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Original article

Maternal complications induced by digoxin treatment of fetal tachycardia: A retrospective series of 18 cases

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ABSTRACT

Objective. – To evaluate maternal tolerance to digoxin, used alone or associated to other antiarrhythmic drugs in the management of fetal tachycardia.
Patients and Methods. – This retrospective study was conducted at Rouen University Hospital between January 2009 and July 2016. All women who have received a treatment by either digoxin alone or associated with another antiarrhythmic drug for fetal tachycardia were included in the study. Maternal cardiac and extracardiac adverse effects were reported and comparisons between electrocardiograms before and during treatment with digoxin alone were performed.
Results. – Eighteen women were treated by digoxin, either alone or associated with another antiarrhythmic (sotalol, flecainide or amiodarone). During treatment, digoxin overdosing (> 2 ng/mL) was observed in 11 women (61%), among which 4 women had toxic levels of digoxinemia (> 3 ng/mL) that was symptomatic in 3 women. Cardiac complications such as sinus bradycardia, first-degree auriculo-ventricular block and Mobitz I second-degree auriculo-ventricular block were reported in four women (18.2%). Extracardiac side effects i.e. neurosensorial or digestive were diagnosed in 35.3% of women. The parameters of the electrocardiogram were not altered before and after treatment with digoxin alone.
Conclusion. – Antiarrhythmics can cause maternal cardiac complications and extracardiac side effects that can sometimes be severe but rapidly reversible upon treatment arrest.

Introduction

Fetal arrhythmia complicates 1–2% of pregnancies and fetal tachycardia has an incidence of 1 out of 10000 pregnancies, representing 5–15% of fetal arrhythmias [1,2]. Antiarrhythmic drugs are used in pregnant women in order to ensure sustainable cardioversion of supraventricular fetal tachycardia and avoid its complications, such as heart failure with hydrops fetalis complicating 30–40% of cases. Hydrops fetalis is associated to higher risks of cerebral ischemic and/or hemorrhagic lesions (15–40%), as well as stillbirth (15–35%) [3,4]. At the time being, no antiarrhythmic drug showed superiority when compared to others, but most authors use digoxin as a first-line therapy. Many centers administrated Digoxin as first-line therapy because of its relatively safe profile with long history of use during pregnancy but also accumulated evidence of complete transplacental transfer. Digoxin use leads to cardioversion in 60 to 90% of cases, but its efficiency is reduced to as low as 10 to 25% in fetuses with hydrops fetalis [4,5]. Sometimes, it is necessary to increase digoxin therapeutic doses used and/or add another antiarrhythmic drug to obtain sustainable fetal cardioversion and particularly in fetuses with hydrops [3,6,7]. This strategy may expose the mother to possible side effects, or even intoxication by digoxin. We will report our experience regarding maternal tolerance to digoxin therapy used for fetal tachycardia, either alone or combined to another antiarrhythmic drug.

Materials and methods

This retrospective study was conducted in Rouen University Hospital between January 2009 and July 2016. It included all women who received a treatment for fetal supraventricular

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tachycardia (SVT), either by digoxin alone or combined to another antiarrhythmic drug. Women who did not receive a digoxin treatment and fetuses presenting a cardiac malformation concomitant to the arrhythmia were excluded from the study. All women came from Haute Normandie region and were referred to our expert center for specialized cardio-pediatric care for fetal arrhythmia. Fetal echocardiograms were performed by a cardio pediatrician in order to define the arrhythmia, eliminate a concomitant cardiac malformation, evaluate fetal hemodynamic tolerance and introduce antiarrhythmic treatment. All antiarrhythmic drugs were started during an in-woman stay in the obstetrics department, after a thorough health check in order to rule out any maternal contra-indications. This process included a complete verification of personal and family medical and cardiologic history, as well as the drugs used routinely, a thorough cardiac auscultation looking for signs of right or left heart failure, an electrocardiogram (ECG), a blood pressure measurement, and a blood test to rule out any electrolytic anomaly. When amiodarone was used, liver enzymes and thyroid function (TSH, T3 and T4) were also checked. Digoxin was the first-line and gold standard therapy in our hospital. It was administered as a loading dose (1 to 2 mg/day, intravenous or enteral administration over 24 to 48 hours), followed by a maintenance dose (0.25 to 0.75 mg/day, enteral administration to obtain sustainable cardioversion) adjusted to maternal digoxinemia (therapeutic levels comprised between 0.8–2 ng/mL). Maternal levels of digoxinemia was systematically measured at 48 hours and further controlled 3 days later. Controls for digoxinemia levels were also performed every two weeks in women with normal therapeutic range or when any clinical maternal intolerance occurred. Digoxin therapy was immediately stopped when a digoxin over dosage (>2 ng/mL) was observed. Digoxin therapy could be only reintroduced when therapeutic range was further obtained but with lower 0.25 mg dosages. When digoxin therapy failed, the cardio pediatricians added another antiarrhythmic drug i.e. sotalol or flecainide with previous digoxin maintenance dosage or amiodarone with previous digoxin dosage reduced by half. Combination with amniodarone was also mostly administrated after 32 weeks gestation in order to reduce the risk for thyroid fetal dysfunction. Posologies of the other drugs were as follows: sotalol (started at 80 mg/day and increased progressively until cardioversion, with a maximal dose of 320 mg/day), amiodarone (loading dose of 1200 to 1600 mg/day until cardioversion, followed by a maintenance dose ranging between 400 to 600 mg/day), flecainide (started at 200–300 mg/day and adjusted to flecainide therapeutic range, between 0.3 and 0.8 mg/L). Maternal surveillance was performed on a daily basis as long as fetal cardioversion was not obtained or the treatment still had to be adjusted. Women's chart included blood pressure, heart rate, clinical signs of intolerance and/or overdose and ECG. Later in the treatment course, therapeutic levels of antiarrhythmic drugs (digoxin and flecainide), as well as electrocardiogram, hepatic and thyroid functions, were regularly evaluated. Medical charts were reviewed by a cardio pediatrician to ensure a reliable analysis of the ECGs. Median values of therapeutic doses of digoxin, ECG pattern before and after treatment (PR interval, QRS complex, corrected QT interval and heart rate), and cardiac and/or digestive side effects were recorded. We also noted the obtention of sustainable cardioversion and the delay necessary to that, the recurrence of fetal arrhythmia in before or after birth, and perinatal mortality.

