

Fetal tachycardias: management and outcome of 127 consecutive cases

J M Simpson, G K Sharland

Abstract

Objective—To review the management and outcome of fetal tachycardia, and to determine the problems encountered with various treatment protocols.

Study design—Retrospective analysis.

Subjects—127 consecutive fetuses with a tachycardia presenting between 1980 and 1996 to a single tertiary centre for fetal cardiology. The median gestational age at presentation was 32 weeks (range 18 to 42).

Results—105 fetuses had a supraventricular tachycardia and 22 had atrial flutter. Overall, 52 fetuses were hydropic and 75 non-hydropic. Prenatal control of the tachycardia was achieved in 83% of treated non-hydropic fetuses compared with 66% of the treated hydropic fetuses. Digoxin monotherapy converted most (62%) of the treated non-hydropic fetuses, and 96% survived through the neonatal period. First line drug treatment for hydropic fetuses was more diverse, including digoxin (n = 5), digoxin plus verapamil (n = 14), and flecainide (n = 27). The response rates to these drugs were 20%, 57%, and 59%, respectively, confirming that digoxin monotherapy is a poor choice for the hydropic fetus. Response to flecainide was faster than to the other drugs. Direct fetal treatment was used in four fetuses, of whom two survived. Overall, 73% (n = 38) of the hydropic fetuses survived. Postnatally, 4% of the non-hydropic group had ECG evidence of pre-excitation, compared with 16% of the hydropic group; 57% of non-hydropic fetuses were treated with long term anti-arrhythmics compared with 79% of hydropic fetuses.

Conclusions—Non-hydropic fetuses with tachycardias have a very good prognosis with transplacental treatment. Most arrhythmias associated with fetal hydrops can be controlled with transplacental treatment, but the mortality in this group is 27%. At present, there is no ideal treatment protocol for these fetuses and a large prospective multicentre trial is required to optimise treatment of both hydropic and non-hydropic fetuses.

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Keywords: fetal tachycardia; atrial flutter; supraventricular tachycardia

Such arrhythmias can be diagnosed accurately during prenatal life,^{4,5} but the prenatal treatment of tachycardias is controversial. This controversy extends to the type of drugs used and to the optimal route of administration, especially with regard to transplacental versus direct fetal treatment.⁶

In this paper we report the management and outcome of 127 consecutive fetal tachycardias managed at a single centre for fetal cardiology, with the aim of highlighting the problems posed by this group of fetuses.

Methods

All cases of fetal tachycardia presenting between 1980, when the unit was founded, and 31 December 1996, were analysed retrospectively. A tachycardia was defined as a fetal heart rate in excess of 200 beats/min. There were 127 consecutive fetuses in the study group. The median gestational age at presentation was 32 weeks (range 18 to 42).

Tachycardias that were incessant throughout the ultrasound scan, without a break, were defined as "persistent," and those that were interspersed with periods of sinus rhythm were defined as "intermittent." The arrhythmias were classified before any drug treatment by echocardiographic criteria.^{4,5} Supraventricular tachycardia was diagnosed if there was a 1:1 atrioventricular conduction, and atrial flutter when the atrial rate was in excess of the ventricular rate, usually with atrial rates of 300 to 450 beats/min and ventricular rates of 200 to 300 beats/min. A limitation of this classification is that a re-entry supraventricular tachycardia cannot be distinguished from other forms of tachycardia with 1:1 atrioventricular conduction. Fetuses were considered to be hydropic if two or more of the following were detected: ascites, skin oedema, pericardial effusion, or pleural effusion. During follow up, for an arrhythmia to be classified as "controlled" there had to be sustained reversion to sinus rhythm.

ECHOCARDIOGRAPHIC EQUIPMENT

Ultrasound systems used were the ATL Ultrasound 4, Toshiba Sonolayer SSA-270A (Advanced Technology Laboratories, Bothell, Washington, USA), and Hewlett Packard 77020A (Hewlett Packard Co, Andover, Minnesota, USA).

STATISTICAL ANALYSIS

Comparison of variables was performed by the Mann-Whitney U test or χ^2 analysis as appropriate.

