REVIEW

Fetal cardiac interventions: Myths and facts

Cathétérisme fœtal : mythes et faits

Isabelle Van Aerschot\textsuperscript{a}, Jonathan Rosenblatt\textsuperscript{b}, Younès Boudjemline\textsuperscript{a,*,c}

\textsuperscript{a} Centre de référence malformations cardiaques congénitales complexes – M3C, hôpital Necker–Enfants-Malades, cardiologie pédiatrique, assistance publique des hôpitaux de Paris, 149, rue de Sèvres, 75015 Paris cedex, France
\textsuperscript{b} Service de gynécologie-obstétrique et centre pluridisciplinaire de diagnostic prénatal de l’Est-Parisien, hôpital Armand-Trousseau, AP–HP, Paris, France
\textsuperscript{c} Université Paris-Descartes, Sorbonne Paris-Cité, Paris, France

Received 23 December 2011; received in revised form 20 January 2012; accepted 22 January 2012
Available online 19 June 2012

KEYWORDS
Aortic stenosis; Foetal cardiology; Hypoplastic left heart syndrome; Interventions; Pulmonary atresia

Summary  An early, primary, in utero cardiac abnormality may prevent normal heart development and cause irreversible secondary structural changes. The idea of foetal cardiac intervention stems from this understanding and focuses on antenatal intervention targeting the primary abnormality to allow normal flow and haemodynamics and thus normal heart development. Crucial aspects of foetal vascular access, varying foetal lie and structural complexity make it very hard to set procedural standards. The procedures are complex and are associated with significant maternal and foetal morbidity and mortality. The high risk-benefit ratio clearly explains the investigational nature of such therapies. With the development of minimally invasive techniques and continued animal experiments, foetal interventional therapy may see a low rate of morbidity and mortality, improving the prognosis of newborns with congenital heart disease previously considered incurable.

© 2012 Published by Elsevier Masson SAS.


Abbreviations: AoS, aortic stenosis; CHD, congenital heart disease; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; PAIVS, pulmonary atresia with intact ventricular septum; PS, pulmonary stenosis.
* Corresponding author. Fax: +33 1 44 49 57 24.
E-mail address: younes.boudjemline@nck.aphp.fr (Y. Boudjemline).

1875-2136/– see front matter © 2012 Published by Elsevier Masson SAS.
Introduction

Percutaneous, invasive, per utero, foetal therapies have been developed to correct and prevent progression of pathologies diagnosed in utero (such as spina bifida, diaphragmatic hernia, etc.). Such techniques are, however, quite challenging to apply in clinical practice. The same applies to the art and science of foetal cardiac interventions [1]. Congenital heart disease (CHD) is the most common inborn defect, occurring in about 19/1000 live births [2]. Advancements in imaging technology over the past couple of decades, with the development of high-frequency, high-resolution probes, have made accurate diagnosis of most CHDs possible during foetal life. Colour flow and echocardiography-based haemodynamic foetal cardiac assessment in pregnancy allows a better understanding of the pathophysiology of even complex CHDs [3]. Currently, the diagnosis of CHD is possible only at the end of the first trimester of pregnancy [4]. Such scans are crucial for foetuses at risk of CHD due to a strong family history, maternal exposure to toxic drugs or chemicals, specific maternal conditions and nuchal translucency above the 99th percentile [5]. The diagnosis of CHD at an early stage of pregnancy allows enough time for a team approach, with prenatal and genetic counselling by the expert paediatric cardiologist, discussion of the optimal management plan, delivery and postnatal care, and planning for future pregnancies. For example, once diagnosed, duct-dependent CHD should be referred to a maternity hospital with the appropriate neonatal intensive cardiac support to reduce perinatal morbidity and mortality [6]. For conditions with no possibility of biventricular repair, the expectant parents may choose between postnatal palliative management (such as the Norwood procedure for hypoplastic left heart syndrome [HLHS]) or for interruption of pregnancy. The latter option is chosen by most young couples in our country nowadays. Factors like these and our insufficient knowledge of the underlying mechanisms have resulted in slow progress in developing effective intrauterine therapies for the management of CHD.

