Controversy About a High-Risk and Innovative Fetal Cardiac Intervention

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A 20-week-old fetus was diagnosed with critical pulmonary valve stenosis. Given the ultrasound findings, the outcome was difficult to predict. The fetal cardiologists discussed the possibility of a pulmonary valvuloplasty (an experimental procedure) with the parents, wherein the fetal right ventricle would be punctured with a long 18G needle, and through it, a wire advanced across the pulmonary valve, allowing for balloon dilation of the valve. The experimental procedure had been performed at a handful of centers. There were some reports of success. The parents sought an opinion at one of the referral centers that had tried the procedure. The doctors there recommended against it. The doctors at the original center were unsure whether they should try the procedure. The parents wanted it. In this ethics rounds, doctors and the parents discuss the arguments for and against a high-risk, innovative in utero procedure.

Innovative Fetal Cardiac Intervention

Dr Edwards conceptualized and designed the case report, drafted the case report, and reviewed and revised the manuscript; Drs Justino, Feudtner, Lantos, Morris, Rychik, and the parents contributed to the design of this article, the drafting of the manuscript, and the review of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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had never performed this procedure before but a handful of centers had reported some success.

The couple sought a second opinion at one of those centers. There, the cardiologists recommended against the procedure because the tricuspid valve annulus was only mildly hypoplastic and growing. In their opinion, this was a promising sign that the infant might have a good postnatal prognosis. Thus, they thought the risks of a prenatal procedure outweighed the benefits. The family was dissatisfied with this recommendation. They returned to the original center and requested that the procedure be done there. On repeat echocardiogram, the coronary fistulae were larger. This made the procedure somewhat riskier, because piercing one of those fistulae would likely result in catastrophic bleeding.

The cardiology team weighed the risks and benefits. If technically successful, the procedure might improve growth of the fetus’ right heart, perhaps making a postnatal biventricular repair more likely. There was no guarantee of these benefits. The risks of the procedure included fetal arrhythmia, bleeding, hemopericardium, tamponade, premature delivery, and death. If the procedure was not done, this patient was at risk of progressing from critical pulmonary stenosis with intact ventricular septum to pulmonary atresia (ie, an imperforate valve). The worst-case scenario was that this progression could lead to the severest form of pulmonary atresia with intact ventricular septum, that is, right ventricular dependent coronary circulation. In this form of the condition, postnatal perforation and pulmonary valvuloplasty would be contraindicated, rendering the right heart completely irreparable; the child would thus receive single ventricle palliation or an eventual heart transplant.

The parents were eager to do what was best for their child. They were well-educated and asked many questions, seemed to understand and accept the risks, and stated clearly that they preferred a fetal intervention with the hope of achieving a 2-ventricle circulation for their child despite a moderate risk of fetal demise. They were willing to take that risk to avoid progression of the disease such that single ventricle palliation or transplant would be likely.

The cardiology group was divided. The interventionalist argued that innovation cannot happen without risk, that the parents clearly understood the risks, and there was a possibility that intervention would lead to a better outcome for the child. Others disagreed and thought that risks of the procedure were too high, and that the prognosis without the procedure was acceptable. The central question was this: Given that doctors disagreed, the risks were high but acceptable to the parents, and that an experienced center had recommended against the procedure, should this center, which had never done the procedure, perform the procedure on this patient?

Drs Edwards, Justino, and Morris

Comment

Critical pulmonary stenosis and/or pulmonary atresia with intact ventricular septum encompasses a spectrum of congenital heart disease with highly variable outcomes. This fetus, in particular, fell in a gray zone of disease severity in which it was challenging to predict whether the infant would have a biventricular, single ventricle, or 1.5 ventricle repair. When different published prediction models were applied, predicted outcomes were conflicting. The tricuspid valve z score, which is considered one of the best predictors of whether a patient will achieve a biventricular repair, hovered around the discriminatory line of –3.0. The right ventricular cavity was relatively large for this disease, but coronary fistulae, which are associated with a lower likelihood of a biventricular repair, were clearly apparent on fetal imaging. As far as we are aware, no current algorithms predict RV-dependent coronary arteries, the direst co-existing condition in this disease. Our fetal center was divided about whether we should offer intervention. The arguments are described in the subsequent sections.

