Can We Do a Prospective Trial for Fetal Tachycardia? The Barriers to Clinical Trials in Small Patient Populations

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Jaeggi and colleagues have added to the literature with their extensive assessment of 159 fetal tachyarrhythmia cases collected from 3 institutions over a 10-year period. However, before we comment on their study, it is worth reviewing some of the relevant issues for management of fetal arrhythmias. An estimated 0.4% to 0.6% of pregnancies have a fetal arrhythmia at some point during the pregnancy. Although the vast majority are not of clinical significance and require no treatment, a much smaller percentage have a sustained tachyarrhythmia that can be life-threatening to the fetus. The most frequent serious arrhythmias in the fetus are supraventricular, most commonly from atrioventricular reentry tachycardia involving an accessory atrioventricular connection (supraventricular tachycardia [SVT]) or atrial flutter, but occasionally from atrioventricular node reentry (also SVT) or ectopic atrial tachycardia. Here, we refer to all these mechanisms together as supraventricular arrhythmias (SVAs) and the subgroups of interest as SVT or atrial flutter. Importantly, SVAs can lead to tachycardia-induced cardiomyopathy because of prolonged decreased cardiac output and myocardial fatigue, which can lead to hydrops fetalis and rare fetal death, as reviewed by Jaeggi et al. Treatment options include careful observation, maternal drug therapy, or delivery of the fetus.

More than 20 studies have looked at outcomes of drug therapy for fetal SVA, some of which are reviewed by Jaeggi et al. The most commonly used antiarrhythmics are digoxin, flecainide, sotalol, and amiodarone, but many drugs have been used less frequently, and results vary widely. In the studies using digoxin as first-line therapy, successful conversion has been reported in 50% to 100% of fetuses without hydrops, but only 0% to 20% of patients with hydrops. Flecainide has resulted in sinus rhythm in 58% to 100% of fetuses without hydrops and 43% to 56% of those with hydrops, whereas sotalol has been successful 40% to 100% of the time without hydrops and 50% of the time in fetuses with hydrops. Finally, amiodarone had conversion success in 50% to 93% of fetuses with SVA. The results from the larger of these studies also often vary by SVA mechanism, SVT versus atrial flutter. Despite the varied results, this brief summary makes a few points clear: (1) No single agent is universally effective; (2) the presence of hydrops makes conversion less likely; and (3) the literature is confounded by data from only retrospective studies of series biased by physician and institutional preferences. Consequently, without controlled efficacy data, there can be no clear guidelines for the treatment of fetal tachycardias.

The study in this month’s journal by Jaeggi et al is a retrospective review of 159 patients managed for fetal SVA, of whom 111 underwent first-line drug therapy with digoxin (n = 24), sotalol (n = 52), or flecainide (n = 35). Patients who were started on combined therapy with digoxin plus either sotalol or flecainide were placed in the sotalol or flecainide group, respectively. A third of the fetuses received a second antiarrhythmic drug by day 10 of treatment. After 5 days of treatment for SVT, 59% of the flecainide group, 57% of the digoxin group, and 38% of the sotalol group had converted to a normal rhythm. However, sotalol tended to be more effective in the fetuses with atrial flutter, with 29% conversion by day 5 compared with 13% with flecainide and 21% with digoxin. The investigators also reported that when the SVT persisted beyond day 5, digoxin and flecainide were more effective than sotalol at reducing the ventricular rate, perhaps improving outcome. Overall, these results are confirmatory, adding a relatively large patient group to the retrospective literature, but do not really define an evidence-based best choice for initial therapy or a protocol for overall management. In fact, the authors ended up speculating that a combination of heart rate lowering and conversion therapies might be the optimal first choice for SVA, using digoxin plus flecainide for SVT and digoxin plus sotalol for atrial flutter, but could only recommend a “larger prospective study.”

