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Case Series

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Spectrum of liver diseases occurring solely in pregnancies carrying male fetuses: A case series

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Abstract

Liver disease affects nearly 3% of pregnancies. It is a challenging topic for obstetricians as it can be fatal for both, the mother and the fetus. They carry a high mortality rate reaching 25%. Sex-specific effect on the expression of pregnancy-related liver diseases is largely unknown. We present several cases of familial pregnancy-related liver diseases that were expressed solely when the mothers had male fetuses, ending with deleterious outcomes. Liver disease was not expressed when they had female fetuses. These cases provide a novel insight into the diversity of pregnancy-related liver disease complications expression among sex.

Abbreviations: ICP: intrahepatic cholestasis of pregnancy; ICN: intensive care nursery; CMV: cytomegalo virus; EBV: epstein-barr; Hbs: hepatitis B surface antigen; HCV: hepatitis C virus.

Introduction

Liver disease affects nearly 3% of pregnancies [1,2]. It is a challenging topic for obstetricians as it can be fatal for both, the mother and the fetus [1,3]. Pregnancy-related liver diseases are numerous, and they follow trimester-specific characteristic in their occurrence [4]. Hyperemesis Gravidarum (HG) occurs at early pregnancy, whereas Intrahepatic Cholestasis of Pregnancy (ICP), preeclampsia with liver involvement including hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and Acute Fatty Liver of Pregnancy (AFLP) affect the liver in late pregnancy [4]. Pregnancy-related liver disease carry a mortality rate reaching up to 25% [5]. Thus, rapid diagnosis and action are essential [1]. Maternal prognosis is firmly related to the degree of impaired synthetic, metabolic and excretory liver function, and timing of delivery [5]. Sex-specific effects on the expression of liver diseases during pregnancies is largely unknown. Here we present a spectrum of familial pregnancy- related liver diseases occurring in a family only with pregnancies carrying male fetuses ending with deleterious outcomes.

Case series

Case 1

A 24 years old lady, Gravida 2 Para 1 Living 0, previously healthy, presented at 35 weeks of gestation with a female fetus. The current pregnancy has a smooth course; contrary to the previous one. She presented for the first visit at 10+4 weeks where she was started, preventively, on ursodeoxycholic acid 250 mg PO once daily because of a previous history of ICP. At 16 weeks of pregnancy, her lab tests were within the normal ranges. Of interest, Serum Glutamic Oxaloacetic Transaminase (SGOT) was 14 IU, Serum Glutamic Pyruvic Transaminase (SGPT) was 10 IU, total bilirubin was 3.4 mg/dl, direct bilirubin was 1.3 and her INR was 1,1. Ultrasound showed a female fetus with a nuchal translucency of 2.2 cm. She was shown, later on, at 34 weeks, still on ursodeoxycholic acid, with her third trimester labs that were within normal limits: SGOT of 14 IU; SGPT of 11 IU, total bilirubin of 0.19 mg/dl and direct bilirubin of 0.09 mg/dl, INR of 1.1. Ultrasound measurements were commensurate with dates without obvious gross congenital anomalies or

chromosomal markers detected. The patient is scheduled for a repeat cesarean at 37 weeks of gestation.

By contrast to the second pregnancy, her previous pregnancy with a male fetus was not smooth. It was complicated since the first trimester by jaundice which was investigated. Labs showed elevated direct bilirubin that was initially 0.7 mg/dl which increased to 1.8 mg/dl. At 18 weeks of gestation, she was admitted to the hospital for worsening jaundice and pruritis. Further elevation in direct bilirubin has reached a value of 12.48 mg/dl. Infectious causes were ruled out as of normal results of HIV IgM antibodies; Cytomegalo Virus (CMV) antibodies, Epstein-Barr (EBV) IgM antibodies, Hepatitis B surface (HBs) antigen and anti- Hepatitis C Virus (HCV) antibodies. Immunologic panel revealed results within normal limits: ANA level 1/100; copper and ceruloplasmin levels of 59 ug/24 hrs and 53.4 mg/dl respectively. Prednisone 40 mg once daily along with ursodeoxycolic acid 250 mg per os three time daily were started for suspicion of Intra-hepatic cholestasis. At 23+5 weeks, she had spontaneous preterm labor and rupture of membrane and was admitted for latency antibiotics and steroids for fetal lung maturation. Upon presentation, worsening of the jaundice was noticed, and direct bilirubin level was 7.3 mg/dl. Prednisone was continued throughout hospitalization for pruritis and the patient was followed closely. At 25+3 weeks of gestation, chorioamnionitis was suspected. She had an emergency cesarean section and delivered a dead baby boy. Broad spectrum antibiotics was continued for three days after cesarean. In the immediate postpartum period, jaundice has improved, itching has resolved, and direct bilirubin has dropped to 5.2 mg/dl.

