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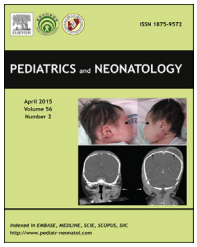

REVIEW ARTICLE

Fetal Cardiac Interventions

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Abstract The present article aims to highlight fetal cardiac interventions (FCIs) in terms of indications, strategies, and fetal prognoses. FCIs of the early years were predominantly pharmacological therapies for fetal arrhythmia or heart block. A transplacental transmission of therapeutic agents has now become the main route of pharmacological FCIs. There have been various FCI strategies, which can be categorized into three types: pharmacological, open FCIs, and closed FCIs. Rather than as a routine management for materno-fetal cardiac disorders, however, FCIs are only applied in those fetal cardiac disorders that are at an increased risk of mortality and morbidity and warrant an interventional therapy. Pharmacological FCIs have been well applied in fetal arrhythmias but require further investigations for novel therapeutic agents. The development of open FCI in humans is an issue for the long run. Closed FCIs may largely rely on advanced imaging techniques. Hybrid FCIs might be the future goal in the treatment of fetal heart diseases.
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1. Introduction

With the steady development of medical imaging techniques, fetal cardiac interventions (FCIs) have drawn considerable attention due to the potential merits of prenatal diagnosis and successful management of fetal cardiovascular anomalies, arrhythmias, and heart failure.[1] FCIs are carried out to improve fetal cardiac function, promote fetal intrauterine development and survival, and enhance postnatal survival.[2] Rather than being a routine management for materno-fetal cardiac disorders, however, FCIs are only applied in those fetal cardiac disorders that have an increased risk of mortality and morbidity and warrant an interventional therapy.[3] There are now various FCI strategies, which can be categorized into three types: pharmacological, open FCIs, and closed FCIs. Of these, closed FCIs can be further subtyped into indirect and direct closed FCIs. The present article aims to highlight FCIs in terms of indications, strategies, and fetal prognoses.

2. Principles of FCIs

The theoretical principles for FCIs have been described in guidelines that not only conform to ethics but also take into account the fetal prognoses and maternal safety (Table 1).

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Table 1	Principles for fetal cardiac interventions.
Fetus	✧ The congenital heart defect may have poor postnatal therapeutic effect without prenatal intervention ✧ The intervention may prevent or reduce the development of the cardiac defect and improve postnatal prognosis
Mother	✧ Maternal safety must be guaranteed ✧ Maternal fertility must not be affected
Technique	✧ The *in-utero* intervention is technically feasible ✧ A multidisciplinary team serves to support the technical application

Prenatal intervention is suitable only for a small subset of fetal conditions, including severe aortic stenosis, pulmonary atresia, and intact atrial septum; therefore intervention should only be offered to candidates fulfilling strict selection criteria.[4] Intrauterine valvuloplasty of a severely stenotic pulmonary valve or a pulmonary atresia with intact ventricular septum aims to prevent hypoplasia of the right ventricle and to enable postnatal biventricular repair.[2] The aim of aortic balloon valvuloplasty for critical aortic stenosis with a small left ventricle or a normal sized left ventricle but poor function is to increase the chances of biventricular repair, and to alter the natural history of mid gestation fetal aortic stenosis toward evolving hypoplastic left heart syndrome (HLHS).[3,5] HLHS often presents in late gestation, and therefore it cannot be caught in time for fetal intervention as there would be insufficient time for fetus *in-utero* development after intervention.[6] Successful fetal aortic valvuloplasty may result in improvement of *in-utero* aortic and mitral valve growth, left ventricular ejection fraction, bidirectional flow across the foramen, and antegrade flow in the transverse arch.[7] Aortic stenosis with a high velocity, good ventricular function, and forward flow in the arch are important preconditions for fetuses to transit to postnatal treatment. A small ventricle may suggest non-eligibility for a prenatal procedure.[4] The most important selection criterion for fetuses is critical aortic valve stenosis evolving HLHS. Other selection criteria include a left ventricular long-axis Z-score of >-3, retrograde flow in the aortic arch, and left-to-right shunt across the foramen ovale.[8] Under these principles, the inclusion criteria (i.e., indications) for the treatment of fetal cardiac disorders are primarily arterial level and atrial level abnormalities, whereas the exclusion criteria are predominantly from maternal aspects (Table 2).

