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MINIREVIEWS

Anesthetic considerations for liver diseases unique to pregnancy

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Abstract

Liver diseases that are most unique to pregnancy consist of hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hemolysis, elevated liver enzymes and low platelets syndrome. In this review, risk factors, etiology, symptoms, diagnosis, prognosis and treatment of each entity followed by principles of anesthetic management based on the case reports or retrospective records will be addressed.

Key words: Liver disease; Pregnancy; Anesthesia

Core tip: Liver diseases like hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy and hemolysis, elevated liver enzymes and low platelets are challenging for anesthesiologists because of the increased risk of morbidity and mortality. Therefore, general and specific anesthetic management strategies are of utmost important. In this review, the risk factors, etiology, symptoms, diagnosis, prognosis and treatment of these liver diseases during pregnancy and general principles of anesthetic management based on our case report and retrospective records will be addressed.

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INTRODUCTION

Most unique liver diseases that occur during pregnancy are hyperemesis gravidarum (HG), acute fatty liver of pregnancy (AFLP), intrahepatic cholestasis of pregnancy (IHCP), and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome[1,2]. We aim to present risk factors, etiology, symptoms, diagnosis, and prognosis briefly and as well as discuss the treatment of each

entity, principles of anesthetic management based on the current literature.

HG

HG, generally occurs generally at 4-10 wk of gestation up to 20 weeks' gestation[3-5]. There are risk factors such as history of HG, hyperthyroidism, psychiatric illness, molar pregnancy, preexisting diabetes, multiple gestations, multiparity, increased body mass index, and excessive daily intake of saturated fat before pregnancy are some of the common risk factors[1]. Female fetus and maternal *Helicobacter pylori* infection might be considered as additional risk factors[6]. The incidence, etiology, symptoms, diagnosis and treatment of the disease were summarized in Table 1[5,7-17].

We would like to underline our established therapeutic plan based on a 21-year-old woman (G1, P0) with a diagnosed HG without remarkable medical history. She was admitted to our unit at 19[1] weeks' gestation. She was suffering from nausea, vomiting and weight loss refractory to medical treatment though she was treated in another hospital before admission. Her current weight was 56 kg (Pre-pregnancy weight 73 kg), and BMI was 18.3 kg/m^2. Her vital signs including blood pressure and heart rate were 90/60 mmHg and 90 beat/min, respectively. Blood and urine laboratory results and thyroid function tests were within normal clinical limits. Obstetric and abdominal USG were unremarkable. Medical treatment was started with metochlopramide and vitamin B during IV total parenteral nutrition. Fluid intake and urine output were adjusted accordingly. Because of persistent refractory nausea and vomiting, metoclopramide was switched to domperidon. For differential diagnosis, endoscopy was planned but 1st endoscopy attempt without sedation was unsuccessful. Therefore, 2nd endoscopy was planned using propofol under monitored anesthesia care (MAC). The endoscopy revealed minimal superficial gastritis and motility dysfunction (with no pyloric stenosis and helicobacteria presence). Although there was rarely need for anesthesia in HG since that disease usually seen during early pregnancy period, we performed sedation with propofol which was a safe intravenous anesthetic agent in liver diseases under MAC.

AFLP

The AFLP is observed 1 in 10000-15000 pregnancies[18]. It often develops between 27-40 weeks' gestation, but may be undiagnosed until the postpartum period[1].

Advanced maternal age, primiparity, multiple pregnancies, preeclampsia, male fetus, being underweight, the use of non-steroidal anti-inflammatory drugs and previous AFLP are considered to be some of the risk factors[1,19]. The incidence of AFLP is high in women with a genetic mutation. Basically, mitochondrial fatty acid oxidation pathway is affected. Fetus has a long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency[7,20]. The incidence, etiology, symptoms, diagnosis and treatment of AFLP were shown in Table 1[7,18,20-29].

Primary obstetric management is to make immediate delivery decision since recovery before delivery is not possible. The anesthesia technique either regional or general must be discussed. General anesthesia is required in patients with coagulopathy because of the concern for regional anesthesia related hematoma risk[1]. Most of the patients recover within 48-72 h after delivery with improved aminotransferase levels[22]. However, patients with coagulopathy, encephalopathy, or hypoglycemia require intensive care admission[26].

Perioperative care includes establishing adequate intravenous accesses readily available for cross-matched blood and blood products against increased risk of postpartum hemorrhage (PPH)[28].

Clinical and laboratory findings, anesthetic managements with maternal and neonatal outcomes of 28 cases from Shanghai Public Health Center were retrospectively reviewed over 5 years. Cesarean delivery was performed under either neuraxial (n = 16) or general anesthesia (n = 12) with rapid sequence induction (RSI). Two maternal deaths (7.1%) without fetal deaths were recorded. As a result of this retrospective study, recommendation of general anesthesia with RSI in case of severe coagulopathy was reconfirmed[29].

IHCP

The incidence of IHCP is approximately 1-2 in 1000 pregnancies. Generally it manifests either in the second or third trimester, around 30 weeks' gestation. After delivery, symptoms generally resolve[30]. According to the recent reports, the incidence varies between 1.5%-4%[1].

Accused common risk factors are advanced maternal age, multiparity, family history, preexisting liver disease, or history of cholestasis while taking oral contraceptives[31,32].

The incidence, etiology, symptoms, diagnosis and treatment of IHCP were also shown in Table 1[1,30-51].

