

First Trimester Recurrent Severe Cholestasis and Jaundice: A Case Report on ABCB11 Gene Mutation and hCG-Mediated Pathogenesis with Successful Management

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Case Report

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Abstract

Background Intrahepatic cholestasis of pregnancy (ICP) typically presents in the second or third trimester with pruritus and elevated serum bile acid levels, resolving postpartum. Early-onset ICP in the first trimester is rare and poses diagnostic and therapeutic challenges.

Case presentation We report a case of a 25-year-old female patient who presented with recurrent severe cholestasis and jaundice during the first trimester of pregnancy. The patient had a history of similar symptoms during her first pregnancy, which resolved following termination. Patient's liver function was normal when not pregnant. Comprehensive laboratory tests and imaging ruled out other potential causes of liver disease. Genetic sequencing revealed a heterozygous mutation in the *ABCB11* gene, which is associated with impaired bile salt export pump (BSEP) function. The onset of symptoms correlated with elevated human chorionic gonadotropin (HCG) levels, indicating that HCG, rather than estrogen, is a major factor. The patient showed limited response to standard treatments, including ursodeoxycholic acid (UDCA) and S-adenosyl-L-methionine (SAME). However, after treatment with cholestyramine, a bile acid sequestrant, her clinical condition improved significantly.

Conclusions These findings suggest that severe cholestasis and jaundice in early pregnancy can be managed through symptomatic treatment and vigilant monitoring, ensuring the safety of both mother and fetus without the need for termination. Further studies are warranted to investigate the role of HCG in the pathogenesis of early-onset ICP.

Background

ICP is a common idiopathic liver disease related to pregnancy. The incidence of ICP varies significantly across different regions and ethnicity, ranging from < 1–27.6% worldwide, with an incidence of 6.06% in the Chinese population [1]. The clinical symptoms of ICP include skin pruritus and elevated serum total bile acid (TBA) levels, which typically resolve rapidly within 1 to 3 weeks postpartum for most patients. ICP is generally considered a benign condition for the mother, and clinical treatment primarily focuses on alleviating maternal pruritus. However, elevated maternal bile acids have the potential to cross the placental barrier, accumulate in the amniotic fluid and fetal tissues, thereby imposing substantial risks to the fetus. The incidence of fetal death, meconium-stained amniotic fluid, preterm birth, and neonatal respiratory distress syndrome is significantly increased with elevated TBA levels. The risk of fetal complications increases by 1%-2% for each additional micromol/L of serum bile acids [2]. When TBA levels reach or exceed 100 $\mu\text{mol/L}$, the risk of stillbirth significantly increases to 18.2%, and the risk of preterm birth increases to 30.5% [3].

ICP typically occurs in the second and third trimester, and cholestasis developing in early pregnancy is extremely rare. To date, only a few cases reported cholestasis occurring in early pregnancy (before 12 weeks), which may be associated with mutations in the *ABCB4* gene and elevated estrogen levels [4]. For these patients, clinicians must carefully evaluate the possibility of underlying liver diseases and the safety of pharmacological intervention during early pregnancy, a period of increased risk for teratogenic

effects on embryonic development. This complexity renders both diagnosis and treatment highly challenging.

Here, we report a case of recurrent severe cholestasis and jaundice in early pregnancy. The etiology may be attributed to the combined effects of mutations in the *ABCB11* gene and elevated HCG levels. Additionally, we share our successful management of this case throughout the pregnancy, which may provide valuable insights for diagnosing and treating such rare conditions.

Case presentation

The patient, a 25-year-old woman without personal or family history of liver disease, developed generalized pruritus and jaundice at 10 + weeks of gestation during her first pregnancy five years ago. Laboratory tests showed elevated alanine aminotransferase (ALT, 206 IU/L), aspartate aminotransferase (AST, 85 IU/L), total bilirubin (TBIL, 111.5 $\mu\text{mol/L}$), direct bilirubin (DBIL, 32.3 $\mu\text{mol/L}$), and total bile acid (TBA, 182 $\mu\text{mol/L}$). Despite 5 weeks of treatment with UDCA, reduced glutathione, and polyene phosphatidylcholine, her symptoms persisted. Follow-up tests showed improved ALT (56.9 IU/L) and AST (50.0 IU/L), but TBIL (197.3 $\mu\text{mol/L}$), DBIL (109.2 $\mu\text{mol/L}$), and TBA (545.0 $\mu\text{mol/L}$) continued to rise. The patient opted for induced abortion at 15 + 1 weeks. Two months after abortion, her symptoms resolved, and bilirubin and bile acid levels returned to normal.

