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Pediatric Cardiology

Comparison of Transplacental Treatment of Fetal Supraventricular Tachyarrhythmias With Digoxin, Flecainide, and Sotalol
Results of a Nonrandomized Multicenter Study

Edgar T. Jaeggi, MD, FRCPC; Julene S. Carvalho, MD, PhD; Ernestine De Groot, MD; Olus Api, MD; Sally-Ann B. Clur, MBBCh, MSc, FCP; Lukas Rammeloo, MD; Brian W. McCrindle, MD, FRCPC; Greg Ryan, MB; Cedric Manlhiot, BSc; Nico A. Blom, MD, PhD

Background—Fetal tachyarrhythmia may result in low cardiac output and death. Consequently, antiarrhythmic treatment is offered in most affected pregnancies. We compared 3 drugs commonly used to control supraventricular tachycardia (SVT) and atrial flutter (AF).

Methods and Results—We reviewed 159 consecutive referrals with fetal SVT (n=114) and AF (n=45). Of these, 75 fetuses with SVT and 36 with AF were treated nonrandomly with transplacental flecainide (n=35), sotalol (n=52), or digoxin (n=24) as a first-line agent. Prenatal treatment failure was associated with an incessant versus intermittent arrhythmia pattern (n=85; hazard ratio [HR]=3.1; $P<0.001$) and, for SVT, with fetal hydrops (n=28; HR=1.8; $P=0.04$). Atrial flutter had a lower rate of conversion to sinus rhythm before delivery than SVT (HR=2.0; $P=0.005$). Cardioversion at 5 and 10 days occurred in 50% and 63% of treated SVT cases, respectively, but in only 25% and 41% of treated AF cases. Sotalol was associated with higher rates of prenatal AF termination than digoxin (HR=5.4; $P=0.05$) or flecainide (HR=7.4; $P=0.03$). If incessant AF/SVT persisted to day 5 (n=45), median ventricular rates declined more with flecainide (−22%) and digoxin (−13%) than with sotalol (−5%; $P<0.001$). Flecainide (HR=2.1; $P=0.02$) and digoxin (HR=2.9; $P=0.01$) were also associated with a higher rate of conversion of fetal SVT to a normal rhythm over time. No serious drug-related adverse events were observed, but arrhythmia-related mortality was 5%.

Conclusion—Flecainide and digoxin were superior to sotalol in converting SVT to a normal rhythm and in slowing both AF and SVT to better-tolerated ventricular rates and therefore might be considered first to treat significant fetal tachyarrhythmia. (***Circulation***. 2011;124:1747-1754.)

Key Words: arrhythmia ■ atrial flutter ■ fetus ■ tachycardia, supraventricular ■ therapy

Atrial flutter (AF) and paroxysmal supraventricular tachycardia (SVT) are the most common causes of an abnormally fast fetal heart rate. The vast majority of fetal SVT is produced by atrioventricular reentrant tachycardia (AVRT), whereas atrial ectopic tachycardia (AET) and permanent junctional reciprocating tachycardia (PJRT) are infrequently observed. Although the tachycardia may be well tolerated, at the more severe end of the spectrum, it may cause low cardiac output and demise. Fetal hydrops is associated with a mortality rate as high as 35% compared with 0% to 4% in nonhydropic fetuses.[1] The risk of fetal hydrops increases if the arrhythmia presents at a younger gestational age and is rapid, incessant, and enduring, although even intermittent rhythm disorders may have serious consequences.[2,3] Drug treatment to prevent or treat heart failure is therefore offered to most mothers who present with frequent or persistent fetal AF/SVT.

Editorial see p 1703
Clinical Perspective on p 1754

Numerous retrospective studies have demonstrated that transplacental therapy with digoxin, flecainide, sotalol, or amiodarone is useful in terminating fetal tachyarrhythmias.[4–18] Nonetheless, in the absence of comparative drug studies, the optimal treatment remains contentious. Digoxin is the most often used first-line antiarrhythmic drug,[5,6,8,9,13,14] albeit its efficacy in controlling fetal SVT within a reasonable time frame has been questioned.[7] Others have suggested that

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Table 1.   Institutional Differences in Their Choice of First-Line Fetal Antiarrhythmic Therapy

	Total	Institution 1	Institution 2	Institution 3	P
Proportion treated, n (%)	111/159 (70)	55/63 (87)	38/64 (59)	18/32 (56)	<0.001
First-choice drug, n (%)					<0.001
Digoxin	24	5 (9)	17 (45)	2 (11)	
Flecainide	35	3 (5)	16 (42)	16 (89)	
Sotalol	52	47 (87)	5 (13)	0 (0)	

flecainide and sotalol are more effective in terminating AF and SVT[4,6–8,12,15]; however, rare reports of unexplained fetal deaths have raised concerns that flecainide and sotalol may provoke fatal proarrhythmia, although there has been no objective evidence to support such concerns.[4,12]

The aim of this retrospective multicenter study was to compare the safety and efficacy of transplacental digoxin, flecainide, and sotalol when used as first-line medications to treat fetal AF/SVT.

