The Pathogenesis of Liver Diseases in Pregnancy

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Key Points

- Liver diseases in pregnancy can include acute fatty liver of pregnancy (AFLP); hyperemesis gravidarum; hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; severe eclampsia; and hepatic cholestasis of pregnancy.
- Acute fatty liver of pregnancy is a serious disease, with current mortality rates still as high as 5%.
- While hyperemesis gravidarum usually occurs early in pregnancy, the others occur in the later trimesters.
- The pathogenesis of AFLP may be defect in fatty acid metabolism, such as a deficiency of long-chain 3-hydroxyl acyl CoA dehydrogenase (LCHAD).
- The pathogenesis of HELLP may be similar to that of severe preeclampsia and may involve a microangiopathy and activation of the coagulation system, but other factors such as complement, fatty acid metabolism, and the renin-angiotensin system may play a role.
- The pathogenesis of hyperemesis gravidarum is unknown but is probably multifactorial, with genetic, environmental, and epigenetic factors involved.
- The incidence of intrahepatic cholestasis of pregnancy varies widely, suggesting a genetic component to the pathogenesis, although estrogen levels may play a role as well.

Introduction

Pregnancy is a normal physiologic process. However, pregnancy is associated with changes in multiple organ systems in order to adapt to a growing fetus. Physiologic changes resulting from pregnancy are shown in Table 33.1. In addition to changes in vascular circulation and flow, the state of pregnancy also affects the gastrointestinal, cardiovascular, and respiratory systems. But changes also occur in other systems, including the skin and musculoskeletal, neurological, and psychological systems. Changes in lipid metabolism [1, 2] and liver enzymes [3] also occur although structurally the liver is unchanged [4].

New-onset liver disease can present during pregnancy, while patients with preexisting liver disease may experience an increase or exacerbation of their disease [5, 6]. The commonly recognized liver diseases that are associated with pregnancy include acute fatty liver of pregnancy (AFLP); hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; hyperemesis gravidarum; intrahepatic cholestasis of pregnancy; preeclampsia/eclampsia; and pregnancy-related hemolytic-uremic syndrome (HUS) [5, 7–10]. There is some

Table 33.1 Physiologic and immunologic status related to the liver during pregnancy

Liver
Normal liver structure
Gall bladder
Normal biliary tract
Increased fasting and residual gallbladder volume
Serum chemistries and liver function
Reduced serum albumin beginning in first trimester (resulting from hemodilution)
Increased serum cholesterol
Increased serum triglycerides
Increased alkaline phosphatase levels
Reduced gamma-glutamyl transpeptidase
Slightly increased ALT levels in serum
Unchanged AST levels in serum
Reduced total and free bilirubin levels

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evidence that HELLP may be merely a more severe form of preeclampsia, in which case the two conditions may share a common pathogenesis. However, our knowledge of the pathogenesis of most of these conditions is far from complete.

Physiologic Changes in the Liver During Pregnancy

Any liver disease that occurs in pregnancy must be assessed in the context of normal physiologic changes that occur in the liver and other organs or systemically during pregnancy. For example, spider angiomas and palmar erythema are two skin changes that can occur in liver diseases but are also found in higher frequency during normal pregnancy. On the other hand, there has been no evidence that there are histological or structural changes within the liver during pregnancy [4]. On physical examination, the liver is pushed upward by the uterus; therefore, if the liver is palpable on examination, then this is considered to be abnormal. Biochemical changes can also occur during pregnancy; hemodilution can cause a reduced albumin level [3], but cholesterol and triglycerides are significantly increased [1, 2].

Liver enzymes may also change during normal pregnancy [3]. Alkaline phosphatase levels are usually at least twice that of normal. Serum alanine aminotransferase (ALT) is slightly elevated but not serum aspartate aminotransferase (AST). Serum gamma glutamyl transferase levels decrease during pregnancy, accompanied by increased 5'nucleotidase levels. Overall, indirect and direct bilirubin levels tend to trend lower during pregnancy.

The clinical presentation of hepatobiliary disease includes nausea, vomiting, abdominal pain, jaundice, malaise, and pruritus. When there is jaundice, such as in intrahepatic cholestasis of pregnancy, the itch can be very severe and debilitating. Unfortunately, itching can be very difficult to treat. The correct diagnosis of liver diseases that occur during pregnancy depends on timing [11], as some, such as hyperemesis gravidarum, are more frequently seen early, as in the first trimester, whereas others, such as intrahepatic cholestasis of pregnancy, occur more often in late pregnancy. Acute fatty liver of pregnancy and HELLP usually occur late in the second or in the third trimester, but earlier onset has been reported [11]. A comparison of the different liver diseases seen in pregnancy is shown in Table 33.2.

