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Fetal cardiac interventions: an update of therapeutic options

Intervenções cardíacas fetais: atualização de opções terapêuticas

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Abstract
Objective: This article aims to present updated therapeutic options for fetal congenital heart diseases.

Methods: Data source for the present study was based on comprehensive literature retrieval on fetal cardiac interventions in terms of indications, technical approaches and clinical outcomes.

Results: About 5% of fetal congenital heart diseases are critical and timely intrauterine intervention may alleviate heart function. Candidates for fetal cardiac interventions are limited. These candidates may include critical aortic valve stenosis with evolving hypoplastic left heart syndrome, pulmonary atresia with an intact ventricular septum and evolving hypoplastic right heart syndrome, and hypoplastic left heart syndrome with an intact or highly restrictive atrial septum as well as fetal heart block. The advocated option are prenatal aortic valvuloplasty, pulmonary valvuloplasty, creation of atrial communication and fetal cardiac pacing.

Conclusion: Fetal cardiac interventions are feasible at midgestation with gradually improved technical success and fetal/postnatal survival due mainly to a well-trained multidisciplinary team, sophisticated equipment and better postnatal care.

Descriptors: Fetal Heart. Heart Defects, Congenital. Prognosis.

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**Abreviations, acronyms & symbols**

| Abbreviation | Description                                |
|--------------|--------------------------------------------|
| AS           | Aortic stenosis                             |
| CHD          | Congenital heart disease                   |
| HLHS         | Hypoplastic left heart syndrome             |
| PA/IVS       | Pulmonary atresia with intact ventricular septum |

**INTRODUCTION**

Cardiac malformations can be a result of intrinsic myocardial disease or a secondary adaptive mechanism of fetal heart during in utero development[1]. Pressure and volume stimuli of blood flow through the fetal heart are important determinants of the development of fetal heart and circulation during the second and third trimesters[1]. In order to reduce perinatal morbidity and mortality, an early diagnosis of the fetal congenital heart disease (CHD) in the parturients who are at an increased risk of CHD is imperative, particularly for those with a family history of CHD[2]. About 5% of prenatally diagnosed CHDs including severe aortic stenosis (AS) (1.6%), pulmonary atresia with intact ventricular septum (PA/IVS) (1.9%) and severe pulmonary valve stenosis (1.5%) can be critical and therefore require intrauterine therapeutic interventions[3]. Early diagnosis of treatable CHDs may improve fetal intervention outcomes[4], allowing ventricular growth and angiogenesis for fetus with semilunar valve stenosis for successful adaptation to extraterine life[5]. Advanced imaging technology and equipment have made an accurate diagnosis of most fetal CHDs possible[6]. Among them, echocardiography is a reliable means for prenatal diagnosis of a wide spectrum of CHDs[7]. At present, diagnosis of CHDs at midgestation (18-24-week gestation) has become feasible in almost all situations[7]. However, minor errors might occur in echocardiographic visualization of a CHD probably due to poor image quality, early (<20 weeks) or late (>34 weeks) gestation, or maternal obesity[7].

Prenatal interventions for structural CHDs are now plausible with high rates of technical success at midpregnancy[8]. Boston experiences have confirmed candidates for fetal cardiac interventions, which are critical AS with evolving hypoplastic left heart syndrome (HLHS), PA/IVS and evolving hypoplastic right heart syndrome, and HLHS with an intact or highly restrictive atrial septum[9]. Moreover, fetuses with hypoplasia of the tricuspid valve anulus seem to be good candidates for pulmonary valve intervention, allowing sufficient right heart growth[6]. Minimal invasiveness (percutaneous access, only one cardiac puncture, and placental avoidance) and free from complications (fetal bradycardia, effusions and thrombus) are regarded as an ideal procedure[10].

