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In utero intervention for severe congenital heart disease

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A B S T R A C T

The aim of foetal cardiac therapy is to treat an abnormality at the developmental stage so that the process of cardiac growth, which is complex and relies on the volume and direction of circulating blood as well as genetic determinants, can continue. In reality, most cardiac interventions are palliative; hence, major abnormalities are still present at birth. Nevertheless, tangible benefits following successful foetal intervention include improved haemodynamics and reduction in secondary damage leading to better postnatal outcomes.

In cases of semilunar valve stenosis, or atresia, foetal valvuloplasty aims to achieve a biventricular, rather than univentricular, circulation. Opening and stenting a restrictive atrial foramen may preserve the pulmonary function in cases of hypoplastic left heart syndrome, thereby increasing the chances of successful postnatal surgery.

More recent endeavours include percutaneous implantation of a miniaturised pacemaker to treat complete heart block and the promotion of left-sided heart growth by chronic maternal hyperoxygenation.

The true clinical benefit of these interventions over natural history remains uncertain because of the paucity of appropriate randomised controlled trials (RCTs). Foetal cardiac therapy must now move from a pioneering approach to one that is supported by evidence, as has been done successfully for other foetal therapies.

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Introduction

In the 1990s, interventional and surgical outcomes for babies born with critical aortic stenosis (AoS) were poor, and before widespread expertise in the Norwood procedure, there was no successful palliative surgery for hypoplastic left heart syndrome (HLHS). Similarly, poor long-term outcomes exist for children with pulmonary atresia or critical pulmonary stenosis with intact ventricular septum (PAIVS). The first foetal valvuloplasties were performed as an alternative to these very limited postnatal therapeutic options but proved technically difficult and hence were abandoned [1].

Surgical and interventional catheter outcomes for these lesions have improved since this period, and it is important to be able to demonstrate that there is substantial benefit from foetal therapy before establishing valvuloplasty as a standard of care. The exception is for babies with HLHS, born with a restrictive atrial septum, where there is still at least 30% mortality, and prenatal perforation and stenting of the foetal atrial septum, although challenging, is considered worthwhile [2].

Currently, foetal valvuloplasty is offered for critical AoS, pulmonary stenosis (PS) (Fig. 1) and PAIVS(Fig. 2). Balloon atrial septostomy and stenting may be offered in AoS or HLHS with a restrictive or intact atrial septum(Fig. 3).

The overall goal is to optimise a baby's maturity at delivery, improve perinatal health and, thereby, increase the postnatal treatment options. For example, in addition to optimising the chances of a biventricular circulation, these therapies have been performed to prolong pregnancies complicated by hydrops as a result of high systemic venous pressures [3,4] and reduce secondary pulmonary damage in HLHS with restrictive or intact atrial septum to optimise the chances of good univentricular surgical outcomes [2,5].

The therapeutic approach to obstructed semilunar valve disease (aortic or pulmonary stenosis/atresia) or restrictive inter-atrial septum in the foetus has developed from postnatal treatment strategies. However, prenatal cases are often different, lying towards the severe end of the spectrum; hence, foetal 'valve' disease is rarely isolated, and there is often already hypoplasia or damage to the supporting ventricle at the time of diagnosis, requiring more extensive postnatal surgery than those detected after delivery. This explains why foetal valvuloplasty is only rarely successful as the sole therapy and two or three episodes of postnatal surgery are usually required for most infants. While a good biventricular circulation has a better short- or medium-term outcome than a good, univentricular palliation, a borderline-successful biventricular circulation is associated with very high morbidity and mortality, particularly where there is a systemic morphological right ventricle [6–8]. Therefore, foetal

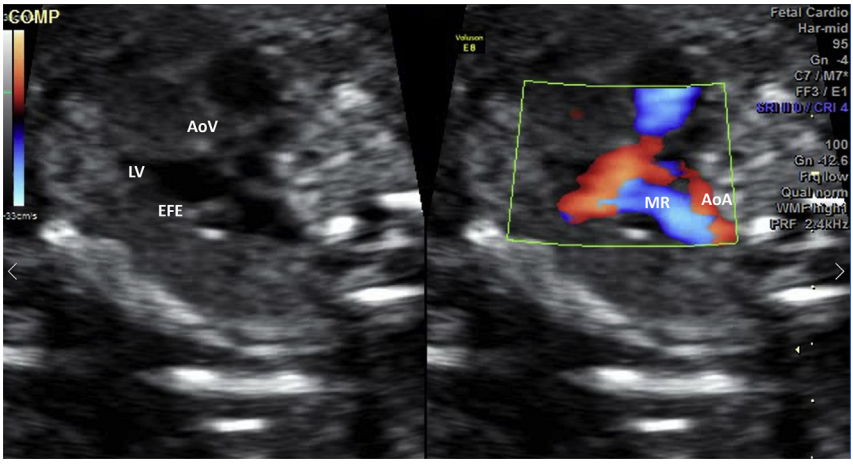

Fig. 1. Left ventricular outflow tract in foetal aortic stenosis. The left ventricle (LV) is damaged with endocardial fibroelastosis (EFE) along the mitral valve chordae resulting in mitral regurgitation (MR) in blue. There is reversed flow (red) along the ascending aorta (AoA) towards the closed aortic valve (AoV).

