

Liver Disease During Pregnancy: A Challenging Clinical Issue

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Source / Izvornik: **Medical Science Monitor, 2018, 24, 4080 - 4090**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.12659/MSM.907723>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:184:442668>

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Download date / Datum preuzimanja: **2024-05-13**



Repository / Repozitorij:

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Received: 2017.10.24
Accepted: 2017.12.14
Published: 2018.06.15

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Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: Self financing

One of the least studied topics in the field of obstetrics is liver disease during pregnancy, which creates a challenge for both gynecologists and hepatologists. Approximately 3% of pregnant women are affected by some form of liver disease during pregnancy. Some of these conditions can be fatal for both the mother and child. In addition, 3 types of liver disease need to be differentiated during pregnancy. One type is liver disease directly related to pregnancy, which can occur at a specific time during pregnancy. Another type is liver disease not related to pregnancy, which can occur at any time, such as viral- or drug-induced hepatitis. Furthermore, pregnancy can occur in women with pre-existing liver disease. It is essential that the clinicians are familiar with this disorder so they can respond promptly and appropriately in all of these situations, especially when emergency delivery is needed and must not be postponed.

MeSH Keywords: **Delivery, Obstetric • Liver Diseases • Pregnancy**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/907723>

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Background

Liver disease during pregnancy is relatively poorly studied and poses a challenge for the consulting gynecologist and hepatologist. Nearly 3% of pregnancies are complicated by some form of liver disease, and severe pregnancy-related liver diseases can have fatal consequences for both mother and child. Diagnostic and therapeutic decisions must consider the implications for both the mother and child, and rapid diagnosis is indispensable for severe cases because the decision of immediate delivery is important for maternal and fetal outcome. Pregnant women undergo some physiological changes that can mimic liver disease; therefore, they must be considered in the diagnostic approach to women with suspected liver disease [1–6]. Pregnancy is associated with a hyperdynamic circulatory status, as maternal cardiac output and heart rate increase during pregnancy. On the other hand, the blood supply to the liver remains unchanged [2–6]. Spider angioma and palmar erythema, which are typical clinical markers of liver disease, are commonly seen during pregnancy as a consequence of the hyperestrogenic state. These physical changes usually disappear after delivery. Gall bladder motility is decreased, increasing the incidence of cholelithiasis in pregnant women [3–6]. Biochemical and hematological tests during normal pregnancy show decreased albumin in all trimesters due to hemodilution, and the decline in albumin levels becomes more pronounced as pregnancy advances. Alkaline phosphatase (ALP) is increased in the third trimester, but it is of placental origin due to fetal bone development. Alpha fetoprotein (AFP) levels also increase because it is produced by the fetal liver [1–7]. In contrast, other liver biochemical tests, such as total bile acids concentration, serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), and bilirubin, remain within the normal range during normal pregnancy. However, because of hemodilution, their ranges can change, with a reduction in the upper limit [1,3]. Pregnancy is a pro-coagulant state in which clotting factors (I, II, V, VII, X, and XII) and fibrinogen are increased, whereas the ranges for prothrombin time (PT) and activated partial thromboplastin (APT) time are within normal values [1,3]. Therefore, elevations in transaminases, bilirubin, fasting total bile acids, or the PT above the normal range during pregnancy are abnormal and indicate a pathological state that requires prompt evaluation [1].

In pregnant women with suspected liver disease we should distinguish the 2 main categories of liver disease: non-pregnancy-related liver diseases and the few diseases directly related to pregnancy [1,2]. Pregnancy-related liver disorders, in their occurrence, exhibit trimester-specific characteristics, whereas non-pregnancy-related liver diseases can occur at any time [3]. The timing of the occurrence of clinical manifestations and abnormal liver tests is critical in determining diagnosis and

treatment strategies. For example, hyperemesis gravidarum (HG) is a pregnancy-related liver disorder of early pregnancy, whereas intrahepatic cholestasis of pregnancy (ICP), pre-eclampsia with liver involvement including hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and acute fatty liver of pregnancy (AFLP) are conditions affecting the liver in late pregnancy [1,3,7]. According to the literature, a mortality rate of 0 to 25% has been reported among mothers with pregnancy-related liver diseases. The main factors determining the maternal prognosis are the cause of the liver disease, the degree of impaired synthetic, metabolic, and excretory liver function, and timing of delivery (i.e., the delay in delivery in HELLP or AFLP) [8–10]. Liver disorders that are coincidental with pregnancy can be classified as those that are present *de novo* during pregnancy, or pregnancy can occur in women with pre-existing chronic liver disease (CLD) [1,3]. Due to limited space, this group of diseases will not be discussed in this review.

Recent investigations and subsequent advances in medical treatment have resulted in improved, but still unsatisfactory, maternal and fetal outcomes. Here, we review recent advances in understanding the etiologies, clinical courses, and management of liver disease in pregnancy, especially liver diseases unique to pregnancy.

