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Drug-induced Liver Injury from Intravenous Immunoglobulin for Prevention of Recurrent Gestational Alloimmune Liver Disease: A Clinical Catch-22

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Abstract

Gestational alloimmune liver disease (GALD) is a rare autoimmune syndrome in which maternal antibodies lead to in utero fetal hepatocyte destruction, often presenting as neonatal liver failure and hemochromatosis. Antenatal intravenous immunoglobulin (IVIG) is generally accepted to be safe in pregnancy with demonstrable benefits for reducing GALD recurrence risk in subsequent pregnancies. Here we present a case of a 33-year-old woman with a prior neonatal demise due to GALD who received multiple prophylactic IVIG infusions in a subsequent twin pregnancy complicated by maternal jaundice and acute hepatitis. A liver biopsy demonstrated hepatocellular injury with bridging necrosis and cholestatic features consistent with drug-induced liver injury. This case demonstrates the importance of close clinical monitoring during IVIG therapy and the need for further research into alternative prophylaxis options for GALD.

Keywords

- gestational alloimmune liver disease
- drug-induced liver injury
- pregnancy
- transaminitis
- liver
- hepatocellular damage
- liver dysfunction
- antibodies
- intravenous immunoglobulin

Key Points

- GALD is a rare antibody-mediated autoimmune syndrome with high recurrence risk.
- IVIG can be effective in reducing risk of GALD recurrence and fetal loss.
- Patient's receiving ongoing IVIG therapy should be closely monitored for developing adverse effects, including DILI.

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Background

Gestational alloimmune liver disease (GALD) occurs in 4 of 100, 000 pregnancies, characterized by maternal antibody-facilitated destruction of fetal hepatocytes.[1,2] As there are usually no prenatal indicators of the underlying disease process, GALD is often diagnosed postnatally in the setting of acute-onset fulminant neonatal liver failure. Recurrence risk is significant (~90%), but preventative treatment with intravenous immunoglobulin (IVIG) can improve outcomes in subsequent pregnancies.[3–5] We describe a case of a pregnant patient receiving IVIG for a history of GALD who developed drug-induced liver injury (DILI) precluding further IVIG treatment.

Case

A 33-year-old G3P0110 at $19^{6/7}$ weeks with a dichorionic diamniotic twin pregnancy was transferred to our tertiary center for prenatal care given her complex obstetric history.

In the preceding year, she had had a 36-week medically induced preterm vaginal delivery for oligohydramnios following an otherwise uncomplicated pregnancy. The infant's postnatal course was complicated by neonatal hypotonia, hypoglycemia, and hypotension requiring vasopressor support on the day of life (DOL) #2, followed by the development of acute kidney injury, hepatic failure with coagulopathy, and respiratory failure requiring extracorporeal membrane oxygenation on DOL #3 to 4. Although initially concerning for sepsis, extensive postnatal workup, including liver and salivary gland biopsies, were suggestive of gestational alloimmune liver disease (GALD; ►**Fig. 1**). Despite exchange transfusions and IVIG), the neonate continued to decompensate and ultimately died secondary to massive acute pulmonary hemorrhage on DOL #28; underlying GALD diagnosis was confirmed on neonatal autopsy (►**Fig. 1**).

The patient's early prenatal care in this subsequent twin pregnancy was uncomplicated with negative routine prenatal screening labs and low-risk cell-free DNA screening. Anatomy sonogram demonstrated normal-appearing, appropriately and concordantly grown, dichorionic diamniotic twins with normal amniotic fluid levels, normal-appearing placentas, and a cervical length of 4 cm. She transferred to our higher-level prenatal care center for initiation of IVIG prophylaxis for the remainder of the pregnancy given her high risk for GALD recurrence.

Weekly IVIG (Privigen 60 g) was initiated for fetal hepatoprotection. Her complete blood cell counts, basic metabolic panels, and liver function tests were serially monitored as an outpatient, initially notable for transient, mild elevations in transaminases after infusions. Moderate transaminitis was noted after her third infusion, progressing to severe transaminitis with new scleral icterus following her fourth infusion. She was admitted at $25^{0/7}$ weeks for closer monitoring and expedited evaluation.

