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Atrial Flutter in the Perinatal Age Group: Diagnosis, Management and Outcome

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OBJECTIVES The aim of this retrospective study was to evaluate perinatal atrial flutter (AF) and the efficacy of maternally administered antiarrhythmic agents, postpartum management and outcome.

BACKGROUND Perinatal AF is a potentially lethal arrhythmia, and management of this disorder is difficult and controversial.

METHODS Forty-five patients with documented AF were studied retrospectively.

RESULTS Atrial flutter was diagnosed prenatally in 44 fetuses and immediately postnatally in 1 neonate. Fetal hydrops was seen in 20 patients; 17 received maternal therapy, 2 were delivered and 1 was not treated because it had a severe nontreatable cardiac malformation. In the nonhydropic group of 24 patients, 18 were treated and the remaining 6 were delivered immediately. In the hydropic group, 10 received single-drug therapy (digoxin or sotalol) and 7 received multidrug therapy. In the nonhydropic group, 13 received a single drug (digoxin or sotalol) and 5 received multiple drugs. One patient with rapid 1:1 atrioventricular conduction (heart rate 480 beats/min) died in utero and another died due to a combination of severe hydrops because of the AF, sotalol medication, stenosis of the venous duct and hypoplastic placenta. Of the 43 live-born infants, 12 were in AF at birth. Electrical cardioversion was successful in eight of nine patients. No recurrences in AF have occurred beyond the neonatal period. Four patients with fetal flutter and hydrops showed significant neurological pathology immediately after birth.

CONCLUSIONS Fetal AF is a serious and threatening rhythm disorder; particularly when it causes hydrops, it may be associated with fetal death or neurological damage. Treatment is required and primarily aimed at reaching an adequate ventricular rate and preferably conversion to sinus rhythm. Digoxin failed in prevention of recurrence at time of delivery in a quarter of our patients, whereas with sotalol no recurrence of AF has been reported, suggesting that class III agents may be the future therapy. Once fetuses with AF survive without neurological pathology, their future is good and prophylaxis beyond the neonatal period is unnecessary. (J Am Coll Cardiol 2000;35:771–7) © 2000 by the American College of Cardiology

Atrial flutter (AF) is an uncommon form of tachycardia in infancy and childhood, the management and particularly the pharmacological treatment of which continue to pose a challenge to clinicians and electrophysiologists. This pertains even more to perinatal AF, a rhythm disorder in which the rate differs from that seen in adult patients and of which underlying etiology and pathophysiology (in the presence or absence of structural heart disease and secondary atrial dilation) still need to be determined in humans. The description of intrauterine AF by Carr and McLure (1) in 1931 is probably the first published report; Blumenthal et al. (2) documented intrauterine AF with the use of fetal electrocardiography in 1968. Currently, fetal echocardiography is the best method and remains the cornerstone for in utero diagnosis.

Observations from the early reports (1–5) of AF in the fetus and newborn infant include a rapid intrauterine heart rate and an abrupt irregular rhythm. Postnatal electrocardiograms (ECGs) show typical AF waves type I, the common form of AF. In 1965, Hassenruck et al. (6) were the first to report successful direct current cardioversion

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Abbreviations and Acronyms

AF = atrial flutter
AV = atrioventricular
CTG = cardiotonography
DCC = direct current cardioversion
HLHS = hypoplastic left heart syndrome
TVAOP = transvenous atrial overdrive pacing

(DCC) of a newborn with AF. The next successful outcome was not published until 1972 by Barclay and Barr (7). The purpose of our retrospective study was to present our experience with 45 fetuses with AF, 44 diagnosed in utero. The course, management and outcome are analyzed.

PATIENTS AND METHODS

Our multicenter, retrospective study comprised 45 patients, 44 fetuses with AF diagnosed in utero and one neonate with long-standing AF (probably from 24 weeks' gestation) diagnosed only at birth. The review includes patients with AF referred from obstetrical units because of an irregular or fast fetal heart rate from January 1984 to December 1998.