Pregnancy-Related Liver Disorders

Hyperemesis gravidarum

HG is defined as nausea and intractable vomiting that results in dehydration, ketosis, and weight loss >5% of body weight [1,11]. HG complicates approximately 0.3–2.0% of pregnancies during the first trimester. Symptoms usually start before the 9th week of gestation and disappear by the 20th week of gestation [1,2,11]. HG is not a true liver disease, but it is associated with abnormal liver test results in approximately half of cases [1,3,7]. Multiple gestations, increased body mass index (BMI), pre-existing diabetes, psychiatric illness, and HG in a previous pregnancy have been shown to be risk factors for HG development [7].

Clinical signs lead to dehydration and increased renal values, electrolyte abnormalities, metabolic alkalosis, and erythrocytosis [1,2,7,12]. Abnormal liver test results are observed in approximately half of all pregnant women [2,13–15]. Elevations in serum aminotransferases usually go up to 200 U/L and this is the most common abnormal liver test result. Other biochemical abnormalities, such as increased serum amylase and lipase values, may also be seen [1,3,7]. In addition to laboratory tests, an abdominal ultrasound must demonstrate normal liver parenchyma without biliary obstruction, and an obstetrical

ultrasound can exclude hydatidiform mole and multiple gestation [1–3,7,12]. In pregnant women presenting with abnormal liver enzymes with or without HG in the first trimester, other causes of abnormal liver enzymes must be ruled out [1,3].

The management of HG is supportive and includes intravenous fluid replacement, correction of electrolyte abnormalities, use of antiemetics, possible parenteral nutrition, and vitamin supplementation [1,2,7,14,16].

Intrahepatic cholestasis of pregnancy

ICP is the most common cause of cholestasis during pregnancy and the most common pregnancy-related liver disease. ICP is a form of liver disease characterized by a reversible cholestatic condition that usually occurs during the late second and third trimester, although rarely it is present as early as 7 weeks of gestation. ICP has rapid postnatal resolution, with signs and symptoms usually disappearing spontaneously within 6 weeks of delivery. ICP recurs in more than half of subsequent pregnancies [1–3,7,17–20]. The incidence of ICP varies widely, with geographic variations in the rate of disease. The incidence rate in Europe has been reported to range from 0.5% to 1.8% of pregnancies. The highest peak of incidence was reported in South American countries (up to 28%) and in Scandinavia. Interestingly, ICP is more common during colder months in Scandinavian and South American countries, for unknown reasons [1,7,17–21]. The risk factors reported to be associated with increased incidence of ICP are maternal age >35 years, multiparity, history of oral contraceptive use, history of fertility treatment in women, and history of ICP during previous pregnancies [1,5,20,22,23].

Pathophysiologically, in ICP there is an abnormal biliary transport across the canalicular membrane, with multifactorial etiology [3,20,24–28]. Genetic, hormonal, and environmental factors have been reported to play a role in ICP etiopathogenesis [3,5,20]. ICP appears late in pregnancy, when serum concentrations of estrogen reach their peak; it has a higher incidence in twin pregnancies, which have higher estrogen levels, and resolves after delivery, when sex hormone levels fall [2,3,5,20,28–30]. Another interesting observation in the context of ICP is its seasonal variability in some countries. Environmental factors may induce ICP in genetically susceptible patients. According to epidemiological data, ICP is more common in the winter. Seasonal variations in ICP have been assumed to be associated with dietary factors related to low maternal levels of selenium and zinc and high levels of copper [20,28,30].

The main symptom of ICP is pruritus, which typically predominates on the palms and soles of the feet and worsens at night [1,20]. Pruritus often develops after 25 weeks of

gestation, with 80% of cases occurring after the 30th week [3]. Other symptoms of ICP can include steatorrhea, malabsorption of fat-soluble vitamins, and weight loss due to cholestasis [5]. Jaundice has an incidence of 14–25% and may develop 1 to 4 weeks after the onset of pruritus, with dark urine and pale feces in some women [20,31]. The most important biochemical test in the context of ICP is total bile acids concentration, which can be the first, and sometimes only, laboratory abnormality [1,20]. Serum bile acid values may fluctuate and increase with advancing pregnancy; therefore, it is advisable to check it weekly in women with ICP [1]. The levels of serum bile acids also have a prognostic value. According to earlier reports, there is an association between the maternal serum bile acid concentration and the risk of undesired pregnancy outcome (spontaneous and iatrogenic preterm labor, stillbirth, and admission to the neonatal unit) [1,31,32]. Recently, Geenes et al. [32] prospectively analyzed the relationship between the risk of adverse perinatal outcomes, including stillbirth, and non-fasting serum bile acid levels in women with ICP. The most important finding of the study was that the risk of perinatal complications is increased in women with non-fasting serum bile acid levels ≥ 40 $\mu\text{mol/L}$ [32,33]. Therefore, >40 μmol serum bile acids in severe ICP is currently considered to be associated with adverse pregnancy outcomes [1,7,32]. Aminotransferases are usually increased by 2 to 10 times, but may be elevated by up to 20 times; the serum GGT levels are normal or moderately elevated in less than one-third of cases, whereas bilirubin levels rarely exceed 100 $\mu\text{mol/L}$ [3,5,20,33]. ALP is also elevated, but this increase is non-specific due to placental production of the enzyme [5]. PT is often normal, but may be prolonged due to vitamin K malabsorption [3,5]. On abdominal ultrasound, there are no abnormal findings for the liver parenchyma and no dilatation of biliary ducts. Liver biopsy is rarely necessary and is not routinely performed. When performed, histopathology is characterized by intrahepatic cholestasis without parenchymal inflammation [3,5,20]. However, in some cases of uncertain diagnosis, considering liver biopsy is advisable, such as in women with jaundice but without pruritus, symptoms beginning before 20 weeks of gestation, and persistent abnormal laboratory findings beyond 8 weeks after delivery [20,34]. In patients with suspected ICP, other hepatobiliary diseases must be excluded [20].

