Fetal tachycardia: A role for amiodarone as first- or second-line therapy?

Tachycardies foetales : y a-t-il une place pour l’amiodarone en première ou deuxième intention?

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Supraventricular tachycardia;
Atrial flutter

Summary
Background. — Fetal tachycardias result in serious prenatal and postnatal morbidity and mortality. Intrauterine treatment can improve prognosis dramatically and the therapeutic protocol is well defined. Currently, amiodarone is used as third-line therapy and is reserved for refractory cases.
Aims. — Our aim was to review the management and outcome of fetal tachycardia, giving particular consideration to the efficacy and safety of amiodarone therapy.
Methods. — This was a retrospective study of 24 consecutive cases of sustained fetal tachycardia, treated mainly with digoxin and/or amiodarone administered by the transplacental route.
Results. — The 24 fetal tachycardias comprised 16 supraventricular tachycardias with 1:1 atrioventricular conduction, seven atrial flutters and one ventricular tachycardia. Seven fetuses were hydropic and eight experienced less severe cardiac failure. Digoxin monotherapy converted 5/12 non-hydropic fetuses and 0/2 hydropic fetuses, with one intrauterine death. Amiodarone monotherapy converted 5/5 fetuses, including two hydropic fetuses: one ventricular tachycardia, two atrial flutters and two supraventricular tachycardias. When administered with digoxin, amiodarone converted all but two fetuses (7/9). No deaths were associated.

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with amiodarone, but there was moderate morbidity, with six transient elevations of thyroid stimulating hormone at birth, two of which required short-term thyroid hormonal substitution therapy.

**Conclusion.** Maternal oral amiodarone seems to be effective and relatively safe, even in hydropic fetuses. We suggest that this treatment could be used earlier than is currently advised.

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**Resumé**

**Objectifs.** Évaluer l’efficacité et la sécurité d’emploi de l’amiodarone administrée par voie transplacentaire pour traiter une tachycardie fœtale in utero.

**Méthodes.** Étude rétrospective de 24 tachycardies fœtales soutenues consécutives traitées principalement par digoxine et/ou amiodarone par voie transplacentaire.

**Résultats.** Il a été observé 16 tachycardies supraventriculaires (TSV) avec conduction 1/1, sept flutter auriculaires et une tachycardie ventriculaire (TV). Sept fœtus étaient en anasarque et huit présentaient des signes de mauvaise tolérance moins sévères. La digoxine seule a régularisé 5/12 fœtus sans anasarque et 0/2 avec anasarque, avec un décès in utero. L’amiodarone en monothérapie a régularisé 5/5 tachycardies : une TV, deux flutter et deux TSV 1/1, dont deux chez des fœtus en anasarque. L’association digoxine—amiodarone a été efficace dans 7/9 cas. Il n’y a pas eu de décès sous amiodarone, mais il a été observé six élévations transitoires de la TSH à la naissance, dont deux ont justifié un traitement substitutif durant les premières semaines de vie.

**Conclusion.** L’administration d’amiodarone par voie orale à la mère semble efficace et relativement bien tolérée, même en cas d’anasarque. Cette série suggère qu’il est envisageable de recourir à ce traitement de façon plus précoce qu’il n’est admis habituellement.

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AET</td>
<td>atrial ectopic tachycardia</td>
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<td>GW</td>
<td>gestational weeks</td>
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<td>SVT</td>
<td>supraventricular tachycardia</td>
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<td>TSH</td>
<td>thyroid stimulating hormone</td>
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<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
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</table>

**Methods**

We reviewed all cases of sustained fetal tachycardia (excluding sinus tachycardia) managed by the prenatal unit of Angers University Hospital between 1986 and 2007, which comprised 23 cases of SVT and one case of VT.

**Diagnosis**

Diagnosis of the arrhythmia was established by M-mode fetal echocardiography using the following criteria:

- fast and identical atrial rate and ventricular rate (> 200 bpm) (SVT with atrioventricular conduction ratio of 1:1 conforming to a re-entry SVT or an AET);
- fast atrial rate (> 300 bpm) associated with a lower ventricular rate demonstrating 2:1 or greater atrioventricular block conforming to an atrial flutter;
- complete dissociation between fast ventricular rate (> 200 bpm) and lower atrial rate, conforming to VT.