Cross-sectional echocardiography, M-mode and echo-Doppler were used for diagnosis. Conventional fetal echocardiographic views of the heart were obtained to exclude structural heart malformation. Atrial rate was determined using M-mode echocardiography, while ventricular rate was determined with the use of M-mode and/or echo-Doppler. A complete fetal scan was simultaneously performed to determine indices of fetal growth, the presence of hydrops, hydramnion or associated anomalies.

The decision to institute maternofetal therapy was related to gestational age at presentation, state of lung maturity and the presence of hydrops. Mode of delivery was decided based upon the fetal condition and the further stress that vaginal delivery might impose.

RESULTS

Forty-four fetuses with in utero AF were diagnosed at a median gestational age of 31.5 weeks, range 19 weeks to 40 weeks. At time of presentation, mean atrial rate was 450/min (median 440, SD 42.8) and mean ventricular rate was 224/min (median 220, SD 21.8). At time of diagnosis, 20 out of 44 fetuses were hydropic.

Maternofetal therapy. As outlined in Figure 1, 17 out of 20 hydropic fetuses received therapy. Nine of these received single-drug therapy with digoxin (loading dose of 1500 μg and maintenance dose of 250 μg twice daily) and one with

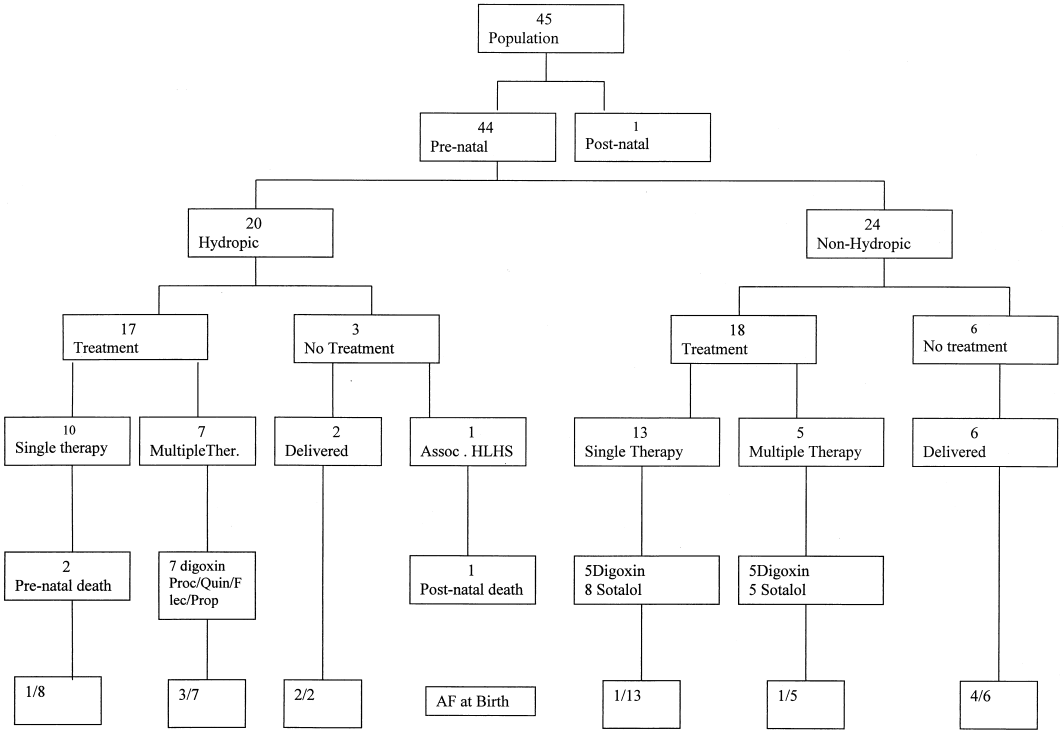

Figure 1. Allocation of fetal patients with atrial flutter into two study groups at time of recognition: hydropic and nonhydropic. Patients are further subdivided into treated and nontreated for each group. Assoc. HLH = associated hypoplastic left heart syndrome; Dig/Sot/Proc/Quin/Flec/Prop = digoxin/sotalol/procainamide/quinidine/flecainide/propaphenone. The bottom boxes describe the number of cases with atrial flutter at birth per number of infants born alive.

