Milestones in the Development of Fetal Cardiac Interventions

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ABSTRACT: Cardiac patients of all ages were managed in the past by internists who specialized in cardiology. During the past 50 years, the medical field has witnessed great strides in the management of congenital heart disease, and thus pediatric cardiology has become a subspecialty in many countries. This review article focuses on the advances in fetal cardiac interventions (FCI) since its inception by our group in 1975. Three major modes of FCI have evolved during the past 42 years: pharmacologic, closed FCI, and open FCI. All treatments require a careful approach by the heart team and are reserved for severe fetal cardiac conditions. They call for prenatal intervention in view of the severity and progressive nature of the diseases that are associated with high fetal morbidity and mortality if left untreated. The well-established pharmacologic FCI approach includes several new and effective agents with recommendations often varying between class I and class IIa and IIb. The advances in prenatal echocardiographic imaging and color flow Doppler has given an impetus to the development of the other FCI modes; however, the need for uterine incision and fetal cardiac bypass in the open technique have limited its advance. Long-term outcomes are still unknown and definite conclusions as to the efficacy and safety of FCI need further investigation, including multicenter trials with long-term data.

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KEY WORDS: congenital heart disease, fetal cardiac interventions (FCI), pharmacology, fetal imaging, heart team

Until a few decades ago, both adult and pediatric cardiology services were provided by internists who specialized in cardiology. This care included the management of children with congenital heart diseases. In the 1960s, the Association of European Pediatric Cardiology was founded and pediatric cardiology became a subspecialty in the United States. In 1981, the first World Congress of Pediatric Cardiology was held in London. Due to our interest in perinatal medicine in a general cardiology service, in 1969 we first introduced the use of the transumbilical vein route for performing Rashkind atrial septostomy in the newborn [1], which simplified the procedure dramatically. With the advent of echocardiography to monitor the procedure at the bedside, the transumbilical route became the fastest, simplest, and easiest way to perform the procedure, and was the preferred method in centers around the world [2-4]. Prompted and motivated in the early 1970s by the department of obstetrics and gynecology at our medical center, we turned our attention to the investigation and management of cardiac problems afflicting the fetus.

Three major modes of fetal cardiac interventions (FCI) are pharmacologic, closed FCI, and open FCI

HEART TEAM APPROACH

In an electrocardiographic study of intrauterine bradyarrhythmias published in 1976 [5] we stressed the need for closer teamwork between the obstetrician and the cardiologist throughout the pregnancy, which would encourage the future development of the field of fetal cardiology. The heart team approach at our institution evolved at an early stage and included senior cardiologists and obstetricians with expertise and experience in Doppler echocardiography techniques, including knowledge of congenital heart defects and their recognition by fetal echocardiography using transabdominal and transvaginal approaches. Joint evaluation and analysis of fetal status including Doppler echocardiography data, decisions for further therapy, and fetal interventions were reached after in depth discussions among the team members.

ERA OF FETAL CARDIAC INTERVENTIONS.

Advances in prenatal ultrasonic screening and fetal imaging technologies have enabled early and accurate detection of congenital heart disease, which stimulated the search for possible fetal cardiac interventions (FCI) in severe cases. The correct diagnosis of fetal cardiac structural diseases and further understanding of their hemodynamics and natural history in utero, as well as the diagnosis of tachyarrhythmias and bradyarrhythmias, have contributed to the development of FCI.

Leading authorities in the field of congenital heart disease and FCI [6,7] have acknowledged our work as being the first FCI ever reported. The earliest reported human fetal cardiac therapy of any kind was in 1975 and involved maternal-fetal transplacental administration of a beta blocker in the setting

of fetal ventricular arrhythmia [6]. In 1975, we reported a sustained fetal ventricular arrhythmia that was successfully controlled by propranolol administered intravenously to the mother under continuous electrocardiographic monitoring of both mother and fetus [8]. Labor ended in a normal vaginal delivery with no undue maternal or fetal side effects. This study heralded the new era of FCI. As early as 1976 [5], we stressed the need for closer teamwork between the obstetrician and the cardiologist, which would give an impetus to the future development of fetal cardiology.

The evolution of FCI originated out of necessity to manage the care of high-risk fetuses with serious and potentially fatal cardiac conditions, both arrhythmic and structural, that mandated urgent intrauterine interventions. Advances in transducer technology and computer processing, as well as improved resolution, led to better definition of complex structural defects and evaluation of cardiac function with the introduction of the Doppler technique in the study of the fetus. FCI mandated proper and accurate anatomic diagnosis and cardiac function evaluation, which prompted the incorporation of Doppler technology to the already improved echo-imaging. In 1985, I coauthored a symposium article on pulsed Doppler fetal echocardiography [9] and concluded that Doppler provided added value in the quantitation of fetal hemodynamics, characterization of cardiac rhythm, and identification of shunt and regurgitant lesions.

