Chapter 18
Pregnancy-Specific Liver Disorders: Preeclampsia and HELLP Syndrome

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Abbreviations

CI	Confidence interval
CT	Computed tomography
DIC	Disseminated intravascular coagulation
HTN	Hypertension
Mg	Milligrams
MHC	Major histocompatibility complex
Mmol	Millimol
MR	Magnetic resonance
NK	Natural killer
PGI2	Prostacyclin
PlGF	Placental growth factor
PP13	Placental protein 13
sFLT1	Soluble FMS-like tyrosine kinase receptor 1
TXA2	Thromboxane

Introduction

Central to understanding these two disorders of pregnancy is being aware of the normal physiology and hemodynamics of pregnancy. Cardiac output increases greatly during pregnancy, especially in the first two trimesters [1–3]. After the second trimester, cardiac output typically will stay steady and level off. In pregnancy as the cardiac output increases, the peripheral vascular resistance decreases. The

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mother's blood plasma volume also increases by around 30–50% during gestation [2, 4]. With all of these dramatic physiologic changes, it is important to note that the absolute hepatic blood flow does not change, but the percent of cardiac output to the liver decreases [2, 3].

In the pregnant state, several changes must occur, not only physically and physiologically in order for the body to accept and allow the fetus to grow, but there is also significant immunologic adaptation that must occur on the part of both mother and fetus. Our current understanding of the precise immunologic adaptions that occur is still under investigation. It seems likely that through a multifactorial process, adaptations occur at the maternal-fetal interface so that a tolerogenic state exists. It is known that the fetal trophoblast cells lack HLA-A and HLA-B antigens [5]. They do however have HLA-C, HLA-G, and HLA-E nonclassical antigens [5]. These nonclassical antigens are major histocompatibility complex (MHC) Class I molecules. Thus they act as tolerogenic ligands for inhibitory receptors expressed by maternal natural killer (NK) cells. It is important to note that fetal trophoblast cells completely lack MHC Class II molecules [5]. MHC Class II molecules are important in complexing with antigen presenting cells in order to introduce foreign entities to the body's immune system. As the fetal trophoblast cells lack these, it allows them to be more tolerogenic and less likely to attack the maternal cells. Additionally these immunologic adaptations occur in response not only to maternal antigens but also to paternal antigens. Seminal fluid exposure will in a dependent manner induce regulatory T cells [1, 5]. This is one of the reasons it is postulated that those undergoing infertility treatments may be at higher risk for preeclampsia and HELLP due to reduced exposure and therefore less induced immunity to paternal antigens by this mechanism.

Maternal-fetal tolerance is a necessary immunologic adaption to allow pregnancy to occur. In most cases preeclampsia includes liver involvement, and in all cases HELLP has liver involvement. As such it stands that there may be some maladaptation of immunology that occurs to allow these two conditions to exist. The liver is an organ that is known to mediate immunological tolerance. Instead of reacting to the variety of antigens it is exposed, the liver responds with relative immunosuppression not activation. An example of this is portal circulation in which the digestive tract is continuously exposing the liver to bacterial antigens [5]. In immunocompetent patients this hardly causes any malady. This balance can be offset in patients with immunosuppressed states, such as those with cirrhosis, and is sometimes the culprit for infections in this population. Another good example of the liver's immunogenicity is seen in solid organ transplant. Organs that have been co-transplanted along with the liver see far less rates of rejection overall than those respective individual organs being transplanted themselves.

Preeclampsia

What symptoms should I expect to feel?
Most of the time, there are few to no symptoms associated with preeclampsia. The most common symptoms if felt include nausea, vomiting, and right upper quadrant

pain. Often hypertension will be diagnosed (blood pressure greater than or equal to 140 mmHg/90 mmHg). Additionally you may have protein leaking in the urine as well, known as proteinuria.

What are the risk factors for having or being predisposed to getting Preeclampsia?
Having previously been diagnosed with preeclampsia or having a family history of preeclampsia puts you at greatest risk for being diagnosed with this disorder. Other risk factors that exist are having a body mass index greater than 35, having high blood pressure going into pregnancy, and maternal age greater than or equal to 40. Also having any preexisting autoimmune disease can place you at a higher risk for developing preeclampsia.