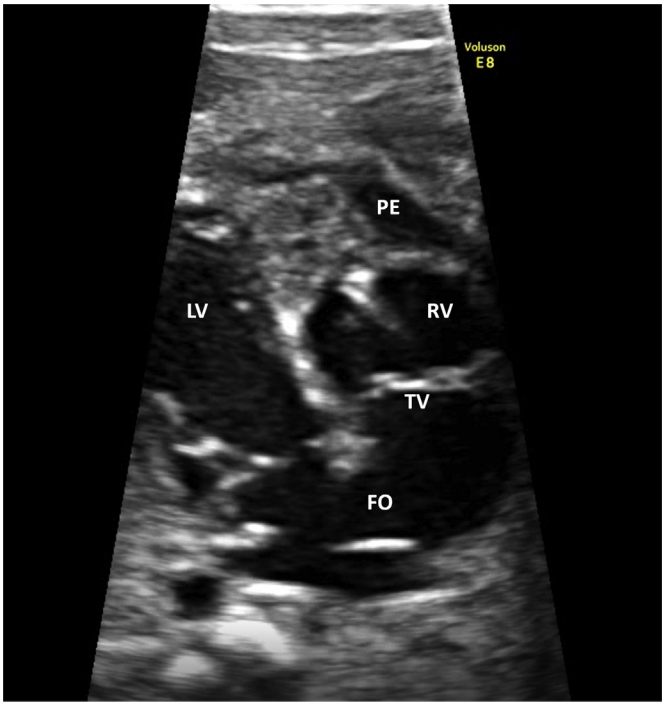

Fig. 2. Four-chamber view of pulmonary atresia with intact ventricular septum. There is pericardial effusion (PE). The right ventricle (RV) is rounded and shortened when compared with the left ventricle (LV). The tricuspid valve (TV) has a normal diameter but is displaced apically. The foramen ovale is stretched, and the flap is aneurysmal (FO).

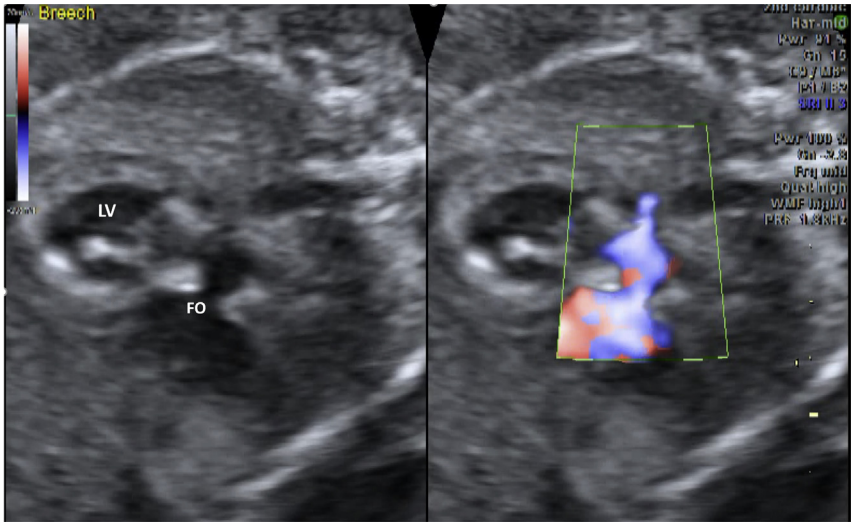

Fig. 3. Four-chamber view in aortic stenosis with a dilated left ventricle (LV). The interatrial septum is thickened with a potentially restrictive foramen ovale (FO). Atrial flow is bidirectional showing left to right flow in blue.

valvuloplasty aims not only to increase the proportion of individuals with a biventricular circulation but also to improve the developing myocardium and pulmonary bed to optimise the quality of future surgery, whether it is for a univentricular or a biventricular strategy. Foetal therapy then becomes a logical extension of past trends to intervene at an early stage rather than a delay until later in childhood [9].

Chronic maternal hyperoxygenation (CMH), a recent novel intervention, has been proposed to stimulate the growth of left-sided foetal heart structures by increasing pulmonary venous return to the left atrium, thereby increasing preload to the left heart. This involves chronic administration of oxygen to a mother for several hours a day during the third trimester. This intervention requires the evaluation of both maternal and foetal safety, and a robust investigation of preliminary claims that it may prevent the need for postnatal surgery in lesions such as coarctation of the aorta and the borderline-sized left heart [10–12].

Foetal cardiac pacing is not yet a technically successful therapy; pacing may increase survival to birth of the hydropic foetus with isolated complete atrioventricular block (CAVB) but requires further development [13–15].

At the present time, no foetal cardiac interventions have been tested by RCTs with appropriate controls, in contrast to other foetal therapies such as for twin-to-twin transfusion syndrome [16] and spina bifida [17]. For foetal cardiac therapies to have a stronger foundation in the future, there must be more evidence of the effectiveness of an intervention to alter the natural history of the disease.

Benchmarking foetal cardiac procedures

Currently, there are no externally verified databases for foetal cardiac interventions. There are published individual-centre series and research reports from the Foetal Working Group of the Association for European Paediatric and Congenital Cardiology and voluntary International Foetal Cardiac Interventions Registry (IFCIR) [18–23]. Single-centre case series of foetal intervention are inevitably biased [24], and medium-term survival is infrequently reported, while the IFCIR foetal registry only reports survival and circulation type at the time of the first hospital discharge [23]. This reduces the ability to extrapolate their results to other healthcare systems and foetal populations.

In contrast, postnatal outcomes are reported in several externally verified, national or international, interventional surgical and interventional cardiology databases including the Society of Thoracic Surgeons–Congenital Heart Surgery database (STS-CHS, https://www.sts.org/), European Congenital Heart Surgeons Association (ECHSA-Congenital, http://www.echsacongenitaldb.org/) and National Institute for Cardiovascular Outcomes Research – Congenital Heart Disease portal (NICOR-Congenital) [25], in North America, Europe and UK, respectively. The International Nomenclature and Database Committee has established an international nomenclature for Congenital Heart Surgery, which allows data aggregation and comparisons between populations. These provide data on anticipated prenatal prevalence of each lesion with outcomes. Foetal pulmonary and AoS account for 5.5% and 4.1%, respectively, of foetal series, which is similar to large postnatal population-based studies. One extrapolation from the NICOR-Congenital database is that approximately 60 cases of semilunar valvular stenosis (AoS and PS) occur in 700,000 annual live births in the UK, which might be considered suitable for foetal intervention [25]. In practice, this estimate would be reduced by intrauterine demise (approximately 6% of cardiac diagnoses) and by families declining foetal intervention following prenatal counselling. These calculations could guide the growth of foetal centres performing foetal cardiac procedures.

