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Selective feticide reverses intrahepatic cholestasis of pregnancy in twins discordant for growth: A case report

Kyriaki Mitta, Ioannis Tsakiridis *, Themistoklis Dagklis, Georgios Michos, Fotios Zachomitros, Apostolos Mamopoulos, Apostolos Zavlanos, Apostolos Athanasiadis

Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece

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ABSTRACT

Twin gestations are associated with an increased risk of intrahepatic cholestasis in pregnancy (ICP), probably attributed to the elevated pregnancy hormones. We report a case of a dichorionic diamniotic twin pregnancy, at the third trimester, complicated with ICP and severe, selective fetal growth restriction (sFGR). A 32-year-old primiparous woman with a dichorionic, diamniotic twin gestation conceived via in vitro fertilization (IVF) presented with pruritus at the maternity care unit at 26^{+4} weeks of pregnancy. Following a detailed assessment, she was diagnosed with severe sFGR and ICP. During her hospitalization, selective feticide of the FGR fetus was decided and a remarkable improvement in the symptoms and the laboratory findings of ICP was noticed. The incidence of ICP is reported to be higher in twin pregnancies, especially those conceived via IVF, compared with singletons. The optimal timing of delivery and management of twin pregnancies complicated with ICP remain unclear. In our case, selective reduction of the FGR fetus led to the resolution of ICP.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease unique to pregnancy, characterized mainly by maternal pruritus and elevated total bile acids (TBA) [1]. Its reported incidence varies widely, between 0.4% and 15% in singleton pregnancies and up to 25% in twin pregnancies, with a geographical distribution [2,1]. ICP is related to an increased risk of adverse fetal outcomes [3], while twin gestations are associated with an increased risk of ICP [4].

The etiopathogenesis of ICP is unclear, and various factors have been proposed, including genetic, ethnical, environmental and hormonal [1,5]. High estrogen and progesterone levels are considered to play a significant role in the onset of ICP [5]. Twin pregnancies, which are characterized by higher levels of hormones than singleton pregnancies, have been increasing over the last years, especially in high-income countries, mainly due to the increasing use of assisted reproductive techniques (ART) such as in vitro fertilization (IVF) [6]. Notably, ICP appears to develop earlier, more frequently and severely in twin pregnancies following ART than in those conceived naturally [6].

We report a case of an IVF twin pregnancy complicated with ICP and severe selective fetal growth restriction (sFGR), with resolution of ICP following selective feticide of the FGR fetus.

2. Case presentation

A 32-year-old primiparous woman with an IVF dichorionic diamniotic (DCDA) twin pregnancy presented at the maternity care unit at 26^{+4} weeks of pregnancy complaining of pruritus. Regarding her medical history, she reported Hashimoto's thyroiditis, treated with levothyroxine; she had a previous history of laparoscopic bilateral salpingectomy because of bilateral hydrosalpinx and had been taking aspirin from the first trimester because of the high risk of preeclampsia (1:75).

On physical examination, all the vital signs were normal: temperature 36.1 °C, heart rate 85 beats/min, blood pressure 110/65 mmHg, O_2 saturation 99% and respiration rate normal. Her body mass index (BMI) was 29.9 kg/cm^2. On admission, at 26^{+4} weeks, a growth scan was performed; the first fetus was at the 49th centile with normal Doppler studies, whereas the growth of the second twin was at the 6th centile with absent end-diastolic flow in the umbilical artery (AEDF) and increased blood flow resistance of the ductus venosus.

Regarding laboratory findings, the total serum bile acids were 105 micromol/L, while she also had elevated alanine transaminase (ALT/SGPT: 399 U/L) and aspartate aminotransferase (AST/SGOT: 196 U/L), with normal gamma-glutamyl transferase (γGT), serum bilirubin, total

* Corresponding author at: Konstantinoupoleos 49, 54642 Thessaloniki, Greece.
E-mail address: iotsakir@gmail.com (I. Tsakiridis).