3. Pharmacological FCIs

FCIs of the early years are predominantly pharmacological therapies for fetal arrhythmia or heart block[3] to preserve the intrauterine growth environment with the precondition of maternal safety, in order to achieve a favorable delivery in due course after a general evaluation of fetal growth and development that would thereby facilitate postnatal treatment.[9] At present, transplacental transmission of therapeutic agents is the main route of pharmacological FCIs. Alternative approaches include umbilical vein transmission, fetal intramuscular injection, and fetal intravascular passages. The use of invasive approaches is very limited in clinical practice, and they were only recommended in those with a very low transplacental passage rate due to severe hydrops.[9] Fetal arrhythmias can be divided into three types: fetal tachycardia (heart rate >180 beats/minute), bradyarrhythmias (heart rate <110 beats/minute), and fetal ectopy (irregular rhythm).[9]

Fetal supraventricular tachycardia is characterized by a 1:1 atrioventricular conduction, usually with a heart rate of 200–300 beats/minute, either paroxysmal or incessant, and it is associated with fetal hydrops in 36–64%.[10] Supraventricular tachycardia is regarded as a cause of nonimmune hydrops fetalis with an increased risk of perinatal mortality.[10] Sustained supraventricular tachycardia (>12 hours) and lower gestation showed direct correlations with hydrops.[11] Clinical observations revealed that the gestational age at delivery was significantly greater in those with intrauterine management than those without.[11] In 1975, Eibschitz et al[12] reported successful intrapartum treatment by intravenous propranolol for fetal ventricular tachycardia. Atasaral et al[10] reported that a fetus developed tachycardia at a heart rate of 240 beats/minute in the 34th week of gestation, which was managed with maternal administration of sotalol 120 mg twice/day on Day 1 of treatment, then tapered to 80 mg twice/day. The fetal heart rate dropped to 140 beats/minute and the fetus was stable until normal vaginal delivery.

The prognosis for fetal atrioventricular heart block related to congenital heart defects can be extremely poor, with a combined fetal and neonatal mortality of >80%. Scheduled early delivery, pacing at a reduced ventricular rate, and dual-chamber pacing have proved to be

Table 2	Inclusion and exclusion criteria of cardiac disorders for fetal cardiac interventions.
	Congenital heart defect
Inclusion	
Left heart system	✧ Critical aortic valve stenosis evolving hypoplastic left heart syndrome ✧ Restrictive atrial level communication evolving hypoplastic left heart syndrome ✧ Severely stenotic mitral valve
Right heart system	✧ Pulmonary atresia with intact septal septum ✧ Pulmonary atresia with ventricular septal defect with hypoplasia of the pulmonary artery ✧ Tetralogy of Fallot with hypoplasia of the pulmonary artery
Others	✧ Severe type of double outlet right ventricle ✧ Complete transpositions of great vessels with restrictive atrial level communication
Exclusion	
Fetus	✧ Associated with severe malformations of other organs ✧ Multiple gestations
Mother	✧ Cervical incompetence ✧ Contraindications for the use of narcotics or uterine contraction inhibitor

ineffective. Isolated, complete atrioventricular block without SSA/Ro antibody positivity normally has a good prognosis. Isoimmune atrioventricular block develops as a result of placental transfer of maternal autoantibodies. The fetus may develop atrioventricular block in 2% of pregnancies with SSA/Ro or SSB/La autoantibodies. Like hydrops, isoimmune heart block may be associated with pericardial effusion related to the inflammatory process, but there are no ascites or pleural effusions. Fetuses with third-degree atrioventricular block and nonreactive ventricular rates <55 beats/minute are at increased risks of hydrops fetalis and neonatal heart failure.[9]

