Unique Liver Disease in Pregnancy

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EXTRACT

The approach of the unique liver disease in pregnancy has not changed much. For most of the liver diseases that manifest during the 2nd and 3rd trimester, the important concept is to consider delivery promptly or at the appropriate time by consideration of maternal health and newborn maturity, and providing continuous intensive monitoring before delivery and at postpartum period. Because the clinical management of the patients with unique liver diseases in pregnancy is alike, liver biopsy is not always indicated, especially if preeclampsia, eclampsia, HELLP syndrome and AFLP are the differential diagnosis. Nowadays, genetic testing and counseling for inherited genetic diseases in newborns and the women becomes more crucial. The risk of disease recurrence in subsequent pregnancy needs to be acknowledged to the women and their family.

Key words: liver disease, pregnancy, clinical management

Normal Physiologic Changes in Pregnancy

During pregnancy, there are many physiologic changes due to increased estrogen and progesterone levels leading to the alteration of liver biochemical tests. Hemodilution from increased total plasma volume results in 1 g/dl reduction of serum albumin(1) whereas the levels of ceruloplasmin, fibrinogen, cholesterol and triglyceride may be elevated during pregnancy.(1) Blood tests that are fairly normal in pregnant women are serum transaminases, gamma-glutamyl transferase (GGT), 5’ nucleotidase, bilirubin and total bile acid(1,2). In more advanced gestational age, the level of serum alkaline phosphatase can be elevated due to the production of placental isoenzyme and the secretion of bone isoenzyme of alkaline phosphatase(1,2). As a result, further investigation for the cause of liver disease is required in pregnant women with the elevation of serum transaminases, GGT or bilirubin. Moreover, spider angiomata and palmar erythema are physical signs that present temporarily during pregnancy.

Approach to Liver Diseases in Pregnancy

Pregnant women who develop nausea, vomiting, anorexia, jaundice, dark urine, itching or abdominal pain need to receive much attention. Initial blood tests should consist of complete blood count, liver function

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test, glucose, uric acid, coagulogram, viral hepatitis B and viral hepatitis C markers. The differential diagnosis should include not only unique liver disease in pregnancy but also concurrent liver problems that can occur in normal subjects. It is recommended to use the gestational age of the pregnancy as the best guide for the differential diagnosis of liver disease in pregnancy.(3)

The common liver diseases presenting during each trimester are demonstrated in Table 1. The changing pattern of liver enzymes (except serum alkaline phosphatase) may also be another clue used to guide the diagnosis.

### Unique Liver Disease in Each Trimester of Pregnancy

**First trimester: Hyperemesis gravidarum**

- **Incidence and onset** Hyperemesis gravidarum occurs in about 1-20 per 1,000 pregnancies.(2,4) Severe vomiting with weight loss and electrolyte imbalance is common during the first trimester.(2,4) As a general rule, hyperemesis gravidarum resolves by week 20 of the gestation.(3) Women who develop severe vomiting at late pregnancy should be looked for eclampsia, preeclampsia, HELLP and acute fatty liver of pregnancy (AFLP).(4) Increased serum aminotransferase level, usually less than 1000 U/L, is seen in 50% of patients.(2,3) Liver biopsy, which is not required for the diagnosis, shows non-specific changes.(5)

**Predisposing factor and pathophysiology** Hyperemesis gravidarum is likely to happen in pregnancy with multiparity, female fetus, high intake of saturated fat prior to pregnancy, gestational trophoblastic disease and congenital fetal abnormalities.(4,6) The underlying pathophysiology is poorly understood. It may be related to elevated estrogen level(7), altered regulation of emetic center at central and enteric nervous system(8), and gastrointestinal smooth muscle dysfunction.(4)

- **Outcome and complication** Hyperemesis gravidarum leads to maternal complications from repeated vomiting.(2) However, in modern era, maternal and fetal complication from this condition is almost negligible.(2,3)

- **Treatment** Supportive treatment for severe vomiting includes intravenous fluid and antiemetics such as promethazine, odansetron, or droperidol.(9,10)

**Second trimester: Intrahepatic cholestasis of pregnancy (ICP)**

- **Incidence and onset** The prevalence of ICP varies from 0.7% in the United States to 6.5% in Chile, and 27.6% among Araucanian Indians in Chile.(1-3,11,12) Pruritus involving mostly the palms and the soles is the main symptom of ICP which usually begins in the second trimester, and resolves within days after delivery. Jaundice develops in only 10% to 20% of patients with ICP.(2,3,11,12) The hallmark of ICP is an elevation of serum bile acid level.(2,3,11,12) In most patients with ICP, AST and ALT levels are elevated 2 to 10 folds above the upper normal limit.(2,3,11,12) Elevated alkaline phosphatase level is difficult to interpret for diagnosis of cholestasis during pregnancy.(11,12) Liver biopsy is rarely indicated because it shows only bland cholestasis without any characteristic feature of ICP.(11,12) Severe fatigue and psychological distress can occur in women with intense pruritus.(12)