The goals of ICP treatment are to reduce maternal symptoms, improve laboratory test results, and improve fetal outcome. The first-line therapy for ICP is ursodeoxycholic acid (UDCA) at a dose of 500 mg twice a day or 15 mg/kg per day [20,35]. UDCA is safe in the third trimester because no maternal or fetal adverse effects have been reported regarding the use of this medication in ICP [20]. Other medications, such as cholestyramine and S-adenosyl-methionine, have not had satisfactory results [5,20,36,37]. In women who do not respond to

UDCA, combining rifampicin with UDCA improves their symptoms and laboratory abnormalities [38].

ICP has a high recurrence rate (40–70%) in subsequent pregnancies [1]. Generally, ICP is a benign condition for the mother, and pruritus often disappears in the first days following delivery, with the normalization of laboratory tests (i.e., serum bile acid concentrations and other liver tests). Liver tests and bile acid concentrations controls are recommended 6 to 8 weeks after delivery. If a woman has biochemical liver impairment for more than 3 months postpartum, she should undergo additional clinical investigations to exclude other or co-existing liver diseases [1]. According to recent data, ICP is associated with an increased risk of developing other hepatobiliary diseases, such as hepatitis C, cirrhosis, and gallstones. In addition, patients with underlying chronic liver disease (e.g., hepatitis C or chronic hepatitis of different etiologies) have an increased risk of developing ICP [5,21]. The cause of this effect is not known, but in light of observations of a strong positive association between ICP and hepatitis C both before and after ICP diagnosis, authors advocate testing for hepatitis C in women with ICP [1,5,21].

In contrast to the favorable prognosis for women with ICP, it may be associated with poor perinatal outcome and increased risk of preterm labor, fetal distress, and sudden intrauterine fetal death, which is the most concerning issue. As mentioned above, severe ICP with adverse pregnancy outcome is associated with serum bile acids $>40 \mu\text{mol/L}$ [1,7,39].

In summary, the main clinical symptom of ICP is pruritus, which often develops after 25 weeks of gestation, with most cases occurring after 30 weeks [3]. Serum total bile acids concentration is the most useful biochemical test, as it may be the first and possibly only test result that is abnormal, but the values may fluctuate with advancing pregnancy, making weekly checks advisable in women with ICP [1]. Generally, ICP is a benign condition for the mother, but it may be associated with poor perinatal outcome and increased risk of preterm labor, fetal distress, and sudden intrauterine fetal death. The first-line therapy for ICP is 500 mg UDCA twice a day or 15 mg/kg per day [20].

Acute fatty liver of pregnancy

AFLP is a microvesicular fatty infiltration of hepatocytes that is also known as acute yellow atrophy or acute fatty metamorphosis [1,3]. AFLP is a medical and obstetric emergency because it can be fatal for both the mother and child in the absence of early recognition and appropriate management [1,7]. AFLP is a rare condition, usually occurring in the third trimester, with an approximate incidence of 1: 7000 to 1: 16 000 pregnancies. Rarely, AFLP can occur as early as 22 weeks of

gestation [7,40,41]. Risk factors include multigravidas, pre-eclampsia, multiple gestation, and male fetus and it is possibly more common in women who are underweight [1,7,41].

The pathogenesis of AFLP is not fully understood, but investigations over the past few years suggest that it may result from mitochondrial dysfunction in most cases [5,41]. Some cases of AFLP have a defect in mitochondrial fatty acid oxidation in both the mother and fetus. Two enzymes are involved in mitochondrial fatty acid oxidation, and mutations in these enzymes are thought to be closely associated with AFLP: mitochondrial trifunctional protein and its alpha subunit long-chain 3-hydroxyacyl-CoA-dehydrogenase (LCHAD) [3,42]. Earlier reports demonstrated that mothers of neonates with LCHAD deficiency have a 79% chance of developing AFLP or HELLP syndrome [1,3,41,43,44]. AFLP usually occurs in the third trimester, rarely before the 30th gestational week, but up to 20% of cases present postnatally [1,45]. Clinical presentation is variable and includes non-specific symptoms such as nausea, vomiting, abdominal pain, headache, and malaise. The clinical course can rapidly progress to acute liver failure and its complications, such as encephalopathy, jaundice, and coagulopathy [1,3,7,41,46].