Two years ago, during her second pregnancy, she underwent manual abortion at 8 weeks of gestation due to embryonic arrest. She did not experience pruritus or jaundice during this pregnancy, and liver function tests, including transaminases, bilirubin, and bile acids, were not performed.

This pregnancy was conceived naturally, without special food intake or medication use, smoking, or alcohol consumption. Prior to pregnancy, her transaminases, bilirubin, and bile acids were all within normal limits. During early pregnancy, she experienced severe nausea and vomiting. At 8 + weeks of gestation, she developed jaundice of the skin and sclera without any obvious cause, which progressively worsened. Subsequently, she experienced generalized skin pruritus that also progressed over time, affecting the limbs, trunk, and face, with symptoms worsen at night.

At 10 + 5 weeks of gestation, the patient presented to our clinic for evaluation. Initial laboratory tests showed elevated alanine aminotransferase (ALT, 125.3 IU/L), aspartate aminotransferase (AST, 43.5 IU/L), alkaline phosphatase (ALP, 179.8 IU/L), γ -glutamyl transferase (GGT, 22.9 IU/L), total bilirubin (TBIL, 99.4 $\mu\text{mol/L}$), and direct bilirubin (DBIL, 41.4 $\mu\text{mol/L}$). TBA was not measured at this time. The patient was treated with UDCA (0.5 g, twice daily) and SAME (1 g, once daily) for 10 days. However, her symptoms of skin pruritus and jaundice worsened despite treatment. Follow-up laboratory tests showed ALT 58.3 IU/L, AST 36.3 IU/L, TBIL 175.3 $\mu\text{mol/L}$, DBIL 98.2 $\mu\text{mol/L}$, and TBA 415.1 $\mu\text{mol/L}$ (Fig. 1). Given the progressive worsening of her condition, a multidisciplinary team, consisting of obstetricians, gastroenterologists, blood transfusion specialists, clinical pharmacists, and nutritionists worked together to conduct a comprehensive consultation and determined a personalized treatment plan.

Laboratory investigations revealed a red blood cell count (RBC) of $4.04 \times 10^{12}/L$, a reticulocyte count of $79.9 \times 10^9/L$, and a hemoglobin (HGB) level of 119 g/L. The Ham test (acid hemolysis test), sucrose hemolysis test, direct antiglobulin test (DAT), and antibody screening test were all negative. The red blood cell osmotic fragility test showed hemolysis beginning at 4.8 g/L NaCl and complete at 3.6 g/L. Ceruloplasmin was 84.7 mg/dL (normal range), and serum protein electrophoresis showed an albumin fraction of 55.6%. The normal RBC count, HGB level, absence of hemolysis-related abnormalities, normal ceruloplasmin, and albumin fraction collectively ruled out hematological or liver-related abnormalities.

For further investigation, a comprehensive panel of serological tests was performed to screen for autoimmune hepatitis (AIH). The results showed that antinuclear antibody (ANA), anti-soluble liver antigen/liver-pancreas antibody (SLA/LP), anti-neutrophil cytoplasmic antibody (ANCA), anti-mitochondrial antibody (AMA), anti-DNA antibody, anti-liver kidney microsomal antibody (LKM-1), and anti-liver cytoplasmic antibody-1 (LC-1) were all negative. Additionally, immunoglobulin levels (IgA, IgG, IgM, and IgE) were within the normal range.

A comprehensive panel of infectious disease tests was performed, including screening for hepatitis A, B, C, D, and E viruses, Epstein - Barr virus (EBV), the TORCH panel (Toxoplasma gondii, Rubella virus, Cytomegalovirus, and Herpes simplex virus), HIV, and syphilis. All tests yielded negative results.

A panel of hepatobiliary tumor markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigens (CA 19 - 9, CA 125) ruled out liver malignancies as a potential cause of the patient's severe cholestasis and jaundice.

