Imaging of the fetal heart to diagnose congenital heart disease has become commonplace during the past 30 years, to the point that institutions such as the American College of Obstetrics and Gynecology, the American College of Radiology, and the American Institute of Ultrasound in Medicine have established, as a standard of care, routine screening for congenital heart disease in the scanning protocol of fetuses undergoing ultrasound study for any reason during the second or third trimester of pregnancy.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Fetal Cardiac Intervention
Innovative Therapy or a Technique in Search of an Indication?
Charles S. Kleinman, MD

The study of Mäkikallio et al in this issue provides an important insight into the pathophysiology of one form of HLHS, ie, progression of fetal aortic stenosis into HLHS. These investigators have noted that the anatomic characteristics of the fetal heart in the presence of severe valvar aortic stenosis do not provide adequate information for the prediction of growth failure of left heart structures, whereas physiological observations of the direction of foramen ovale blood flow (left-to-right shunting) and left ventricular diastolic filling (monophasic mitral valve flow) are both sensitive and specific predictors of growth failure of left heart structures during later pregnancy. Previous observers had noted a correlation between small foramen ovale size and low transatrial fetal flow volumes in fetuses with left heart obstruction. Berning and colleagues noted the importance of “reverse” flow in the fetal foramen ovale and ductus arteriosus in the clinical recognition of congenital heart diseases involving critical left or right heart obstruction. In the present study, retrograde perfusion of the fetal aortic isthmus and transverse aortic arch proved to have a 100% sensitivity and specificity for the prediction of progressive left heart hypoplasia.

The application of catheter-based therapy for the treatment of fetuses with aortic stenosis is aimed at avoiding the need for Norwood palliation in favor of a biventricular management strategy. With reported Norwood stage 1 survivals in excess of 90% in the current era, the proposed fetal interventions are aimed at an enhanced quality of life, rather than simple survival. The concept of fetal intervention for enhanced quality of survival has involved a paradigm shift for
the maternal-fetal medicine community. This has fueled a heated debate over the role of fetal surgery for the management of myelomeningocele, a procedure that requires the mother to place her well-being and reproductive future at risk in an effort to ameliorate the potential neurological disabilities of a fetus who otherwise would likely survive to have neonatal surgery without fetal intervention. A multicenter National Institutes of Health (NIH) study (MOMS) has been undertaken to assess the efficacy of this procedure, but that study did not begin until >100 fetuses nationally had been referred for this procedure. The NIH study has thus encountered difficulties with underenrollment, in part due to the reluctance of referring physicians to participate because of preconceived notions concerning the efficacy of this procedure.20

The initial application of catheter therapy for fetal aortic stenosis with secondary myocardial failure was undertaken because of the almost-uniform neonatal mortality encountered among such fetuses.21 Within 6 years of their initial report, these investigators imposed a moratorium on further interventions, due in part to improved surgical and interventional catheterization survival among these patients.22 A subsequent multicenter review indicated uniformly dismal outcomes for fetal balloon aortic valvuloplasty during the ensuing decade.23

The use of this technique for alteration of severe fetal aortic stenosis certainly represents a technical tour de force for the investigators.15 Initial reports have suggested that a small percentage of patients have been able to undergo biventricular management after such interventions. The current study suggests that all untreated fetuses with retrograde perfusion of the aortic arch will go on to require Norwood palliation and univentricular management. It should be noted, however, that the decision-making algorithm for deciding on a surgical management strategy for neonates with “borderline” left ventricles remains somewhat subjective, despite efforts to apply objective criteria through the use of mathematical formulas such as the Rhodes equation.24 A candidate for biventricular management at 1 institution, for example, might well undergo Norwood palliation at a second institution.

The rationale behind the performance of aortic balloon valvuloplasty in fetuses with severe aortic stenosis, left ventricular dysfunction, and retrograde aortic arch perfusion is that it is best to avoid Norwood and subsequent Fontan palliation. This is based on the presumption that the overall quality of life will be compromised with the latter approach, with impaired neurodevelopmental outcomes and an inexorable deterioration in cardiovascular function, resulting in the onset of arrhythmias, protein-losing enteropathy, thrombotic complications, and progressive systemic ventricular failure. The assumption is that the patient undergoing biventricular repair after fetal palliation will have a greater likelihood of a happy, robust, and longer life. It is unclear whether the latter will necessarily be the case, especially in neonates who have had to undergo endocardial resection to remove endocardial fibroelastosis. The hope is that these neonates will enjoy further growth of their ventricles and will maintain adequate systolic and diastolic performance.