Methods

Study Population
We reviewed 159 consecutive cases with a prenatal diagnosis of AF/SVT at our tertiary care centers between 1998 and 2008. We excluded cases in which drug therapy had been initiated at another institution. The study was approved by the research ethics boards.

Patients and Diagnosis
Charts and ultrasound examinations were evaluated for arrhythmia characteristics, clinical findings, management, and outcome. The tachycardia was considered incessant if present ≥50% of the echocardiographic monitoring time; otherwise, it was classified as intermittent. Doppler echocardiography and M-mode echocardiography were used to distinguish AVRT, AET/PJRT, and AF.[19–21] If applicable, the mechanism was further established by postnatal ECG. If there was a tachycardia ≥180 bpm with 1:1 AV conduction and long-AV/short-VA intervals, AVRT was diagnosed. If the atrial rate was ≥170 bpm either with 1:1 (AET or PJRT) or variable (AET) AV conduction and short-AV/long-VA intervals, AET or PJRT was diagnosed. When the atrial rate exceeded 300 bpm, which was associated predominantly with 2:1 (range, 1:1 to 4:1) AV conduction and ventricular response rates between 120 to 350 bpm in this study, AF was diagnosed. Cases with multiple arrhythmias were classified according to the dominant mechanism. Fetal hydrops was characterized by the presence of at least two of the following findings: ascites, pleural or pericardial effusions, or skin edema.

Pregnancy Management
The choice of therapy depended on the fetal condition, arrhythmia characteristics, gestational age, maternal health, and willingness to undergo treatment. We usually observed brief arrhythmia that was present <1 to 2 minutes during the echocardiogram without any therapy. Delivery with postnatal treatment was considered if the tachycardia was more persistent or early fetal hydrops was documented after 35 weeks' gestation. Before 35 weeks, pharmacological treatment to obtain permanent fetal sinus rhythm was preferred because the hazard associated with premature delivery was believed to outweigh the risks of drug therapy. Antiarrhythmics were started in the hospital to allow serial monitoring of maternal well-being, serum electrolytes, cardiac rhythm, and ECG. Fetal well-being was monitored by frequent biophysical profile scoring, as well as Doppler and ultrasound examinations, until cardioversion or near-normal heart rate control was achieved.

Prenatal treatment was not randomized, but varied among study centers (Table 1). Primary choices were sotalol in institution 1, digoxin or flecainide in institution 2, and flecainide in institution 3,

which were used in 87%, 87%, and 89% of treated cases, respectively. Sotalol was usually given twice daily at a median dose of 160 (range, 80–320 mg/d), and the dosage was increased within a few days if the SVT/AF remained unresponsive to a maximum dose of 480 mg/d. The starting dose of sotalol for fetal hydrops was 320 mg/d. The daily dosage of flecainide was 300 mg/d (range, 200–450 mg/d) in 3 doses, and if applicable, this was adjusted to obtain therapeutic drug levels between 0.2 and 1 μg/mL. The oral loading dose of digoxin was 1.5 to 2 mg over 2 days, followed by maintenance dosages between 0.375 and 1 mg/d, aiming to obtain maternal drug levels in the upper therapeutic range between 2 and 2.5 ng/mL.

Definitions and Outcome Measures
Analyses were based on the initial treatment intent to avoid the effects of crossover therapy. Patients started with a monotherapy of sotalol, flecainide, or digoxin were assigned to their respective drug cohort. If digoxin was started simultaneously with sotalol or flecainide, which was the case in 7% of SVT and 8% of AF patients, these patients were included in the sotalol or flecainide cohorts. Changes in first-line prenatal management such as the addition of other drugs and delivery were also analyzed. Primary outcome measures were the time interval from treatment initiation to permanent cardioversion and, once established, the freedom from arrhythmia recurrence from the time of conversion until birth on maintenance treatment. Only the final outcome was considered to classify cases; fetuses with a recurrence who eventually achieved permanent sinus rhythm were counted as a treatment success but only after the final cardioversion. Intrauterine demise and delivery for tachyarrhythmia were considered treatment failures. Any recurrence of fetal SVT/AF after documentation of a completely normal cardiac rhythm by echocardiography was classified as maintenance treatment failure. Postnatal outcome was characterized as self-limiting (resolution of the tachycardia and no need for drug treatment within a year of birth), controlled (no tachycardia on treatment), or drug refractory (incomplete control despite drug treatment).

