From HELLP to Hepatic Rupture:

The Spectrum of Liver Diseases Associated with Pregnancy

"Lily Pads" by Christina Luksza-Paravacini

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Dr. Mayo's interests are in cholestatic and autoimmune liver diseases, including primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and intrahepatic cholestasis of pregnancy. She studies the immunopathobiology and process of liver fibrosis in these diseases. She has a particular interest in the pathophysiology and management of pruritus in patients with cholestatic liver disease

Normal Liver Changes of Pregnancy

During pregnancy, plasma volume increases 40%, leading to hemodilution of several standard liver tests. A prospective study of 103 pregnant women in 1996 showed that AST, ALT, bili, and GGT were about 20% lower than in matched non-pregnant women, although they still remain within the normal range. (1) GGT levels may also lower during liver disease of pregnancy than in non-pregnant individuals because estrogen and progestational compounds affect the liver such that less GGT is released into the blood with hepatocellular injury. (2) By the third trimester, albumin, urea, and uric acid concentrations are decreased, and triglycerides, cholesterol, ceruloplasmin, transferrin, and alpha globulins are increased. The average decrease in albumin is about 1 g/dl. Alkaline phosphatase levels begin to rise during the first several months of pregnancy and rise sharply in the third trimester, peaking at 2-4X the upper limit of normal (ULN). This is due mostly to placental production of this enzyme, but increased maternal bone turnover may also contribute. (3) During labor, AST rises, probably secondary to leakage from contracting uterine muscle.

On examination, palmar erythema and spider telangiectasias present in up to 60% and thus cannot be used as accurate markers of liver dysfunction. (4) In contrast to experimental animals, the human liver does not increase in size during pregnancy. In a 1963 study from Parkland Hospital by Burton Combes et al, the average liver weight in 16 pregnant women who died after a brief illness was no different than non-pregnant women.(5) Microscopically, the liver also appears essentially normal.

Hyperemesis Gravidarum

Hyperemesis gravidarum represents the extreme end of the spectrum of morning sickness, with dehydration and often ketosis. It has been documented in the medical literature as early as 1609 and reportedly led to the death of Charlotte Bronte, author of Jane Eyre, during her first pregnancy.(6)

Epidemiology

Hyperemesis gravidarum occurs in approximately 1-20 patients per 1000 pregnancies Risk factors include: a female baby, multiparity (7), obesity, maternal age less than 25, nonsmokers, and hyperthyroidism. (8)

Clinical Presentation

Hyperemesis gravidarum usually occurs in the first trimester of pregnancy.
50% will require hospitalization, and up to 25% of hospitalized patients will have abnormal liver enzymes. (9) Transaminases are mildly elevated, usually <1,000. Amylase may be elevated due to leakage from the salivary glands. Jaundice is rare, but possible.

Diagnosis

The clinical diagnosis of hyperemesis is usually not difficult, but is, nevertheless, one of exclusion. The differential diagnosis includes viral hepatitis, gastroenteritis, pancreatitis, and biliary obstruction. (8) A liver biopsy is only indicated if another hepatic process is suspected and needs to be ruled out. The liver biopsy changes in hyperemesis gravidarum are subtle and nonspecific.

Clinical Course and Complications

Hyperemesis is usually resolved by gestation week 20, but sometimes may persist for the entire pregnancy. (10) Complications are related to repeated vomiting: electrolyte disturbances, acid-base disturbances, esophageal rupture, retinal hemorrhage, pneumomediastinum, and pre-renal kidney failure. Fetal outcomes are the same or better than in the general population (11), although those with very severe symptoms have smaller babies. (12) Liver function tests return to normal within a few days of good nutrition

Pathophysiology

The cause of hyperemesis gravidarum and the reason it may cause elevated liver tests are completely unknown. Proposed theories include:

1) *Psychological.* A 1988 study in which all patients underwent psychological screening found that more than half of the pregnancies were unplanned and most were either ambivalent or did not want to have a child. (13)
2) 2) *Hyperthyroidism/hyperparathyroidism.* Some patients with hyperemesis have elevated thyroid function studies which abate at the same time as the hyperemesis. The correlation, however, is far from perfect. There may be another circulating substance that can stimulate these glands in patients with hyperemesis gravidarum. (8)
3) *Gestational hormones.* Beta HCG, in particular, peaks and falls within the first 20 weeks of pregnancy. However, studies conflict as to whether there is a correlation between the level of this hormone and the incidence and/or severity of nausea and vomiting.(14, 15) Estrogen levels rise most rapidly during the first trimester, and some speculate that slow adaptation to the increased hormonal load is responsible. (8)
4) *Altered autonomic function.* Riely et al demonstrated an association between abnormalities of sympathetic adrenergic function and electrogastric activity of the stomach in patients with hyperemesis. (16)
5) *Nutritional deficiencies.* Although an attractive hypothesis, there is no difference in serum copper or zinc levels between pregnant patients with or without hyperemesis. (17)

Treatment

There are, surprisingly, no randomized placebo-controlled trials addressing therapy of hyperemesis gravidarum. Supportive measures including IV fluids, are recommended, Anecdotally, anti-emetics such as promethazine, ondansetron, droperidol and diphenhydramine (18), and corticosteroids have been useful and relatively safe in pregnancy. One pilot study (N=30) compared the efficacy of 10 mg IV ondansteron to 50 mg IV promethazine and found that symptoms improved similarly in both

groups.(19) Without a placebo group, however, one cannot determine whether it was the medication or supportive care (NPO and IV hydration) that was therapeutic. Ondansetron is considerably more expensive than promethazine, but caused significantly less sedation. Rarely, parenteral or enteral feeding is necessary.
A few case reports have illustrated a dramatic response to oral prednisone (40 mg/day), but controlled trials are lacking. (20)

Hemolysis, Elevated Liver tests and Low Platelets (HELLP) Syndrome

HELLP is a severe form of pre-eclampsia (hypertension, proteinuria, peripheral edema) in which the placental ischemia leads to a DIC-like picture, with thrombocytopenia, hemolysis, coagulopathy, and microthrombi in the liver. Evidence that HELLP is an extreme variant of HELLP stems from the observation that 90%-100% of pts with HELLP have pre-eclampsia (21,22) and that some patients appear to have pre-eclampsia with partial HELLP syndrome, for example elevated liver tests but normal platelet counts and no hemolysis. This intermediate variant is sometimes called " pre-eclampsia with liver involvement". HELLP as a distinct syndrome was first described as a separate entity in 1982. (23)

Epidemiology

Pre-eclampsia (hypertension, proteinuria, edema) affects 3-10% of all pregnancies. HELLP occurs in about 10% of patients with severe pre-eclampsia (incidence 1:1000 pregnancies). HELLP recurs in 3-27% of future pregnancies. (24) Although pre-eclampsia is more common in young and nulliparous mothers; women who are older, multiparous, and Caucasian have a higher risk of HELLP.

Clinical Presentation

In the present era, most HELLP syndrome patients are identified when routine screening for proteinuria or hypertension indicates pre-eclampsia and further laboratory work-up shows HELLP. Of those who present clinically, right upper quadrant abdominal pain is the most common symptom (65%), followed by malaise, nausea and vomiting. One third have headaches and 10% will have visual changes. (24,25) The majority (60%) are diagnosed between 27 and 37 weeks gestation, but 33% are diagnosed after delivery and 7% are diagnosed before 27 weeks. (24)

Diagnosis

The differential diagnosis includes gallstone disease, appendicitis, pancreatitis, viral hepatitis, ITP, TTP, HUS, sepsis, DIC, abruption placentae, and amniotic fluid embolism. Serum AST derives from both liver damage and hemolysis and can achieve very high levels (70-6000, median 250).The INR is only mildly elevated (<1.5). About 5%) become clinically jaundiced (Bili 0.5-25, median 1.5). Platelet levels are usually in the 20,000-100,000 range. Hemolysis is evident by elevated LDH (300-24,000, median 850). schistocytes, burr cells, low haptoglobin, and anemia. Liver biopsy reflects that this is a disorder of increased clotting, with fibrin deposition and periportal hemorrhage. Steatosis is seen in about one third of cases, illustrating the connection between HELLP and acute fatty liver of pregnancy (discussed below). The severity of histological

changes does not correlate well with transaminases, (26) and liver biopsy is not needed to establish a diagnosis.