An abdominal ultrasound was performed to further evaluate the patient's hepatobiliary system, which showed a coarse gallbladder wall and a polyp of 0.55 cm in diameter. The intrahepatic bile ducts and common bile duct were normal. No abnormalities were detected in the liver, pancreas, spleen, or kidneys on two-dimensional and color Doppler ultrasound. The portal and hepatic veins also appeared normal. Given that the patient is in the early stage of pregnancy, she declined to undergo magnetic resonance cholangiopancreatography (MRCP) due to concerns about potential risks to the fetus.

The white blood cell count (WBC) and the platelet count (PLT) were within the normal ranges. Stool examination revealed no parasites or red blood cells. Urinalysis showed dark yellow urine containing bilirubin and ketone bodies, while urine protein, glucose, and urobilinogen were negative. Renal function tests, thyroid function tests, lipid profiles, and blood glucose levels were all within normal limits.

Since the comprehensive laboratory and imaging investigations did not find any potential cause for patient's severe cholestasis and jaundice, genetic sequencing for hereditary liver diseases was performed. The genetic analysis identified a missense mutation in the ABCB11 gene (c.3382C > T, p.Arg1128Cys), which is associated with impaired function of the bile salt export pump (BSEP) and progressive familial intrahepatic cholestasis (PFIC).

The patient declined plasmapheresis and chose pharmacological treatment instead. We adjusted the pharmacological treatment regimen by increasing the doses of UDCA and SAME, and adding cholestyramine (Chol) 8 g/day (divided into two doses) (Fig. 1). Other pharmacological intervention include supplementation with multivitamin tablets and a combination of vitamin B6 and doxylamine to alleviate nausea and vomiting. Additionally, a balanced dietary plan was formulated for the patient.

Following treatment adjustment, the patient's symptoms of jaundice, pruritus, and nausea/vomiting improved, and her bilirubin, bile acid, and transaminase levels returned to normal. At 19 weeks of gestation, follow-up tests showed TBA 15.7 $\mu\text{mol/L}$, TBIL 41.4 $\mu\text{mol/L}$, DBIL 16.9 $\mu\text{mol/L}$, ALT 51.2 IU/L, and AST 36.2 IU/L. We de-escalated pharmacological treatment regimen (Fig. 1).

At 21 weeks of gestation, follow-up tests showed TBA 17.9 $\mu\text{mol/L}$, TBIL 24.1 $\mu\text{mol/L}$, DBIL 7.9 $\mu\text{mol/L}$, ALT 61.1 IU/L, and AST 26.1 IU/L. We continued to de-escalate the pharmacological treatment regimen. (Fig. 1).

At 23 weeks of gestation, follow-up tests showed TBA 8.3 $\mu\text{mol/L}$, TBIL 14 $\mu\text{mol/L}$, DBIL 4.8 $\mu\text{mol/L}$, ALT 25.5 IU/L, and AST 17.7 IU/L. We discontinued all pharmacological treatment. We performed follow-up tests for bile acids, bilirubin, and transaminases every 2 to 3 weeks, with all values staying within normal ranges until 33 + 4 weeks of gestation, when pruritus reoccurred (Fig. 1).

At 33 + 4 weeks of gestation, the patient experienced recurrent skin pruritus without jaundice. Laboratory tests showed ALT 134.5 IU/L, AST 45.1 IU/L, TBIL 9 $\mu\text{mol/L}$, DBIL 2.7 $\mu\text{mol/L}$, and TBA 38.9 $\mu\text{mol/L}$ (Fig. 1). After administering dexamethasone injections (5 mg every 12 hours, intramuscularly, for 48 hours) to promote fetal lung maturation, the patient underwent cesarean section at 34 + 1 weeks of gestation.

The newborn had a length of 46 cm and a weight of 2120 g, with APGAR scores of 10-10-10, indicating excellent condition at birth. On postoperative day one, the patient's skin pruritus resolved. Follow-up tests showed ALT 46.9 IU/L, AST 28.7 IU/L, TBIL 9.1 $\mu\text{mol/L}$, DBIL 2.0 $\mu\text{mol/L}$, and TBA 5.6 $\mu\text{mol/L}$. At 43 days postpartum, all laboratory indicators were normal (Fig. 1). We followed up with the patient one year after childbirth. The child's growth and development were normal, and no genetic testing for hereditary liver disease was performed.

Throughout the pregnancy, the patient underwent screening for Down syndrome, non-invasive prenatal testing (NIPT), thalassemia, and amniocentesis, all of which yield normal results.

