Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 434–436

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Successful treatment of atrial flutter by repeated intraperitoneal and intra-amniotic injections of amiodarone in a fetus with hydrops

Pei-Hsuan Lin, Hsin-Hung Wu, Horng-Der Tsai, Charles Tsung-Che Hsieh*

Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan

ARTICLE INFO

Article history:
Accepted 26 May 2014

Keywords:
amiodarone
fetal atrial flutter
fetal direct treatment
hydrops fetalis

ABSTRACT

Objective: We report a case of nonimmune hydrops fetalis caused by atrial flutter, which was successfully treated by intraperitoneal and intra-amniotic injections of amiodarone.
Case Report: A 27-year-old woman presented at 30 weeks of pregnancy with hydrops fetalis caused by a fetal atrial flutter. As the transplacental passage of antiarrhythmic agents is impaired in hydrops fetalis, we chose direct treatment using fetal intraperitoneal and intra-amniotic injections (75–300 mg) of amiodarone. We managed to successfully convert the fetal atrial flutter to normal sinus rhythm. The woman delivered a live female baby at 33 weeks of gestation with normal sinus rhythm and neurological development.
Conclusion: Intrauterine antiarrhythmic treatment can reduce perinatal morbidity and mortality. This report suggests that direct fetal therapy using intraperitoneal or intra-amniotic injections of amiodarone constitutes an effective treatment for atrial flutter in cases of hydrops fetalis.

Introduction

The reported incidence of fetal tachycardia is 0.3 cases per 1000 births [1], whereas fetal atrial flutter (AF) accounts for approximately one-third of fetal tachyarrhythmia [2]. Fetal tachycardia complicated with hydrops fetalis carries a high risk of intrauterine fetal death [3]. Therefore, if these occur before 34 weeks of gestation, intrauterine therapy is preferred to premature delivery. In reviews of the agents used for fetal antiarrhythmic therapy, transplacental treatment was usually used as the first-line treatment, and direct fetal treatment through intramuscular, intraperitoneal, or umbilical vein injection was left for refractory cases [4–6]. Intraperitoneal administration of antiarrhythmic drugs into the fetal ascites has been found to be effective since its first use by Gembruch et al in 1988 [7,8]. According to fetal pharmacokinetics of antiarrhythmic agents, their transplacental passage is decreased in the presence of hydrops fetalis. We therefore chose to use amiodarone for direct fetal therapy due to its availability and efficacy in cases of refractory arrhythmia.

Case Report

A 27-year-old woman (G2P0A1) was referred to our hospital at 30 weeks of gestation for investigation and treatment of hydrops fetalis, which had been observed at 29 weeks of gestation by her local health care provider. Investigations for intrauterine infection (antibody titers for toxoplasmosis, cytomegalovirus, rubella, and parvovirus B19) were all normal. On ultrasonography, a single live fetus with ascites, pleural effusion, and skin edema was seen. No structural cardiac defect was noted. Fetal AF with 2:1 atrioventricular block was diagnosed using M-mode echocardiography (Figure 1A); fetal atrial and ventricular rates were approximately 480 bpm and 240 bpm, respectively. Amniotic fluid index was normal (14.74 cm). The fetus was diagnosed with heart failure secondary to fetal AF.

As the transplacental passage of antiarrhythmic agents is impaired in the presence of hydrops fetalis, we decided on direct treatment using fetal intraperitoneal injection of 75 mg amiodarone. At 5 minutes after the first injection into the fetal ascites, cardioversion to normal sinus rhythm was achieved (Figure 1B). The patient was admitted for fetal surveillance, and 0.25 mg digoxin was administered daily. The first cycle of betamethasone for fetal lung maturation was given at 30 weeks. During the 4 days

* Corresponding author. Department of Obstetrics and Gynecology, Changhua Christian Hospital, 135 Nanxiao Street, Changhua 500, Taiwan.
E-mail address: 40129@cch.org.tw (C.T.-C. Hsieh).

