Fetal Arrhythmia Diagnosis and Pharmacologic Management

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Abstract

One of the most successful achievements of fetal intervention is the pharmacologic management of fetal arrhythmias. This management usually takes place during the second or third trimester. While most arrhythmias in the fetus are benign, both tachy- and bradyarrhythmias can lead to fetal hydrops or cardiac dysfunction and require treatment under certain conditions. This review will highlight precise diagnosis by fetal echocardiography and magnetocardiography, the 2 primary means of diagnosing fetuses with arrhythmia. Additionally, transient or hidden arrhythmias such as bundle branch block, QT prolongation, and torsades de pointes, which can lead to cardiomyopathy and sudden unexplained death in the fetus, may also need pharmacologic treatment. The review will address the types of drug therapies; current knowledge of drug usage, efficacy, and precautions; and the transition to neonatal treatments when indicated. Finally, we will highlight new assessments, including the role of the nurse in the care of fetal arrhythmias. The prognosis for the human fetus with arrhythmias continues to improve as we expand our ability to provide intensive care unit–like monitoring, to better understand drug treatments, to optimize subsequent pregnancy monitoring, to effectively predict timing for delivery, and to follow up these conditions into the neonatal period and into childhood. Coordinated initiatives that facilitate clinical fetal research are needed to address gaps in knowledge and to facilitate fetal drug and device development.

Keywords

antiarrhythmic drugs, arrhythmia, congenital heart block, fetal arrhythmia, fetal magnetocardiography, fetal echocardiography, fetal pharmacology, fetal tachycardia, long QT syndrome, torsades de pointes

Collaborations between pediatric cardiologists and obstetricians to implement drug treatments for tachy- and bradyarrhythmias have led, in some of the cases, to dramatically successful outcomes for rhythm disturbances that had previously resulted in premature birth, hydrops, and death. Fetal echocardiography became a mainstay of both anatomic and rhythm diagnosis and improved over the decades, implementing advanced 2-dimensional, M-mode, color Doppler, and pulsed Doppler techniques.

Diagnostic Approach of Fetal Arrhythmia

Electrocardiographic monitoring never developed in the fetus, due mainly to technical reasons such as the near-complete insulating effect of the fetal vernix and maternal tissues that made it impossible to consistently record a fetal cardiac signal from the maternal abdominal surface. Fetal electrocardiography was complicated further by fetal movement. Cardiotocography, a Doppler-based fetal heart rate monitoring technique, remains largely restricted to normal fetal rhythm and heart rate (HR) assessments in the third trimester and during labor, leaving a major gap in arrhythmia assessment of the high-risk fetus.

During the early parts of the 21st century, a small number of medical physics laboratories from around the world were recognizing that fetal electrocardiographic monitoring would likely never offer the capabilities that electrocardiography offers postnatally. They began evaluating super-conducting quantum interference devices, that capture the electrocardiogram-analogous magnetocardiogram. Rather than catching on, with implementation in every fetal care center, super-conducting quantum interference devices have been largely restricted to a few labs due to the expense of helium and magnetically shielded rooms.

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Fetal SVT at 25 wks GA, transplacental Dig/Flecainide
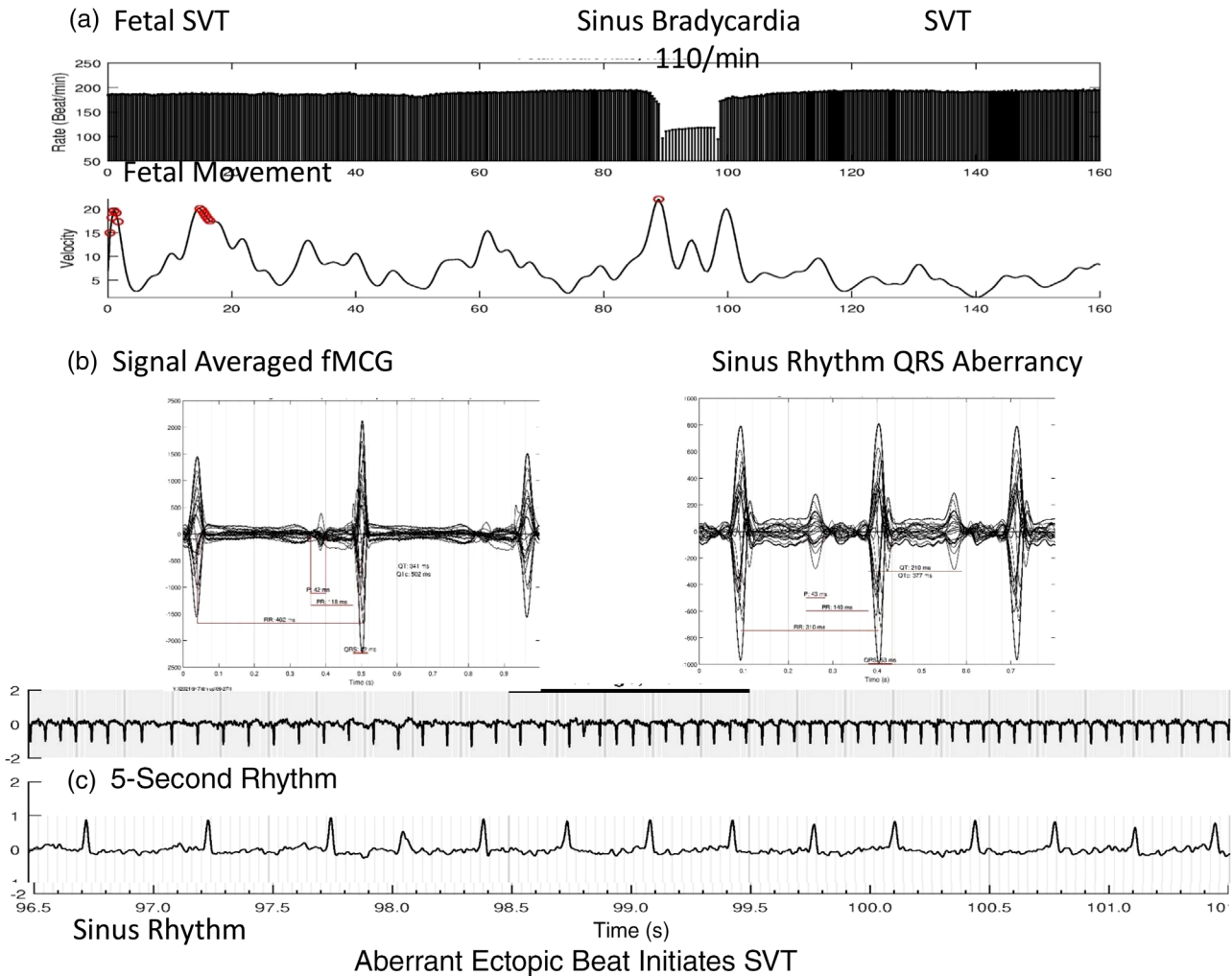
Figure 1. Fetal SVT. (a) Heart rate trend over 5 minutes. In this case, the fetus is in SVT at about 194/min for nearly the entire tracing. Sinus bradycardia at 110/min is likely due to the transplacental effects of digoxin and flecainide. (b) cardiac time intervals in both sinus rhythm and SVT with 1:1 VA conduction. Note that the QRS is wider during SVT, likely related to flecainide effect. (c) Aberrantly conducted PAC that initiates SVT. Note that T-wave inversion is present. This could be due to digoxin. Dig, digoxin; fMCG, fetal magnetocardiogram; GA, gestational age; PAC, premature atrial contraction; SVT, supraventricular tachycardia.