Statistics
Data are presented as mean±SD, median with minimal and maximal values, frequency, hazard ratio (HR), and 95% confidence interval (CI) as appropriate. Differences between cohorts were estimated with the χ^2 test and ANOVA or nonparametric Kruskal-Wallis ANOVA as appropriate. Time to permanent cardioversion was assessed by Kaplan-Meier estimates with Cox proportional hazard model for group comparisons (PHREG on the SAS system). Multivariable survival regression models were created to test whether treatment effect was independent of important covariates known or hypothesized to be associated with the probability of conversion to sinus rhythm. Analyses were performed with SAS Statistical Software version 9.2 (SAS Institute, Inc, Cary NC) and Prism 5 (GraphPad Software, San Diego, CA).

Results

Fetal Tachycardia Presentation
Table 2 shows the characteristics of the AF and SVT cohorts. Of 159 referrals, 45 had AF and 114 had SVT; AVRT was the main cause of fetal hydrops (34 of 41, 83%). Compared with

Table 2. Characteristics of 159 Cases With Fetal Atrial Flutter or Supraventricular Tachycardia

	Total	Institution 1	Institution 2	Institution 3	P
Total fetuses, n	159	63	64	32	1 vs 2 vs 3
Fetuses with AF, n (%)	45/159 (28)	20/63 (32)	14/64 (22)	11/32 (34)	0.32
Age at diagnosis, wk	33.2±3.5	33.6±2.8	33.6±4	31.8±4.1	0.43
Heart rate, bpm	223±37	216±17	210±41	250±47	0.08
Incessant arrhythmia, n (%)	38 (84)	19 (95)	11 (79)	8 (73)	0.20
Fetal hydrops, n (%)	6 (13)	1 (5)	1 (7)	4 (36)	0.04
Prenatally treated cases, n (%)	36 (80)	18 (90)	10 (71)	8 (73)	0.32
Fetuses with SVT, n (%)	114/159 (72)	43/63 (68)	50/64 (78)	21/32 (66)	0.32
SVT mechanism, n (%)					0.63
AVRT	98 (86)	36 (84)	45 (90)	17 (81)	
AET	14 (12)	6 (14)	5 (10)	3 (14)	
PJRT	2 (2)	1 (2)	0 (0)	1 (5)	
Age at diagnosis, wk	29.1±6	27.8±5.6	30.7±5.6	28.2±7.1	0.05
Heart rate, bpm	242±35	247±27	248±40	220±29	0.003
Incessant arrhythmia, n (%)	69 (61)	31 (72)	26 (52)	12 (57)	0.13
Fetal hydrops, n (%)	35 (31)	17 (40)	15 (30)	3 (14)	0.12
Prenatally treated cases, n (%)	75 (66)	37 (86)	28 (56)	10 (48)	0.001

AF indicates atrial flutter; SVT, supraventricular tachycardia; AVRT, atrioventricular reentrant tachycardia; AET, atrial ectopic tachycardia; and PJRT, permanent reciprocating junctional tachycardia.

well-tolerated AVRT, fetal hydrops was associated with an incessant arrhythmia pattern (91% versus 47%; $P<0.001$) and faster heart rates (253±26 versus 239±33 bpm; $P=0.01$) independently of gestational age. On average, AF was diagnosed 4 weeks later than SVT ($P<0.001$) with slower ventricular rates ($P<0.001$), whereas fetal hydrops was less common ($P=0.03$). Hydropic fetuses with AF were younger than those presenting without hydrops (30.2±2.6 versus 34±3.3 weeks; $P=0.008$), whereas tachycardia rates ($P=0.77$) and patterns ($P=0.57$) did not differ. Finally, AET/PJRT cases had the slowest rates of tachycardia (200±18 bpm; $P<0.001$) and were the least likely to be hydropic (1 of 16, 6%).

Overall, 9 fetuses (6%) also had structural heart disease. These included 3 AF cases, 1 each with left isomerism, aortic

stenosis, and coarctation of the aorta. Of 6 SVT cases, 2 had cardiac tumors, 2 had ventricular septal defects, 1 had Ebstein anomaly, and 1 had left heart hypoplasia.

Prenatal Management Characteristics

Tables 3 and 4 compare treated and untreated cohorts with AF and SVT. Treated fetuses were younger and more likely to be hydropic, whereas cohorts treated with digoxin, flecainide, or sotalol were largely comparable in clinical presentation, treatment duration, and outcome. Overall, 80% of AF cases (36 of 45) and 66% of SVT fetuses (75 of 98) received sotalol (n=52), flecainide (n=35), or digoxin (n=24).

