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Sudden Fetal Deterioration in Severe Intrahepatic Cholestasis of Pregnancy

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1. Abstract

1.1. Background: Intrahepatic cholestasis of pregnancy is a reversible cholestasis typically beginning in the second or third trimester and associated with increased rates of stillbirth, preterm birth, fetal asphyxia, and neonatal care unit admission. The etiology of adverse outcomes in gestational cholestasis seems related to maternal bile acids levels, but recommendations for management, particularly regarding fetal surveillance and timing of delivery, have been limited due to the paucity of data and the low-quality of the evidence.

1.2. Case: A patient with severe gestational cholestasis (bile acids level >100 µmol/L) was hospitalized at 32.3 weeks of gestation for close fetal surveillance inclusive of non-stress test three times daily, and maternal treatment. At 34.1 weeks, fetal bradycardia lasting 7 minutes was noted at fetal heart rate monitoring. At emergency cesarean delivery a liveborn appropriately grown infant was found, with Apgar scores of 5, 7 and 8 at 1, 5 and 10 minutes, respectively, and umbilical artery acidemia (pH of 7.19, base excess of -5.4 mMol/L). The child did eventually well.

1.3. Conclusion: Severe maternal cholestasis can cause acute fetal acidemia; close inpatient surveillance or delivery could be necessary in such cases to prevent stillbirth.

2. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a gestational liver disease characterized by pruritus without rush or typical dermatologic lesions, with elevated serum bile acid concentrations in the absence of other systemic or hepatobiliary disorders [1-4]. ICP is associated with increased risk of adverse perinatal outcomes, including preterm delivery (both spontaneous and iatrogenic), fetal death, and neonatal respiratory distress syndrome. Elevated total bile acids concentrations are more predictive of adverse perinatal events, including stillbirth, than other biomarkers [3, 5, 6]. A recent meta-analysis has revealed that the stillbirth risk increases significantly with total bile acid concentrations of ≥100 µmol/L at any point in the pregnancy compared with the pooled national prevalence of stillbirth [3]. A maternal blice acids level ≥100 µmol/L was found to be a predictor of higher risk of stillbirth also in large multicenter study [6]. The actual risk may be higher since management strategies (including fetal testing and timed delivery) may have mitigated the risk.

The cause of stillbirth in ICP is uncertain; several studies and case reports have described stillbirths occurring within days of reassuring fetal surveillance tests [7]; such findings, as well as data from animal models showing a toxic effect of bile acids on the fetal cardiac conduction system resulting in fatal arrhythmias [8, 9], have led to the hypothesis that fetal deaths caused by elevated bile acids may not be preventable with traditional fetal surveillance [10]. However, the known association between meconium-stained amniotic fluid and ICP, with nearly 80% of stillbirths occurring in the context of meconium-stained fluid, and the significant association between maternal bile acids level and rates of meconium-stained

amniotic fluid, suggest a role for fetal hypoxia in the causation of at least some stillbirths, since sudden arrhythmias would be unlikely to result in meconium passage [6, 11]. Alternative explanations for the causation of fetal deaths in ICP have been proposed. Acute placental vessel spasms have been reported in vitro in the presence of bile acids, suggesting a potential for hypoxia as causative mechanism [12]. A cohort study has shown that a protocol inclusive of monitoring of fetal well-being with twice weekly non-stress tests, search for meconium-stained fluid via transcervical amnioscopy, and elective delivery at 37 weeks significantly reduced the stillbirth rate compared with a historic cohort which had not undergone fetal surveillance [13]. Of interest, in 2% of cases in such series, urgent delivery was prompted by non-reassuring fetal surveillance. Such observations justify a role for fetal surveillance in the presence of ICP with elevated total bile acids levels. Despite limited evidence to document its benefit, antenatal fetal surveillance is commonly implemented and recommended in ICP [4, 14]. However, opinions vary as to the appropriateness of fetal surveillance, its frequency, and timing of delivery [14-16].

We present a documented case of rapid fetal deterioration associated with cord blood gas analysis evidence of acidemia in a woman hospitalized for severe ICP undergoing frequent daily fetal surveillance.