Fetal heart block may result from the myocardial inflammation and the further fibrosis of the conduct system due to the deposits of anti-Ro and anti-La antibodies in the placentas.[13,14] Such an immune injury may lead to heart block at 16th—17th week of gestation.[15] Fetal bradyarrhythmias warrant electrocardiographic monitoring, especially in the event of long QT intervals.[9] When echocardiography demonstrated a fetal heart rate drop to <56 beats/minute, maternal administration of oral terbutaline 2.5—7.5 mg every 4—6 hour (10—30 mg/day) becomes necessary. Mothers with fetal isoimmune complete heart block can take oral dexamethasone (4 mg/day until 30 weeks, and then tapered by 1 mg every other week) from the date diagnosis was established until the 36th week of gestation or delivery.[16] There is currently no effective intrauterine therapy for fetal slow arrhythmias, which are mainly managed with adrenomimetic drugs and dexamethasone. Adrenomimetic drugs, such as salbutamol and terbutaline, can increase the fetal heart rate by 15—25% and improve fetal cardiac output. Transplacental dexamethasone cannot reverse high-degree heart block, but it can prevent immune first-degree heart block from developing into a second- or third-degree condition.[15] The use of antenatal steroid therapy is not widely accepted in the treatment of fetal immune-mediated heart block owing to the risks to the fetus. Direct fetal cardiac pacing has rarely been attempted.[14]

Hydrops fetalis is an accumulation of fluid or edema in at least two fetal compartments, including the subcutaneous tissue, pleura, pericardium, or abdomen.[10] Nonimmune hydrops fetalis may be due to maternal and placental disorders, with common etiologies of cardiovascular abnormalities, infectious disease, aneuploidy,[17] and critical aortic valvular stenosis.[18] For severe heart failure and hydrops fetalis, transplacental passage of digoxin is often declined due to poor outcomes.[19] The treatment success rate with digoxin is about 50% in the presence of hydrops, which is often associated with poor placental transfer of digoxin.[20] One case of nonimmune fetal hydrops, diagnosed as mucopolysaccharidosis VII with hypoalbuminemia, was even subjected to intrauterine albumin transfusions via cordocentesis on five occasions, but no improvement was obtained for the hydrops after the albumin transfusions.[21]

Fetal heart failures were considered a result of neurohumoral stimuli and biomechanical stress on cardiomyocytes, the resultant adverse cardiac pathological remodeling and pathway activations.[22] It has been reported that digoxin improves fetal cardiac function and maintains a prolonged and successful gestation for the normal twin.[23] For tachyarrhythmia-induced fetal congestive heart failure, the maternal dose of transplacental digoxin is 0.25—0.5 mg/day, whereas for nonimmune hydrops fetalis caused by supraventricular tachycardia and flutter, the maternal dose is 0.125—0.5 mg/day.[24] Under treatment with transplacental digoxin with an initial dosage of 0.25 mg/day until delivery, the placental transportation efficiency (neonate/mother ratio of serum digoxin concentration) was 76.45—84.31%, with no postnatal reoccurrence of arrhythmias[25] A retrospective case series of fetuses with congestive heart failure were treated with transplacental digoxin and were evaluated by using a ten-point cardiovascular profile score (CVPS). The overall mortality was 32%. A CVPS of ≥6 was proved to be the best predictor of survival.[26]

4. Open FCI

Open FCIs provide insight into the pathophysiology of fetal cardiac bypass on the basis of animal experiments. In 1986, *in-utero* ventricular pacing for complete heart block was attempted in a human fetus.[27] Later, in fetal lambs, pacing leads were inserted into the superior vena cava and ascending aorta through a neck incision by a hysterectomy. The procedure led to a reduced right ventricular output, whereas cardiac output remained constant when the right atrium was paced at ≥ 300 beats/minute.[28] Also in lambs, left ventricular pacing was later proved to be effective in the treatment of complete atrioventricular heart block in hydropic fetuses.[29] Preliminary researches into fetal cardiac bypass illustrated that without nitroprusside, placental blood flow decreased by 25—60%, whereas cardiac output increased by 15—25% after bypass with non-decreasing flows to other fetal organs. Decreased placental blood flow after bypass was accompanied by a fall in partial pressure of oxygen (PO_2) and a rise in partial pressure of carbon dioxide (PCO_2). Nitroprusside improved placental blood flow, cardiac output, and arterial blood gases after bypass.[30] At normothermia, the placenta may tolerate a 30-minute umbilical blood flow cessation. As indomethacin improves placental blood flow after fetal cardiac bypass, placental perfusion on bypass without indomethacin causes severe placental dysfunction. Reddy et al[31] compared in-line axial-flow pump and a roller pump with a venous reservoir for cardiac bypass for 30 minutes in fetal sheep at 118—122 days of gestation. Three fetuses in the control group died during the study, whereas all eight fetuses in the Hemopump group remained stable throughout the study period. During and after bypass, placental blood flow was significantly higher, and placental vascular resistance was significantly lower in the former group than the latter. In 2007, Baker et al[32] reported that the addition of calcium or bicarbonate adversely affected fetal gas exchange during 30-minute bypass in ovine fetuses of 104—110 days of gestation.