Laboratory tests can show abnormal liver values, including elevated aminotransferase levels (from mild elevation to 1000 IU/L, but usually 300–500 IU/mL) and hyperbilirubinemia (frequently $>5 \text{ mg/dL}$). Often, leukocytosis, normochromic anemia, and thrombocytopenia are present, as well as hypoalbuminemia, elevated uric acid, renal dysfunction, metabolic acidosis, hyperammonemia, and biochemical pancreatitis. Ketonuria and proteinuria can be present. Hypoglycemia is characteristic and predicts a poor prognosis. In severe cases, prolonged PT and reduced fibrinogen levels may be found, whereas disseminated intravascular coagulation (DIC) is seen in approximately 10% of patients with AFLP. A number of women with AFLP have complications, such as ascites, pleural effusions, and acute pancreatitis, or respiratory and renal failure. Infections are common, as well as vaginal bleeding or bleeding from Caesarean section wounds because women with AFLP are extremely susceptible to developing coagulopathies due to impaired synthetic liver function and/or DIC [1–3,7,41,47].

The diagnosis of AFLP is based on clinical and laboratory findings. Microvesicular steatosis on liver biopsy is the criterion standard, but is rarely necessary [7,41]. Imaging may be useful to exclude other disorders (e.g., hepatic infarct or hematoma). On abdominal ultrasonography or computed tomography (CT) there are signs of fat infiltration, and current imaging methods have limited utility in the diagnosis of AFLP. However, further research is needed to determine non-invasive imaging methods that will be acceptable as a part of the standard workup for AFLP in the future [1,5,41]. Fifteen years ago,

Table 1. Proposed Swansea diagnostic criteria for the diagnosis of acute fatty liver of pregnancy [49].

Nausea/vomiting	Leukocytosis ($>11 \times 10^6/L$)
Abdominal pain (mainly epigastric)	Elevation in serum ammonia (>47 mmol/L)
Polydipsia/polyuria	Elevated transaminases (>42 IU/L)
Encephalopathy	Ascites or bright liver on ultrasound
Elevated bilirubin (>14 mmol/L)	Renal failure (creatinine >150 mmol/L)
Hypoglycemia (<4 mmol/L)	Coagulopathy (PT >14 s or APTT >34 s)
Elevated uric acid (>340 mmol/L)	Microvesicular steatosis on biopsy

PT – prothrombin time; APTT – activated partial thromboplastin time.

Ch'ng et al. [48] published a study in which they proposed diagnostic criteria, known as the Swansea criteria, for the diagnosis of AFLP (Table 1). According to these criteria, presence of 6 or more of these features in the absence of other etiologies is suggestive of AFLP [48]. The Swansea criteria have a sensitivity of 100% and specificity of 57%, with positive and negative predictive values of 85% and 100%, respectively, for the diagnosis of AFLP [5,49,50].

The main differential diagnosis is HELLP syndrome due to the great overlap between AFLP and HELLP syndrome. Thus, distinguishing between these 2 disorders is often very difficult, potentially delaying diagnosis [7,17,41]. Early recognition of the disease and delivery of the fetus regardless of gestational age are the keys to successful management, followed by maternal care, which is mainly supportive. There are no reports in the literature of recovery before the delivery of the child. The life-threatening condition associated with AFLP is acute liver failure. Thus, aggressive maternal stabilization in an intensive care setting is necessary, with correction of coagulation, hypoglycemia, and other abnormalities [1–3,5,41]. In some non-randomized reports, the use of plasma exchange (PE), as well as PE in combination with continuous renal replacement therapy (CRRT), following delivery was associated with improved clinical outcomes, including reduced maternal mortality [51–53]. Liver transplantation (LT) has been reported sporadically as a last-chance measure [1,54]. In a retrospective analysis, Westbrook et al. [54] evaluated 54 cases of pregnancy-related liver disease; 18 had AFLP and 32 had hypertension/eclampsia-related disease. The survival rates were 43/48 if not listed for LT and 4/6 if listed. Of the 4 transplanted patients, 3 survived. The study shows the overall favorable prognosis in pregnancy-related liver failure, but also shows that elevated lactate levels in the presence of encephalopathy best identify women at greater risk of morbidity or death or for LT, whereas the King's College criteria were not effective in predicting outcome [54].

