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Digoxin for Fetal Tachyarrhythmia: Toxicity in an Underweight Mother

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To editor:

The use of digoxin for the transplacental treatment of sustained fetal tachyarrhythmia (FT) was first reported in 1980.[1] This medication is the first-line and most common antiarrhythmic in nonhydropic fetuses. Digoxin is administered to usually healthy mothers. Due to the intermediate solubility and low molecular weight of this drug, digoxin is readily delivered to the fetus via the placenta. The reported feto-maternal digoxin concentration ratio is 0.6–0.9 in normal pregnancies and lower in cases of hydrops fetalis (0.1–0.4) due to impaired transplacental transfer.[2,3] Despite the long history of safe use in pregnancy, 6% to 78% of patients have experienced digoxin side effects.[4,5] Therefore, the maternal serum concentration of digoxin must be monitored to ensure drug safety and efficacy. Below is a case of FT treated using standard doses of digoxin and flecainide as adjunctive treatment. The patient experienced symptoms of digoxin toxicity, requiring dosage reduction. The patient gave her consent for the case to be reported.

Case presentation

A 23-year-old, 47 kg, primigravida at 28 weeks was referred from the health clinic to the hospital for fetal tachycardia. The patient has no known medical illnesses besides having a low baseline albumin level of 30 g/L and being underweight (16 kg/m^2) during her first antenatal clinic visit at 12 weeks of gestation. The transabdominal scan indicated a singleton in a breech position with an estimated fetal weight of 1414 g and nonsustained fetal tachycardia with a heart rate of 248 beats per minute (bpm). Fetal echocardiography revealed normal cardiac structures and function without evidence of hydrops fetalis. The M-mode echocardiography assessment revealed the presence of atrial flutter with an atrial rate of up to 400 bpm and ventricular rate of 200 bpm. Otherwise, fetal growth was satisfactory as all fetal parameters were within the 25–75th percentile for gestational age (Table 1). The maternal baseline electrocardiogram (ECG) showed that a sinus rhythm, electrolyte levels, and thyroid function test were normal. Maternal TORCHes (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) screening was negative.

Transplacental therapy with oral digoxin was initiated at 250 micrograms (mcg) daily. One week later, the follow-up fetal echocardiography scan showed sustained supraventricular tachycardia with a heart rate of 234 bpm and apical pericardial effusion. No other features of hydrops were observed. The maternal ECG showed a sinus rhythm. The patient was admitted for an intravenous loading dose of digoxin at 400 mcg eight hourly, followed by an oral maintenance dose of digoxin 250 mcg twice daily. Serum digoxin concentration as well as signs and symptoms of digoxin toxicity, such as nausea, vomiting, bradycardia, and visual disturbances, were monitored to ensure the safety and efficacy of the treatment. Fetal heart rate (FHR) monitoring via the fetal Doppler was performed at every shift.

On day 3 of admission, the patient experienced epigastric discomfort with three episodes of vomiting. The patient's hemodynamics were normal. Maternal ECG indicated a flat T with an ST segment sagging at lateral leads and shortened QTc intervals, which is a normal presentation among patients treated with digoxin and not a marker of digoxin toxicity. The serum digoxin concentration was 1.6 mcg/L. As maternal vomiting persisted in the subsequent days and the repeated serum digoxin concentration exceeded the therapeutic range at 2.9 mcg/L, the digoxin administration was withheld. However, maternal hemodynamic status and the serial ECG tracing remained reassuring. Oral digoxin was restarted at 125 mcg twice daily when the level normalized, and the patient was asymptomatic. Subsequently, repeated serum digoxin concentrations were within the therapeutic range at 0.8–1.1 mcg/L (Fig. 1).

As the FT persisted with FHR ranging between 215 and 220 bpm, oral flecainide (100 mg twice daily) was administered a week later. FHR control was achieved within 48 hours of initiation of oral flecainide therapy. At discharge, the FHR remained stable (130–160 bpm), and the mother was healthy with a normal ECG and hemodynamic status. During a clinic visit at 32 weeks and 2 days of gestation, the patient complained of blurring and seeing double

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Table 1

Serial fetal biometry, biophysical profile score, and other sonographic findings.