**Fetal tolerance**

Fetal tolerance was subdivided into three groups according to the severity of two-dimensional and Doppler echographic findings of fetal haemodynamic compromise:

- poor tolerance with hydrops, with at least two of the following signs present — ascites, pleural effusion, abundant pericardial effusion, moderate to severe tricuspid valve regurgitation, skin oedema and polyhydramnios;
- intermediate tolerance, when a small pericardial or abdominal effusion, a hydrocoele and/or a mild tricuspid valve regurgitation were present and disappeared after conversion to sinus rhythm;

**Background**

The management of fetal tachycardia is one of the most stimulating fields in prenatal cardiology. Fetal tachycardias result in serious prenatal and postnatal morbidity and mortality [1,2], particularly if a non-immune fetal hydrops is present [3,4]. Intrauterine treatment can, however, improve prognosis dramatically. Over the past 25 years, almost all antiarrhythmic agents have been tested via different administration routes, either transplacental or directly to the fetus by intracordinal, intramuscular or intraperitoneal injections [5—10]. This extensive experience has enabled the selection of four main drugs (digoxin, Flecainide®, sotalol, and amiodarone) and the definition of their means of administration [11—13]; it has also identified the risks and complications associated with the use of antiarrhythmic drugs during fetal life [14,15].

The literature published on this topic usually reports on the use of two or three lines of treatment, with amiodarone being used as a last resort and reserved for refractory cases [6,8—10,15,16]. Our retrospective study of 24 cases of fetal tachycardia documents the earlier and more extensive use of amiodarone both as monotherapy and as first-line treatment.
Fetal tachycardia: A role for amiodarone as first- or second-line therapy?

621

Treatment

Transplacental treatment was always initiated in the hospital setting. Digoxin and amiodarone were administered to the mother by the oral route in the following ways:

• amiodarone, loading dose 1600–2400 mg/day two to four times daily usually halved every 24 hours, maintenance dose 200–400 mg/day twice daily;
• digoxin, loading dose 1–1.5 mg/day twice daily, maintenance dose 0.5 mg/day.

To enable assessment of the neonate without treatment, amiodarone was withdrawn 15–21 days before term and digoxin was discontinued a few days before delivery.

Statistical analysis

When appropriate, statistical analysis was performed using the non-paired Student’s t test. Differences were considered to be significant at a p-value of less or equal to 0.05.

Results

About 70,000 births occurred in our centre during the study period; we identified 24 cases of fetal tachycardia, which gives an approximate incidence of 0.3 cases per 1000 births.

Clinical characteristics

The principal data on the 24 tachycardias are summarized in Tables 1–3, according to the intensity of fetal haemodynamic failure.

The tachycardia mechanism was supraventricular in 23 cases and originated from the ventricle in one case (confirmed postnatally). It became apparent that out of the 14 SVT with a 1:1 atrioventricular conduction ratio, 11 were re-entry tachycardias and four were AET. Seven cases corresponded to atrial flutter (35%). In one case, the mechanism of the SVT could not be ascertained in utero (one short run with spontaneous resolution) and was confirmed only after the recurrence of re-entry SVT after birth.

The ventricular rate was slower in cases of atrial flutter (200 ± 37 bpm, range 160–270 bpm) than in re-entry SVT (263 ± 44 bpm, range 210–360 bpm; p < 0.05). The ventricular rates of the four AET ranged from 225 to 280 bpm.

The gestational age at presentation ranged from 21 to 37 GW (mean 30.1 ± 4.6 GW) with 12 arrhythmias occurring before 32 GW and 12 at or after 32 GW. All cases of atrial flutter were discovered after 30 GW.

At initial evaluation, seven fetuses were hydropic (29%; four SVT, one AET and two atrial flutters) and eight fetuses had signs of intermediate tolerance (33%; five re-entry SVT, one AET and two atrial flutters), with the remaining nine fetuses showing no apparent haemodynamic disturbance (35%; three re-entry SVT, two AET, three atrial flutters and one VT). None of the 24 fetuses had any associated cardiac or extracardiac morphological abnormalities.

Treatment

A sustained sinus rhythm was obtained medically in 18 cases, and spontaneously (i.e. before any treatment was administered) in one case. First-line therapy was successful in 10 cases. Six cases required second-line therapy, and two cases required third-line therapy.

In four fetuses (two AET and two re-entry SVT), treatment failed to restore sinus rhythm but resulted in a slower ventricular rate with haemodynamic improvement, allowing the pregnancy to continue for a further 4–15 weeks.

One intrauterine death was observed after eight days of treatment with digoxin that had failed to produce any noticeable effect on a 34 GW fetus with no cardiac malformation (confirmed by autopsy) and who presented initially with atrial flutter (ventricular rate 160 bpm) and severe hydrops.