Department of Fetal Cardiology, 15th Floor, Guy's Hospital, London SE1 9RT, UK
J M Simpson
G K Sharland

Correspondence to:
Dr Simpson.

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Fetal tachycardias result in a significant prenatal and postnatal mortality, particularly when associated with non-immune fetal hydrops.¹⁻³

(a) Type of arrhythmia

	Number (%)
SVT	105 (83)
AF	22 (17)

(b) Duration of arrhythmia

	SVT	AF	Total (%)
Persistent	68	15	83 (65)
Intermittent	37	7	44 (35)

(c) Incidence of hydrops

	SVT	AF	Total (%)
Hydrops	41	11	52 (41)
No hydrops	64	11	75 (59)

(d) Cardiac structure

	n
Normal	122
Structural Abnormality	5
<u>Types of defect</u>	
Ventricular septal defect	2
Ebstein's anomaly	2
Tricuspid valve dysplasia	1

Figure 1 Characteristics of 127 fetuses with tachycardias. AF, atrial fibrillation; SVT, supraventricular tachycardia.

STUDY LIMITATIONS

This study was retrospective and the treatment regimens employed were allocated in a non-random fashion, based on the preference of the attending fetal cardiologist. Postnatally, many babies were treated by other paediatricians and paediatric cardiologists, so treatment protocols varied, and in some cases follow up data are incomplete.

DRUG DOSAGE

The drugs used for oral treatment included digoxin, verapamil, and flecainide. Maternal digoxin treatment was given orally at a dose of 0.25 mg three times daily, and the dose was adjusted to achieve a maternal serum concentration in the therapeutic range (0.8 to 2.0 ng/ml). Maternal verapamil was given orally at a dose of up to 80 mg three times daily. Flecainide was given orally at an initial dose of 100 mg three times daily and the dose was altered to achieve a maternal serum concentration of 300 to 800 µg/l. Direct fetal treatment included use of amiodarone, adenosine, digoxin, and verapamil. The drug doses for direct fetal treatment were individualised according to the estimated fetal weight.

Results

The main features of the study group are shown in fig 1. The majority (83%) of the fetuses had supraventricular tachycardia. The arrhythmia was persistent in 65% of cases, and 41% had associated non-immune fetal hydrops. The cardiac structure was abnormal in five cases (4%). Seven fetuses presented initially with multiple atrial ectopic beats and subsequently developed prenatal tachycardias.⁷ The median ventricular rate at presentation was 240 beats/min (range 210 to 300), which did not differ significantly between hydropic and non-hydropic fetuses.

PRENATAL TREATMENT

Non-hydropic fetuses

The treatment regimen of the 75 non-hydropic fetuses is shown in fig 2. Nine fetuses were not treated because of advanced gestational age (range 34 to 42 weeks), two because the tachycardic episodes were short lived, and one because the parents declined treatment.

Oral digoxin was used as first line treatment in all 63 treated fetuses. Conversion to sinus rhythm occurred in 39 cases on this treatment alone, with a median response time of 14 days. Twenty four cases did not respond to digoxin alone and 17 had further treatment. Maternal oral verapamil was added in 14 cases, which converted 10 fetuses. Oral flecainide was substituted for digoxin in three cases, all of whom converted. Two of the latter had become hydropic before starting on flecainide, and hydrops resolved after treatment. Overall, control of the arrhythmia was established in 52 (83%) of the 63 fetuses who received drug treatment.

Supraventricular tachycardia versus atrial flutter—Five of eight fetuses with atrial flutter (63%) and 47 of 55 fetuses with supraventricular tachycardia (85%) converted to sinus rhythm following drug treatment. There was no significant difference in response to drug treatment between atrial flutter and supraventricular tachycardia ($p = 0.25$, χ^2 analysis).