sotalol (80 mg q 8 h). In this group, one patient died in utero shortly after diagnosis and 2 h after maternal loading with intravenous (IV) digoxin. The AF was associated with 1:1 atrioventricular (AV) conduction, with a ventricular rate of 480/min. This ventricular rate, and not the initiation of digoxin therapy, probably caused the demise of this fetus. Another patient was treated with sotalol and died abruptly intrauterine at 38 weeks' gestation within 24 h after the oral sotalol medication was increased to 160 mg q 12 h, because of persisting AF. This could very well be a pro-arrhythmic effect, but in this hydropic patient an associated hypoplastic ductus venosus was found at autopsy. Of the remaining eight patients, one was in AF at time of birth.

Seven of the 20 hydropic fetuses received more than one drug, digoxin, as the drug of first choice in each. Drug combinations included digoxin and procainamide, quinidine, flecainide, propaphenone and sotalol. One of these patients received direct umbilical vein digoxin and procainamide. Of these seven patients, three (including the latter) were born in AF. Of the 24 nonhydropic patients, 18 were treated. Thirteen of them had single therapy, five with digoxin and eight with sotalol. The remaining five patients received a combination of digoxin and sotalol. Table 1 contains a summary of clinical data, and dosages for the different drugs are indicated in Table 2.

Surveillance of mother and fetus occurred twice weekly. Fetal heart rate was examined, and the mother was questioned on subjective maternal complaints; but no maternal problems other than slight dizziness occurred. All mothers had an ECG made before therapy initiation, but no irregular heart rates were found. No blood levels were measured during the period of this review, but recently this policy has been changed, and blood levels are monitored. Before a second drug was introduced, the initial therapy was maximized (sotalol 3*160 mg and digoxin 3*0.125 mg).

Nontreated fetuses. Three of the 20 hydropic patients were not treated, one due to an associated hypoplastic left heart syndrome (HLHS) and the other two were delivered soon after diagnosis because they were near term. Six of the 24 nonhydropic fetuses received no medication, as they were delivered within a week of diagnosis and beyond 35 weeks of gestation (when the lungs were assumed to be mature).

Structural heart disease. Only one of the 44 fetuses was found to have a cardiac malformation. Atrial flutter in this fetus was detected at 19 weeks' gestation, and a HLHS was diagnosed. In light of the prognosis a decision was made not to treat, and spontaneous delivery occurred at 29 weeks' gestation.

Mode of delivery. Delivery through means of a cesarean section was deemed necessary in 10 of the 44 fetuses (median gestational age 37 weeks, range 30 to 40 weeks) as normal vaginal delivery was considered to impose further stress on an already compromised heart. Cesarean section was performed soon after presentation and diagnosis of AF in five cases, which were not treated. A hydropic fetus diagnosed at 33 weeks was treated with digoxin for 24 h with no improvement and was therefore delivered by cesarean section. In another fetus presenting at 34 weeks, maternofetal digoxin was administered for four weeks before cesarean section delivery. In a third patient presented at 35 weeks, sotalol and digoxin failed to establish normal sinus rhythm, and delivery was performed at 39 weeks by cesarean section.

Atrial flutter at birth. Of the original 45 patients, 2 patients died in utero, and 12 of the 43 live-born infants were in AF at birth. Twelve-lead ECG confirmed AF with monomorphic undulating negative flutter waves in leads II, III, and avF (common type). Flutter waves were commonly seen in lead V_1. No sign of aberrant conduction was noted on these ECGs. Three infants were in serious trouble with poor Apgar scores at birth.