**Fetal Cardiac Intervention**

**Intrauterine balloon aortic valvuloplasty**

Severe AS is associated with left ventricular outflow obstruction and may lead to irreversible left ventricular dysfunction secondary to volume overload with right heart failure and hydrops fetalis[11]. It may develop into HLHS prenatally and is associated with poor postnatal survival if left untreated in the uterus[12]. Retrograde flow in the transverse aortic arch, severe left ventricular dysfunction, monophasic and short mitral valve inflow and left-to-right flow across the foramen ovale can be determinants of AS progression into HLHS, in which very few chances of left heart growth and function can be available for a biventricular outcome[13]. Clinical observations also confirmed pre- and postnatal evolution of HLHS were associated with not only prenatal critical AS, but also endocardial fibroelastosis of the left ventricle[14]. By echocardiography, endocardial fibroelastosis is also implicated in post-interventional outcomes and postnatal heart growth[15].

The entry criteria for prenatal intervention for critical AS have been advocated as severe AS or atresia with severe left ventricular dysfunction and the left ventricular length was not <2 SD below the mean for gestational age at diagnosis. The timing of intervention should be on an urgent basis because of the potential for rapid progression into left ventricular growth failure in fetuses[16].

The first intrauterine balloon aortic valvuloplasty was reported in 1989 for the treatment of critical AS in two fetuses[12]. However, one died intrauterine post-intervention and the other died postnatally. The problem encountered during the maneuver was difficulty of needle withdrawal after the access to the fetal heart, which was afterwards resolved by the utilization of a stilette needle. Tworetzky et al.[16] reported successful aortic valvuloplasty, preventing the evolution of HLHS in fetuses with AS in 2004. Of the 20 pregnancies at 21-29-week gestation, technical success rate was 70% and subsequent postnatal biventricular repair rate was 21%. Further observations by echocardiography revealed left heart growth arrest in unsuccessful or declined cases, but ongoing left heart growth in successful cases. Resumed left heart growth leading to a biventricular circulation at birth was observed in three babies[16]. Arzt et al.[17] reported 24 aortic valvuloplasties in 23 fetuses with critical AS at 26 (range, 21-32)-week gestation, both technical success and postnatal biventricular repair rates were 66.7%. Recently, Goldstein et al.[18] introduced a standard 0.014-inch PrimeWire Prestige coronary guidewire for aortic valvuloplasty. With the aid of a micromanometer pressure sensor 3 cm from the tip, it was directed into the left ventricle and across the severely stenotic aortic valve. Immediate aortic pressure drop was seen after the procedure. This technique allows several potential advantages over conventional procedures in continuous monitoring of pressure waveforms, improvement of intraprocedural fetal hemodynamic monitoring and responsiveness to resuscitation.

Intrauterine aortic valvuloplasty for AS is technically feasible. Success depends on a series of predictive factors, including cardiac structural changes (severe endocardial fibroelastosis),
devices available (angle of cannula entry, cannula designs and catheter and wire configurations), fetal positioning, ultrasound imaging, maneuver sophistimations and post-interventional care, etc. In addition, quick maneuvers may minimize the progressive fetal bradycardia. A successful procedure was anyway achieved in 81% at 21-26-week gestation fetuses[19]. The mortality and morbidity of fetal AS were mainly due to technical errors and due to the degree of the hemodynamic effects of the stenosis and left ventricular adaptation, development and function during fetal life[19].

However, fetal aortic valvuloplasty was not a definitive solution for fetal AS. In order to have a biventricular outcome, postnatal interventions are often required, such as repeated aortic valvuloplasty in most cases, temporary left atrial decompression, and frequent surgical interventions, such as coarctation repair, resection of endocardial fibroelastosis, mitral valvuloplasty, etc.[20].

**Intrauterine pulmonary valvuloplasty**

PA/IVS is characterized by complete obstruction to right ventricular outflow tract with varying degrees of right ventricular and tricuspid valve hypoplasia[21]. Intrauterine pulmonary valvuloplasty in fetuses with PA/IVS allows potential growth and functional improvement of the right heart thereby increasing postnatal survival and biventricular repair[22-25]. Prenatal treatment of the lesion may prevent development of non-immune hydrops and intrauterine death[22], however, only limited cases have been reported[26]. Fetal cardiac intervention for PA/IVS is a challenging procedure because of the anatomical features of the right ventricular outflow tract and the difficult access to the pulmonary valve. With advancing gestation, a steady increase of the right ventricle-to-pulmonary artery gradient could lead to a high rate of pregnancy termination (61%) and some intrauterine death (5%) if left untreated[27].

