

Liver diseases in pregnancy: Diseases unique to pregnancy

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Abstract

Pregnancy is a special clinical state with several normal physiological changes that influence body organs including the liver. Liver disease can cause significant morbidity and mortality in both pregnant women and their infants. This review summarizes liver diseases that are unique to pregnancy. We discuss clinical conditions that are seen only in pregnant women and involve the liver; from Hyperemesis Gravidarum that happens in 1 out of 200 pregnancies and Intrahepatic Cholestasis of Pregnancy (0.5%-1.5% prevalence), to the more frequent condition of preeclampsia (10% prevalence) and its severe form; hemolysis, elevated liver enzymes, and a low platelet count syndrome (12% of pregnancies with preeclampsia), to the rare entity of Acute Fatty Liver of Pregnancy (incidence of 1 per 7270 to 13000 deliveries). Although pathogenesis behind the development of these ailments are not fully understood, theories have been proposed. Some propose the special physiological changes that accompany pregnancy as a precipitant. Others suggest a constellation of factors including both the mother and her fetus that come together to trigger those unique conditions. Reaching a

timely and accurate diagnosis of such conditions can be challenging. The timing of the condition in relation toward which trimester it starts at is a key. Accurate diagnosis can be made using specific clinical findings and blood tests. Some entities have well-defined criteria that help not only in making the diagnosis, but also in classifying the disease according to its severity. Management of these conditions range from simple medical remedies to measures such as immediate termination of the pregnancy. In specific conditions, it is prudent to have expert obstetric and medical specialists teaming up to help improve the outcomes.

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Key words: Liver; Pregnancy; Hyperemesis gravidarum; Intrahepatic cholestasis; Hemolysis, elevated liver enzymes, and a low platelet count; Preeclampsia; Eclampsia; Acute fatty liver

Core tip: Pregnancy is a special clinical state with several normal physiological changes that influence body organs including the liver. Liver disease can cause significant morbidity and mortality in both pregnant women and their infants. Challenges involve making the diagnosis and the methods of treatment and their safety for both the mother and the baby. This review summarizes liver diseases that are unique to pregnancy.

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HYPEREMESIS GRAVIDARUM

Although nausea and vomiting of pregnancy affect up to 90% of pregnancies, hyperemesis gravidarum (HG) oc-

curs in approximately 1 out of every 200 pregnancies^[1]. Women with HG present with severe and persistent vomiting in the first trimester that can cause dehydration, metabolic disturbances, and nutritional deficiencies. HG may result in weight loss and ketonuria. Risk factors for HG include multiple gestations, molar pregnancies, fetal anomalies such as hydrops fetalis and trisomy 21^[2,3]. Not all women with HG develop liver disease. Half of the patients who require hospitalization for HG suffer from liver disease^[4]. HG was the cause in up to 94% of pregnant women with elevated liver transaminases in their first trimester in one series^[5]. Veenendaal *et al*^[6] conducted a meta-analysis that showed women with HG are more likely to have low birthweight < 2500 kg (OR = 1.42; 95%CI: 1.27-1.58), small for gestational age (OR = 1.28; 95%CI: 1.02-1.60), and premature delivery (OR = 1.32; 95%CI: 1.04-1.68) than those with no HG. On the other hand, no correlations with Apgar scores, congenital anomalies or perinatal death were identified. Some of those poor outcomes were more likely in pregnant women with low gestational weight gain (< 7 kg)^[7].

Pathogenesis

Despite several hypotheses, the pathogenesis of liver disease in HG is not well understood and likely multifactorial. Starvation injury was proposed as an etiology since 1968^[8,9]. Over expression of cytokine-producing cells was implicated as a potential cause for pregnancy-related liver diseases such as preeclampsia and HG. Other hypotheses predicted damage to the liver resulting from impaired maternal or fetal mitochondrial fatty acid oxidation, implicating deficiency in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) as a reason for accumulation of fatty acids in the placenta and eventually causing liver damage^[10]. Other report linked fetal deficiency of hepatic carnitine palmitoyltransferase I, the enzyme responsible for transporting long chain fatty acids from the cytoplasm of cells across the outer mitochondrial membrane, to HG^[11-16].

Clinical presentation

The clinical presentation of HG with liver disease can range from mild aminotransferase elevation to rarely severe elevation. No fulminant hepatic failure has been reported with HG^[17,18]. Patients usually are acutely ill with signs of dehydration. Rarely, it can present with jaundice and electrolyte disturbances such as hypokalemia and hyponatremia as well as metabolic alkalosis and erythrocytosis. It seems that the severity of nausea and vomiting correlates well with the degree of liver enzymes elevation^[4]. No specific abdominal ultrasound findings are associated with HG. Liver biopsy may show necrosis, steatosis or bile plugs^[19,20], and usually is not indicated.