The mean time interval from diagnosis to conversion to sinus rhythm was 5.8 ± 4.7 days (range 1–17 days; n = 15). The mean time interval between the start of the efficient treatment and conversion to sinus rhythm was 4.9 ± 3.6 days (range 1–15 days; n = 18).

The antiarrhythmic agents used were mainly digoxin (16 cases) and amiodarone (14 cases). The peak digoxin serum level was 1.69 ± 1.09 ng/ml (n = 15), with a significantly higher level when digoxin was associated with amiodarone (2.36 ± 1.27 ng/ml) than when used alone (1.08 ± 0.44 ng/ml; p < 0.05). Verapamil, Flecainide®, cibenzoline and sotalol were used infrequently (five cases only); of these, only sotalol was shown to be effective (Case 21; re-entry SVT). Cibenzoline reduced STV runs without sustained conversion to sinus rhythm (Case 10; AET).

To summarize, the conversion to sinus rhythm could be attributed to:

• digoxin alone in five cases (two re-entry SVT and three atrial flutters);
• amiodarone alone in five cases (two re-entry SVT, two atrial flutters and one VT);
• amiodarone–digoxin dual therapy in seven cases (five re-entry SVT, one AET and one atrial flutter);
• digoxin–sotalol dual therapy in one case (one re-entry SVT).

Digoxin monotherapy was never effective when hydrops was present; it enabled conversion to sinus rhythm in only 2/7 fetuses, all of whom had intermediate haemodynamic tolerance. Amiodarone monotherapy was effective in all cases in which it was used (two cases with hydrops and one case with intermediate tolerance). In one AET case (Case 23), in whom digoxin–amiodarone dual therapy had failed, the association of digoxin 0.5 mg/day with Flecainide® 300 mg/day also failed, despite serum levels of these drugs being in the therapeutic range in maternal samples (digoxin 1.9 ng/ml; Flecainide® 0.7 mg/l) and cordonal samples (digoxin 0.7 ng/ml; Flecainide® 0.6 mg/l). Conversion was obtained with amiodarone after birth.

Birth and postnatal progression

The mode of delivery was caesarean section in seven cases, only two of which were partially (Case 5) or totally (Case 23) related to the arrhythmia. Other than
<table>
<thead>
<tr>
<th>Initial presentation</th>
<th>Age (GW)</th>
<th>Heart rate (bpm)</th>
<th>Treatment</th>
<th>Result (delay in days)</th>
<th>Birth mode</th>
<th>Age (GW)</th>
<th>Weight (g)</th>
<th>Follow-up ECG</th>
<th>Recurrence</th>
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</table>

Cases are numbered in chronological order. AET: atrial ectopic tachycardia; bpm: beats per minute; caesarean: programmed caesarean section; delivery: vaginal delivery; ECG: electrocardiogram; GW: gestational weeks; SVT: supraventricular tachycardia; WPW: Wolff-Parkinson-White syndrome; VT: ventricular tachycardia.
Table 2  Presentation of SVT with intermediate haemodynamic tolerance.

<table>
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<tr>
<th>Initial presentation</th>
<th>Age (GW)</th>
<th>Heart rate (bpm)</th>
<th>Treatment</th>
<th>Result (delay in days)</th>
<th>Birth mode</th>
<th>Age (GW)</th>
<th>Weight (g)</th>
<th>Follow-up ECG</th>
<th>Recurrence</th>
<th>Thyroid</th>
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</table>

Cases are numbered in chronological order. AET: atrial ectopic tachycardia; bpm: beats per minute; delivery: vaginal delivery; ECG: electrocardiogram; GW: gestational weeks; IUD: intrauterine death; SVT: supraventricular tachycardia; TSH+: thyroid stimulating hormone elevation; WPW: Wolff-Parkinson-White syndrome.

a Emergency caesarean section indicated by worsening of fetal status.
these two cases, the mean gestational period at delivery was similar for the 11 fetuses treated with amiodarone (38.9 ± 1.5 GW) and for the six fetuses treated with digoxin alone (38.2 ± 1.9 GW). We observed a slightly lower birth weight after amiodarone treatment (3165 ± 329 g) than after digoxin treatment (3400 ± 365 g), although this difference was not statistically significant.

Thyroid function was explored in all cases treated with amiodarone. TSH levels were elevated in six neonates and were associated with a goiter in two cases, leading us to administer transient substitutive hormonal treatment for five weeks and two months, respectively.

Of the 21 neonates for whom we have follow-up information (ranging from two months to 17 years), nine infants had recurrence of tachycardia: eight SVT required postnatal maintenance therapy (38% of follow-up), including all four cases that had evidence of pre-excitation on neonatal electrocardiogram. The fetus with VT had some runs of VT after birth, with spontaneous recovery at one month of life.