Most women recover during the first month after delivery, but cholestasis may persist longer. Histological changes resolve after delivery, but may persist for up to 5 weeks. If there are no signs of pre-existing CLD, recovery is complete. All women and their children should be screened (by molecular testing) for LCHAD mutations, mainly for the most common G1528C mutation [1–3,5,41,55].

In summary, AFLP is a medical and obstetric emergency because it can be fatal for both the mother and child. AFLP is a rare disease and usually occurs in the third trimester [7,40]. Diagnosis is usually reached according to clinical and laboratory findings, exclusion of other liver diseases, and the Swansea diagnostic criteria [1,48]. The main differential diagnosis is HELLP syndrome, but signs of liver failure with coagulopathy, hypoglycemia, and encephalopathy, as well as renal impairment, are more common in women with AFLP [3]. Early recognition of the disease and prompt delivery regardless of gestational age are key to successful management, in addition to aggressive maternal supportive care, mainly in the intensive care unit [1–3,5,41]. In the absence of signs of pre-existing CLD, most women recover completely during the first month after delivery. However, more research is needed to understand the epidemiology of AFLP and evaluate the long-term maternal outcome [41].

Preeclampsia, eclampsia, and HELLP syndrome

According to the international society that studies hypertension during pregnancy, preeclampsia is a multisystem disorder defined by *de novo* hypertension after the 20th week of pregnancy with blood pressure (BP) $\geq 140/90$ mmHg and proteinuria of >300 mg/day in association with other organ dysfunction of the mother, such as renal impairment, liver involvement, neurological or hematological complications, and uteroplacental dysfunction, as well as fetal growth restriction [1,56]. The main feature that distinguishes eclampsia from preeclampsia is the presence of seizures [2].

Table 2. Tennessee HELLP diagnostic criteria [60].

Platelets $\leq 100 \times 10^9/L$
AST ≥ 70 IU/L
LDH ≥ 600 IU/L

AST – aspartate aminotransferase; LDH – Lactate dehydrogenase.

HELLP syndrome is a variant of severe preeclampsia that occurs in up to 12% of patients with preeclampsia, but can also occur in normotensive patients [5,57]. Risk factors for HELLP are advanced maternal age and multiparity [7]. The syndrome is characterized by the presence of hemolysis, elevated liver aminotransferases, and low platelet counts [3]. The disorder can be diagnosed antepartum (in 70% of women between 27 and 30 weeks) or postpartum [7]. In the postpartum period, the HELLP syndrome often develops within the first 48 h, usually in patients who had proteinuria and hypertension prior to delivery [58].

Pathophysiologically, it is assumed that some molecules released from the placental tissue, such as nitric oxide, prostaglandins, and endothelin, can induce platelet aggregation, endothelial dysfunction, and hypertension. Consequently, endothelial injury and fibrin deposition in blood vessels is responsible for the development of microangiopathic hemolytic anemia (schistocytes and Burr cells on smear), with platelet activation and consumption [1,3]. Liver dysfunction is considered to be secondary to fibrin deposition within the hepatic sinusoids, resulting in sinusoidal obstruction, vasospasm of the liver vascular bed, and liver ischemia. This may sometimes lead to large hematomas, capsular tears, and intraperitoneal hemorrhage [1,3,59].

The diagnosis of HELLP syndrome is based mainly on clinical features. Women often present with fluctuating colic-like pain in the upper abdomen, usually epigastric or in the right upper quadrant. In addition, non-specific symptoms such as nausea, vomiting, and malaise are often present. Arterial hypertension and proteinuria are noted in most women. Due to microangiopathic hemolytic anemia, unconjugated bilirubin and LDH are increased, whereas liver enzymes are moderately elevated (ALT 2–30 fold). Low haptoglobin may be used as another parameter for the diagnosis of hemolysis. The presence of schistocytes or Burr cells on smears reflects the development of microangiopathic hemolytic anemia. Furthermore, renal impairment is common. In pregnant women, thrombocytopenia (PLTs $< 150 \times 10^9/L$) can be a consequence of gestational thrombocytopenia (59%), immune thrombocytopenic purpura (11%), preeclampsia (10%), or HELLP syndrome. In addition, $< 100 \times 10^9$ PLTs/L is relatively rare in preeclampsia and gestational thrombocytopenia, but is frequent in immune

Table 3. Mississippi HELLP diagnostic criteria [60].

HELLP class	Criteria
I	Platelets $\leq 50 \times 10^9/L$ AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
II	Platelets $\leq 100 \times 10^9/L$, $\geq 50 \times 10^9/L$ AST or ALT ≥ 70 IU/L LDH ≥ 600 IU/L
III	Platelets $\leq 150 \times 10^9/L$, $\geq 100 \times 10^9/L$ AST or ALT ≥ 40 IU/L LDH ≥ 600 IU/L

HELLP – hemolysis, elevated liver function tests, and low platelet counts; AST – aspartate aminotransferase; ALT – alanine aminotransferase; LDH – lactate dehydrogenase.

thrombocytopenic purpura and obligatory in HELLP syndrome. In severe cases, DIK may occur with evidence of elevated fibrin degradation products, low fibrinogen, and an increased PT [1–3,5,58,60,61]. According to the literature, there are 2 classifications of HELLP syndrome: the Tennessee (Table 2) and Mississippi classifications, which classifies the disorder by PLT values (Table 3) [60]. In the Mississippi classification system, class 3 HELLP syndrome is considered to be a clinically significant transition phase of HELLP syndrome, which has the ability to progress [58,60].