Clinical Course and complications

Serious maternal complications in HELLP include DIC (21%), abruption placentae (16%), acute renal failure (8%), severe ascites (8%), pulmonary edema (6%), and pleural effusions (6%). Rare (<1%), but very serious complications include cerebral edema, ARDS, venoclusive disease, and liver infarction leading to subcapsular liver hematoma and possible hepatic rupture. Risk Factors for more severe clinical course of HELLP syndrome include: abdominal pain, nausea/vomiting, platelets <50,000, CPK >200 IU/ml, LDH >1400 IU/ml, AST >150 IU/ml, ALT>100 IU/ml, Uric Acid >7.8 mg/dl, Cr >1l, and 4+ proteinuria. (27) The Mississippi 3 class system divides patients into classes of severity based on platelet count (<50K, 50K-100K, and 100K-150K). However, the clinical utility of this classification system has been debated.

Priori to 1980, mortality from HELLP was approximately 25%, but now it is 1%-9% (22) Fetal mortality used to by 62-77%, but is now also lower. (28) Studies of maternal mortality in HELLP show that most die from cerebral hemorrhage, cardiopulmonary arrest, or DIC, but 20% die from hepatic hemorrhage. (29) Mortality from hepatic rupture remains high: 50% maternal mortality and 70% fetal mortality.

Hepatic Rupture

Hepatic rupture is almost always preceded by hepatic infarction and intraparenchymal hemorrhage that extends to the subcapsular space. When the pressure of the subcapsular hematoma exceeds the strength of Glissen's capsule, rupture into the peritoneum occurs. Clinically, the patient with hepatic rupture may have a prodromal period that can last up to a month with malaise, headache, and vague abdominal discomfort that probably correlates to the hemorrhage, followed by acute worsening (the rupture). Hepatic infarction can be recognized by very high aminotransferases (>5,000), anemia, and fever. It is best diagnosed and monitored by CT or MRI and hopefully will resolve spontaneously. The majority of hematomas (74%) occur in the superior anterior right lobe, while rupture usually occurs on the inferior edge of the right lobe (28).

It is important to remember that complications can develop 24-72 hrs after delivery in pts with sever pre-eclampsia/HELLP, so mothers should receive continued monitoring, correction of coagulopathy and thrombocytopenia after delivery. In fact, in the Kings College series of 46 women admitted to their liver failure unit, patients frequently got worse after delivery before they get better. 80% of the patients admitted to their unit had already delivered at the local hospital prior to transfer. (22)

Although usually a sequelae of HELLP, hepatic rupture may also occur as a complication of hepatic adenoma, hepatocelular carcinoma, cavernous hemangiomas, and hepatic infarction due to cocaine use.

Pathophysiology

HELLP syndrome is a multi-system disease variant of severe pre-eclampsia. Pre-eclampsia and HELLP appear to be initiated by placental ischemia, leading to activation of endothelium, alteration of vasomotor tone, initiation of the coagulation cascade, increased adhesion of platelets, and increased thrombogenicity (30) Nitric oxide, endothelin-1, thromboxane, lipid peroxidases, and isoprostanes are elevated and prostacyclin (PG12) levels are reduced, leading to altered vascular tone. Another important mediator may be Fas (CD95) ligand, which is produced in the placenta and may contribute to hepatocellular damage.(31) Homozygosity of the HLA-DR gene in the fetus has also been associated with the development of pre-eclampsia, although this may be a linkage phenomenon. (32) Evidence is emerging that fatty acid metabolism defects implicated in the pathophysiology of acute fatty liver of pregnancy (discussed below) are also responsible for a portion of HELLP cases.

Treatment

Use of aspirin and anti-platelet drugs is controversial. One trial of antithrombin III did not support the clinical use of this drug. (33) Recombinant human activated protein C has been proposed as therapy but not yet adequately tested. (34) Severe coagulation abnormalities should be corrected with FFP and platelets. Use of magnesium to prevent seizures in patients with pre-eclamspsia/eclamspia may also reduce platelet clumping.