Sonographic characteristic	28 weeks of gestation	32 weeks of gestation	36 weeks of gestation
Fetal biometry (mm)			
Biparietal diameter	81	86	93
Head circumference	289	314	331
Abdominal circumference	275	287	347
Femur length	56	61	72
Estimated fetal weight (kg)	1.7	2.1	3.4
Deepest vertical pocket (cm)	4	4	5
Uterine artery pulsatility index	0.9	0.8	1.0
Biophysical profile score	-*	>4	>4

*Fetal biophysical variables are not assessed at or before 28 weeks of gestation.

vision after taking flecainide, which lasted 2 to 3 hours and resolved spontaneously. The patient was reassured, and the oral digoxin and flecainide treatments were continued.

The fetal echocardiography during the subsequent clinic visit at 35 weeks and 3 days of gestation demonstrated a recurrence of FT (atrial flutter). The tachyarrhythmia relapse was caused by the patient's nonadherence to both medications. The patient was advised to be admitted to the hospital for the reinitiation of digoxin and flecainide. However, she declined and assured her adherence to the prescribed treatment at home. No digoxin levels were recorded during the period of nonadherence. Despite the claimed adherent, the atrial flutter persisted during the patient's clinic visit at 36 weeks and 5 days of gestation, with A:V conduction of 2:1. The atrial rate was 350 bpm, and the ventricular rate was 160–190 bpm. No features of fetal hydrops were observed. Oral flecainide was increased to 100 mg thrice daily.

The FHR control was reachieved on the subsequent follow-up. An elective cesarean delivery was performed at 37 weeks and 5 days of gestation. Maternal oral digoxin and flecainide were stopped after delivery. A baby boy weighing 3000 g was delivered with a good APGAR score. He has multifocal ectopic atrial tachycardia with difficult rate control. His atrial flutter did not respond to synchronized cardioversion. Furthermore, the infant developed ventricular tachyarrhythmia and was treated with oral propranolol and flecainide. A good rate control was observed in the patient when administered with oral propranolol (2 mg/kg, q8h), ivabradine (0.15 mg/kg, q12h), and digoxin (5 mcg/kg, q12h). The digoxin levels measured ranged between 0.9 and 1.9 mcg/L throughout therapy. The patient was discharged home after 6 weeks of hospitalization.

Discussion

Digoxin for transplacental therapy to treat FT is initiated with a loading dose to ensure the digoxin level reaches the therapeutic range rapidly. This can be administered intravenously or orally at 375–500 mcg every 8 hours for three doses or 500 mcg every 12 hours for four doses.[6] The treatment is followed by an oral maintenance dose of 250–500 mcg 12 hourly,[6] optimized to clinical effect and target range. In the case described above, the fetus's cardiac condition was detected in the early third trimester. Given the nonsustained tachyarrhythmia, the treatment was initiated with a low oral maintenance dose of digoxin to control the cardiac rhythm. One week later, the ultrasound indicated a sustained abnormal cardiac rhythm with a localized apical pericardial effusion, possibly due to the inadequate initial dosage of digoxin. The loading and maintenance doses of digoxin were reinitiated according to the consensus guidelines.

Digoxin is known for its narrow therapeutic range. In this case, early and routine monitoring of digoxin levels was performed to ensure that the drug reached the therapeutic level, sufficient to attain the desired clinical effect while avoiding digoxin toxicity. Although our center uses the digoxin target range of 0.8–2 mcg/L,[3] other target digoxin ranges that are reported in the literature for transplacental therapy of FT: 1.0–2.5 mcg/L,[6,7] 1.5–2 mcg/L,[5,8] and 2–3 mcg/L.[9] The variable targets resulted from the concerns regarding maternal adverse events and a range of feto-maternal digoxin concentration ratios. Digoxin is a hydrophilic compound that