Table 33.2 Comparison of the different liver diseases seen in pregnancy

Parameter	AFLP	Hyperemesis gravidarum	HELLP	Intrahepatic cholestasis	Preeclampsia with severe features (liver involvement)
Incidence	1 in 7000–20,000 pregnancies	Approximately 1 in 300 pregnancies	0.1–1% of pregnant women, 1–2% of preeclampsia	0.32–5.6% in the United States, 0.5–1.5% in Europe, 27.6% in Araucanos Indians in Chile	1% of all pregnancies
Trimester	Third	First	Late second to third	Late second to third	Late second to third
Presentation	Nausea, vomiting, abdominal pain, malaise, headache, anorexia, hypertension, jaundice, ascites, encephalopathy, DIC	Vomiting persistent enough to lead to a 5% weight loss	Abdominal pain, nausea, vomiting, malaise	Pruritus, right upper quadrant pain, nausea, poor sleep, reduced appetite	Hypertension, proteinuria, end-organ dysfunction, headache, may have pulmonary edema, renal insufficiency
Laboratory findings	Elevated ALT; AST usually below 500 μ/l; elevated WBC; decreased platelets; elevated uric acid, creatinine, and ammonia; decreased glucose, fibrinogen, and antithrombin levels; increased APTT, PT; burr cells on peripheral smear; proteinuria	Ketonuria, elevated ALT, less elevated AST, usually both below 1000 μ/l	Elevated AST, platelets less than 100,000/mm^3, elevated LDH, Total bilirubin greater than 1.2 mg/dl, elevated uric acid	Elevated ALT, AST, elevated total bilirubin (usually less than 6 mg/dl), direct bilirubin, elevated serum bile acids	ALT, AST greater than 2 times normal range, platelets less than 100,000/mm^3, elevated uric acid, increased serum creatinine, protein/creatinine ration in urine is increased
Defined criteria	Swansea criteria	No	Yes	No	Yes (ACOG)

Table 33.2 (continued)

Parameter	AFLP	Hyperemesis gravidarum	HELLP	Intrahepatic cholestasis	Preeclampsia with severe features (liver involvement)
Mortality	Decreased from 75% to less than 5% over past decades	Never	Variable	Rare (though prematurity and stillbirth have been reported)	1 per 100,000 live births, case-fatality rate of 6.4 deaths per 100,000, liver involvement present in 10–15% of maternal deaths associated with preeclampsia
Pathogenesis	20% associated with LCHAD deficiency, presumed defective fetoplacental fatty acid metabolism		Unclear, thrombotic microangiopathy, complement dysregulation, LCHAD deficiency	Unknown, possibly related to estrogen and progesterone metabolism (reduced 5-alpha and 3-alpha progesterone and saturation of liver transport system)	Poor placental perfusion, shallow placentation, failure to remodel spiral arteries of decidua and myometrium, antiangiogenic factors such as sFLT-1, endoglin
Predominant gender of fetus	Male	Female	N/A		N/A
Risk factors	Fetal LCHAD deficiency, multiple gestation, previous AFLP, low BMI (less than 20 kg/m^2), preeclampsia or HELLP, male fetus	Young maternal age, primigravida, female fetus	Previous history of preeclampsia or HELLP	History of liver disease, in vitro fertilization, multiple pregnancy, personal or family history of IHC	Risk factors or preeclampsia: past history of preeclampsia, multiple gestation, primigravida, family history of preeclampsia, advanced maternal age, prior pregnancy associated with placental insufficiency, existing medical conditions including pregestational diabetes, chronic hypertension, SLE, APS, prepregnancy BMI greater than 25 kg/m^2, chronic kidney disease
Treatment	Delivery of the fetus		Delivery of the fetus, antihypertensive therapy, magnesium sulfate, steroids	UDCA, S-adenosyl-methionine, cholestyramine, rifampin, hydroxyzine or steroids	Delivery of the fetus, antihypertensive therapy

AFLP acute fatty liver in pregnancy; *APTT* activated partial thromboplastin time; *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *BMI* body mass index; *DIC* disseminated intravascular coagulation; *HELLP* hemolysis, elevated liver enzymes, and low platelet count; *IHC* intrahepatic cholestasis of pregnancy; *LCHAD* long-chain 3-hydroxyl CoA dehydrogenase; *PT* prothrombin time; *UDCA* ursodeoxycholic acid

Liver Diseases Unique to Pregnancy

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) is estimated to occur in about 1 in every 7000–20,000 pregnancies [12–15]. It is a severe illness, and while mortality rates have decreased significantly with improved recognition and care, it is still a potentially fatal condition. Mortality rates for the mother and child used to be up to 75% and 85%, respectively. This has dropped to a still significant 18% and 23%, respectively, and some reports suggest that with improved care, the mortality rates have now dropped to 5%. AFLP usually presents in the third trimester. The symptoms include nausea and vomiting, abdominal pain, tiredness, loss of appetite, and headache. Patients may suffer from hypertension, but this is more common in HELLP. Risk factors include a history of AFLP in previous pregnancies, a history of HELLP, low body mass index, and multiple gestation [16, 17]. In contrast to hyperemesis gravidarum, it is more common in those with male fetuses.