Changes from first-line therapy over time were comparable among arrhythmias and drugs (Figure 1). Treatment modifications were rare during the initial 5 days of therapy, but by

Table 3. Pregnancy Management and Outcome of 45 Fetuses With Atrial Flutter

	Fetal Therapy			First-Line Treatment (n=36)			
	No	Yes	P	Sotalol	Flecainide	Digoxin	P
Fetuses, n (%)	9 (20)	36 (80)		17 (47)	9 (25)	10 (28)	
Age at diagnosis, wk	36.1±3.1	32.4±3.3	0.003	32.7±2.5	31.2±4.4	32.8±3.4	0.48
Heart rate, bpm	224±61	225±27	0.50	216±17	247±33	222±24	0.01
Incessant arrhythmia, n (%)	6 (67)	32 (89)	0.37	17 (100)	7 (78)	8 (80)	0.13
Fetal hydrops, n (%)	1 (11)	5 (14)	1.00	2 (12)	2 (22)	1 (10)	0.71
Time from diagnosis to delivery, d	1 (0–60)	28 (2–98)	0.002	28 (7–71)	29 (5–77)	26 (2–98)	0.88
Treatment duration, d	NA	28 (2–98)		28 (7–71)	28 (4–73)	23 (2–98)	0.83
Fetal demise, n (%)	0 (0)	1 (3)	1.00	0	1	0	0.21
Postnatal demise, n (%)	2 (22)	0 (0)	0.04	0	0	0	1.00
Age at delivery, wk	37.2±2.3	37.3±2.5	1.00	37.4±2.7	36.7±3.1	37.6±1.7	0.70
Birth weight, kg	3.4±0.4	3.3±0.6	0.56	3.0±0.6	3.6±0.6	3.5±0.4	0.04

Table 4.   Pregnancy Management and Outcome of 114 Fetuses With Supraventricular Tachycardia

	Fetal Therapy			First-Line Treatment (n=75)			
	No	Yes	P	Sotalol	Flecainide	Digoxin	P
Fetuses, n (%)	39 (34)	75 (66)		35 (48)	26 (35)	14 (19)	
Age at diagnosis, wk	31.9±6.5	27.7±5.2	<0.001	27.3±5.5	27±5.5	30.2±3.6	0.15
Heart rate, bpm	235±51	248±29	0.16	246±28	252±30	245±29	0.64
Incessant arrhythmia, n (%)	16 (41)	53 (71)	0.003	27 (77)	18 (69)	8 (57)	1.97
Fetal hydrops, n (%)	7 (18)	28 (37)	0.036	15 (43)	10 (38)	3 (21)	1.98
Time from diagnosis to delivery, d	28 (0–169)	65 (1–181)	0.006	66 (1–140)	75 (4–181)	50 (12–143)	0.32
Treatment duration, d		65 (1–158)		64 (1–140)	72 (2–158)	50 (12–143)	0.41
Fetal demise, n (%)	0 (0)	4 (5)	0.30	2	2	0	1.08
Postnatal demise, n (%)	3 (8)	2 (3)	0.34	1	0	1	1.79
Age at delivery, wk	38.9±2.2	38±2.5	0.07	37.8±2.2	38.2±2.5	37.8±3.1	0.78
Birth weight, kg	3.6±0.6	3.2±0.6	<0.001	3.1±0.6	3.3±0.6	3.0±0.6	0.30

day 10, one third of mothers had received a second antiarrhythmic drug or had been delivered. Overall, 13 of 24 women (54%) treated with digoxin received another medication (5 sotalol, 7 flecainide) or had been delivered (n=1) at a median of 6 treatment days (range, 3–33 days). Of 35 flecainide-treated cases, 14 (40%) ended up with modified management (9 digoxin, 2 sotalol, 1 amiodarone, 2 deliveries) at 9 treatment days (range, 2–15 days). Of 52 sotalol-treated cases, 26 (50%) required modified management (17 digoxin, 7 flecainide, 2 deliveries) at 7 treatment days (range, 2–15 days). Finally, 3 hydropic fetuses with therapy-resistant AVRT on oral flecainide/digoxin converted to sinus rhythm after direct fetal administration of adenosine and amiodarone or digoxin as third-line agents.

Because AF was diagnosed later, the duration of fetal therapy was shorter (P<0.001) and delivery by caesarean section more likely than with SVT (55% versus 32%; P=0.03). Figure 2 compares the cardioversion rates of SVT and AF during the first month of treatment. Atrial flutter responded more slowly to drug therapy (HR=2; 95% CI=1.2–3.3; P=0.005); rhythm control at 5 and 10 days was achieved in 50% and 63% of fetuses with SVT but in only 25% and 41% of similarly managed fetuses with AF. The rate of treatment failure was higher if SVT (HR=2.6; 95% CI=2.0–8.9; P<0.001) and AF (HR=4.9; 95% CI=4.3–311.8; P=0.001) were incessant and if SVT was associated

with fetal hydrops (HR=1.8; 95% CI=1.0–3.1; P=0.04) at the time of diagnosis (Figures 3 and 4). It took more than twice as long (9 versus 4 days) for conversion of 50% of SVT cases to a normal rhythm if fetuses were hydropic.