Figure 1 shows typical fetal magnetocardiogram (fMCG) tracings from a case of fetal supraventricular tachycardia (SVT) evaluated using fetal magnetocardiography.

A recent breakthrough in the field of biomagnetism has led to the introduction of optically pumped magnetometers, which are compact, inexpensive, and can be used within a person-sized noise-reducing shield rather than requiring a large shielded room.[1,2] These may be ready for Food and Drug Administration (FDA) approval within 2 years. Meanwhile, some centers continue to try to develop fetal electrocardiography, but to date no commercial models are approved for precise arrhythmia diagnosis.

Unique Aspects of Pharmacologic Treatment of the Fetus

The treatments for various arrhythmias are rhythm specific and, to a large extent, still based on limited actual pharmacologic drug data due to the invasive nature of sampling the fetus.

Table 1 shows the unique aspects of treatment of the fetus as compared to treatment of the infant.

Treatment of the fetus is quite different from treatment of the infant or child. The most common approach is transplacental therapy (TPT), where the pregnant patient is given escalating and sometimes top-therapeutic doses of antiarrhythmic or other

Table 1. Differences in Pharmacological Treatment Between the Fetus and Neonate/Infant

	Fetus	Neonate/Infant
Knowledge of treatment of arrhythmias	Limited published experience (<20% of the infant studies), mainly from fetal care centers, within the past 4 decades, even less published for direct fetal therapies	Small to medium case series have been published for most major cardiac drugs used in infants
Pharmacologic assessment	Requires cordocentesis for direct drug measurement; not routine Maternal serum levels and corresponding umbilical cord concentrations can be obtained at delivery Amniotic fluid drug concentration may be higher than maternal serum for some drugs	Serum levels available for digoxin, propranolol, procainamide, flecainide, amiodarone, lidocaine, mexiletine, +/– sotalol Not routinely available for sotalol and beta blockers other than propranolol ECG and heart rate changes used as surrogate to assess drug effect
Electrophysiologic assessment	Maternal home hand-held Doppler and/or frequent obstetric monitoring critical to detecting SVT recurrence, or bradycardia; if available, fMCG can provide QRS and QTc, HR variability, and STT changes; maternal ECG helpful	Outpatient: Cardiac monitor or Transtelephonic transmitter, Holter monitor, periodic ECGs; transesophageal pacing before discharge may identify fetuses that will never have SVT again and thus do not require treatment or follow-up
Drug administration	Physiologic changes in later pregnancy (higher cardiac output and volume of distribution), play an important role in transplacental drug delivery; single transplacental drug therapy, followed by combination drug therapy or direct fetal IM or IC therapy No clearly superior first-line drug for SVT or atrial flutter; currently under study Upward dose adjustment may be needed in the third trimester.	Single drug therapy, followed by dual or combination drug therapy for refractory cases Reduced Compliance with medication administration can be seen if twice-daily or 4-times-daily dosing of drug Drug levels can be used to assess longer-term compliance; with rapid neonatal/infant growth, drug adjustment every other week is recommended on a mg/kg/day basis. Important to teach neonatal resuscitation to caregivers, and also poison prevention measures for siblings and infant. Maternal postpartum depression can impact medication compliance for infant
Drug withdrawal	Once treatment is initiated, it is usually continued to delivery	Infants after fetal tachycardia should be weaned from treatment at birth unless recent SVT. Most recurrences are within 72 hours. TEP may be useful. If postnatal antiarrhythmics are used, wean off at 6-12 months of age. Long-term, if SVT persists, radiofrequency ablation is usually done after 4-7 years of age
Long-term prognosis	87% with fetal SVT will wean from drug therapy by 1 year; 13% will still require treatment; higher for those with long-RP tachycardia	About 90% will wean from therapy; however, late recurrences can be seen in up to one-third. RF ablation is generally performed over 4-7 years of age. Younger age risks coronary injury with RF ablation

ECG, electrocardiogram; fMCG, fetal magnetocardiogram; HR, heart rate; IC, intracordal; IM, intramuscular; RF, radiofrequency; SVT, supraventricular tachycardia; TEP, transesophageal pacing.

For references, see text.

medication alone or in combination in order to reach the fetus. Most drugs are of small molecules that readily cross the placenta. Another means is direct administration to the fetus via intracordal, intramuscular, or intraperitoneal instillation. Fetal vascular access has significant risk, which will be addressed.

During the latter part of pregnancy, the physiologic changes in pregnancy that result in a higher cardiac output and volume of distribution, are an important factor in TPT. This is because increased cardiac output and decreased vascular afterload result in higher peripheral tissue and organ perfusion. A larger volume of distribution provides for higher net distribution for the drug. This often "outstrips" the gains in free drug in the circulating volume (which is increased due to

lower albumin levels).[3] Recurrences of well-controlled tachyarrhythmias can occur when maternal drug levels fall (higher distribution and lower patient compliance) or when hydrops develops (impaired transplacental flow). Digoxin has poor transplacental transfer during hydrops, and when hydrops resolves, the impact of high maternal digoxin dosing may manifest as fetal bradycardia.[4] Fetal drug effects may rise during long-term therapy with sotalol or flecainide due to accumulation of certain drugs in the amniotic space.[5,6] The placenta was once felt to be the only means of transfer of drug into or out of the amniotic fluid space, but Menon[7] has suggested that fetal membranes also contain the same enzymes as the placenta and may be important in drug transfer (both ingress and egress).