Nine of the 12 patients in AF received DCC as initial treatment. Eight of these converted to sinus rhythm. One patient remained in AF despite undergoing subsequent transvenous atrial overdrive pacing (TVAOP). This baby received a multitude of medications including IV digoxin and procainamide. Loading with IV amiodarone and repeat TVAOP were successful in conversion to sinus rhythm.

One other patient born with AF initially underwent unsuccessful TVAOP and reverted to sinus rhythm after electrocardioversion.

Two patients were treated medically, one with digoxin alone, the other with digoxin and quinidine. Both reverted to sinus rhythm on medication.

In one other patient, AF had not been diagnosed before birth. At 26 weeks' gestation polyhydramnion had been detected, and an irregular CTG (cardiotonography) suggested a possible existence of AF, but this was not recognized and no further investigations or treatment were performed. Delivery at 39 weeks revealed a hydropic and acidotic baby with extremely poor Apgar score requiring immediate resuscitation and artificial ventilation. On referral, the pulse was irregular, between 120 and 140 beats/min. Blood pressure was low, 40/22, mean 29 mm Hg. A narrow QRS rhythm could be seen on ECG, but no detectable P waves. Twelve-lead ECG confirmed AF at a rate of 480 to 540 beats/min with varying AV block. On cross-sectional echocardiography the atria were markedly dilated and seen to flutter, while the ventricles were dilated. Synchronized electrocardioversion was successful. The infant was digitalized. Over the ensuing 4 h the rhythm changed from AF with varying block to AV reentry supraventricular tachycardia with ventricular rates of up to 300/min. Six hours later the infant was in sinus rhythm with a good blood pressure and improved peripheral perfusion. Ultrasound of the head showed evidence of cortical necrosis most likely on the basis of long-standing cerebral hypoperfusion. Two days later the child died from cerebral inactivity. Figure 2 indicates

Table 1. Summary of Clinical Data

Pt	GA at Recognition (Weeks)	Hydrops	In Utero Treatment	Delivery Mode	GA (Weeks)	AF at Birth	Treatment at Birth	Duration of Prophylaxis (Months)
1	40	−	no	cs	40	yes	DCC	12
2	36	−	yes	nvd	40	no	no	1.25
3	33	+	yes	cs	33	yes	DCC	7.5
4	37	−	no	cs	37	yes	DCC	6
5	34.3	−	yes	cs	35	yes	DCC	7
6	39	−	no	nvd	40	no	no	no
7	34	−	yes	nvd	36	no	no	9
8	37	−	no	nvd	38	no	no	no
9	35	−	no	cs	35	yes	TVAOP	12
10	19	+	yes	nvd	38	no	no	12
11	29	+	yes	cs	30	yes	yes	6
12	35	+	no	cs	35	yes	DCC	3
13	24	+	yes	nvd	39	yes	yes	6
14	19	+	no	nvd	29	no	HLHS	no
15	28	+	yes	nvd	38	yes	yes	12
16	36	−	yes	nvd	40	no	no	no
17	37	−	no	nvd	37	yes	DCC	9
18	37	−	yes	nvd	41.5	yes	DCC	12
19	34	−	yes	cs	38	no	no	12
20	34	−	yes	nvd	38	no	no	12
21	—	+	no	nvd	39	yes	DCC	died day 2
22	32	+	yes	nvd	37	no	no	3
23	33	+	yes	nvd	38	no	no	12
24	36	+	yes	nvd	38	no	no	6
25	36	−	yes	nvd	38	no	no	no
26	34	+	yes	nvd	37	no	no	3
27	34	+	yes	nvd	37	no	no	6
28	35	+	yes	nvd	39	no	no	3
29	28	+	yes	nvd	36	no	no	no
30	31	+	yes	nvd	38	died in utero	died in utero	died in utero
31	36	+	yes	nvd	38	no	no	no
32	38	+	yes	nvd	39	no	no	no
33	—	+	yes	nvd	36	no	yes	yes
34	31	+	no	cs	35	no	no	no
35	−	yes	nvd	34	no	no	no	
36	35	−	yes	cs	39	no	no	no
37	36	−	yes	nvd	—	no	no	no
38	30.2	−	yes	nvd	—	no	no	no
39	20.5	−	yes	nvd	40.2	no	no	no
40	31	−	yes	nvd	39	no	no	no
41	34	−	yes	nvd	34.3	no	no	no
42	—	−	yes	nvd	36	no	yes	0.75
43	30	−	yes	nvd	−	no	no	no
44	36	−	yes	nvd	39	no	yes	yes
45	33.3	+	yes	nvd	39	died in utero	died in utero	died in utero