Diagnosis is based on clinical signs and laboratory tests. Elevated bilirubin levels (< 6 mg/dL), and elevated transaminases (approximately 20 times than normal values). The most sensitive diagnostic biomarker is the elevation in the fasting serum bile acid level. Parturients generally have bile acid levels higher than 10 μmol/L. The degree of disease as mild, moderate or severe is made according to bile acid levels (Mild: 10-39 μmol/mL, moderate: 40-99 μmol/mL and severe: ⩾ 100 μmol/mL)[38].

We have retrospectively documented maternal, fetal and neonatal outcomes of parturients with IHCP delivered in Gazi University. Maternal outcomes were generally good as indicated in many previous reports[28,37,47,48]. Twenty-seven percent of our cases had normal spontaneous vaginal delivery, while the rest (73%) underwent cesarean delivery. Approximately

Table 1 The incidence, etiology, symptoms, diagnosis and treatment of the liver disease unique to pregnancy

Disease	Incidence	Etiology	Symptoms	Diagnosis	Prognosis	Treatment
Hyperemesis gravidarum[3-17]	1-20/1000 pregnancies (< 2%)[5]	Psychological predisposition Hormones (human chorionic gonadotropin, estradiol)[7]	Severe nausea and vomiting Dehydration Malnutrition Poor weight gain[1,7]	Diagnosis by clinical presentation (persistent vomiting, acute starvation and weight loss) Increaed levels of liver enzymes (aminotransferase, alkaline phosphatase and amylase)[1,3,8-12] Rarely, liver biopsy is needed[1,11,12]	Unchanged maternal and fetal outcomes after use of safe antiemetics Increased risk of low-birth-weight infants, preterm birth, preeclampsia, and placental abruption in the 2nd trimester[8,16,17]	Avoid nausea triggering substances Medical and supportive therapy (ginger, multivitamin or Vit B6 with H1 receptor antagonist doxylamine) Treatment of dehydration (intravenous infusion of fluids, metoclopramide or promethazine with another H1 receptor antagonist dimenhydramine)[1,8,13-15]
Acute fatty liver of pregnancy[18-29]	1/10000-15000 pregnancies[18]	Mutations in LCHAD[1,21]	Nausea, vomiting, anorexia lethargy, abdominal pain, ascites, progressive jaundice Polyuria and polydipsia due to transient diabetes insipidus Acute renal failure Hepatic encephalopathy Hypertension, proteinuria and edema[1,4,22,23]	Diagnosis by clinical and laboratory findings (increased levels of aminotransferases, ammonia, bilirubin, leukocytosis, hypoglycemia, thrombocytopenia, neutrophilia, coagulopathy, renal dysfunction)[20,22,24] Tomography and ultrasonography are unremarkable[7] Liver biopsy reveals microvesicular steatosis[25]	Liver function improves within a week to months[27] Preterm delivery (75%) approximately at 34 wk gestation Check all mothers with AFLP for defects in fatty acid oxidation[1]	Immediate hospitalization Supportive measures (glucose infusion, readily availbale blood products) Prompt delivery
Intrahepatic cholestasis of pregnancy[1,30-51]	1-2/1000 pregnancies[1]	Multifactorial genetic (mutations in the *MDR3* gene) Hormonal Exogenous factors (*e.g.*, progesterone) Abnormal biliary transport[25,33-35]	Generalized peripheral pruritus (1st sign) Chills and abdominal pain Diarrhea or steatorrhea[36,37]	Diagnosis by clinical symptoms and/or laboratory tests (increased levels of fasting serum bile acid and elevated bilirubin and transaminase levels)[38] Liver biopsy is needed only in severe cases and biopsy reveals cholestasis with minimal or no inflammatory changes[39]	Good maternal outcome (laboratory results resolve within 2-8 wk postpartum)[7] Compromised fetal outcome (spontaneous preterm labor, meconium-stained fluid with some perinatal mortality) in moderate and severe forms[1,42-46]	Symptomatic medical treatment (ursodeoxycholic acid: UDCA which is B Class safe drug for pregnancy and breastfeeding by FDA)[40,41] Optimal timing of delivery at the best possible fetal maturity[45]
HELLP syndrome[1, 51-62]	0.1%-0.6%[1,52]	Usually presents with preeclampsia (4%-12% are with severe preeclampsia) Endothelial injury with fibrin deposit is the underlying mechanism of the disease[54]	Right upper quadrant or epigastric pain Nausea and vomiting Malaise Nonspecific viral-like symptoms headache visual symptoms[55]	Liver biopsy is not necessary but if performed sinusoidal fibrin thrombin, hemorrhage, and hepatocellular necrosis might be observed[25] Laboratory findings Platelet count < 100000/μL Serum aspartate aminotransferase > 70 U/L Serum lactic dehydrogenase > 600 U/L[56]	Maternal death (1%) Perinatal death (7.4%-20.4%) Pulmonary edema Acute renal failure DIC Abruptio placenta Liver hemorrhage or failure ARDS Retinal detachment Stroke Blood transfusion related complications	Provide transfer to tertiary care center after confirmed diagnosis Delivery > 34 weeks' gestation is recommended if possible Prophylaxis of seizures with magnesium during labor and 24 h postpartum[58]

HELLP: Hemolysis, elevated liver enzymes and low platelets; LCHAD: Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase; ARDS: Acute respiratory distress syndrome; AFLP: Acute fatty liver of pregnancy; FDA: Food and Drug Administration.