Procedure-based surgical databases have several design limitations: (1) they are procedure based and a child may be represented more than once; (2) follow-up is usually mortality at one month and one year, but many outcomes are recorded as unknown and (3) they reflect postnatal procedures, and hence, terminations of pregnancy and affected babies dying before or not offered surgery will not be recorded. Therefore, to assess the number of foetal cardiac interventional programmes required for a given population and benchmark the circulatory outcomes one expects to achieve, healthcare providers will need to estimate true prenatal workload. In addition to the procedure-based limitations listed above, there are prenatal ascertainment issues: for example, true foetal population prevalence

includes cases of AoS that progress to HLHS [26], but this proportion is unknown because the prenatal detection of AoS is low. In a single-centre series, only 10% of babies born with AoS had prenatal detection, which limits the assessment of the role of foetal therapy [27]. Additionally, because the risk-to-benefit ratio for therapeutic efficacy remains uncertain, fewer cases may be referred for consideration of foetal valvuloplasty than are diagnosed prenatally, reducing the power to test the benefit of foetal therapy [28]. There are UK national guidelines (https://www.nice.org.uk/search?q=fetal+valvuloplasty, accessed January 4, 2019) and scientific statements from the American Heart Association guiding clinical practice for foetal aortic and pulmonary valvuloplasty [29].

Risks of foetal therapy compared with postnatal therapy

Early foetal valvuloplasties had limited success, mostly because the catheter equipment available was not suitable for the small foetal heart. Technical improvements have led to renewed interest in foetal therapy, and most programmes report above 80% technical success using high-pressure small coronary artery catheters with low profiles, suitable for small hearts [3,4,18–23,30–32]. Success is usually defined as the passage of a balloon across a valve followed by sonographic evidence of improved forward flow and/or new regurgitation [19,30]. A larger balloon-to-valve ratio is used in the foetus than postnatally to achieve technical success. New regurgitation is usually well tolerated by the foetus compared to that occurring following childhood valvuloplasty [3,18,19,31].

The major theoretical risks are maternal (haemorrhage, respiratory, and thrombotic), foetal (demise, haemorrhage, cardiac tamponade and cerebral ischaemia or haemorrhage) and miscarriage [20,28]. There have been no reports of important maternal morbidity, although volume loading and wound haematomas were reported in the early experience following laparotomy and usually associated with maternal general anaesthesia and longer procedure times [32]. There are acknowledged dangers of general anaesthesia in pregnancy, and this is avoided in most centres. However, a general anaesthetic is helpful in foetal cardiac procedures where a good foetal lie is pivotal to the success of the procedure, as it relaxes the uterus and allows for a degree of manipulation. However, manipulation poses the risk of placental abruption, and the duration of the procedure may be longer in the anesthetised woman. If the approach is percutaneous, through a 16- to 18-gauge needle, the risks to the mother and of miscarriage are probably less then when using a fetoscopic approach, although the latter may have the benefits of improved imaging and access to the foetal heart.

In experienced centres, foetal demise occurs in 5%–10%; however, less experienced teams have reported mortality of up to 32% [22,23]. Mortality may be attributed to team inexperience and technical difficulties, which result in cardiac tamponade or cerebral haemorrhage, or because the foetus is hydropic. The underlying pathology, for example, a heavily mineralised myocardium that fails to seal around the puncture site, is a risk factor for tamponade, which is unlikely to diminish with experience, and this complication may only be resolved by case selection [28]. Even minimal haemorrhage at the time of intervention may be poorly tolerated by the foetus because the delicate watershed area in the foetal brain is easily damaged, resulting in cerebral haemorrhage and risk of substantial handicap.

The postnatal databases report procedural mortality between 1% and 3% for neonatal balloon aortic valvuloplasty. This is now as low as for most catheter-based procedures at any age [25] and raises the bar for performing prenatal aortic valvuloplasty. However, as some cases of foetal AoS will progress to HLHS, the mortality for Norwood stage 1 as well as long-term morbidity and mortality for a univentricular circulation should be factored into the risk–benefit equation. Thirty-day mortality for Norwood stage 1 is reported as approximately 7%, but for the more high-risk cases offered by the Hybrid procedure – those of low birth weight or with restrictive interatrial septum – the mortality remains high at approximately 30% [25]. Five-year survival for Norwood-type procedures is 75%–80%, and for Fontan-type, it is approximately 85%. Thirty-day mortality for systemic to pulmonary arterial shunting in PAIVS is approximately 12%, higher than procedure-related mortality for foetal valvuloplasty in some, but not other series [4,31,33]. While foetal pulmonary valvuloplasty may be performed with acceptable mortality, it will not necessarily reduce the proportion of neonates requiring a shunt to improve pulmonary blood flow [31].

Semilunar valve stenosis

Natural history outcomes

The natural postnatal history of ductal-dependent critical AoS, critical PS or PAIVS is neonatal death, unless immediate postnatal treatment is available to maintain systemic or pulmonary blood flow, respectively, until valve obstruction is relieved. Progression of AoS to HLHS is reported to occur between 12 and 16 weeks of gestation [26], while progressive involution of the right ventricle occurs in PAIVS [3,31,33]. The right ventricle is composed of three morphological segments: the inlet – the tricuspid valve, the trabecular portion – the ventricular cavity, and the outlet portion – the infundibulum and pulmonary valve. Hearts with only one developed part of the three segments (unipartite) and most with two developed segments (bipartite) will go along a postnatal single ventricle surgical pathway. Foetal Z-scores and composite scores for the right heart have been used to predict eventual circulation [34,35].

Valve stenosis or atresia is managed by balloon valvuloplasty in the newborn period [36,37] if a biventricular circulation is thought possible, otherwise by univentricular palliation using the Fontan or Norwood surgical pathway for right and left heart obstructions, respectively. Cardiac outcomes diagnosed prenatally tend to be worse than those with a postnatal diagnosis, particularly in univentricular circulation; the overall survival for HLHS following prenatal diagnosis followed through to 5 years was 46.9% (23/49) compared with overall 70% survival in the current era [38,39]. In a more recent multinational study reporting the natural history of 80 foetuses diagnosed with AoS and treated in the neonatal period, 52% had a biventricular outcome with a significantly better median 6-year survival advantage (75% vs 54%) than those following a univentricular surgical pathway [40]. A retrospective multinational PAIVS study reported that approximately one-third of children have an eventual two-ventricle repair, with a 5-year survival rate of 68% [41].