Discussion and Conclusions

Here, we present a case of 25-year-old woman with recurrent cholestasis and jaundice in early pregnancy, demonstrating the diagnostic and therapeutic complexities of severe liver dysfunction during this period. The patient's history of symptom resolution following pregnancy termination and normal hepatic parameters during non-pregnant period strongly suggests a pregnancy-specific condition, likely

ICP, although several features were different from classical ICP presentation. Although ICP is the most common cause (71%) of pregnancy-related pruritus after excluding other etiologies, it typically occurs in mid-to-late pregnancy [2]. Also, classical ICP usually presents with relatively mild jaundice occurring 4 weeks after the onset of pruritus in only 10–15% of cases [5]. The patient's atypical early onset, severe symptoms, progressive clinical deterioration, and refractoriness to standard UDCA and SAME therapy suggest the presence of other genetic or pathological factors beyond typical ICP.

The comprehensive laboratory and imaging investigations, including negative results for hemolysis, AIH, infectious diseases, and hepatobiliary malignancies, highlight the importance of ruling out other potential etiologies of liver dysfunction. Our comprehensive medical history review also rules out etiologies related to food, medication, and alcohol. The normal results of the hepatobiliary ultrasound preliminarily exclude biliary obstruction or pathology as etiologies of the patient's severe cholestasis and jaundice. Furthermore, the patient's decision to decline MRCP preventing us from definitively identifying any subtle obstructions or pathologies in the intrahepatic bile ducts.

Identifying a significant mutation in the *ABCB11* gene through genetic sequencing provided critical insights into the underlying pathophysiology. The *ABCB11* gene encodes BSEP, a protein responsible for transporting bile salts into the canaliculi of hepatocytes. Defects in this gene can impair BSEP function, leading to the accumulation of bile salts within hepatocytes and causing PFIC [6]. The inheritance pattern of *ABCB11* follows an autosomal recessive mode; heterozygous mutations are typically asymptomatic, as the residual BSEP function is usually sufficient to meet the physiological demands for bile salt transport under normal conditions. However, during pregnancy, elevated levels of circulating female sex hormones and metabolites can inhibit *ABCB11* transcription and reduce the expression of the normal allele, thereby exacerbating bile stasis [7].

Estrogen levels rise progressively during pregnancy, peaking in the third trimester and declining rapidly postpartum [8]. ICP predominantly occurs in the mid-to-late pregnancy and resolves promptly after delivery, correlating with the trend of estrogen levels. Therefore, estrogen has been identified as a significant etiologic factor in ICP [8]. However, this mechanism does not explain the severe bile stasis and jaundice observed in our patient during early pregnancy.

HCG levels peak at 8 to 10 weeks of gestation and then decline gradually, remaining relatively stable from 20 weeks until term [9]. The clinical presentation of our patient, characterized by severe bile stasis and jaundice during early pregnancy, alongside hyperemesis gravidarum (an HCG-related disorder), suggests that HCG rather than estrogen may be the primary etiologic factor. This hypothesis is further supported by the absence of bile stasis and jaundice recurrence between 23 and 32 weeks of gestation, without pharmacologic intervention. Additionally, patients with embryonic arrest usually have lower HCG levels compared with those with normal pregnancies [10]. This finding may explain why our patient did not experience severe bile stasis or jaundice during her second pregnancy, which ended in spontaneous embryonic arrest. At 33 weeks and 4 days of gestation, the patient experienced a recurrence of bile

stasis, although with lower total bile acid (TBA) levels and without jaundice. We believe that elevated estrogen levels during late pregnancy may be the underlying cause of this scenario.