18.5% of cesarean deliveries were not elective or planned. When anesthesia and/or analgesia choices were evaluated in whole, we performed combined spinal epidural (CSE) for labor analgesia only in 1 patient. According to the records of cesarean deliveries, rates of neuraxial and general anesthesia were 85% and 15%, respectively. Among neuraxial anesthesia choices, spinal anesthesia (96%) was the mostly preferred one. Regarding neonatal outcomes, birth weight and Apgar scores were good as well. However,

there were 2 preterm births and 2 preterm labors from mild and severe IHCP cases (one from each). Hepatitis in 2 newborns was observed in parturients with mild IHCP. But the worst fetal outcome observed in a parturient having severe IHCP was perinatal fetal death at the 34 weeks' of gestation. Anesthesia choices for delivery might be challenging in IHCP. Due to the physiologic decrease in gall bladder contractility, pregnant women tend to have a sort of physiologic cholestasis. The cholestasis might lead to malabsorption of vitamin K. Vitamin K is a cofactor responsible from synthesis of coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ. Therefore, coagulation abnormalities might be expected in parturients with IHCP. Additionally, increased liver enzymes; aspartate aminotransferase (AST) and predominantly ALT are considered to be determinants of liver diseases[1,28,37,47-49]. However, in a recent retrospective study investigating the incidence of coagulopathy in parturients with IHCP, no abnormal coagulation studies were found even in the presence of significantly increased liver enzymes[50]. The authors reported that the presence of coagulopathy in parturients with isolated IHCP was low and the routine coagulation studies were not necessary except patients having IHCP with coexisting preeclampsia[50]. Similarly, we had neither abnormal coagulation parameters nor we came across any patient with coexisting preeclampsia in our study.

Severity of IHCP, especially bile acid levels higher than 40 μmol/L, may affect pregnancy outcomes[46,51]. Based on these studies, we similarly classified our cases having bile acid level ⩾ 10-39 μmol/L, 40-99 μmol/L and ⩾ 100 μmol/L as mild, moderate and severe IHCP, respectively. In the present study the rates of mild, moderate and severe IHCP were 65%, 21% and 14%, respectively. When we compared our studies in this regard, the incidence of mild IHCP was higher but severe IHCP was less than that of study by Brouwers *et al*[51]. In mild cases obstetric management includes delivery at 38 weeks' gestation but early delivery at 36 weeks' can be considered in severe cases due to the high risk of fetal distress/death, jaundice or unbearable maternal pruritis despite ursodeoxy cholic acid (UDC) treatment[28,37,47-51]. In contrast to the 14% of CS rate in Brouwers *et al*[51]'s study, we documented much higher CS rate, which was 73%. However, our high CS rate was consistent with 65% rate of DeLeon *et al*[50]. Currently, we have observed adverse outcomes including preterm labor and birth and perinatal fetal death in severe IHCP class parturients.

Pregnancy associated liver diseases and/or abnormalities in conjunction with their interpretation have been extensively studied[2,25,26,32]. Our maternal and fetal-neonatal outcomes according to the elevated bile acid levels were comparable to recent retrospective studies[50,51]. However, the present retrospective records including 37 cases with IHCP delivered in Gazi University in one-year period might be helpful to provide better understanding of anesthetic management. Consequently, parturients with IHCP having normal coagulation parameters despite increased liver enzymes preoperatively underwent cesarean delivery mostly under spinal anesthesia uneventfully. Although maternal outcomes were generally good, adverse fetal and neonatal outcomes may occur more likely in severe IHCP.

HELLP SYNDROME

HELLP syndrome is commonly associated with hypertension, proteinuria, and edema develop either in the second or third trimester. HELLP syndrome has an incidence of 0.1%-0.6% that develops usually in the 3rd trimester. The rate of HELLP patients with severe preeclampsia is 4%-12%[52]. While 70% of patients with HELLP syndrome present before delivery, 30% of them develop in the postpartum period[1].

Some of the risk factors for HELLP syndrome are nulliparity and advanced maternal age[53]. The incidence, etiology, symptoms, diagnosis and treatment of HELLP syndrome were indicated in Table 1 as well[1,51-62].

Fifty percent of patients with HELLP syndrome might be free of all diagnostic criteria. Maternal morbidity varies due to the degree of thrombocytopenia. According to the Mississippi classification for HELLP, class 1 corresponds to platelet count ⩽ 50000/μL, class 2 corresponds to platelet count greater than > 50000 but ⩽ 100000/μL, while class 3 corresponds to platelet count 100000-⩽ 150000/μL[57].

HELLP syndrome often progresses and may eventually compromise maternal and fetal outcome. If diagnosis is controversial, hypertension should be controlled by available intravenous antihypertensive drugs (hydralazine or labetalol)[58].

Delivery is recommended ⩾ 34 weeks' gestation. Intravenous magnesium sulfate (4-g loading dose followed by 2 g/h) should be administered for seizure prophylaxis during labor and for 24 h postpartum[58]. In case of active labor, a vaginal delivery may be proceeded if there is no fetal distress or risk of disseminated intravascular coagulopathy. Additionally, in case of coexistence with multi-organ dysfunction, renal failure, or abruption, immediate cesarean delivery should be performed because induction of labor is not indicated.

Patients with HELLP syndrome generally receive platelet transfusion if the platelet count is < 20000/μL, if < 50000/μL and cesarean delivery is mandatory. There is no need to transfuse platelet more than once, since thrombocytopenia improves after delivery[59].