Critical AoS: evidence of benefit following foetal valvuloplasty

Foetal valvuloplasty for critical AoS has been practised anew for almost two decades [18–23,30,42], but evidence of its efficacy over natural history outcomes has only recently been reported using suitable controls [30,40]. In a multicentre study, two foetal cohorts, one undergoing foetal valvuloplasty, were matched using propensity scoring, and approximately one-third of each cohort had a biventricular outcome out to 8 years. Considering survivors of the foetal intervention only, a biventricular circulation conferred survival advantage.

The potential of foetal valvuloplasty to improve cardiac growth was overestimated initially, and foetuses with damaged ventricles were included in early treatment groups and developed HLHS despite successful foetal valvuloplasty or had unsuccessful postnatal attempts to achieve a biventricular outcome [8,42]. This has led to a change in selection criteria for valvuloplasty, and most select only foetuses where Doppler ultrasound suggests the foetal heart is likely to progress to HLHS, yet the anatomy and physiology are favourable for a biventricular circulation following successful foetal valvuloplasty [18,19]. Echocardiographic prediction of myocardial mineralisation or endocardial fibroelastosis (EFE) was thought unreliable in the past, but its sonographic features may be better identified in the modern era. Mineralisation increases the risk for tamponade following cardiac puncture, as the myocardium cannot close around the puncture site; therefore, should such cases be avoided? Successful valvuloplasty may allow improved diastolic function and better ventricular filling and promote normal division of myocardial cells during the remainder of pregnancy, thus increasing the proportion of healthy myocardial cells in the myocardium. This may improve outcomes for both biventricular and univentricular surgical pathways after birth. Currently, the earliest gestation foetus reported to undergo foetal cardiac intervention has been at 20 weeks, and some attribute poor foetal survival to procedures performed at earlier gestational ages [20].

In the absence of a randomised trial, the quality of information remains insufficient to create robust prospective criteria. Two recent reports compared the predictive ability of the 2009 criteria [19] for eventual circulation in a hypothetical situation where no foetal intervention was performed. One

retrospective single-centre historical series of 10 foetuses with a reported circulatory outcome found them predictive [43], while the larger cohort of 80 foetuses did not [30].

Haemodynamic improvement following foetal aortic valvuloplasty

Foetal aortic valvuloplasty improves left ventricular haemodynamics [30]. Tissue Doppler studies conducted before and immediately after foetal valvuloplasty correlated with circulatory outcomes in a cohort of 23 liveborn foetuses [44]. Improved left ventricular filling pressure was a good predictor of a future biventricular circulation, as was a reduction in the Tei index in this cohort. These results were not confirmed by others in a smaller series, but they reported that a more spherical LV was associated with worse diastolic function and was more likely to have EFE and less likely to achieve biventricular outcome [45]. Longer term evidence is still lacking whether foetal improvements will predict normal diastolic function in childhood. Persistent pulmonary hypertension, in part secondary to left ventricular damage such as EFE, leads to significant long-term morbidity and childhood mortality and may not be improved by foetal valvuloplasty [7].

Ventricular and valvular growth

Successful valvuloplasty for foetal AoS fails to promote significant growth of the mitral valve or left ventricle [18,19]. This is not surprising, as the disease process may involve all left-sided cardiac structures including EFE and pulmonary hypertension. This extensive pathology reduces the likelihood of a biventricular outcome in spite of a technically successful foetal procedure and extensive postnatal surgery [8,30,42].

Critical pulmonary stenosis and pulmonary atresia with intact ventricular septum: evidence of benefit following foetal valvuloplasty

The response of two foetal hearts with a bipartite right ventricular anatomy to foetal valvuloplasty in the mid-second trimester was described in 2002 [3]. Since then, only two small series and case reports have been published [4,31,33]. Tulzer and colleagues reported good technical success and improved foetal function post valvuloplasty correlating with an increased likelihood of a biventricular circulation compared with historical natural history reports [31], but there is insufficient power to assess its value, and others report verbally poor technical success and high mortality associated with foetal valvuloplasty.

Haemodynamic improvement following foetal pulmonary valvuloplasty

Pulmonary valvuloplasty decompresses the right ventricle and leads to a change in Doppler assessment of tricuspid regurgitation [3,31].The duration of regurgitation is reduced, thereby increasing ventricular filling time, and reduced velocity indicates lowering of right ventricular pressures, and although it is temporary in some foetuses, it may improve the circulation and hydrops, thus allowing for increased maturity at delivery and improved perinatal survival.

Ventricular and valvular growth

In PAIVS or critical PS, growth of the tricuspid valve and right ventricle in foetuses may be better when there is tricuspid regurgitation and a high right atrial pressure score [34]. Following successful foetal valvuloplasty, relief of the pulmonary valve obstruction leads to a better appreciation of the anatomy and size of the tricuspid valve and right ventricle because of reduced afterload and better ventricular filling. The preprocedural measurements are likely to be underestimated, and therefore, a good initial 'response' to foetal valvuloplasty is often identified. However, despite improved flow through the valves, growth velocities in the right heart are low compared with those in normal foetuses [31].