5. Closed FCIs

5.1. Indirect fetal intervention

Kohl[33] set two examples of indirect fetal interventions: fetoscopic laser ablation of the placental vascular

anomalies and ultrasound-guided thoracoamniotic shunt insertion. It has been recognized that twinetwin transfusion syndrome (TTTS) can be the underlying cause of fetal cardiac failure, and twin demise might occur in up to 10% of monochorionic twin gestations. De Lia et al[34] reported that fetoscopic laser ablation of the placental vascular anomalies resulted in 66.7% survival of the mother and twins. One (33.3%) patient was complicated by a placental vessel perforation and developed severe preeclampsia at 29 weeks, necessitating delivery. Fetal cardiac failure associated with generalized hydrops in untreated fetuses with a severe bilateral hydrothorax may cause fetal demise. Ultrasound-guided thoracoamniotic shunt insertion can decrease the intrathoracic pressure, improve heart function, and enhance pulmonary re-expansion.[35] To improve fetal heart function, ultrasound-guided fetal pericardial effusion evacuation can be used as an indirect fetal intervention.[36] Laser treatment of the twinetwin communications or cord ligation with acardiac twins can alleviate fetal heart failure as well.[37]

5.2. Direct fetal intervention

In 1991, Maxwell et al[38] reported aortic valvuloplasty performed in two fetuses with initiated success; however, the first fetus died 24 hours after the procedure, and the second died of renal failure on postnatal Day 28. Later, they reported another case of fetal aortic valvuloplasty with longer survival.[2] In 2002, Tulzer et al[39] performed pulmonary valvuloplasty successfully for critical pulmonary stenosis in two fetuses at 28- and 30-weeks of gestation, respectively. In 2004, intrauterine atrial septostomy was attempted by Marshall et al[40] in seven fetuses at 26—34 weeks of gestation with HLHS and intact or highly restrictive atrial septum. One fetus died, and six remained well until delivery.

Some patients are diagnosed with aortic valve stenosis and a normal-sized or dilated left ventricle evolving into HLHS during the second trimester. Echocardiographic parameters including retrograde flow in the transverse arch, severe left ventricular dysfunction, monophasic and short mitral valve inflow, and left-to-right shunt across the foramen ovale may predict the development of HLHS. The potential benefit of fetal cardiac intervention for evolving HLHS is to decrease the left ventricular afterload and enhance left heart circulation for the prevention of progressive left heart dysfunction and hypoplasia.[3,5] When fetal movements have stopped, an 18—19 gauge needle can be introduced through the maternal abdomen under ultrasound guidance and then into the left ventricle through an intercostal space of the fetal thorax.[8] If the fetus has a complete pulmonary atresia *in utero*, perforation of the pulmonary valve by a needle or a radiofrequency wire is mandatory prior to balloon valvoplasty.[4] A few large series of fetal aortic valvuloplasties for severe aortic stenosis and evolving HLHS have obtained a technical success of 67—86%,[3,8,41] a biventricular repair rate of 24—65%,[3,8,41] and a mortality of 13%.[8] In a retrospective study, Selamet Tierney et al[7] discovered that mid-gestation fetal balloon aortic valvuloplasty may effectively improve fetal left ventricular function. Arzt et al[8] performed 24 procedures in 23 fetuses with aortic stenosis. The complications included bradycardia in 39.1% (9/23), left ventricular thrombus in 21.7% (5/23), pericardial effusion $>$ 3 mm in 13% (3/23), balloon tear off in 8.7% (2/23), and *in-utero* fetal demise in 13% (3/23) (Figure 1). Bradycardia and/or right ventricular dysfunction is complicated in 50% of fetal aortic valve interventions.[5] Even though biventricular circulation is not achieved, a functioning left ventricle may support systemic circulation for further postnatal operations.[3]

