Abnormal liver chemistries seen in approximately 3-5% of pregnancies can represent benign processes that will not alter the course of pregnancy, however, can also be a manifestation of life-threatening problems that warrant urgent intervention. Liver disease in pregnancy can be broadly divided into three categories: liver disease that is unique to pregnancy (which will be the focus of this syllabus), newly acquired liver disease not specific to, but more prevalent or serious in pregnancy, and pregnancy occurring in a patient with pre-existing liver disease. For a concise review of non-pregnancy related liver disease during pregnancy, the reader is directed to a recent review on the topic.1

Liver Disease Specific to Pregnancy
Abnormal liver chemistries during pregnancy should prompt an evaluation for pregnancy specific diseases guided by gestational period. (Figure 1) (Table 1)

Early Pregnancy
Hyperemesis Gravidarum
Hyperemesis gravidarum (HG) is a diagnosis of exclusion, thus a careful evaluation for preexisting liver disease or other gastrointestinal illness is essential. Although nausea and vomiting are common in pregnancy, HG is characterized by intractable nausea and vomiting that often requires hospitalization. It occurs, by definition, in the first trimester, in 0.3-2.0% of pregnancies. Abnormalities in liver chemistries occur in up to 50% of cases of HG. A hepatocellular injury pattern is typical, with elevations in ALT and AST ranging from mild to as high as 10 times the upper limit of normal.2 Jaundice is rare and when present may suggest underlying liver or biliary tract disease. Symptoms are often severe enough to result in weight loss, dehydration, ketonuria, and electrolyte imbalances. In 10% of women, symptoms persist throughout pregnancy and resolve only with delivery of the fetus. HG is more common in the setting of molar pregnancy, twin pregnancies, preexisting diabetes or hypothyroidism, and psychiatric disorders.3 Treatment is supportive, and includes correction of dehydration and electrolyte abnormalities. Thiamine supplementation is recommended to prevent Wernicke’s encephalopathy. While the role of corticosteroids is not well established, it may be useful in refractory cases.4 Successful treatment of HG leads to correction of abnormal liver chemistries without lasting liver complications.

Mid to Late Pregnancy
Intrahepatic Cholestasis of Pregnancy
Intrahepatic cholestasis of pregnancy (ICP) is characterized by generalized pruritus and biochemical evidence of cholestasis that typically affects women during the last trimester of pregnancy, though it can also present in the late second trimester. While rare, it is the most common pregnancy-related liver disorder, with a prevalence of 1 in 1,000 to 1 in 10,000.5 Geographically, it appears to be more common in South America, particularly in Chile (14%) and in Scandinavia (1-2%), particularly in the winter months.6-8 In North America, the incidence is less than 1%. Risk factors for developing ICP include multi-parity, advancing maternal age, twin pregnancies, and a history of cholestasis secondary to oral contraceptive use. The condition recurs in 60-70% of subsequent pregnancies, suggesting a genetic predisposition with incomplete penetrance.

The etiology of ICP not well described, but likely includes genetic, hormonal and exogenous factors. Evidence for a strong genetic component is supported by familial clustering, increased prevalence in specific ethnic groups, higher incidence levels in twin pregnancies, and increased risk in siblings of women affected with ICP.9 The majority of genetic variation in ICP has been identified in the biliary transporters ABCB4 and ABCB11 and others in the placenta, with various mutations conferring increased susceptibility to ICP.10-13 Hormonal factors also appear to play a role with increased symptom severity during the third trimester, when reproductive hormone concentrations are the highest. Pruritus has also been described in women taking exogenous hormones and at particular points in the menstrual cycle, implying a further correlation between hormonal changes and pruritus.14 Both estrogens (mainly estradiol-17β-D-glucoronide) and progesterone metabolites can promote cholestasis.6,15

The development of ICP has little lasting consequence for the mother. Morbidity is typically limited to pruritus, which often begins in the palms and soles of the feet and resolves after delivery, with normalization of serum bile acid (SBA) levels. Some women may present with jaundice, malabsorption, and clinically significant gallstone disease. In contrast, morbidity and mortality for the fetus is increased, particularly in women with serum bile acid levels ≥ 40μmol/L.16 Specifically, ICP increases the risk of preterm delivery (19-60%), fetal distress (22-41%), and fetal loss (0.4-1.6%).17-21 The incidence of fetal hypoxia, meconium-stained amniotic fluid,
and intrauterine death also appears to be higher, and recent studies have shown that delivery at 38 weeks may improve perinatal outcomes. Perinatal outcomes in patients with SBA \(< 40\) \(\mu\)m do not appear to be significantly worse, thus these patients should be managed symptomatically, without induction of pre-term labor.\(^8\)

While several compounds have been studied, UDCA is the most effective in the treatment of pruritus as well as in the prevention of adverse fetal outcomes.\(^{22, 23}\) In patients with SBA \(< 40\) \(\mu\)m do not appear to be significantly worse, thus these patients should be managed symptomatically, without induction of pre-term labor.\(^8\)

For development of severe preeclampsia and HELLP include history of diabetes, chronic hypertension, multi-parity, and older age.