It has been shown that pulmonary valvuloplasty in fetal life is also techniically feasible in midgestation. With optimal fetal positioning with the aid of adequate echo imaging, a limited maternal laparotomy without uterine exteriorization or incision could be attained. Fetal pulmonary balloon valvuloplasty can be performed at 21-32-week gestation under maternal local anesthesia and sedation by inserting a needle through maternal abdominal wall into the uterine cavity under ultrasound guidance. Fetal analgesia is then injected before advancing the needle through the fetal chest wall into the right ventricular infundibulum of the fetus. A guidewire is inserted through the needle and across the pulmonary valve. A balloon catheter is inserted and then inflated to dilate the stenotic valve. Access to the right ventricular outflow tract is achieved through direct puncture by using a 19-gauge cannula via a subcostal approach on the fetal chest or an intercostal space next to the sternum, the cannula tip is directed into the right ventricular outflow tract and the atretic pulmonary valve is dilated by inflating a coronary angioplasty balloon. After the final balloon deflation, the wire, balloon and cannula are removed. The catheter and needle are then withdrawn[26].

Since 2002, prenatal intervention for fetal PA/IVS has been performed for membranous pulmonary atresia with identifiable pulmonary valve leaflets or membrane, an intact or highly restrictive ventricular septal defect and right heart hypoplasia with a tricuspid valve annulus z score of <-2. Compared with control fetuses with PA/IVS who did not undergo prenatal intervention with postnatal univentricular circulation, the tricuspid valve annulus, right ventricle length and pulmonary valve annulus grew significantly more from mid- to late gestation in the six fetuses that underwent successful interventions[25]. Gómez Montes et al.[29] reported fetal intervention was performed for PA/IVS in four fetuses with technical success in all of them and with some improvement of the right heart growth and hemodynamics early after the procedure, thereby increasing the chances for a biventricular repair.

Polat et al.[29] also adopted a 0.014-inch floppy tipped coronary guide wire in the maneuver. The wire-catheter assembly was introduced through the needle until the balloon emerged. After deployed in the left pulmonary artery, the balloon was pulled back across the perforated valve with three consecutive inflations. Post-interventional echocardiography showed slight improvement in right ventricular compliance. They performed a successful valvulotomy of the pulmonary valve in a fetus with PA/IVS at 28-week gestation and fetal intervention was performed for a Z-score>3 and good tricuspid valve growth are the important factors leading to postnatal biventricular repair in fetuses with PA/IVS. According to the Boston experience, a Z-score >=3 is associated with biventricular outcome and a <3 score with univentricular palliation[30].

**Prenatal intervention on the atrial septum**

Hypoplastic left heart syndrome is potentially detectable in fetuses of 18-22-week gestation with a four-chamber view on echocardiography. With left heart obstruction, the existence of an intratral communication is important for oxygenated blood to be distributed to the body and to prevent pulmonary congestion[31]. Prenatal intervention on the atrial septum is indicated for an intact or highly restrictive atrial septum, which promotes profound cyanosis and pulmonary edema after birth, leading to little effective pulmonary blood flow and resulting in chronic pulmonary venous hypertension and lymphatic dilatation. This can in turn result in increased perioperative morbidity and mortality with stage I Norwood procedure. Postnatal atrial septotomy, albeit rapid
and effective, may not reverse pulmonary vasculature pathologies and further mortality in the first few weeks or months of life. Therefore, midgestation intervention on atrial septum is imperative for preventing pulmonary vasculature changes, reducing the need for additional or urgent procedures and improving the infant’s surgical outcome.