Different Types of Fetal Arrhythmias

The most common arrhythmias are isolated ectopic atrial contractions, which occur in about 1% to 2% of pregnancies. It is important to distinguish these from premature ventricular contractions. Premature atrial contractions (PACs) are commonly caused by redundancy of the septum primum or flap of the foramen ovale. They do not require antiarrhythmic treatment. They can produce bradycardia (heart rate <110/min) when PAC's alternately block at the atri-oventricular (AV) node (blocked atrial bigeminy). PACs are associated with the SVT in about 1% of ectopy cases; however, this risk climbs to 10% to 14% risk for blocked atrial bigeminy. Thus, when ectopy develops, close weekly observation or hand-held home monitors should be employed to detect SVT before the onset of hydrops, which can develop in within several days. Isolated premature ventricular contractions also do not require treatment; however, care should be taken to exclude commonly associated conditions such as ventricular aneurysms or diverticuli, tumors, congenital heart disease or cardiomyopathy, or familial long QT syndrome and other inherited arrhythmia syndromes.

Treatment of Fetal Tachyarrhythmia

Pharmacologic Treatment of Fetal Tachyarrhythmia—A Historical Perspective

Tachyarrhythmias of severity to require intrauterine treatment are seen in about 1 in 2500 pregnancies. The most serious complication is the development of fetal congestive heart failure or hydrops fetalis. Digoxin was the first drug used to treat fetal tachyarrhythmia and fetal heart failure.[8–12] This was followed shortly by the use of verapamil,[13–15] beta blockers,[15] procainamide,[15,16] quinidine,[9,15] and amiodarone.[15,17] During the 1990s, new drugs such as flecainide and sotalol came along with good transplacental transfer and effectiveness for severe life-threatening tachyarrhythmia, and these were used, alone and in combination, in fetuses with drug-refractory tachycardia.[5,6,11,12,18–23] While digoxin was about 60% effective in the absence of hydrops, it had very poor transplacental transfer in fetuses with hydrops (<20%), and beta blockers also appeared to be minimally effective. Verapamil,[13–15] which was quite efficacious for reentrant arrhythmias, had a side effect profile that included sudden demise and renal failure. Procainamide, while also effective, increased uterine irritability, and with intravenous maternal administration, could actually trigger preterm labor. Quinidine caused gastrointestinal side effects. Amiodarone, while exceedingly effective even in drug-refractory fetal tachyarrhythmia, also had many side effects, including thyroid dysfunction in both mother and fetus, and potential fetal neurodevelopmental concerns, limiting its broader application, though it is still used for the most life-threatening maternal and fetal arrhythmias.[23–27]

While direct fetal therapy with intracordal adenosine for rapid conversion or instilling other potent drugs into the fetal cord seemed enticing, the risk of direct cord access had to be weighed against the risk of fetal death from the arrhythmia. Several studies have shown higher mortality (25%-50%) in fetuses treated directly via the cord, than in those treated only with maternal medication or by intramuscular injection.[25] Intracordal adenosine has been effective in converting SVT; however, premature beats lead to reinitiations, rendering adenosine overall ineffective.

One approach, however, has proven useful for fetuses with hydrops. Intramuscular digoxin has been reported to both shorten time to conversion and improve the rate of conversion, but it has been associated anecdotally with sciatic nerve injury in about 1 in 20 cases where injection was given into the thigh or buttocks.[4]

Pharmacologic Treatment of Fetal Tachyarrhythmia—Current Perspective

The advent of the 21st century has seen more systematic evaluation of fetal tachyarrhythmia through multicenter approaches.[28] Miyoshi et al[2] published a protocol for the fetus without hydrops, starting with digoxin and adding other drugs (digoxin/sotalol then digoxin/flecainide). Overall survival was 96%, and loss was only in those with hydrops. Miyoshi et al showed that oral digoxin loading was comparable to intravenous digoxin dosing, making administration in the hospital setting safer. SVT conversion to sinus rhythm in utero was 89% without hydrops and 75% with hydrops. Those with long-RP tachycardia were responsive to sotalol. Jaeggi[29] and colleagues are currently conducting a multicenter randomized clinical trial, called the FAST trial, of 600 fetuses with SVT or atrial flutter (AFl) from at least 70 centers (and also a registry for those unable to be randomized). This study is evaluating digoxin, sotalol, and flecainide monotherapy for fetuses without hydrops with SVT; digoxin or sotalol monotherapy for fetuses with AFl (digoxin+sotalol for AFl with hydrops); and digoxin+flecainide vs digoxin+sotalol for SVT with hydrops. The study is blinded, and results will not be released until total enrollment is reached.

Impact of Fetal Tachycardia Treatment on Maternal and Child Health

Studies have shown relatively high rates of maternal side effects and premature delivery related to fetal transplacental treatment. Maternal nausea and anorexia can lead to poor weight gain. In hydrops, once sinus rhythm is restored, preterm labor can be triggered due to rapid fetal diuresis into the confined

intra-amniotic space, leading to polyhydramnios. In Miyoshi's[2] series, 20% of fetuses delivered prematurely. Rarely, amniotic fluid reduction procedures have been necessary. To our knowledge, maternal death from fetal tachyarrhythmia drug treatment has not been reported, but side effects are common and usually well tolerated.[30] These are often specific to the drug and are more common when drugs are given concurrently, in quick succession, or rapidly escalated. Daily inpatient electrocardiograms and heart monitoring or telemetry are indicated during initiation of drug therapy. For the fetus, third-trimester biophysical profiles or non-stress-testing assessments are indicated. Generally, if good control of the rhythm has been achieved, as is the case in about 75% to 90% of cases, vaginal delivery is possible.[31] The infant should be monitored in a neonatal intensive care unit (ICU) setting during the withdrawal phase from medication, and if SVT or AFl has not recurred during the first 72 hours, home heart rate monitoring or transesophageal electrophysiologic study can be considered.[31]

