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Intrauterine therapy for structural congenital heart disease: Contemporary results and Canadian experience

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ABSTRACT

Percutaneous, ultrasound-guided fetal cardiac intervention (FCI) is increasingly used to alter the prognosis of specific forms of congenital heart disease. Careful patient selection and postnatal management strategy are essential for optimal outcomes. This article discusses the rationale, patient selection criteria, procedural techniques, and contemporary results of FCI. Sources of information included published patient series, the International Fetal Cardiac Intervention Registry, and the Toronto experience as the Canadian referral center.

Key words: Congenital heart disease, Fetal, Interventions, Therapy, Echocardiography.

Introduction

Most congenital heart disease can be diagnosed by prenatal echocardiography. While complex lesions usually occur early in pregnancy with no or little change to birth, some conditions may deteriorate as gestation advances. For example, a semilunar valve may become progressively more stenotic or atretic, leading to dysfunction and underdevelopment of the ventricle and great artery. Nonetheless, 2 adequate sized, functional ventricles are required to sustain the postnatal pulmonary and systemic circulation as the arterial duct closes. If an obstructed valve can be dilated in utero before irreversible damage occurs, ventricular function and growth may recover to permit a postnatal biventricular circulation. Since 25 years, the first attempts [1] to dilate the stenotic aortic valves of 2 fetuses with balloon valvuloplasty, a steadily increasing number of fetal cardiac interventions (FCI) have been performed as fetal therapy have become more widely available. Nonetheless, the global experience is still limited to a few hundred procedures. This review addresses the main lesions that are potentially amenable to prenatal interventions: (1) critical valvar aortic stenosis, (2) a severely restrictive atrial septum with severe left heart obstruction, and (3) valvar pulmonary atresia with an intact ventricular septum. The rationale of FCI, patient selection criteria, procedural techniques, risks, and outcomes will be

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reviewed for each of these lesions. Sources included the International Fetal Cardiac Intervention (IFCI) Registry [2], published single center series, and our published and previously unpublished institutional experience as the Canadian referral center. A total of 34 cases with aortic stenosis ($n = 23$) or pulmonary atresia ($n = 11$) from this ($n = 11$) and other ($n = 23$) centers have been previously included in the Registry.

Risks of FCI and precautions

A basic principle of FCI is to minimize the procedure-related risks for the mother and fetus. The vast majority of direct fetal interventions at our center are done under local anesthetic with 2% lidocaine, intravenous (IV) sedation with remifentanyl ± midazolam and propofol, and a single dose of IV antibiotics [3]. We do not use general anesthesia and almost never use regional anesthesia. All procedures are performed percutaneously and we have never had to resort to maternal laparotomy to improve access. We feel that a minimal invasive approach is paramount when any procedure is evolving experimentally, as is still the case with FCI. In case of fetal malposition, we wait until the lie is optimal to allow access to the relevant heart structures and, if necessary, we use external version to improve the lie. As soon as access is optimized, we perform an ultrasound-guided fetal blood sample (FBS) and give IV rocuronium for paralysis and IV fentanyl for sedation. The maternal risks of FCI are thus minimized, but would include rare events such as adverse drug reactions to sedation or antibiotics. In an experience of over 1000 more complicated fetal interventions, no significant maternal adverse reaction occurred to any of these agents [3]. All procedures are done as an outpatient and bed rest is discouraged to minimize the risk of venous thromboembolism.

Transient fetal bradycardia and ventricular dysfunction occur commonly after the ventricle is punctured with the 18-G needle. For this reason, we give IV atropine to the fetus prophylactically, at the time of initial FBS. If a hemopericardium develops that causes any significant degree of hemodynamic compromise, we drain it immediately with a 22-G needle. If cardiac resuscitation is required, we give intracardiac epinephrine, atropine and/or calcium gluconate as appropriate via a 22-G needle. As with any fetal invasive procedure, there is a very small risk of preterm premature rupture of membranes and premature labor. There is a risk of fetal loss during or after the procedure, that is, influenced by the type of procedure, the gestational age at delivery, and the expertise of the interventional team with FCI.

Critical valvar aortic stenosis (CAS)

Pathophysiology

Valvar aortic stenosis causes myocardial hypertrophy due to left ventricular (LV) pressure overload. As the obstruction progresses to CAS, the LV begins to dilate and heart failure ensues as the cardiac function deteriorates. CAS with LV dilation and heart failure has a poor prognosis in adults. In contrast, since the fetal circulation has 2 parallel working ventricles, even severe LV dysfunction can remain clinically silent. LV dilation, especially if accompanied by mitral regurgitation (MR), may however, is severe enough to interfere with right ventricular (RV) filling and contraction secondary to septal shift, which may result in low cardiac output and hydrops in a subgroup of fetuses. Hypoplastic left heart syndrome (HLHS), the most common sequela of severe left heart obstruction, was thought to originate early in cardiac morphogenesis, until fetal echocardiography demonstrated that HLHS may develop much later, long after the heart has formed [4]. Allan observed a 22-week fetus with CAS and a poorly contractile dilated LV, which progressed to HLHS by 32 weeks and at term was found to have LV and aortic dimensions arrested at the 22-week stage. Reduced growth of left heart structures was subsequently demonstrated in larger fetal patient cohorts without [5] and with fetal aortic valve dilation [6]. Endocardial fibroelastosis (EFE), characterized by a thickening of the ventricular endocardium from proliferation of collagen and elastic fibers, is frequently associated with CAS and presumably arises from a response to the increase in fetal LV pressure. Fetuses with left heart disease display a lower cardiac index than normal. Lower cerebral blood flow may contribute to the smaller brains and white matter abnormalities that are found in these neonates [7,8].

Rationale for FCI

There are 2 overlapping reasons to consider FCI. Firstly, to rescue a fetus from intrauterine death, so that it can be delivered at term and receive postnatal treatment. Fetal CAS can result in hydrops, which can be reversed by aortic valvuloplasty [9,10]. Secondly, to alter disease progression and improve postnatal outcomes. The proposed benefits include avoiding HLHS and increasing the aortic and cerebral blood flow with potentially beneficial effects on brain development.

Patient selection

Criteria for FCI are still evolving. It is currently easier to identify cases that will progress to HLHS, rather than those that may achieve a biventricular repair, as the latter outcome is dependent on a variety of postnatal management strategies. According to Makikallio et al. [11], retrograde or bidirectional flow in the transverse arch, severe LV dysfunction, monophasic mitral inflow, and left-to-right atrial shunting were predictors for the development of HLHS. The best characterized predictor of eventual LV outcome was a "threshold score" derived from 70 aortic FCI cases done at Boston Children's Hospital, excluding those with severe MR, hydrops, or a restrictive atrial septum [12]. The current Boston criteria for offering aortic FCI are as follows [12]:

(1) Aortic valve stenosis;
(2) LV long-axis z-score > -2; and
(3) a "threshold score" ≥ 4 of the following 5 parameters:
    (a) LV long-axis z-score > 0,
    (b) LV short-axis z-score > 0,
    (c) aortic valve annulus z-score > -3.5,
    (d) mitral valve annulus diameter z-score ≥ -2, and