Preeclampsia

With that background in mind, clinically, preeclampsia is a condition in pregnancy where de novo hypertension occurs in the second half of pregnancy. This is characterized by systolic blood pressure greater than or equal to 140 mmHg and a diastolic blood pressure greater than or equal to 90 mmHg [2]. It is important to note that this new diagnosis of HTN occurs in this condition after 20 weeks of gestation [1, 2]. It is further characterized by the presence of greater than 300 mg/day of protein in the urine or a spot urine/creatinine ratio of >30 mg/mmol [1]. Until recently, proteinuria alongside hypertension was a signature defining trait of this condition, but more recent studies have found that proteinuria is not necessary for this condition to exist. Alternately preeclampsia can have a more severe presentation with HTN and either renal failure, pancreatitis, pulmonary edema, or seizures, also known as eclampsia.

The incidence of preeclampsia is ten times more common than HELLP and so more likely to be encountered in practice [2, 4]. It occurs in 3–5% of all pregnancies and can extend beyond the gestational period of 20 weeks to up to 2 weeks postpartum [1, 2, 4]. Often this condition is comanaged alongside a high-risk obstetrician or maternal fetal medicine specialist. It has long been postulated that preeclampsia may be a predisposing or precursor condition to the development of HELLP.

There are several hypothesized risk factors for the development of preeclampsia. There does appear to be some penchant toward development of this if the mother already has HTN [2]. Similarly, if there is a prior history of preeclampsia or a family history of preeclampsia than there is a higher likelihood to develop preeclampsia (RR 7.19, CI 5.85–8.83) [6]. Additionally as preeclampsia and HELLP are both thought to emanate from the improper implantation of the trophoblast early in pregnancy which can lead to restricted perfusion of the placenta, it stands that autoimmune diseases may predispose to the development of this maladaptive implantation with background inflammation [6]. In preeclampsia it also appears that the systemic vascular resistance does not decrease as it does so in proper pregnancy, and there is an increased sensitivity to vasospasm. Other risk factors for preeclampsia include a BMI >35, preexisting insulin-dependent diabetes mellitus type II (DMII), nulliparity, and advanced maternal age greater than 40 [2, 6].

Clinically preeclampsia may be relatively asymptomatic upon presentation. If symptoms do surface, they are usually headaches, visual changes, right upper quadrant pain, and nausea or vomiting [7]. Unfortunately these are symptoms that are quite nonspecific and relatively germane to some stage of pregnancy. Ceruloplasmin may be a marker for the development of preeclampsia, but this has yet to be used clinically [8]. It is assumed that placental hypoxia associated with preeclampsia increases placental expression of ceruloplasmin [8].

Once preeclampsia is diagnosed, magnesium sulfate should be administered to help reduce the likelihood of seizures during delivery, and antihypertensives are used to manage elevated blood pressures [1]. There are conflicting data as to oral calcium supplementation potentially reducing the risk of preeclampsia [1, 9], and current guidelines do not support its use. The use of aspirin in women identified at high risk for developing preeclampsia is currently recommended at a dose of 81–162 mg [10]. It is theorized that aspirin helps through the inhibitory effects on cyclooxygenase on thromboxane (TXA2) and prostacyclin (PGI2) [10]. When commenced before 16 weeks, it is thought to help improve placental blood flow and reduce risk of placental thrombosis [10].

HELLP Syndrome

What is HELLP syndrome?
Hemolysis, elevated liver test, and low platelets make up the syndrome known as HELLP. It can occur in the third trimester of pregnancy to up to 2 weeks postpartum.

What symptoms should I expect to feel?
Most of the time, there are few to no symptoms associated with HELLP until the very end. The most common symptoms include nausea, vomiting, right upper quadrant pain, swelling in the legs, and headache, much of what is experienced in preeclampsia. Often high blood pressure will be diagnosed (blood pressure greater than or equal to 140 mmHg/90 mmHg), and you may have protein leaking in the urine as well, known as proteinuria.

HELLP

Dr. Louis Weinstein first described the syndrome of HELLP in 1982. He had studied case reports dating as far back as 1954 that seemed to describe hemolysis and elevated liver enzymes in a toxemia of pregnancy which he postulated was actually the first description of this disorder [11]. He himself had studied 29 obstetric patients with these constellation of symptoms of hemolysis, elevated liver enzymes, and low platelets. Truly remarkable was that up until his discovery and description, the

treatment for patients with these combination of symptoms was conservative watchful waiting. Weinstein's assertion that one be aggressive in the treatment of HELLP with expeditious delivery, even if by way of cesarean section, was a bold and novel declaration [11].

