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Case Report

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# Therapeutic drug monitoring on the use of transplacental digoxin in fetal tachyarrhythmia: a case report

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## ABSTRACT

Fetal tachycardia (FT) is a rare disorder and is associated with significant mortality of fetus. Digoxin is one of the antiarrhythmic agents used to treat FT via transplacental therapy. In this report, we describe a therapeutic drug monitoring (TDM) case of digoxin during the treatment of FT. A 40-year-old woman, gravida 2 para 1, hospitalized to control FT as the fetal heart rate (FHR) showed over 200 bpm on ultrasonography at 29 weeks of gestation. She did not have any medical or medication history and showed normal electrolytes level on clinical laboratory test results. For the treatment of FT loading and maintenance dose of intravenous digoxin (loading dose: 0.6 mg; maintenance dose: 0.3 mg every 8 hours) were administered. To monitor the efficacy and safety of the treatment, TDM was conducted with a target maternal serum trough digoxin concentration of 1.0 to 2.0 ng/mL, as well as ultrasonography and maternal electrocardiogram. The observed digoxin serum concentrations were 0.67, 0.83, and 1.05 ng/mL after 1, 2, and 5 days after the initiation of digoxin therapy, respectively. Although the serum digoxin concentrations reached the target range, the FHR did not improve. Therefore, digoxin was discontinued, and oral flecainide therapy was started. The FHR adjusted to the normal range within 2 days from changing treatment and remained stable. TDM of digoxin along with the monitoring of clinical responses can give valuable information for decision-making during the treatment FT.

**Keywords:** Therapeutic Drug Monitoring; Digoxin; Fetal Therapy

## INTRODUCTION

The prevalence of sustained fetal tachyarrhythmias (FT) is 1 per 1,000 pregnancies [1]. Sustained FT may cause fetal heart failure, hydrops fetalis, and even death [1-3]. Transplacental medical interventions have been applied for nearly 40 years to control fetal rhythm and conversion to sinus rhythm [2].

Digoxin is a commonly used antiarrhythmic drug as it has been used for a long with its safety profile for the mother and fetus [3-5]. Digoxin is highly lipophilic and a low molecular weight drug that can rapidly cross the placenta and reach equilibrium [6]. Reports reveal its equal maternal and fetal serum concentrations: 60% to 90% of maternal serum levels, or 11% to 26% in cases of hydrops fetalis [6,7]. Flecainide, sotalol, and amiodarone are generally

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used as other choices of therapies [5,8]. Digoxin and flecainide are preferred in cases of fetal supraventricular tachycardia, whereas sotalol is preferred in cases of atrial flutter [4,5].

Here, we report a case of a pregnant woman in whom therapeutic drug monitoring (TDM) of digoxin contributed effectively to determining alternative treatment.

## CASE REPORT

A 40-year-old woman, gravida 2 para 1, was referred to our hospital at 29 weeks of gestation to manage FT. She had no surgical or medical history. Fetal ultrasound revealed a grossly normal fetus with an estimated fetal weight of 1,671 g and an amniotic fluid index of 11.95 cm. Electronic fetal heart rate (FHR) monitoring revealed cardiomegaly and an FHR of > 200 beats per minute (bpm) sustained over 50% of the monitoring time. Fetal echo in M-mode revealed an atrial rate of up to 500 bpm, with a ventricular rate of 228–236 bpm (A:V = 2:1). Maternal baseline electrocardiogram (ECG) and electrolyte levels were normal.

Transplacental digoxin therapy was planned to control the fetal rate. Digoxin was administered with a 0.6 mg intravenous (IV) load over the first 20 minutes, followed by IV maintenance of 0.3 mg every 8 hours. To monitor the efficacy and safety of the treatment, TDM was conducted in the target maternal serum through a digoxin concentration of 1.0 to 2.0 ng/mL, along with daily ultrasonography and maternal ECG. The observed digoxin serum concentrations were 0.67, 0.83, and 1.05 ng/mL on the first, second, and fifth days after initiation of digoxin therapy, respectively. On the fifth day of digoxin treatment, the FT duration increased, although the serum digoxin concentrations reached the target range (**Fig. 1**). Therefore, digoxin was discontinued, and oral flecainide therapy was started on the sixth day. Flecainide was orally administered at a fixed dose (100 mg 3 times a day) until cesarean delivery. The FHR was adjusted to the normal range within 2 days of changing treatment to flecainide and remained stable. Mild prolongation of the maternal QT interval (< 480 milliseconds) from 360 milliseconds was observed after flecainide therapy without any symptoms. A cesarean section was performed at 38 weeks and 1 day of gestation. At birth, the baby measured 45 cm in length, weighed 3,800 g, and had Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. His heart rate was 100–130 bpm. Echocardiography revealed an atrial septal defect with a left-to-right shunt (4.1 × 5.6 mm) and a patent ductus arteriosus (5.1 mm).