3. Case

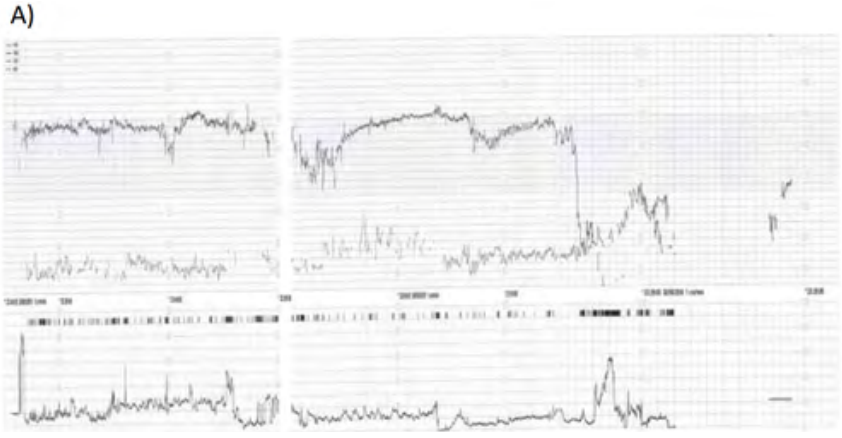
The patient was a 33-year-old woman Gravida 2 Para 1001 hospitalized at 32.3 weeks of gestation due to severe cholestasis, with complaints of severe, widespread pruritus day and night, bile acids level of 103.5 µmol/L, ALT 469 U/L (8-41), AST 357 U/L (11-34), and normal bilirubin 0.8 mg/dL (0.4-1.2 mg/dL). Hepatitis A, B and C markers showed absence of acute or chronic viral hepatitis. An ultrasound exam of the liver showed normal size and consistency, without dilatation of the intrahepatic or extrahepatic bile ducts or signs of portal hypertension or vascular abnormalities, and normal gallbladder.

During her first pregnancy, she was hospitalized at 34.4 weeks due to severe ICP (bile acids level of 107.5 µmol/ L), for thrice-daily non-stress test and treatment with ursodeoxycholic acid. Induction of labor at 36 weeks' gestation resulted in a healthy neonate, birth weight 2280 gr (22nd centile), Apgar score of 9 at 5 minutes.

During the hospitalization in the index pregnancy, ursodeoxycholic acid was administered (300 mg orally every 8 hours), fetal non-stress tests were performed three times daily, and biophysical scores were obtained twice a week. Fetal biometry was appropriate for gestational age. Induction of labor was scheduled for 36.0 weeks. Despite therapy, serum bile acids levels increased to 170.9 µmol/L at 33.2 weeks of pregnancy, whereas transaminase levels decreased (AST 95 U/L, ALT 214 U/L). The daily dose of ursodeoxycholic acid was increased to 1,200 mg/daily in divided doses; antihistamine therapy was added due to worsening symptoms. Throughout the hospitalization, fetal movements were normally perceived by the patient, the non-stress test was reactive, and biophysical profile scores were normal.

At 34.1 weeks, during a routine non-stress test, a prolonged deceleration with fetal heart rate reaching a nadir of 80 beats/min was detected (Figure 1, A). After 7 minutes of persistent bradycardia despite resuscitative measures, an emergency cesarean section was decided, with a decision-to-delivery interval of 13 minutes, and interval between completion of general anesthesia and delivery of 5 minutes. At entrance into the amniotic cavity, meconium-stained amniotic fluid was present. A female neonate was delivered with birth weight of 2210 gr (50th centile) and Apgar scores of 5, 7, and 8 at 1, 5, and 10 minutes, respectively. Umbilical artery pH was 7.19, base excess -5.4 mMol/L, lactate 3.7 mMol/L. The neonate showed respiratory distress, cyanosis, bradycardia, and generalized hypotonia; she was admitted to the neonatal intensive care unit and required continuous positive pressure ventilation for 3 days, empiric antibiotic therapy with ampicillin (though all culture results were negative). Her breathing improved rapidly; she was transferred to a normal ward on day 4 and she was discharged home on day 9 from birth.

The patient's therapy with ursodeoxycholic acid was discontinued after delivery, and values of bile acids, AST and ALT normalized within the following 4 weeks. Histological examination of the placenta showed no evidence of meconium-laden macrophages; mild decidual vasculopathy, areas of villus hypermaturity, and increased perivillous fibrin deposits were noted, with normal membranes and umbilical cord.