Management

Patients with HG usually require hospitalization for intravenous fluid replacement, anti-emetics, bowel rest, and possible parenteral nutrition.

Prognosis

Hyperemesis gravidarum is usually a reversible condition with no permanent damage to the liver and almost never fatal.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) is a reversible condition of cholestasis that happens usually in the third trimester. Findings such as pruritus, high serum bile acids levels, and abnormal liver function tests usually resolve after delivery. ICP is more prevalent in Scandinavian and South American countries^[21,22]. Prevalence in Europe, United States, Canada and Australia is 0.1% to 1.5%^[23]. In a recent review, although no causality effect can be claimed, ICP was associated with an increase in the risk of developing hepatobiliary diseases later in life, such as hepatitis C, cirrhosis, and gallstones. Having underlying chronic liver disease (hepatitis C or chronic hepatitis) increased the odds of developing ICP^[24].

Pathogenesis

Genetic predisposition and hormonal factors have been implicated in the pathogenesis of ICP. The familial tendency and the observation of clustering of ICP in families led to the belief that genetics play a role in its development. Although some studies revealed results connecting MDR3 (*ABCB4*) gene with ICP, several other studies failed to demonstrate such relation^[25-29]. Other genes such as *ABCB11* and *ATP8B1* were examined but showed weaker linkage to ICP^[30-32]. Explaining ICP on a molecular basis in relation to sex hormones has gained interest^[33]. The facts that ICP happens late in pregnancy and has a higher incidence in multiple gestation pregnancies, and that it resolves after delivery when sex hormones levels fall, make a logical connection between sex hormones and ICP. The estrogen metabolite estradiol-17β-glucuronide and differences in progesterone metabolites between pregnant women with and without ICP were also implicated^[34-38].

Clinical presentation

ICP usually commences in the third trimester although earlier start in the second trimester has been reported^[39]. The most common symptom is pruritus. Severity of pruritus increases at night and can involve the palms and soles. Other symptoms include steatorrhea, malabsorption of fat-soluble vitamins, and weight loss. ICP seems also to increase the incidence of gallstones and cholecystitis^[40]. ICP tends to return in subsequent pregnancies with variable severity^[41]. Elevated fasting serum bile acids level (> 10 μmol/L) confirms the diagnosis. Aminotransferases can be elevated as well up to 2-10 folds^[42]. Alkaline phosphatase levels might not be helpful due to higher physiological levels in late pregnancy. Clinical jaundice is detected in 10%-15% of the cases only and bilirubin levels rarely exceed 100 μmol/L^[23,43]. As in all

cholestatic patients, women with ICP tend to have higher low-density lipoprotein cholesterol and triglycerides^[44]. Liver biopsy can reveal bland cholestasis (intrahepatic cholestasis without parenchymal inflammation). Liver biopsy is usually not indicated.

Management

Bile acids sequestrants such as cholestyramine, antihistamines and opioid antagonists have been used to alleviate the pruritus. Cholestyramine is an exchange resin that binds bile acids and other anions in the intestine and increases their fecal excretion. Cholestyramine does not improve biochemical parameters or fetal outcomes in ICP^[45]. *S*-adenosyl-methionine has shown limited efficacy in ICP^[46,47]. Ursodeoxycholic acid (UDCA) is the first line therapy for ICP. UDCA has shown significant decrease in serum bile acids, serum aspartate aminotransferase and alanine aminotransferase, serum bilirubin, and was effective for pruritus^[48-50]. Weekly non-stress testing did not prove to make a difference in ICP-related fetal deaths^[51]. Some studies suggested 40 $\mu\text{mol/L}$ as a cutoff level of bile acids, after that fetal complications may happen^[52,53]. Others did not observe such correlation until bile acids are $> 100 \mu\text{mol/L}$ ^[54]. No evidence is strong enough to recommend early delivery (at 37 wk of gestation) for mothers with high bile acids levels, although this strategy is still used in some practices^[55].

Prognosis

Although ICP is a benign condition for the mother, poor fetal outcomes can occur. In some studies ICP resulted in premature births up to 60%. Other complications such as fetal distress and intrauterine fetal death were reported at 61% and 1.6% respectively^[23,39,56]. The onset of pruritus and higher maternal fasting serum bile acids were associated with higher risk for premature delivery^[57].