http://dx.doi.org/10.1016/j.tjog.2016.04.022

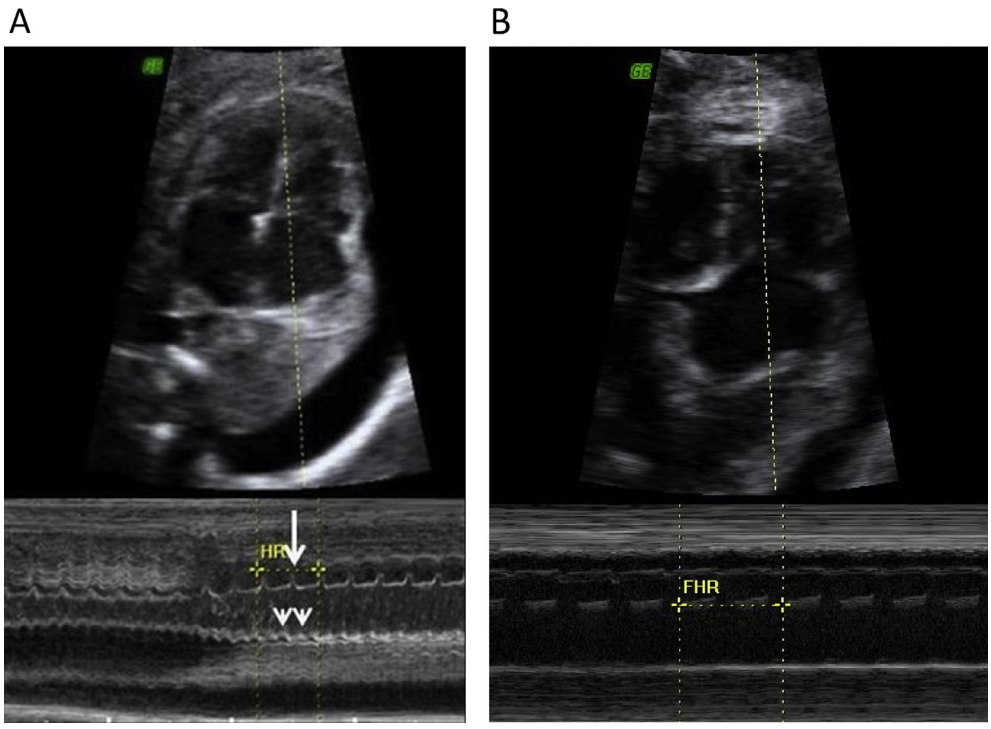

Figure 1. (A) Fetal cardiac M-mode of a 30-week pregnancy shows atrial flutter with 2:1 AV block with an atrial rate of 480 bpm and ventricular rate of 240 bpm (short arrow: atrial beat; long arrow: ventricular beat). (B) After the first intraperitoneal treatment at 30 weeks of pregnancy, fetal cardiac M-mode showed normal sinus rhythm. AV = atrioventricular; HR = heart rate; FHR = fetal heart rate.

of hospital stay, no recurrence of fetal AF was detected. She was discharged and received ultrasonographic follow-up every 2nd day.

At the first outpatient department follow-up, ultrasonography showed normal sinus rhythm and the ascites had almost disappeared. At 31 weeks of gestation, a recurrence of AF was detected on ultrasonography without progression of hydrops fetalis. Intra-amniotic injection of 75 mg amiodarone was administered, and cardioversion to normal sinus rhythm was observed within 5 minutes after treatment. At 32 weeks of gestation, AF was again detected at ultrasonographic follow-up and another intra-amniotic injection of 300 mg amiodarone was administered, with cardioversion soon observed after treatment. The injection was repeated after 4 days due to AF recurrence. During the 3 weeks of treatment, AF occurred occasionally; however, hydrops fetalis improved greatly (i.e., ascites disappeared and right pleural effusion was minimal).

A decrease in fetal movement was observed at 33 weeks of gestation, and a cesarean section was arranged after the patient's second course of betamethasone treatment. She delivered a female baby weighing 1.76 kg with an Apgar score of 7 at 1 minute and 9 at 5 minutes. The baby had a normal sinus rhythm after delivery. She still had mild right pleural effusion, and therefore received digoxin and furosemide treatment for 4 days. After that, no antiarrhythmic drug was needed. Echocardiography showed normal left ventricular function and no chamber enlargement. A thyroid profile survey was normal. The baby remained under hospital care for 24 days and was then discharged with a body weight of 2.1 kg. She is now 4 years old and has not had any recurrence of tachyarrhythmia.