The maneuver of prenatal interventions on atrial septum has been described. After accessing the fetal heart, a communication is created by directing the needle across the atrial septum. A wire and small balloon are forwarded into the left atrium and a small atrial communication is enlarged by inflation of the balloon. A larger series of intraterine atrial septoplasty in fetuses with HLHS was reported by Marshall et al.[41]. Of 21 fetuses at 24-34-week gestation who received this procedure, there were 19 technical successes and two fetal deaths. An atrial septal defect of at least 3 mm in diameter was confirmed to allow postnatal benefit. However, postnatal outcomes were disappointing with a mortality of 58%. In order to keep septectomy open, a stent can be deployed across the atrial septum. Chaturvedi et al.[34] performed percutaneous ultrasound-guided stenting of the atrial septum in 10 fetuses. Two fetuses developed stent stenosis and died postnatally from pulmonary hypertension and sepsis, respectively. Kalish et al.[35] reported that nine fetuses at 24-31-week gestation with HLHS/IAS received fetal atrial septal stent placement, with technical success in five and failure in four cases. Stent deployment may decompress the left atrium. Additionally, there were no maternal complications.

**Fetal cardiac pacing**

Complete heart block can be life-threatening in fetuses. The etiologies were considered to be inflammation and fibrosis at the atrioventricular node associated with the production of antibodies. Heart block can progress during pregnancy and may result in hydrops fetalis and eventual fetal demise. There are few effective treatment options for fetal heart block, and may result in hydrops fetalis and eventual fetal demise. Isoproterenol can be an indication for permanent pacemaker implant before birth. In order to keep septectomy open, a stent can be deployed across the atrial septum. Chaturvedi et al.[34] performed percutaneous ultrasound-guided stenting of the atrial septum in 10 fetuses. Two fetuses developed stent stenosis and died postnatally from pulmonary hypertension and sepsis, respectively. Kalish et al.[35] reported that nine fetuses at 24-31-week gestation with HLHS/IAS received fetal atrial septal stent placement, with technical success in five and failure in four cases. Stent deployment may decompress the left atrium. Additionally, there were no maternal complications.

The initially proposed approach was an epicardial pacing lead on the fetal heart with an extra-uterine pulse generator implanted in the mother. However, a lack of myocardial fixation and dislodgment of the percutaneous lead due to fetal movement were the major limitations of the percutaneous approach. To resolve this problem, an entire single chamber pacing system without exteriorized leads without risk of dislodgement of the pacing system was therefore developed. Such a design is now possible because of significant advances made in fetal surgery and fetal intervention, allowing the pacing system to be deployed through the maternal abdomen under ultrasound guidance.

Furthermore, Assaad et al.[36] designed a novel prototype T-shaped lead for secure fixation onto the fetal myocardium and prevention from electrode dislodgement, which could be introduced via an 18-gauge needle and therefore an open surgery was not needed. The new lead was tested in fetal goats, suggesting that a gradual increase in the fetal rate, beginning at 80 beats per minute after implantation would be more reliable for an adequate fetal cardiac output. Boudjemline et al.[37] developed an implantable fetal pacing lead, which was made of a flexible quadrifilar coil with outer silicone insulation and a fixed screw on its distal tip. Attempts in 12 pregnant Pre-Alp ewes at 110-112 day gestation were successful for anchoring the lead on the ventricular wall in all 12 and on the atrium in three of them.

**DISCUSSION**

The reverse remodeling phenomenon should be even more pronounced in fetal life. Thus, fetal cardiac interventions were attempted aiming at promoting ventricular growth and function, decreasing intrauterine death and increasing survival. Fetal cardiac interventions have been advocated for fetuses with semilunar valve stenosis or with HLHS with an intact or highly restrictive atrial septum. In the early years, fetal cardiac interventions showed poor outcomes, probably related to poor ultrasound imaging, limitations of equipment availability and poor fetal conditions. Technical success of fetal cardiac interventions has greatly enhanced postnatal biventricular outcome, thereby avoiding the need for three-stage palliation or cardiac transplant. Despite the progress made in this field, these fetal cardiac interventions remain controversial in both indications and results.