Her admission labs revealed elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT; 1,866 U/L and 1,089 U/L, respectively), elevated total bilirubin (11 mg/dL), elevated alkaline phosphatase (238 U/L), prolonged prothrombin time (PT; 14.4 seconds), hypoalbuminemia (3.2 g/dL), and elevated International Normalized Ratio (INR; 1.16). Her workup was notable for elevated ceruloplasmin 65 mg/dL, ammonia 42 Umol/L, and total bile acids 140 Umol/L. Fibrinogen, lactate dehydrogenase, glucose, creatinine, white blood cells, platelets, urine protein/creatinine ratio, ammonia, acute viral serologies (Hepatitis A/B/C/E, Epstein–Barr virus, Cytomegalovirus, Herpes Simplex virus), and autoimmune antibodies (anti-nuclear, anti-smooth muscle, anti-mitochondrial, anti-liver kidney microsomal) were all within normal range. The patient was mentating appropriately with normal vital signs and no reported pain, gastrointestinal upset,

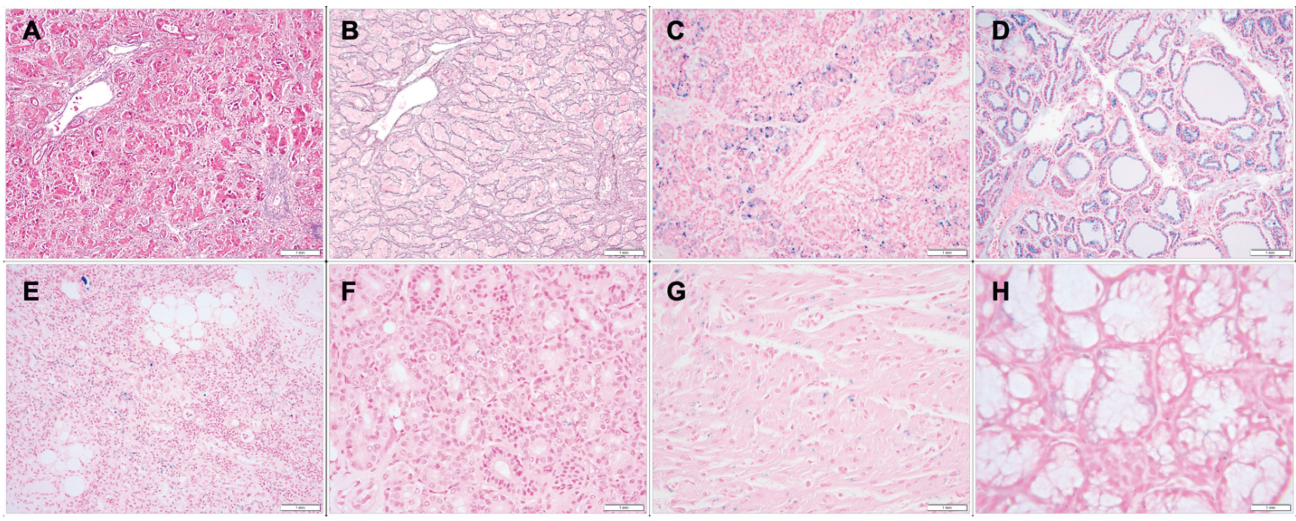

Fig. 1 Hepatic and extrahepatic tissue histopathology from neonatal autopsy consistent with gestational alloimmune liver disease with neonatal hemochromatosis phenotype (GALD-NH). Microscopic examination notable for extensive lobular collapse with pericellular and perivenular fibrosis on trichrome and reticulin stains (**A, B**), marked cholestasis with reactive bile ductular proliferation, hepatocyte giant cell transformation with pseudorosette formation, as well as extensive ballooning degeneration with cytoplasmic rarefaction. Extrahepatic iron deposition was observed in (**C**) pancreas, (**D**) thyroid, (**E**) thymus, (**F**) submandibular gland, (**G**) heart, consistent with findings on (**H**) premortem neonatal salivary gland biopsy.