All fetal cardiac interventions and treatments should be managed by a heart team and reserved for severe fetal cardiac conditions

The study of fetal arrhythmias evolved in parallel with the available technologies at that time. Thus, in the 1970s, we utilized electrocardiography [5,8], followed by echocardiography and Doppler [9,10].

CATEGORIES OF FETAL CARDIAC INTERVENTIONS

Pharmacological FCI

Indications: fetal tachyarrhythmias and fetal bradycardias

Eleven years after our initial publication [8], the first open in utero pacemaker implantation for fetal complete heart block was performed in 1986 [11]. Results of the first case of fetal balloon aortic valvuloplasty were published in 1991 [12].

Pharmacological FCI was the first and most established mode of FCI, which has evolved since our first description in 1975 [8]. It now includes several old and more recent drugs for transplacental delivery for the control of tachyarrhythmias and bradyarrhythmias, including heart block. Drugs such as digoxin, beta blockers, amiodarone, sotalol, flecainide, and terbutaline have been used. If left untreated, signs of fetal hydrops may appear in some cases that may lead to fetal demise.

Fetal bradycardia may be caused by sinus node dysfunction, atrioventricular block (AVB), or blocked premature beats. It can also be the result of fetal hypoxia. Common AVB may lead to hydrops fetalis and may be associated with structural congenital heart disease or maternal autoimmune disease treated with steroids and beta-agonists. A few open FCI procedures for pacemaker fetal implantations have been reported, but this method has not been successfully adopted clinically. In the early 1980s, we treated a fetal complete AVB by close echocardiography follow-up [13], and after progressive cardiomegaly and hydrops appeared, an early Cesarean section was performed at 34 weeks followed by immediate temporary transvenous pacing at birth. An epicardial permanent pacemaker was then implanted at 3 weeks of age. The patient is alive and well, having averted certain intrauterine demise.

Fetal medical therapy for sustained supraventricular or ventricular tachycardias (VT) has a class I recommendation [14]. The remaining indications reach class IIa for sympathomimetics for AV block and medications for intermittent VT or IIb for dexamethasone in immune-mediated AV block and class IIb for digoxin in fetal heart failure although its usefulness is not well established. Class IIa indicates that the treatment is reasonable and can be useful, while a IIb recommendation indicates that the treatment might be considered but its usefulness and effectiveness is not well established.

CLOSED FCI

The term *closed FCI* is reserved for mechanical percutaneous fetal interventions without a surgical opening of the uterus or gaining access via a port over 3 mm in diameter. The first case of closed FCI was that of a balloon aortic valvuloplasty reported by Maxwell and coauthors in 1991 [12]. In depth details of this technique are beyond the scope of this review. Other lesions amenable to this approach are pulmonary valvuloplasty for critical stenosis, atrial septostomy for highly restrictive or intact atrial septum in hypoplastic left heart syndrome (HLHS), pulmonary atresia (PA) with intact ventricular septum (IVS) with evolving hypoplastic right heart syndrome (HRHS). Closed FCI is conducted under general anesthesia and ultrasound guidance via an 18–19 gauge needle introduced through the maternal abdomen and fetal intercostal space reaching the fetal heart. After an initial learning curve, technical success was achieved in 75–80% of aortic valvuloplasty [7]. Further improvements have been recently been documented [15]. These include 123 fetuses who underwent aortic valvuloplasty: 71 in early periods (2000–2008) vs. 52 in later (2009–2015) periods. A 95% success rate was achieved in the more recent period compared to 73% in the early era. Moreover, among live born babies, biventricular circulation was more likely in the more recent group.

The improved technical success rate of the fetal aortic valvuloplasty and modification of selection criteria led to the improved biventricular outcome. In those with evolving HLHS, aortic valvuloplasty may improve left heart physiology and the growth of the aortic and mitral valves. The aim of catheter mediated FCI is to alter the intrauterine natural history and

the negative course of such lesions to prevent fetal death or to improve the status of the newborn, which translates to the reduction of morbidity and mortality.

All lesions that qualify for closed FCI have class IIb recommendations with a level of evidence B/C (14). Moderate quality of evidence (Level B) is based on one or more randomized controlled trials and observational or registry studies. Level C is based on observational or registry data with limitations of design and meta analysis of such studies. The fetuses have severe aortic stenosis (AS) with antegrade flow and evolving HLHS, AS, severe mitral regurgitation, restrictive atrial septum, HLHS with a severely restrictive or intact atrial septum, or with PA and IVS. The objective of FCI is to open the stenotic semilunar valves and restrictive/intact atrial septum to promote antegrade flow and to encourage growth of left and right sided structures to facilitate future biventricular repair. Opening of the atrial septum provides relief of left atrial hypertension and prevents pulmonary vasculopathy.