- **Predisposing factor and pathophysiology** ICP is more common in women with advanced maternal age, in multiparous women and in the winter season.(2) The pathogenesis of ICP is multifactorial and poorly understood.(12) Potential contributing factors include genetic predisposition (as occur more frequently in some ethnic groups), derangement of estrogen level...
and its metabolism, and environmental factors.\(^{(1\text{-}3,11,12)}\)

**Outcome and complication**  The risk of postpartum hemorrhage is increased if vitamin K is deficient before delivery.\(^{(12)}\) The fetal outcome is not favorable. ICP is associated with an increased risk of fetal prematurity, stillbirth, meconium-stained amniotic fluid and perinatal mortality.\(^{(1\text{-}3,11,12)}\)

**Treatment**  ICP recurs in 60% to 70% of subsequent pregnancy.\(^{(11)}\) A recent report showed that a low dosage estrogen birth control can be prescribed for women with history of ICP with a low risk of cholestasis.\(^{(14)}\) The treatment of choice for ICP is ursodeoxycholic acid (UDCA).\(^{(1\text{-}3,11,12,15)}\) UDCA treatment is showed to decrease pruritus, serum bilirubin, ALT and bile salt levels without causing maternal and fetal toxicity.\(^{(1\text{-}3,11,12,15)}\) It helps increase the number of fetal delivery at term and birth weight.\(^{(15)}\) Cholestyramine improves pruritus but does not improve biochemical parameter or fetal outcome.\(^{(12)}\) Hydroxyzine at a dose of 25 to 50 mg/day helps alleviate the itching.\(^{(11)}\) Definite treatment of ICP is delivery. The decision to terminate pregnancy should be made by weighing the risk of prematurity resulting from early delivery versus the risk of intrauterine death.\(^{(12)}\)

**Third trimester : Preeclampsia and eclampsia**

**Incidence and onset**  Preeclampsia, which complicates 5-10% of pregnancy, is characterized by hypertension, edema and proteinuria.\(^{(1,2,16,17)}\) The additional development of seizure signifies eclampsia, which affects 0.1-0.2% of pregnancy.\(^{(1)}\) Preeclampsia usually develops during the 2nd and 3rd trimester of pregnancy.\(^{(1,2,16,17)}\) Liver involvement in preeclampsia commonly manifests as upper abdominal pain, nausea and vomiting. Elevation of serum transaminases (5-100 times above the upper normal limit) occurs in approximately one-quarter of patients with mild preeclampsia and up to 90% of those with eclampsia.\(^{(1,2,16,17)}\)

**Predisposing factor and pathophysiology**  Pregnant women with primiparous, hypertension, diabetest, extreme ages, multiple gestations or having the history of the condition are at increased risk of preeclampsia and eclampsia.\(^{(1)}\) Its etiology is unknown but available evidences suggest that uteroplacental ischemia may play a major role.\(^{(2,17,18)}\) The activation of the endothelium from placental hypoxemia leads to an increase in vascular tone and initiation of coagulation pathway.\(^{(1,2,16,17)}\) Liver biopsy in this condition shows periportal fibrin deposition, hemorrhage and hepatocellular necrosis.\(^{(1,2,16,17)}\)

**Outcome and complication**  Nowadays, the maternal mortality rate is less than 1%, however 80% of maternal death is resulted from seizure and cerebral edema.\(^{(1,2,16,17)}\) The remaining causes of death are subcapsular hematoma, hepatic infarction and rupture, and liver failure.\(^{(1,2,16,17,19)}\) Fetal mortality is affected by abruptio placenta, prematurity and intrauterine growth retardation.\(^{(1,2,16,17)}\)

**Treatment**  Besides intensive monitoring and effective management, the only effective treatment is delivery of the fetus when the development of fetal maturity is confirmed.\(^{(1,2,16,17)}\)