In utero natural history and therapeutic perspectives

The impact and outcomes of invasive, per utero, foetal therapies are still debated and there are differing opinions among the various experts [1]. It is hard to predict the natural history and intrauterine course of events. There is a school of thought that the natural history of CHD worsens over time and that it is best to perform corrective surgery as early as possible (previously performed in childhood and now carried out in the neonatal period or infancy) [7]. Others believe that the outcome of CHD is definitively defined from an anatomical point of view at the second trimester in most cases and that foetal intervention would not alter the natural history, except in case of foetal hydrops. The first school of thought is based on the flow-driven mechanistic approach that might help the understanding of the pathophysiology of some severe heart diseases. With this understanding, it is believed that myocardial chamber growth is related to the increasing blood flow into the cavities. Thus, with in utero alteration of haemodynamics and blood flow — and the resultant morphological and functional changes — CHD may progress and may be worse at birth than originally predicted. Valvular stenosis may result in poor chamber development by reducing the blood flow. Thus, aortic valve stenosis may be the root cause and instigating defect leading to HLHS, small or virtual left ventricle, mitral atresia and aortic arch abnormalities. Once the crucial phase of chamber development is reached, it becomes irreversible, despite correction of stenosis. These findings have inspired the idea of in utero catheter intervention, restoring the flow through the stenotic valve in order to allow the development of the respective chamber and thus leave the option for a biventricular repair after birth. Similar interventions could improve the global prognosis of such heart malformations. The feasibility of an interventional approach is heavily dependent on the access to the foetal vascular compartment and on acceptable maternal and foetal morbidity and mortality.

Access to foetal vascular compartment

Cordocentesis

Ultrasound-guided cordocentesis was first described in 1983 by Daffos et al. [8]. The procedure involves percutaneous access to the foetal vascular compartment to draw foetal blood for cytological, biochemical and cytogenetic studies; it is also used for foetal transfusion in cases of foetal anaemia due to maternofetal alloimmunization. Furthermore, cordonal access allows perfusion of
therapeutic agents to the foetus for sedation analgesia during technical procedures on the foetus, such as setting up a pleuroamniotic drain in the management of hydrothorax or for intracardiac interventions. The risk of foetal loss related to the cordocentesis is estimated at 1–2%. The length of the umbilical cord and its highly tortuous course make progression with a guide both dangerous (due to risk of perforation) and technically impracticable.

Cardiocentesis

Percutaneous, per utero, foetal, transthoracic, direct ventricular access was proposed as an alternative to cordonal access for foetal transfusion in cases of maternofetal rhesus alloimmunization when cordonal access was technically impossible or after failure [9]. Cardiocentesis is performed with local anaesthesia to the maternal skin and direct needle puncture of the foetal chest wall to enter the foetal left ventricle.

Besides technical problems such as difficult access with varying foetal lie and catheter/balloon fragmentation, the rate of foetal loss is estimated at around 5.5–6.5%. Currently, cardiocentesis is seldom or not used in the indication of foetal transfusion. Its current indications are mainly for foetal reduction in dichorionic twin pregnancies if one of the foetuses satisfies the indication for selective termination of pregnancy, such as aneuploidy. This technique is also used for therapeutic acts in utero on foetuses with CHD. It requires experience in percutaneous puncture under ultrasound guidance as well as in foetal echocardiography. The access has to be focused on the area to be treated (e.g. transventricular access in case of valvular lesion). The right ventricle is usually more accessible given its subparietal location. It is essential to precisely locate atrioventricular valves, valve chordae and interventricular septum (containing the bundles of conduction) in order to avoid injury to these structures if the pregnancy is expected to continue.

Foetoscopic access

Kohl et al. first described foetoscopic access in a foetal sheep: with three to four trocars percutaneously placed in the uterus and videofoetoscopic equipment, they achieved a limited thoracotomy to obtain minimally invasive, direct, foetal cardiac access [10]. This approach was tested on 15 foetal sheep for foetal cardiac pacing or antegrade foetal cardiac catheterization. The technique was achieved in 10 foetal sheep (five failures because of bleeding or technical complications); eight were alive at the end of the procedure. Six ewes continued gestation; three non premature lambs (20% of cases) were born. Foetal death occurred in seven cases, maternal death by sepsis in two cases and technical complications, such as bleeding of the puncture site, and technical difficulty in identifying the subxyphoid region were also noted. Foetoscopic access has some advantages compared with maternal hysterectomy but this technique is not done in humans because of the high rate of complications.