Although the technique is feasible and success is possible for fetal aortic, pulmonary, and atrial septal plasties, general widespread application of FCI remains inappropriate and should be restricted to highly trained medical professionals. Moreover, successful fetal catheter intervention does not always lead to clinical improvement after birth; hence, patient selection for such intervention is critical. Thus, although FCI is supposed to enhance neurodevelopment by increasing fetal cerebral oxygenation and improve hemodynamics postnatally consequent to a biventricular circulation, their neurodevelopmental status was similar to HLHS without FCI (16). The authors suggested that innate patient factors and morbidity during infancy play a dominant role in neurodevelopmental outcomes.

Due to the complex nature of the procedure, both closed and open fetal cardiac interventions should be performed in highly specialized centers

A recent systematic review and meta-analysis concerning outcomes and complications following FCI was based mostly on case reports and a few larger series [17]. Limitations included lack of randomized controlled trials and low quality of evidence. However, current data regarding aortic valvuloplasty revealed superior results compared to older studies with recent fetal mortality of 11–17% compared to 83% in the past, and a live-birth rate of 65%. Live birth rates for pulmonary valvuloplasty, septoplasty, and pericardiocentesis were 56%, 84%, and 71%, respectively. Still, the authors concluded that well-designed randomized controlled trials are needed to ascertain the value and contribution of FCI.

OPEN FCI

Open FCI entails surgical opening of the uterus or access through a trocar that is 3 mm or more in diameter. The first report of open FCI in a human fetus in whom a pacemaker was placed was published in 1986 [11]. Isolated cases have been reported but this mode of FCI has not been accepted clinically. Fetal bypass due to maternal placental dysfunction consequent to an increase in vascular resistance and reduction in fetal blood flow leading to fetal hypoxia has also not been accepted.

CONTRAINDICATIONS TO FCI

Maternal contraindications

Significant maternal diseases that would jeopardize the mother and fetus related to the anesthetic administration and to the procedure itself are maternal contraindications. Additional relative contraindications include obesity, severe diabetes, human immunodeficiency virus (HIV) infection, and coagulopathies. Maternal risks are relatively minor and include risks from anesthesia, placental abruption, premature labor, and hemodynamic strain.

Fetal contraindications

Significant chromosomal and major extracardiac anomalies, and co-morbidities, and multiple gestations are some of the fetal contraindications for FCI. Risks to the fetus include bradycardia consequent to the needle puncture of the heart, hemopericardium, tamponade, and possible fetal death. If the fetal cardiac defect is too complex to allow FCI, or if insufficient time is available to allow for fetal intrauterine adjustment after FCI, the latter should not be undertaken.

FUTURE POTENTIAL

Although some of the expectations expressed 3 to 4 decades ago have been partially realized, both parents and physicians are often confronted with treat or terminate situations. The technique and outcomes of FCI need to improve as even after successful fetal valvuloplasty many result in postnatal univentricular repair. Better selection of patients, greater understanding of the intrauterine natural history, improvement of equipment and technique, as well as correct timing of FCI is mandatory. Due to the complexity of the subject, FCI should be confined to highly specialized departments.

CONCLUSIONS

Even though 43 years have elapsed since we embarked on the FCI venture, there remains much to be explored in this often uncharted territory. Compared to the other categories of FCI, the nonsurgical pharmacologic approach has been better established and adopted by the medical profession. The nonsurgical approach is followed by the closed mode. Although FCI has made great strides since its inception, its routine clinical application remains elusive and not without hazards.

Advances in imaging, equipment, minimally invasive techniques, as well as superior expertise of highly trained medical teams in specialized departments should increase

safety, precision, success, and possibly impact on the natural history of fetal heart diseases and widen the indications for FCI. Earlier fetal diagnosis and referrals to highly specialized centers is crucial to avoid the proliferation of FCI at multiple centers unlikely to reach a critical number of cases required to ensure appropriate expertise and proficiency. These cases are further reduced in number, especially in countries where parents often prefer to terminate pregnancies with such complex fetal cardiac diseases.

Closer collaboration of the various disciplines is mandatory to further improve techniques and achieve better safety goals for both mother and fetus as fetal interventions have a great potential in the management of complex congenital heart disease. Indeed, a journey of a thousand miles began with a single step 43 years ago, but so far we have not reached our final destination.

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Capsule

Restorative effects of human neural stem cell grafts on the primate spinal cord

Rosenzweig and co-workers grafted human spinal cord-derived neural progenitor cells (NPCs) into sites of cervical spinal cord injury in rhesus monkeys (*Macaca mulatta*). Under three-drug immunosuppression, grafts survived at least 9 months post-injury and expressed both neuronal and glial markers. Monkey axons regenerated into grafts and formed synapses. Hundreds of thousands of human axons extended out from grafts through monkey white matter and synapsed in distal gray matter. Grafts gradually matured over 9 months and improved forelimb function beginning several months after grafting. These findings in a pre-clinical trial support translation of NPC graft therapy to humans with the objective of reconstituting both a neuronal and glial milieu in the site of spinal cord injury.

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Eitan Israeli

"The one real object of education is to have a man in the condition of continually asking questions"

Bishop Mandell Creighton, (1843–1901), British historian and a bishop of the Church of England