**Discussion**

The population we studied shares similarities with those described in other reports [3,6,10,17], particularly with regard to the frequency of fetal cardiac failure and the distribution of arrhythmias. All our cases of atrial flutter were discovered after 30 GW, in line with our current knowledge of the pathophysiology of this arrhythmia [18]. However, our case series had an important difference in terms of the therapeutic regimen adopted, and it is on this topic that we will focus our discussion.

Fetal tachycardia requires specific management as soon as it is sustained or if it is present for over half the time when under observation [18]. Before 34–36 GW, and especially if fetal hydrops is present, in utero management is preferred to premature delivery, because it reduces cardiac failure and neonatal mortality. In a study by Simpson et al., the mortality rate of hydropic fetuses was 9.7% when in utero conversion was successful and 56% in other cases [3]. The choice of an antiarrhythmic agent is a compromise between efficacy and side effects, both for the mother and the fetus. The customary dosage per kilogram used is the same for fetuses as for adults. When the transplacental route is adopted, the mother is inevitably exposed to high doses of the agent. Our current understanding of the pharmacokinetics and the sensitivity of the fetal myocardium to antiarrhythmic drugs is embryonic. Oudjik et al. contend, however, that the pro-arrhythmic effect of sotalol is more pronounced in fetuses than in adults [12]. This risk is illustrated by the difficulties reported by Simpson et al. in their attempt to manage fetal tachycardia via cord injection [3], and by the fetal deaths reported by others [10,14,15].

After 20 years of accumulated experience, the therapeutic protocol consists of the use of four main agents and a three-stage strategy. Digoxin is administered as first choice, and if it fails it is followed by Flecainide® [5,19] or sotalol [7] either on their own or with digoxin as second-line therapy. In this scheme, amiodarone remains on reserve for refractory cases and is only used as a third-line agent [20].

Digoxin is used as first choice for several reasons: it is a well-known drug with a good evidence-based in neonates and children. Transplacental transfer of digoxin is good, at least in the absence of hydrops. Maternal blood levels can be monitored easily, as long as the frequent presence of digoxin-like substances during pregnancy is taken into account (up to 0.5 nmol/l in our series) [21]. Digoxin monotherapy is known to be relatively effective, regulating 60–85% of fetal tachycardias in the absence of hydrops and 30–50% when it is present [3]. Our own experience, however, is more disappointing. Digoxin alone reduced only 50% of SVT without cardiac failure and was never effective when fetuses were hydropic. Three elements may explain these mediocre results: the exclusive use of the oral route, when the reduced gastrointestinal absorption of digoxin during pregnancy usually favours intravenous administration; the fact that maternal blood levels were often below 2 ng/ml (although levels as low as 0.45 ng/ml have proved sufficient at times); and the replacement or combination of digoxin with another drug in the absence of conversion within 48–72 h.

Our team adopted a therapeutic strategy that differs from what is usually reported: we used amiodarone widely and early, sometimes as first-line therapy (four SVT and one VT) and always as second-line therapy except in three cases. This choice was based on a number of considerations. In the early stages of our experience, two failures occurred while using digoxin monotherapy for approximately 1 week (followed by a digoxin—verapamil association that also failed), causing the only death of this series. Consequently, we decided to introduce the second line of treatment earlier on, particularly if hydrops was present. In addition, the digoxin–amiodarone association proved to be efficient and to have a rapid onset of action, illustrated by a mean conversion time of less than six days. Finally, despite the positive results reported with sotalol and Flecainide®, we chose not to use these drugs because of their more marked myocardial depressive and/or pro-arrhythmic effects compared with amiodarone, as suggested by the fatalities reported after treatment by sotalol [18] or Flecainide® [12,21].

Our study showed amiodarone to be effective for all fetuses, whether they were hydropic or not, and whether the agent was used alone or in association with digoxin, with the exception of two cases: one partial effect, and one failure for which Flecainide® also proved ineffective. Our series confirms observations made by Kosteth et al. [22], Jouannic et al. [6] and Strasburger et al. [9].

Jouannic et al. used amiodarone as first-line therapy in the four most severe cases among 25 hydropic fetuses with SVT. They observed two conversions and one reduction in fetal heart rate without conversion. The fourth observation was cut short by a decision to terminate the pregnancy at 24 GW due to worsening hydrops. They used amiodarone as second-line therapy, alone or in association with digoxin in nine cases, resulting in five conversions and three fetal heart rate reductions compatible with the continuation of pregnancy. An intrauterine death occurred in the last fetus, who was presenting severe hydrops, major ventricular hypokinesia, and an intraventricular haemorrhage [6].