AFLP can be confused with HELLP. One differentiating factor is the fibrinogen level, wherein a fibrinogen level greater than 300 mg/dl is more common in patients with AFLP. Other biomarkers that can differentiate AFLP from HELLP include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low blood sugar, and abnormally high creatinine levels. The Swansea criteria were introduced and validated in the United Kingdom for the diagnosis of AFLP. In a small study of women who underwent liver biopsies, positive and negative predictive values were established at 85% and 100%, respectively [18].

Table 33.3 Swansea criteria for the diagnosis of AFLP

Clinical criteria
Abdominal pain
Encephalopathy
Polydipsia or polyuria
Vomiting
Laboratory criteria
Acute kidney injury with creatinine over 1.7 mg/dl
Elevated ammonia greater than 47 μmol/l
Elevated bilirubin over 0.8 mg/dl
Elevated transaminases over 42 IU/l
Elevated uric acid greater than 5.7 mg/dl
Hypoglycemia less than 72 mg/dl
Leukocytosis over 11,000 cells/μl
Prothrombin time greater than 14 s or other evidence of coagulopathy
Imaging
Ascites or bright liver diagnosed by ultrasound
Biopsy
Microvesicular steatosis determined by liver biopsy

Any six of the above criteria are required to make the diagnosis of AFLP

The criteria are shown in Table 33.3. Six of the fourteen criteria in the absence of an alternative cause of liver disease must be present to make the diagnosis of AFLP [19].

AFLP can be more dangerous than HELLP, in that AFLP can progress to liver failure, severe hypoglycemia, and encephalopathy. One study reported that in 46 patients with liver failure or imminent liver failure, 70% had AFLP and 15% had HELLP [20].

Pathogenesis

The pathogenesis of AFLP is unknown. It has been postulated that it may be related to an abnormality in fetal fatty acid metabolism. In the latter stages of pregnancy, there is an increase in free fatty acids. This is necessary to support fetoplacental growth. Women with an inherent defect in fatty acid metabolism, such as a deficiency of long-chain 3-hydroxyl acyl CoA dehydrogenase (LCHAD) [21], are not able to keep up with the metabolism of the increased fatty acid burden and fatty acids accumulate in hepatocytes, leading to cellular damage [22].

LCHAD catalyzes the conversion of 3-hydroxyacyl-CoA to 3-ketoacyl-CoA. If a fetus is homozygous for a pathogenic variation in LCHAD, then the fetoplacental unit is incapable of the beta-oxidation of mitochondrial fatty acids, and intermediate products are released into the maternal circulation. Since the mother is heterozygous for a pathogenic variant, she is unable to metabolize long-chain fatty acids and this leads to maternal liver dysfunction, which then causes a coagulopathy, along with electrolyte imbalances and eventually multi-organ failure.

It is estimated that LCHAD deficiency is responsible for up to 20% of AFLP [13, 14]. The most common pathogenic mutation is G1528C, p.Glu474Gln. Though not as frequently seen as LCHAD, deficiencies in short-chain acyl-CoA dehydrogenase [23], medium-chain acyl-CoA dehydrogenase [24], and carnitine palmitoyltransferase [25] can also lead to AFLP.

The role of the placenta in the pathogenesis of AFLP cannot be discounted. An animal model was developed to study AFLP. Microvesicular steatosis was induced using sodium valproate, and this led to structural alterations in the mitochondria and evidence of oxidative stress in organelles of the liver. These changes were also seen in the placenta of patients with AFLP [26].

HELLP Syndrome

HELLP is an acronym for hemolysis, elevated liver enzymes, and low platelet, a syndrome that occurs during pregnancy. The term was first coined in 1982 by Louis Weinstein following a review of 29 patients with common complications of pregnancy [27]. The pathophysiology of HELLP syndrome is unknown. HELLP is sometimes thought of as a more severe form of preeclampsia, although it has not been definitively determined that these two conditions are related. There are observations seen in preeclampsia, such as a higher incidence with nulliparity, which are not seen in HELLP [28]. HELLP patients have more inflammation of the liver and abnormalities in coagulation than patients with preeclampsia [29–31]. The incidence of HELLP is between 0.1% and 1.0% of pregnancies [32]. Risk factors include a history of preeclampsia or HELLP during a previous pregnancy. Complications of HELLP include liver hemorrhage in the mother and prematurity in the fetus.