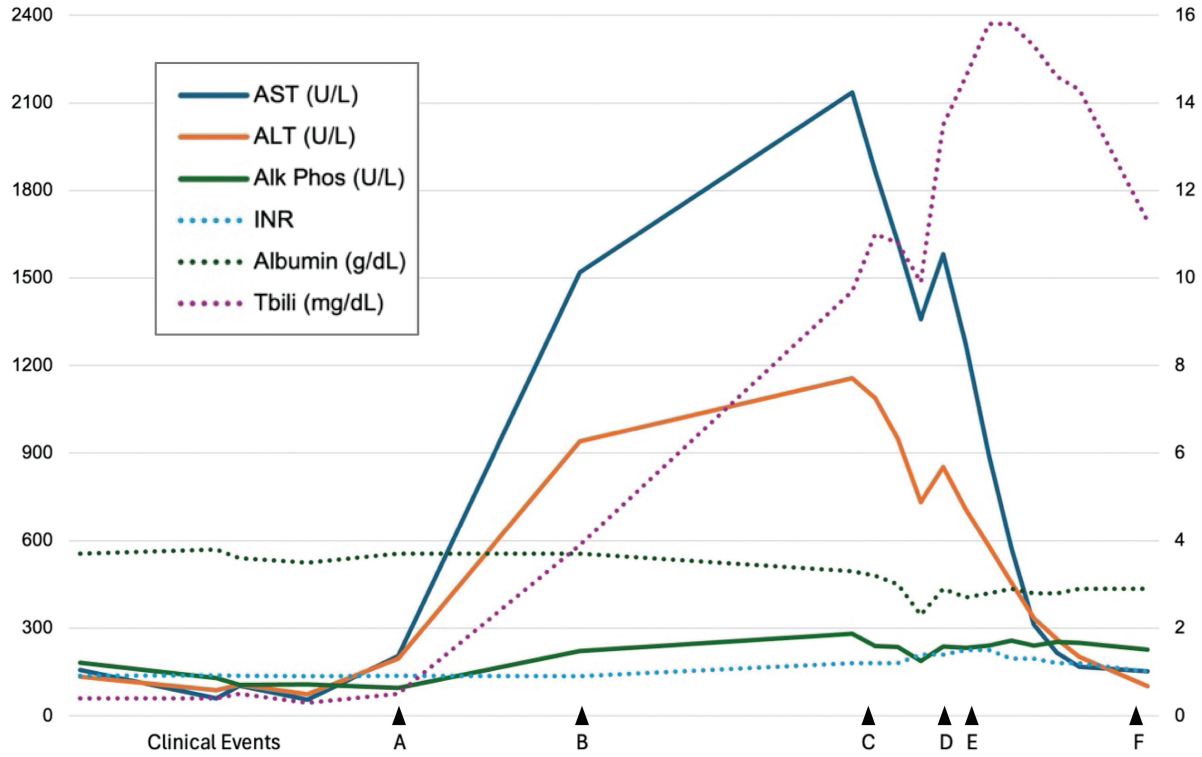

Fig. 2 Clinical course of hepatitis lab abnormalities and interventions. *Lab values plotted on two separate axis scales, according to similar units (AST, ALT, Alk Phos—solid lines corresponding to the left vertical axis; INR, Albumin, Tbili—dotted lines corresponding to the right vertical axis). *Clinical events over time are reflected on the horizontal axis. (**A**) IVIG infusion #3, (**B**) IVIG infusion #4 (no further IVIG infusions given thereafter), (**C**) admission for hepatitis evaluation, (**D**) liver biopsy, (**E**) initiation of prednisone therapy, (**F**) postpartum admission. Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio; IVIG, intravenous immunoglobulin; Tbili, total bilirubin.

or persistent pruritis. She reported taking only a daily prenatal vitamin with no new medications other than IVIG. Fetal heart rate tracings were reassuring throughout admission. She had an abdominal ultrasound only notable for prominent portal triads, suggestive of acute hepatitis. As her transaminitis was persistent with worsening hepatic synthetic function (INR peak 1.5, albumin nadir 2.3 g/dL), the decision was made to perform an ultrasound-guided liver biopsy (►**Fig. 2**).

Pathology revealed markedly active hepatitis with bridging necrosis, cholestatic features, widespread mononuclear infiltrates, and negative staining for iron and periodic acid–Schiff with diastase, findings suggestive of DILI (►**Fig. 3**). In consultation with gastroenterology, the patient was initiated on prednisone (60 mg daily) with gradual improvement in her labs, and she was discharged home at $26^{2/7}$ weeks on an oral steroid taper.

The patient represented 3 days later following an extramural delivery at $26^{5/7}$ weeks due to preterm labor. The subsequent neonatal demise of Twin A on DOL #1 was autopsy-confirmed due to sequelae of extreme prematurity. Twin B's course was notable for normal coagulation panels, transaminases, ferritin, and serial abdominal ultrasounds, but markedly elevated alpha-fetoprotein of >375,000 ng/mL. As definitive diagnosis by salivary gland biopsy was precluded by the neonate's small size, empiric IVIG was given for GALD risk and no further clinical concerns for GALD were observed. The neonate progressed appropriately with discharge home on DOL #75. The patient's postpartum course was uncomplicated with continually downtrending liver function tests on low-dose prednisone (5 mg daily).

