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EDITORIAL COMMENT

The Power Is in the Numbers

Using Collaboration and a Data Registry to Answer Our Burning Questions Regarding Fetal Cardiac Intervention*

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Technological advances in fetal cardiac imaging have given us a window into the womb, creating the field of fetal cardiology, where the fetus is considered an individual patient from the time of diagnosis. One of the challenges we face as fetal caregivers is that we must strive to understand the "prequel" of what we already know; the natural history and progression of congenital heart disease in utero. More than 25 years ago, researchers reported that structural heart disease, specifically aortic stenosis, evolves in utero (1). Fetal therapy, either by catheter intervention or surgery, is based on the fundamental principle that intervention will alter the natural history of the disease process. To prove that this is true, we must first gain an understanding of the unaltered progression of heart disease in utero. In addition, we must have measurable goals that we hope to achieve, whether it be to completely reverse the process of progression of valve disease to hypoplastic right or left heart syndrome or to minimize myocardial and/or end-organ injury in fetuses with impaired perfusion or myocardial performance. Foremost in the design of fetal intervention techniques is the principle that there are 2 patients to consider and the risk to the mother must be minimized. For this reason, catheter-based intervention is appealing.

The concept of fetal intervention is not new, with techniques and outcomes reported for fetal diagnoses that include twin-twin transfusion, hydrocephalus, myelomeningocele, obstructive uropathy, and diaphragmatic hernia (2). Fetal cardiac intervention, as well, is no longer a new idea. Maxwell et al. (3) are credited with the first report of intervention in 2 fetuses for evolving hypoplastic left heart syndrome (HLHS) performed in 1991. The technique was abandoned after a series of cases was reported (4), partly due to improved surgical outcomes for HLHS. Subsequently, review of the world experience of fetal aortic valvuloplasty showed disappointing outcomes, with only 1 of 12 fetuses going on to have a 2 ventricular repair (5), further discouraging advancement of the field. A similar fate was had for fetuses with severe pulmonary valve disease with the first report in 2002 (6) and limited acceptance thereafter. In 2004, Tworetzky et al. (7) published the experience at Boston Children's Hospital, rejuvenating both interest and controversy. Aortic valvuloplasty was successfully performed in 14 of 20 fetuses, of whom 3 went on to have a biventricular circulation. In 2009, the group reported additional outcomes in 70 fetuses (8), 52 of whom had a technically successful intervention with 17 achieving a biventricular circulation. Since their original report, the group has gone on to perform >100 procedures and has reported on technique, outcomes, and criteria for successful intervention (8,9). Other investigators have achieved similar results. In Austria, 16 of 23 fetuses had a successful intervention for aortic stenosis, with 10 achieving a biventricular circulation (10).

Despite single-center reports of success, uncertainty persists, and acceptance of fetal cardiac intervention remains limited, partly due to unanswered questions regarding the natural progression of aortic stenosis to HLHS in utero and the lack of formalized study of the procedure and outcomes. Recently, the American Heart Association released the first scientific statement on the diagnosis and treatment of fetal cardiac disease (11). Comprehensive reviews of published reports revealed that there was not significant

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evidence to support the widespread recommendation for fetal cardiac intervention, given that studies had small sample sizes, no control groups, and no long-term follow-up. The statement concluded, "Given the rarity of many conditions, national and international multidisciplinary collaboration is essential as we embrace our role as specialized caregivers for fetuses with cardiovascular disease" (11).

This is not a new concept. In 2005, Kleinman (12) compared the experience and challenges of fetal cardiac intervention to that of treating myelomeningoceles, in a U.S. National Institutes of Health trial in which enrollment was affected by anecdotal clinical experience, setting up a bias that the procedure was effective. The author stated "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" (12). He suggested a prospective multicenter trial to address the nuances of technical performance of the procedure, to evaluate short-term and mid-term results, and to compare these results with those of children undergoing various forms of palliation for HLHS. An alternative plan proposed by Mellander et al. (13) to create a registry, though not ideal, offered a reasonable alternative. The authors state, "Although randomized trials would be desirable, the practical issues of recruiting sufficient sample sizes and controlling for variation in practice across multiple sites is not to be underestimated. Multicenter registries, analyzed free of bias, may be an alternative way to improve the evidence base of fetal cardiac therapy."