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protein, albumin, and prothrombin time (PT). The hepatitis panel (HAV, HBV, HCV, HEV), the anti-smooth muscle antibody test (ASMA) for autoimmune hepatitis and the anti-mitochondrial antibodies (AMA) for primary biliary cirrhosis were all negative. Immunoglobulin M antibodies for TORCH and Epstein-Barr virus were negative, as well. An ultrasound scan of the upper abdomen was performed without any abnormal findings. Therefore, the diagnosis of ICP was made and treatment with ursodeoxycholic acid (UDCA) was initiated.

During the patient's hospitalization, a serial evaluation of the liver function was performed; the transaminases had a gradual increase (Table 1). Additionally, Doppler studies were offered every other day and computerized cardiotocography daily. A growth scan was performed one week later; the 1st fetus was at the 39th centile with normal Doppler, whereas the second one was at the 3rd centile with AEDF and increased blood flow resistance of ductus venosus. As survival without severe morbidity was unlikely for the FGR fetus and maternal liver function was deteriorated, thus prejudicing extreme preterm delivery, the option of selective feticide was discussed with the couple. The couple opted to proceed with this and informed consent was given. An uncomplicated procedure was performed. Four days after the selective feticide, an improvement in her liver function, the total bile acids (36 micromol/L), and the symptoms were noticed; the patient was discharged under close outpatient follow-up.

On follow-up 14 days after the feticide, the total bile acids were 5.2 micromol/L (29^{+4} weeks of pregnancy) and aminotransferases were normal. At 34^{+2} weeks, the total bile acids were 6 micromol/L. At 37^{+1} weeks, she had a spontaneous onset of labor and delivered vaginally a healthy neonate of 2600 g.

3. Discussion

This was a case of a DCDA IVF twin pregnancy, complicated with ICP at 26^{+4} weeks of gestation and severe sFGR. Following extensive counseling, selective feticide of the FGR fetus was offered one week after admission, due to sFGR with AEDF and deterioration of maternal liver function. The symptoms and the liver function test, including total bile acids, were improved; she had an uneventful vaginal delivery, with spontaneous onset, at 37^{+1} weeks.

Selective second-trimester feticide of an abnormal twin has been previously reported, either to prevent the birth of an abnormal twin or to protect the normal twin from perinatal complications related to the anomaly [7]. Moreover, published data suggest that selective feticide may be an option for treating preeclampsia in some twin pregnancies, by causing involution of the pathologic placenta; selective feticide could lead to resolution of maternal illness, such as preeclampsia in twin gestations discordant for severe sFGR or other conditions in which the abnormal twin is not viable [8]. Nevertheless, there are no data regarding resolution of ICP after selective feticide in discordant twins. In our case, we hypothesized that since preeclampsia may be resolved, other maternal conditions such as ICP may be resolved after selective feticide, as well.

Table 1
Timeline of the pregnancy management (inpatient).

	Day 1 *Admission*	Day 8 *Selective reduction of the FGR fetus*	Day 12 *Discharge*
AST/SGOT U/L	196	206	114
ALT/SGPT U/L	399	523	340
Total bile acids micromol/L	**105**	**120**	**36**
Upper Abdomen U/S	√		
ASMA, AMA,	√		
Rest laboratory findings	√	√	√
Growth scan	**1st fetus:** 49th centile, normal dopplers **2nd fetus:** 6th centile, AEDF, ↑PIV ductus venosus	**1st fetus:** 39th centile, normal dopplers **2nd fetus:** 3th centile, AEDF, ↑PIV ductus venosus	

With regard to pregnancy complications associated with ICP, in a large cohort study of twin gestations, ICP was associated with an increased risk of preterm delivery and stillbirth, which occurred at a gestational age of 33–35 weeks, earlier than reported in singleton pregnancies [4]. Twin gestations may have significantly higher serum levels of fasting total bile acids than singleton gestations; thus, severe ICP is more common among [9] and the onset of symptoms of ICP occurs earlier in twin than singleton gestations [4].