The treatment of choice is delivery around 36 weeks. NIH consensus guidelines indicate that if the platelet count is <50,000 and the baby is >34 weeks, delivery should occur within 24 hrs. If the gestation is 24-34 weeks, fetal mortality can be improved by optimization of hypertension, coagulopathy, and corticosteroids to enhance fetal lung maturity. (35) Markers of DIC are a poor prognostic sign, and von Dadelszen has proposed that an anti-thrombin III <79%, D-dimers >4 mcg/mL, and TAT complexes > 26 mg/ml could be considered criteria for terminating pregnancies in patients with HELLP. (36) Continuing steroids after delivery can avoid rebound thrombocytopenia in mother. Some recommend plasmaphereses in mothers who have not improved by 72 hours post partum.

Subcapsular hematoma, intraparenchymal hemorrhage, and/or hepatic rupture are best handled by trauma surgeons experienced in liver lacerations. Although subcapsular hematomas can be managed conservatively in stable patients, frank hepatic rupture should not. In one retrospective analysis, conservative non-surgical management of hepatic rupture led to a maternal mortality rate of 96%, as compared to 33% in those receiving surgical management. (37) In patients with unstable hepatic hematomas, evacuation with packing and drain placement is better tolerated (82% survival) than hepatectomy (25% survival). (37) Occasionally, angiography and embolization may be used to control hepatic bleeding. Once the mother is stabilized, the baby must be delivered, but fetal mortality is high. Large ruptures require total hepatectomy and listing for liver transplantation.

Acute Fatty Liver of Pregnancy (AFLP)

In 1934, "acute yellow atrophy" of the liver was first described by Stander et al. (38) This entity has also been called "acute obstetric fatty metamorphosis of liver" and now goes by the acronym AFLP. Clinical overlap of AFLP with the HELLP syndrome has been well documented. In the 1997 Kings College series, 50% of patients with AFLP also had HELLP (22), and lesser degrees of microvesicular fatty infiltration of the liver can be seen in pts with HELLP alone.(39) AFLP is considered by some to be just a severe extension of the HELLP syndrome.

Epidemiology

AFLP is a rare event, occurring in approximately 1/13,000 pregnancies. (4) It affects all ages and races and is more common in twin pregnancies (20% of all AFLP), male births, and primiparous women. Traditionally, it was thought that AFLP uncommonly recurs in subsequent pregnancies, but recurrences are difficult to quantify because AFLP is so uncommon to begin with and many AFLP mothers do not have a second pregnancy, either by choice or by death. There are clearly several well-documented cases of AFLP recurring in subsequent pregnancies.

Clinical presentation

AFLP usually presents in the third trimester, although there are rare reports of second trimester presentation; and, just like HELLP syndrome, it may also present post-partum. The symptoms are similar to that of severe HELLP: headache, fatigue, and nausea and vomiting. RUQ/epigastric pain is present in 50-80%. However, most patients are jaundiced, and many progress to liver failure.

Diagnosis

As mentioned, there may be significant clinical overlap with HELLP. However, AFLP is distinguished by prominent picture of liver failure. Ultrasound/CT may or may not show the fat, as it is microvesicular. (40) The liver is usually normal sized, but may be small. Patients are usually jaundiced (Bili 4-40). Transaminases are only modestly elevated (usually <1,000, median ALT 300) despite the fact that AFLP is a disease of true hepatic failure with hypoglycemia, hyperammonemia, and coagulopathy. AFLP is frequently associated renal failure. In the Kings College liver failure unit, 97% of patients with AFLP had an elevated creatinine. (22) Hemolysis is not a feature of AFLP itself, and thus the LDH is usually < 600. The diagnosis of AFLP is usually made based upon clinical and laboratory findings. The gold standard for diagnosis is liver biopsy, but this is rarely done for two reasons: first, because there is "no time to waste," as this is a medical and obstetrical emergency; second, coagulopathy is usually present. If done, a liver biopsy will show central zone pallor, vacuolization, and microvesicular fat. Mitochondrial disruption can be seen on electron microscopy. Of note, 25% have a portal inflammatory infiltrate, often misinterpreted as viral hepatitis.

Clinical Course and Complications

AFLP may progress rapidly to multi-organ failure. Infectious complications occur in over half (45-53%). (22) Other complications include renal failure (60%), hypoglycemia (53%) cerebral edema (33%), GI hemorrhage (33%), coagulopathy (30%). Delivery is often

complicated by severe post partum hemorrhage. Maternal DIC can lead to placental infarcts and fetal asphyxiation. Maternal mortality is 1-10%, depending on referral base. Fetal mortality is about 20%. Prior to 1980, maternal mortality rates were generally greater than 80%.