As the study by Jaeggi et al demonstrates, retrospective clinical trials have multiple limitations, including various methods of diagnosis, disease definitions, severity assessments and, most important, therapy initiation, maintenance, and assessment. All of these metrics may vary by center and physicians within centers, as was the case with Jaeggi et al. For the case of fetal SVA, the additional issues of the need for any initial drug therapy and the possibility of delivery as therapy must also be taken into account; both factors are significant in the Jaeggi et al study, in which 48 of 159 patients (30%) never received drug therapy. Assessment of the results of both retrospective and prospective trials becomes even more complicated when staged therapy must be used, as is the case for fetal SVA. Finally, the institution-specific nature of the therapy bias in this trial leads to additional confusion in the interpretation of the data because the center populations varied in terms of...
disease severity, as assessed by tachycardia rate and the presence of hydrops fetalis.

Given all the above issues with retrospective studies, one might ask why these 3 centers did not perform a prospective trial or, even better, why no one has performed one for the management of fetal SVA. As is the case for so many pediatric heart conditions, the reasons (or should we say the excuses) are multifactorial. Of course, the primary limiting factors for randomized clinical therapy trials in pediatric heart disease are the generally small patient population and the clear need for a multicenter trial. Other important factors for a fetal tachycardia trial include the following: (1) hydropic fetuses may need more aggressive therapies than the nonhydropic group in a trial (26% in the study by Jaeggi et al); (2) no single or even 2 therapies have dominated in the literature, potentially leading to the need for a multiarm trial and for many more subjects; (3) staged therapy is probably appropriate, again increasing the number of necessary subjects; (4) there are many physician and institutional biases for therapy, as seen in the Jaeggi et al study; and perhaps most important, (5) pediatric cardiologists and perinatologists/obstetricians are typically involved in the care of the mothers/fetuses, with 1 group or the other dominating the care in different centers. Finally, a placebo-controlled trial would of course be ideal; however, in other planned trials for rare pediatric arrhythmias, in which drug therapy has been a standard of care, it has not been possible to convince investigators to design a placebo-controlled trial (eg, intravenous amiodarone trial15). Despite the above limitations, one can estimate both the number of subjects needed for a randomized trial and the number of subjects available for enrollment. The simplest trial to design and perform would include 2 therapy arms for all fetuses with tachycardia (hydropic or not), such as digoxin versus flecainide, digoxin versus sotalol, or flecainide versus sotalol. If we hypothesize that a 20% difference in efficacy exists between therapies (50% versus 70%), a trial with 80% power and an α of 0.05 would require ≈80 subjects in each arm (160 in total).17 A still-straightforward 3-arm trial with differences between groups of 20% (30 versus 50 versus 70%) would require ≈100 subjects per group (300 in total).18 Without specifics, it is hard to estimate the subjects needed for more complex trials (eg, including placebo, amiodarone, double, crossover, and staged therapy), but there is no doubt that the number would be even higher. With an estimated 80% consent rate, the number of required subjects would be 200 to 500, depending on the study design. It is worth noting that it took Jaeggi et al 10 years to collect 111 therapy cases from 3 prominent centers; however, we do not know the denominator for the number of deliveries at those centers or the number of fetuses with SVA not included in the study. Looking at it another way, one could estimate the total US deliveries at those centers or the number of deliveries at those centers or the number of patients with hypoplastic left heart syndrome were enrolled from 15 centers over a period of 3 years in a randomized trial of 2 different Norwood procedure surgical techniques.20 With ≈1000 live births with hypoplastic left heart syndrome per year in the United States (3000 over 3 years), these 664 infants represent ≈20% of all the eligible US infants in that 3-year period, a larger percentage than would be required for a fetal tachycardia study. There also may be a unique opportunity to combine the capabilities of the 9 PHN clinical centers with the 14 clinical centers (~150 000 deliveries per year) of the Maternal Fetal Medicine Unit Network of the National Institute of Child Health and Human Development, which perform randomized trials in pregnant mothers and by chance has minimal institutional overlap with the PHN. Together, these 23 centers (PHN plus Maternal Fetal Medicine Unit Network) should have access to more than enough eligible fetuses with tachycardia and would have the expertise and the necessary funding to perform a randomized trial of fetal SVA therapy.

So back to the question posed in the title: Can we do a prospective trial for fetal tachycardia? The answer appears to be “yes.” The only real question is, Do we have the interest and will?

Disclosures
None.

References


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