UDCA and SAME are the most commonly used medications to treat ICP. However, due to the rarity of ICP cases presenting in early pregnancy, there is currently a lack of safety data regarding exposure to UDCA and SAME during this period. Currently, there is no definitive consensus on treatment strategies, with UDCA and SAME remaining the primary therapeutic agents in existing case reports [4]. In our case, the patient's symptoms of jaundice and cholestasis progressed despite adequate treatment with UDCA and SAME. Additionally, given that the patient was in a high-risk period for embryonic development, it was imperative to identify a safe and effective alternative treatment. Cholestyramine, a bile acid sequestrant, is not absorbed in the gastrointestinal tract and binds to bile acids in the small intestine to form insoluble complex which is excreted in the feces. This results in a partial removal of bile acids from the enterohepatic circulation by preventing their absorption. Therefore, we considered it safe to use during early pregnancy. However, cholestyramine may lead to fat malabsorption and vitamin K deficiency. To mitigate these risks, we supplemented the patient with fat-soluble vitamins and monitored for vitamin K deficiency. After adding cholestyramine, the patient's jaundice and cholestasis significantly improved. She discontinued all medications at 23 weeks of gestation and remained recurrence-free until 32 + 3 weeks. In summary, we believe that the patient's clinical improvement was due to both declining HCG levels and the combined therapeutic effects of the medications. The decision to proceed with cesarean section at 34 + 1 weeks was made to ensure fetal well-being, given the patient's recurrence of cholestasis at 33 + 4 weeks and the potential risks associated with ongoing severe cholestasis, which is most commonly linked to fetal death. The excellent condition of the newborn and the resolution of maternal symptoms postpartum further support the effectiveness of the management strategy.

This case indicated that the interplay between the ABCB11 gene mutation, which is associated with impaired bile salt export pump (BSEP) function, and elevated human chorionic gonadotropin (HCG) levels, rather than estrogen, might play a critical role in severe intrahepatic cholestasis during the first trimester of pregnancy. The successful treatment with cholestyramine, a bile acid sequestrant, highlights the significance of personalized treatment strategies for managing ICP, especially in cases that are refractory to standard therapies or present in the first trimester. The findings suggested that severe cholestasis and jaundice in early pregnancy can be managed through symptomatic treatment and vigilant monitoring, ensuring the safety of both mother and fetus without the necessity of pregnancy termination. Further studies are warranted to investigate the role of HCG in the pathogenesis of early-onset Intrahepatic Cholestasis of Pregnancy (ICP).

Abbreviations

Intrahepatic cholestasis of pregnancy (ICP)

bile salt export pump (BSEP)

human chorionic gonadotropin (HCG)

ursodeoxycholic acid (UDCA)

S-adenosyl-L-methionine (SAdMe)

total bile acid (TBA)

aminotransferase (ALT)

aspartate aminotransferase (AST)

total bilirubin (TBIL)

direct bilirubin (DBIL)

alkaline phosphatase (ALP)

γ-glutamyl transferase (GGT)

red blood cell count (RBC)

hemoglobin (HGB)

direct antiglobulin test (DAT)

autoimmune hepatitis (AIH)

antinuclear antibody (ANA)

anti-soluble liver antigen/liver-pancreas antibody (SLA/LP)

anti-neutrophil cytoplasmic antibody (ANCA)

anti-mitochondrial antibody (AMA)

anti-liver kidney microsomal antibody (LKM-1)

anti-liver cytoplasmic antibody-1 (LC-1)

Epstein - Barr virus (EBV)

alpha-fetoprotein (AFP)

carcinoembryonic antigen (CEA)

carbohydrate antigens (CA)

magnetic resonance cholangiopancreatography (MRCP)

white blood cell count (WBC)

platelet count (PLT)

progressive familial intrahepatic cholestasis (PFIC)

Declarations

Ethics approval and consent to participate

We would like to note that Xinqiao Hospital does not require ethical approval for reporting individual cases or case series.

Consent for publication

Written informed consent for the publication of personal/clinical data and any accompanying images was obtained from the patient.

Availability of data and materials

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (Nucleic Acids Res 2022), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA012934) that are publicly accessible at <https://ngdc.cncb.ac.cn/gsa-human> [11-12].

Competing interests

The authors have no competing interests to declare.

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Authors' contributions

SYQ and JJL contributed equally to this work. SYQ and JJL analyzed the clinical data and drafted the manuscript. HL, LF, and XW critically revised the manuscript and prepared the figures. ZQC conceived the study and supervised the clinical management. PG conceived the study, administered the project, and obtained funding. All authors read and approved the final manuscript.