For choosing method of analgesia, epidural block is generally contraindicated if platelet count is less than 75000/μL but is also up to the experience of the anesthesiologist. Patients should be monitored for at least 48 h in the postpartum period to avoid pulmonary edema. Laboratory abnormalities usually regress 24 h postpartum and almost completely recover 48 h postpartum[1].

HELLP syndrome is associated with increased risk of maternal and fetal morbidity and mortality. Rate

of maternal death is approximately 1%. Noteworthy maternal complications include pulmonary edema, acute renal failure, DIC, abruptio placenta, liver hemorrhage or failure, ARDS, retinal detachment, stroke and adverse events due to blood transfusion[1].

The rate of perinatal death varies between 7.4%-20.4%, depending on the gestational age and concurrent factors related to the pregnancy. The highest morbidity and mortality rates are observed < 28 weeks' gestation[60]. Most perinatal morbidity is due to prematurity that may cause to RDS, bronchopulmonary dysplasia, intracerebral hemorrhage, and necrotizing enterocolitis.

General anesthesia for CS has been the most commonly preferred technique in HELLP syndrome. However, high rate of use of regional anesthesia for CS has been documented in a review of 102 cases with preterm HELLP syndrome[61]. According to review of 102 charts, number of antepartum and postpartum HELLP were 95 and 7, respectively. Mean gestational age was 30.6 ± 2.7 (23-36) wk. Most of the parturients underwent regional anesthesia (n = 65). Cases having preoperative mean platelet count of 113000/μL (n = 53) underwent CS under CSE, while spinal anesthesia was performed in pregnant women (n = 12) having preoperative platelet count of 95000/μL. Interestingly, 2 patients with mean platelet count < 50000/μL underwent CS with CSE. One of these patients received platelet transfusion immediately before CSE. Luckily, epidural hematoma has not been reported in none of the patients received regional anesthesia[61].

However, subarachnoid hematoma following spinal anesthesia in a 39-year-old having G3, P2 (151 cm and 52 kg) with severe preeclampsia associated HELLP delivered at 27 weeks' gestation was reported. A 23 G Quincke spinal needle was used to inject 2.5 mL of hyperbaric bupivacaine for spinal block. Apgar scores of a 696 g of baby were 6 and 9 at 1 and 5 min, respectively. Duration of surgery was approximately 37 min with approximately 400 mL blood loss. Complete recovery of motor block was achieved 5 h after spinal anesthesia. Although preoperative platelet count was 91000/μL, it declined progressively to 30000/μL postoperatively (2nd day). Patient was suffering from numbness on the posterior aspect of her thigh and the toes of her right leg and her bladder was insensitive to fullness (urinary retention). Neurologic examination revealed flaccid paraparesis. Power in her right hip was 4/5, while it was 3/5 in her right knee, ankle and toes. There was sensory deficit in her right leg between L3-S5 dermatomes, while it was between L4-S5 dermatomes in her left leg. Spinal subarachnoid hematoma compressing cauda equina was observed in the magnetic resonance imaging. Medical treatment including Vit B12 and PG E1 against neurologic deficit, oral neostigmine + bladder exercise for urinary retention, flurbiprofen for relieving headache and neck pain and rehabilitation for paraparesis were performed. Complete recovery was observed 3 mo after conservative treatment (hematoma regression)[62].

PRINCIPLES OF ANESTHETIC MANAGEMENT

Regional anesthesia is recommended in patients with advanced liver disease whenever possible because of the less systemic effects of the locally administered drugs. Regional anesthesia is superior than general anesthesia due to possible liver dysfunction leading to delayed metabolism of general anesthetic drugs. Either central or peripheral blocks could be considered in liver dysfunction and/or failure. Total drug dose used in peripheral block should be cautiously calculated and close monitoring is advocated for side effects[49]. Regarding local anesthetic drugs, $t_{1/2elim}$ of lidocaine increases 3 fold from 108 to 296 min. Meanwhile, increased volume of distribution (Vd) of lidocaine offers some protection against toxicity. α1 acid GP is synthesized even in end stage liver disease which provides some protection against toxicity as well. However, clearance of ropivacaine is less in the end stage liver disease than normal. For ester type local anesthetic drugs, though pseudocholin esterase enzyme production in the liver may decrease in disease state, overall clearance of chloroprocaine is unclear.

Although coagulopathy is an absolute contraindication for regional anesthesia, it can be recommended in selected patients having acceptable coagulation profile. Regional anesthesia blunts hemodynamic effects of stress hormones in the circulation. These hormones depress immune function as well[63]. In all cases, arterial blood pressure should be maintained and sympathetic stimulation should be avoided.

Considering general anesthesia, isoflurane seems to be a better choice[64]. When sevoflurane or desflurane were compared with isoflurane, sevoflurane could have some advantages over others without significant differences among them[65,66]. Nitrous oxide was used to be an inhalation anesthetic despite risk of accumulation of gas in the closed spaces leading to distension[49]. However, liver cell injury with xenon anesthesia has been shown to be impossible which might be a promising alternative agent[67].

Successful use of opioids has been reported in liver disease despite there were concerns with delayed drug clearance and prolonged half-life. Fentanyl, if used in relatively moderate doses, is a good choice without affecting oxygen supply, or requirements of the liver[68,69].