Preeclampsia is defined by the development of hypertension (HTN) \((\geq 140/90\) mmHg) occurring at \(> 20\) weeks of gestation plus proteinuria \((\geq 0.3\) g/24-hours). Severe preeclampsia is characterized by blood pressure \(\geq 160/90\) mmHg and \(\geq 5\) g protein/24-hours or by the presence of end organ damage (oliguria, cerebral or visual problems, pulmonary edema, impaired liver function, thrombocytopenia, or fetal growth restriction). Seizures in the setting of any of the above findings, defines eclampsia. Finally, the finding of hemolysis, along with thrombocytopenia and elevated liver enzymes, suggests the development of HELLP syndrome, which carries the highest risk both for the mother and the fetus. Distinguishing between these three entities is important, as management and prognostic implications differ.
The diagnosis of HELLP syndrome requires a high index of suspicion. The majority of patients endorse non-specific fatigue and malaise prior to presentation, and 50% report epigastric or right upper quadrant pain. The degree of jaundice is usually mild, and other clinical signs and symptoms may be absent. The main abnormalities noted on biochemical examination include varying degrees of thrombocytopenia and elevated liver enzymes, elevated LDH due to hemolysis, and microangiopathic hemolytic anemia. Sinusoidal obstruction likely explains the right upper quadrant pain experienced by most patients. The Mississippi classification stratifies severity based on platelet count and aminotransferase elevation. Generally, thrombocytopenia less than 100,000/mm³, LDH > 600 U/L, and aminotransferases > 70 U/L are consistent with a diagnosis of HELLP. Worsening thrombocytopenia is associated with poor outcomes. Complications decrease significantly with advanced gestational age as fetal risk diminishes, and some studies have shown this is irrespective of the diagnosis of HELLP versus severe preeclampsia.

The management of HELLP requires immediate hospitalization, often in an intensive care unit. Management of patients with preeclampsia includes institution of intravenous magnesium sulfate as prophylaxis against seizures, and antihypertensives to lower blood pressure below 160 mm Hg systolic. Fetal well-being should be assessed using standard methods, and finally, the timing of delivery should be established. Definitive management for HELLP is delivery of the fetus, which typically results in resolution of symptoms within 5 days, though complications can still present post-partum. The general approach is to deliver the fetus if gestational age is greater than 34 weeks. For less than 34 weeks, the administration of glucocorticoids followed by delivery in 48 hours is preferred. It is important to note that there is considerable debate regarding the timing of delivery and the utility of administering corticosteroids in cases of HELLP. Randomized control trials are needed to validate current practice. In most cases, both maternal and fetal complications are common without prompt delivery. In the setting of hemodynamic instability from development of hepatic subcapsular hematoma and hemorrhagic shock, surgical exploration, percutaneous embolization of the hepatic artery, and liver transplantation have all been pursued with some success.

Acute Fatty Liver of Pregnancy
AFLP is a rare condition that affects 1 in 7,000-20,000 pregnancies, almost exclusively in the third trimester. It is more common in nulliparous women, and in twin pregnancies. It is characterized by microvesicular fatty infiltration of the liver, and is associated with varying degrees of hepatic failure. It can be complicated by encephalopathy, thrombocytopenia, disseminated intravascular coagulopathy, and renal failure, potentially resulting in maternal and fetal death. It never develops after delivery, though the clinical course can linger after delivery, and can be difficult to distinguish from HELLP, as 50% of patients with AFLP have coexisting preeclampsia.

The pathophysiology of AFLP is largely unknown, but many cases have been linked to fetal defects in mitochondrial fatty acid oxidation, specifically in defects in two key enzymes: the mitochondrial tri-functional protein and its alpha subunit, long-chain-3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD). The exact mechanism by which deficiencies in these enzymes lead to clinical AFLP is unknown. However, one hypothesis suggests that the accumulation of 3-hydroxyacyl metabolites produced by the fetus is toxic and can lead to disease in a predisposed mother. Despite the association between LCHAD deficiency and AFLP, only 20% of babies born to mothers with AFLP have the mutation.

Women typically present in the third trimester with nausea, vomiting, and abdominal pain, in the setting of elevated serum aminotransferases. Jaundice is not common, and signs of preeclampsia may be present. In cases of acute liver failure, encephalopathy and coagulopathy may be part of the initial clinical presentation. The diagnosis of AFLP is based on clinical criteria, imaging suggestive of steatosis (though because it is microvesicular fat, it is not reliably seen on imaging), and liver biopsy showing microvesicular fatty change. While liver biopsy is the gold standard, it carries risk and should only be pursued when the diagnosis is in question and/or urgent delivery is not optimal.

AFLP is an obstetric emergency that requires urgent delivery to prevent maternal and fetal complications. Signs of acute liver failure (coagulopathy, encephalopathy) require monitoring in an intensive care unit, with supportive care, which may include intracranial pressure monitoring in some centers. Delivery results in the resolution of symptoms and hepatic recovery for the mother. After birth, close monitoring is required for the child due to the risk of an associated fatty acid oxidation defect. Some advocate screening newborns of mothers with AFLP to assist with genetic counseling and nutritional therapy. Thanks to advances in intensive care support, early detection of AFLP, and improved principles of early delivery, maternal mortality has decreased from 90% to less than 10% over the past 30 years. Fetal mortality was previously reported to be 50%, but has also substantially decreased to levels similar to current maternal outcomes. It is important to emphasize that maternal complications may still occur in the early post-partum period and patients should be monitored with these in mind.

Conclusion
Liver disease in a pregnant patient can occur as a result of or irrespective of pregnancy. Diseases of the liver unique to
pregnancy reliably occur at specific points in the gestational spectrum. Thus, gestational age, a comprehensive history and a clinically driven evaluation can help narrow the differential diagnosis and guide management. Early recognition of these conditions is essential in order to optimize maternal and fetal outcome.

REFERENCES