GA = gestational age; cs = cesarean section; nvd = normal vaginal delivery; DCC = direct current cardioversion; AF = atrial flutter; TVAOP = transvenous atrial overdrive pacing; HLHS = hypoplastic left heart syndrome pacing.

outcome and treatment strategy after birth for the whole study group.

Neurological complications. In four of the 45 patients, including the one described above, neurological morbidity was documented immediately postnatally, suggesting an association with the prenatally existing arrhythmia. The neurological damage ranged from severe cerebral hypoxic-ischemic lesions to intraventricular hemorrhage, resulting in a hydrocephalus. One patient had a small periventricular infarction that is resolving.

Management and follow-up. Prophylactic antiarrhythmic medication was given to 25 of the infants. Median duration

Table 2. Drugs Used for Control of Fetal AF

Drug	Dose	Maternal Therapeutic Concentration	Fetal:Maternal Concentration Ratio
Digoxin	Loading: IV 3 dd 1.5 mg Maintenance: po 0.25 to 1.0 mg/day	1–2 mg/ml	0.6:1
Flecainide	Loading: po 2 dd 150 mg Maintenance: po 2 dd 100 mg	0.2–1 μg/ml	0.86:1
Sotalol	Maintenance: po 160–320 mg/24 h	2–7 μg/ml	1.05:1
Amiodarone	Loading: po 1200 mg/24 h Maintenance: po 400–600 mg/24 h	Amiodarone: 1–2.5 μg/ml Desethylaminodarone 0.2–2.6 μg/ml	0.1–0.3:1

IV = intravenous; po = per os.

of prophylaxis was 7.25 months and ranged from three weeks to 12 months. Prophylactic antiarrhythmic drugs included digoxin alone in 17 patients, digoxin and quinidine in one patient, digoxin and sotalol in one patient and sotalol alone in six patients.

Recurrence of AF after initial conversion to sinus rhythm did not occur in any of the patients. Long-term follow-up for the group ranges between six months to 10 years and three months, median five years and two months.

DISCUSSION

Early reports. Atrial flutter is a primary atrial tachyarrhythmia confined solely to the atrium. The specialized AV conduction system does not participate in the primary mechanism. Early reports (1–5,8) of AF in the fetus and newborn stressed that the intrauterine heart rate was rapid, the rhythm was abruptly irregular. Digoxin did not seem to be effective in converting the rhythm to sinus and after birth