History taking, physical examination and laboratory evaluation help to rule-in the diagnosis and rule out other disorders in differential diagnosis. Several guidelines mention that the differential diagnosis of ICP should include pregnancy-specific dermatopathies such as pruritic urticarial papules and plaques of pregnancy, pemphigoid gestationis, the atopic eruption of pregnancy, polymorphic eruption of pregnancy and non-pregnancy-specific conditions, such as atopic dermatitis [10,11]. Other pregnancy-specific causes of hepatic impairment that should be ruled out are preeclampsia, hemolysis, elevated liver enzymes and low platelets syndrome (HELLP), acute fatty liver of pregnancy and hyperemesis gravidarum [10,11]. Preexisting causes of hepatic impairment such as viral, autoimmune hepatitis, biliary tract obstruction, primary biliary cirrhosis, primary sclerosing cholangitis [10–12] and drug-induced liver injury should be considered, as well [12].

ICP should be suspected in any pregnant woman with pruritus unrelated to rash in the late second or third trimester. Diagnosis is confirmed when pruritus is associated with elevated total bile acids (fasting total bile acid>10 micromol/L) [1]. Furthermore, ICP is classified as mild if the bile acid concentrations are 19–39 micromol/L, moderate if they are 40–99 micromol/L and severe if the bile acids are ≥100 micromol/L [10]. In our case, ICP was characterized as severe; the total bile acid levels on admission were 105 micromol/L.

With regard to management, UDCA is recommended as first-line treatment [13], as it has been shown to reduce maternal pruritus and improve laboratory findings [14,15]. Notably, UDCA has no impact on the reduction of adverse perinatal outcomes [16]. A dose of 10–15 mg/kg/day is recommended, with a maximum daily dose of 2500 mg [13]. In our case, the maximum dose of UDCA was 1250 mg and no other medication was administered.

Regarding the optimal timing of delivery, according to the most recently published guidelines, most algorithms propose delivery between 38 and 40 weeks or sooner, taking into consideration the previous obstetrical history, antenatal monitoring and gestational age [10]. Regarding twin gestations, there are some studies in the literature that propose earlier delivery, at 35–36 weeks, depending on the severity of the disease [9]. In our case, there was resolution of ICP after the feticide of the FGR fetus and spontaneous onset of labor occurred at 37^{+1} weeks.

The recurrence rate of ICP is reported to be as high as 90% [11]; women with severe familial forms of ICP are suggested to be at increased risk of chronic liver disease later in life [17]. As for long-term outcomes, according to cohort studies, women with a history of ICP have increased rates of hepatitis C, chronic hepatitis, cirrhosis, gallstones disease, cholangitis, hepatobiliary cancer, cardiovascular disease and immune-mediated diseases [3,18].

4. Conclusions

This is a case of a DCDA twin pregnancy, complicated with severe ICP and severe sFGR, which had a resolution of ICP following selective feticide of the FGR fetus. Our case highlights the need for close follow-up of twin pregnancies complicated with ICP, especially those following IVF. Notably, there is a lack of guidelines and strategies regarding the optimal management and delivery time of twin gestations complicated with ICP. Our case provides an indication that twin pregnancies manifest

a more severe form of ICP compared than singleton pregnancies. Potentially, ICP was linked with disease in one but not both twins. This case may also suggest that selective feticide may be an acceptable option for maternal ICP in twin gestations discordant for severe FGR with a poor prognosis, in which the abnormal fetus is unlikely to be viable and when ICP occurs at early gestational age, obviously in settings where this intervention is legal and there is expertise.

Contributors

Kyriaki Mitta contributed to the literature review and drafting of the manuscript.

Ioannis Tsakiridis contributed to the conception of the case report and drafting of the manuscript.

Themistoklis Dagklis was involved in patient care and revision of the article.

Georgios Michos participated in the literature review and data acquisition.

Fotios Zachomitros participated in the literature review and data acquisition.

Apostolos Mamopoulos was involved in patient care and revision of the article.

Apostolos Zavlanos was involved in patient care and revision of the article.

Apostolos Athanasiadis contributed to the conception of the case report and the revision of the article.

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Patient consent

Written informed consent was obtained from the patient for the publication of this case report.

Provenance and peer review

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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