Abdominal imaging methods, such as ultrasonography, CT, and MRI, should be performed in all women with HELLP syndrome in order to investigate liver complications, such as liver infarction, intraparenchymal hemorrhage, subcapsular hematoma, and hepatic rupture [1,3,62]. In cases in which liver biopsy was performed, histological changes in the liver in HELLP syndrome include periportal changes with hemorrhage, sinusoidal fibrin deposition, and hepatocyte necrosis [1,63].

As mentioned above, HELLP syndrome and AFLP share similar presentations. The differential diagnosis among AFLP and HELLP syndrome is shown in Table 4 [1,5]. In addition, HELLP syndrome must be distinguished from other rare, but life-threatening, diseases such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome [3,58].

After HELLP develops, the only definitive treatment is delivery of the fetus and stabilizing the maternal clinical condition. Steroids should be given only for fetal lung maturity, but their use is unclear and remains controversial [57,58,64,65]. In a recent meta-analysis, Mao et al. [64] investigated the efficacy of corticosteroid therapy in patients with HELLP syndrome, reporting that treatment with corticosteroids significantly improved the PLT count, LDH levels, and ALT levels, but the decrease in AST levels was not significant. Corticosteroid treatment was

Table 4. The differential diagnosis among AFLP and HELLP syndrome [1,5,41].

	HELLP	AFLP
Prevalence	0.10%	0.01%
Timing of occurrence	Late second trimester to early postpartum	Third trimester
Clinical findings	Abdominal pain, nausea/vomiting, overlap with findings in preeclampsia – often hypertension and proteinuria	Abdominal pain, nausea/vomiting, hypoglycemia, signs of more significant liver disease and possibly liver failure, ascites
Laboratory findings	Increased ALT, up to 2–30-fold; total bilirubin, up to 1.5–10-fold; Decreased platelets in all; LDH ≥ 600 IU/mL; renal impairment; PT may remain normal, normal fibrinogen	Increased ALT, up to 3–15-fold; total bilirubin, up to 3–15-fold; not necessarily associated with low platelets; Leukocytosis, decreased serum glucose concentration, renal impairment, decreased antithrombin III, prolonged PT, low fibrinogen, DIC
Management	Rapid delivery	Rapid delivery, plasmapheresis, liver transplantation

HELLP – hemolysis, elevated liver function tests, and low platelet counts; AFLP – acute fatty liver of pregnancy; ALT – alanine aminotransferase; LDH – lactate dehydrogenase; PT – prothrombin time; DIC – disseminated intravascular coagulation.

also associated with a significantly lower blood transfusion rate and shorter hospital/intensive care unit stay [64].

After delivery, the mother should continue to be closely monitored. The PLT counts and other laboratory abnormalities often return to normal levels within 2 weeks of delivery [2]. The prognosis of maternal mortality is approximately 1.1%, but higher maternal mortality of up to 25% has been reported. The rate of maternal mortality in hepatic rupture ranges from 18% to 86% [58,66–68]. The perinatal mortality rate related to HELLP syndrome is between 7.4% and 34% [58,69–71]. Complications, such as prematurity or placental insufficiency, with or without intrauterine growth restriction and placental abruption, are the main causes of neonatal death. Hepatic rupture has a perinatal mortality rate of up to 80% [58,72–75].

In summary, HELLP syndrome is a variant of severe preeclampsia that occurs in up to 12% of patients with preeclampsia, and 10–20% of cases are normotensive patients [5,57]. HELLP syndrome is defined by the presence of hemolysis, elevated liver aminotransferases, and low PLT counts [3]. This disorder is primarily diagnosed antepartum (between 27 and 30 weeks in 70% of women), but is diagnosed postpartum in approximately 30% of cases [7]. Diagnosis is based mainly on clinical features and laboratory findings. The differential diagnosis among AFLP and HELLP syndrome is the main diagnostic challenge, but HELLP syndrome must also be distinguished from some other rare, but life-threatening diseases, such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Thus, once HELLP develops, the only definitive treatment is delivery of the fetus and stabilization of the maternal clinical condition. Laboratory abnormalities often return to normal levels within 2 weeks of delivery [2,3,58].