Hydropic fetuses

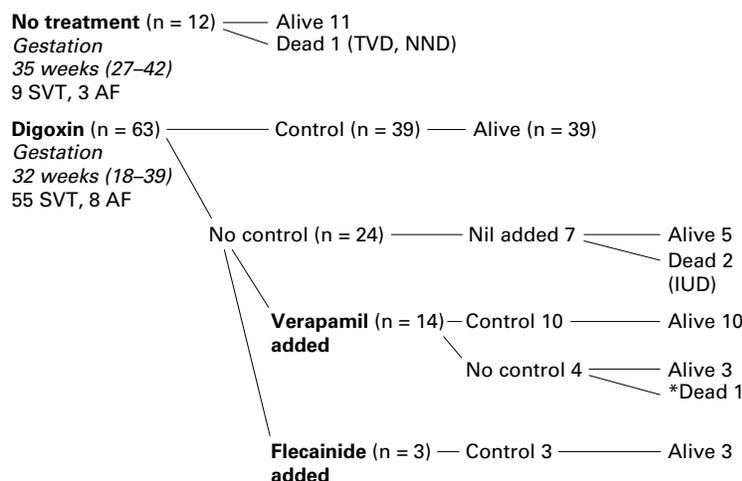
The treatments used for hydropic fetuses are summarised in fig 3. There were no statistical differences in gestational age between the treatment groups. Five fetuses did not receive any drug treatment at all, four of whom were delivered within 48 hours after the detection of the arrhythmia.

First line treatment—The treatment regimen for this group was variable, as there was a policy change in the choice of first line treatment following the introduction of flecainide in 1989.⁸ Before this, hydropic fetuses were treated either with digoxin, or digoxin plus verapamil, given orally to the mother.

Five fetuses were treated with digoxin alone, of whom only one converted. Digoxin in conjunction with verapamil was used as first line treatment in 14 cases of whom eight (57%) converted to sinus rhythm. Resolution of hydrops occurred in two (25%) of these fetuses before delivery. Oral flecainide was used as first line treatment in 27 hydropic fetuses. In 16 of

Median gestation (range) at presentation is shown in italics

Total number of fetuses = 75



*Death from pneumococcal meningitis at the age of 2 years

Figure 2 Treatment and outcome of non-hydropsic fetuses with tachycardias. AF, atrial fibrillation; SVT, supraventricular tachycardia; TVD, tricuspid valve dysplasia; NND, neonatal death; IUD, intrauterine death.

the 27 there was conversion to sinus rhythm, and in 10 (63%) of these the hydrops resolved before delivery.

Direct fetal treatment was used as first line treatment in one fetus at 33 weeks' gestation. Two doses of adenosine (300 µg then 400 µg) were injected into the umbilical vein, which led to reversion to sinus rhythm. The mother was started on oral digoxin, 500 µg three times daily, but 48 hours later supraventricular tachycardia recurred, so the fetus was treated with two doses of amiodarone (20 mg each) directly into the umbilical vein. Following these injections the fetus became bradycardic and was treated with intracardiac adrenaline. The mother was continued on digoxin (250 µg three times daily) and two days later the fetus was in sinus rhythm, which was maintained until delivery at 36 weeks' gestation.

Second line treatment—Two of the six fetuses who failed to respond to digoxin in conjunction with verapamil received further treatment. One received flecainide, which resulted in conversion to sinus rhythm. The other received verapamil (0.2 mg) directly into the umbilical vein, which immediately led to asystole from which the fetus could not be resuscitated.

There were 11 babies who failed to respond to initial flecainide treatment. Maternal oral treatment with digoxin and verapamil was substituted in three of these, of whom two converted. Oral digoxin was added to the flecainide in a further case and this baby converted to sinus rhythm.

Direct fetal treatment was undertaken in two cases. One of these had not responded to transplacental treatment with flecainide and subsequently to a combination of digoxin and verapamil. The right ventricle was punctured directly and two boluses of adenosine were injected (100 µg and 200 µg), which led transiently to sinus rhythm before the supraventricular tachycardia recurred. Two boluses

of amiodarone (7.5 mg over 20 minutes) were then given, which caused fetal bradycardia. At the end of the procedure the fetus was in sinus rhythm interspersed with short periods of supraventricular tachycardia. The mother was started on oral amiodarone. Seven days later the fetus was still in intermittent supraventricular tachycardia, so a further 10 mg amiodarone was given through the umbilical vein. Two weeks later the baby delivered spontaneously at 34 weeks' gestation. The postnatal course was complicated by renal failure, disseminated intravascular coagulation, and supraventricular tachycardia refractory to treatment with digoxin, amiodarone, and dc cardioversion. The baby died on the second postnatal day.