Pro-Intervention Faction

Although we could not predict with certainty the progression of this fetus’ right heart hypoplasia and postnatal outcome, the models by Roman et al and Gardiner et al both predicted a nonbiventricular repair, and the model by Gómez-Montes et al predicted a probable nonbiventricular repair. Only Salvin’s et al model, which is based solely on tricuspid annulus z score, predicted a biventricular repair. In utero pulmonary valvuloplasty may improve growth of the fetus’ right heart and make a biventricular repair more likely. It may also decompress the RV and prevent development of RV-dependent coronary circulation, a condition which requires single ventricle repair and significantly worsens the prognosis. Children undergoing single ventricle repairs with RV-dependent coronary circulation carry high interstage mortality because of a high risk of myocardial ischemia. Although there is certainly risk to the procedure, Boston Children’s Hospital, the center with the most experience, reported 0 mortality as a result of procedural complications. Furthermore, the parents understood and accepted the risk and wanted to move forward with fetal intervention. Given the potential to alter the course of the disease, and with definite parental understanding of risks and a desire to proceed, we argued we should move forward with the procedure.
The benefit of in utero pulmonary valvuloplasty in neonates with critical pulmonary stenosis and intact ventricular septum is not well established, and it is possible we could perform the procedure, have negligible growth of the right heart, and still need to proceed with a single ventricle palliation. It is also possible that without any fetal intervention, the child would have a biventricular repair or a 1.5 ventricle repair with a relatively good prognosis. The serious risks of the procedure, however, are definite. If the mother went into labor or the child developed an arrhythmia or hemopericardium that necessitated delivery, the neonate would have an extremely poor prognosis with this gestational age and heart defect. The procedure is also technically challenging, and physicians at the Boston Children’s Hospital reported technical failure of their first 4 attempts of 10 total published procedures although with no related mortality. Physicians associated with The International Fetal Cardiac Intervention Registry, which has reported the largest series of fetal pulmonary valve interventions (n = 16), reported a 25% procedure-related fetal death rate. Although we had performed other fetal interventions, we had not performed a fetal pulmonary valvuloplasty. We questioned whether our first attempt should be a patient with questionable indication and particularly technically challenging features because of the presence of large coronary fistulae. Finally, we questioned whether we should incur a significant risk of fetal demise to try to prevent a 1.5 or single ventricle outcome with a functioning left ventricle (LV). Furthermore, authors of long-term studies of this disease do not clearly show a difference between patients with single ventricle palliation, 1.5 ventricle palliation, or biventricular repair. We believed the real risks of the procedure outweighed the theoretical benefit and argued against the procedure.

**The Parents (John and Katie)**

We first found out about our infant’s (JJ) congenital heart defect during a fetal echocardiogram indicated because of my (Katie) autoimmune disorder. The echocardiogram was initially performed to check for fetal heart block. An unrelated structural defect was an unexpected finding.

I remember sitting in the examination room while our doctor sketched what a “normal” heart should look like and immediately being overwhelmed with emotions and fear for our unborn infant. The initial diagnosis was thought to be moderate pulmonary stenosis. After a thorough explanation of what this meant, John and I were reassured that although this was serious and the full prognosis unknown, that most likely a routine valve replacement after birth would be all he needed.

Two weeks later, a follow-up echocardiogram revealed that the pulmonary stenosis had gone from moderate to severe and was borderline atresia. A whole new wave of emotions hit. We had gone from “scary but fixable” to something significantly more serious. Our infant might need multiple open-heart surgeries and possibly even a heart transplant. We were afraid. If this change had occurred in a mere 2 weeks, what was going to happen over the remainder of my pregnancy? A daunting 18 weeks of helplessness stood ahead.