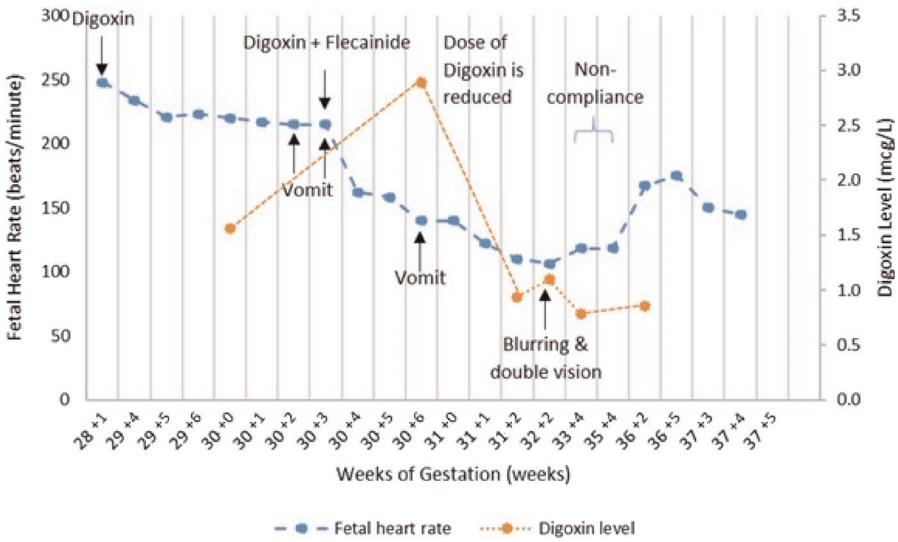

Figure 1. Treatment of digoxin and flecainide with the digoxin levels and fetal heart rate. Target maternal serum digoxin concentration is 0.8–2 mcg/L.

transfers poorly across the hydropic placenta, resulting in a low feto-maternal digoxin ratio. Therefore, a higher target range of up to 3 mcg/L has been cautiously administered in several cases.[9]

The incidence of digoxin side effects is approximately 80%, and are often gastrointestinal symptoms.[4] Nausea and vomiting are experienced by more than half (54%) of the patients,[3] and should be considered an early sign of digoxin toxicity, besides fatigue, visual disturbances, bradycardia, heart block, atria, and ventricular fibrillation, and bigeminy.[3,6] While specific ECG changes such as flat T with ST-segment depression and shortened QTc intervals are normal presentations of patients on digoxin therapy (as observed in the case discussed), the ECG changes such as ventricular tachycardia, AV block, and bigeminy are signs of digoxin toxicity. Therefore, performing daily ECG monitoring at the initial phase is essential while titrating digoxin levels to effective therapeutic doses.[3] Factors that may potentiate digoxin toxicity include electrolyte imbalances and hypothyroidism.[3] It should be noted that the patient in this case was underweight during her first antenatal clinic visit and had low albumin (28–30 g/L) throughout her pregnancy. Low albumin level and muscle mass have been associated with an increased unbound fraction of digoxin and a risk of digoxin toxicity,[10] as experienced by the patient in this case. A decrease in dose rapidly reversed the symptoms.

Flecainide is another drug used for the transplacental therapy of FT. It is a lipophilic compound with good transplacental transfer, even in cases of hydrops.[9] The recommended oral dose of flecainide is 200–300 mg twice or thrice daily[6,7] and to be adjusted to target maternal serum flecainide level of 200–1000 mcg/L.[2,3] In this center, oral flecainide is primarily used as an adjunct medication, such as in the case discussed, or in cases of tachyarrhythmia with fetal hydrops.[6] Given that this center does not test flecainide levels, the efficacy and safety of this drug are entirely based on the patient's clinical responses and electrocardiographic monitoring.

Conclusion

Digoxin treatment for FT should be performed cautiously and monitored closely especially in underweight pregnant woman, hence the importance of monitoring the maternal serum concentration of digoxin as well as the signs and symptoms of digoxin toxicity.

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Conflicts of Interest

None.

Data Availability

All data generated or analyzed during this study are included in this published article.

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