Pre-Existing Liver Diseases and Pregnancy

Cirrhosis and portal hypertension

Pregnancy is relatively rare in women with liver cirrhosis. When pregnancy occurs, the risk of spontaneous abortion, prematurity, and perinatal death are very high. However, with advancements in the medical field, pregnancy is not contraindicated in these women, as previously believed [3,4,7]. The outcome of pregnancy is related to the severity of the maternal liver disease. The model for end-stage liver disease (MELD) has been shown to be a good model for predicting the risk of decompensation of maternal liver disease during pregnancy [1]. A few years ago, Westbrook et al. [76] showed that a pre-conceptional MELD score ≥ 10 had 83% sensitivity and specificity for predicting liver decompensation during pregnancy [1,76].

In pregnant women with cirrhosis, the most common and most serious complication is variceal bleeding. Due to worsening of portal hypertension (PH) because of increased circulating blood volume and direct pressure of the gravid uterus on the inferior vena cava, impairing venous return, variceal bleeding occurs mainly during the second trimester and the in the second stage of labor [1,3,75–80]. Therefore, active management of varices is essential before and during pregnancy [80].

Upper gastrointestinal (GI) bleeding from varices has high mortality and morbidity rates in women with pre-existing cirrhosis and PH because it is often complicated by liver decompensation with worsening synthetic, metabolic, and excretory function of the liver, manifesting as jaundice, hepatic encephalopathy, coagulopathy, and ascites [1,3]. In contrast to women with PH due to liver cirrhosis, women with non-cirrhotic PH usually have preserved synthetic liver function and

the reproductive system is rarely affected. Although the incidence of variceal upper GI bleeding in these women is similar to the incidence in women with cirrhosis, the overall prognosis is significantly better [1,77,78]. For women with varices that lack “high-risk stigmata”, prophylaxis with beta-blockers (propranolol or nadolol) should be initiated [1,7]. In contrast, spironolactone should be discontinued [1,3,7,77]. In women who did not have an upper GI endoscopy prior to pregnancy and those with no varices before pregnancy, upper GI endoscopy should be performed during the second trimester for the reasons mentioned above [1,7].

In women with an episode of an acute variceal bleeding during pregnancy, treatment should be focused on the resuscitation and hemodynamic stabilization of the mother, antibiotic prophylaxis, and endoscopic therapy. The preferable endoscopic method for bleeding esophageal varices is endoscopic variceal band ligation [1,3]. Although sclerotherapy is avoided in most centers due to the risk of injecting sclerotherapeutic chemicals, there have been reports of successful hemostasis with sclerotherapy [1,3,79]. The use of vasopressin is not recommended during pregnancy and the use of octreotide is controversial [3,7,80]. The insertion of a transjugular intrahepatic portosystemic shunt has been reported as emergency salvage therapy when endoscopic techniques fail to control variceal bleeding [1,81].

Chronic hepatitis B and C in pregnancy

All pregnant women should be screened for hepatitis B virus (HBV) early in pregnancy [1,7,81–83]. According to recent EASL recommendations, for a woman of child-bearing age without advanced fibrosis and cirrhosis who plans a pregnancy in the near future, it may be prudent to delay therapy until the child is born [82]. In contrast, for pregnant women with chronic HBV infection and advanced fibrosis or cirrhosis, therapy with nucleoside analogs (NAs) is recommended, specifically tenofovir disoproxil fumarate (TDF) [82].

Vertical infection of infants born to hepatitis B surface antigen (HBsAg)-positive mothers is associated with a higher risk of chronic infection, and the main risk factors for vertical transmission are the presence of HBe antigen and the maternal viral load. Therefore, vaccination and anti-HBs immunoglobulin should be administered to all newborns from HBV-positive mothers within 12–24 h after delivery. However, some newborns will develop HBV infection despite adequate prophylaxis. The risk of immunoprophylaxis failure increases with increased maternal viral load [1,3,7,82–84]. Immunoprophylaxis failure occurs almost exclusively in HBeAg-positive women with high HBV DNA levels ($>200\,000$ IU/mL) and/or HBsAg >4.5 log₁₀ IU/mL [82]. Therefore, NA therapy is suggested during the third trimester of pregnancy to prevent vertical HBV transmission [1,82].

Pegylated interferon (PEG-IFN) is contraindicated during pregnancy. When treatment is indicated, the literature and recent EASL recommendations propose TDF as the first-line NA in pregnancy. Safety data is available for 2 other NAs during pregnancy – lamivudine and telbivudine [1,3,7,82,85,86] – but TDF is the preferable NA because it has a better resistance profile and more extensive safety data in pregnant HBV-positive women [82]. In women who do not need long-term therapy, NA therapy should be discontinued at 1–3 months postpartum, but these women should be monitored up to 6 months postpartum because of the risk of HBV flare-up upon withdrawal of antiviral therapy [1,84]. The safety of continuing treatment during breast-feeding is uncertain [1,7,82].

