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Two Cases of Atrial Flutter with Fetal Hydrops : Successful Fetal Drug Therapy

We describe two cases of fetal atrial flutter associated with severe fetal hydrops which were unresponsive to digoxin but were successfully treated with flecainide acetate. Two cases of fetal atrial flutter were identified in fetuses with severe fetal hydrops on 3rd trimester ultrasonogram(28 weeks' gestation and 30 weeks' gestation). Following failed digoxin monotherapy, flecainide acetate was added to digoxin. On the 7th day and 13th day after combined therapy, fetal heart rate converted to normal sinus rhythm without recurrence. Our cases showed that the combined therapy of digoxin and flecainide acetate can effectively treat fetal atrial flutter associated with fetal hydrops unresponsive to digoxin monotherpy.

Key Words: *Atrial flutter; Hydrops fetalis; Flecainide; Drug therapy, fetal*

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INTRODUCTION

Uncontrolled fetal tachyarrhythmias may cause cardiac failure and fetal hydrops which consists of massive generalized edema, cardiomegaly, hepatosplenomegaly, or circulatory collapse. Polyhydramnios is a commonly associated sign and is often the presenting symptom (1). Perinatal morbidity and mortality are increased in this condition due to either hydramnios-related preterm labor or iatrogenic preterm delivery (2). Fetal drug therapy may prevent those problems by correcting arrhythmia and reversing hydrops and hydramnios. Digoxin has been the first-line drug in many of the reported series. The successful intrauterine cardioversion with flecainide in a hydropic fetus resistant to transplacental digoxin therapy has prompted more widespread use. We describe two cases of fetal atrial flutter associated with severe fetal hydrops unresponsive to digoxin that were successfully treated with flecainide.

CASE REPORT

Case 1

A 27-year-old primigravid woman was referred to our department at 30 weeks' gestation because of fetal ascites and irregular heart rhythm. Sonographic examination revealed a structurally normal baby except for hydrops fetalis (ascites, pleural effusion and skin edema) and mild polyhydramnios [Amniotic Fluid Index (AFI) = 26 cm, Fig. 1A]. Fetal M-mode echocardiography showed a 400-440 beats/min of atrial rate with a 2:1 atrioventricular (AV) relation (Fig. 1B). The mother was given three oral doses of digoxin (0.25 mg every 8 hours for 6 days). Although the maternal serum digoxin level was within the therapeutic range (1-2 ng/mL), echocardiography showed a persistent atrial flutter. On the 6th day of treatment, flecainide acetate was added orally 50 mg twice a day. On the 8th day of treatment, there was a notable change of fetal heart rate. The fetal heart rate fluctuated between normal sinus rhythm (150 beats/min) and tarchycardia. This pattern of fetal heart rate continued for several days. On the 14th day of treatment, the dosage of flecainide acetate was increased to 75 mg twice a day. On the 16th day of treatment, the fetal heart rate completely converted to normal sinus rhythm (141 beats/min). Fetal ascites and pleural effusion were resolved on the 18th day of treatment. The dosage of flecainide acetate was decreased to 50 mg twice a day on the 26th day of treatment. Administration of digoxin and flecainide acetate was stopped on the 29th day of