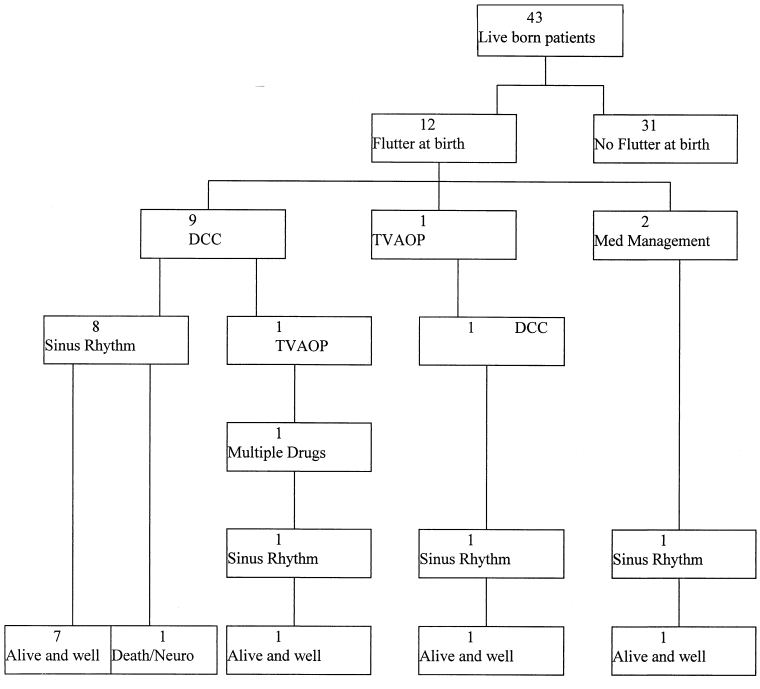

Figure 2. Outcome for the entire study group and treatment strategy for neonates in atrial flutter after birth. DCC = direct current cardioversion; TVAOP = transvenous atrial overdrive pacing; Death = death due to a neurological cause.

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the ECG showed typical flutter waves. Furthermore, if the infant had a cardiac malformation, the prognosis was poor. Even in the absence of associated structural heart disease the prognosis has been reported to be poor.

Our series. In our series of 45 patients with perinatal AF, the mortality and neurological morbidity were each 9% and were confined to the subgroup of hydropic fetuses. One patient died postnatally from severe associated structural heart disease (hypoplastic left heart syndrome) and another intrauterine after treatment with digoxin. We do not consider this patient's death a consequence of digoxin therapy, because under ideal circumstances, transplacental passage of this drug is slow (up to a few days) in order to achieve an adequate therapeutic level in the fetus. In this patient with a hydropic placenta, the transplacental transfer of digoxin was further hampered. At autopsy an accessory AV connection was identified, which we contend was responsible for the 1:1 AV conduction.

In the third severely hydropic patient, AF had been missed before birth, but was present immediately after birth. Despite successful DCC after birth, the patient ultimately died from cerebral damage probably due to long-standing and/or fluctuating cerebral hypoperfusion as a result of intrauterine AF.

Three patients were delivered by cesarean section, although no cases of hydrops were present, because patients were near term and at that time therapy was considered to be more effective out of utero. Since then the policy has been changed in favor of vaginal delivery as no positive effect of cesarean section has been discovered.

Potential mortality and morbidity. The potentially lethal outcome in perinatal AF is not to be underestimated. Moller et al. (3) were the first to report increased birth weight, which suggested to them the presence of anasarca from intrauterine cardiac failure secondary to arrhythmia. In 1970 van der Horst (9) reported a case of fetal hydrops secondary to intrauterine AF. In 1969, Moller et al. (5) reviewed the outcomes in 36 infants with AF. Nine infants died, of whom six had received digoxin but failed to respond.

Even more worrisome were the four patients in the present study with neurological damage. In a previous publication we reported the assumption that AF was responsible for the disturbance of the maintenance of adequate cerebral perfusion (10). This causes loss of cerebrovascular autoregulation and will result in a pressure-passive phenomenon, whereby a reduction or increase in mean arterial blood pressure is accompanied by a concomitant reduction or increase in cerebral blood flow. In the distressed newborn, cerebral autoregulation is lost, exposing the brain to ischemia in even moderate hypotension and to an increased pressure gradient across the capillary wall in even moderate hypertension, with increased risk of intracranial hemorrhage (11). Experimental studies in the fetal lamb have shown that this certainly applies to the distressed fetus in utero; a period of intrauterine distress causes abolition of cerebral autoregulation leading to severe impairment of the maintenance of constant cerebral perfusion (12,13). A fetus presenting with hemodynamic compromise and hydrops secondary to fetal tacharrhythmia is therefore at increased risk of development of a pressure-passive cerebral circulation and the cerebral complications that may result from this.