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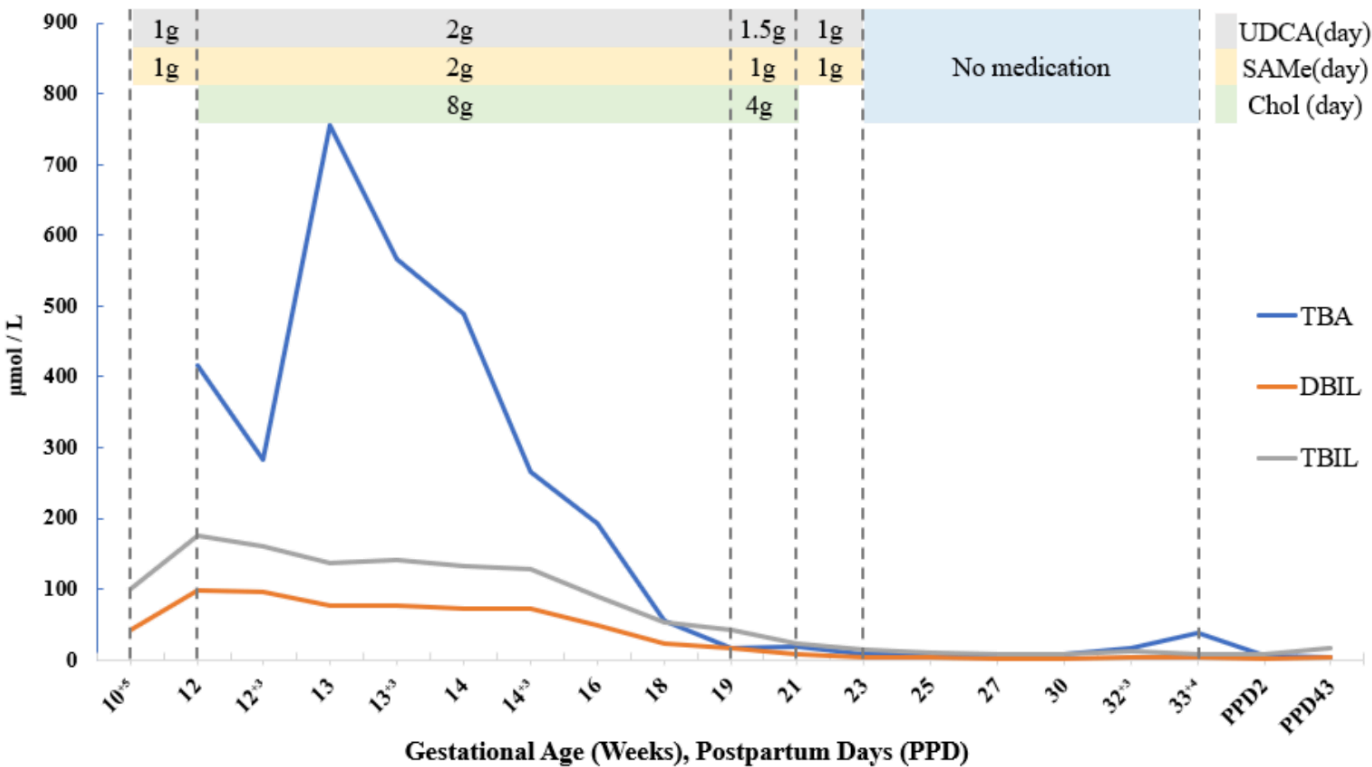
listed as authors in this work. Their dedication and expertise were instrumental in the successful management of the cases presented herein. Additionally, we would like to express our appreciation for the financial support provided by the Chongqing Municipal Health Commission, which facilitated our research endeavors.

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<https://doi.org/10.1093/nar/gkab951> [PMID=34718731]Thank you for submitting data to GSA-Human.

Figures



UDCA: ursodeoxycholic acid; SAMe :and S-adenosyl-methionine; Chol:cholestyramine; TBA: total bile acid; TBIL: total bilirubin; DBIL: direct bilirubin. PPD: Postpartum Days. From 10 + 5 to 12 weeks of gestation, the patient was administered oral UDCA 1 g/day and SAMe 1 g/day. From 12 to 19 weeks of gestation, the doses were increased to UDCA 2 g/day, SAMe 2 g/day, and Chol 8 g/day. From 19 to 21 weeks of gestation, the doses were adjusted to UDCA 1.5 g/day, SAMe 1 g/day, and Chol 4 g/day. From 21 to 23 weeks of gestation, the patient was given UDCA 1 g/day and SAMe 1 g/day. From 23 weeks to 33 + 4 weeks of gestation, no medications were used.

Figure 1

Changes in TBA, DBIL and TBIL during pregnancy and postpartum period with different treatment regimens.