In 2004, Strasburger et al. [9] reported on the pooled experience of several American and Dutch teams with 26 fetuses with hydrops or left ventricular dysfunction treated by digoxin and a loading dose of amiodarone after the failure of one or two first-line treatments. This treatment...
strategy converted 93% of re-entry SVT, 100% (2/2) of VT or junctional tachycardia and 33% of atrial flutter, without any deaths at delivery. Transitory side effects were observed in eight mothers and five neonates. This paper also reported on the relative ineffectiveness of amiodarone in cases of atrial flutter, an observation that differs from ours and that of Jouannic et al. [6]. More recently, Strasburger [20] contended that no fetal death linked to amiodarone has been reported and consequently proposed the use of amiodarone with digoxin on admission in severe cases.

Fetal VT are very rare. In their case report, Schleich et al. also resorted to amiodarone, with partial success, although their case was more severe than ours, with hydrops at initial evaluation. The authors suggested that amiodarone could be the treatment of choice for this form of tachycardia [23].

Our study suggests that amiodarone, which has been reported to be effective after direct fetal administration [3,10,16,17], is equally so after maternal oral administration (even in hydropic cases), with a relatively rapid onset of action despite its mediocre transplacental passage. The fetal heart may therefore be particularly sensitive to antiarrhythmic agents, which would explain why a weak dose of amiodarone can be effective and conventional doses of other antiarrhythmic agents can be potentially toxic.

In our case series, maternal tolerance to amiodarone was good, apart from transient prolongation of the PR interval in three mothers. No maternal thyroid complications were observed. Two patients given the amiodarone–digoxin combination showed elevated levels of serum digoxin (up to 5 ng/ml) and clinical signs of digitalis intolerance, leading to the discontinuation of the digoxin treatment and the administration of amiodarone alone. Amiodarone is known to raise the plasma levels of digoxin, which therefore necessitates careful dosage adjustments [24].

Fetal cardiac tolerance was also acceptable. No conduction defects or deterioration of haemodynamic status were observed in utero or at birth. However, as feared, thyroid dysfunction was observed, with the appearance of a fetal goiter leading to discontinuation of the treatment in two fetuses, and an elevation of TSH levels in six neonates, two of whom required short-term thyroid substituting hormonal treatment. Our experience is therefore similar to Jouannic et al. observation that 2/11 fetuses treated with amiodarone had an elevated TSH at birth and needed hormonal treatment for two and three months, respectively [6]. Prematurity and small for dates are risks reported with amiodarone use [25]. Our series did not notice the first effect but cannot exclude the second.

To our knowledge, pulmonary and ocular complications linked to the use of amiodarone in fetuses have not been reported. In adults, ocular complications only appear after two months of treatment. Although Bartalena et al. suggest that amiodarone is directly neurotoxic during fetal life, this hypothesis has not been confirmed by Grosso et al. [26,27]. Nevertheless, we must attempt to keep the duration of amiodarone administration during fetal life as short as possible. One possibility would be to use amiodarone as first-line therapy, either alone or combined with digoxin, and to discontinue its use as soon as conversion occurs. Another antiarrhythmic agent (preferably digoxin) could be used as maintenance therapy if indicated. This protocol was used in our last case (Case 24), allowing for a rapid conversion to sinus rhythm with a very short exposure to amiodarone (three days) and normal thyroid hormone levels at birth.

Study limitations

This study was retrospective and spanned 20 years, without strict standardization of the treatment regimen. Data on drug serum levels in mothers or neonates were missing in some cases. Three children born in another maternity after conversion to sinus rhythm could not be followed up.

Conclusion

This study suggests that, despite poor placental transfer, amiodarone is efficient in the treatment of fetal tachycardias after oral maternal administration. When amiodarone is used as first-line monotherapy in hydropic fetuses, its benefits seem to outweigh the risks, both for the fetus and mother. The study also suggests that amiodarone may be a valuable first-line choice for the treatment of less severe forms of fetal STV, despite uncertainty regarding possible long-term effects of prolonged administration on the fetus. By resorting to this drug only during the acute phase of treatment and withdrawing it as soon as there is conversion to sinus rhythm, it may be possible to benefit from the positive therapeutic effects of amiodarone while limiting exposure time to this heavily iodinated molecule and its potential adverse effects.

Conflict of interest

None.

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References

Fetal tachycardia: A role for amiodarone as first- or second-line therapy? 627