Criteria for the Diagnosis of HELLP Syndrome

Criteria for diagnosing HELLP are shown in Table 33.4. There are two sets of criteria, the Mississippi and the Tennessee criteria. In addition to a peripheral smear demonstrating evidence of hemolysis, such as schistocytes and burr cells, there should also be anemia, increased serum bilirubin, and low haptoglobin. To satisfy the features of thrombocytopenia and liver disease, the platelet count should be less than 100,000 cells per microliter and the AST or ALT two times more than the normal. Other biomarkers include an elevated lactate dehydrogenase (LDH).

The differential diagnosis of HELLP includes AFLP, thrombotic thrombocytopenic purpura (TTP), and pregnancy-related atypical hemolytic-uremic syndrome (HUS). How to distinguish HELLP from AFLP was already discussed in the

Table 33.4 Criteria for the diagnosis of HELLP

Criteria for the diagnosis of HELLP (Tennessee) [32]		
Hemolysis	Elevated liver enzymes	Low platelets
At least two of the following	*And*	*And*
Severe anemia	AST or ALT must be at least 200% of upper limits of normal	Less than 100,000 platelets per microliter
Serum bilirubin greater than or equal to 1.2 mg/dl		
Peripheral smear showing burr cells and schistocytes		
Low serum haptoglobin (less than 25 mg/dl) or elevated lactate dehydrogenase (greater than twice upper limits of normal		

Criteria for the diagnosis of HELLP (Mississippi) [130]			
Class	Liver enzymes	LDH	Platelets[a]
1	AST or ALT greater than or equal to 70 IU/ml	Greater than or equal to 600 IU/ml	Less than 50,000 platelets per microliter
2	AST or ALT greater than or equal to 70 IU/ml	Greater than 600 IU/ml	Platelet count less than or equal to 100,000 and greater than 50,000 per microliter
3	AST or ALT greater than or equal to 40 IU/ml	Greater than 600 IU/ml	Platelet count less than or equal to 150,000 or greater than 100,000 per microliter

[a]Platelet count is the nadir during the course of the disease

section above. TTP can also present with elevated LDH, but transaminases are generally normal. Clotting parameters are more likely to be prolonged in HELLP compared with TTP, where only platelet counts are decreased. TTP also tends to occur earlier in pregnancy than HELLP, predominantly in the second trimester compared with the third trimester for HELLP. Pregnancy-related atypical HUS usually presents with a higher incidence of renal disease. The renal disease is often severe enough to lead to dialysis, whereas liver involvement in Pregnancy-related HUS is generally absent to mild. The distinction between preeclampsia, pregnancy-related HUS, and HELLP is not always clear.

A case of transfusion-related acute lung injury (TRALI) has been reported after a Caesarean section in a patient with HELLP [33].

Histology in HELLP Syndrome

Pathologic changes of the placenta in HELLP syndrome have been studied, comparing the normal placenta with the placenta in patients with preeclampsia with and without HELLP. In one study, the preeclampsia patients with HELLP syndrome tended to have higher placental weights than those without HELLP [34], but this was not confirmed in another study [35]. Small-sized villi with increased syncytial knotting may occur, which may be indicative of poor placental perfusion [36]. Additional changes in the placenta are discussed in the next section.

Pathogenesis of HELLP

HELLP may represent more than one disease that may have varying pathogenetic mechanisms. For example, there is a small number of HELLP patients with a fetal long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, similar to AFLP [21]. Two series of 6 and 19 cases found that 100% and 79% of pregnancies in which there was a deficiency of LCHAD developed HELLP, respectively [22, 37].

The pathogenesis of most cases of HELLP is thought to be related to a microangiopathy and activation of the intravascular coagulation pathway. The pathological changes include vascular spasms, platelet aggregation, vascular endothelial damage, platelet consumption, deposition of fibrin, and ultimately, end-organ ischemia and failure.