The rate of oddi sphincter spasm was nearly 3% due to opioids. Medical treatment can be provided with atropine, naloxane, glucagon, nitroglycerin, volatile anesthetics, or antispasmodic drugs. Anesthesia induction and maintenance are provided with possibly safe drugs and pulmonary and cardiovascular measures should be maintained. Anesthetic management using inhalation agents (isoflurane, desflurane or sevoflurane), alone or in combination with small doses of fentanyl

seems to be reasonable. Anesthetist must consider the altered pharmacokinetics in liver disease. Half-life of lidocaine and benzodiazepines may increase by more than 300% and 100%, respectively. Drugs, like sodium thiopentone, highly bound to albumin have a decreased Vd. Therefore, doses should be adjusted accordingly. Among intravenous anesthetic agents, propofol is the most favorable one for liver diseases. It has a short half-life even in cirrhosis. However, either edema or increased gamma globulin resulting in the increased Vd may require to increase the first effective dose of many drugs[49].

Long acting narcotics and sedatives should be avoided in cirrhotic patients. Fentanyl or sufentanil and oxazepam or lorazepam, in conjunction with sevoflurane or propofol are recommended[40,70].

For non-depolarizing muscle relaxants, vecuronium and atracurium are recommended because these muscle relaxants are not metabolized mainly in the liver. Clearance and elimination half-life of atracurium are preserved even in impaired liver or renal function. Because of larger Vd, elimination half-life is shorter in severe hepatorenal dysfunction than that of healthy individuals. Therefore, muscle relaxants are used guided by neuromuscular block monitoring[49].

Suxamethonium which is a depolarizing muscle relaxant is used for providing RSI. It has a prolonged half-life due to decreased serum cholinesterase concentrations in liver dysfunction and during pregnancy.

Both vecuronium and rocuronium have prolonged elimination in severe cases. Either atracurium or cisatarcurium may be a better option because of independent metabolism of liver and kidney[71].

Consequently, rational selection of anesthetic drugs and close monitoring are the key factors for providing safe anesthesia.

POSTOPERATIVE CARE

Even though delayed clearance is a concern in severe liver disease, intravenous opioids can be administered for postoperative analgesia. Neuraxial opioids, especially a single dose of morphine, may obviate any accumulation issues. Advanced liver disease can lead to hepatic encephalopathy. Neurologic deterioration in the postoperative period may result from the residual effects of anesthetic agents, acute liver decompensation, or an intracranial process. Neurologic observation and liver function monitoring is essential to the proper postoperative management of pregnant women with advanced liver disease[49].

SPECIFIC ANESTHETIC CONSIDERATIONS

Pregnant woman with either mild IHCP or uncomplicated liver transplantation may be managed in the same manner as a healthy parturient assuming that hepatic synthetic and metabolic functions were intact. Only coagulopathy should be excluded or corrected before regional anesthesia if possible[1].

According to a retrospective cohort study including 319 parturients with or without coagulation tests, no neuraxial hematoma was observed even in case of liver enzyme elevations > 5 times than normal. Postpartum hemorrhage after vaginal or cesarean delivery was 2.4% and 6.3%, respectively. Based on these results, routine coagulation test monitoring in IHCP to minimize neuraxial anesthesia complications or predict postpartum hemorrhage was not necessary. Therefore, neuraxial anesthesia is not necessarily be delayed or avoided in pregnant patient with IHCP[50].

Anesthesia selection for AFLP should be individualized. General anesthesia with RSI is recommended in case of severe coagulopathy. Perioperative anesthetic care includes establishing adequate iv access with readily available cross matched blood and blood products since PPH is anticipated[49].

In summary, particularly spinal anesthesia is the 1st choice for patients with HELLP syndrome scheduled to undergo CS if there is no progressive thrombocytopenia. Close patient monitoring is a must against hemorrhagic complications, DIC or ecclampsia at all times. If neuraxial anesthesia is contraindicated, general anesthesia with RSI should be performed especially in hypertensive patients. Additionally, risk of aspiration due to full stomach and/or difficult airway should be taken into account. General anesthesia is indicated as a 1st option when platelets < 80000/μL (class 1 or partially class 2 HELLP syndrome)[71].

In conclusion, selection of either general or regional, or MAC alone may not be sufficient enough for good survival and better outcomes because induction of a safe anesthesia in this specific group needs special attention and care with rational choice of drugs under constant careful monitoring. Prevention of further liver injury can be provided by optimizing hepatic blood flow and oxygenation. Effects of anesthesia type and local and general anesthetic drugs on the liver should be carefully considered as well.

REFERENCES

1 **Sasaki KJ**. Liver Disease and Pregnancy. [updated 2015 Aug 27]. Available from: URL: http://emedicine.medscape.com/article/188143-overview#a1

2 **Hepburn IS**, Schade RR. Pregnancy-associated liver disorders. *Dig Dis Sci* 2008; **53**: 2334-2358 [PMID: 18256934 DOI: 10.1007/s10620-007-0167-9]

3 **Riely CA**. Liver disease in the pregnant patient. American College of Gastroenterology. *Am J Gastroenterol* 1999; **94**: 1728-1732 [PMID: 10406228 DOI: 10.1111/j.1572-0241.1999.01199.x]

4 **Lee NM**, Brady CW. Liver disease in pregnancy. *World J Gastroenterol* 2009; **15**: 897-906 [PMID: 19248187 DOI: 10.3748/wjg.15.897]

5 **Fairweather DV**. Nausea and vomiting in pregnancy. *Am J Obstet Gynecol* 1968; **102**: 135-175 [PMID: 4877794 DOI: 10.1016/0002-9378(68)90445-6]