Right ventricular to coronary artery fistulae

Procedures are not usually offered in PAIVS with coronary fistulae. Right ventricular to coronary artery fistulae are detected by colour Doppler in up to a third of foetuses with PAIVS and in

approximately 46% investigated by catheter in postnatal series [41]. Coronary fistulae connect the coronary arterial system to a hypoplastic high-pressure (usually right) ventricle in PAIVS. After birth, if the semilunar (usually pulmonary) valve is opened, the right ventricular pressure falls, resulting in coronary artery steal with myocardial ischaemia and infarction. Prenatally, high-pressure retrograde flow in the coronary system may lead to stenosis and atresia of the coronary arteries, thereby resulting in fatal neonatal myocardial infarction [28]. The majority of large fistulous communications occur in unipartite right ventricles, unlikely to result in a biventricular circulation and hence would not be considered for a foetal intervention. However, some fistulae are small, or more rarely, the right ventricle is of a reasonable length, and hence, their impact on the postnatal choice of circulation is uncertain until postnatal angiography can be performed. As these babies are at increased risk of neonatal death, an argument could be made for foetal intervention, with the rationale being that early decompression of the ventricle may allow regression of the fistulae and improve survival. Moreover, as foetal ventricular pressures are almost equal, opening the right ventricular outflow tract will not result in coronary steal and is a relatively safe procedure [28].

Restriction of the interatrial septum

Patency of the foramen ovale is essential to allow unrestricted flow returning from the placenta to fill the foetal left ventricle. Approximately 10%–12% of HLHS and AoS show thickening and/or closure of the interatrial septum. Some affected foetuses develop hydrops with subsequent intrauterine death [2,7]. Closure of the atrial septum is associated with pulmonary venous Doppler abnormalities, which may indicate irreversible pulmonary damage such as lymphangiectasis and pulmonary venous hypertension, leading to pulmonary haemorrhage and neonatal death. It is difficult for affected neonates to resuscitate after delivery; they often do not reach a cardiac centre and, therefore, are not documented in surgical registries. Surgical outcomes are poor, as it may not be possible for babies to be weaned from cardiopulmonary bypass [2].

Evidence of benefit of interatrial septostomy and stenting

Successful opening of a restrictive atrial septum normalises pulmonary venous waveforms and may indicate better left atrial filling and a normalisation of wall stresses in the pulmonary veins. Theoretically, this may reduce the risk of developing pulmonary lymphangiectasia and optimise perinatal lung function. However, the relationship between the duration of Doppler abnormality and irreversible pulmonary damage remains poorly understood. The thickened atrial septum is difficult to perforate using a high-pressure balloon alone. Several groups have stented the foramen ovale following its dilation with varying degrees of short-term success [5,20]. The procedure is technically difficult with the risk of tamponade following perforation of the small, relatively thin-walled atrium. Research in animal models has not improved procedural success in the human foetus to date [20]. In the absence of a safe and successful foetal intervention, clinical options include repeating the foetal intervention or early delivery with immediate surgical atrial septectomy.

Isolated complete heart block

Isolated CAVB develops in approximately 2% of foetuses of anti-Ro-positive pregnancies, where only a proportion of mothers have symptoms of connective tissue disease. It is rare, and as these foetuses have normally connected hearts, we refer to this as isolated CAVB. Foetuses born at term generally do well initially. In one large observational study, approximately 90% of foetuses with isolated complete heart block survived, with most born at term, but at least 70% were paced by three months [46]. CAVB is associated with significant myocardial disease and severe cardiac dysfunction with the development of hydrops (usually in those with foetal heart rates below 55 beats per minute), leading to foetal demise in approximately 9% [46]. Evidence is poor that foetuses presenting with CAVB will benefit from transplacental medical therapy [46,47], although administration of steroids has been proposed as beneficial

in preventing later cardiomyopathy [48]. More recently, early administration of steroids has again been proposed to prevent the development of established CAVB [49].

Evidence for benefit of foetal cardiac pacing

Cardiac pacing was attempted first in 1986 in a human foetus to prevent in utero demise but has not been a successful therapy to date [13–15]. However, a miniaturised pacemaker that can be implanted percutaneously was recently developed, and it has shown proof of principle in animals [50]. This may be a suitable therapy for hydropic human foetuses with CAVB before 34 weeks, but after this gestation, delivery and pacing may be easier.

Chronic maternal hyperoxygenation

Maternal hyperoxygenation (MH) is an established test of the responsiveness of the pulmonary bed in foetuses with restrictive or closed inter-atrial septum, where a single-ventricle surgical pathway is anticipated [51,52]. In this test, 100% oxygen is administered to the mother for 15 min and Doppler changes in foetal pulmonary blood flow measured. More recently, CMH has been offered with the objective of increasing pulmonary venous return to the left side of the heart in responders, thus promoting its growth [10,11]. CMH involves chronic administration of 100% oxygen to mothers for several hours a day over several weeks from approximately 30 gestational weeks. Oxygen therapy has also been proposed to improve brain growth in foetuses with congenital heart defects and perhaps for better neurological outcomes [53].

Evidence for benefit of CMH

CMH is reported to result in improved growth of left-sided cardiac structures. However, small series reports have shown unconvincing incremental cardiac growth and no convincing improvements in outcome when applied to small heterogeneous cohorts, without control data [10,54]. More recently, cardiovascular growth and functional outcomes have been reported from a controlled study of foetuses enrolled because of suspicion of coarctation and treated with either CMH or maternal air administration (sham treatment) and compared with a second control cohort of normal foetuses [11,12]. These studies report that improved growth of cardiac structures and improved myocardial deformation indices occur in treated foetuses compared with those treated with air, and fewer foetuses required postnatal surgery after CMH. These are promising preliminary results, but randomisation methods are unclear, and within CMH, a sub-group did not respond. Diagnostic precision of foetal CoA is poor, and it is possible that foetuses without CoA were included in this study and good outcomes from CMH assumed. Thus, its incorporation into clinical practice should be cautious and its future role determined by a large well-designed RCT. No adverse events were documented in this study, but oxygen is a powerful therapy, and there are concerns about its safety, as reduced head growth has been reported at six months in babies treated with CMH [55].

Controversies

1 Regulation (Benchmarking)

When a new therapy is proposed, investigators benchmark it against a gold standard, or current, practice in the form of an RCT. This approach has not been adopted for foetal cardiac procedures. One reason offered has been the rarity of suitable cases of foetal semilunar valve stenosis or atresia, interatrial restriction or isolated complete heart block. Therefore, procedures have been offered in an unregulated manner by many low-volume centres worldwide with little or no progress in defining

who might benefit from the procedure and higher mortality at foetal intervention in some centres than following current postnatal surgery [21–23,25].