To provide alternative approaches for human foetal cardiac interventions, the same team described transumbilical foetal cardiac catheterization in sheep by minimally invasive foetoscopy, guided by foetal transoesophageal echocardiography [11]. The umbilical cord was punctured in 6/6 cases, with the possibility of antegrade catheterization into the foetal heart. However, all foetuses died secondary to dissection, total thrombosis of umbilical vein or blood loss after sheath dislodgment or removal. Interestingly, a suture at the sheath insertion site ensured foetal survival for 1–2 weeks.

The translation of cardiocentesis to a human foetus seems inconceivable at present; its interest lies in the simplicity of ultrasound guidance but its morbidity and mortality rates in animals is close to 100%.

Transhepatic access

The technical deadlock in performing transumbilical foetal cardiac catheterization led to the suggestion of transhepatic access [12]. The aim was to reproduce the conditions of catheterization using Seldinger’s technique as it is done in the postnatal period and to improve foetal tolerance.

The feasibility of antegrade, echocardiography-guided, cardiac catheterization through a transhepatic approach of the intra-abdominal foetal vessels was tested on ten foetal lambs. Access to the subdiaphragmatic portion of the inferior vena cava was performed by ultrasound guidance via a transhepatic approach. A guide was placed into the subhepatic vein and cardiac catheterization was performed according to Seldinger’s technique, allowing the heart chambers to be reached in all cases, with atrial or ventricular pacing in six foetuses and ballooning of the pulmonary valve in nine cases (Fig. 1). Three foetuses died after the procedure and five foetuses were born at term, with an autopsy showing no significant cardiac or peritoneal injury. The simplicity of the procedure, with its shallow learning curve, has successfully lowered complication rates in subsequent studies. In the future, this method could become an alternative to percutaneous transventricular catheterization. The perioperative bleeding risk could be reduced by peritoneal reabsorption of red blood cells. However, variations in foetal positions and hepatic vein diameter add to the challenges; the latter limits this method to the second part of pregnancy when a needle can be safely inserted.

Possible foetal cardiac interventions

In theory, foetal cardiac catheterization can be planned for various types of aortic and pulmonary valve obstructions: pulmonary atresia with intact ventricular septum (PA/IVS) (perforation/ballooning); HLHS with restrictive atrial septal defect (enlargement or creation of an atrial septal defect); antenatal closure of the ductus arteriosus (sten in the ductus arteriosus); rhythm abnormalities such as supraventricular tachycardia or atrioventricular block (electrophysiology study, ablation, in utero pacing [lead]); total aberrant pulmonary venous drainage with collector vein obstruction (sten in the collector vein); and a few other exceptional abnormalities poorly tolerated before birth, such as the aorta-left ventricular tunnel with hydrops (occlusion of the shunt).

Although technically feasible, these invasive interventions still have to be performed only in cases with a low risk-benefit ratio. In other words, the risk of foetal death from the cardiac invasive method must remain lower than the risk of spontaneous foetal death (in utero or early
neonatal death). Thus, the intervention must provide survival of the foetus until the end of pregnancy if there is risk of intratable foetal death, along with improved long-term outcomes by modification of cardiac growth and/or cardiac function.

With the proposed mechanistic theory, each heart chamber grows proportionately to its blood flow during foetal life and each primitive cardiac defect (such as blood flow obstruction) causes secondary heart lesions. So, invasive interventions performed during the foetal development period will aim to remove this primary lesion and allow a better and theoretically sufficient blood flow through the heart cavity, to ensure cardiac myocyte proliferation and heart cavity growth.

The three acceptable indications where foetal intervention therapy may have a positive impact include: balloon aortic valvuloplasty for the prevention of HLHS; balloon pulmonary valvuloplasty for the prevention of hypoplastic right heart syndrome (HRHS); and balloon atrial septostomy to improve outcomes in patients with HLHS and restrictive or intact interatrial communication.

