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Fetal intervention for cardiac disease: The cutting edge of perinatal care

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Summary Fetal cardiac valvuloplasty has been proposed for progressive cardiac disease with a poor prognosis, such as critical aortic stenosis and pulmonary atresia with intact ventricular septum and balloon atrial septostomy for hypoplastic left heart syndrome, or simple transposition of the great arteries with closed or restrictive inter-atrial communication. It is anticipated that early rescue of ventricles or the pulmonary veins from an unfavourable environment may promote healthier ventricular and vascular growth and improve postnatal outcomes. While close collaboration between the fetal medicine specialist and perinatal cardiologist may optimize the chances of technical success, obstacles to progress include the relative rarity of suitable cases and late referral for therapy. In common with other interventions in fetal medicine, there is a learning curve, and it would benefit progress if the procedures were initially concentrated in just a few centres to enable them to develop skills and experience. Following careful evaluation, it may then be desirable to train further centres and roll out best practice models.

Introduction

Twenty years ago the first fetal cardiac intervention in humans was reported when fetal pacing was attempted in a hydropic fetus with complete heart block due to maternal anti-Ro/La antibodies.[1] Temporary pacing was achieved, but fetal demise occurred within hours, probably due to the severity of the hydrops. The authors postulated that pacing might be successful in the future if performed in fetuses that are less sick, as it might increase the duration of pregnancy and reverse a less severe hydrops. The next publication on fetal cardiac therapy, in 1991, described fetal aortic valvuloplasty in two fetuses in London; the technique was successful in one at 34 weeks, and she is now 15 years old with a biventricular circulation.[2] The place of fetal intervention has yet to be determined in the current era. For most children with congenital heart disease, surgery can be performed with a mortality of <5% and expectation

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of a good quality of life. This is not so for children born with left or right heart hypoplasia. These conditions are the most difficult to manage surgically, with an overall 5-year survival of about 60% for those with a univentricular circulation, depending on institutional case selection.[3–6] Postnatal surgical modifications and interventional catheter approaches for hypoplastic left heart syndrome have improved early survival,[7,8] but ventricular function is impaired in a single-ventricle circulation,[9] and long-term prognosis for an individual is guarded.

New innovations in fetal medicine are frequent.[10] Current management of difficult fetal pathophysiological situations—such as twin–twin transfusion syndrome—has benefited from carefully conducted multicentre research produced through collaborative initiatives.[11] However, this approach has not yet been instituted for the assessment of fetal cardiac interventions, and until recently our knowledge was based on mostly isolated reports of fetal valvuloplasty during the 1990s, none earlier than 26 weeks' gestation, and summarized in a collected review.[12] More recently larger case series have been published, as have reports using new technology in animal models, but to date there remains a lack of a large evidence base for fetal cardiac interventions.[13–21]

In this article we explore the reasons behind the renewed interest in fetal therapy and perceived successes and limitations of procedures reported to date.

Rationale for fetal procedures

Individuals diagnosed before birth tend to have poorer outcomes, presumably because the more advanced cases are detected antenatally, and these progress rapidly in the second- and third-trimester fetus, resulting in a greater chance of secondary damage to the rapidly growing pulmonary bed and ventricles.[3,22–25] Deterioration of ventricular growth and function can be documented on serial fetal echocardiograms in most individuals with aortic or pulmonary stenosis.[26–28] Fetal critical aortic stenosis may progress to hypoplastic left heart syndrome (HLHS) in a proportion of cases,[26,29] resulting in an eventual univentricular circulation, but even for those in whom an eventual biventricular circulation is possible, the overall 5-year survival is only about 72%, and more than half (54%) will have undergone further surgery before they are 5 years old.[30] The outlook is similar for pulmonary atresia with intact septum (PAIVS), where 5-year survival was only 64% from an unselected population-based study in the UK and Eire. Only one third of these children were reported to have a biventricular circulation at 10-year follow-up.[4] Fetuses with an intact inter-atrial septum (complicating simple transposition of the great arteries and hypoplastic left heart syndrome) may show compromise of the fetal circulation, with hydrops and intrauterine death. For the survivors, the prognosis is much poorer than for those born with a good inter-atrial communication because of in-utero damage to the developing pulmonary vasculature.[3]

There are few studies that document the natural history of cardiac growth and physiological changes in individual fetal malformations, and we know little of the genes driving these mal-developments, or their timing. Unfortunately there is no animal model of progressive heart disease sufficiently similar to that in humans to provide accurate insights into the pathophysiological mechanisms involved and to aid in developing management strategies. The major reason for fetal intervention is to improve postnatal outcome and encourage a biventricular outcome, or the best possible univentricular circulation. To achieve this aim, prevention of secondary damage is desirable. Cases diagnosed in utero have a particularly poor prognosis because the left ventricle usually shows severe afterload mismatch, and the ventricle shows a variety of maladaptive responses leading to worsening biventricular function.[26,27,31] However, the primary morphology is probably also less favourable in these cases. The 'monocuspid' aortic valve is far commoner in neonates requiring urgent aortic valvuloplasty soon after birth than in children or adults undergoing this procedure, and we can estimate that it is present in at least one third of fetuses presenting with critical aortic stenosis.[32] In cases of critical aortic and pulmonary stenosis, the supporting ventricle develops under increased pressure, and the resultant ventricular hypoplasia, fibrosis, and abnormalities of coronary arterial and pulmonary venous morphology and function are common and major determinants of poor outcome.[31]

The learning curve

Training

The fetal medicine specialist is the person most skilled in placing the needle in the correct position in the fetal heart for valvuloplasty or balloon atrial septostomy. This is not a technique for all to attempt, and the learning curve in achieving technical success seen in some series may be due to differences in training opportunities resulting in a lack of experience in cardiac puncture. In some countries fetocide performed via fetal cardiac puncture is recommended before late termination of pregnancy, and fetal medicine specialists will perform this under supervision during their specialist training and regularly thereafter. This provides them with the basic skills to reliably access the fetal heart in the correct plane to position the needle in the appropriate outflow tract for a cardiac intervention. If this is not routine practice, the skills of fetal cardiac puncture will form the major part of the learning curve during the initial cardiac interventions, and more complex manoeuvres such as mini-laparotomy may be required to achieve access to the fetal circulation.

Teamwork

Fetal cardiac intervention requires close collaboration between fetal medicine specialists and cardiologists. It is still considered an experimental therapy, and as such requires institutional ethical approval. The establishment of a multidisciplinary team is essential to the success of any interventional programme.[13,14,16] Of paramount importance is the safety of the mother, and the procedures should ideally be performed in a fetal medicine centre that can provide comprehensive care for the pregnant woman. The team comprises not only the fetal cardiologist but also the