Pathophysiology

AFLP likely results from mitochondrial dysfunction. The mitochondrial fatty acid beta-oxidation spiral consists of a series of multiple transport steps and enzymatic reactions. One of these enzymes is long chain 3-hydroxylacyl-CoA dehydrogenase (LCHAD), part of the mitochondrial trifunctional complex on chromosome 2. Recent evidence clearly links deficiency in LCHAD with a risk of developing AFLP. Babies who are homozygous deficient in LCHAD suffer from hepatic failure, cardiomyopathy, hypoglycemia, microvesicular steatosis, and death. Mothers (obligate heterozygotes) carrying homozygous deficient babies appear to be at great risk of developing liver disease during pregnancy.

A sentinel report in 1991 described a baby with LCHAD deficiency born to a mother with recurrent acute fatty liver of pregnancy. (42) A retrospective review of 19 Finnish families with LCHAD deficiency then found that 79% of pregnancies carrying LCHAD deficient fetuses were complicated by AFLP (12/19) or HELLP (3/19) No complications of pregnancy were seen if the fetus was wild type or heterozygote, only homozygous or compound heterozygote, implying that the interaction of maternal and fetal factors was critical to the pathogenesis. (43) In another retrospective review of 63 pregnancies of 18 of the Finnish families with LCHAD deficiency, fetal outcome was studied. A higher risk of prematurity, asphyxia, intrauterine growth retardation, and intrauterine death was found. (44)

How does LCHAD deficiency cause AFLP? The pathophysiology is not entirely clear. However, most speculate that hepatotoxic long chain 3-hydroxylacyl fatty acid metabolites produced by the fetus and placenta overwhelm the mitochondrial-oxidation capacity of the heterozygous mother, who is already under stress from the demands of late pregnancy. In addition, the deficient fetus is unable to assist with mitochondrial oxidation. Human placenta is a known site of fatty acid oxidation. Normally there is a high level of LCHAD and SCHAD activity in the placenta, but this is markedly reduced in homozygous deficient fetuses. (45,46). This hypothesis also fits well with the observation that AFLP pregnancies are frequently multiple gestation. The most common mutations in LCHAD are the G152C mutation, present in over 60% of cases, and a E474Q mutation, present in 19% of cases. (47)

LCHAD deficiency alone, however, does not account for the majority of AFLP cases. One French study did not find the common LCHAD mutations (G1528 and C1132T) in any of their 14 cases of AFLP. (48) Overall, approximately 19% of AFLP cases are associated with fetal LCHAD deficiency. (49) Thus, there must be other disorders to account for the majority of cases AFLP.

There are more than 20 described deficiencies in the fatty acid oxidation cycle described thus far. They are recognized and feared because they may be unrecognized until they cause sudden infant death syndrome. They may also present as Reye-like syndrome, (which is very much like an acute fatty liver of infancy), infantile hypoglycemia, cardiomyopathy, neuropathy, or myopathy. Reports that some of these other recessive fatty acid oxidation defects may be responsible for liver disease of the mother during pregnancy are beginning to emerge. Carnitine palmitoyl transferase 1 (CPT-1) deficiency, carnitine-acylcarnitine translocase deficiency, SCAD short chain acetyl-Co A dehydrogenase, MCAD (medium chain acetyl-Co A dehydrogenase), and complete trifunctional protein deficiency have all been reported to be associated with HELLP or AFLP in individual cases. (50-53)

A recent report from Harvard compared 50 pregnancies of infants diagnosed with various fatty acid oxidation defects to 1250 controls and found that multiple different fatty acid oxidation defects were associated with HELLP or AFLP. (54) Long chain defects were 50 times more likely to develop maternal liver disease, and short and medium chain defects were 12 times more likely. Overall, maternal liver disease was found in 16% of all fatty acid oxidation defect pregnancies, compared with 0.88% of the general population.