Mechanisms of Fetal Tachycardia and the Drugs That Are Used to Treat These

Reentrant SVT. The vast majority of fetal SVT is reentrant SVT. In this case, the fetal heart rate (FHR) is usually 220 to 320/min and regular, with a 1:1 relationship of atrium and ventricle. SVT is usually initiated by PACs.[32] The average time to conversion/control is 6 to 7 days. The fetus with sustained durations of tachycardia lasting >12 hours and with rates in excess of 200/min, with a gestation <36 weeks should receive TPT.[33] For the fetus >36 weeks, delivery can be considered, but given the need for cesarean section when delivering a baby in SVT, several major centers have now begun treating transplacentally even at this mature gestation, in the hopes that tachycardia control might afford a vaginal delivery and avert the developmental risks associated with late-preterm births. Likewise, fetuses with hydrops are sometimes treated transplacentally at gestations >36 weeks, since resolution of hydrops can improve respiratory resuscitation (E Jaeggi and BF Cuneo, personal communication, June 2022). Argument for delivery after SVT presentation >36 weeks' gestation includes the potential for directly administering drugs to the infant, as well as averting stillbirth potential and not exposing the mother to the side effects of transplacental antiarrhythmic drugs. Shared decision making with the care team and patient is optimal.

Transplacental dosing does not always lead to adequate fetal efficacy, which may necessitate higher maternal doses or even the addition of multiple concurrent drugs in order to control the tachycardia. Three drugs are generally used in the first-line treatment of SVT: digoxin, flecainide, and sotalol. Currently, none have been found to be superior for reentrant SVT. Sotalol, flecainide, and other drugs can concentrate in the amniotic fluid to levels up to 28 times the maternal serum level.[6] Maternal clearance through the placenta and possibly through fetal membranes is often sufficient to prevent fetal reabsorption of significant quantities.[34]

Atrial Flutter. Atrial flutter, which accompanies SVT in up to 30% of cases and is associated with a much higher atrial rate than SVT (atrial rates of 375-550 bpm, with ventricular rates of 190-230/min) is treated in the same way as SVT. Digoxin and Sotalol are drugs of choice for atrial flutter. Amiodarone, despite its high side effects profile, is >90% effective for controlling drug-refractory SVT; it is less so for AFl and often simply slows the flutter rate.[25]

Table 2 shows the mechanism, side effects profiles, and transplacental maternal-fetal drug concentration ratios for the commonly used drugs to treat SVT and AFl.

These doses are based on often small case series. Even when treatment goes well, these drugs have been reported to have a stillbirth rate of 4% and prematurity rate of almost 20%.[2] Much of the prematurity is due to inadequate time for transplacental conversion (which can take 3-7 days per each drug administered), and there is no question that the fetal and neonatal morbidity of delivering a very premature infant in SVT or AFl far surpasses the morbidity of transplacental treatment. There is a tendency to underestimate the time to conversion of SVT. By delivering the infant prematurely, the effective drug processing power of the placenta and maternal circulation is exchanged for the immature drug processing of the premature infant's liver and kidneys.[35] At least 40% to 60% of infants will require neonatal drug treatment[31]; therefore, having a mature neonate delivered in sinus rhythm is a marked advantage. The need for transfusions for anemia from bone marrow suppression, exchange transfusions for hyperbilirubinemia due to drug displacement of bilirubin-binding sites, and prolonged neonatal ICU care for regulating drug therapy are much higher for the premature infant. In addition, premature infants often have markedly different metabolic rates. For example, digoxin half-life can be as long as 30 hours.[35] This is an area for research.

Tachycardia. Rare forms of slower fetal tachycardia have a long VA interval (atrial ectopic tachycardia and permanent junctional reciprocating tachycardia) with a predominantly 1:1 AV relationship and can respond to sotalol, flecainide, or amiodarone. These also have

Table 2. Drugs to Treat Fetal SVT and Atrial Flutter[a]

Drug[2,6,12,25,27,28,31,74–84]	Type of Arrhythmia	F:M Drug RatioRoute	Efficacy Acute and Chronic	Elimination	Intra-amniotic	Side Effects
Digoxin Na,K-ATPase inhibitor Class C	SVT, AFl	0.8:1, ↓ if hydrops to 0.2:1 PO, IV, fetal IM/IC	50%-60%, combined with other AA 80%	Renal	Higher, not reflected in fetal	N/V, arrhythmias, anorexia, poor weight gain
Flecainide Calcium channel inhibitor Class C	SVT, AFl, AET, PJRT, VT (non-LQTS)	1:1(+) PO	60%	Renal	Up to 27× maternal serum level	CNS, bradycardia, ↑QRS, ↑QTc
Sotalol Potassium channel inhibitor/beta blocker Class B	SVT, AFl, AET, PJRT	0.9:1(+) PO	50%-60% for SVT, up to 80% for AFl	Renal	1.6-28× maternal serum level	CNS, bradycardia, ↑QTc
Amiodarone Multichannel inhibitor Class D	SVT, AFl (±), AET, PJRT, JET, VT not if ↑QTc	0.4:1, long half-life after PO loading Rare IC or peritoneal administration	90+%	Hepatic	Lipophilic, all tissues	Bradycardia, M/F hypothyroidism, ↑QTc, breastfeeding CI
Adenosine	0	Not recommended, Direct IC administration	Low	Erythrocytes	0	Short-acting

AA, antiarrhythmic agent; AET, atrial ectopic tachycardia; AFl, atrial flutter; CI, contraindicated; CNS, central nervous system; F:M, fetal:maternal; IC, intracordal; IM, intramuscular; IV, intravenous; JET, junctional ectopic tachycardia; LQTS, long QT syndrome; M/F, maternal/fetal; N/V, nausea/vomiting; PJRT, permanent junctional reciprocating tachycardia; PO, per os (orally); QTc, corrected QT interval; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
[a] For individual drug dosages, see Donofrio et al[33] or Joglar et al.[98]

a greater tendency to persist beyond 1 year of age and may require radio frequency ablation.

Fetal ventricular tachycardia (VT) or junctional ectopic tachycardia are much rarer than SVT and AFl. These are treated differently depending on the etiology. fMCG is extremely helpful in assessing these types of rare arrhythmias and in risk stratifying the cases. Many of the drugs cause corrected QT (QTc) prolongation and are contraindicated in torsades de pointes (TdP).

Table 3 lists drugs for TdP as well as for VT not associated with QTc prolongation.