First- and Second-Line Therapy

Estimates of treatment-resistant tachyarrhythmia with first-line digoxin, flecainide, and sotalol are shown in Figure 5. For patients with fetal SVT, in multivariable models adjusted for hydrops and arrhythmia pattern and including both first- and second-line therapy in the same model, the use of digoxin (HR=2.9; 95% CI=1.3–6.5; P=0.01) or flecainide (HR=2.1; 95% CI=1.3–3.8; P=0.02) as first-line therapy was associated with a higher rate of arrhythmia termination compared with sotalol (Figure 5A). None of these agents as second-line therapy were associated with a greater rate of arrhythmia termination. Five days after treatment was begun, 59% of flecainide-treated and 57% of digoxin-treated SVT cases but only 38% of sotalol-treated cases were in normal rhythm. The median time to conversion of SVT cases was 3 days with digoxin, 4 days with flecainide, and 12 days with sotalol.

For patients with AF, in multivariable models adjusted for incessant versus intermittent arrhythmia pattern and including first- and second-line therapy in the same model, first-line
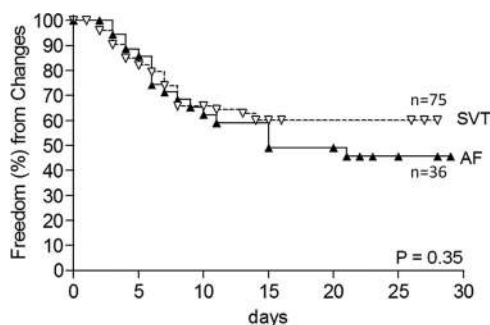

Figure 1. Freedom from changes in first-line treatment of fetal atrial flutter (AF) and supraventricular tachycardia (SVT).
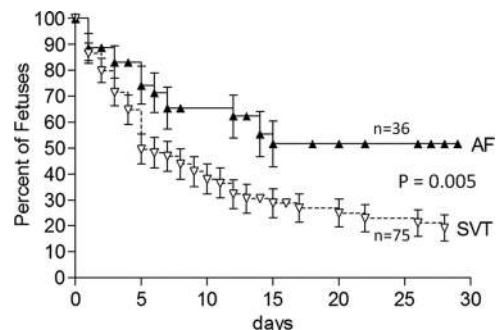

Figure 2. Freedom from prenatal conversion of atrial flutter (AF) vs supraventricular tachycardia (SVT) to persistent sinus rhythm despite transplacental antiarrhythmic therapy.
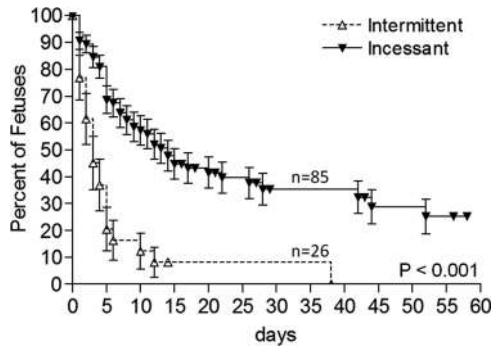
Figure 3. Freedom from prenatal termination of incessant vs intermittent supraventricular tachycardia and atrial flutter to anti-arrhythmic treatment.

sotalol was associated with a higher rate of arrhythmia termination compared with digoxin (HR=5.4; 95% CI=1.0–30.0; P=0.05) or flecainide (HR=7.4; 95% CI=1.2–46.1; P=0.03; Figure 5B). The same observation was made with the second-line therapy, although it did not reach statistical significance because of too few cases (P=0.11 for sotalol versus digoxin; P=0.13 for sotalol versus flecainide). At day 5 of treatment, only 13% of fetuses on flecainide, 21% on digoxin, and 29% on sotalol had a normal heart rhythm. The median time to conversion of AF cases was 12 days with sotalol, whereas this was not achieved with digoxin or flecainide before delivery. Nonetheless, when incessant SVT (n=23) or AF (n=22) persisted to day 5 of treatment, ventricular rates were lowered more significantly with flecainide (median, −22%) and digoxin (−13%) than with sotalol (−5%; P<0.001; Figure 6).

Maintenance Therapy and Outcome
Maintenance treatment failure was uncommon (Figure 7). Fetal hydrops resolved in the majority (76%) of treated cases before delivery. Most babies, treated and untreated, were born near term with normal birth weights. Only 9 of the 159 fetuses with arrhythmia (6%) were delivered at ≤35 weeks' gestation. Neonatal arrhythmia was more common in fetuses who had been untreated than in those who were treated (44% versus 24%; P=0.02) and was documented in 46% of AF cases, 21% of AVRT cases, and 31% of AET/PJRT cases. Atrial flutter did not recur after postnatal cardioversion either with (11%) or without (89%) prophylactic antiarrhythmic
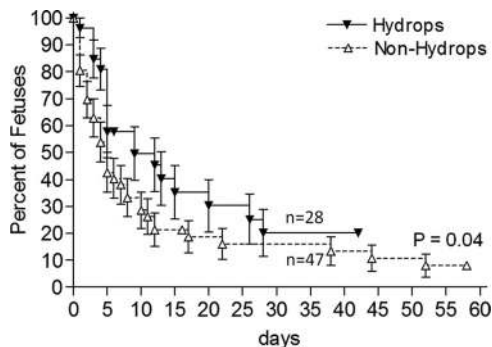