With the dedicated search for associations between fatty acid oxidation defects and AFLP, it has become apparent that there is also an increased risk of not only AFLP, but also HELLP in pregnancies affected by fatty acid oxidation disorders. Placental insufficiency in fatty acid oxidation deficiencies could be caused by accumulation of fat in the placental vessels. Two pathological studies have reported the presence of fatty placenta and placental infarcts in HELLP. (44,55)

Treatment

As with HELLP, expedient delivery is the treatment of choice. Broad spectrum antibiotics should also be administered, as the rate of sepsis is very high. Coagulopathy is usually prominent and should be treated with vitamin K, FFP, and cryoprecipitate. Patients progressing to liver failure despite delivery or loss of the fetus can be considered for liver transplantation. However, many patients will either recover or will not be eligible for transplantation due to progressive complications such as sepsis and multi-organ failure.

Offspring of AFLP pregnancies should be screened for LCHAD deficiency. In families with proven LCHAD deficiencies, prenatal diagnosis by CVS can be done. The risk of recurrent AFLP in LCHAD-related cases is around 25%. Biochemical, enzymatic and molecular studies on fluids can be performed on tissue collected from stillborn fetuses. To date, all reported recurrent cases of AFLP have occurred in women whose fetuses had LCHAD deficiency. (43)

LCHAD-deficient babies should be given medium chain triglyceride formula and followed carefully. Small, frequent feedings and low fat diet are recommended for

babies and have been considered as treatment for the pregnant mothers, but have not been tested in controlled trials

Intrahepatic Cholestasis of Pregnancy (ICP)

Intrahepatic cholestasis of pregnancy is a condition that results in very bothersome pruritus for the mother and poses an increased risk of complications to the baby.

Epidemiology

Cholestasis of pregnancy is estimated to occur in about 1/1,000-1/10,000 pregnancies. It is more common in women from Chile and Bolivia (prevalence 6.5-24%) (56) and Scandanavia (1-2%) than in Australia (0.2%) or the United States (0.7%). (57) It is more common with advanced maternal age, twin/triplet pregnancies, and in the winter months. A positive family history is identifiable in 50% of cases, suggesting a genetic component. Patients with ICP also have an increased incidence of gallstones (25% versus 7.7%) (58) and/or a personal history of cholestasis with oral contraceptives. (59)

Clinical Presentation

ICP typically presents in the third trimester (mean 30 weeks), sometimes the second trimester. Interestingly, a urinary tract infection precedes the onset of clinical symptoms in 50%. (60) The main symptom is pruritus, which often has the peculiar distribution of starting in the palms and soles and moving more centrally to the trunk and face as it advances. Severe cases may involve the eyelids or oral cavity. No rash is evident, unless the patient develops secondary skin changes from scratching such as excoriations, lichenification, or prurigo nodules. Typically the pruritus is worse in the evenings, and it can lead to profound insomnia and distress in third trimester patients who are already uncomfortable. Jaundice follows the onset of pruritus in 20-60% about 1-4 weeks later. Steatorrhea from fat malabsoprtion is actually common if sought, but is usually subclinical. (61)

Diagnosis

The diagnosis of ICP is best established by elevated serum bile acid levels. Serum bile acids are typically 10-25 fold elevated in ICP. In contrast to other cholestatic disorders, the alkaline phosphatase and GGT are not very useful. Alkaline phosphatase is usually 1-4X ULN, which is within the expected range for late pregnancy. GGT is relatively suppressed during pregnancy and may be normal in patients with ICP. Serum bilirubin may be mildly elevated (1-6 mg/dl), as may the serum AST and ALT (2-10X ULN). Liver biopsy is rarely needed, but will show a "bland cholestasis." Bile plugs may be found in the hepatocytes and cannaliculi, predominantly in the centrilobular region. Bile duct injury, portal tract inflammation or edema, necrosis, and proliferating bile ductules are not usually seen and their presence should prompt consideration of an alternate diagnosis.

Clinical Course/complications

Maternal outcome is good, but there is an increased risk of fetal distress, spontaneous premature delivery, and sudden intrauterine death. Fetal mortality in untreated patients

is 11%-20%. (62) Even in expertly managed cases, there is a an increased incidence of fetal distress (16%-25%), premature delivery (12%-44%), and perinatal mortality (1.3%-3.5%) (63) Pruritus symptoms resolve 1-4 weeks post partum, although a few atypical cases of cholestasis lasting beyond this period are reported. (64) There are no known long-term sequelae for the mother or baby.