6 **Golberg D**, Szilagyi A, Graves L. Hyperemesis gravidarum

and Helicobacter pylori infection: a systematic review. *Obstet Gynecol* 2007; **110**: 695-703 [PMID: 17766620 DOI: 10.1097/01.AOG.0000278571.93861.26]
7 **Schutt VA**, Minuk GY. Liver diseases unique to pregnancy. *Best Pract Res Clin Gastroenterol* 2007; **21**: 771-792 [PMID: 17889807 DOI: 10.1016/j.bpg.2007.05.004]
8 **American College of Obstetrics and Gynecology**. ACOG (American College of Obstetrics and Gynecology) Practice Bulletin: nausea and vomiting of pregnancy. *Obstet Gynecol* 2004; **103**: 803-814 [PMID: 15051578 DOI: 10.1097/00006250-200404000-00045]
9 **Adams RH**, Gordon J, Combes B. Hyperemesis gravidarum. I. Evidence of hepatic dysfunction. *Obstet Gynecol* 1968; **31**: 659-664 [PMID: 5646397 DOI: 10.1097/00006250-196805000-00011]
10 **Larrey D**, Rueff B, Feldmann G, Degott C, Danan G, Benhamou JP. Recurrent jaundice caused by recurrent hyperemesis gravidarum. *Gut* 1984; **25**: 1414-1415 [PMID: 6510771 DOI: 10.1136/gut.25.12.1414]
11 **Abell TL**, Riely CA. Hyperemesis gravidarum. *Gastroenterol Clin North Am* 1992; **21**: 835-849 [PMID: 1478739]
12 **Hay JE**. Liver disease in pregnancy. *Hepatology* 2008; **47**: 1067-1076 [PMID: 18265410 DOI: 10.1002/hep.22130]
13 **Matthews A**, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev* 2015; **(9)**: CD007575 [PMID: 26348534 DOI: 10.1002/14651858.CD007575]
14 **Sahakian V**, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. *Obstet Gynecol* 1991; **78**: 33-36 [PMID: 2047064]
15 **Quinla JD**, Hill DA. Nausea and vomiting of pregnancy. *Am Fam Physician* 2003; **68**: 121-128 [PMID: 12887118]
16 **Bolin M**, Åkerud H, Cnattingius S, Stephansson O, Wikström AK. Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study. *BJOG* 2013; **120**: 541-547 [PMID: 23360164 DOI: 10.1111/1471-0528.12132]
17 **Veenendaal MV**, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. *BJOG* 2011; **118**: 1302-1313 [PMID: 21749625 DOI: 10.1111/j.1471-0528.2011.03023.x]
18 **Watson WJ**, Seeds JW. Acute fatty liver of pregnancy. *Obstet Gynecol Surv* 1990; **45**: 585-591 [PMID: 2204851 DOI: 10.1097/00006254-199009000-00004]
19 **Ibdah JA**. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. *World J Gastroenterol* 2006; **12**: 7397-7404 [PMID: 17167825 DOI: 10.3748/wjg.v12.i46.7397]
20 **Browning MF**, Levy HL, Wilkins-Haug LE, Larson C, Shih VE. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006; **107**: 115-120 [PMID: 16394048 DOI: 10.1097/01.AOG.0000191297.47183.bd]
21 **Benjaminov FS**, Heathcote J. Liver disease in pregnancy. *Am J Gastroenterol* 2004; **99**: 2479-2488 [PMID: 15571598 DOI: 10.1111/j.1572-0241.2004.30231.x]
22 **Nelson DB**, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. *Am J Obstet Gynecol* 2013; **209**: 456.e1-456.e7 [PMID: 23860212 DOI: 10.1016/j.ajog.2013.07.006]
23 **Minakami H**, Morikawa M, Yamada T, Yamada T, Akaishi R, Nishida R. Differentiation of acute fatty liver of pregnancy from syndrome of hemolysis, elevated liver enzymes and low platelet counts. *J Obstet Gynaecol Res* 2014; **40**: 641-649 [PMID: 24428400 DOI: 10.1111/jog.12282]
24 **Ko H**, Yoshida EM. Acute fatty liver of pregnancy. *Can J Gastroenterol* 2006; **20**: 25-30 [PMID: 16432556 DOI: 10.1155/2006/638131]
25 **Joshi D**, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. *Lancet* 2010; **375**: 594-605 [PMID: 20159293 DOI: 10.1016/S0140-6736(09)61495-1]
26 **Kia L**, Rinella ME. Interpretation and management of hepatic abnormalities in pregnancy. *Clin Gastroenterol Hepatol* 2013; **11**: 1392-1398 [PMID: 23707777 DOI: 10.1016/j.cgh.2013.05.016]
