reduced LV size and volume. The alteration of LV pressure as a result of the aortic stenosis has led to impaired LV filling and redirection of flow across the foramen ovale to the right ventricle (reversed shunting across the foramen ovale from left to right). LV growth slows down and stops, whereas the right ventricle (RV) grows at an increased rate and takes care of the total cardiac output.[5] Echocardiographic features include a small LV (LV long-axis *Z*-scores <-2) with muscular hypertrophy and echogenic endocardium, caused by endocardial fibroelastosis (EFE). The mitral valve is hypoplastic, too (*Z*-scores <-2), usually with monophasic inflow and without significant regurgitation. The gradient across

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the aortic valve is low and there is reversed flow in the aortic arch and ascending aorta. It has been shown that these fetuses all develop hypoplastic left heart syndrome (HLHS)[6] and it was speculated they would be good candidates for an in-utero intracardiac intervention. Relief of the aortic obstruction should lead to improved LV filling and growth.

2.1.2. LV dilation and dysfunction

In these fetuses the LV pressure increase can no longer be maintained by the myocardium and leads to a rapid and significant LV dilatation. There is no more synchronous LV contraction, shortening fraction is markedly decreased and signs of EFE appear probably as a result of impaired coronary perfusion.[7] There is progressive myocardial damage, which may become irreversible. The mitral valve is involved in this process, too. Ventricular dilatation may lead to progressive mitral valve regurgitation, and involvement of papillary apparatus into EFE may cause mitral stenosis. If dilatation occurs in mid or late gestation, LV size at birth may still be within normal limits or even enlarged. However, severe myocardial dysfunction associated with mitral valve disease puts these patients at high risk for postnatal valvuloplasty and towards a univentricular circulation.[8] If dilatation occurs early in gestation, there will be LV growth arrest as described above, which results in LV hypoplasia at birth and HLHS.[9] A timely fetal aortic valve dilation shortly after the onset of dilatation or, even better, shortly before the onset of dilatation should be able to reverse or prevent LV dilatation, LV dysfunction and ischemia and allow better or normal LV filling and growth, so that these patients become favourable candidates for a postnatal valvuloplasty with preserved LV contractility.

2.1.3. LV dilation with dysfunction, congestive heart failure and hydrops

In addition to the pathophysiology described in the preceding section, right ventricular function also becomes affected. The dilated high pressure LV compresses the RV, resulting in RV dysfunction, tricuspid regurgitation and an increase in RV filling pressures. At a certain point, the RV is no longer capable of maintaining the combined cardiac output; CHF and hydrops will appear leading to intrauterine death.[10,11] Reduction in LV pressure and size by a successful intracardiac intervention should improve or restore RV function and cardiac output. This should improve CHF, reverse fetal hydrops and ensure survival until birth.

2.1.4. Severe mitral regurgitation with giant left atrium

In these fetuses with CAS the pressure rise in the LV results in progressive severe mitral regurgitation. The reason could be a primary mitral valve abnormality or a secondary involvement of the mitral valve in this disease by annulus dilatation, altered papillary muscle geometry or EFE. The resulting increased left atrial pressure can cause a premature narrowing or closure of the foramen ovale. As a result the left atrium cannot decompress into the right atrium and increases in size; pulmonary veins become dilated and congested, affecting pulmonary vascular development. If the large LV compresses the RV, as described above, hydrops may occur.[12] Aortic valve dilation should be able to decrease the severity of mitral regurgitation by lowering LV pressure and the stress on the mitral valve.

Therefore, except in fetuses with end-stage CHF and hydrops, where an intervention may be life-saving, the rationale is to achieve an enhanced quality of life. There is no doubt that two ventricles are better than one ventricle in terms of quality of life, life expectancy and the potential of late problems such as thrombotic events, protein loosing enteropathy, plastic bronchitis, arrhythmias or early ventricular dysfunction.

The neurological outcome of fetuses with congenital heart disease has become an important issue. Fetuses with CAS all have retrograde flow in the aortic arch and therefore their brains are perfused with less-oxygenated blood from the right ventricle. An altered cerebral perfusion and brain volume, assessed by Doppler interrogation and magnetic resonance imaging, has been described.[13–15] Establishment of antegrade aortic arch flow by a prenatal intracardiac intervention may therefore have beneficial effects, even if LV size remains too small for a biventricular postnatal circulation.

2.2. Critical valvar pulmonary stenosis or pulmonary atresia with intact septum

Pulmonary atresia with intact ventricular septum carries a significant morbidity and mortality.[16] As in fetuses with CAS, a pulmonary valve stenosis can progress in severity and even become atretic during fetal life.[17,18] Intrauterine death occurs in ~5%; if there is a wide patent foramen ovale most fetuses will reach term without major problems. Pulmonary obstruction leads to increased RV pressures, but, unlike the LV, the RV does not dilate but develops massive muscular hypertrophy, so becoming restrictive with impaired filling and growth. Severe RV hypoplasia may preclude a biventricular circulation postnatally. Survival rates at 1 year range from 65% to 92% and at 10 years from 43% to 76%.[19–22] It is interesting to note that the survival rates of children with univentricular and biventricular circulation was not different in most reports. Impaired RV growth and function in biventricular children might be responsible for this.[23,24] In univentricular patients it has been shown that their left ventricular function can be negatively affected by a high-pressure right ventricle with unknown long-term consequences.[25] So the rationale for in-utero pulmonary valvuloplasty would be to ensure better RV growth with a biventricular outcome in fetuses who would otherwise end up with a univentricular circulation, and also a better RV in patients with a biventricular repair.

2.3. Closed or severely restrictive foramen ovale in fetuses with critical left heart obstructive lesions

In fetuses with HLHS or critical left ventricular outflow obstruction there is reversed left-to-right shunting through the foramen ovale. However, increased left atrial pressure may cause premature closure of the foramen ovale, resulting in left atrial hypertension. Pulmonary venous congestion and hypertension are responsible for secondary changes in pulmonary vessel morphology and pulmonary lymphangiectasia.[26] Therefore these patients have a substantially high morbidity and mortality even if an urgent atrioseptostomy is performed immediately after birth.[27] Therefore decompression of the left atrium by creation of a large atrial septal defect should allow unobstructed pulmonary venous drainage, remodelling of the pulmonary vessel walls and continuing normal pulmonary vascular development.

2.3.1. Risks

There are, of course significant risks associated with this procedure and there are two patients involved: a healthy mother and a fetus with congenital heart disease.

As the amniotic cavity has to be entered transabdominally with a 18 or 19 gauge needle, there are inevitable risks for the mother such as premature rupture of the membranes, premature labour, placental abruption, bleeding or infection. Until now, we have not encountered any of these maternal complications during all our 53 procedures and the team at Boston Children's Hospital has reported the same for all their cases, totalling more than 120.[28–30]

There is a significant chance of severe fetal complications. Sustained bradycardia and/or hemopericardium are frequent complications, that can lead to hemodynamic instability and fetal death.