Pathophysiology

Epidemiologic observations suggest that there are both genetic (strong family history) and environmental (more frequent in the winter) factors involved in the pathogenesis of ICP. ICP is presumed to be an exaggerated cholestatic response to pregnancy hormone levels, similar to the abnormal response to oral contraceptives that these patients also exhibit. Estrogen levels are no different in ICP patients than in non-ICP pregnancies. Under the hormonal stress of pregnancy, excretion of bile acids into bile is impaired, resulting in damage to the liver and increased bile acids in the serum. Estrogen probably increases hepatocyte sensitivity to bile acids because it stiffens hepatocyte membranes by increasing the cholesterol and cholesterol ester content of hepatocyte membranes. (65) Selenium deficiency may also contribute in some individuals. Finnish women with ICP have a higher rate of selenium deficiency than the general population. (66) Selenium acts as a coenzyme for glutathione peroxidase, which protects membranes from free radical damage. Thus, selenium deficient individuals may also be more susceptible to hepatocyte damage from retained bile acids.

Fetal complications are probably also directly related to the toxicity of circulating bile acids. Bile acids, particularly cholic acid, have a dose-dependent vasoconstrictive effect on placental chorionic veins. (67) They also increase fetal colonic activity, which may predispose to meconium staining, and may increase uterine contractions, predisposing to premature delivery. (68) In a retrospective analysis of 693 Swedish cases of ICP, fetal complications only occurred if the serum bile acids were >or= 40 micromol/L, and the rate of fetal complications increased by 1%-2% per additional micromole/L of serum bile acids. (69)

In addition to bile acids, sulfated progesterones have been implicated another pruritogenic and toxic agent in ICP. Women with ICP make more sulfated progesterone than glucoronated progesterone (70), and these metabolites compete with bilirubin for excretion. Exogenous administration of progesterone during the 3rd trimester (given to delay premature delivery) is associated with elevated serum bile acids and elevated ALT. In one case series, 62% of patients with ICP had received oral micronized progesterone. These patients developed pruritus much earlier during pregnancy than usual. (71)

The susceptibility of mothers with ICP to environmental factors that impair bile acid secretion appears to be genetic in origin. A major breakthrough was achieved when Jacquemin first noted that ICP occurred in mothers of children with progressive familial intrahepatic cholestatic (PFIC 3), a homozygous recessive disorder caused by a mutation in the multidrug resistance 3 (MDR3, now termed ABCB4). He described a

large kindred of ICP patients related to an index case of PFIC3. He was able to sequence MDR3 and show that the heterozygous state was present in all the patients with ICP. (72)

MDR3 (ABCB4) flips phosphatidylcholine across the cannalicular membrane so that it is available to make micelles. Without sufficient ability to make micelles, the free hydrophobic bile acids in the cannaliculus destroy the biliary membranes. Damage to biliary cells explains why individuals with PFIC3 usually have elevated GGT. Lack of micelles also promotes lithogenicity of bile, crystallization of cholesterol and small duct obstruction. Heterozygous mutations in MDR3 have now been associated with both cholesterol gallstones and the tendency to develop jaundice following oral contraceptives. (73)

Others have confirmed that the heterozygous state for MDR3 mutations is a risk factor for ICP, even in mothers of healthy children. More than 13 different heterozygous MDR3 mutations have now been associated with ICP. (74)

Mutations may be nonsense or missense, leading to either loss of function (stop codon) or misfolding leading to impaired trafficking to membrane. Although both are associated with ICP, there is a genotype-phenotype correlation suggesting that the missense mutations have a less severe phenotype. (75)

Although the association between heterozygous MDR3 mutations and ICP is clear, it does not account for all cases of ICP. In one German study, only 1/49 patients with ICP had a defect in MDR3. (76) It has been hypothesized that defects in other proteins involved in bile acid transport (for example bile salt export protein or ATP8B1) may also be related to ICP. In fact, in the original report of Byler's disease (a progressive cholestatic disorder later discovered to be a defect in ATP8B1), two of the four mothers of the affected children had severe pruritus in the third trimester, and one of these had 4 repeated episodes of ICP. (77)