Complement may play a role in pathogenesis of HELLP. The activation of complement may be triggered by an immunological rejection of the fetus by the mother. This loss of tolerance leads to activation of complement and the release of C3a, C5a, and the later components of the complement cascade. Complement has many functions in the human immune system, but those relevant to HELLP may include stimulation of macrophages and leukocytes leading to the release of vasoactive substances, ultimately causing those pathological changes noted in the mentioned previously. This leads to the clinical manifestations including thrombocytopenia, hemolysis, and liver enzyme elevation [38–40]. Complement activation appears to be involved in the pathogenesis of preeclampsia and spontaneous abortion in women with systemic lupus erythematosus or positive antiphospholipid antibodies. This study utilized the PROMISSE database of 250 pregnant patients with lupus or positive antiphospholipid antibodies to demonstrate mutations in three complement regulator proteins (complement factors H and I and membrane cofactor protein (MCP)) [41]. In a case report, a woman with severe HELLP that developed relatively early in pregnancy was treated with eculizumab, a monoclonal antibody directed against C5, and displayed significant clinical improvement and resolution of laboratory abnormalities. The period of remission lasted 16 days, but then the symptoms of HELLP recurred [42].

Other factors that may play a role in the pathogenesis of HELLP include the renin-angiotensin system. Elevated angiotensin II levels are known to play a role in hypertension and renal disease [43]. Agonistic autoantibodies to the type 1 angiotensin II receptor leads to their activation, which can potentially lead to regulation of the activity of intracellular Protein Kinase C, leading to angiotensin II-induced vascular

abnormalities. It has also been shown that the renin-angiotensin system plays a role in hepatic fibrosis and chronic liver disease. Inhibitors of this pathway have been shown to reduce fibrosis scores compared to controls [40]. Also reduced were the serum fibrosis markers including TGF-β1, collagen I and IV, TIMP-1, and MMP2. In other studies, investigators noticed an improvement in mean arterial pressures in patients treated with renin-angiotensin system inhibitors compared with controls.

Some authors have suggested that HELLP syndrome originates as a result of placental ischemia which may either cause or result from aberrant placental development and abnormal function. It has been proposed that liver ischemia causes release of mediators that leads to endothelial damage including vasoconstrictive agents. Platelet activation ensues [44]. Which involves remodeling of the placental arteries and defective placentation, placental infarction and abruption [34].

Hyperemesis Gravidarum

Hyperemesis gravidarum is a pregnancy-related condition that is characterized by excessive nausea and vomiting, weight loss, and dehydration. It usually occurs in the earlier phases of pregnancy and usually resolves by about the 20th week of pregnancy but in some cases may persist throughout pregnancy. It is fairly common, occurring in about 1 in every 300 pregnancies. Risk factors include young age of the mother, primigravida, and multiple pregnancy. It is also associated with elevated serum aminotransferase and bilirubin levels. Given that nausea and vomiting are so common in the early stages of pregnancy (up to 90% incidence) and are part of normal expected changes in physiology, the name hyperemesis gravidarum must be applied only to those patients on the extreme end of the symptom spectrum. In many cases, hyperemesis gravidarum affects quality of life, leading to direct and indirect work performance issues.

The risk factors associated with hyperemesis gravidarum are unclear [45–47]. There may be a genetic risk, based on the increased occurrence in family members and on twin studies [48–55]. One of the most intriguing observations is that hyperemesis occurs significantly more frequently with female fetuses, with an odds ratio of 1.27, 95% CI 1.21–1.34 [56]. The things that you should never do during pregnancy, including drinking alcohol and cigarette smoking, are ironically associated with a lower risk of hyperemesis gravidarum [47].

In addition to symptoms of nausea and vomiting, patients with hyperemesis gravidarum also may present with elevated liver enzymes. In one study, this occurred in about half of the patients admitted for hyperemesis [57]. The ALT elevation is generally higher than that of AST. The levels typically do not go over 1000 units/l. The total bilirubin level may also be elevated but generally it is mild [58].

Many of the patients with hyperemesis also have elevated thyroid levels, which has been blamed on the higher activity of human chorionic gonadotropin and its ability to stimulate the thyroid gland [59]. Other laboratory findings in hyperemesis gravidarum include elevated serum amylase and lipase [60], decreased magnesium and calcium levels, electrolyte derangements, and elevated hematocrit; the latter are due to persistent vomiting and hypovolemia, respectively [61]. In cases where liver biopsies were done to exclude other liver diseases, findings were either normal or showed nonspecific findings including a lack of inflammation but with areas of necrosis and central vacuolization [58, 62].

Pathogenesis of Hyperemesis Gravidarum

The mechanisms by which nausea and vomiting occur in pregnancy is unknown. Hormones such as estrogen and progesterone have been implicated, but there is no formula for their relative amounts that have been found to definitively cause these symptoms. Estrogen levels have been blamed, but these are highest in the third trimester which is contrary to this argument. Human chorionic gonadotropin (hCG) levels are highest in the first semester, so this suggested a possible role in early pregnancy nausea and vomiting, but studies have not shown a correlation between high hCG levels and these symptoms.