**HELLP syndrome**

**Incidence and onset**  HELLP syndrome is a variant of severe preeclampsia that is characterized by microangiopathic hemolytic anemia, elevated liver enzymes, low platelet count (<100,000 /mm\(^3\)).\(^{(16,17)}\) HELLP syndrome and acute fatty liver of pregnancy should be considered in the differential diagnosis of liver dysfunction in the second half of pregnancy.\(^{(3)}\) The majority (70%) of the patients with HELLP syndrome develop symptoms antepartum, usually in the third trimester, and 30% of the patients present postpartum.\(^{(1\text{-}3,12,16,17)}\) The condition affects 0.1-0.6% of overall pregnancies. There is a 4-12% incidence of HELLP complicating preeclampsia and it occurs in 20% of patients with severe preeclampsia.\(^{(1\text{-}3,12,16,17)}\) Nausea and upper abdominal pain are the most frequent symptoms. Patients with HELLP may present with the symptoms of preeclampsia or eclampsia. Laboratory abnormalities include marked elevation of serum transaminases, increasing LDH levels (>600 IU/L) and thrombocytopenia.\(^{(1\text{-}3,12,16,17)}\)

**Predisposing factor and pathophysiology**  The HELLP syndrome is more common among older multiparous women.\(^{(16,17)}\) HELLP and preeclampsia share common etiologies. The major mechanisms are vasoconstriction and the activation of platelet aggregation and coagulation pathway.\(^{(1\text{-}3,12,16,17)}\) Liver biopsy, which is usually unnecessary for diagnosis of HELLP, shows the typical features similar to that of preeclampsia.\(^{(1\text{-}3,12,17)}\)

**Outcome and complication**  The risk of recurrent HELLP syndrome in subsequent pregnancy is 3-27%.\(^{(20)}\) Maternal mortality from HELLP syndrome ranges between 1-3.5%.\(^{(12,21)}\) Maternal complication includes DIC, postpartum hemorrhage, abruptio placentae, hepatic hemorrhage, infarction and rupture, sub-
capsular hematoma, eclampsia, renal failure and hypertension.\(^{(2,3,12,17)}\) The perinatal mortality ranges from 10-20%.\(^{(2,16)}\) More than one-third of fetuses are born with premature or intrauterine growth retardation.\(^{(2)}\)

**Treatment** Management is obstetrical, with careful fetal monitoring and prompt delivery.\(^{(1,3,16,17)}\) Vaginal delivery is a preferred route however caesarian section may be necessary in some circumstances.\(^{(17)}\) Physicians need to be aware of the manifestation of hepatic hemorrhage, infarction and rupture which rarely complicate HELLP syndrome. These complications may occur in the peri- and postpartum period.\(^{(17)}\)

**Acute fatty liver in pregnancy (AFLP)**

**Incidence and onset** The incidence of AFLP is much lower than that of HELLP syndrome. The latter is found in 1:5,000 deliveries while the former is seen in 1:13,000-16,000 deliveries.\(^{(1,2,16,22)}\) Preeclampsia is present in 50% of cases with AFLP.\(^{(2,3)}\) AFLP, as opposed to HELLP syndrome, is a condition that true liver dysfunction exists.\(^{(3)}\) Severe coagulopathy, jaundice, hepatic encephalopathy, ascites, hypoglycemia and mild to moderate elevation of transaminases are the key features of AFLP.\(^{(3,17,23-5)}\)

**Predisposing factor and pathophysiology** AFLP is common in twin pregnancies, male pregnancy and nulliparous.\(^{(1,2,17)}\) AFLP has characteristic features of the liver histology distinctive from other liver abnormalities that occur during pregnancy. It is unfortunately that liver biopsy is hardly achievable for confirmation of the diagnosis (and so, it is not indicated\(^{(3)}\)) because patients usually develop severe coagulopathy at the time of diagnosis. The liver histology of AFLP reveals microvesicular fatty infiltration of the swollen hepatocytes predominantly at perizonal area of the liver lobule.\(^{(3,17,23)}\) To date, the pathogenesis of AFLP remains unclear.

**Outcome and complication** Recently, an association between AFLP and a deficiency of the enzyme long chain 3-hydroxyl-acyl CoA dehydrogenase (LCHAD) has been reported.\(^{(1,12,26,27)}\) The most common mutations are localized to a G1528C mutation in over 60% of cases, and a E474Q in 19% of cases.\(^{(26,27)}\) Twenty percent of infants born to mothers with AFLP are homozygous or compound heterozygous for mutation causing LCHAD deficiency.\(^{(26)}\) When women with AFLP have fetuses with homozygous long chain 3-hydroxyl-acyl CoA dehydrogenase (LCHAD) deficiency, they are found to be heterozygous deficiency for LCHAD.\(^{(2,3,16,17,23,24,28)}\) It is possible that the heterozygous mothers faces a relative insufficiency of the beta-oxidation of fatty acids to meet high energy demand during the third trimester of pregnancy and are overloaded with long chain fatty acid.\(^{(3,12,22)}\) These factors lead to the disclosed features of AFLP in susceptible women.\(^{(3,12,22)}\) Children born with this defect failure to thrive and are prone to develop liver failure with microvesicular steatosis and hypoglycemia, or a Reye-like syndrome.\(^{(2,3,17,23,24,28)}\) Screening newborns and pregnancies that are complicated by AFLP for the gene mutation is recommended.\(^{(1,2,16)}\) AFLP recurs occasionally in subsequent pregnancy.\(^{(2)}\)