Neonatal Antiarrhythmic Therapy for Tachyarrhythmias

The need for postnatal antiarrhythmic therapy varies, but conservatively, only 50% to 70% of fetal tachycardia cases will need treatment for SVT once born, since the natural history is for accessory AV connections to regress with time, and because blood flow dynamics change at birth. AFl that has been direct-current cardioverted or converted using transesophageal pacing is even less likely to recur and require neonatal antiarrhythmic agents.[36–40] Both VT and junctional ectopic tachycardia require treatment. When fetal SVT recurrences occur, about 80% will recur in the first 3 days. For this reason, a drug-free period is usually instituted shortly after birth. For those that recur, treatment is usually instituted with a beta blocker or sometimes digoxin or flecainide. Recurrence is more common with long-RP types of tachycardias. Sometimes fetal bundle branch block is noted immediately after delivery.[41–43] This is most common with flecainide, especially when its

treatments are overlapped with sotalol or amiodarone. Drug levels should be sent and the drug withheld if possible, until conduction normalizes.

Recognition and Treatment of Fetal Bradyarrhythmias

Sinus Bradycardia. Bradyarrhythmias such as persistent sinus bradycardia can be underrecognized. They can be markers for fetal long QT syndrome (LQTS), inherited bradycardia syndromes, congenital heart disease (heterotaxy with low atrial rhythm), isoimmune disease, and other life-threatening conditions. Many of the fetal arrhythmias that contribute to fetal demise are hidden from existing types of clinical assessment.[44–49] Obstetricians have generally used American College of Obstetricians and Gynecologists guidelines to establish FHR ranges, with normal FHRs being between 110 and 180 bpm.[50] But this largely ignores the gestation effect on FHR, which is significant. Several gestation-based HR norms exist[51–55] and can and should be applied to better recognize those fetuses with HRs outside the normal range for gestation. In general, bradycardia does not require treatment; however, recognition of underlying cause is important, as many of these diseases do require treatment in the fetus or neonate.

Atrioventricular Block. Sustained second- or third-degree AV block is seen most commonly in Sjogren's Antibody A isoimmunization from maternal collagen vascular disease. Currently, the StopBloQ study[56] is enrolling women at risk for development of congenital

Table 3. Antiarrhythmic Agents for VT[a]

Drug[70,74,85–92]	F:M Drug Ratio	Efficacy Acute and Chronic	Elimination	Intra-amniotic Accumulation	Side Effects
Drugs to treat all VT, including torsades de pointes					
Magnesium sulfate Class D after 48 h	1:1(+) IV, PO coadministered with Vit D if 25-OH Vit D level is low	80+%	Renal	Baseline high	CNS
Propranolol, other beta blockers Class C	0.25:1 IV, PO	Partial, ↓QTc, lowers ventricular fibrillation risk; metoprolol less effective in LQTS	Hepatic	2-4×	Bradycardia; nadolol concentrates in breast milk
Lidocaine/Mexiletine Calcium channel inhibitor	0.5:1 IV/PO	50+%	Hepatic, renal	0.5-1.0	CNS, Paradox ↑QTc
Drugs to treat VT with normal QTc, not torsades de pointes					
Flecainide Calcium inhibitor Class C	1:1	60%	Hepatic, renal	1.6-27× serum level	CNS, brady, ↑QTc
Sotalol Potassium inhibitor/beta blocker class B	0.9:1(+)	50%-60%	Renal	28× serum level	CNS, bradycardia, ↑QTc
Amiodarone Class D	0.4:1, long-term after loading	90+%	Hepatic, biliary excretion, long half-life	All tissues	Bradycardia, no breastfeeding

CI, contraindicated; CNS, central nervous system; IV, intravenous; LQTS, long QT syndrome; PO, per os (orally); QTc, corrected QT interval; VT, ventricular tachycardia.

[a] For individual drug dosages see Donofrio et al[33] or Joglar et al.[98]

atrioventricular block (CAVB). CAVB is seen in about 1% to 2% of pregnant lupus patients, 5% with active disease, and after an affected pregnancy, this risk increases to 16%.

Figure 2 shows an example of a fetus with isoimmune CAVB.

It is important to realize that maternal autoimmune disease is a risk factor for stillbirth, growth restriction, and other complications of pregnancy even without fetal AV block (AVB). AVB onset is commonly between 18 and 24 weeks' gestational age, and rarely develops after 28 weeks' gestational age.[57–59] Based on what we have learned from fMCG and echocardiography, the early stages of AVB are associated with frequent ectopy, junctional and ventricular tachycardia, STT wave changes, and QT prolongation. After several weeks of adapting to the lower FHR, which is often in the 50 to 70/min range, the fetus will show stabilization for the majority of the remainder of pregnancy. The HR may continue to fall and lose variability and for rates <50 bpm with low variability, and most of these infants will require pacemaker implantation in the newborn period. If the HR is < 50 bpm, augmentation with terbutaline may raise ventricular rate, though it has not been linked to better survival. The use of dexamethasone

both in partial (second-degree AVB) and complete (third-degree AVB) has been shown in some cases to prevent progression to a higher-grade AVB, as well as to reverse partial block in up to 25%. Dexamethasone's use in third-degree AVB is controversial still, with some centers finding reduced long-term cardiomyopathy and others not finding this.[60] Additionally, intravenous immunoglobulin has been shown to prevent mortality in most fetuses with hydrops due to CAVB. Many centers are using intravenous immunoglobulin to reduce inflammation in high-risk cases where extensive endocardial fibroelastosis or ventricular dysfunction is present. Hopefully, the StopBloq trial will provide more insight into its role.

Table 4 lists the common medications used to treat fetal AV block.

Recognition and Treatment of Fetal Arrhythmias That Are Not Picked Up by Echocardiography

Recently, we and others have gained a much better understanding of the impact of silent arrhythmias and conduction defects on fetal morbidity and mortality. Genetic conditions are known to be associated with high rates of stillbirth and sudden infant death syndrome. Ion channelopathies may play a role.