One proposal mentions *Helicobacter pylori* as a cause of nausea and vomiting. However, the results are inconsistent. A systematic review and meta-analysis published in 2014 found that, collectively, the studies showed a significant higher incidence of *H. pylori* in patients with hyperemesis gravidarum than in normal pregnant controls, but it was also noted that there was a large variability between studies. The studies also did not distinguish between past or active infection.

Abnormal gastrointestinal motility has also been cited, as well as reduced esophageal sphincter integrity, suggesting that in pregnancy, there is increased gastrointestinal reflux [63]. However, this does not explain why nausea and vomiting would improve as the pregnancy progresses.

Finally, genetic studies have identified certain alleles that convey a higher risk of nausea and vomiting, including the placental proteins GDF15 and IGFBP7 and the hormone receptors GFRAL and PGR [64, 65].

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis presents during the late second or early third trimester and resolves quickly upon delivery of

the fetus. The incidence is variable and ranges from less than 1% in European studies [66] to 27.6% in Araucanos Indians in Chile [67]. While variability depends on geography and environmental factors, there are no specific triggers that have been identified. Some studies have found a seasonal predominance in the winter months [66].

Even within the United States, variability is high and can range from 0.32% to 5.6%, the higher incidence being found in a primarily Hispanic population [68, 69]. Patient-related risk factors have been identified to include advanced maternal age, a family history of intrahepatic cholestasis, chronic hepatitis C infection, and a prior pregnancy with the disease [70]. Intrahepatic cholestasis is the most common liver disease that is unique to pregnancy.

Pathogenesis of Intrahepatic Cholestasis of Pregnancy

It is believed that the etiology of intrahepatic cholestasis of pregnancy is multifactorial, with genetic, environmental, and hormonal factors all playing a role. The genetic component is supported by a familial predisposition to develop the condition. There are also increased risks in certain ethnic groups and in first-degree relatives.

Although no specific environmental factors have been identified, a contribution of the environment to the pathogenesis is supported by a seasonal pattern seen in some studies as well as the wide-ranging geographic variation mentioned above. Other environmental factors that have been implicated are low vitamin D levels resulting from a lack of sunlight exposure and low selenium levels resulting from poor diet [71].

Hormonal factors include elevated estrogen levels. This seems to be consistent with the timing of intrahepatic cholestasis. It most often occurs in the second trimester when estrogen levels are at their highest, and it often occurs in twin pregnancies which are also associated with higher estrogen levels compared to uniparous pregnancies [72, 73].

A 2019 randomized study of 600 women with intrahepatic cholestasis of pregnancy showed that ursodeoxycholic acid was better than placebo in controlling pruritus, but did not perform better than placebo in composite measures including neonatal unit admissions, perinatal deaths, and preterm delivery and also did not change the incidence of stillbirth [74].

Preeclamptic Liver Dysfunction (Preeclampsia with Severe Features)

Particularly severe cases of preeclampsia are labeled as preeclampsia with severe features. This terminology was changed from severe preeclampsia in 2013. As mentioned above, there is considerable overlap between preeclampsia and HELLP. Criteria for the diagnosis of severe preeclampsia are shown in Table 33.5. With preeclampsia with severe features, the overlap is even more significant. The severe features include seizures, pulmonary edema, hypertensive encephalopathy, stroke, retinal detachment, cortical blindness, disseminated intravascular coagulation, placental abruption, renal failure, and hepatic failure or rupture. Death can ensue from many of these complications. Liver disease can be present in both HELLP and in preeclampsia with severe features [75]. The incidence of preeclampsia with severe features in the United States is about 1% of all pregnancies [76]. The incidence is higher in women who have never given birth [77, 78].

Table 33.5 Criteria for the diagnosis of preeclampsia

Systolic blood pressure greater than or equal to 160 mmHg, diastolic blood pressure greater than equal to 110 mmHg (after 20 weeks' gestation, confirmed[a])
or
Systolic blood pressure greater than or equal to 140 mmHg, diastolic blood pressure greater than or equal to 90 mmHg (after 20 weeks' gestation, confirmed[a]), plus new onset of at least one of the following:
Cerebral or visual symptoms (including headache, blurry vision, scotomas, photophobia)
Liver transaminases higher than twice the upper limit of normal for local laboratory
Platelet count less than 100,000/mm^3
Proteinuria greater than 0.3 g in a 24-h urine collection or greater than 0.3 mg/mg in a random urine sample
Pulmonary edema
Serum creatinine greater than 1.1 mg/dl or twice the normal creatinine