Intrauterine treatment. In light of these findings, we have opted for a policy to treat all fetuses with AF at time of presentation, unless immediate delivery is possible. Despite active treatment in most cases, we were confronted with AF at birth in 18% of patients (six out of 34 live-born patients). Conversion to sinus rhythm in our patients while receiving maternofetal therapy is a debatable issue. Was this indeed a result of the antiarrhythmic medication or was it part and parcel of the natural history of AF in these patients? One may postulate that both a paroxysmal and sustained form of AF exists in the fetus and newborn infant, as is seen with adult patients. Alternatively, we are unsure whether the stress of delivery and release of catecholamines may have an influence on retriggering the onset of AF, such as seen in fetuses with supraventricular tachycardia (14).

Digoxin may be useful through its action in slowing ventricular rate, allowing more ventricular filling, and improving cardiac output. Its inability in breaking or converting AF to sinus rhythm in pediatric and adult patients has been well documented (14–16). In the collaborative study reported by Garson et al. (17), digoxin used alone was successful in preventing recurrences of AF in only 44% of patients. Wellens (18) stresses that digoxin is contraindicated in the presence of an accessory pathway, which conducts anterogradely. This is most likely to have been the case in our fetus with 1:1 AV conduction.

These studies suggest that although digoxin has been used for treatment in the past, it might have lost some of its attraction for the treatment of AF. Alternatively, antiarrhythmic drug treatment with class I drugs is often unsuccessful in the conversion of AF to sinus rhythm, possibly explained by experimental data, suggesting that prolongation of the atrial-effective refractory period is more critical than slowing conduction in the termination of reentrant atrial flutter (19). Action potential prolongation in the absence of conduction slowing seems more effective in terminating human AF than depression of the excitability (19).

Current literature in adult patients advocates the use of class III agents such as sotalol. Sotalol appears to be an effective agent in the treatment of AF, seems suitable in treating the fetus, and has excellent transplacental passage in a dosage regimen of 160 mg twice daily (20,21). Monitoring of the maternal QT interval is essential in excluding maternal pro-arrhythmia; fetal pro-arrhythmia, however, is a troublesome aspect of this therapy and might force the fetal cardiologist eventually to abandon this agent. Amio-

darone, also a class III agent, has been used for fetal arrhythmias but has many side effects and does not cross the placenta as readily as does sotalol (22).

Dophitilide, a new class III agent, may be even more promising in the future for both in utero treatments and in the newborn infant (19). Although current data on the use of dophitilide in the fetus and neonate are lacking, dophitilide is found to be more effective than flecainide in the conversion of AF to sinus rhythm in adult patients, yet flecainide produces a more prolonged flutter cycle length (19).

Although both digoxin and sotalol are effective drugs in the treatment of fetal AF, we use sotalol as the drug of choice because digoxin transplacental passage is slower, relapse into AF occurs more often at birth, and subjective maternal complaints are more prominent than with sotalol.

Postnatal flutter and treatment. The relapse of patients at birth into AF remains a troublesome issue and requires intensive-care admission of these fragile patients. Synchronized DCC (eight out of nine patients) was useful in the conversion of AF to sinus rhythm (6,7), and TVAOP was successful in one of two patients, and only after loading with amiodarone. Esophageal or TVAOP has been used in children to terminate atrial flutter (23,24).

Once AF is converted to sinus rhythm, one may elect to wait and observe if flutter recurs (25). Alternatively, one may elect to treat for six months to a year, although it appears from this review that recurrence of AF is exceedingly rare beyond the neonatal period. This questions the need for prophylaxis; our current policy is not to treat prophylactically.

Conclusions. Finally, we can state that AF is a serious and life-threatening rhythm disorder of the human fetus. Specifically, when it causes hydrops it is associated with fetal death or neurological damage. Treatment therefore is required, primarily aiming at reaching an adequate ventricular rate and preferably conversion to sinus rhythm. It seems important that relapses back and forth and in and out of flutter should be prevented at all cost to protect the fetal brain. Once fetuses with AF survive, their future is bright, and prophylaxis beyond the neonatal period is unnecessary.

Acknowledgments

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