(a)

24 wk GA Fetus: Isoimmune 2:1 AV Block, Ventricular Tachycardia, Intermittent Complete Bundle Branch Block
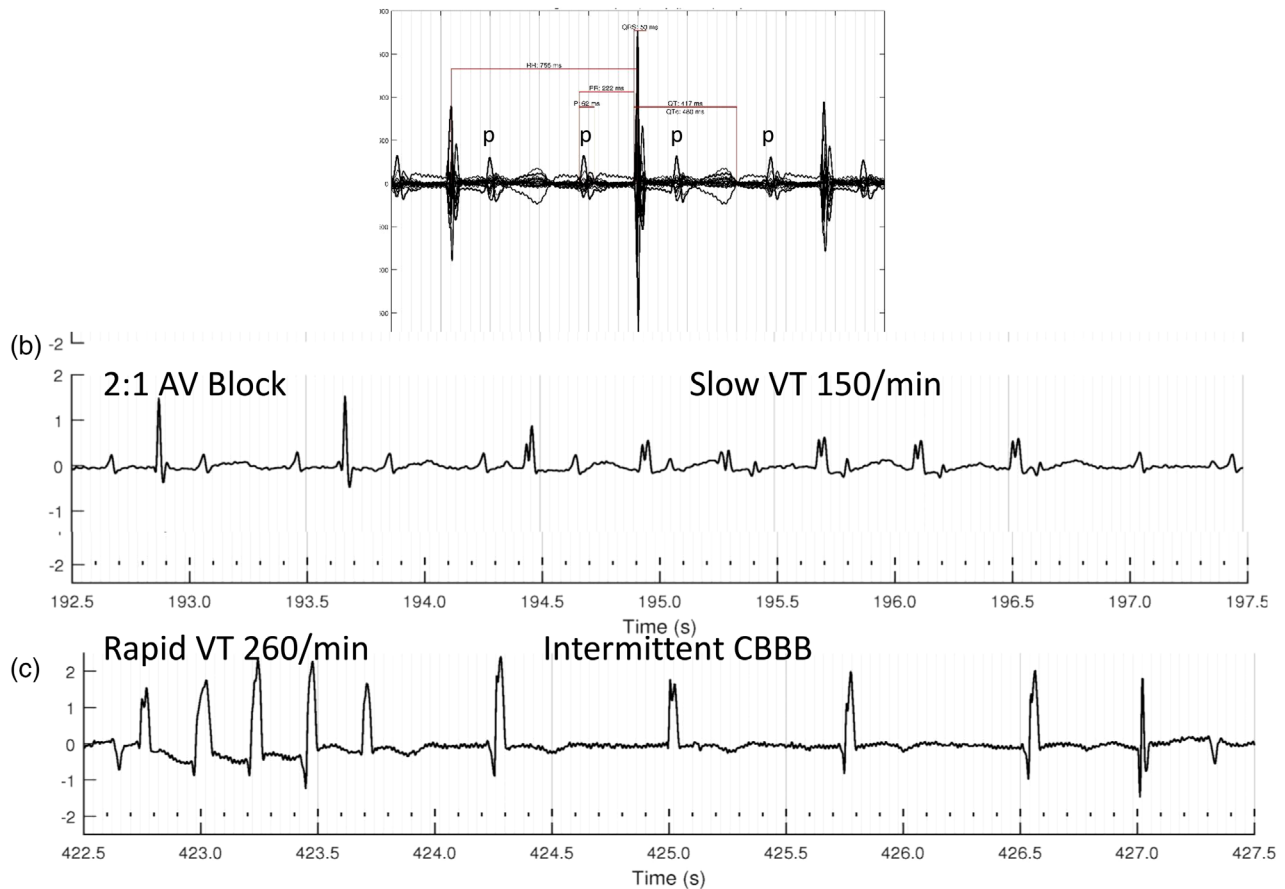
Figure 2. 24-week GA fetus with complex 2:1 isoimmune AV block, HR 75/min. (a) The signal averaged wave form, which documents 2 P waves for each QRS and a stable but prolonged PR interval. (b) Slow ventricular tachycardia is shown, which is common during the first several weeks of AV block. (c) Image shows that this fetus also had periods of rapid ventricular tachycardia and complete AV block with wide QRS escape rhythm (complete bundle branch block). These unstable findings are most common during the early adaptive phase, when the fetus is adjusting to the sudden drop in heart rate associated with AV block. AV, atrioventricular; CBBB, complete bundle branch block; GA, gestational age; VT, ventricular tachycardia.

Vitamin D and magnesium or calcium deficiency and maternal QT prolonging or HR-augmenting medications have the potential to increase risk in susceptible populations.[61–66] One of the most important impacts of newer cardiac monitoring such as fMCG will be in uncovering the predisposition for fetal QT prolongation. We recently reported that 16 of 33 fetuses with congenital heart disease had either QTc >500 milliseconds (10/33), complete bundle branch block (4/33), or both (2/33) (Wacker-Gussmann et al[67]). Unlike manifest fetal arrhythmias, many of the most serious rhythm disorders occur when the FHR is within the normal range, and rhythm may be entirely normal, making these arrhythmias nearly impossible to detect using standard obstetrical monitoring techniques alone. It is within this group of rhythm disturbances that the majority of fetal deaths occur. Even postnatally, this group represents a challenge to

detect, though electrocardiography will detect these if performed. Some countries have adopted universal electrocardiographic screening techniques (Japan, Italy) to recognize these infant conditions that account for 10% to 15% of sudden infant death syndrome and up to 30% of sudden deaths in older children.[68,69] In the fetus, 5% to 10% of all unexplained stillbirths have been linked in several studies to these inherited repolarization abnormalities, and in families with LQTS the risk of miscarriage in doubled and stillbirth is 8 times higher than in the general population.[49] The mechanism of death in the inherited channelopathy group is likely due to TdP VT, and has been associated with markedly prolonged fetal QTc >600 milliseconds. T-wave and systolic mechanical alternans (echocardiographically), and late-coupled premature ventricular contractions discovered with fMCG can be warning signs preceding TdP or lethal events (B. Hughes,

Table 4. Drugs for Treatment of Isoimmune AV block[a]