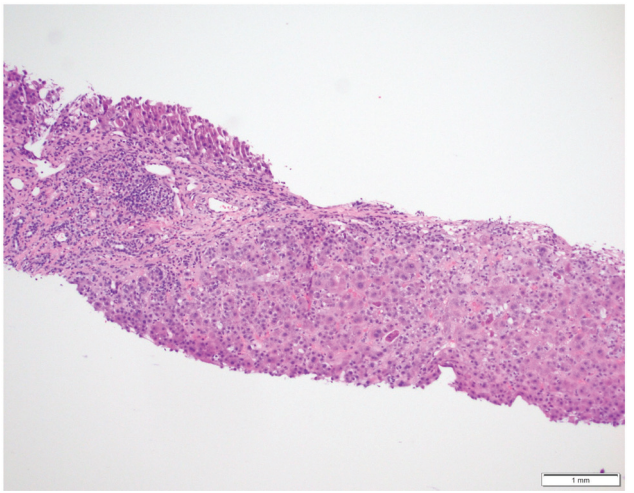

Fig. 3 Histopathology from liver biopsy demonstrating evidence of drug-induced liver injury. Hematoxylin and eosin (H&E)-stained section showing markedly active hepatitis with bridging necrosis, cholestatic features, and widespread mononuclear infiltrates.

Discussion

GALD is a rare autoimmune syndrome characterized by maternal antibody-mediated destruction of fetal hepatocytes. A similar pathophysiology is seen in the more common example of Rh alloimmunization in which an RhD-negative mother develops antibodies that target and destroy red blood cells in an RhD-positive fetus, leading to fetal anemia. In the case of GALD, placentally transferred maternal IgG antibodies target a hepatocyte protein that is uniquely expressed on fetal hepatocytes (vs. a paternally inherited alloantigen).[1,6] The mechanism of initial sensitization is unknown but can incite disease even in a first pregnancy.[6,7] Maternal antibody attachment to a fetal hepatocyte protein activates the fetal complement cascade with the formation of the membrane attack complex and osmolytic hepatocyte death.[6] Consequently, major metabolic functions of the fetal liver are compromised (such as iron dysregulation via loss of hepcidin enzymes), leading to fetal iron toxicity and extrahepatic iron deposition—the classic phenotype of in-utero GALD with neonatal hemochromatosis (GALD-NH).[8]

Diagnosing GALD can be challenging. It is often only identified postnatally during the evaluation of acute-onset fulminant neonatal liver failure with a definitive diagnosis of GALD-NH usually made by extrahepatic iron deposition seen on neonatal salivary gland biopsy.[6] In the rarer cases lacking congenital extrahepatic findings, pathologic diagnosis may be made via diffuse immunohistochemical staining for the terminal complement complex (C5b-9) in fibrotic hepatocytes.[9–11] Prenatal diagnosis is rare, especially in the absence of pertinent history, as sonographically detectable sequelae of GALD are nonspecific and highly variable in presentation. Some case reports have identified fetal growth restriction, ascites, oligohydramnios, placentomegaly, and even hydrops fetalis as early signs of the underlying alloimmune hepatic disease, but these may all also be seen secondary to more common etiologies.[11] This patient's index pregnancy was affected by oligohydramnios but otherwise had no features of congenital liver disease, and all fetal imaging in the current described pregnancy was normal. Regardless of the timing of diagnosis, knowledge of maternal sensitization is relevant to the care of all subsequent pregnancies as recurrence risk is upwards of 90%.[4]

Since GALD is an antibody-mediated disorder, prevention of recurrence in an ongoing pregnancy focuses on maternal immunomodulation. The use of IVIG for this purpose has been well-studied for RhD alloimmunization with efficacy in preventing and even reversing fetal anemia.[12] Optimal outcomes are seen when therapy is initiated early (~13 weeks, aligning with the physiologic onset of placental IgG transfer) and is uninterrupted throughout gestation (to account for the competing half-lives of IVIG vs. maternal antibodies).[5,12] The underlying mechanism for IVIG prophylaxis in alloimmunization is not entirely clear but is proposed to be related to the downregulation of the maternal immune response, competitive binding to Fc receptors, or direct inhibition of circulating alloantibodies.[12] The literature on IVIG prophylaxis for GALD is growing. There are several case studies that have shown high-dose IVIG can reduce the risk of fetal/neonatal loss and overall GALD recurrence (as much as a 68% disease reduction in one study—94% with no liver disease after IVIG vs. only 30% after no antenatal treatment).[3–5,13] A recent study proposed a treatment protocol of IVIG (dosed at 1 g/kg, maximal dose 60 g) at 14, 16, and 18 weeks, advancing to weekly thereafter until 1 week prior to delivery—our intended treatment plan for this patient.[5] Our patient began infusions at approximately 20 weeks due to late transfer of care, and her duration of therapy was short-lived due to the unanticipated development of DILI necessitating IVIG discontinuation.