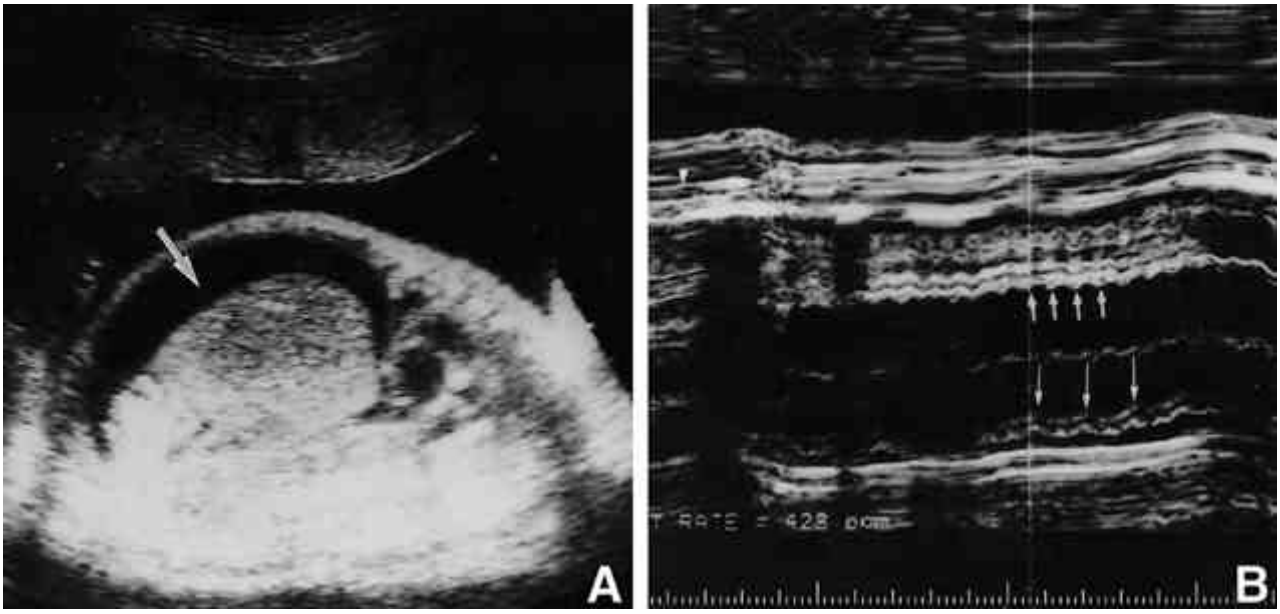

Fig. 1. Case 1. A: Initial ultrasonography shows fetal hydrops and polyhydramnios (arrow: ascites). B: Fetal cardiac M-mode shows atrial flutter recorded atrial rate of 400-440 bpm with a 2:1 atrioventricular relation (short arrow: atrial beat, long arrow: ventricular beat).

treatment. The fetus stayed in sinus rhythm after that period. A male infant, weighing 3,218 g, was born in good condition at 41 weeks of gestation. The neonatal echocardiogram was normal. The baby remained in sinus rhythm until a 18-month follow-up.

Case 2

A 27-year-old multigravid woman was admitted at 28 weeks' gestation because of fetal tachycardia (230 beats/min) on routine prenatal care. Fetal M-mode echocardiography showed supraventricular tachycardia (230-260 beats/min). The heart was structurally normal, but mild ascites was noted (Fig. 2A). The mother was given two oral doses of digoxin (0.5 mg every 12 hours and then 0.75 mg daily). Follow-up M-mode echocardiography on the 3rd day of treatment showed irregular rapid atrial beats (380-420 beats/min) and regular ventricular beats (194 beats/min) with 2:1 AV conduction (Fig. 2B). Although the maternal serum digoxin level was within

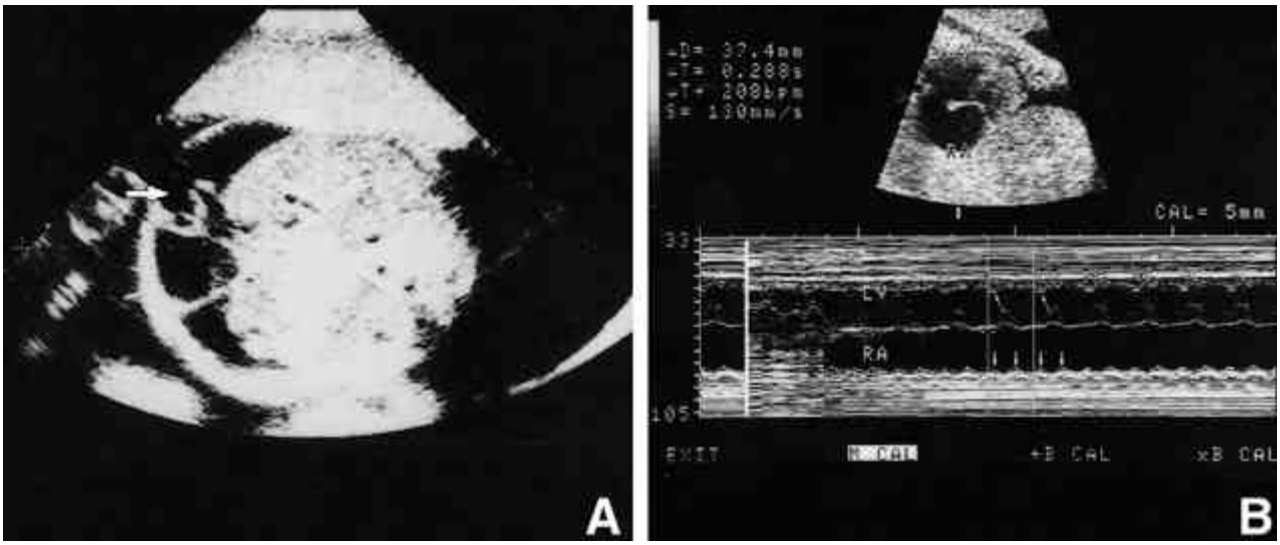

Fig. 2. Case 2. A: Initial ultrasonography shows hydrops fetalis (arrow: ascites). B: Fetal cardiac M-mode shows atrial flutter recorded atrial beat 380-420 bpm with 2:1 atrioventricular relation.

