Management of drug-induced hyperbilirubinaemia in early pregnancy

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No reports have described effects on the fetus of maternal jaundice caused by drug-induced hepatotoxicity during pregnancy, particularly in the first trimester. We report on two pregnant women who developed severe drug-induced hepatic failure and hyperbilirubinaemia during the period of fetal organogenesis. Both were diagnosed and treated promptly, and neither of the newborns had organic abnormalities. Prompt discontinuation of the drug suspected to be causing the condition is the optimal management, immediately decreasing the maternal bilirubin level and improving the perinatal prognosis. It appears that brief exposure of the fetus to maternal hyperbilirubinaemia during the first trimester may not affect fetal development, even if the mother's bilirubin level temporarily exceeds 171.0 µmol/l.

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Hyperbilirubinaemia occurs in 1 in 2 000 obstetric patients. Severe hepatic disorders in pregnancy are rare, but remain clinically important because of serious adverse effects on both mother and fetus.[1] Maternal hyperbilirubinaemia during pregnancy worsens perinatal outcomes because of the increased risks of preterm delivery and intra-uterine death.[2] However, the effects of maternal hyperbilirubinaemia on the fetus, particularly during the first trimester, have not yet been reported. Furthermore, there are no clear guidelines for management of maternal hyperbilirubinaemia during the first trimester, a period during which the fetus is highly sensitive to harmful environmental factors.[2]

We report on two women with hyperbilirubinaemia caused by drug-induced hepatotoxicity in early pregnancy. Our therapeutic and management approaches may have contributed to favourable fetal neurodevelopmental outcomes. We therefore present these cases, with a review of the relevant literature, in the hope of providing information that will help others improve maternal and fetal outcomes in similar situations.

Case reports

Case 1

A 36-year-old primipara complained of general fatigue and noted the onset of jaundice from the 8th week of gestation. She visited our prenatal care centre during the 9th week. She had been medicated with aspirin since the 6th gestational week because of a history of multiple spontaneous abortions. Personal and family histories were unremarkable. Biochemical examinations on admission showed elevated liver enzymes and hyperbilirubinaemia. Her total serum bilirubin level was 215.5 µmol/l, with an unconjugated fraction of 71.8 µmol/l. Her blood type was AB-Rh positive; the direct Coombs test was negative. Hepatitis B surface antigen and hepatitis C antibody were negative. Antinuclear antibodies and antimitochondrial antibodies were negative, ruling out an auto-immune condition. An abdominal ultrasound scan revealed no abnormalities.

As soon as the patient stopped taking aspirin, the hyperbilirubinaemia and abnormal liver enzymes began to normalise. Drug-lymphocyte stimulation tests for aspirin were positive. We therefore diagnosed drug-induced hepatotoxicity caused by aspirin. From the 15th gestational week her bilirubin level remained stable within the normal range and the jaundice did not recur. Fetal growth was appropriate, with no prenatal evidence of abnormalities.

The patient gave birth vaginally to a healthy male infant at the 39th gestational week. His bilirubin level was within the normal range for newborns, and his neurological development and the results of neurological examination were normal at 12 months of age.

Case 2

A 36-year-old primipara had noticeable jaundice after the 11th week of gestation, and visited our prenatal care centre during the 13th week. She had been medicated with piperidolate hydrochloride for threatened abortion since the 6th week. Her past and family histories were unremarkable. Biochemical examinations on admission showed elevated liver enzymes and hyperbilirubinaemia. Her total serum bilirubin level was 389.9 µmol/l, with an unconjugated fraction of 53.0 µmol/l. Viral hepatitis, auto-immune disorders and liver and biliary tract disease were ruled out.

We withdrew the piperidolate hydrochloride and treated the patient with a liver-protective drug. The jaundice and abnormal liver enzymes immediately improved and soon normalised. Drug-lymphocyte stimulation tests for piperidolate hydrochloride were negative, but in view of the patient's clinical course we concluded that her hyperbilirubinaemia was caused by drug-induced hepatotoxicity.