[a]Confirmed means detected on two occasions 4 hours apart

Pathogenesis of Preeclampsia

While the pathophysiology of preeclampsia is most likely dependent on both maternal and fetal factors, there is evidence that the placenta plays a significant role as well. The development of preeclampsia is dependent on the placental tissue, not the fetus. The disease resolves after delivery of the placenta, but full recovery may take weeks. Abnormal structural development of the placenta has been demonstrated in patients with preeclampsia. Normal placental development involves remodeling of the spiral arteries during the late first trimester [79, 80]. Maternal spiral arteries are the terminal branches of the uterine artery which supplies nutrients to the fetus and placenta. It has been shown that in preeclampsia these spiral arteries do not penetrate the myometrium and do not develop into the normal large vascular channels, instead remaining narrow and causing reduced perfusion to the placenta [81, 82]. In addition, ineffective trophoblast develop-

ment has been shown to be related to defective spiral artery invasion. The pseudo-vasculogenesis from adhesion molecule expression to endothelial cell expression [83] that is seen in normal placental development is impaired in women with preeclampsia [79, 80]. The impaired trophoblast differentiation may be under the control of semaphorin 3B, which inhibits the vascular endothelial growth factor signaling pathway [84]. All this leads to decreased perfusion to the placenta. The ischemic placenta can generate factors such as soluble frns-like tyrosine kinase 1 (sFLT-1) which may play a role in the maternal features of preeclampsia [85, 86].

Immunological factors that have been shown to play a role in preeclampsia are analogous to those seen in transplant rejection. After all, the fetus is to some extent foreign to the mother, and the mother must be able to develop tolerance to the fetus to carry it to term. The development of tolerance is dependent on the expression of HLA class I antigens HLA--A–C, HLA-E, and HLA-G by extravillous trophoblast cells and the ability for natural killer cells to express the appropriate receptors such as killer immunoglobulin receptors (KIR) to recognize these class I molecules. One study showed polymorphisms in KIR and HLA-C were associated with a higher risk of preeclampsia [87].

The role of antibodies to the angiotensin II type 1 (AT-1) receptor has also been suggested in the pathogenesis of preeclampsia. The angiotensin AT-1 receptor may stimulate the sFLT-1 receptor mentioned above and may also play a role in the mobilization of intracellular free calcium, increased plasminogen activator-1 production, and the defective trophoblast invasion that occurs in preeclampsia [88–91]. In addition, signs of exaggerated levels of inflammation have been detected in mothers with preeclampsia, including complement activation or dysregulation [92, 93], nitric oxide production [94], increases in cell-free DNA [95, 96], and circulating syncytiotrophoblast debris [97, 98].

Genetic factors in preeclampsia have been identified. Variants in the DNA sequence near the FLT1 locus on chromosome 13 in the human fetal genome has been associated with preeclampsia [99]. Genetic evidence has also suggested that the genetic factors that play a role in HELLP may be different than those in preeclampsia with severe features [100]. Other polymorphisms reported to play a role in preeclampsia include those in the SERPINE1 (PAI-1) 4G/4G insertion/deletion promoter [101, 102].

The critical function of the endothelium in pregnancy is demonstrated by the potential role of endothelial dysfunction in the development of preeclampsia. Deficiency in the function of VEGF (as mentioned earlier) and placental growth factor (PIGF) has been implicated in the pathogenesis of preeclampsia [103]. sFLT-1 has a direct role in inhibiting the biological activity of these growth factors. Another endothelial factor that may play a role in preeclampsia is soluble endoglin. Endoglin is a co-receptor of transforming growth factor (TGF)-β that is highly expressed in the vascular endothelium and syncytiotrophoblasts. Soluble endoglin function as an anti-angiogenic protein which may affect the trophoblast development within the placenta [104–106].

Liver Diseases Not Unique to Pregnancy

Neonatal Lupus

While heart block is the most well-known manifestation of neonatal lupus, the disease can also affect the skin, liver, spleen, as well as hematological and neurological systems. The liver diseases that occur in the neonate as a result of neonatal lupus are most commonly intrahepatic cholestasis and/or hepatitis [107, 108], usually manifested by jaundice, icterus, and transient elevation of liver enzymes. The incidence of liver involvement in neonatal lupus is between 10% and 24%. This is usually mild and resolves spontaneously within the first 6 months of life, as do other noncardiac manifestations of neonatal lupus [109–111].