Discussion

Fetal AF is defined as an atrial rate of >250 bpm with a fixed (usually 2:1) or variable atrioventricular block observed [2]. A fetus with tachyarrhythmia without hydrops has a good prognosis after transplacental treatment. Jaeqqi et al [2] presented their experience of 15 AF cases between 1988 and 1995. Eleven AF fetuses were treated with maternal digoxin, of which four cases showed conversion to normal sinus rhythm within 2 days of treatment and seven still had AF at birth. They also noted that patients with therapy-resistant AF without 1:1 atrioventricular conduction have a good prognosis because they observed no deterioration to hydrops. Obviously, their conclusion is not compatible with our presenting case where we found that AF with a 2:1 atrioventricular block could be complicated with hydrops. Furthermore, Simpson and Sharland [9] reported that intrauterine fetal therapy for fetal tachycardia could reduce the mortality rate of hydropic fetuses from 56% to 9.7%. Therefore, in our presenting case involving hydrops at 30 weeks of gestation, intrauterine therapy was preferred to premature delivery.

The main drugs used to combat fetal antiarrhythmic therapy are digoxin, flecainide, sotalol, and amiodarone. Digoxin is used as first choice, followed by flecainide or sotalol either alone or in combination with digoxin. Amiodarone is usually reserved for refractory cases [9]. The choice of drug for the first-line treatment of fetal tachycardia with hydrops is still controversial. Digoxin alone is considered a poor choice for the hydropic fetus by several studies because of low placental transfer [1,9–11], and, as per retrospective case reviews, no antiarrhythmic agents have shown constant efficacy for hydrops. Some studies mentioned that sotalol is an effective treatment for fetal AF and should be considered the most successful drug in recent years [11–14]. Sotalol can cross the placenta completely with a high fetal-to-maternal ratio (up to 1.1) [13]. In a case report, Wu et al [14] treated AF with digoxin and sotalol for 3 weeks before delivery. During the period of treatment, the fetal heart beat was partially controlled with a decreased ventricular rate and no hydrops observed. However, normal sinus rhythm was not achieved. Even sotalol alone or combined with digoxin shows a high conversion

rate of up to 83–85% [11,13]. Flecainide also had a good fetal-to-maternal ratio of 0.9 in the study of Krapp et al [15]. In addition, flecainide has a good sinus conversion rate (59–95%) in treating fetal tachyarrhythmia [4,15,16]. However, although it has a good placental transfer ratio, flecainide use was limited due to its possible proarrhythmic effect with 14.8% mortality rate in hydrops cases [9]. In our hospital, sotalol and flecainide are not available.

Amiodarone is considered a broad-spectrum antiarrhythmic medication for treating many arrhythmias when other antiarrhythmic drugs have failed. It is easily available and was selected for this case. It was suggested as first- or second-line therapy for the treatment of fetal tachycardia by Pezard et al [1]. They suggested daily oral administration (loading dose 1600–2400 mg daily and maintenance dose 200–400 mg daily), and this monotherapy was effective in five cases including two of hydrops with a rapid onset of action at around the 5th day. One case of hydrops was caused by AF and was converted to normal sinus rhythm after 10 days of treatment. The mothers received long-term amiodarone treatment till 15–21 days before term, and there were no fetal deaths in the amiodarone treatment group. Although transient thyroxine stimulating hormone elevation was noted in six cases, only two needed short-term thyroxine supplement. Their study suggested that transplacental amiodarone treatment was safe and effective even in cases of hydrops. The conclusions of this group differed from those of earlier studies. Gembruch et al in 1989 [8] presented the first case of fetal supraventricular tachycardia with severe hydrops that was successfully treated using direct repeated umbilical vein amiodarone injections after the failure of transplacental treatment with combined antiarrhythmic drugs. According to their experience, the dosage of umbilical vein injection should start at 2.5 mg/kg with stepwise increments up to 5 mg/kg of estimated fetal weight (without hydrops). In the study, they also tested the fetal blood from the umbilical vein and detected a low placental transfer of digoxin and amiodarone in hydrops (fetal-to-maternal transfer in digoxin 0.2–0.4 and in amiodarone 0.015–0.028). Amiodarone was chosen as the drug for direct fetal therapy because of its long elimination half-life [1], which could reduce the frequency of direct treatment.