**Incidence and onset** The maternal mortality before 1970 could reach 100%.\(^{(29)}\) Currently, maternal mortality decreases to less than 10% because of early recognition of the disease, prompt delivery, and intensive care at post-partum.\(^{(2,3,12,16,30)}\) If patients are in labor, in good condition and do not have signs of fetal distress, vaginal delivery may be tried.\(^{(31)}\) However, caesarean section is strongly recommended for severe cases after coagulopathy is corrected.\(^{(23)}\) In general, the condition of the ailing patients improves gradually after delivery.\(^{(23,24)}\) AFLP is considered to be a reversible form of acute liver failure, and it does not usually require liver transplantation except in very few cases whose liver failure arises or progresses after delivery.\(^{(3,21,24,32,33)}\)

**Hepatic infarction, hemorrhage and rupture**

**Incidence and onset** Hepatic infarction, hemorrhage and rupture are extreme rare conditions, with an estimated incidence of 1 in 40,000 to 1 in 250,000 pregnancies.\(^{(34)}\) Eighty percent of the affected women are multiparous with an average age of 32 years old.\(^{(35)}\) Hepatic hemorrhage precedes hepatic rupture, which usually involves the right lobe and occurs just before delivery or postpartum.\(^{(2)}\) The clinical presentation of hepatic infarction, hemorrhage and rupture is generally non-specific with malaise, abdominal pain, nausea and vomiting.\(^{(1,2,36-38)}\) Hepatic rupture may present as a clinical triad of preeclampsia or eclampsia, abdominal pain and hypotension.\(^{(36)}\) A high index of suspicion is essential for early diagnosis.\(^{(37)}\) Computed tomography (CT) scan with contrast remains the best diagnostic method.\(^{(37)}\)

**Predisposing factor and pathophysiology** Associated factors including AFLP, HELLP syndrome, preeclampsia, eclampsia, DIC, cocaine abuse, hemangioma, hepatic adenoma, cavernous hemangioma, liver abscess and trauma have been reported.\(^{(1,2,37,39)}\) Spontaneous hemorrhage into the liver is a frequent com-
Vascular injury from endothelial damage and vasospasm are believed to be the underlying pathophysiology of these conditions. Pathological examination of the liver biopsy shows periportal areas of necrosis, occlusive fibrin deposit in the periportal capillary and extensive periportal hemorrhage.

Outcome and complication Over the past two decades, maternal mortality has dropped from 59% to 33% but fetal mortality has hardly changed from 62%.

Treatment The management of these catastrophic conditions requires a multidisciplinary approach. Close monitoring, intensive therapy, aggressive resuscitation with intravenous fluid and blood component transfusion are the most important parts of early management. If the liver capsule is intact, conservative management with close monitoring with CT follow-up is recommended. Delivery by a caesarian section may be preferable because the strain of vaginal delivery may trigger rupture of a subcapsular hematoma. Once a rupture liver capsule is detected, aggressive resuscitation and emergent surgery is mandate.

CONCLUSION

To date, the approach of the unique liver disease in pregnancy has not changed much. For most of the liver diseases that manifest during the 2nd and 3rd trimester, the important concept is to consider delivery promptly or at the appropriate time by consideration of maternal health and newborn maturity, and providing continuous intensive monitoring before delivery and at postpartum period. Because the clinical management of the patients with unique liver diseases in pregnancy is alike, liver biopsy is not always indicated, especially if preeclampsia, eclampsia, HELLP syndrome and AFLP are the differential diagnosis. Nowadays, genetic testing and counseling for inherited genetic diseases in newborns and the women becomes more crucial. The risk of disease recurrence in subsequent pregnancy needs to be acknowledged to the women and their family. (Table 2)

Table 2 Recurrent rate of liver disease in pregnancy in subsequent pregnancy

<table>
<thead>
<tr>
<th>Pregnancy-associated liver disease</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic Cholestasis of Pregnancy</td>
<td>40-60%</td>
</tr>
<tr>
<td>HELLP</td>
<td>4.27%</td>
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<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Occasionally</td>
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<tr>
<td>Preeclampsia</td>
<td>2-43%</td>
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REFERENCES