HELLP occurs in 0.2–0.8% of pregnancies and exclusively occurs in the third trimester to postpartum period [2, 5]. The maternal mortality associated with this disorder is 1.1–2.0%, and perinatal mortality is as high as 33% [2, 5]. There clearly is a marked fold difference in maternal to fetal mortality in this disorder. HELLP includes up to 80% of the cases of preeclampsia, and this is why it is so difficult to learn about HELLP without also knowing about preeclampsia [5] (Fig. 18.1, Table 18.1).

There are two widely accepted classification systems for describing and diagnosing HELLP. These are the Mississippi classification system and the Tennessee classification system [4]. In the Mississippi classification system, there are three classes based on severity of presentation, and these are dictated by platelet count (Table 18.2).

As expected most maternal deaths occur in Class I patients [12]. The clinical presentation of HELLP typically includes symptoms such as severe abdominal pain, vomiting, and the most dreaded complication of liver rupture. In reality hepatic hematoma is far more likely to occur than hepatic infarction [7] (Fig. 18.2). In those that develop hepatic hematomas, there is a 12% incidence of hepatic rupture [7]. This leads to a maternal mortality of 32% and a fetal mortality of up to 51% [7]. Capsular rupture occurs in 0.53–2.0% of women with preeclampsia and HELLP [7]. In this clinical scenario, maternal mortality is 17%, and fetal mortality is 38% [7]. The exact culprit for the intrahepatic hematoma is not clearly known. It has been hypothesized that fibrinoid thrombin within sinusoids from disseminated intravascular coagulation (DIC) that is associated with HELLP leads to periportal hematomas and necrosis (Fig. 18.3). Ultrasound is still first line to detect any hepatic abnormalities that may precede capsular rupture [7]. If any abnormalities are found, it is appropriate to proceed with magnetic resonance (MR) or multidetector CT imaging. In a severely ill patient with hemodynamic instability and HELLP, a multidetector CT

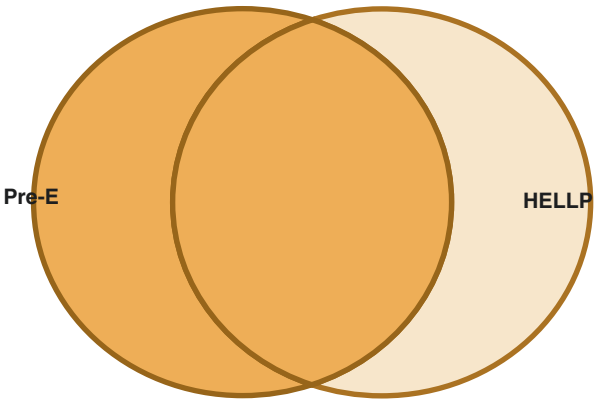

Fig. 18.1 The interrelatedness of preeclampsia and HELLP

Table 18.1 Clinical features and laboratory findings

	HELLP	Preeclampsia
Clinical features	Abdominal pain, vomiting, proteinuria, headache, peripheral edema	Abdominal pain, hypertension, proteinuria, headache, blurred vision, peripheral edema
Trimester	Third (less common second an postpartum)	Late second or third
Ascites	–	–
Thrombocytopenia	+	+
Bilirubin	<5 mg/dL (ULN 1.9 mg/dL)	<5 mg/dL (ULN 1.9 mg/dL)
Bile acid elevation	–	–
Hypoglycemia	–	–
Coagulopathy	DIC	–
Proteinuria	+/–	+
Aminotransferases	1–100×	1–100×
Uric acid elevation	+	+
Hemolysis	+	+/–
Renal dysfunction	+/–	+
Histopathology	Fibrin deposition, hemorrhage, hepatocellular necrosis	Fibrin deposition, hemorrhage, hepatocellular necrosis
Treatment	Delivery	Delivery