27 **Knight M**, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut* 2008; **57**: 951-956 [PMID: 18332072 DOI: 10.1136/gut.2008.148676]
28 **Kamimura K**, Abe H, Kawai H, Kamimura H, Kobayashi Y, Nomoto M, Aoyagi Y, Terai S. Advances in understanding and treating liver diseases during pregnancy: A review. *World J Gastroenterol* 2015; **21**: 5183-5190 [PMID: 25954092 DOI: 10.3748/wjg.v21.i17.5183]
29 **Zhou G**, Zhang X, Ge S. Retrospective analysis of acute fatty liver of pregnancy: twenty-eight cases and discussion of anesthesia. *Gynecol Obstet Invest* 2013; **76**: 83-89 [PMID: 23796980 DOI: 10.1159/000351565]
30 **Knox TA**, Olans LB. Liver disease in pregnancy. *N Engl J Med* 1996; **335**: 569-576 [PMID: 8678935 DOI: 10.1056/NEJM199608223350807]
31 **Reyes H**. Sex hormones and bile acids in intrahepatic cholestasis of pregnancy. *Hepatology* 2008; **47**: 376-379 [PMID: 18220280 DOI: 10.1002/hep.22139]
32 **Than NN**, Neuberger J. Liver abnormalities in pregnancy. *Best Pract Res Clin Gastroenterol* 2013; **27**: 565-575 [PMID: 24090943 DOI: 10.1016/j.bpg.2013.06.015]
33 **Jacquemin E**, Cresteil D, Manouvrier S, Boute O, Hadchouel M. Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. *Lancet* 1999; **353**: 210-211 [PMID: 9923886 DOI: 10.1016/S0140-6736(05)77221-4]
34 **Reyes H**, Simon FR. Intrahepatic cholestasis of pregnancy: an estrogen-related disease. *Semin Liver Dis* 1993; **13**: 289-301 [PMID: 8235718 DOI: 10.1055/s-2007-1007357]
35 **Meng LJ**, Reyes H, Axelson M, Palma J, Hernandez I, Ribalta J, Sjövall J. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. *Hepatology* 1997; **26**: 1573-1579 [PMID: 9398000 DOI: 10.1002/hep.510260627]
36 **Kondrackiene J**, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. *World J Gastroenterol* 2008; **14**: 5781-5788 [PMID: 18855975 DOI: 10.3748/wjg.14.5781]
37 **Bacq Y**. Liver diseases unique to pregnancy: a 2010 update. *Clin Res Hepatol Gastroenterol* 2011; **35**: 182-193 [PMID: 21310683 DOI: 10.1016/j.clinre.2010.11.011]
38 **Lata I**. Hepatobiliary diseases during pregnancy and their management: An update. *Int J Crit Illn Inj Sci* 2013; **3**: 175-182 [PMID: 24404454 DOI: 10.4103/2229-5151.119196]
39 **Steven MM**. Pregnancy and liver disease. *Gut* 1981; **22**: 592-614 [PMID: 7021334 DOI: 10.1136/gut.22.7.592]
40 **Liu Y**, Qiao F, Liu H, Liu D. Ursodeoxycholic acid in the treatment of intraheptic cholestasis of pregnancy. *J Huazhong Univ Sci Technolog Med Sci* 2006; **26**: 350-352 [PMID: 16961291 DOI: 10.1007/BF02829573]
41 **Kondrackiene J**, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology* 2005; **129**: 894-901 [PMID: 16143129 DOI: 10.1053/j.gastro.2005.06.019]
42 **Rioseco AJ**, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. *Am J Obstet Gynecol* 1994; **170**: 890-895 [PMID: 8141222 DOI: 10.1016/S0002-9378(94)70304-3]
43 **Falconer JD**, Smith AN, Eastwood MA. The effects of bile acids on colonic motility in the rabbit. *Q J Exp Physiol Cogn Med Sci* 1980; **65**: 135-144 [PMID: 6902962 DOI: 10.1113/expphysiol.1980.sp002497]
44 **Kirwan WO**, Smith AN, Mitchell WD, Falconer JD, Eastwood MA. Bile acids and colonic motility in the rabbit and the human. *Gut* 1975; **16**: 894-902 [PMID: 1193418 DOI: 10.1136/gut.16.11.894]
45 **Roncaglia N**, Arreghini A, Locatelli A, Bellini P, Andreotti C, Ghidini A. Obstetric cholestasis: outcome with active management. *Eur J Obstet Gynecol Reprod Biol* 2002; **100**: 167-170 [PMID: 11750958 DOI: 10.1016/S0301-2115(01)00463-8]
46 **Glantz A**, Marschall HU, Mattsson LA. Intrahepatic cholestasis