**Prenatal balloon valvuloplasty in aortic valve stenosis**

Stringent criteria are established as an indication for this procedure. Only midtrimester foetuses with a dominant aortic stenosis (AoS) lesion and a potentially salvageable left ventricle must be considered for intervention. The left ventricular length should not be more than two standard deviations below the mean for the gestational age, with severe AoS demonstrated by retrograde flow in the ascending aorta. Kohl et al. collected data on foetal cardiac intervention worldwide and reported that among 14 foetuses, eight of whom had isolated aortic valve stenosis, there was only one long-term survivor [10]. Kohl and Gembruch later pointed out that the poor outcomes were more due to poor results of postnatal treatment than to failure of the intrauterine interventions.

Tworecki et al. first reported a series of 20 cases of in utero balloon valvuloplasty for severe foetal AoS [13]. In this first series, the procedure failed technically in six cases, all of which evolved into HLHS (three newborns, one medical termination of pregnancy and two foetal deaths). In the other 14 cases, a percutaneous left ventricular approach was achieved, with a limited maternal laparotomy for adequate exposure in half of the cases. In each case, a balloon was inflated through the aortic valve stenosis. Foetal death was observed in two cases and six newborns evolved into HLHS. Finally, the procedure was technically successful in three cases, with a functional biventricular heart at birth. These results show that the intervention is technically feasible in three quarters of cases, but raise questions about the identification of foetuses who would benefit from such procedure [14]. A limited maternal laparotomy could be performed to minimize technical constraints but it carries significant risks, particularly infections. Patient selection is difficult because no ultrasonographic variable has yet been identified to accurately predict the effectiveness of the technique [15]. Only some criteria have been described as predictors of the natural course to HLHS [16]. In midgestation foetuses with AoS and normal left ventricular length, reversed flow in the transverse aortic arch and foramen ovale, monophasic mitral inflow and left ventricular dysfunction are predictive of progression to HLHS. Another series published in 2009 by the same team included 70 foetuses [17]. The technical success rate reached 74% with a similar technique. Fifteen children (22%) were born with a functional biventricular heart. The study of biometric and biophysical ultrasonographic criteria (Doppler) failed to reveal reliable variables for predicting the success of the procedure (predictive positive value of 38%).

**Prenatal balloon valvuloplasty in PAIVS and pulmonary stenosis**

Based on the flow theory described earlier in the text, PAIVS and pulmonary stenosis (PS) are two phenotypes of the same disease, one being an extension of the other. Some studies support this hypothesis, showing that about 10% of PS will evolve into pulmonary atresia, but the natural course of these right heart pathologies remains unclear. Taking into consideration the lack of knowledge and invasiveness of the prenatal intervention with the aim of decompressing the right ventricle, the unfavourable forms of pulmonary atresia with HRHS have yet to be defined [18].

Few ultrasonographic data are currently available. Based on retrospective data on foetuses with pulmonary atresia, several authors defined the foetal tricuspid valve size as a predictor of postnatal outcome [19]. If the tricuspid annulus measured less than three standard deviations at any time of pregnancy, the risk of progression to an extreme hypoplastic right ventricle with coronary fistula was important. In addition, a progressively narrowing tricuspid annulus during pregnancy, especially when very small in early gestational age, is another important predictor of hypoplastic right ventricle. The antenatal measure was quite reliable as it correlated closely with the postnatal measure [20]. In summary, foetuses with hypoplasia of the tricuspid valve annulus seem to be good candidates for foetal pulmonary valve dilation, with the hope of improving right heart growth and thereby the prognosis of postnatal management.

This technique has been applied in humans in several small series, with fewer than 30 foetuses altogether [18,21]. The rate of technical success is close to that for aortic valve dilation (around 75–80%). The risk for the foetus (foetal death and preterm birth) is similar but with an increased risk of haemopericardium due to the use of a thicker needle and a bigger balloon. Most cases require additional endovascular valvuloplasty at birth to achieve effective dilatation. It is too early to say whether prenatal dilatation of the pulmonary valve changes the natural history of this heart disease, as the number of patients treated to date is too low.

**HLHS with intact or restrictive atrial septum**

Restrictive atrial septal defect during foetal life leads to severe haemodynamic and anatomical lesions (pulmonary...
Vein wall thickening) because of the chronic, high-level pressure in the left atrium. These lesions are fatal in case of HLHS, as demonstrated by the high neonatal mortality rate (around 85%) despite an early opening of the atrial septum at birth.