We were overwhelmed with questions: Would the pulmonary stenosis even allow the right side of his heart to grow? How can an infant survive with only half a functioning heart? How many surgeries will he need? Will his life be one of repeated painful procedures with no guarantee of ultimate success?

John and I immediately met with the cardiologists at our top-rated children’s tertiary center. It has a large pediatric cardiology center and experience performing open-heart procedures. They talked us through the typical postnatal treatment of a pulmonary stenosis patient: everything from first few days of life to Blalock-Taussig shunt, Glenn shunt, Fontan procedure, etc. It seemed like the list of procedures and operations was endless. They informed us that based on the current echocardiogram images, JJ’s prognosis was concerning but ultimately unknown. They estimated the likelihood of a successful biventricular repair to be minimal. He was most likely heading toward a path of a single ventricle heart, which was one of our biggest fears. We were crushed. Through our research we had learned about the true reality of what that meant. Although doctors quoted us low mortality rates for subsequent surgeries, we were concerned about his future quality of life. Was there something other than the already proposed postnatal options that would give him a better chance at living a healthy life?

Just when we thought we had no options, our fetal cardiologist mentioned that in rare cases of pulmonary stenosis and/or atresia, a life-altering fetal intervention can be performed that would open up the pulmonary valve and possibly allow for a biventricular system, which was our best outcome. She referred us to 3 fetal cardiology centers that have experience with early cardiac fetal intervention to see if JJ was a candidate for the procedure. The next few days were spent holding our breath, anxiously waiting to hear if any of the doctors would take our case.

Over the next few weeks we incurred the expense and turmoil of traveling back and forth to 2 of the fetal centers to meet with fetal interventionists to have them review our case. We learned what the fetal intervention would entail.
and the potential benefit it could have for JJ’s heart. All of the sudden, we felt like we had a shot for a biventricular repair; JJ’s whole heart could have the chance to function. However, the procedure had only been performed a handful of times and the doctors were not certain it was worth the risk. We had to weigh putting JJ through the risk of the fetal procedure against holding off and “waiting” to see how his heart functioned after he was born.

As we went back and forth on the decision to move forward the optimism from the cardiology teams seemed to ebb and flow. No one could give us a clear-cut answer. We became obsessed with the numbers and z scores. We asked many questions.

Had the tricuspid valve annulus grown?
Yes.
By how much?
Not enough.
Is there still flow across the pulmonary valve?
Barely.
What is the velocity?
Low.
Had the RV grown?
Yes, but it was still small.

At each echocardiogram, we were happy to see some growth but that also meant his prognosis remained in this gray zone. It was growing enough for the doctors to think that the right heart could have the potential to be viable but not growing enough to fully relieve our concern.

At this point 1 institution had offered us the procedure and 1 had recommended against it. After numerous discussions with doctors and each other, we felt like the fetal intervention was right for JJ. We understood the risk was high, and in the worst case could result in losing our infant, but the thought of not doing anything and subsequently having an infant who could suffer the rest of his life swayed our decision.

We met with the institution willing to perform the procedure and set a date. One last fetal echocardiogram was performed and to our dismay, large coronary fistulas were found, which further complicated the procedure and brought back into question the safety of moving forward. The team was unsure whether they would be willing to proceed. Our families had all come to town to support us.

We could not believe that the decision was not ours alone to make. We were comfortable with the fact that JJ’s heart would never be perfect and understood that the intervention had risks, but we were still eager to do anything in our power to give JJ the best chance to lead a healthy life. We didn’t understand why, in this gray zone, our willingness to move forward was not the only opinion that mattered.

**Drs Rychik and Feudtner Comment**

Three interrelated but distinct questions arise from this case:

First, which treatment strategy (fetal intervention or conventional postnatal therapy) is most likely to result in the best outcome, that of a close-to-normal 2-ventricle system?