Treatment

The most effective treatment is delivery by 38 weeks (36 weeks or sooner if fetal lungs are mature), which has reduced perinatal mortality from 10-15% to 2-3%. (77, 78) Part of this decrease in mortality over the past 20 years is also due to an increased awareness of the disease. During this time, there was also a 2-fold increase in the diagnosis of milder cases. Fetal monitoring is controversial and has not been shown to affect outcome, but nonetheless is done by many. In Chile, patients are screened prenatally with serum bile acid levels, a policy which has resulted in same fetal death rate as non-ICP pregnancies. (79)

UDCA

Ursodeoxycholic acid (UDCA) at 15 mg/kg/d can improve pruritus symptoms, liver enzymes, serum bile acid levels, and fetal outcomes. It appears to be safe for both mom and the baby. (80) There have been multiple randomized and placebo controlled trials

of UDCA in ICP. (81-85). UDCA appeared to be beneficial in all trials, although in slightly different ways in each study.

One study using 20-25 mg/kg/day showed an even greater decrease in bile acid levels in maternal blood, amniotic fluid, and cord blood, (80) and another study showed that those patients with very elevated bile acids show statistical improvement. ICP is a heterogeneous disorder, and the response to UDCA may be different in various subgroups. In PFIC 3, those with a missense MDR3 mutation have a clinical response to UDCA, whereas those with a non-sense mutation do not, and they progresses to death by age1.(86)

UDCA has multiple beneficial effects in cholestasis. Importantly, UDCA upregulates expression of MDR3. It also modifies the bile acid pool composition, replacing lithocholic acid, cholic acid, and chenodeoxycholic acid, so that the bile is less toxic to hepatocyte membranes. It improves bile flow and also improves progesterone metabolism and decreases serum levels and urinary excretion of sulfated steroids. .

S- adenosyl methionine (SAM-e)
SAM-e is a nutritional supplement that increases sulfation of bile acids and methylates liver plasma membrane phospholipids resulting in enhanced fluidity. It also has anti-depressant effects. Randomized placebo controlled trials have found conflicting results, but most are supportive that SAM-e controls pruritus in ICP (81, 87-89). As opposed to UDCA, SAM-e has not been reported to improve fetal outcomes. In a head to head comparison of SAM-e and UDCA, both were capable of improving pruritus symptoms, but UDCA was superior at reducing total bile acid concentrations (81).

Bile-Acid Biding resins
Cholestyramine (12-24 g/d) may relieve itching, but Vitamin K deficiency is a real concern in pregnancy. Bile acid binding resins should be prescribed with supplemental vitamin K, to be taken at another time of day. Some experts recommend that all ICP patients receive supplemental vitamin K, even if they are not taking bile acid binding resins, because of an increased risk of hemorrhage with delivery.

Steroids
Corticosteroids decrease fetal dihydroepiandosterone (a precursor for placental estrogen), effectively reducing maternal estrogen levels and also maturing the fetal lung. One small study administered steroids (12 mg X7 days, then 3 day taper) with remarkable improvement in pruritus. (90) However, these findings could not be confirmed in a larger study. (85)

One exciting possibility for the future is cell-based therapy for ICP and PFIC3. In mdr2 knockout mice (the murine equivalent of PFIC3), liver disease is corrected by transplantation of mdr2+/+ hepatocytes. Growth of the transplanted cells is favored because they are resistant to bile salt damage. (91)

Summary:
New molecular technologies have elucidated the association between genetic mutations in fatty acid oxidation enzymes and phospholipid transporters, and the liver disease unique to pregnancy. Pre-eclampsia, HELLP, and AFLP overlap clinically and are regarded by many as presentations along a spectrum of a single liver disease. A mother who is a heterozygous carrier for a mutation in the LCHAD gene is at particularly high risk for HELLP and/or AFLP. A mother who is a heterozygous carrier for a mutation in the PFIC3 gene is at risk for ICP. New mutations in genes for proteins of similar function continue to be discovered and linked to these liver diseases of pregnancy. Environmental factors such as elevated estrogen levels still appear to contribute to disease expression. Expedient delivery of the baby remains the best therapeutic option. Improved intensive and neonatal care has dramatically reduced mortality of the mother and child.

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