The prevalence of anti-hepatitis C virus (HCV) positivity among pregnant women in Europe is 1.7–2.5% [7,87,88]. Pregnancy does not seem to modify the natural course of HCV disease, and does not worsen maternal liver disease or other adverse complications in the mother and child [7]. Although chronic HCV infection is thought to rarely influence the course of pregnancy [7,89,90,91], a meta-analysis by Huang et al. [90] found that maternal HCV infection is significantly associated with an increased risk of preterm birth. Therefore, further studies on this topic are needed. Vertical transmission via the mother's HCV RNA is actually low, occurring in approximately 3–5% of cases [1,3,92].

Autoimmune liver disease during pregnancy

In the setting of autoimmune hepatitis (AIH), the maternal course is highly variable and depends on the timing of the pregnancy and preconception preparation of the mother. Westbrook et al. [93] analyzed 81 pregnancies in 53 women, with 41% of pregnancies occurring in the context of cirrhosis. The live birth rate (LBR) was 73%. In cases in which the mother had cirrhosis at the time of conception, the LBR rate was lower, with higher incidence of admissions to the neonatal intensive care unit. Disease activity flared up in 33% of pregnancies [1,93].

Generally, and in accordance with earlier observations, if a pregnancy occurs during an acute episode of AIH, the mother's liver disease may have a fulminant course with a small chance of the baby's survival. On the other hand, for the women who are in remission from AIH and do not have cirrhosis of the liver and PH, the outcome of the pregnancy may be favorable [1,7,94,95]. If women have poor disease control in the year before pregnancy and lack of drug therapy, the risk of poor outcome is high. The most common complication of AIH during pregnancy is a flare-up of autoimmune disease, which happens more frequently after delivery (11–81% of cases) [1,96]. The use of azathioprine during pregnancy and lactation is thought to be safe [1,7,94,95].

Liver transplantation and pregnancy

Long-term survival following LT is expected in the majority of patients. Following LT, fertility is restored in most women with a liver transplant, especially after the first year [1]. The first case of successful pregnancy in a patient with transplanted liver was described by Walcott et al. [1,97] in 1978. Subsequently, there were several publications on pregnancy in transplanted liver patients [1,98–100]. The most important issues in this context are maternal and graft risk, optimal immunosuppression, and fetal outcomes [1,98].

According to a recently published study [98], 117 conceptions were achieved in 79 women with liver transplant (median patient age 29 years). Maternal adverse effects were preeclampsia/eclampsia (15%), acute cellular rejection (ACR; 15%), gestational diabetes (7%), graft loss (2%), and bacterial sepsis (5%). Remarkably, more cases of ACR were observed in women who became pregnant within 12 months after LT. The LBR was 73%. In addition, the authors reported that 24 (29%) of the neonates had low birth weight, and prematurity occurred in 26 (31%) cases. They reported that the choice of immunosuppressive therapy (cyclosporine vs. tacrolimus) had no significant influence on adverse effects and pregnancy outcomes [98]. Therefore, according to the literature, the incidence of ACR can be reduced by delaying pregnancy for 1 or 2 years following LT in order to achieve stable immunosuppressive therapy and ensure that the transplanted organ is functioning well [1,98].

LT patients require life-long immunosuppression, and it should be continued throughout pregnancy. Drugs that can generally be used safely during pregnancy are steroids, azathioprine, and the calcineurin inhibitor (CNI) tacrolimus. On the other hand, the use of mycophenolate during pregnancy is not recommended. Moreover, mycophenolate should be discontinued 6 months before conception [1]. Thus, pregnant women with LT should be closely and regularly monitored by a multidisciplinary

team consisting of hepatologists, doctors specializing in transplantation medicine, and obstetricians.

Conclusions

Liver disease during pregnancy is a poorly studied topic and poses a challenge for both the gynecologist and hepatologist. Challenges involve diagnosis and determining the appropriate treatment for the safety of both mother and baby. Liver disease in pregnancy is a complex issue that deserves a multidisciplinary approach. Nearly 3% of pregnancies are complicated by liver disease, and severe pregnancy-related liver disease can have fatal consequences for the both mother and child. Diagnostic and therapeutic decisions must consider the implications for both, and rapid diagnosis is indispensable for severe cases because the decision of immediate delivery is important for maternal and fetal outcomes [1–3,5]. In pregnant women with suspected liver disease, it is essential to distinguish between the 2 main categories of liver disease: non-pregnancy-related liver disease and the few diseases that are directly related to pregnancy. Pregnancy-related liver disease is the most frequent cause of liver dysfunction during pregnancy. We also need to keep in mind that pregnancy is associated with many normal physiological changes that should be considered in the diagnosis of liver disease [1–3]. Pregnancy-related liver disorders exhibit trimester-specific characteristics in their occurrence, whereas non-pregnancy-related liver diseases can occur at any time [3]. The timing of clinical manifestations and liver test result abnormalities can be critical for determining the diagnosis and treatment strategies [1,3,7]. More research is needed to understand the epidemiology of pregnancy-related liver disease and to evaluate the long-term maternal outcome [41].

Conflict of interest

None.

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