Even in pregnancy, IVIG is generally considered a safe therapy. Late adverse effects are typically renal or hematologic, but overall rare.[14–16] Transaminitis from IVIG is even more infrequently reported and usually limited to a transient inflammatory reaction.[2] This was the suspected etiology for this patient's early mild transaminitis after starting therapy and was not a contraindication to continued treatment when initially limited to mild, transient elevations with no concerning symptoms. Such transaminase elevations have historically been thought to be triggered in part by sugar-based diluents (especially maltose) used in some formulations of IVIG, although the exact mechanism of transaminitis is unknown.[2,17] In this case, Privigen was used, which is a human plasma-derived product containing IgA with an L-proline stabilizer and no carbohydrate stabilizers or preservatives.

Severe DILI from IVIG has not yet been reported in the obstetric literature. A 1996 case report has described the development of concomitant aseptic meningitis and hepatitis in a non-pregnant woman who received an IVIG infusion.[18] Some monoclonal antibody therapies (infliximab, pembrolizumab, and rituximab) have been rarely associated with DILI, but these differ from IVIG in composition and pharmacokinetics.[19] Our patient demonstrated an acute hepatitis phenotype following multiple infusions of IVIG with an otherwise negative hepatitis workup. She did have mildly elevated ammonia and significantly elevated bile acids, which could be concerning for acute fatty liver of pregnancy or intrahepatic cholestasis of pregnancy. However, the timing of onset after IVIG, the severity of transaminitis, hyperbilirubinemia, and evolving synthetic dysfunction, as well as the absence of gastrointestinal upset, encephalopathy, persistent pruritus, or other associated lab abnormalities (such as hyperglycemia or leukocytosis) make these alternative diagnoses less likely.[20,21] Further, liver biopsy histopathology was consistent with drug-induced hepatocellular injury.[22]

Most cases of DILI will recover following cessation of the inciting drug, though severe cases may progress to acute liver failure even after discontinuation. Hepatocellular DILI, especially when associated with hyperbilirubinemia (more than twice the upper limit of normal) and ALT elevations (more than three times the upper limit of normal) may portend a particularly poor prognosis with a greater risk for acute liver failure, transplant requirement, and mortality.[23] Aside from

drug discontinuation, there are no definitive therapies for DILI. Corticosteroids may be considered, though the literature is mixed regarding their efficacy for this purpose.[24] Thus, prompt diagnostic evaluation of DILI is crucial to reducing morbidity by ensuring timely discontinuation of the causative drug. In pregnancy, this may be even more prudent to optimize obstetric outcomes. It is likely that this patient's preterm labor and preterm birth may have been related to the preceding acute hepatitis as other known etiologies of hepatitis (viral and autoimmune) are associated with increased preterm birth risk.[25,26]

This patient strongly desires future fertility. An alternative GALD prophylaxis would be needed in future pregnancies as reexposure to the inciting IVIG after confirmed DILI is not recommended.[24] In neonates, GALD-NH therapy often involves both IVIG and plasma exchange.[6,27] Antenatal use of plasmapheresis for GALD prevention has not yet been studied but may be a promising option. A recent case described good obstetric outcomes after dual therapy with IVIG and double-filtration plasmapheresis for maternal antibody depletion in the setting of anti-M alloimmunization.[28]

Understanding of the pathophysiology, prenatal diagnosis, and antenatal prevention of GALD is growing, but many questions remain unanswered. This case demonstrates that while IVIG is an accepted, effective preventative therapy for GALD, it may not be entirely benign, warranting close lab and symptom monitoring throughout treatment. Persistent or worsening transaminitis, particularly if accompanied by hyperbilirubinemia or clinical jaundice, should prompt concern for possible DILI and discontinuation of IVIG until the hepatitis workup has been completed.