Several teams tried to remove the restriction by creation of an atrial septal defect as soon as possible during pregnancy, to prevent the development of lesions encountered after birth. The Boston experience, with a cohort of 21 foetuses, reported poor results: an atrial septal defect was created in 19 foetuses with a restrictive atrial septal defect but postnatal mortality remained higher (58%) than in cases of HLHS without restriction, given that for technical reasons the procedure was feasible only at the beginning of the third quarter of the pregnancy [22]. The rate of early mortality by haemopericardium reaches around 10%, as for aortic valvuloplasty. In the future, with technical advances, better results could be expected with an earlier and more

Figure 1. Still echographic frames showing the various steps of pulmonary balloon dilatation after hepatic vein puncture: (A and B) the catheter is seen entering and advancing in the inferior vena cava; (C) short-axis view showing the catheter across the right ventricle and the pulmonary valve; (D) the balloon is shown inflated in the pulmonary valve area.

Figure 2. Still echographic frames showing the various steps of epicardial stimulation: (A) the needle is shown in contact with the external border of the heart; (B) the pacing lead has been anchored on the atrial wall; M-mode still frames showing heart rate (C) acceleration and (D) deceleration, after pacing has been turned on and off.
aggressive intervention, such as stenting, rather than single dilation to prevent the risk of restenosis.

The way forward

There are several aspects that need significant work to improve the technique and outcomes of foetal interventions. Despite the timing of foetal valvuloplasty during the second quarter of pregnancy, the results are generally disappointing; about 70% of foetuses with successful valvuloplasty evolve to postnatal univentricular-type management. Several points need to be addressed; better understanding of the in utero natural history of CHD for better selection of patients; improvement of the interventional armamentarium and evolution of techniques to facilitate intervention earlier in the natural course for favourable haemodynamic and structural outcomes; and evaluation of long-term outcomes of foetal cardiac interventions (e.g., compare evolution of successfully dilated and biventricular-repaired patients with patients receiving palliative management for an equivalent heart disease). With better imaging techniques and a better understanding of in utero CHD, the number of foetuses requiring such interventional procedures may increase. Foetal cardiac catheterization through a transhepatic access is being well studied in animals and could potentially become a new interventional approach in human foetuses.

Work on foetal epicardial pacing is also ongoing; with a specially designed lead, transcutaneous, echo-guided, foetal acute pacing is feasible in foetal sheep (Fig. 2) [23]. Additional refinement of both the equipment and the operative technique is required before considering permanent pacing in the human foetuses. This technique may prove to be highly valuable in cases of hydrops foetalis secondary to either congenital complete heart block or due to incessant supraventricular tachycardia where there may be the option to pace-terminate. Cordinal puncture for the administration of antiarrhythmic agents can also be an option. In brief, interventional foetal cardiac catheterization shows promise for the treatment of the human foetus.

Conclusion

Understanding the development and progression of structural abnormalities in utero is quite challenging. An early, primary, in utero abnormality may prevent normal heart development and cause irreversible secondary structural changes. The idea of foetal cardiac intervention stems from this understanding and focuses on antenatal intervention to target the primary abnormality, to allow normal flow and thus normal heart development. Access to the foetal heart, however, is the most crucial aspect of this ambitious project. The tremendous variations in the amount of amniotic fluid, foetal lie and structural complexity make it very hard to set standards. Various techniques have been developed in animals to facilitate approaching the foetal vascular compartment. Currently, the percutaneous transventricular approach is most commonly used for interventional foetal cardiac catheterization. Technical improvement and experience of different teams show varying results. These invasive procedures are designed for foetuses with CHD whose postnatal management is deemed palliative. In France, the development of these procedures is poor, as many young couples opt for medical termination of the pregnancy with such pathologies. Moreover, these procedures are complex and associated with significant maternal and foetal morbidity, which clearly explains the high risk-benefit ratio and the investigational nature of such therapies. With the development of minimally invasive techniques and continued animal experiments, foetal interventional therapy may see a low rate of morbidity and mortality, improving the prognosis of newborns with CHD, who were previously considered incurable.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

Acknowledgements

The authors thank Dr. Mehul Patel for his help in editing the paper.

References