The second baby who received direct treatment had failed to respond to flecainide and sotalol. The direct treatment, which was given at another hospital, involved both intravenous and intraperitoneal administration of amiodarone to the fetus, and has been described previously.⁹

In all 47 hydropsic fetuses who received drug treatment, control of the arrhythmia was achieved in 31 (66%) compared with 83% of non-hydropsic fetuses ($p = 0.07$, χ^2 analysis). *Supraventricular tachycardia versus atrial flutter*—Seven of 10 fetuses with atrial flutter (70%) and 23 of 37 fetuses with supraventricular tachycardia (62%) were converted back to sinus rhythm following drug treatment. The response rates were not significantly different ($p = 0.93$, χ^2 analysis).

OUTCOME

Non-hydropsic fetuses

The outcome for this group is shown in fig 2. Of the 12 fetuses receiving no treatment, one died. This baby had tricuspid valve dysplasia and died from severe pulmonary hypoplasia within 12 hours of birth. Of the 63 cases who did receive treatment, there were three deaths. Two deaths occurred in utero, without control of the arrhythmia, and there was one late death from pneumococcal meningitis at the age of two years. Overall, 72 babies (96%) survived through the neonatal period.

Hydropsic fetuses

The outcome for this group is shown in fig 3. Of the five babies who received no treatment, one pregnancy was terminated and one baby died following surgery for a tracheo-oesophageal fistula.

One of the five babies treated with digoxin alone died in utero, less than 24 hours after starting oral digoxin treatment. In the group treated with digoxin and verapamil as first line treatment, two deaths occurred: one following direct fetal treatment with verapamil, and the other was a neonatal death from multiorgan failure in a fetus who delivered preterm at 33 weeks' gestation.

In the fetuses given flecainide as first line treatment, there was one death when control of the rhythm had been achieved. This baby, who was on no treatment, died suddenly at the age of four months. There had been no recurrence