Figure 4. Freedom from prenatal termination of supraventricular tachycardia to antiarrhythmic treatment in fetuses with vs without hydrops.
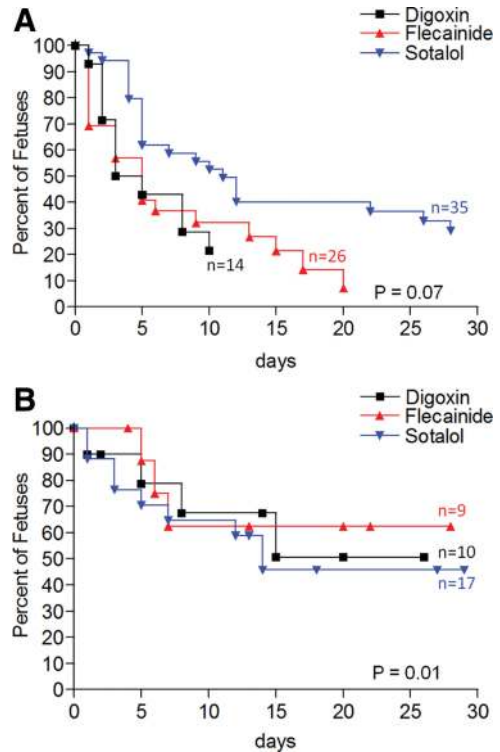

Figure 5. A, Freedom from prenatal termination of supraventricular tachycardia (**A**; n=75) and atrial flutter (**B**; n=36) over time with digoxin (D), flecainide (F), and sotalol (S).

therapy. Finally, of 106 survivors with SVT, 11 (10%) with only brief periods of SVT were lost to follow-up, whereas 62 had self-limiting, 29 had drug-controlled, and 4 had drug-resistant SVT (1 AET, 1 PJRT, 2 AVRT) during their first year of life.

Morbidity and Mortality
Arrhythmia-related mortality of nonhydropic and hydropic cases was 0% (0 of 118; 95% CI=0–3) and 17% (7 of 41; 95% CI=9–31), respectively (P<0.001). The first hydropic fetus succumbed within a day after transplacental digoxin/sotalol and direct fetal adenosine were given for incessant AVRT at 30 weeks. Three other fetuses, 2 with AVRT and 1 with AF, failed to respond to sotalol (n=1), flecainide (n=2), and second-line medication and died between 6 and 42 days

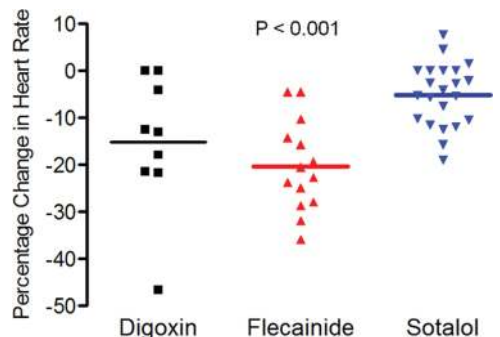**Figure 6.** Percentage changes in fetal ventricular rate if incessant atrial flutter (n=22) and supraventricular tachycardia (n=23) persisted after 5 days of digoxin (n=9), flecainide (n=14), and sotalol (n=22) administration.
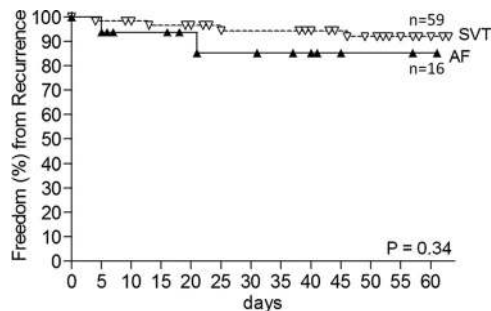
Figure 7. Freedom from prenatal recurrence of atrial flutter (AF) vs supraventricular tachycardia (SVT) on antiarrhythmic maintenance therapy.

after initiation of therapy. The fifth case with AVRT had sudden onset of severe bradycardia before any prenatal treatment could be started and died during delivery by emergency caesarian section at 25 weeks. The sixth case with AVRT refractory to both digoxin and flecainide for 3 weeks died of multiorgan failure after delivery at 32 weeks. The final case had incessant AF and was delivered at 32 weeks after the mother went into spontaneous labor. The newborn developed broad-complex tachycardia at 2 days of age and could not be resuscitated. Five additional deaths occurred as a result of non–arrhythmia-related causes: 1 was a stillbirth with umbilical cord strangulation, and 4 babies received palliative care for perinatal asphyxia (n=1), cardiac tumors (n=2), or glutaric aciduria type 2 with dilated cardiomyopathy and encephalopathy (n=1).