From the 17th week of gestation her bilirubin level was stable and remained within the normal range. Jaundice did not recur. Fetal growth was appropriate, with no prenatal evidence of abnormalities.

Spontaneous labour began at 39 weeks' gestation, but fetal distress necessitated an emergency caesarean section. A healthy female infant was delivered. The newborn's bilirubin level was within the normal range. The findings on neurological examination were normal, and her neurological development was normal at 12 months of age.

Discussion

To our knowledge, no reports in the relevant literature describe the effects on the fetus of maternal hyperbilirubinaemia during the first trimester. Our two patients had severe hepatic dysfunction and hyperbilirubinaemia during the period of fetal organogenesis. However, their newborns suffered no organic abnormalities such as kernicterus or neurodevelopmental disorders. Prompt diagnosis and treatment of drug-induced hyperbilirubinaemia, with immediate discontinuation of the medication, appear to allow fetal development to remain unaffected.

Fetal bilirubin metabolism is characterised by accumulation of unconjugated bilirubin because of immature enzymatic activity of bilirubin-uridine-glucuronosyltransferase.[3] Most unconjugated bilirubin in the fetus is readily transferred across the placenta to the maternal circulation and excreted in the maternal bile. A smaller fraction of unconjugated bilirubin is conjugated by the fetal liver. Because conjugated bilirubin does not cross the placenta from the fetal into the maternal circulation, it is excreted into the fetal bile or amniotic fluid, where it is then transferred to the maternal circulation.[3] When maternal bilirubin metabolism is normal, unconjugated bilirubin does not accumulate in immature fetal organs. On the other hand, when maternal or fetal unconjugated bilirubin levels exceed the maternal capacity for catabolism, the excess bilirubin is transferred to the fetal circulation and may accumulate in fetal organs.[3] If pregnant patients with hepatotoxicity can be treated, avoiding prolonged exposure of the fetus to even a modest amount of unconjugated bilirubin *in utero*, the effects of hyperbilirubinaemia on the fetus can be minimised. Oladokun *et al.* also insisted that efforts be made to shorten the period of maternal exposure to hyperbilirubinaemia.[2] At present, the theory that up to a certain amount of bilirubin exposure the fetus might have an inherent capacity to protect itself from hyperbilirubinaemia during organogenesis remains speculative.

We searched the electronic database of Medline for publications containing the terms 'drug-induced hyperbilirubinaemia' in combination with 'pregnancy' and found no reports providing evidence that maternal hyperbilirubinaemia during organogenesis could result in organic abnormalities in a surviving infant. We also reviewed the outcomes of pregnant women with Crigler-Najjar syndrome, caused by bilirubin-uridine-glucuronosyltransferase gene mutations, a disease complicated by unconjugated hyperbilirubinaemia. The metabolism of bilirubin in Crigler-Najjar syndrome is similar to that in a fetus, i.e. it is immature. There is only one case report describing high levels of unconjugated bilirubin in a pregnant patient with Crigler-Najjar syndrome as a cause of quadriplegia in the neonate.[4] Passuello and Puhl suggested that the fetus would not develop kernicterus if the mother's total bilirubin level could be kept below 171.0 μmol/l by treating her hyperbilirubinaemia.[5]

In managing patients with hyperbilirubinaemia during pregnancy, particularly the first trimester, it is important to suspect drug-induced hepatotoxicity and to rule out other hepatic diseases. A diagnosis of drug-induced hepatotoxicity can be made by drug sensitivity tests (e.g. a drug-lymphocyte stimulation test, or a skin test) or in response to discontinuation of the medication suspected to be responsible.[6] In a patient with drug-induced hepatotoxicity, discontinuation of the suspected drug is the best way to achieve a rapid decrease in the maternal bilirubin level and thereby improve the perinatal prognosis of both mother and newborn. Based on reports of maternal hyperbilirubinaemia and our experience, if the period of fetal exposure period to bilirubin is brief, hyperbilirubinaemia during first trimester may not affect fetal development, even when the maternal bilirubin level temporarily exceeds 171.0 μmol/l.

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