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In this issue of the *Journal*, Moon-Grady et al. (14) have taken on the task of pulling together experts in the field to collaborate and create the International Fetal Cardiac Intervention Registry (IFCIR) to build the platform needed to gather the data we have been calling for over the past decade. This article represents the initial report of the registry and sets the groundwork for future publications from this rich and expanding dataset. Established in 2010, the IFCIR collects data for maternal/fetal dyads and newborns who were referred and evaluated as possible candidates for fetal cardiac intervention. Forty institutions from 15 countries are represented, and 370 cases have been entered thus far, 245 of whom had an intervention, including 186 aortic valvuloplasties (of which 100 from 1 institution were excluded in order to remove overlap and facilitate comparison), 16 pulmonary valvuloplasties, 37 atrial septal cases of HLHS, and 6 unclassified cases. The majority of interventions were performed percutaneously with either regional or local anesthesia. Of 15 centers reporting an intervention, case volume ranged from 1 to 132, with 7 performing 3 or fewer cases and 2 reporting more than 20 cases.

Exploratory analysis of the data was performed to compare outcomes of the intervention group versus those of patients who met criteria but who had no intervention or had an unsuccessful one. Overall survival was not affected by intervention; fetal survival to live birth was 80.0% in the intervention group and 85.2% in the nonintervention group; survival to discharge was 57.5% and 59.3%, respectively. In the subgroup of fetuses with aortic stenoses and evolving HLHS, live-born infants were more than twice as likely to be discharged with a biventricular circulation after successful fetal intervention than those who had no fetal intervention or the intervention was unsuccessful (42.9% vs. 19.4%, respectively). When fetal deaths were counted as intervention failures, outcomes were similar, with an increased percentage of patients discharged with a biventricular circulation after successful intervention (31.3% vs. 18.5%, respectively). Of HLHS fetuses considered for atrial septal intervention, 37 underwent interventions. There were no differences in overall survival, although diagnostic criteria for intervention were not uniform. Finally, 16 fetuses underwent pulmonary valvuloplasty; of these, 42.9% were discharged with biventricular circulation compared to 37.5% who were discharged without intervention.

Comparison of IFCIR outcomes after fetal aortic valvuloplasty to those of recently published data from single-center reveals similar findings. In Boston (9), 77% of fetuses had a successful intervention, with 45% resulting in a biventricular outcome. In Austria (10), after an early "learning curve," 79% of interventions were successful, with 67% of interventions achieving biventricular circulation. Similarly, registry data revealed that 81% of fetuses with aortic stenoses had a technically successful intervention and that 43% of those who were live-born were discharged with biventricular circulation. Additionally, despite concerns regarding differences in post-natal care and catheter and surgical strategies, the percentage of registry patients who ultimately had biventricular repair matched the outcomes in the larger, single-center Boston and Austrian experiences (9,10). Finally, the overall registry procedure-related complication rates were similar to those of the Boston and Austria experiences. These data all support the concept that the procedure can be done successfully in specialized centers as long as expertise is present.

There are inherent limitations of using registry data to draw overarching conclusions and make definitive recommendations. First and foremost, the lack of randomization precludes a true control group to determine whether those who receive intervention have outcomes similar to those who do not. Although this issue is addressed by using fetuses with unsuccessful interventions as control subjects, this is not ideal and not truly representative of the affected population. Second, there is no uniformly accepted strategy for determining post-natal surgical care for these patients, including accepted criteria for biventricular repair. It is important to note that post-natal management is essential to treating newborns with aortic stenoses and a borderline left ventricle. Key factors, including access to specialized interventional catheterization procedures and innovative surgical techniques, must be considered. Different care strategies from individual practices may introduce center bias, making it difficult to ascertain whether fetal intervention or specialized post-natal care determines success. Also, although most practitioners believe it is more beneficial for a patient to have biventricular repair than single-ventricle palliation, the long-term benefits of strategies that begin with fetal intervention remain unknown. Comparative analysis of long-term outcomes of fetal intervention as an alternate strategy through detailed follow-up is imperative. Finally, alterations in brain development and brain injury in fetuses with aortic stenosis versus those with HLHS will need to be addressed. Data suggest that lack of antegrade aortic flow may have an impact on brain maturation in the third trimester (15). Careful assessment of brain development and injury in fetuses with aortic stenosis post-fetal intervention will need to be investigated.

In conclusion, the power is truly in the numbers. Individual centers have shown that fetal cardiac intervention can be performed successfully, with minimal risk to the mother and encouraging outcomes for fetuses, particularly in those with aortic stenoses evolving to HLHS. This first IFCIR report (14) has shown that fetal cardiac intervention is being performed successfully worldwide, that the procedure has now become safer using percutaneous access and local or regional anesthesia, and that pregnancy outcomes and survival rates are similar, despite different practices in post-natal care. Given the small number of fetuses with cardiac defects amenable to fetal intervention, a multicenter randomized trial is unlikely. It is imperative, however, that we continue to move forward in the field. Only if we work together and collaborate as a medical community, pooling our experiences and data, will we succeed. The IFCIR represents a major step forward in the field of fetal cardiology. Hopefully, the answers to our burning questions are close at hand.

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