Drug[84,93–97]	Indication/Duration Route	F:M Drug Ratio	Efficacy Acute and Chronic	Elimination	Side Effects
Dexamethasone Fluorinated glucocorticoid	PR on echo >170 ms or AV block onset PO	0.5 F:M, ↓ Mab levels	20%-40% reversal of 2:1 block, may ↓ postnatal cardiomyopathy	Hepatic and renal	Maternal HTN, ↑ glucose, Cushing syndrome, CNS, osteoporosis, etc; transfer to breast milk
IVIG Anti-inflammatory, blocks F2/FAB receptors in placenta	Hydrops IV	0.5-1.0:1	In HF, ↓ mortality from 80%-25% $$$, preapproval needed	Depends on target, mostly renal	Allergic Rxn, vaccines
Hydroxychloroquine TLR blocker, ↓ endosomal pH	Prior infant with NLE PO	1.04:1	↓ heart block risk from 16% to 7% in subsequent pregnancy	Half-life, 40-50 days; mostly renal, some retained long-term	↑QTc
Terbutaline Beta agonist (isoimmune and nonisoimmune AV block)	FHR <50/min, if CHD <55/min or with hydrops PO	1-1.5:1	↑ FHR by 5-10 beats/min, not proven to ↑ survival	Renal	↑ maternal HR, arrhythmias, CNS

AV, atrioventricular; CHD, congenital heart disease; CNS, central nervous system; FAB, fragment antigen-binding; FHR, fetal heart rate; F:M, fetal:maternal; HF, hydrops fetalis; HR, heart rate; HTN, hypertension; MAb, monoclonal antibody; NLE, neonatal lupus erythematosus; Rxn, reactions; TLR, toll-like receptor.
[a] For individual drug dosages, see Donofrio et al[33] or Joglar et al.[98]

personal communication, August 2022). While TdP is usually associated with rapid development of heart failure and hydrops, it is better tolerated in the fetus than in the neonate due to the placental perfusion pressure that maintains fetal circulation. Unlike other forms of VT, TdP is very difficult to recognize echocardiographically because the semilunar valves (aortic and pulmonary) do not open consistently and the rate appears slower than what it actually is (Wacker-Gussmann et al[67]; Bolin et al[70]).

Figure 3 shows a case of a fetus with familial LQTS type 2 and 2:1 AVB, where TdP was discovered only at the time of fMCG. Serial follow-up in this fetus demonstrated that transplacental mexiletine, added to oral propranolol, to stabilize the fetal rhythm was actually proarrhythmic, making the TdP worse. The fetus was taken off mexiletine, left on high-dose propranolol, and adequately managed despite some ongoing fetal torsades until birth, when nadolol and pacemaker therapy were instituted. She is now 2 years old. Her mother, interestingly, had also presented with 2:1 block, and required neonatal pacemaker.

The mechanisms of fetal demise in cardiomyopathies (noncompaction, idiopathic) and inherited metabolic syndromes are different than for LQTS, and many of these are not associated with repolarization abnormalities, but rather depolarization abnormalities. Complete right or left bundle branch block is common. Unfortunately, unlike inherited arrhythmias that can often be effectively treated once recognized, many cardiomyopathies with such profoundly wide QRS complexes will go on to experience severe de-

celerations, ST-T abnormalities, hypertrophic changes, and fetal demise. A widely divergent group of additional conditions and arrhythmias, some of which are acquired, such as myocarditis, cardiac rhabdomyomas from tuberous sclerosis, cardiac fibromas, congenital heart defects (heterotaxy syndrome, Ebstein malformation, etc), and ventricular aneurysms, can manifest both overt and hidden rhythm and conduction abnormalities.

With the use of fMCG, we and others have begun to recognize electrophysiological signs of fetal risk in such conditions as fetal growth restriction, hydrops, mono-twins, gastroschisis, pregnancies subsequent to a stillborn infant, and others. These are often the same types of findings that one might notice on a cardiac monitor in an ICU setting, such as ST depression, T-wave inversion, QT prolongation, pathologic FHR decelerations, J waves, intermittent preexcitation, bundle branch block, arrhythmias, and more. Although not a part of regular practice at this time, with advances in newer types of inexpensive magnetometers, it is likely that in the future, obstetric care will marry the diagnostic benefits of the ultrasound/echocardiogram with the advanced monitoring capabilities of fMCG. These will be most helpful in serial follow-up of certain high-risk maternal/fetal conditions.

Another underrecognized problem in electrophysiology of the fetus is the complexity of rhythm disturbances. With those LQTS fetuses who were stillborn, novel fetal rhythms were often found, including AVB with 3:1 conduction ratio, QRS alternans in 2:1 AVB, long-cycle-length TdP, and slow monomorphic VT, that

fMCG Maternal LQTS 2: 29 6/7 wks GA
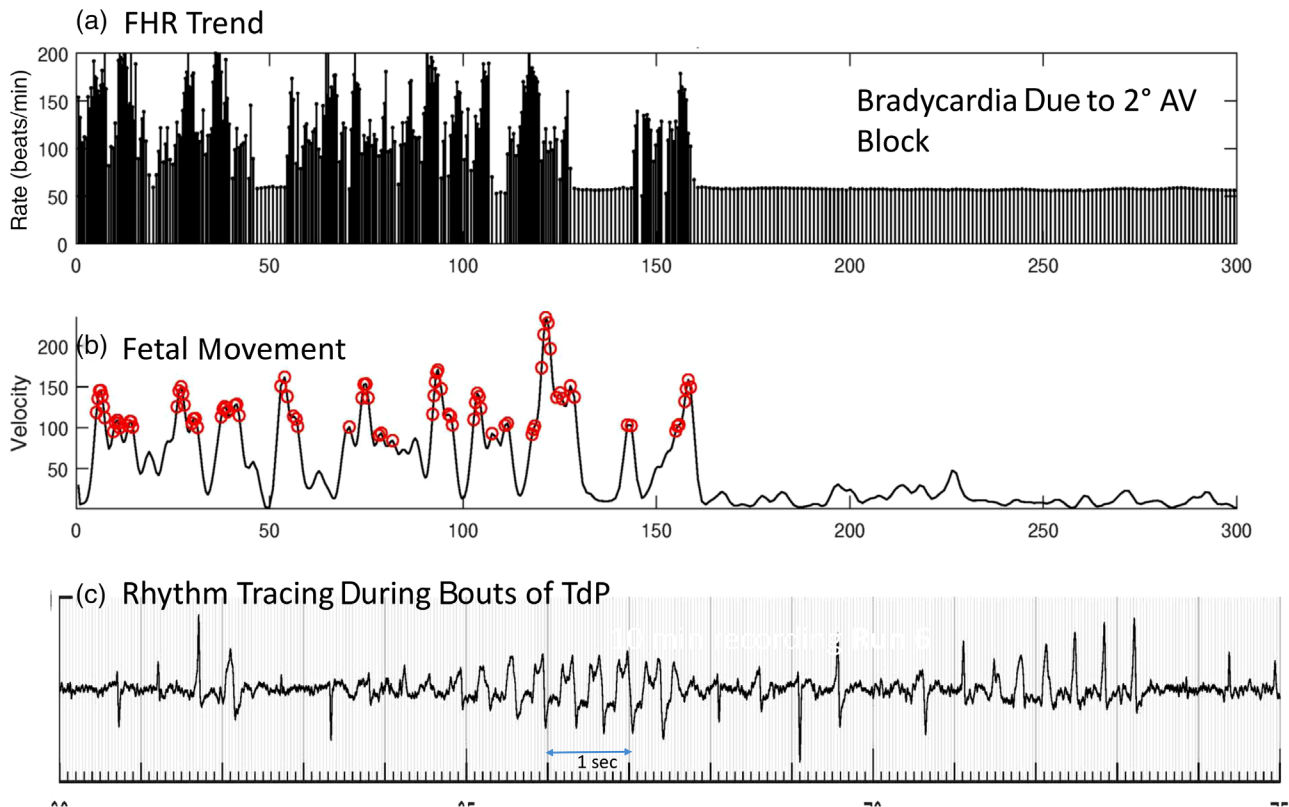
Figure 3. 29-week GA fetus with familial LQTS type 2. The top tracing shows low fetal heart rates of 52/min due to functional 2:1 AV block. Irregular tachycardia is seen (left half) with rates of 100-200/min. The bottom panel shows the rhythm associated with the higher rates, which is torsades de pointes and not sinus rhythm with ectopy as suspected by referral echocardiogram. AV, atrioventricular; FHR, fetal heart rate; fMCG, fetal magnetocardiogram; GA, gestational age; LQTS, long QT syndrome; TdP, torsades de pointes; VT, ventricular tachycardia.