of pregnancy: Relationships between bile acid levels and fetal complication rates. *Hepatology* 2004; **40**: 467-474 [PMID: 15368452 DOI: 10.1002/hep.20336]
47 **Ahmed KT**, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. *World J Gastroenterol* 2013; **19**: 7639-7646 [PMID: 24282353 DOI: 10.3748/wjg.v19.i43.7639]
48 **Goel A**, Jamwal KD, Ramachandran A, Balasubramanian KA, Eapen CE. Pregnancy-related liver disorders. *J Clin Exp Hepatol* 2014; **4**: 151-162 [PMID: 25755551 DOI: 10.1016/j.jceh.2013.03.220]
49 **Rahimzadeh P**, Safari S, Faiz SH, Alavian SM. Anesthesia for patients with liver disease. *Hepat Mon* 2014; **14**: e19881 [PMID: 25031586 DOI: 10.5812/hepatmon.19881]
50 **DeLeon A**, De Oliveira GS, Kalayil M, Narang S, McCarthy RJ, Wong CA. The incidence of coagulopathy in pregnant patients with intrahepatic cholestasis: should we delay or avoid neuraxial analgesia? *J Clin Anesth* 2014; **26**: 623-627 [PMID: 25439411 DOI: 10.1016/j.jclinane.2014.04.013]
51 **Brouwers L**, Koster MP, Page-Christiaens GC, Kemperman H, Boon J, Evers IM, Bogte A, Oudijk MA. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. *Am J Obstet Gynecol* 2015; **212**: 100.e1-100.e7 [PMID: 25046809 DOI: 10.1016/j.ajog.2014.07.026]
52 **Mihu D**, Costin N, Mihu CM, Seicean A, Ciortea R. HELLP syndrome - a multisystemic disorder. *J Gastrointestin Liver Dis* 2007; **16**: 419-424 [PMID: 18193124]
53 **Fitzpatrick KE**, Hinshaw K, Kurinczuk JJ, Knight M. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. *Obstet Gynecol* 2014; **123**: 618-627 [PMID: 24499757 DOI: 10.1097/AOG.0000000000000140]
54 **Groot E**, de Groot PG, Fijnheer R, Lenting PJ. The presence of active von Willebrand factor under various pathological conditions. *Curr Opin Hematol* 2007; **14**: 284-289 [PMID: 17414220 DOI: 10.1097/MOH.0b013e3280dce531]
55 **Audibert F**, Friedman SA, Frangieh AY, Sibai BM. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. *Am J Obstet Gynecol* 1996; **175**: 460-464 [PMID: 8765269 DOI: 10.1016/S0002-9378(96)70162-X]
56 **Rose CH**, Thigpen BD, Bofill JA, Cushman J, May WL, Martin JN. Obstetric implications of antepartum corticosteroid therapy for HELLP syndrome. *Obstet Gynecol* 2004; **104**: 1011-1014 [PMID: 15516393 DOI: 10.1097/01.AOG.0000143262.85124.e8]
57 **Martin JN**, Blake PG, Lowry SL, Perry KG, Files JC, Morrison JC. Pregnancy complicated by preeclampsia-eclampsia with the syndrome of hemolysis, elevated liver enzymes, and low platelet count: how rapid is postpartum recovery? *Obstet Gynecol* 1990; **76**: 737-741 [PMID: 2216215 DOI: 10.1097/00006250-199011000-00001]
58 **Padden MO**. HELLP syndrome: recognition and perinatal management. *Am Fam Physician* 1999; **60**: 829-36, 839 [PMID: 10498110]
59 **Geary M**. The HELLP syndrome. *Br J Obstet Gynaecol* 1997; **104**: 887-891 [PMID: 9255078 DOI: 10.1111/j.1471-0528.1997.tb14346.x]
60 **Habli M**, Eftekhari N, Wiebracht E, Bombrys A, Khabbaz M, How H, Sibai B. Long-term maternal and subsequent pregnancy outcomes 5 years after hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. *Am J Obstet Gynecol* 2009; **201**: 385.e1-385.e5 [PMID: 19716544 DOI: 10.1016/j.ajog.2009.06.033]
61 **Palit S**, Palit G, Vercauteren M, Jacquemyn Y. Regional anaesthesia for primary caesarean section in patients with preterm HELLP syndrome: a review of 102 cases. *Clin Exp Obstet Gynecol* 2009; **36**: 230-234 [PMID: 20101854]
62 **Koyama S**, Tomimatsu T, Kanagawa T, Sawada K, Tsutsui T, Kimura T, Chang YS, Wasada K, Imai S, Murata Y. Spinal subarachnoid hematoma following spinal anesthesia in a patient with HELLP syndrome. *Int J Obstet Anesth* 2010; **19**: 87-91 [PMID: 19945267 DOI: 10.1016/j.ijoa.2009.05.007]
63 **Lautt WW**. The 1995 Ciba-Geigy Award Lecture. Intrinsic regulation of hepatic blood flow. *Can J Physiol Pharmacol* 1996; **74**: 223-233 [PMID: 8773400 DOI: 10.1139/y96-029]
64 **Gelman S**. General anesthesia and hepatic circulation. *Can J Physiol Pharmacol* 1987; **65**: 1762-1779 [PMID: 3319112 DOI: 10.1139/y87-276]
65 **Armbruster K**, Nöldge-Schomburg GF, Dressler IM, Fittkau AJ, Haberstroh J, Geiger K. The effects of desflurane on splanchnic hemodynamics and oxygenation in the anesthetized pig. *Anesth Analg* 1997; **84**: 271-277 [PMID: 9024014 DOI: 10.1097/00000539-199702000-00007]
66 **O'Connor CJ**, Rothenberg DM, Tuman KJ. Anesthesia and the hepatobiliary system. In: Miller RD, editor. Miller's Anesthesia. 6th ed. Philadelphia: Churchill Livingstone/Elsevier, 2005: 2209-2229
67 **Dabbagh A**, Rajaei S. Xenon: a solution for anesthesia in liver disease? *Hepat Mon* 2012; **12**: e8437 [PMID: 23300498 DOI: 10.5812/hepatmon.8437]
68 **Hoetzel A**, Ryan H, Schmidt R. Anesthetic considerations for the patient with liver disease. *Curr Opin Anaesthesiol* 2012; **25**: 340-347 [PMID: 22450699 DOI: 10.1097/ACO.0b013e3283532b02]
69 **Kiamanesh D**, Rumley J, Moitra VK. Monitoring and managing hepatic disease in anaesthesia. *Br J Anaesth* 2013; **111** Suppl 1: i50-i61 [PMID: 24335399 DOI: 10.1093/bja/aet378]
70 **Kurosawa M**, Unno T, Aikawa Y, Yoneda M. Neural regulation of hepatic blood flow in rats: an in vivo study. *Neurosci Lett* 2002; **321**: 145-148 [PMID: 11880193 DOI: 10.1016/S0304-3940(01)02509-5]
71 **del-Rio-Vellosillo M**, Garcia-Medina JJ. Anesthetic considerations in HELLP syndrome. *Acta Anaesthesiol Scand* 2016; **60**: 144-157 [PMID: 26446688 DOI: 10.1111/aas.12639]

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