Case 2

Of a specific concern, her maternal cousin had also liver trouble during pregnancy. She had three pregnancies of which the first and the third were both complicated by ICP. While the second one, with a female fetus, had a smooth course. The first pregnancy ended up with a preterm normal vaginal delivery at 34 weeks of gestation due to worsening ICP and delivered a live baby boy that was transferred to Intensive Care Nursery (ICN). The third pregnancy was also complicated by ICP that was started early on in that pregnancy. She was hospitalized at 23 gestational weeks of gestation due to jaundice, worsening itching and hematemesis with several episodes of otorrhagia and epistaxis. Labs revealed INR of 4.4, thromboplastin time (86%) and direct bilirubin reaching 14.8 mg/dl remarking liver failure and acute fatty liver of pregnancy. Her condition was immediately stabilized by fresh frozen plasma transfusions and vitamin k administration. Termination of pregnancy was highly recommended by the gastroenterologist. She delivered a dead baby boy by normal vaginal delivery after induction of labor at 23 weeks of gestation and transferred to intensive care unit afterwards for three days until her liver condition was stabilized.

Interestingly, among further family detailed history, the patient mentioned that her maternal grandma had a number of her previous pregnancies that were complicated by jaundice and itching, that were not investigated, and were assumed to be normal findings of pregnancies at that time for the lack of medical advice. She also revealed that her brother and her maternal cousin, both died at the age of 15 years old due to an autoimmune liver disease.

Discussion & conclusion

In our cases, mothers expressed liver disease during pregnancy only when they carried male fetuses, which, were born dead, or needed ICN admission. However, when carrying female fetuses, their pregnancies were smooth and uncomplicated.

In fact, Intrahepatic Cholestasis of Pregnancy (ICP) is the most common pregnancy-related liver disease [6]. It affects 0.2-2% of pregnant women [6,7]. It usually manifests in the second to third trimester, although rarely it is present as early as 7 weeks of gestation [1,2,6,7]. It is characterized by pruritis, as the result of bile acid deposition in the skin, predominantly of the palms and soles [6-8]. It is typically a reversible cholestatic disease that resolve spontaneously after delivery [6]. Although essentially benign for the mother, Pathak et al, and Azzardi et al, mentioned that ICP might be associated with adverse fetal outcome raging from fetal distress to sudden (intrauterine) fetal death [6,9,10]. The pathogenesis of ICP is unclear and largely unknown; it was suggested that specific mutations in bile transporter genes, hormonal milieu (estrogen, progesterone) and environmental factors might probably influence the expression of the disease [6-10]. It increases with parity, multiple pregnancies, maternal age (> 35 years) and a family history of biliary disease [7-9]. The recurrence rate is around 80% [6].

A meta-analysis confirmed that effect of fetal gender on pregnancy-induced maternal pathologies is less clear. Despite that, Di Renzo et al have confirmed that sex-specific difference, more specifically male fetus, is an independent risk factor for adverse pregnancy outcomes [11]. In our cases, the mother was susceptible to ICP only when she had a male fetus. This was not consistent with Gowda et al who concluded that fetal sex does not appear to influence maternal susceptibility to common pregnancy- related pathologies; however, it may affect neonatal outcomes [12]. A particular finding of their study is that, no association exists between fetal sex and maternal intrahepatic cholestasis expression.

Of a special concern, Papacleovoulou et al have demonstrate that maternal ICP is associated with offspring adiposity and metabolic abnormalities, both in human and mice [13]. Importantly, they mentioned that maternal ICP was associated with sex-specific increased susceptibility to diabetes and obesity, more specifically in male children [13].

Acute Fatty Liver of Pregnancy (AFLP) is an uncommon fatal complication [14]. It was first recognized by Sheehan in 1940 who distinguished it from fulminant hepatitis [14,15]. It occurs in the third trimester; however earlier expression has been documented in the literature [16]. Perinatal morbidity and mortality have decreased from 85% to 23 % with prompt diagnosis and treatment [14,15,17]. Optimal maternal-fetal outcomes are achieved by supportive care and expeditious delivery [14]. It was postulated that primigravidas, preeclampsia, male fetus and multiple gestations are risk factors of AFLP [14,18]. However, no causal relationship identified between these risk factors and AFLP [14].