Second, why do reasonable people (parents and clinicians) answer the first question differently? And third, how should we resolve disagreement about what to do, between parents and clinicians or among clinicians, when conflict arises?

Regarding the first question about treatment strategy, let’s focus briefly on the LV before considering the RV. Criteria for fetal prediction of a single ventricle outcome when the LV is small exist and are generally agreed on. If these criteria are met, recruitment of the LV has been successfully demonstrated by experienced centers through fetal balloon valvuloplasty of the aortic valve.\(^{11}\)

The situation for the RV is different. Predicting for a small, nonviable RV is much more challenging. Currently, no community-wide accepted criteria exist for predicting RV inadequacy long-term after birth based on fetal findings. In addition, we poorly understand which fetus with mild RV hypoplasia and pulmonary stenosis will evolve and develop toward pulmonary atresia and a prohibitive RV for 2-ventricle repair during fetal life. One point that is clear, though, is that the likelihood of a fetus with pulmonary stenosis (as in the current case, and not pulmonary atresia) ultimately resulting in a single ventricle outcome is relatively low.\(^{12}\)

Why is the RV so different from the left? Essentially, smallness or inadequacy of the RV is much more forgiving than would be the case for the LV, with a greater degree of abnormality and hypoplasia amenable to a 2-ventricle system outcome. Although the left-sided systemic circulation needs a well-defined LV structure and good LV myocardial function to perform the task of systemic arterial perfusion, the right-sided pulmonary circulation is more accommodating. Significant RV structural hypoplasia and marked abnormality can be well-tolerated and, importantly, surgical strategies toward recruitment can take place well after birth. Said differently, the LV has to be fit and ready for work at birth, whereas the RV can be impaired, with surgery undertaken to support the pulmonary circulation while the RV grows and develops over the first few months or years of life. Specifically, even small RVs can be recruited through surgical or catheter-based opening of the RV outflow tract, and placement of a shunt as a temporary support for pulmonary blood flow. This strategy is well-defined and will often result in the goal of a 2-ventricle system.\(^{13}\)

For these reasons, we believe that the treatment strategy most likely to result in the most desirable outcome, that
of a successful 2-ventricle result, is a conventional postnatal therapeutic approach, not a fetal intervention. Indeed, the likelihood of failure with a conventional postnatal strategy in this individual case seems low.

Regarding the second question of why reasonable people would reach a different and strongly held conclusion about the optimal treatment strategy, answers typically point to differing values, perspectives, or preferences; to different tolerances of risk or making decisions under conditions of uncertainty; or to the substantial problems we humans have in thinking about probability. Although these are all important factors, we are going to focus here on 2 factors that are especially pertinent to this case.

First, the medical details and outcome data that could inform decision-making in this case are wrapped in a large set of narratives and considerations that may influence decision-makers, often unwittingly. Fetal intervention offers the promise of altering nature and changing the human substrate before birth, and this concept is extremely attractive. Fetal intervention is also imbued with a seemingly magical, almost other worldly mysticism. And attempting any new and exciting procedure can be alluring. All these factors would shade decision-making toward a fetal intervention. In the other direction, a strong policy argument can be made that such rare, uncommon procedures should be limited to highly experienced centers in a regionalized manner. This shades decision-making in the other direction. From an ethics point of view, all these considerations are not specific to this case, and their influence on decision-making for this particular patient should be limited.