2 Technical Developments

The current method remains the original percutaneous Seldinger approach: directing a needle into the foetal heart and passing an 'over a wire' coronary catheter through a flexible introducer under ultrasound guidance and maternal general or local anaesthesia. Alternative approaches to the percutaneous route have been investigated in animal models, which are more invasive and lengthy and have not been adopted in the treatment of human foetuses [20,56].

Ultrasound imaging may be limited once equipment has been introduced into the uterus, and transesophageal imaging produces spectacular ultrasound images in animals and in one reported human foetus undergoing intervention for a restrictive or intact atrial septum [57]. However, as it is more invasive and requires a fetoscopic approach, it may increase the risk of miscarriage and there is potential for rupture of the foetal oesophagus.

3 Assessment of Benefit

Although more is known about the natural history of foetal AoS in the current era, uncertainties remain with regard to case selection, timing and benefit of foetal valvuloplasty [30,42]. Unlike neonatal surgery, where evidence supports that earlier repair improves the chances of ventricular and vascular remodelling [9], most foetal procedures are palliative and neonatal surgery will be required. Therefore, the contribution of the foetal procedure to eventual postnatal outcome in individual cases remains unknown. Moreover, there is concern that foetal interventions are currently offered to those who will not benefit from them, whether it is because foetal disease appears mild or the ventricle is already too damaged. Efficacy cannot be assessed until childhood, as an initial biventricular outcome may become univentricular, and vice versa, particularly in PAIVS. Paradoxically, foetal therapy may result in poorer overall outcomes in surgical series that follow more aggressive approaches for borderline hearts because institutional expectations are for a biventricular circulation [8,42]. Conversely, others adopt a conservative approach performing Norwood in newborns with AoS and a well-developed left heart [24]. Survival and circulatory outcomes are relatively easy to document, but a formal assessment of quality of survival and neurodevelopmental outcomes is rarely reported. This information is essential to increase knowledge of the tolerance limits of the human foetal brain and guide future therapeutic endeavours.

Summary

Foetal therapy is offered for a variety of disorders diagnosed before birth; guided by the hypothesis, it will improve outcomes compared with natural history and postnatal therapy alone. Although a few have been introduced following RCTs, others including foetal cardiac therapy have entered the clinical arena in a more piecemeal fashion. Although cardiac malformations are common with major lesions affecting approximately 3.5 per thousand pregnancies, only approximately 5% of foetuses with major CHD are likely to benefit from an intrauterine intervention, resulting in too many practitioners with too little experience chasing rare cases for intervention. As a result, the overall role of foetal cardiac intervention remains uncertain almost two decades after its re-introduction in 2000. To assess the benefits or adverse effects of foetal cardiac interventions, it is necessary to have linked prenatal and postnatal data with long-term outcomes, including neurodevelopmental assessment and later changes in circulatory type out to school years. This re-emerging field deserves a more rigorous scientific approach by the leaders in foetal cardiac therapy to ensure it has a place in future clinical practice.

Conflicts of interest

The author has no conflicts of interest.

Practice points

- Foetal AoS often includes secondary damage of the ventricle, its inlet valve, myocardium, and aortic arch.
- Low prenatal detection of AoS limits our ability to assess the potential for foetal valvuloplasty to alter outcomes.
- Case selection, timing of foetal cardiac therapy and a streamlined postnatal program are pivotal to outcomes.

Research agenda

- Improved power is required to assess treatment benefits.
- The role of CMH requires more study to ensure maternal and foetal safety and determine its efficacy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bpobgyn.2019.01.007.

References

[1] Maxwell D, Allan L, Tynan MJ. Balloon dilatation of the aortic valve in the fetus: a report of two cases. Br Heart J 1991;65:256–8.
[2] Rychik J, Rome JJ, Collins MH, DeCampli WM, Spray TL. The hypoplastic left heart syndrome with intact atrial septum: atrial morphology, pulmonary vascular histopathology and outcome. J Am Coll Cardiol 1999;34:554–60.
[3] Tulzer G, Arzt W, Franklin RC, Loughna PV, Mair R, Gardiner HM. Pulmonary valvuloplasty for critical pulmonary stenosis or atresia with intact septum. Lancet 2002;360:1567–8.
[4] Tworetzky W, McElhinney DB, Marx GR, Benson CB, Brusseau R, Morash D, et al. In utero valvuloplasty for pulmonary atresia with hypoplastic right ventricle: techniques and outcomes. Pediatrics 2009;124:e510–8.
*[5] Marshall AC, van der Velde ME, Tworetzky W, Gomez CA, Wilkins-Haug L, Benson CB, et al. Creation of an atrial septal defect *in utero* for fetuses with hypoplastic left heart syndrome and intact or highly restrictive atrial septum. Circulation 2004;110:253–8.
[6] Delius RE, Rademecker MA, de Leval MR, Elliott MJ, Stark J. Is a high-risk biventricular repair always preferable to conversion to a single ventricle repair? J Thorac Cardiovasc Surg 1996;112:1561–8. Discussion 1568–1569.
[7] Burch M, Kaufman L, Archer N, Sullivan I. Persistent pulmonary hypertension late after neonatal aortic valvotomy: a consequence of an expanded surgical cohort. Heart 2004;90:918–20.
[8] Emani SM, Bacha EA, McElhinney DB, Marx GR, Tworetzky W, Pigula FA, et al. Primary left ventricular rehabilitation is effective in maintaining two-ventricle physiology in the borderline left heart. J Thorac Cardiovasc Surg 2009 Dec;138(6):1276–82.
[9] Di Donato RM, Jonas RA, Lang P, Rome JJ, Mayer Jr JE, Castaneda AR. Neonatal repair of tetralogy of Fallot with and without pulmonary atresia. J Thorac Cardiovasc Surg 1991;101:126–37.
[10] Kohl T. Chronic intermittent materno-fetal hyperoxygenation in late gestation may improve on hypoplastic cardiovascular structures associated with cardiac malformations in human fetuses. Pediatr Cardiol 2010;31:250–63.
[11] Zeng S, Zhou J, Peng Q, Deng W, Zhang M, Zhao Y, et al. Sustained maternal hyperoxygenation improves aortic arch dimensions in fetuses with coarctation. Sci Rep 2016;6:39304.
[12] Zeng S, Zhou J, Peng Q, Deng W, Zang M, Wang T, et al. Sustained chronic maternal hyperoxygenation increases myocardial deformation in fetuses with a small aortic isthmus at risk for coarctation. JASE 2017;10(30):992–1000.