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is a rare but a serious condition that is unique to pregnancy and happens in the third trimester. AFLP can lead to significant maternal and fetal morbidity and mortality^[20,58]. Although rare, incidence of 1 per 7270 to 13000 deliveries, outcomes can be grave with acute liver failure and death^[20,59-61].

Pathogenesis

Until recently the pathogenesis of AFLP was unknown and still has not been fully elucidated. However, molecular advances over the past decade suggest that AFLP may result from mitochondrial dysfunction. Defects in fetal mitochondrial fatty acid β -oxidation have been linked to development of maternal AFLP, particularly fetal defects in LCHAD, which is part of the mitochondrial trifunctional protein (MTP) complex^[14,62-66]. In a retrospective study, Ibdah *et al.*^[14] examined the association between MTP defects in children and liver disease in their mothers during pregnancy in 24 families with documented pe-

diatric defects in MTP. Fifteen of 24 women (62%) were diagnosed to have had maternal liver disease consistent with AFLP, although in two cases a clear distinction between AFLP and hemolysis, elevated liver enzymes, and a low platelet count (HELLP) syndrome was not possible. Nine of the 24 women had normal pregnancies. All 15 pregnancies with maternal liver disease were associated with fetal LCHAD deficiency. Molecular analysis revealed a common LCHAD mutation, G1528C in the offspring of women who developed AFLP. The results from this study show that when carrying a fetus that is LCHAD deficient, the mother has a high risk of developing AFLP. In a subsequent study, Ibdah *et al.* evaluated fetal genotypes and pregnancy outcomes in 83 pregnancies in 35 families with documented pediatric MTP defects^[66]. This study provided further evidence that carrying a fetus with LCHAD deficiency is associated with a high risk for developing AFLP. With the growing evidence suggesting that carrying an LCHAD-deficient fetus is associated with AFLP, it was recommended that neonates born to pregnancies complicated by AFLP be tested for the common G1528C mutation and that this testing when done early after birth can be lifesaving as it may identify LCHAD-deficient children before they manifest the disease allowing early dietary intervention by institution of a diet low in fat, high in carbohydrate, and by substitution of the long chain fatty acids with medium chain fatty acids (for complete review on the association between AFLP and pediatric LCHAD deficiency^[61]).

The precise mechanism by which an LCHAD deficient fetus causes AFLP in a heterozygote mother is still unclear. However, several factors appear to contribute to this fetal-maternal interaction. First, the heterozygosity of the mother for an MTP defect reduces her capacity to oxidize long chain fatty acids. Second, third trimester is accompanied by changes in metabolism, an increased lipolysis, and a reduction in mitochondrial fatty acid oxidation, all increase the susceptibility of the mother who carries a fetus with LCHAD deficiency. Thus it has been speculated that potentially hepatotoxic long-chain 3-hydroxyacyl fatty acid metabolites, produced by the affected fetus or placenta, accumulate in the maternal circulation^[61].

Clinical presentation

Although there were few reports of AFLP starting in the second trimester, it usually presents in the third trimester between the 30th and 38th week of gestation^[67-70]. It is more frequent in primiparous women and can return in subsequent pregnancies^[12,62,71]. Nonspecific symptoms such as nausea, vomiting, headache, and fatigue can be the initial presentation. Right upper quadrant pain or epigastric pain can occur. Jaundice common and early jaundice may indicate severe disease^[72]. Other features such as hypoglycemia, renal failure, coagulopathy, ascites, and encephalopathy were reported frequently. AFLP can result in maternal and fetal demise^[73]. Although hypertension can be present, severe hypertension is likely

Table 1 Proposed (Swansea) diagnostic criteria for acute fatty liver of pregnancy

Vomiting	Abdominal pain
Polydipsia/polyuria	Encephalopathy
Elevated bilirubin	Hypoglycaemia
Elevated uric acid	Leucocytosis
Ascites or bright liver on US	Elevated transaminases
Elevated ammonia	Renal impairment
Coagulopathy	Microvesicular steatosis on liver biopsy

To meet the criteria the patient should have 6 or more of these clinical findings. Source: Ref. [80], with permission; US: Ultrasound scan.