There have been relatively fewer prenatal pulmonary valve interventions comparing with prenatal aortic valve intervention. On the other hand, prenatal interventions for the management of pulmonary atresia and intact ventricular septum were often associated with increased risks of preterm delivery and neonatal mortality. Furthermore, pulmonary valve stenosis may be alleviated with the intraterine right heart growth and the impact of interventional therapy on the pulmonary cir-
culation does not seem to be as forceful as that on the systemic circulation secondary to fetal aortic valvuloplasty.[55]

Candidates for fetal arrhythmic interventions have been considered supraventricular tachycardia refractory to conventional drug with a potential for progression into hydrops fetalis and fetal demise.[54,56] Immune complete heart block with low ventricular rate may cause significant decrease in fetal cardiac output, cardiac failure and hydrops fetalis[56,57]. The poor prognosis of these fetal arrhythmias has incited the development of alternative therapeutic strategies. Fetal ventricular pacing has been found to improve ventricular output in experimentally induced complete atriовentricular block.[58] However, initial attempts of fetal pacing have failed in human fetuses.[4,42] As open fetal surgery for intrauterine pacemaker insertion has been associated with unacceptable maternal morbidity and fetal demise, minimally invasive approaches using either transcutaneous ultrasound-guided[39] or fetoscopic approaches[47] have been favored. Both endovascular route for intracardiac[42] and epicardial lead anchorages[59] were attempted. Adaptations of new leads to the fetal anatomy for a secure anchorage are crucial for obtaining better outcomes of fetal pacing. Fetal cardiac interventions by direct cardiac puncture are associated with significant fetal morbidity. In order to avoid direct cardiac puncture, Nugent et al.[60] have employed successfully an in vitro fetal heart model of approximating a 32-week gestation with magnetically steerable guide wires from the hepatic vein to the descending aorta and balloon to the aortic valve, in between 5 and 10 minutes.

The treatment of critical left ventricular outflow tract obstruction in the neonate and infant remains a significant challenge.[61] Postnatal surgical options include biventricular repair (surgical aortic valvotomy, balloon aortic valvotomy, Ross/Konno procedure and arch repair with or without other lesion repair), single ventricular repair (Norwood type), biventricular repair after initial single ventricular repair and cardiac transplantation[61]. Biventricular repair presents obvious advantages over univentricular type of repair in terms of better survival and lower hospitalization costs.[62] Rhodes scores have been taken as reliable indicators for the determination of a biventricular or univentricular repair.[63] For conditions with no possibility of biventricular repair, the expectant parents may choose, between postnatal palliative management (such as the Norwood procedure for HLHS) or for interruption of pregnancy[64]. Heart transplantation can be a third option for the parents in saving the baby with life-threatening, critical AS, which fails to other surgical interventions[64].

At the beginning, the technical success and biventricular repair rates were low, which were now considered to be mostly attributed to postnatal care other than prenatal intervention, while technical failure was only responsible for small parts[47]. Only small part of the mortality could directly correlate with the prenatal intervention; whereas the greater part died postnata-

CONCLUSIONS

Fetal cardiac interventions (intrauterine balloon aortic valvuloplasty, intrauterine pulmonary valvuloplasty, prenatal intervention on the atrial septum and fetal cardiac pacing) for four types of congenital heart defects are feasible during midgestation aiming at improving fetal cardiac function, minimizing loss of fetus and enhancing postnatal biventricu-
lar repair. The postnatal deaths are more likely to be a result of candidate selection, effects of improvement of ventricular circulation secondary to fetal cardiac interventions and surgical technical errors and probably a limited intensive care. For improving success rate and post-interventional outcomes, a well-trained team with sophisticated equipment is warranted. With improved patient selection, technical modifications, for example with a robotic interventional approach, promising outcomes may be achieved in future cases. Moreover, with the advances of fetal bypass techniques, it is anticipated that open fetal heart operations would become feasible to facilitate the early treatment of fetal CHDs in the future.

| Authors’ roles & responsibilities |
|-----------------------------------|
| SMY Main author                   |

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