would not have been recognized without fMCG.[71] It is apparent that a subset of these extremely lethal arrhythmias will not be seen postnatally due to their complete lethality.

The best antiarrhythmic treatments are based on a precise electrophysiologic assessment of rhythm. This is true at all ages. Personalized pharmacologic treatment strategies may need to be developed in the future, especially for the rarer genetic conditions.[72]

Nurse's Role in the Care of Patients With Fetal Arrhythmia

The fetal nurse in the United States provides an array of care for patients with fetal cardiology and rhythm diagnoses. These roles can include support for complex diagnoses, including obstetric issues, structural anomalies, and/or arrhythmias. Thus, the nursing background necessary overlaps medical disciplines. Critical roles in the care of these patients, include care coordination, patient education, and collaboration with the various inpatient and outpatient team members, including fetal cardiology, perinatology, obstetric care teams and

pharmacy, and the patient and family members. It is critical in the care of these complex patients that all are aware of the medications including over-the-counter vitamins and supplements as well as prescription antiarrhythmic agents. Often, these medications are titrated to anthropometric measures that change throughout the progression of pregnancy.

The current standard of practice for the nurse includes regular medication reconciliation at each visit (in-person, phone, or virtual visits) verbally with the patient as well as documentation in the electronic medical record for accuracy. It may be necessary to retrieve send-out drug levels. Patients receive extensive education at each visit regarding the administration, dosing, and effects of the medications (over-the-counter medications, prescriptions) including side effects, interactions, and potential dietary recommendations. It is advisable that written supportive documents such as after-visit summaries are provided. The nurse is required to remain up to date with these multiple effects of the medication and required monitoring guidelines using multiple online resources. For example, some

drugs may be newly listed to the long QT list, or have new indication based on emerging scientific statements. In addition, new FDA warnings can be posted. The fetal nurse will frequently collaborate with pharmacies to ensure drug availability, especially at initial discharge from the hospital; ensure accurate formulations; and verify any drug-drug interactions.

Often in the care of fetal cardiology patients, monitoring the maternal and fetal HR is necessary to optimize pharmacologic treatment. The fetal nurse will order the equipment necessary to monitor the maternal and fetal HRs, provide patient and family instruction, and regularly check on the patient to record results. The fetal nurse is responsible for contacting the corresponding care providers when the results are concerning or if any questions arise from the patient. Often, the fetal nurse will arrange for evaluation with the provider when abnormal data arises. Anticipation is key to the nursing role.

Areas for Future Research

More research in pharmacokinetic modeling for drug effect as well as for ion channel effects are needed. Randomized controlled clinical trials like the FAST trial, and StopBloq trial are important for defining proper treatment. In addition, drug usage registries should be actively funded by the National Institutes of Health and the FDA to accurately assess the clinical effects of antiarrhythmic drug treatment on both mother and fetus, and should include data during the breastfeeding period.

Electrophysiologic modeling of the rhythm and conduction has reached an advanced state for adults; however, such modeling during pregnancy, and also in the fetus, where different proteins and enzymes exist, is badly needed. The fetus exists in a buoyant environment, which can impact QTc, as well as a hypoxemic environment, which can trigger arrhythmias more readily. Fetuses are exposed to drugs through transplacental transfer and through intra-amniotic accumulation and reabsorption that alter cardiac time intervals.[73] Having better pharmacologic and electrophysiologic modeling to predict what effects these may have can benefit the clinician.

Finally, as outlined by Kogutt and Satin[41] in a recent article, research innovations in obstetrics lag far behind those of other medical disciplines with regard to funding, industry investment, patents, and companies producing products. This could be addressed by establishing a fetal drug and device consortium, funded by the National Institutes of Health or FDA to promote research and the translation of promising device technologies and drugs, including future gene therapies, for the human fetus in need of treatment. This coordination effort could substantially reduce the delays in innovative fetal treatments, as has already been experienced for pediatric patients through current FDA drug and device initiatives.

In summary, the needs of the fetus should be identified, and a multidisciplinary effort should be made to address these needs as quickly as possible, through policy changes that facilitate fetal research, technological advances, and more careful monitoring of drug and device treatments for the fetus.

Data Availability Statement

Data for this manuscript involves vulnerable groups (fetuses, infants), and as such is not openly shared on public databases. Requests for data will be reviewed individually. Research teams can addressed requests to Janette Strasburger, MD (Children's Wisconsin, Herma Heart Institute, MS 713, 9000 W. Wisconsin Ave, Milwaukee, WI 53226).

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