secondary to the reduction in peripheral vascular resistance associated with liver failure. AFLP is a medical and obstetric emergency and diagnosis relying on clinical and laboratory findings should be prompt. Liver biopsy can be helpful in early and mild cases of AFLP especially if diagnosis is not clear^[74]. Liver biopsy is not necessarily needed and should be avoided in more severe cases where the risk of bleeding is high and prompt therapeutic intervention is needed. Although elevated aminotransferases is expected, the severity of liver dysfunction is not always reflected by the degree of elevation. Alkaline phosphatase is usually elevated. Other findings such as leukocytosis, thrombocytopenia, disseminated intravascular coagulopathy (DIC), abnormal prothrombin time, partial thromboplastin time, and normal fibrinogen can occur^[74-76]. Ketonuria and proteinuria can be present. Elevated blood urea nitrogen and creatinine indicate renal insufficiency. Low serum albumin and hypoglycemia can occur. Uric acid and ammonia levels can be increased. Hyperuricemia can be an early indicator and develop before hyperbilirubinemia^[77,78]. In comparison with diffuse or microvesicular steatosis, Swansea criteria had a sensitivity of 100% (95%CI: 77-100) and specificity of 57% (95%CI: 20-88), with positive and negative predictive values of 85% and 100% in one report (Table 1)^[79-81]. Ch'ng *et al*^[80] proposed a set of clinical findings, known as Swansea criteria, to help reach the diagnosis of AFLP. Those diagnostic criteria have not been validated in different populations. Liver biopsy usually displays microvesicular steatosis^[82]. Electron microscopy can show mitochondrial disruption. Imaging studies can be useful to exclude other pathologies; but have limited utility in the diagnosis of AFLP.

Management

Stabilization of the mother and early recognition and delivery are the keys for successful management. Close monitoring and management of associated complications is necessary to improve outcomes. Plasmapheresis was used in few series in severe cases with reported success^[83,84].

Prognosis

AFLP is severe disease with high maternal (18%) and fetal (23%) mortality. Prenatal diagnosis can provide

Table 2 Hemolysis, elevated liver function tests, and low platelet counts syndrome diagnostic criteria

HELLP class	Tennessee classification	Mississippi classification
1	Platelets $\leq 100 \times 10^9/L$ AST ≥ 70 IU/L LDH ≥ 600 IU/L	Platelets $\leq 50 \times 10^9/L$ AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
2		Platelets $\leq 100 \times 10^9/L, \geq 50 \times 10^9/L$ AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
3		Platelets $\leq 150 \times 10^9/L, \geq 100 \times 10^9/L$ AST or ALT ≥ 40 IU/L LDH ≥ 600 IU/L

AST: Aspartate aminotransferase; Source: Haram *et al.* BMC Pregnancy and Childbirth 2009 9:8 doi:10.1186/1471-2393-9-8; ALT: Alanine aminotransferase; HELLP: Hemolysis, elevated liver function tests, and low platelet counts; LDH: Lactate dehydrogenase.

benefit for both the mother and her fetus in subsequent pregnancies.

PREECLAMPSIA/ECLAMPSIA AND HELLP SYNDROME

Preeclampsia is a syndrome that is unique to pregnancy. Manifestations include hypertension and proteinuria, and can result in fetal growth retardation. By far, preeclampsia is the most common serious medical disorder in pregnancy with prevalence up to 10%. It is associated with up to 20% of maternal mortality in developed countries^[85,86]. Organ involvement such as liver, brain and kidneys signifies severe disease. Elevated aminotransferases occurs up to 10% of severe preeclampsia cases^[86,87]. Although preeclampsia can start as early as the second trimester, liver involvement is mainly seen in the third trimester. Severe preeclampsia can be life threatening to the mother and can result in fetal morbidity and mortality. Eclampsia usually refers to preeclampsia with seizures. HELLP syndrome is a variant of severe preeclampsia that happens in up to 12% of patients with preeclampsia, and entails constellation of findings including hemolysis, elevated liver aminotransferases of and low platelet counts. Table 2 shows the diagnostic criteria of HELLP syndrome.

Pathogenesis

In reviewing liver biopsies and autopsies of cases with preeclampsia, eclampsia and unclassified toxemia, from the Armed Forces Institute of Pathology between 1920 and 1984, Rolfes *et al*^[88] reported that despite that large cerebral and midbrain hemorrhages, extensive thrombosis and infarction as well as cerebral edema with herniation were the major causes of deaths, liver disease contributed to 17 deaths out of the 102 cases reviewed. Extensive periportal lesions producing widespread parenchymal hemorrhage and necrosis were described. Large areas of infarction, wide bands of fibrin replacing liver cells, extravasation of red blood cells, and capillary