Courtesy of Dr. Sheila Eswaran
ULN upper limit of normal

Table 18.2 Mississippi classification system for HELLP

Type	Platelet count
Class I	<50,000/μL
Class II	50,000–100,000/μL
Class II	100,000–150,000/μL

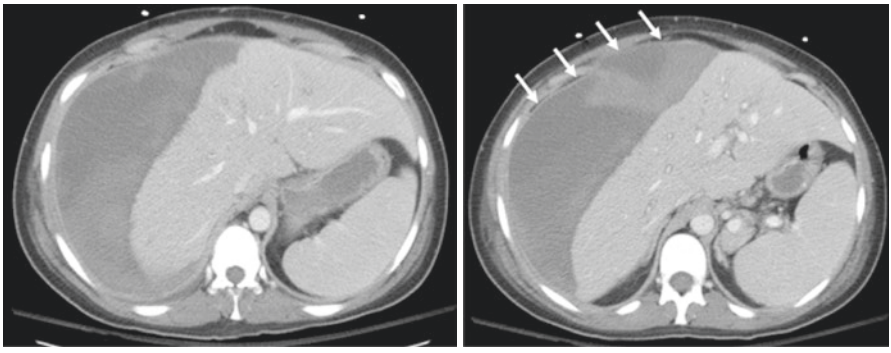

Fig. 18.2 Thirty-three-year-old female at 28 weeks 3 days gestation who presented with nausea and vomiting and then developed acute severe right upper quadrant pain. CT shows acute subcapsular hematoma exerting substantial mass effect on the liver parenchyma. (Courtesy of Dr. Daniel Myers)

imaging is recommended as first line [7]. If capsular rupture should occur, there exist both surgical and nonsurgical treatment options. Transcatheter arterial embolization can be used and has been shown to decrease maternal and fetal mortality from 17% to 0% and 38% to 30%, respectively [7]. The surgical options that exist consist of surgical packing, arterial ligation, partial liver resection, and orthotopic liver transplant.

Some of the risk factors that are known to exist for the development of HELLP include nulliparity, the instance of having a gestational hypertensive disorder in previous pregnancy, and having essential HTN in nulliparous women (not so if multiparous) [13]. There is no worldwide genetic cause for preeclampsia or HELLP as of yet discovered, and likely there will not be one single causative gene and more likely a multifactorial process that consists of both genetic and environmental influences [1, 5]. The pathophysiology of HELLP is thought to be one where there is an enhanced inflammatory state where maternal immune and endothelial cells react to syncytiotrophoblast cells. The syncytiotrophoblast membrane separates maternal and fetal blood, and it is known in preeclampsia and HELLP; there is an abnormal morphology to its brush border [1, 5, 14, 15]. In HELLP, placental protein 13 (PP13) is abnormally incorporated into the membrane. Additionally there is a shift toward soluble FMS-like tyrosine kinase 1 (sFLT1) protein which favors an overall more antiangiogenic environment [14, 15]. There is a drop in the placental growth factor (PlGF) levels in both preeclampsia and HELLP [14, 15]. This subtle shift in balance toward increased antiangiogenic factors is thought to induce maternal vascular endothelial dysfunction which causes arterial hypertension and increases the inflammatory response and ultimately leads to the downstream cascade of events seen in HELLP. In the later stages of HELLP, near term, there are defects that occur in the complement pathway that leads to thrombotic microangiopathy and hemolysis. With this knowledge of the shift in antiangiogenic factors, there has been development of assays to detect these factors as a potential biomarker to help predict the risk of preeclampsia or HELLP. The ratio of sFLT1/PlGF might be a better predictor of the development of preeclampsia than either biomarker alone. It has been found that a sFLT1/PIGF ratio of 38 or lower had a 99.3% negative predictive value (95% confidence interval [CI], 97.9–99.9) [15].

The damage to the liver that occurs in HELLP is specifically caused by soluble CD95L (sCD95L) [5]. This has been found in increased levels in maternal blood in HELLP and causes liver cell apoptosis [5]. Interestingly the severity of clinical presentation in HELLP does not correlate to histopathology. In the rare instances that a liver biopsy has been performed in HELLP, findings of periportal hemorrhage and fibrin deposition are found, but the degree of this does not correlate with the severity of clinical findings [3, 16] (Fig. 18.3).