Atrial septostomy for highly restrictive or intact atrial septum in HLHS may protect the fetuses from pulmonary vasculature and pulmonary parenchyma damage.[42] Ballooning may not be sufficient to keep an atrial level shunt open for a long time; and atrial septal shunting is thus an alternative that can be done in early to mid of third trimester. Fetuses with an atrial level shunting $<$3 mm may require urgent atrial septostomy after birth. Intrauterine atrial septostomy may largely decrease the need for postnatal interventions. Pulmonary valvuloplasty for pulmonary atresia with intact ventricular septum and hypoplastic right ventricles has been reported in the third trimester. Successful pulmonary valve perforations render significant growth of the right ventricle and tricuspid and pulmonary valve annuli.[43]

6. Discussion

Transplacental digoxin is the main treatment for fetal heart failure and fetal hydrops. During the treatment, comprehensive evaluation and monitoring of the fetal ventricular Tei index, CVPS, umbilical arterial pulsatility index and resistance index are mandatory. Pharmacological FCIs are primarily the study of fetal pharmacokinetics. Miranda-Carús et al[44] created a congenital atrioventricular heart block model by administering SSA/Ro and SSB/La antibodies on pregnant murines, laying a foundation for the treatment of immune fetal atrioventricular heart block, but without reaching a consensus. In order to observe the transplacental transmission rates of flecainide, maternal and fetal distribution concentrations and elimination rates, Dimas et al[45] conducted a transplacental pharmacokinetic study of flecainide in the gravid baboon and fetus, and they provided experimental evidence of safe flecainide use in clinical practice. To date, there are no animal models of

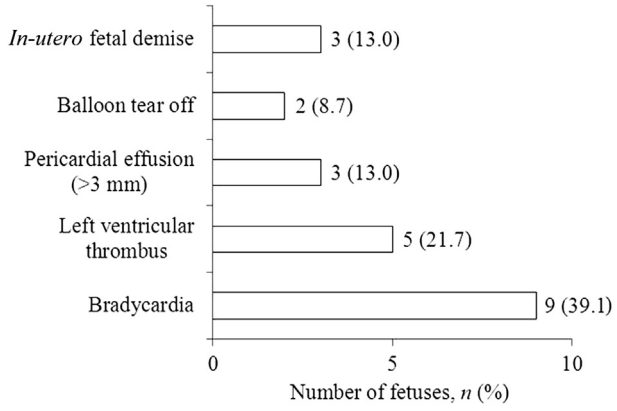

Figure 1 Complications of fetal aortic valvuloplasty.[39]

fetal rapid arrhythmias and fetal cardiac failure. Clinical observations have revealed that fetal exposure to chemotherapy for maternal cancer in the second or third trimester of pregnancy does not impair fetal neurological development or worsen the clinical outcome, indicating a fetal protective effect from the placental barrier-function against maternal chemotherapeutic administration during organogenesis.[46] Nevertheless, the use of warfarin in pregnant patients with a mechanical heart valve prosthesis can lead to a very different situation. Due to the embryopathic effect of warfarin in the first trimester and toxic effects in the last three weeks of gestation, it is suggested that subcutaneous heparin administration is substituted for warfarin during these two periods of gestation.[47]