Table 3 Preeclampsia associated liver diseases

	Severe preeclampsia and eclampsia	HELLP syndrome	Acute fatty liver of pregnancy
Time	After gestational week 22	Late second trimester to early postpartum	Third trimester
Prevalence	Increases in multiple gestation (5%-7%)	0.10%	Increases in male fetus, multiple gestations, primiparous women (0.01%)
Findings	High blood pressure; proteinuria; edema; seizure; renal failure; pulmonary edema	Abdominal pain, nausea/vomiting, overlap with findings in preeclampsia	Abdominal pain, nausea/ vomiting, jaundice, hypoglycemia and hepatic failure
Tests	Platelets > 70000; urine protein > 5 g/24 h; abnormal liver enzymes (10%)	Low platelets; hemolysis; elevated liver enzymes; prothrombin time may remain normal; normal fibrinogen	Platelets < 100000; AST and ALT 300-1000 U/L; low antithrombin III; high prothrombin time; low fibrinogen; high bilirubin; DIC
Management	Blood pressure control; beta-blockers, methyldopa, magnesium sulfate, early delivery	Prompt delivery 5% maternal death 1% hepatic rupture	Prompt delivery; liver transplant ≤ 10% maternal death
Outcome	1% maternal death	1%-30% fetal death	Up to 45% fetal death

HELLP: Hemolysis, elevated liver function tests, and low platelet counts; DIC: disseminated intravascular coagulation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Table 4 Complications of preeclampsia/hemolysis, elevated liver function tests, and low platelet counts syndrome

Maternal complications	Neonatal complications	Labor complications
Eclampsia	Fetal death	Preterm labor
HELLP syndrome	Prematurity	
Hepatic subcapsular hematoma, infarction or rupture	IUGR	
Acute renal failure	Respiratory distress syndrome	
Stroke, cerebral hemorrhage, edema and herniation	Intraventricular hemorrhage	
Pulmonary edema and acute respiratory distress syndrome	Sepsis	
Laryngeal edema		
Retinal detachment		

HELLP: Hemolysis, elevated liver function tests, and low platelet counts; IUGR: Intrauterine growth retardation.

thrombi were also seen. Histological changes of the liver in HELLP syndrome include periportal or focal parenchymal necrosis with hyaline deposits of fibrin-like material in the sinusoids^[89]. Other molecular mechanisms such as vascular remodeling and placentation, immunological factors, and fatty acid oxidation defects were proposed as potential factors in the development of this spectrum of diseases^[12,71,90-92].

Clinical presentation

Preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy share similar presentations and differentiating between the three entities can be difficult. All present late in pregnancy and can have similar clinical features. Clinical presentation followed by typical laboratory findings can help in reaching the diagnosis. Although it may be reasonable to do an ultrasound of the liver for pregnant women with abnormal liver enzymes, imaging studies such as computed tomography and magnetic resonance imaging are rarely useful in making the diagnosis. Such

studies can have a role in diagnosing complications such as liver infarcts, hematomas, and liver rupture^[93]. Table 3 presents a comparison between the three preeclampsia-associated liver diseases in pregnancy.

Management

Successful management strategies rely on early diagnosis and prompt intervention. Women with severe preeclampsia or HELLP syndrome should be hospitalized and closely monitored in labor and delivery units, and placed on bed rest with good blood pressure control (systolic blood pressure < 155 and diastolic blood pressure < 100)^[94]. The use of intravenous magnesium sulfate to prevent seizures is recommended. Close monitoring of mental status and appropriate use of imaging studies as indicated can help in identifying complications early. Prompt delivery can be the only effective therapy. Timing of delivery should be based on gestational age (reflecting the degree of fetal maturity) and the severity of the disease (maternal morbidity and mortality). Prompt delivery is indicated if the syndrome develops after 34 wk of gestation or earlier if complications occur, such as multi-organ dysfunction, liver infarction or hemorrhage, DIC, renal failure, suspected abruption of placenta, or fetal compromise^[95-97]. Fetal lung maturity is not achieved before 34 wk of gestation. Therefore making a determination about terminating the pregnancy before 34 wk of gestation can be difficult^[96,98-102]. Although a favorable effect on the platelet count and the aminotransferases levels has been observed, it's not clear if corticosteroids alter the course of the disease, and therefore their use remains controversial^[101,103,104]. Betamethasone 12 mg intramuscularly every 24 h twice or four doses of intramuscular dexamethasone 6 mg every 12 h is recommended for enhancing fetal maturity^[101]. Fetal and maternal complications are listed in Table 4.

Prognosis

Although not very common, preeclampsia and HELLP syndrome remain a significant cause of morbidity and mortality for both pregnant women and their fetuses. With a maternal mortality of 1% in severe preeclamp-



sia, up to 5% in HELLP syndrome, and up to 30% fetal death rate, early diagnosis and prompt delivery remain the only effective treatment strategy.

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