Two fetuses (1.2%) who were delivered prematurely had therapy-resistant SVT and developed post-hemorrhagic hydrocephalus suggestive of arrhythmia-related insults. One needed ventriculoperitoneal shunt drainage, but neither had any developmental sequelae.

One third of mothers reported adverse symptoms that were probably drug related. Their main complaints were nausea and dizziness attributed to the use of digoxin (38%), flecainide (20%), or sotalol (10%) and visual disturbances with flecainide (14%). In most cases, these symptoms were minor, so no treatment change was required, except for 3 women. In the first, flecainide/digoxin was stopped for 3 days because of low serum magnesium and potassium levels. The second mother became bradycardic on a low dose of sotalol (120 mg/d). On day 25 of treatment, she felt dizzy with a heart rate of 40 bpm. A healthy male baby was delivered the same day at 37 weeks 4 days, and the maternal symptoms resolved. In the third pregnancy, incessant AVRT with severe fetal hydrops could be terminated only with maximal dosages of flecainide (400 mg/d) and sotalol (480 mg/d). This was well tolerated by the mother, but the fetal heart rate decreased to 110 bpm after successful cardioversion. The fetal heart rate normalized after reduction of sotalol to 320 mg/d.

Discussion

This study is the first to establish response-rate curves over time for treatment with digoxin, flecainide, and sotalol. Our multicenter experience shows that the fetal response to transplacental therapy was associated with the fetal state, the type of tachycardia, and the choice of antiarrhythmic. Su-

praventricular tachycardia was significantly better controlled by transplacental medication than AF, whereas fetal hydrops and incessant SVT/AF were independently associated with slower cardioversion rates. Sotalol was associated with the highest rate of prenatal AF termination. On the contrary, flecainide and digoxin were associated with superior conversion rates of SVT to a normal rhythm and greater slowing to better-tolerated ventricular rates of persistent AF and SVT than sotalol.

Fetal State

In the absence of fetal hydrops, arrhythmia-related mortality in this study was 0%, suggesting that transplacental antiarrhythmic therapy is safe and effective regardless of the drug chosen. In hydropic fetuses, however, the rate of arrhythmia-mediated death was 17%, which is comparable to most other reported rates.[6,8,12] Fetal hydrops was strongly associated with incessant AVRT; overall, one third of all AVRT fetuses were hydropic compared with 6% with AET/PJRT and 13% with AF. Therefore, rapid cardioversion to sinus rhythm appears to be most pressing for incessant AVRT. Unfortunately, fetal hydrops itself is associated with treatment failure,[6–8,18] as we confirmed. For digoxin, this has been explained by incomplete passage of the drug across the placenta, so adequate fetal levels are not obtained despite often near-toxic maternal dosages.[22] Flecainide and sotalol, on the other hand, continue to cross the placenta readily even if there is fetal hydrops and thus should be preferred for patients in heart failure.[4,14,16,23] In this study, hydropic fetuses with SVT responded in general more slowly than nonhydropic fetuses, regardless of the choice of medication. Because fetal drug levels were not obtained, it is unclear whether this was due to impaired drug transfer/distribution, changes in electrophysiological properties, eg, resulting from tissue edema, or both. In our series, arrhythmia-related demise occurred predominantly after a lengthy period of unsuccessful treatment in a severely hydropic fetus. These "late" deaths may be preventable with more effective drug choices.

Arrhythmia Type

Previous studies, summarized by Krapp et al,[18] reported comparable prenatal success rates in terminating AF and SVT with digoxin, but response times were usually not evaluated. We found that, although prenatal rhythm control was eventually obtained in a significant proportion of chronically treated fetuses, the response of AF to transplacental therapy differed substantially from other forms of SVT. This should not be surprising because SVT and AF have diverse causes. Cardioversion of AF requires an antiarrhythmic drug to terminate the atrial reentrant circuit. This was achieved in only half of our treated AF cases within the first 2 weeks and in two thirds before delivery. Despite the rather low success rate, arrhythmia-related mortality was relatively low, probably because AF develops predominantly late in gestation and, even in persistent AF, near-normal ventricular rates may be obtained by the pharmacological delay of myocardial/AV nodal conduction. Because AVRT and PJRT involve atrial and ventricular myocardial tissue and conduction through the

AV node and accessory pathway, termination of these arrhythmias is possible by the electrophysiological alteration of one or several tissues. Suppression of enhanced atrial focal automaticity is needed to terminate AET. Treatment of AET/PJRT may occasionally be challenging,[20] although we did not find them to be associated with an increased risk of treatment failure with the limitation that both disorders are rare and our numbers were likely too small to detect differences from AVRT (data not shown). Compared with AF, fetal SVT responded faster and more consistently to pharmacological treatment, whereas both AF and SVT had an 8% to 15% recurrence rate on maintenance treatment. We would therefore recommend at least weekly assessment of the fetal heart rate until delivery once the arrhythmia appears to be controlled.