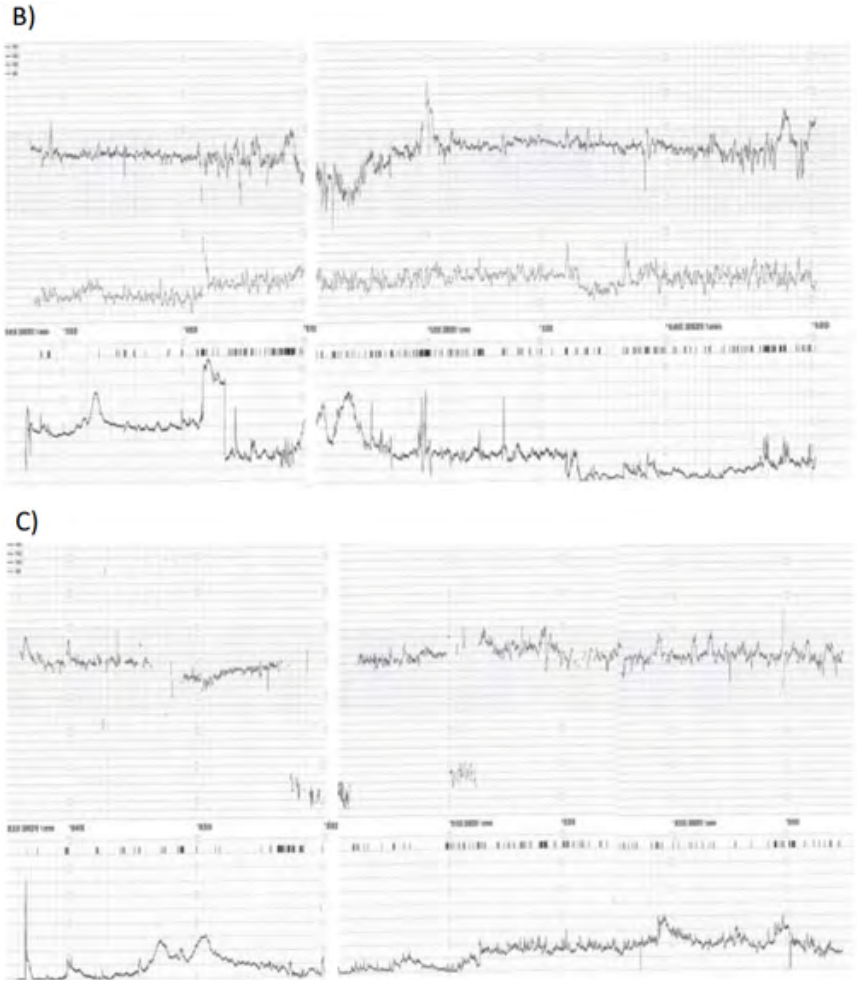


Figure 1:

A. Non-stress test which prompted the emergency cesarean delivery. The test was non-reactive, with two prolonged decelerations followed by a final 7-minute prolonged deceleration.

B. Non-stress test obtained 8 hours prior to delivery. Although the non-stress test was reactive, a 6 minutes prolonged deceleration was observed.

C. Non-stress test obtained 12 hours prior to delivery. The non-stress-test was reactive.

Speed of tracing is 1 cm/min.

4. Discussion

Rapid fetal heart rate deterioration and acidemia can occur in the context of severe maternal ICP. In our case, umbilical artery pH and base excess were lower than expected at cesarean delivery in the absence of labor [17], and they were compatible with the reported decline of 1 mMol of base excess every 2-3 minutes of bradycardia [18]. Although meconium-stained fluid was noted at delivery, no meconium-laden macrophages were present in the placenta, suggesting recent passage of meconium. The non-stress test 8 hours before the fetal bradycardia was reactive, albeit with an isolated prolonged deceleration (Figure 1, B). The occurrence of fetal bradycardia during fetal heart rate monitoring was a fortuitous event, which sheds light on the possible causation of some stillbirths in the context of severe ICP. Despite animal data suggesting fetal arrhythmias in the causation of ICP, acute fetal deterioration and acidemia may occur in the absence of arrhythmia.

As a corollary to our finding, prevention of stillbirth in the presence of maternal bile acids levels ≥100 μmol/L cannot be accomplished with outpatient surveillance. Indeed, a large multicenter study of cases of ICP managed with outpatient serial biophysical profiles and delivery planned between 36 and 37.6/7 weeks of gestation did not obviate the occurrence of stillbirth (15% for women with bile acids ≥100 μmol/L vs 0% for cases with bile acids <100 μmol/L) [6]. Current guidelines by the Royal College of Obstetricians and Gynaecologists are to advise women with ICP to monitor the quality and quantity of the fetal movements, and report any reduction or changes; fetal cardiotocography monitoring or biophysical profile are not recommended to reduce the risk of stillbirth. The Society for Maternal Fetal Medicine (SMFM) recommends fetal surveillance in ICP with frequency determined by criteria such as comorbidities or bile acids levels, with more frequent monitoring for total bile acid levels of 100 mmol/L or greater; however, continuous monitoring is recommended only during labor [4]. The American College of Obstetricians and Gynecologists (ACOG) recommends outpatient fetal surveillance once or twice weekly [14]. Such surveillance may reduce but not eliminate the risk of stillbirth associated with ICP [6, 13]. We suggest that

whereas outpatient fetal surveillance may be adequate for maternal serum bile acids levels <100 μmol/L, continuous in-patient fetal heart rate monitoring should be considered for cases with bile acids levels ≥100 μmol/L.

Alternatively, delivery may be anticipated after administration of corticosteroids. A decision-analytic model study accounting for prematurity morbidity versus stillbirth risk concluded that the optimal gestational age at delivery for women with ICP was 36 weeks, but the study did not stratify by bile acids level [19]. Both SMFM and ACOG recommend that delivery be scheduled at 36 weeks in cases of ICP with bile acids ≥100 μmol/L [4, 14]. We suggest that it is reasonable to offer earlier delivery in the rare cases of ICP with persistent bile acids ≥100 μmol/L, especially if unresponsive to therapy with ursodeoxycholic acid. Of note, treatment with ursodeoxycholic acid has been shown to reduce preterm birth and maternal symptoms, but not the risk of stillbirth [20]. Timed induction of labor may also allow vaginal delivery, while avoiding the risks of emergency cesarean section for both mother and fetus.

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