[13] Carpenter RJ, Strasburger JF, Garson A, Smith RT, Deter RL, Engelhardt Jr HT. Fetal ventricular pacing for hydrops secondary to complete atrioventricular block. J Am Coll Cardiol 1986;8:1434–6.
[14] Walkinshaw SA, Welch CR, McCormack J, Walsh K. In utero pacing for fetal congenital heart block. Fetal Diagn Ther 1994;9:183–5.
[15] Assad RS, Zielinsky P, Kalil R, Lima G, Aramayo A, Santos A, et al. New lead for in utero pacing for fetal congenital heart block. J Thorac Cardiovasc Surg 2003;126:300–2.
[16] Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med 2004;351:136–44.
[17] Adzick NS, Thom EA, Spong CY, Brock 3rd JW, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011 Mar 17;364(11):993–1004. https://doi.org/10.1056/NEJMoa1014379.
*[18] Arzt W, Wertaschnigg D, Veit I, Klement F, Gitter R, Tulzer G. Intrauterine aortic valvuloplasty in fetuses with critical aortic stenosis: experience and results of 24 procedures. Ultrasound Obstet Gynecol 2011;37:689–95.
*[19] McElhinney DB, Marshall AC, Wilkins-Haug LE, Brown DW, Benson CB, Silva V, et al. Predictors of technical success and postnatal biventricular outcome after *in utero* aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation 2009;120:1482–90.
[20] Jaeggi E, Renaud C, Ryan G, Chaturvedi R. Intrauterine therapy for structural congenital heart disease: contemporary results and Canadian experience. Trends Cardiovasc Med 2016;26:639–46.
[21] Pedra SR, Peralta CF, Crema L, Jatene IB, da Costa RN, Pedra CA. Fetal interventions for congenital heart disease in Brazil. Pediatr Cardiol 2014;35:399–405.
[22] Galindo A, Gómez-Montes E, Gómez O, Bennasar M, Crispi F, Herraiz I, et al. Fetal aortic valvuloplasty: experience and results of two tertiary centers in Spain. Fetal Diagn Ther 2017;42(4):262–70. https://doi.org/10.1159/000460247. Epub 2017 Apr 7.
[23] Moon-Grady AJ, Morris SA, Belfort M, Chmait R, Dangel J, Devlieger R, et al. International fetal cardiac intervention registry: a worldwide collaborative description and preliminary outcomes. J Am Coll Cardiol 2015 Jul 28;66(4):388–99. https://doi.org/10.1016/j.jacc.2015.05.037.
[24] Kovacevic A, Roughton M, Mellander M, Öhman A, Tulzer G, Dangel J, et al. Fetal aortic valvuloplasty: investigating institutional bias in surgical decision-making. Ultrasound Obstet Gynecol 2014 Nov;44(5):538–44. https://doi.org/10.1002/uog.13447. Epub 2014 Oct 13.
[25] National Institute for Cardiovascular Outcomes Research: National Congenital Heart Disease Audit Website (NICOR-Congenital), https://nicor4.nicor.org.uk/ [last accessed 11/02/2019].
[26] Axt-Fliedner R, Kreiselmaier P, Schwarze A, Krapp M, Gembruch U. Development of hypoplastic left heart syndrome after diagnosis of aortic stenosis in the first trimester by early echocardiography. Ultrasound Obstet Gynecol 2006;28:106–9.
[27] Freud LR, Moon-Grady A, Escobar-Diaz MC, Gotteiner NL, Young LT, McElhinney DB, et al. Low rate of prenatal diagnosis among neonates with critical aortic stenosis: insight into the natural history in utero. Ultrasound Obstet Gynecol 2015 Mar;45(3):326–32. https://doi.org/10.1002/uog.14667. Epub 2015 Jan 28.
[28] Matsui H, Gardiner HM. Fetal intervention for cardiac disease: the cutting edge of perinatal care. Semin Fetal Neonatal Med 2007;12:482–9.
*[29] Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 2014 May 27;129(21):2183–242. https://doi.org/10.1161/01.cir.0000437597.44550.5d. Epub 2014 Apr 24.
*[30] Kovacevic A, Öhman A, Tulzer G, Herberg U, Dangel J, Carvalho JS, et al. Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. Ultrasound Obstet Gynecol 2017 Oct 4. https://doi.org/10.1002/uog.18913 [Epub ahead of print].
*[31] Tulzer A, Arzt W, Gitter R, Prandstetter C, Grohmann E, Mair R, et al. Immediate effects and outcomes after in-utero pulmonary valvuloplasty in fetuses with pulmonary atresia with intact septum or critical pulmonary stenosis. Ultrasound Obstet Gynecol 2018;52(2):230–7.
[32] Tworetzky W, Wilkins-Haug L, Jennings RW, van der Velde ME, Marshall AC, Marx GR, et al. Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome: candidate selection, technique, and results of successful intervention. Circulation 2004;110:2125–31.
[33] Galindo A, Gutierrez-Larraya F, Velasco JM, de la Fuente P. Pulmonary balloon valvuloplasty in a fetus with critical pulmonary stenosis/atresia with intact ventricular septum and heart failure. Fetal Diagn Ther 2006;21:100–4.
[34] Gardiner HM, Belmar C, Tulzer G, Barlow A, Pasquini L, Carvalho JS, et al. Morphological and functional predictors of eventual circulation in the fetus with pulmonary atresia or critical pulmonary stenosis with intact septum. J Am Coll Cardiol 2008;51:1299–308.
[35] Roman KS, Fouron JC, Nii M, Smallhorn JF, Chaturvedi R, Jaeggi ET. Determinants of outcome in fetal pulmonary valve stenosis or atresia with intact ventricular septum. Am J Cardiol 2007;99:699–703.
[36] McElhinney DB, Lock JE, Keane JF, Moran AM, Colan SD. Left heart growth, function, and reintervention after balloon aortic valvuloplasty for neonatal aortic stenosis. Circulation 2005;111:451–8.
[37] Ashburn DA, McCrindle BW, Tchervebkov CI, Jacobs ML, Lofland GK, Bove EL, et al. Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia. J Thorac Cardiovasc Surg 2003;125:1070–82.
[38] Rasiah SV, Ewer AK, Miller P, Wright JG, Barron DJ, Brawn WJ, et al. Antenatal perspective of hypoplastic left heart syndrome: 5 years on. Arch Dis Child Fetal Neonatal Ed 2008;93:F192–7. Epub 2007 June 29.
[39] Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI, et al. Variation in outcomes for benchmark operations: an analysis of the society of thoracic Surgeons congenital heart surgery database. Ann Thorac Surg 2011;92:2184–91. https://doi.org/10.1016/j.athoracsur.2011.06.008. Discussion 2191–2192.
*[40] Gardiner HM, Kovacevic A, Tulzer G, Sarkola T, Herberg U, Dangel J, et al. Natural history of 107 cases of fetal aortic stenosis from a European multicenter retrospective study. Ultrasound Obstet Gynecol 2016 Sep;48(3):373–81. https://doi.org/10.1002/uog.15876. Epub 2016 Aug 4.