In the meantime, however, it is likely that either the majority of patients with HLHS will present too late in gestation to be considered candidates for fetal intervention or that their anatomic variety of HLHS will not be considered amenable to such palliation. Ongoing efforts to improve the outcome of patients with HLHS, including the Sano modification23 and the use of “hybrid” techniques26 to avoid diastolic “steal” from the systemic circulation and prolonged cardiopulmonary bypass during the immediate neonatal period might well be expected to have a positive impact on neurodevelopment later in childhood, whereas modifications in the performance of the Fontan procedure, including the use of cathereter-based therapies, may be expected to improve the longevity of these patients.

On the other hand, it is fascinating to note that the physiological common denominator among the patients identified by Mäkikallio et al15 is retrograde perfusion of the aortic isthmus and arch. Presumably, fetal aortic balloon valvuloplasty results in improved left ventricular and aortic growth by enhancing forward flow through the arch vessels. This may prove to be more important to the long-term outcome than the avoidance of univentricular palliation. Fournon27 has investigated the importance of the aortic isthmus as a branch point in the fetal circulation and has correlated retrograde arch perfusion with impaired neurodevelopmental follow-up.28 We have found that fetuses with HLHS and retrograde arch perfusion have a high incidence of altered cerebral blood flow with increased end-diastolic flow velocity and decreased arterial pulsatility, consistent with an autoregulatory drop in cerebrovascular resistance.29 These findings are consistent with the altered cerebral-placental ratio of resistance that is observed in fetuses with placental insufficiency and growth retardation in which the centralization of blood flow distribution represents an effort at “head-sparing.”30 Follow-up studies of these children during early childhood have documented a high incidence of neurological and neurodevelopmental abnormalities.31 Similar findings among patients with HLHS have been documented by investigators at the Children’s Hospital of Pennsylvania.32 We are currently participating in a multicenter investigation to determine whether such perturbations in cerebral circulation might identify fetuses at particularly high risk for neurodevelopmental delay in association with congenital heart disease. It is conceivable that fetuses with aortic stenosis and retrograde arch perfusion may derive a neurodevelopmental advantage from the establishment of antegrade arch perfusion by timely aortic balloon valvuloplasty. At present, this is pure speculation, but it should be considered during follow-up of these fetuses through later gestation and after birth into early childhood.

As noted earlier, such fetal interventions pose potential risks to the fetus, as well as to the mother. Most of the promising fetal surgical interventions introduced during the past 2 decades have been abandoned because of the absence of evidence that they provide a functional advantage to the fetuses who undergo such procedures. In the case of in utero shunting of hydrocephaly, for example, improved fetal survival was accompanied by severe developmental disabilities.14
On the other hand, just as the Norwood procedure not only provided the potential for survival of a subgroup of infants with a previously untreatable heart disease but also revolutionized the care of a generation of patients by improving our understanding of preoperative and postoperative management strategies for patients with single-ventricle physiology, the potential exists for fetal cardiac interventions to improve our understanding of the pathophysiology of congenital heart disease and to refine techniques for management of the fetus and neonate with left heart obstruction. That such investigations are undertaken at selected centers, with an institutional commitment to a multidisciplinary fetal treatment and counseling program, with a “fail-safe” mechanism to ensure patient understanding and safety, is totally appropriate. The potential for the proliferation of programs for fetal cardiac intervention elsewhere, before there has been adequate evaluation of the potential volume of such patients and adequate follow-up to characterize the functional results in the surviving patients, is inappropriate.

Although the difficulties that have arisen in the enrollment of fetuses with myelomeningocele into the NIH-sponsored MOMS trial might not have whetted the appetite of the NIH for such multicenter trials, the time is right for such a trial to be undertaken to evaluate the utility of fetal aortic balloon valvuloplasty. Recent articles in the lay press have popularized the notion that fetal cardiac intervention is an innovative but accepted therapy, and multiple centers have attempted a handful of such procedures with variable degrees of success. Rather than await a proliferation of such procedures at centers that are unlikely to amass a critical volume of experience to ensure clinical competence, a prospective multicenter trial should be considered to address the nuances of technical performance of the procedure, to evaluate the short- and midterm results, and to compare these results with those of children undergoing various forms of palliation for HLHS. Only then can we determine whether this is a rational strategy for the management of these patients or merely the application of a technique in search of an indication.

Disclosures
None.

References


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