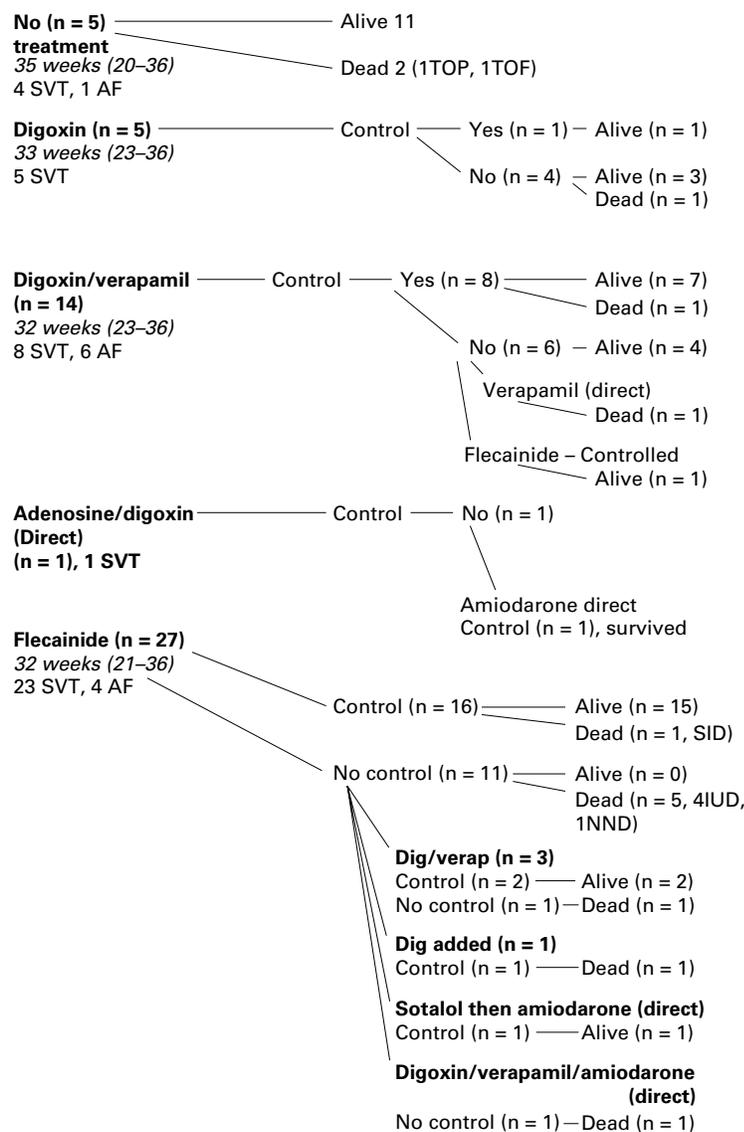


Figure 3 Treatment of hydropic fetuses with tachycardias. AF, atrial fibrillation; IUD, intrauterine death; NND, neonatal death; SID, sudden infant death syndrome; SVT, supraventricular tachycardia; TOF, tracheo-oesophageal fistula; TOP, termination of pregnancy.

of tachycardia postnatally and death was certified as the sudden infant death syndrome.

In the fetuses where control was not achieved, the mortality was much higher. There were four intrauterine deaths, three of which occurred within 24 hours of starting flecainide, and one of which occurred two weeks after starting flecainide without control of the arrhythmia. There was one neonatal death of an infant who delivered at 30 weeks' gestation, one week after starting flecainide.

Of the six babies who received further treatment after the failure of flecainide to convert the rhythm, there were three deaths. An intrauterine death occurred in a fetus in whom control of the arrhythmia had been achieved following amniotic fluid drainage, drainage of fetal ascites, and cordocentesis to measure the fetal flecainide level. The other two babies died in the neonatal period.

In summary there were seven intrauterine deaths, five neonatal deaths, one infant death, and one termination of pregnancy. In the group

overall, including those who did not receive any drug treatment, 38 of 52 hydropic fetuses survived (73%). There were three deaths (9.7%) in the group (n = 31) where the arrhythmia was controlled prenatally, versus nine deaths (56%) in the group (n = 16) where control of the arrhythmia was not documented (p = 0.002, χ^2 analysis). For those fetuses in whom control of arrhythmia was successful, the median time taken to achieve sinus rhythm was three days (range one to 28) in those treated with flecainide, compared with a median of 10 days (range eight to 35) for those treated with digoxin and verapamil (p = 0.001, Mann-Whitney U test).

POSTNATAL DRUG TREATMENT

Non-hydropic fetuses

Initial treatment—Seventy three babies (97%) in this group survived to delivery. Three of these (4%) had pre-excitation on the postnatal ECG. In the neonatal period, 38 babies (52%) received antiarrhythmic treatment. Thirty five babies received digoxin, six received β blockers, six received flecainide, three received amiodarone, and one underwent dc cardioversion. Eleven fetuses received more than one drug in the neonatal period.

Maintenance treatment—The type of postnatal maintenance treatment is known for 67 of the 72 non-hydropic fetuses who survived the neonatal period. Of these, 29 (43%) were not treated with maintenance antiarrhythmic treatment. Twenty eight babies were maintained on digoxin, two on digoxin plus verapamil, one on digoxin plus amiodarone, two on flecainide, and five on β blockers. The median duration of maintenance treatment was six months (range one to 60 months). One child, with Ebstein's anomaly of the tricuspid valve and recurrent supraventricular tachycardia, had radio-frequency ablation of an accessory pathway at the age of five years.

Hydropic fetuses

Initial treatment—Forty four babies (85%) survived to delivery. Seven of the 44 (16%) had evidence of pre-excitation on the postnatal ECG; 35 (81%) received drugs in the neonatal period. Treatment in the neonatal period included digoxin (n = 32), dc cardioversion (n = 7), flecainide (n = 5), verapamil (n = 4), amiodarone (n = 2), and β blockers (n = 6).