Pathogenesis of Neonatal Lupus

The pathogenesis of neonatal lupus can be traced to the presence of autoantibodies to Ro/SSA and La/SSB. U1-RNP autoantibodies can also be seen in neonatal lupus [112–114]. However, it is unclear if these autoantibodies are pathogenic. Mothers who have infants with neonatal lupus do not necessarily have lupus themselves at the time of delivery, but they frequently show positive autoantibodies. The risk of having a child with neonatal lupus is related to the presence of these autoantibodies and is about 2% [115]. If the mother has had a child with neonatal lupus, then the incidence increases with subsequent pregnancies. Other pathogenic mechanisms that have been proposed in neonatal lupus include maternal-fetal microchimerism. In one study, maternal cells were found in the myocardium of male fetus or neonates of Ro and La antibody-positive mothers who developed heart block [116]. Fetal HLA-alleles have been associated with neonatal lupus, with high risk alleles being HLA-DRB1*04 and HLA-Cw*05 and low risk alleles being DRB1*13 and Cw*06 in one Swedish study [117]. It is likely that the pathogenesis of neonatal lupus, as in many other autoimmune diseases, is a combination of genetic and environmental factors [112, 118]. The pathogenesis for developing liver disease in neonatal lupus is not known.

Patients with Preexisting Liver Disease

Autoimmune Hepatitis and Pregnancy

Autoimmune hepatitis is a risk factor for pregnancy and has been associated with a higher frequency of stillbirth, prema-

turity, and spontaneous abortions. Moreover, patients with AIH can experience flare-ups during and after pregnancy. In addition, if the AIH is advanced and there is evidence of portal hypertension, the risk of bleeding is increased. In spite of this, the prognosis for the newborn is generally favorable. A report of nine pregnancies in seven patients who had autoimmune hepatitis revealed 22.2% exacerbations [119]. Six of the pregnancies resulted in live births (two premature), and three were first trimester miscarriages. Flares were treated with azathioprine and prednisolone in 2/3 of the patients.

Pathogenesis of Autoimmune Hepatitis

Like most autoimmune diseases, the pathogenesis of autoimmune hepatitis is multifactorial, with genetic and environmental factors playing a role. Autoimmune hepatitis presents with elevated liver enzymes resulting from inflammation of the liver. There are two forms of autoimmune hepatitis, type 1 and type 2, which are classified according to the autoantibodies detected. Anti-nuclear antibodies and anti-smooth muscle antibodies are characteristic of type 1 autoimmune hepatitis, whereas liver kidney microsomal antibodies (LKM-1) are found in type 2 autoimmune hepatitis.

The role of autoantibodies in the pathogenesis of autoimmune hepatitis is unclear. Other factors can precipitate autoimmunity or a breakdown in tolerance that leads to invasion of the hepatic parenchyma by a dense mononuclear infiltrate that is seen on histological examination of the liver in autoimmune hepatitis. CD4+ helper cells have been shown to be able to recognize an autoantigen that is presented by MHC class 1 molecules, leading to their activation and differentiation into Th1 helper cells. These Th1 cells can activate macrophages and further enhance HLA class 1 expression, priming hepatocytes to be vulnerable to attack by cytotoxic CD8+ T lymphocytes. At the same time, HLA class 2 expression leads to the production of various cytokines that favor the development of autoantibodies. All this occurs in the face of reduced Treg cell numbers and functions which further allows autoreactive T cells to differentiate and proliferate unchecked [120–123].

Multiple studies have shown that patients with autoimmune hepatitis can safely deliver a fetus [124, 125]. However, poor pregnancy outcomes occur more often when disease control of a patient's autoimmune hepatitis is suboptimal [126]. Risk factors for adverse outcomes include the presence of autoantibodies against soluble liver antigen (SLA), Ro (SSA), and liver/pancreas antigen (LP) [127]. Twenty percent of pregnant females have a flare during their pregnancy. The mechanisms that lead to flares during pregnancy is not clear. The postpartum period carries a greater risk for flare-ups in up to 52% of mothers who have delivered their baby [128, 129].

Conclusion

Several different liver diseases can occur during pregnancy. Some of these diseases are unique to pregnancy, whereas others can be exacerbated during pregnancy. The diseases that are unique to pregnancy include acute fatty liver of pregnancy, HELLP, intrahepatic cholestasis, and hyperemesis gravidarum. These disorders can be distinguished by their features and timing. Hyperemesis gravidarum usually presents early in pregnancy, but AFLP, HELLP, and severe preeclampsia are more commonly seen in late pregnancy. Intrahepatic cholestasis can also occur during late pregnancy and is associated with pruritus. The prognosis varies for the different liver diseases, and patients with AFLP can develop severe liver dysfunction and liver failure. The treatment of the more severe forms of liver diseases in pregnancy is to deliver the fetus. The pathogenesis of liver diseases in pregnancy is multifactorial, with genetics and the environment potentially playing relative roles.

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