Conflict of Interest

None declared.

References

1 Rieneck K, Rasmussen KK, Schoof EM, et al. Hunting for the elusive target antigen in gestational alloimmune liver disease (GALD). PLoS One 2023;18(10):e0286432
2 Vijaya Prakash A, Parvathaneni A, Malempati S, Keilson G. Intravenous immunoglobulin induced transaminitis. Cureus 2023;15 (12):e51347
3 Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet 2004;364(9446):1690–1698
4 Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. Pediatrics 2008;121 (06):e1615–e1621
5 Whitington PF, Kelly S, Taylor SA, et al. Antenatal treatment with intravenous immunoglobulin to prevent gestational alloimmune liver disease: comparative effectiveness of 14-week versus 18-week initiation. Fetal Diagn Ther 2018;43(03):218–225
6 Feldman AG, Whitington PF. Neonatal hemochromatosis. J Clin Exp Hepatol 2013;3(04):313–320
7 Taylor SA, Kelly S, Alonso EM, Whitington PF. The effects of gestational alloimmune liver disease on fetal and infant morbidity and mortality. J Pediatr 2018;196:123–128.e1
8 Whitington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. Semin Liver Dis 2012;32(04):325–332
9 Debray FG, de Halleux V, Guidi O, et al. Neonatal liver cirrhosis without iron overload caused by gestational alloimmune liver disease. Pediatrics 2012;129(04):e1076–e1079
10 Tsunoda T, Inui A, Kawamoto M, et al. Neonatal liver failure owing to gestational alloimmune liver disease without iron overload. Hepatol Res 2015;45(05):601–605
11 Zermano S, Novak A, Vogrig E, Parisi N, Driul L. GALD: new diagnostic tip for early diagnosis - a case report and literature review. Front Reprod Health 2023;5:1077304
12 Mayer B, Hinkson L, Hillebrand W, Henrich W, Salama A. Efficacy of antenatal intravenous immunoglobulin treatment in pregnancies at high risk due to alloimmunization to red blood cells. Transfus Med Hemother 2018;45(06):429–436
13 Baruteau J, Heissat S, Broué P, et al. Transient neonatal liver disease after maternal antenatal intravenous Ig infusions in gestational alloimmune liver disease associated with neonatal haemochromatosis. J Pediatr Gastroenterol Nutr 2014;59(05): 629–635
14 Baxley A, Akhtari M. Hematologic toxicities associated with intravenous immunoglobulin therapy. Int Immunopharmacol 2011;11(11):1663–1667
15 Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol 2018;9:1299
16 Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol 2005;29(03):173–184
17 Williams MA, Rhoades CJ, Provan D, Newland AC. In vitro cytotoxic effects of stabilizing sugars within human intravenous immunoglobulin preparations against the human macrophage THP-1 cell-line. Hematology 2003;8(05):285–294
18 Shorr AF, Kester KE. Meningitis and hepatitis complicating intravenous immunoglobulin therapy. Ann Pharmacother 1996;30 (10):1115–1116
19 livertox.nih.gov. Monoclonal antibodies. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
20 Liu J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: Updates in pathogenesis, diagnosis, and management. Am J Gastroenterol 2017;112(06):838–846
21 Lee RH, Mara Greenberg , Metz TD, Pettker CMSociety for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org. Intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2021; 224(02):B2–B9
22 Kleiner DE, Chalasani NP, Lee WM, et al; Drug-Induced Liver Injury Network (DILIN) Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology 2014;59(02):661–670
23 Andrade RJ, Lucena MI, Fernández MC, et al; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology 2005;129(02): 512–521
24 Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Amerian College of Gastroenterology Clinical Guideline: Diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2021;116:878–898
25 Pena Polanco NA, Levy C. Autoimmune hepatitis and pregnancy. Clin Liver Dis (Hoboken) 2024;23(01):e0112
26 Sookoian S. Liver disease during pregnancy: acute viral hepatitis. Ann Hepatol 2006;5(03):231–236
27 Timpani G, Foti F, Nicolò A, Nicotina PA, Nicastro E, Iorio R. Is exchange transfusion a possible treatment for neonatal hemochromatosis? J Hepatol 2007;47(05):732–735
28 Yasuda S, Ono-Okutsu M, Fukuda T, Kyozuka H, Fujimori K. Double-filtration plasmapheresis and high-dose intravenous immunoglobulin therapy in a case of anti-M alloimmunization. AJP Rep 2024;14(02):e101–e105