Maintenance treatment—Beyond the neonatal period, 31 of the 39 survivors (79%) received maintenance antiarrhythmic treatment. The drugs used were digoxin (n = 18), flecainide (n = 4), digoxin plus verapamil (n = 5), digoxin plus β blocker (n = 3), and digoxin plus amiodarone (n = 1). The median duration of antiarrhythmic drug treatment was 10 months (range one month to four years).

LATE MORBIDITY

Two babies, both from the hydropic group of fetuses, have neurological sequelae. One had a hemiplegia diagnosed at the age of 15 months. The other baby, who had a neonatal period complicated by poor left ventricular function,

assisted ventilation, and repeated dc cardioversion, has significant developmental delay.

Discussion

Drug treatment has been advocated in the management of fetal tachycardias in order to control the rhythm disturbance prenatally, and to prevent or treat cardiac failure. Thus, drug treatment was used for the vast majority of patients in this series, even when the fetus was non-hydrops. Although preterm delivery and postnatal treatment avoids the uncertainty of placental transfer of drugs, our previous experience¹⁰ and that of other investigators^{1,2} has shown a high mortality and high incidence of complications in fetuses managed in this way. In this series there was a 9.7% mortality for hydropic fetuses in whom the arrhythmia was controlled prenatally, versus 56% in those in whom the arrhythmia was not controlled. These results show that prenatal control of the tachycardia is associated with an improved rate of survival in babies with signs of intrauterine cardiac failure. The policy in our unit is to avoid preterm delivery and instead to attempt to control the rhythm disturbance before delivery. A wide range of different drugs has been used for prenatal treatment,¹⁻³ often in small numbers of patients¹¹⁻¹³ and by a variety of different routes,^{1,9} so that the optimal treatment for fetuses with tachycardias remains a matter for debate.

The type of tachycardia was diagnosed prenatally by echocardiography in all our cases. The most common type of arrhythmia was supraventricular tachycardia, as in other reports.^{1,2} In contrast to the experience of others, however, no cases of ventricular tachycardia were observed.² Both supraventricular tachycardia and atrial flutter were associated with fetal hydrops, which also occurred even when the arrhythmia was intermittent.¹⁴ There was no difference between atrial flutter and supraventricular tachycardia in the frequency with which conversion to sinus rhythm was achieved. This differs from other series where atrial flutter was more difficult to control.² The use of flecainide as monotherapy for atrial flutter is considered controversial because of the potential hazard of increasing the ventricular response and thereby worsening the tachycardia.¹⁵ Nonetheless, in our series, following treatment with flecainide for atrial flutter, three of four hydropic fetuses reverted back to sinus rhythm and no increase in ventricular rate was observed. Hence, flecainide at present remains the drug of first choice for the hydropic fetus with atrial flutter in our unit.

PRENATAL DRUG TREATMENT

The majority (63%) of the non-hydrops fetuses were converted to sinus rhythm using oral maternal digoxin treatment alone. When this failed, the addition of verapamil, or substitution of digoxin with flecainide, meant that control was established in 83% of cases. This high rate of control for non-hydrops fetuses has been documented in other series.¹⁻³ The use of oral maternal digoxin treatment avoids the need for admission of the mother to hospi-

tal, but has the potential disadvantage of less rapid control of the arrhythmia compared with intravenous loading of the mother.¹² Progression to fetal hydrops was rare (3%), and both fetuses in whom it did occur were successfully managed with transplacental flecainide. However, the potential for development of fetal hydrops is a justification for treating non-hydrops fetuses.

Control of the tachycardias in the hydropic fetuses (66%) was less frequent than in non-hydrops fetuses (83%). Poor transfer of drugs, particularly digoxin, across the placenta in the hydropic fetus may explain these differences.^{1,3} Flecainide does cross the placenta effectively, even when the fetus is hydropic.⁷ Use of flecainide controlled the rhythm more rapidly and caused resolution of hydrops more frequently than the combination of digoxin and verapamil. There were, however, three intrauterine deaths of hydropic fetuses with supraventricular tachycardia within 24 hours of starting flecainide. This is of concern, because of the known negative inotropic effects of flecainide. Intrauterine deaths, however, also occurred in three fetuses (two non-hydrops, one hydropic) treated with digoxin alone. Thus it is impossible to be certain if flecainide was truly associated with an increased incidence of intrauterine death, or whether this is a chance finding in fetuses who are at risk of intrauterine death, regardless of the drug used.