[41] Daubeney PE, Wang D, Delany DJ, Keeton BR, Anderson RH, Slavik Z, et al. UK and Ireland collaborative study of pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 2005;130:1071. e1–e9.
*[42] Freud LR, McElhinney DB, Marshall AC, Marx GR, Friedman KG, del Nido PJ, et al. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation 2014;130:638–45.
[43] Hunter LE, Chubb H, Miller O, Sharland G, Simpson JM. Fetal Aortic Valve Stenosis: a critique of case selection criteria for fetal intervention. Prenat Diagn 2015 Dec;35(12):1176–81.
[44] Wohlmuth C, Wertaschnigg D, Wieser I, Arzt W, Tulzer G. Tissue Doppler imaging in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after fetal aortic valvuloplasty. Ultrasound Obstet Gynecol 2016; 47(5):608–15.
[45] Friedman KG, Schidlow D, Freud L, Escobar-Diaz M, Tworetzky W. Left ventricular diastolic function and characteristics in fetal aortic stenosis. Am J Cardiol 2014 Jul 1;114(1):122–7. https://doi.org/10.1016/j.amjcard.2014.04.013. Epub 2014 Apr 18.
*[46] Eliasson H, Sonesson SE, Sharland G, Granath F, Simpson JM, Carvalho JS, et al. Fetal Working Group of the European Association of Pediatric Cardiology. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation 2011;124:1919–26.
[47] Lopes LM, Tavares GM, Damiano AP, Lopes MA, Aiello VD, Schultz R, et al. Perinatal outcome of fetal atrioventricular block: one-hundred-sixteen cases from a single institution. Circulation 2008;118:1268–75.
[48] Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK. Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 2004;110: 1542–8.
[49] Sonesson S-E, Ambrosi A, Wahren-Herlenius M. Benefits of fetal echocardiographic surveillance in pregnancies at risk of congential heart block: a single center study of 212 anti-Ro 52 positive pregnancies. Ultrasound obstet gynecol 2019 [Epub details pending].
[50] Bar-Cohen Y, Loeb GE, Pruetz JD, Silka MJ, Guerra C, Vest AN, et al. Preclinical testing and optimization of a novel fetal micropacemaker. Heart Rhythm 2015 Jul;12(7):1683–90. https://doi.org/10.1016/j.hrthm.2015.03.022. Epub 2015 Mar 14.
[51] Szwast A, Tian Z, McCann M, Donaghue D, Rychik J. Vasoreactive response to maternal hyperoxygenation in the fetus with hypoplastic left heart syndrome. Circ Cardiovasc Imaging 2010;3:172–8.
[52] Schidlow DN, Donofrio MT. Prenatal maternal hyperoxygenation testing and implications for critical care delivery planning among fetuses with congenital heart disease: early experience. Am J Perinatol 2018 Jan;35(1):16–23. https://doi.org/10.1055/s-0037-1603991. Epub 2017 Jul 26.
*[53] Sun L, Macgowan CK, Sled JG, Yoo SJ, Manlhiot C, Porayette P, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. Circulation 2015 Apr 14;131(15):1313–23. https://doi.org/10.1161/CIRCULATIONAHA.114.013051.
[54] Lara DA, Morris SA, Maskatia SA, Challman M, Nguyen M, Feagin DK, et al. Pilot study of chronic maternal hyperoxygenation and effect on aortic and mitral valve annular dimensions in fetuses with left heart hypoplasia. Ultrasound Obstet Gynecol 2016 Sep;48(3):365–72. https://doi.org/10.1002/uog.15846.
[55] Edwards LA, Lara DA, Sanz Cortes M, Hunter JV, Andreas S, Nguyen MJ, et al. Chronic maternal hyperoxygenation and effect on cerebral and placental vasoregulation and neurodevelopment in fetuses with left heart hypoplasia. Fetal Diagn Ther 2018 Sep 17:1–13. https://doi.org/10.1159/000489123.
[56] Jouannic JM, Boudjemline Y, Benifla JL, Bonnet D. Transhepatic ultrasound-guided cardiac catheterization in the fetal lamb. Circulation 2005;111:736–41.
[57] Kohl T, Muller A, Tchatcheva K, Achenbach S, Gembruch U. Fetal transesophageal echocardiography: clinical introduction as a monitoring tool during cardiac intervention in a human fetus. Ultrasound Obstet Gynecol 2005;26:780–5.