The temporary pacemaker implantation accomplished by Carpenter et al[27] in 1986 was the beginning of open FCIs. The animal experiments thereafter did not achieve any substantial progression to facilitate clinical fetal pacemaker implants. Cardiopulmonary bypass as a mandatory adjunct of fetal cardiac surgery has not been sufficiently developed, which has restricted advances of fetal cardiac surgery. A large-scale randomized clinical observation has revealed that uterine incision is a predictive factor of the fetal prognosis in open FCIs. The premature delivery rates were 100%, 80%, and significantly reduced when the uterine incision was $\geq$5 mm, $\geq$3.3 mm, and $<$3.0 mm, respectively. Open FCI was therefore defined as an operation with a uterine incision of $\geq$3.3 mm including the fetoscopy operations (the diameter of the 10F sheath used in the fetoscopy operations was 3.3 mm).[48] The influence of the operation on hemodynamic changes and the pertinent protective treatment were investigated in fetal lambs undergoing ultrasound-guided intrauterine aortic balloon valvulotomy. In a fetal lamb model of atrial septal stent implantation, relations between the shapes of the stents, the treatment efficacy and endothelialization of the stents were evaluated by three-dimensional ultrasound. In the majority of cases (8/10) the procedure was successful either by piercing the septum primum directly with an 18-gauge needle or by piercing by an 18-gauge needle inserted through the dilator of a 4F sheath.[49]

Fetoscopy operations are an open FCI but with minimal invasion, which makes it appealing for fetal cardiac and noncardiac interventions, and several series of experimental researches have been conducted on this aspect of FCIs.[50,51] Applications of fetoscopy operations in humans have been sporadically reported with limited results; however the risks, especially premature delivery risks associated with fetoscopy operations, have yet to be evaluated in detail.[52]

Closed FCIs are fetal cardiac interventions via a uterine puncture. An 18—19-gauge puncture needle can meet the requirement for a fetal cardiac maneuver by maintaining the integrations of the uterine and the amniotic cavity, thereby avoiding the risks of premature delivery and infection from a fetal operation. Currently, closed FCIs mainly include fetal aortic and pulmonary balloon valvulotomy, and balloon atrial septotomy under the guidance of ultrasound by way of maternal abdominal wall and uterine punctures.

FCI is not an independent interventional therapy. In a minority of cases radical therapeutic outcomes may be attained, but it is a palliative remedy in the majority of the cases, offering an opportunity for further postnatal treatments, such as aortic and pulmonary balloon valvulotomy, balloon atrial septotomy, and staged cardiac operations. The possible cure of fetal cardiac anomalies has to be fully evaluated prior to FCI. If it is impossible for FCI to be performed due to the complexity of the fetal cardiac anomaly, or if there is insufficient time for fetal intrauterine development, FCI will not be an effective remedy. On the contrary, it may bring about ineffective or unfavorable results or even hazards. It is therefore important to set the inclusion and exclusion criteria in terms of the timing of FCI and evaluate the predictive risk factors. Both Z-score and threshold score systems are valuable for the assessment of prognosis of FCIs in fetuses with a restrictive atrial communication. They have been proved to directly correlate with the maximal flow velocity via an atrial shunt, diameter/area ratio of the atrial shunt, and development status of cardiac chambers. A CVPS is a reliable indicator for pre-interventional assessments of fetuses with different cardiovascular anomalies.[1] If the CVPS is $\leq$7 points, etiologic treatment should be recommended; and if the CVPS is $<$5 points, the risks of perinatal mortality could be high.

Successful FCIs could restrain or reverse dysplasia of the fetal heart and systemic-pulmonary vascular beds. The procedure, however, may be associated with hemodynamic instability, which may cause impairment to the fetal brain, placenta, and other vital organs, and the long-term outcomes are unknown.

7. Conclusion

FCIs can be associated with potential short-term risks during the course of treatment of fetal heart disease, while the long-term risks warrant further evaluations. It seems that few pregnant patients may benefit but more may be subject to risks from FCIs. In selected cases, carefully weighing the advantages and disadvantages of FCI is of outstanding importance. Pharmacological FCIs have been successfully applied in fetal arrhythmias, but further investigations are required for novel therapeutic agents. The development of open FCI in humans is an issue for the long term. Closed FCIs may largely rely on advanced imaging techniques. Hybrid FCIs may be the future goal in the treatment of fetal heart diseases.

Conflicts of interest

The author has no conflicts of interest relevant to this article.

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