## DISCUSSION

The recommended dosing regimen for flecainide in FT transplacental therapy is orally 200–300 mg/day, dividing 2 or 3 times a day, and can be increased to 450 mg/day to approach the target plasma range between 0.2 and 1 μg/mL [1,5]. The amount and frequency for dosing flecainide in the case (100 mg 3 times a day) corresponded with the recommended dosage regimen.

Although digoxin is preferred in transplacental therapy because of its long history of use for the mother and fetus, there are discrepancies in the first-choice drug for FT treatment [5]. In a recent systemic review, 4 medications were used as first-line therapy in ten studies: digoxin, flecainide, sotalol, and amiodarone in 54%, 26%, 19%, and 1% of patients, respectively [1]. A recent meta-analysis reported that flecainide was more effective than digoxin concerning the rate of supraventricular tachycardia termination and the incidence of maternal side effects [1,5].


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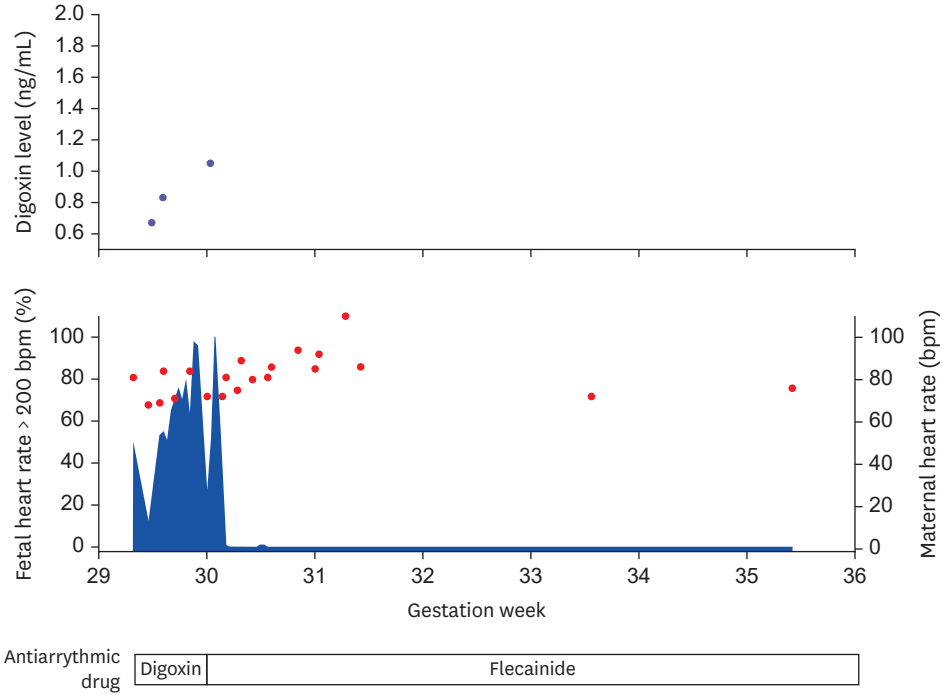


**Figure 1.** Treatment of digoxin and flecainide, the concentration of digoxin, percentage of fetal heart rate > 200 bpm (blue filled area, left y-axis) and maternal heart rate (red circle, right y-axis). The patient was hospitalized at hospital from 29 weeks of gestation and delivered at 38 weeks and 1 day of gestation.
bpm, beats per minute.

Various target digoxin ranges are reported for maternal concentration in FT therapy: between 0.8 and 2.0 ng/mL [3], 1 and 2.5 ng/mL [1], 1.5 and 2.0 ng/mL [5,8] and 2.0 and 3.0 ng/mL [5]. It may be a consequence of clinicians' concerns about maternal adverse events and a wide variety of fetal-to-maternal concentration ratios [9]. Because digoxin is a substrate for P-glycoprotein, the concentration ratio may depend on the gestational age of the placenta [9,10]. Maternal and fetal plasma-binding proteins and placental perfusion can also affect the concentration ratio [9]. Therefore, clinicians should consider the clinical response to maternal digoxin levels when considering alternative management.

TDM of digoxin also helps in minimizing side effects and reducing mortality and morbidity. A high serum digoxin level is considered an essential predictor of digoxin toxicity and is the most important predictor of mortality. In a case series reporting the relationship between maternal digoxin dosage, tolerance, and side effects with digoxin levels, the side effects frequently appeared when the serum digoxin level was > 2 ng/mL [11]. In all cases in which at least one symptom or sign existed, the digoxin level was higher than the therapeutic threshold (2 ng/mL), and all reversed within a maximum of 48 hours after the dose decrease. None of the patients developed side effects with digoxin levels < 2 ng/mL [11].

Our case report indicates the significance of TDM in transplacental digoxin therapy for the appropriate and timely management of FT.


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