In our presenting case, we believed that the placental transfer of digoxin and amiodarone would be poor because of hydrops fetalis; therefore, we selected direct therapy. Intraperitoneal and intra-amniotic injections, but not cordocentesis, were chosen because of their ease of use in daily practice. There were no clear dosage guidelines to follow for these injections. According to the guidelines for amiodarone dosage in newborns, a loading IV dose of 25 mg/kg/mine for 4 hours is followed by a maintenance dose of 4 mg/kg every 8 hours. For intraperitoneal injection, which mimics the intravenous route, we used 75 mg amiodarone (twice the suggested dosage of the IV route), resulting in rapid conversion within 5 minutes as monitored by M-mode ultrasonography. We noted that the AF recurred at approximately 1 week after each injection. For the third and fourth intra-amniotic injections (mimicking the oral route), we increased the amiodarone dosage to 300 mg. After four direct intraperitoneal or intra-amniotic injections, the hydrops fetalis almost resolved at delivery. No AF or elevated thyroxine stimulating hormone level was detected in the baby after birth. We therefore suggest that repeated intra-amniotic amiodarone injections can be used to treat AF with hydrops that is usually refractory to first-line transplacental therapy. We successfully resolved the hydrops and converted AF rapidly at every recurrence without the need to subject the mother to high-dose antiarrhythmic agents.

Thus, intraperitoneal or intra-amniotic amiodarone injections of 75–300 mg can be effective and safe to treat AF with hydrops without long-term side effects. However, further clinical experience is needed to establish the dosage guidelines for the therapy.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Pezard PG, Boussion F, Sentilhes L, Lepinard C, Couvreur MH, Victor J, et al. Fetal tachycardia: a role for amiodarone as first- or second-line therapy? Arch Cardiovasc Dis 2008;101:619–27.
[2] Jaeqqi E, Fouron JC, Drblik SP. Fetal atrial flutter: diagnosis, clinical features, treatment, and outcome. J Pediatr 1998;132:335–9.
[3] Van Engelen AD, Weijtens O, Brenner JL, Kleinman CS, Copel JA, Stoutenbeek P. Management outcome and follow up of fetal tachycardia. J Am Coll Cardiol 1994;24:1371–5.
[4] Bergmans MG, Jonker GJ, Kock HC. Fetal supraventricular tachycardia. Review of the literature. Obstet Gynecol Surv 1985;40:61–8.
[5] Stewart PA, Wladimiroff JW. Cardiac tachyarrhythmia in the fetus: diagnosis, treatment and prognosis. Fetal Ther 1987;2:7–16.
[6] Parilla BV, Strasburger JF, Socol ML. Fetal supraventricular tachycardia complicated by hydrops fetalis: a role for direct fetal intramuscular therapy. Am J Perinatol 1996;13:483–6.
[7] Gembruch U, Hansmann M, Redel DA, Bald R. Intrauterine therapy of fetal tachyarrhythmias: intraperitoneal administration of antiarrhythmic drugs to the fetus in fetal tachyarrhythmias with severe hydrops fetalis. J Perinat Med 1988;16:39–44.
[8] Gembruch U, Manz M, Bald R, Ruddel H, Redel DA, Schlebush H, et al. Repeated intravascular treatment with amiodarone in a fetus with refractory supraventricular tachycardia and hydrops fetalis. Am Heart J 1989;118:1335–8.
[9] Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. Heart 1998;79:576–81.
[10] Pradhan M, Manisha, Singh R, Kapoor A. Amiodarone in treatment of fetal supraventricular tachycardia. Fetal Diagn Ther 2006;21:72–6.
[11] Shah A, Moon-Grady A, Bhogal N, Collins KK, Tacy T, Brook M, et al. Effectiveness of sotalol as first-line therapy for fetal supraventricular tachyarrhythmias. Am J Cardiol 2012;109:1614–8.
[12] Oudijk MA, Michon MM, Kleinman CS, Kapusta L, Stoutenbeek P, Visser GHA, et al. Sotalol in the treatment of fetal dysrhythmias. Circulation 2000;101:2721–6.
[13] Oudijk MA, Ruskamp JM, Ververs FF, Ambachtsheer EB, Stoutenbeek P, Visser GH, et al. Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. J Am Coll Cardiol 2003;42:765–70.
[14] Wu TH, Huang LC, Ho M, Lee CC, Chiu TH, Hung YC. Fetal atrial flutter: a case report and experience of sotalol treatment. Taiwan J Obstet Gynecol 2006;45:79–82.
[15] Krapp M, Baschat AA, Gembruch U, Geipel A, Germer U. Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. Ultrasound Obstet Gynecol 2002;19:158–64.
[16] Won HS, Lee IS, Yoo HK, Yoo SJ, Ko JK, Lee PR, et al. Two cases of atrial flutter with fetal hydrops: successful fetal drug therapy. J Korean Med Sci 1998;13:676–9.