Treatment for HELLP as Dr. Weinstein had proposed several years ago has not changed much over these past few years. Immediate delivery is recommended and expectant supportive management. If gestation is less than 34 weeks, then delivery is recommended within 48 h after administration of corticosteroids, to allow for fetal lung maturity [1].

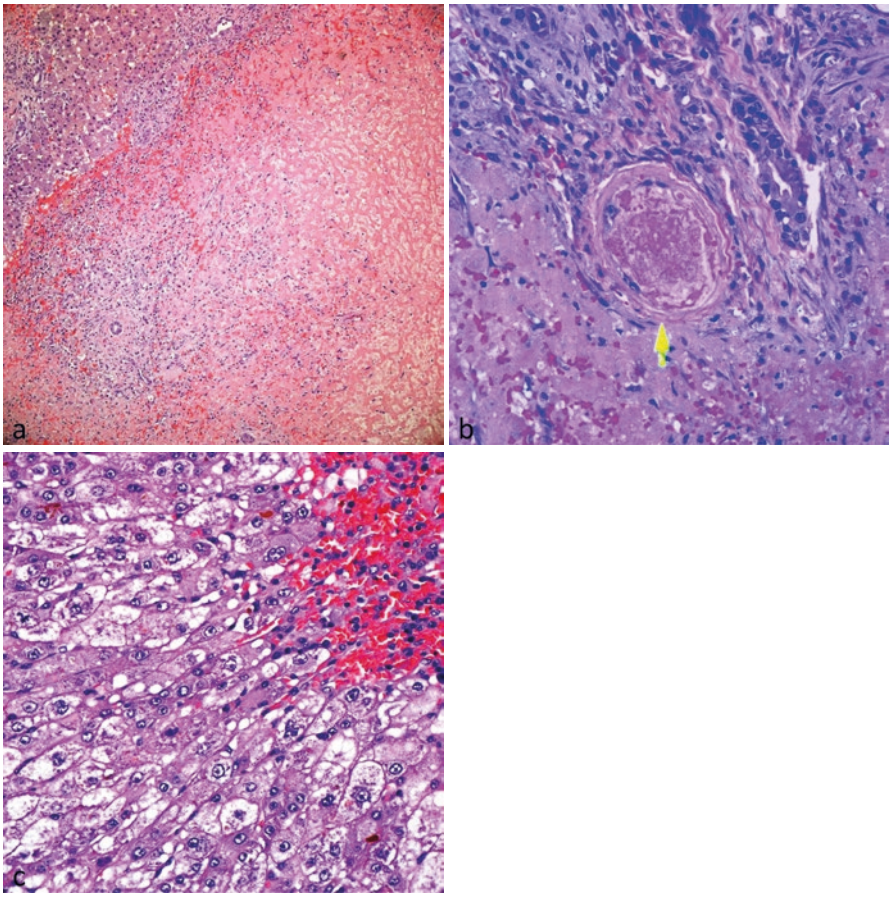

Fig. 18.3 (**a**) Histological findings from a HELLP patient, explanted liver, H&E: showing hepatic parenchyma with extensive necrosis. (**b**) Fibrin thrombus in a vessel adjacent to necrotic hepatic parenchyma. (**c**) Residual viable parenchyma with marked ballooning degeneration. (Courtesy of Dr. Jiang Wang)

Future Trends

While not much has changed with regard to treatments for preeclampsia and HELLP in the past few years, there is much that has been under study. Pravastatin has been shown in mice models to help prevent and treat preeclampsia [17–19]. Statins in general are HMG-CoA reductases that lower LDL but also have antioxidant, anti-thrombogenic, and anti-inflammatory properties. In murine models pravastatin was shown to decrease the increased sFLT1 levels in preeclampsia [19]. It was also shown to increase levels of nitric oxide synthetase, and in this way pravastatin may prove to be a valuable new treatment in both prevention and treatment [8, 17, 19]. There is a phase 1 trial in the United States that is underway and thus far has found

no serious adverse fetal or maternal effects with the use of pravastatin. There is a double-blind randomized placebo-controlled multicenter trial underway in the United Kingdom called StAmP or Statins to Ameliorate early-onset Preeclampsia. Additionally a few case reports have shown success with using salvage postpartum plasma exchange within 24 h in patients with Class I HELLP whose symptoms are persisting after delivery [12].

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