therapeutic range (1.0-2.0 ng/mL) for several days, echocardiography showed a persistent atrial flutter. On the 8th day of treatment, three oral doses of flecainide acetate (100 mg every 8 hours) were added. Because there was no response in the fetal atrial flutter after 48 hours, the dosage of flecainide was increased to 400 mg/day. The fetal tachyarrhythmia converted to normal sinus rhythm on the 14th day of treatment. However, ultrasonographic examination revealed more progressed fetal ascites and pericardial effusion. Administration of digoxin was stopped on the 16th day of treatment and the dosage of flecainide was tapered to 200 mg daily over 3 days. Administration of flecainide acetate was also stopped on the 19th day of treatment. Because irregular fetal tachycardia (180 beats/min) recurred on the 21st day of treatment, flecainide acetate (300 mg/day) was administered again to the mother. The fetal heart rate returned to normal sinus rhythm following administration of flecainide. The fetus stayed in sinus rhythm with flecainide acetate (200 mg daily). Fetal ascites and pleural effusion were resolved on the 39th day of treatment. A male baby, weighing 3,920 g, was born in good condition. Electrocardiography on the infant showed subtle preexcitation but there was no definite preexcitation in electrocardiography at 8-month follow-up. The echocardiography on the infant was normal. The baby remained in sinus rhythm until a 10-month follow-up.

DISCUSSION

The management of fetal arrhythmia depends on the underlying arrhythmias, hemodynamic status of the fetus, gestational age and maturity of the fetus. There are three therapeutic options in the management of fetal arrhythmias such as transplacental drug therapy, direct fetal administration of antiarrhythmic drugs, and delivery. Drug therapy for fetal arrhythmias, especially for tachyarrhythmias, is becoming standard management. Close monitoring of the fetomaternal adverse effects is very important in fetal drug therapy. Digoxin has been the drug of choice and its safety is well recognized in the management of fetal arrhythmias. Digoxin exerts its therapeutic electrophysiologic effects mainly by increasing the refractoriness of the AV node, thereby slowing AV nodal conduction and the ventricular rate in atrial fibrillation, atrial flutter, and supraventricular tachycardia. Digoxin readily crosses the placenta in human beings, and the administration of digitalis to the mother has been the mainstay in the therapy of intrauterine fetal tachyarrhythmias. Maternal administration of digoxin may be orally or intravenously, aiming to achieve maternal plasma levels of 2-3 ng/mL. Increased clearance during pregnancy warrants close monitoring of digoxin serum levels to avoid therapeutic failure. However, digoxin monotherapy is not successful in all cases and this most likely is a result of poor transplacental digoxin transfer (3, 4). Placental transfer varies between 40% and 100% and the correlation between maternal digoxin concentrations and rates of intrauterine cardioversion are poor. Endogenous digoxin-like substance (EDLS) does exist in the fetus (5) and pregnant women (6), as well as in patients with renal failure. The cross reactivity of EDLS in digoxin immunoassays complicates interpretation of data on serum digoxin level. The best approach is to achieve and maintain therapeutic or upper therapeutic serum digoxin concentrations in the mother in the absence of maternal toxicity. Successful cardioversion with digoxin alone can be expected in between 50% and 60% of nonhydropic fetuses with a duration from commencement of treatment to cardioversion of 7-16 days (7). Digoxin alone is less likely to be effective in the hydropic fetus probably because of impaired transplacental transfer.

Flecainide is a sodium channel blocker and produces marked phase-0 depression and slows conduction, especially in the His- Purkinje system. Literatures report the effectiveness of flecainide in the management of fetal tachyarthythmias (8, 9, 10). Flecainide therapy may produce paresthesia or visual disturbances, as well as adverse cardiac events such as proarrhythmic effects, impaired conduction or heart failure in treated adults (11). Flecainide is also associated with nonreactive NST results and poor beat-to-beat variability (9). Surveillance for fetal well-being is important. Fetal and neonatal serum levels of flecainide closely reflect maternal serum levels in the presence and absence of hyrops fetalis.

In our cases, digoxin was used as the first line drug. Although the maternal serum levels of digoxin were maintained within therapeutic range, the fetal heart rates failed to convert to normal sinus rhythms in our cases. Flecainide was added for its additive effect with digoxin. Since monitoring serum flecainide levels was not feasible in our institution, the dosage of flecainide acetate was monitored by means of PR and QRS intervals in the maternal electrocardiogram (<130-140% of baseline). Time for conversion to sinus rhythm after maternal oral dosing ranged from fewer than 2 days (8) to 4 to 7 days (9, 10). Time for conversion to sinus rhythm after maternal oral flecainide in addition to digoxin was 10 days in case 1 and 7 days in case 2. The initial dose of flecainide in case 1 was relatively low compared with other reports (8, 9). This could explain the difference in the time for conversion to sinus rhythm in our cases. After birth, tachycardia was induced by means of transesophageal atrial pacing in our two cases, but, atrial

flutter or other supraventricular tachycardia were not induced. The fetal atrial flutters in both cases seemed to be transient episode in utero.

We conclude that oral flecainide acetate in addition to digoxin can effectively treat fetal atrial flutters associated with hydrops fetalis unresponsive to digoxin alone.

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