Data collection was performed using Excel program. Median values and percentiles were calculated for continuous variables, while percentages were used for qualitative variables. On maternal ECGs, PR, QRS and corrected QT (cQT) before and after digoxin alone were compared using a Mann–Whitney test. A P value strictly inferior to 0.05 was considered statistically significant.

Results

During the study period, 22 women received antiarrhythmic treatment for fetal tachycardia. Four women were excluded because they were not treated by digoxin and 18 women were included. Maternal clinical characteristics and information on fetal tachycardia are presented in Table 1. Main types of fetal tachycardia were as following: permanent ($n=14$), junctional ($n=10$), and/or complicated by hydrops fetalis ($n=5$). Various treatment protocols obtained a sustainable cardioversion in 14 fetuses and a significant reduction in heart rate in 3 fetuses (Fig. 1). One therapeutic abortion was conducted because of a severe hydrops fetalis and failure of several attempts to obtain cardioversion with many antiarrhythmic drugs. One fetus with hydrops diagnosed at 32 weeks of gestation was died in utero in spite of rapid sustainable cardioversion with intravenous Digoxin and normal digoxinemia levels. A persistent severe cardiac insufficiency was then observed and the fetus died four days later. Dosages of antiarrhythmic drugs and the complications recorded are represented in Table 2. Some women were treated by several associations of antiarrhythmics and thus presented many side effects. Seven women (38.8%) presented side effects of antiarrhythmic drugs, among which 5 women presented a digoxin overdosage. Complications were observed only in women treated by digoxin, either alone or associated to sotalol. During treatment, digoxin overdosage (>2 ng/mL) was observed in 11 women (61%), among which 4 women had toxic levels of digoxinemia (>3 ng/mL) that was symptomatic in 3 women. Symptoms were cardiac ($n=1$, digoxin alone) and/or neurosensorial and digestive ($n=2$). Cardiac complications were reported in 4 women (18.2%) either treated by digoxin alone ($n=1$) or digoxin associated to sotalol ($n=3$). The woman treated by digoxin presented a severe intoxication while treated by digoxin 0.75 mg/day for more than 3 months and was admitted for anorexia and vomiting complicated by a weight loss evolving for a week. At admission, digoxin blood level was of 4.4 ng/mL and ECG revealed a first-degree auriculo-ventricular bloc (AVB) characterized by a PR interval of 360 ms and rapidly evolving to second-degree Mobitz 1 AVB. She was admitted to cardiologic intensive care unit and presented a severe bradycardia (30 beats/minute) that did not require a pacemaker but was complicated by acute renal failure. Two out of the three women treated by digoxin (0.75 mg/day) and sotalol (160 mg/day) presented a first-degree AVB, with PR interval of 220 and 260 ms, and digoxin blood level of 2.1 and 1.5 ng/mL, respectively. On the other hand, the third woman who received the digoxin-sotalol regimen with digoxin blood level of 1.3 ng/mL presented a sinus bradycardia as low as 50 bpm with no increased QT interval,

Table 1
Maternal and fetal characteristics ($n=18$).

Maternal characteristics	
Age (yr), median value (1st–3rd Q)	27 (25–32)
Smoking, *n* (%)	4 (23.5)
BMI (kg/m^2), median value (1st–3rd Q)	23,4 (20.2–28.2)
Primiparity, *n* (%)	11 (59)
Fetal characteristics	
GA at diagnosis (weeks), median value (1st–3rd Q)	32,4 (27.1–34.6)
Type of tachycardia, *n* (%)	
Flutter	6 (33.3)
AVRT	9 (50.0)
PJRT	1 (5.5)
Others	2 (11)
Permanent tachycardia, *n* (%)	14 (77.8)
Heart rate (bpm), median value (1st–3rd Q)	230 (220–250)
Hydrops fetalis, *n* (%)	5 (27.8)

BMI: body mass index; bpm: beat per minute; GA: gestational age; Q: quartile; AVRT: atriventricular reentrant tachycardia: PJRT: permanent junctional reciprocating tachycardia.

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