Second, there is the phenomenon of postdecision dissonance. When confronting a complex medical decision with 2 or more plausible treatment strategies, even if a decision-maker initially realizes that there are pros and cons to each of the strategies such that no one strategy is clearly superior, once the decision-maker starts to choose a particular strategy, all former awareness of the uncertainty of which strategy to pick starts to evaporate. In controlled experiments in which participants are asked to choose between 2 options that were previously given equal ratings (eg, a free gift of a toaster or a coffee maker), after the decision participants increase the value ratings of the option they chose and lower the ratings of the other options. The more similar the options are, the greater the rating changes after the decision. One explanation for this is that individuals experience dissonance (a state of unpleasant conflict or arousal) after making a difficult decision, and then seek evidence supporting their decision to reduce their dissonance. The act of reappraisal of the options helps to regulate emotions, and happens at the moment of decision without much deliberation. Conflicts can then ensue between decision-makers who started off ambivalent about each option yet made different choices, in the process becoming more committed to their choices. Such disagreements can worsen if each individual interacts with others who support their decision, causing each individual to become more extreme in their decision.

As for the last question, how to resolve disagreement about what to do when conflict arises, there is of course no easy answer. A useful technique can be to have a discussion in which everyone contributes the pros and cons of each strategy and to have a facilitator write these down where everyone can see them. This helps to reestablish a sense of decisional equipoise both for individuals and for the group as a whole. Further facilitation of dialogue using other tools of mediation can also help. In the end, though, if conflict remains for decisions in which 2 reasonable yet complex treatment strategies exist, no party should be able to compel another party to move in forced partnership down a long, arduous, and risky path.

**OUTCOME OF THE CASE**

The cardiology team ultimately decided not to proceed with the intervention. They felt that the risks were too high and that there was not conclusive evidence that we would improve the postnatal outcome. The tricuspid valve continued to grow over the remainder of gestation period, with stable tricuspid regurgitation, as did the RV, and the fetus did not develop pulmonary atresia. JJ was born at 39 and 2/7 weeks’ gestation via cesarean delivery for nonreassuring fetal heart tones. Apgar scores were 8 and 8 at 1 and 5 minutes. Umbilical lines were placed in the delivery room, and he was started on prostaglandin infusion. An echocardiogram performed shortly after birth revealed critical valvar pulmonary stenosis with trivial prograde flow, moderate tricuspid valve hypoplasia, and moderately hypertrophied and mildly hypoplastic tripartite RV. Curiously, the multiple coronary fistulae arising from the RV were much smaller in appearance compared with the fetal echocardiogram. There was no evidence of heart block.

He underwent catheterization on day of life 2. Angiography confirmed that the coronary circulation was not right ventricular-dependent, so we proceeded with balloon pulmonary valvuloplasty with a decrease in right ventricular pressure from 2 times systemic to 3/4 systemic and a residual gradient of 16 mm Hg across the pulmonary valve with mild to moderate pulmonary regurgitation. He was unable to wean off prostaglandin and so
underwent repeat catheterization for stenting of the ductus arteriosus on day of life 10. JJ was discharged from the hospital at 2 weeks of age with an oxygen saturation of 85%. At 5 months of age, JJ underwent a third catheterization for partial occlusion of his atrial septal defect, with the hopes of augmenting right ventricular filling volumes, growing his RV, and optimizing his chances of a biventricular circulation. In the short-term, he has tolerated partial closure of his atrial septal defect well, with improved saturations and no signs of right heart failure. It remains unclear if his RV will grow adequately to allow for a biventricular repair.

**Dr Lantos Comments**

In 1986, Rothman introduced the concept of “the tentative pregnancy” to describe the new situation created by the widespread availability of amniocentesis. She described how the new field of fetal diagnostics forced women to make decisions that they never had to make before. Since then, advances in fetal diagnosis and fetal intervention have made prenatal decisions exponentially more complex. It used to be that, during pregnancy, the pregnant woman was the only patient and prenatal care was focused on keeping her healthy. Today, there are clearly 2 patients: the pregnant woman and her fetus. This forces doctors and parents alike to deal with a far more complex set of ethical calculations. This thoughtful discussion by the treating physicians, the parents, and outside experts illustrates how complex this can be and how, even with the best evidence, there is still a need to make judgments and choices that may turn out wrong. Fortunately, in this case, they seemed to turn out right.

**ABBREVIATIONS**

LV: left ventricle
RV: right ventricle

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