As in our case, Monga and Kutz reported a case of AFLP diagnosed at 22 weeks gestation that was managed by urgent delivery [16]. In a retrospective analysis of 56 cases, Zhang et al reported that 67% pregnancies complicated with AFLP had

male fetuses. Hence, a male predilection to AFLP expression [19]. This was consistent with Rolfes and Ishak who estimated a male to female ratio for AFLP expression of 3:1 [20]. Gao et al considered male fetus a potential risk factor of bad prognosis and adverse maternal outcomes [18].

Currently there is paucity of literature available to address the correlation of gender related differences linking liver diseases in pregnancy. These cases provide a novel insight into the diversity of pregnancy-related liver disease complications expression among sex. Additional studies of mechanisms, basis for sex-specific effects and prevention of pregnancy-related liver disease will contribute importantly to understanding of ICP and AFLP effects. If confirmed, sex selection could be a potential solution in modern obstetrics to significantly reduce pregnancy complications.

References

1. Mikolasevic I, Filipec-Kanizaj T, Jakopcic I et al. Liver disease during pregnancy: A challenging clinical issue. Medical science monitor. 2018; 24: 4080-4090.
2. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J hepatol. 2016; 64: 933- 945.
3. Ahmed K, Almashhrawi A, Rahman R, et al. Liver diseases in pregnancy: diseases unique to pregnancy. World J gastroenterol. 2013; 19: 7639-7646.
4. Brady C. Liver disease in pregnancy: What's new. Hepatology communications. 2020; 4: 145-156.
5. Knight M, Nelson- Piercy C, Kurinczuk JJ. et al. UK obstetric surveillance system. A prospective national study if acute fatty liver of pregnancy in the UK. Gut. 2008; 57: 951-956.
6. Rook M, Vangas J, Caughey A. et al. Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a northern California cohort. Plos one. 2012; 7: e28343.
7. Ross M, Desai M. maternal cholestasis and offspring metabolic abnormalities. Nat Rev Endocrinol. 2013; 9: 567-568.
8. Bacq Y et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: A meta-analysis. Gastroenterology. 2012; 143: 1492-1501.
9. Pathak B, Shibani l, Lee RH. Cholestasis of pregnancy. Obstet Gynecol Clin North Am. 201; 37: 269-282.
10. Azzardi F, Turco L, Lisotti A, Mazella G. the pharmacological management of intrahepatic cholestasis of pregnancy. Curr Clin Pharmacol. 2011; 6: 12-17.
11. Di Renzo GC, Rosati A, Sarti RD et al. does fetal sex affect pregnancy outcome? Gend Med. 2007; 4: 19-30.
12. Gowda M, Kim Y, Bautista J et al. is there an association between fetal sex and common pregnancy- induced pathologies? Austin J obtet Gynecol. 2014; 1: 5.
13. Papacleovoulou G, et al. Maternal cholestasis during pregnancy programs metabolic disease in offspring. J Clin Invest. 2013; 123: 3172- 3181.
14. Hinko H, Yoshida E. Acute fatty liver of pregnancy. Canadian journal of gastroenterology, 2006; 20: 25- 30.
15. Sheehan HL. The pathology of acute yellow atrophy and delayed chloroform poisoning. J obstet Gynaecol Br Emp. 1940; 47: 49-62.
16. Monga M, Katz AR. Acute fatty liver in the second trimester. Obstet Gynecol. 1999; 93: 811- 813.
17. Varner M, Rinderknecht NK. Acute fatty metamorphosis of pregnancy. A maternal morbidity and literature review. J reprod Med. 1980; 24: 177- 180.
18. Gao Q, Qu X, Chen X et al. Outcomes and risk factors of patients with acute fatty liver of pregnancy: a multicenter retrospective study. Singapore medical journal. 2018; 59: 425- 430.
19. Zhang Y Kong W, Zhou S et al. Acute fatty liver of pregnancy: a retrospective analysis of 56 cases. Chin Med j. 2016: 129: 1208-1214.
20. Rolfes D, Ishak K. Acute fatty liver of pregnancy: A clinicopathologic study of 35 cases. Hepatology. 1985; 5: 1149-1158.