Even though flecainide offers the possibility of effective transplacental treatment of the hydropic fetus, serious questions were raised about flecainide in the cardiac arrhythmia suppression trial (CAST),¹⁶ in which patients with ventricular ectopy following myocardial infarction were investigated. There was an increased incidence of arrhythmia related deaths in the patients treated with either flecainide or encainide compared with placebo. Although post-infarction patients are a different group from pregnant mothers, doubts persist about the safety of flecainide, despite encouraging reports of its use in children.¹⁷ In our unit, flecainide treatment is restricted to hydropic or refractory cases of tachycardias, and whenever flecainide is used the mother is admitted to hospital for monitoring of drug levels and serial electrocardiograms to detect any sign of toxicity. To date, we have not documented any serious effects of flecainide on maternal cardiac rhythm necessitating withdrawal of the drug.

Direct fetal treatment was used in only 3% of our cases, compared with 50% of hydropic fetuses in a series reported by Hansmann *et al.*¹ Our reluctance to use such an approach is because of the high risk of cordocentesis in the hydropic fetus¹⁸ and of direct injection of antiarrhythmic drugs. Of the 13 fetuses in the series reported by Hansmann *et al.*,¹ two cardiac arrests (15%) occurred during direct fetal treatment and multiple injections of antiarrhythmic drugs were often required (up to 25 separate injections in one fetus). The use of oral maternal flecainide has resulted in less frequent direct fetal treatment in our unit, and in the experience of others.³ The overall survival of the hydropic fetuses in our series

(73%) was very similar to the survival rate (76%) in the study reported by Hansmann *et al.* In the four cases in our series in whom direct treatment was used, episodes of significant fetal bradycardia were observed in two cases following amiodarone, and asystole in one following intravenous verapamil. The use of verapamil in this fetus predated reports of serious adverse effects of this drug in the neonatal period.¹⁹ The death of one fetus after cordocentesis for measurement of flecainide levels has led to our abandoning this practice of monitoring fetal drug levels, and now treatment is monitored by measurement of maternal drug concentrations in combination with echocardiographic assessment of the fetus.

POSTNATAL DRUG TREATMENT

Postnatally, drug treatment for individual babies varied widely: 43% of non-hydropic fetuses and 21% of hydropic fetuses did not receive any maintenance treatment beyond the neonatal period. This variation is not surprising as the babies were delivered at several different hospitals with different treatment protocols. Some units elected to observe initially and only treat those newborns who had a recurrence of the tachycardia, but at other units antiarrhythmic treatment was given "prophylactically" for at least six months before any attempt was made to withdraw treatment. The variety of different drugs used in the newborn period suggests that the fetus with a tachycardia should be delivered either at a cardiac centre or at a high level neonatal centre with close cardiological support. Neurological sequelae were documented in only two children (1.6%), which is relatively low given the difficult prenatal and postnatal course which many of these babies had undergone. This justifies the efforts which are made to treat such fetuses both prenatally and postnatally.

CONCLUSIONS

The non-hydropic fetus with a tachycardia has an excellent prognosis with transplacental treatment. The mortality in hydropic fetuses is much higher, but the majority of tachycardias associated with hydrops can still be controlled with transplacental treatment, and the mortality is much lower if the arrhythmia is controlled prenatally. The choice of drug treatment and the method used to deliver the drug to the fetus remains controversial. Although transplacental flecainide is associated with

more rapid control of the arrhythmia and more frequent resolution of hydrops compared with other drugs given by the transplacental route—with results being comparable with other series where direct treatment has been used—it has still not been proved to be the ideal treatment. Thus there still remains an urgent need for a prospective, multicentre, randomised trial to establish the optimum protocol for the management of fetal tachycardias.

We acknowledge the contribution of Professor L D Allan and Mr Darryl Maxwell to the clinical management of some of the fetuses in this series.

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