First-Line Medication

Extensive data from smaller studies exist on the success of fetal therapy with specific antiarrhythmic drugs. A summary of these data was recently published.[24] When these drugs were used as first choice, termination of AF/SVT before birth occurred in 51% of fetuses (115 of 226) with digoxin,[6–9,13,14,19,20,25] in 64% (45 of 70) with flecainide,[4,6–8,16] and in 66% (23 of 35) with sotalol.[10,12,15,19] This implies that sotalol and flecainide may be the most effective drugs regardless of the underlying arrhythmia mechanism. Nevertheless, clinically more relevant than rates of arrhythmia termination at birth is the response time to a particular intervention, and this information is available only for digoxin in 1 study.[26] Our numbers are too small to detect meaningful differences in survival among drug cohorts. Nonetheless, because the risk of demise increases once the fetus is in heart failure, rapid restoration of a normal fetal heart rate is imperative. Two drug effects may be useful in improving fetal hemodynamics: reduction of heart rate to one that is better tolerated and, ideally, cardioversion to a normal rhythm. Our study shows that both transplacental flecainide and digoxin were associated with higher rates of conversion of SVT to a normal rhythm and with greater slowing of persistent tachycardia than sotalol. Flecainide has previously been reported to result in a significant reduction in SVT rate.[14] We found that flecainide and digoxin were similarly effective in reducing AF and SVT rates. Sotalol, on the other hand, was associated with a higher rate in terminating fetal AF, but it had only modest effects on tachycardia rates. This implies that in the future we might combine sotalol with either digoxin or flecainide as first-line therapy if AF control is a matter of urgency because these combinations give the best chance of terminating fetal AF or of reducing ventricular rates in persistent AF. The safety and efficacy of combined drug treatment need to be evaluated in a larger prospective study.

Study Limitations

Several limitations are acknowledged. This is a retrospective review, and pregnancy management was not randomized but depended on institutional preferences. This explains the higher proportion of fetuses treated in institution 1. Caesarean section rates vary between centers and populations; hence, this was not evaluated separately as an outcome variable. We defined treatment as being successful if SVT/AF was terminated because it was not possible to objectively estimate a reduction in arrhythmia duration over time from stored recordings. Finally, unlike flecainide and digoxin, sotalol levels were not monitored because sotalol does not have the same narrow margin between therapeutic and toxic serum levels. This means that, in the absence of fetal hydrops, sotalol was usually started at the lowest dosage considered to be therapeutic (160 mg/d) and then increased until the desired effect was obtained. This may, in part, explain delayed treatment effects compared with flecainide and digoxin.

Conclusions

We found significant differences in the fetal response to pharmacological treatment between SVT and AF. Our results may be useful in improving our understanding of the potentials and limitations of antiarrhythmic drug therapy and, in persistent AF or SVT, helping to define a treatment period after which an alternative management should be considered.

Disclosures

None.

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CLINICAL PERSPECTIVE

Fetal atrial flutter and supraventricular tachycardia may result in low cardiac output and death. Consequently, maternal antiarrhythmic treatment is offered in most affected pregnancies. This retrospective multicenter study is the first to compare the efficacy and safety of transplacental digoxin, flecainide, and sotalol, the most commonly used drugs to treat fetal tachyarrhythmia. In the absence of fetal hydrops, arrhythmia-related mortality was 0%, suggesting that transplacental antiarrhythmic therapy is safe and effective regardless of the drug chosen. In fetal hydrops, however, when rapid heart rate control becomes a matter of urgency to improve the chances of survival, the rate of arrhythmia-mediated death was 17%. We found that the fetal response to drug therapy was significantly associated with the type of tachycardia, fetal state, and choice of antiarrhythmic. Atrial flutter, fetal hydrops, and an incessant arrhythmia pattern were independently associated with slower cardioversion rates. Flecainide and digoxin were associated with increased likelihood of conversion of fetal supraventricular tachycardia to a normal rhythm and significantly greater slowing of ventricular rates of persistent atrial flutter/supraventricular tachycardia than sotalol. The highest rate of prenatal atrial flutter termination was observed with sotalol, albeit this was achieved in only about half of the sotalol-treated patients. Flecainide or digoxin might therefore be considered first to treat significant fetal tachyarrhythmia, perhaps in combination with sotalol to treat poorly tolerated atrial flutter. Our results may also be useful in improving our understanding of the potentials and limitations of antiarrhythmic drug therapy and, in persistent arrhythmia, helping to define a treatment period after which an alternative management should be considered.

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