



## Pregnancy and liver disease

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### **Pregnancy-related liver disorders**

#### *Intrahepatic cholestasis of pregnancy*

Intrahepatic cholestasis of pregnancy (ICP) is a benign cholestatic disorder that occurs usually during the second or third trimester of pregnancy and disappears shortly after delivery. ICP, also called obstetric cholestasis, is characterized by pruritis, serum biochemical abnormalities of liver function, and, occasionally, jaundice. Although not life-threatening, the pruritis affects maternal comfort and sense of well-being and is associated with an increased incidence of postpartum hemorrhage, possibly as a result of vitamin K deficiency [1–3]. At the same time, ICP has been associated with poor fetal outcomes, including increased incidences of meconium-stained amniotic fluid, fetal intolerance of labor, spontaneous preterm delivery, and intrauterine fetal death [1–3].

#### *Incidence*

The incidence of ICP varies geographically, with rates as low as 1 to 2 per 10,000 pregnancies in North America, Asia, and Australia and as high as 10 to 200 per 10,000 pregnancies in Europe [4,5]. The incidence is 2% of births in Sweden, 14% in Chile, and 24% among Araucanian Indians in Chile [5,6]. An environmental role is suggested by seasonal variations in the frequency of ICP in Chile and Sweden, with the highest rates reported in November [6,7]. ICP occurs in women of all ages and in primiparous and multiparous

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women. It can recur in subsequent pregnancies and is more common in multiple gestations [5,8].

### *Pathogenesis*

The pathogenesis of ICP is multifactorial and obscure. Potential etiologic contributors include genetic abnormalities, hormonal exposure, decreased sulphotransferase activity, and endogenous opioids [9,10].

### *Genetics*

Evidence of a genetic predisposition includes the high incidence in specific ethnic groups, such as Araucanian Indians in Chile and Swedish women [5,6]. In a retrospective Swedish study, moreover, the risk of ICP was increased in women whose mothers or sisters had experienced this disorder [5]. The genetic trait is believed to be an autosomal dominant and, possibly, X-linked, related to HLA haplotypes. Fathers may transmit the condition to their daughters [5,11,12]. Two studies revealed no significant difference, however, in HLA haplotype distribution or class II HLA alleles between patients with a history of ICP and control subjects [13,14]. The specific genetic abnormalities are not identified.

### *Estrogen*

Indirect evidence supports the role of estrogen in disease initiation. ICP tends to occur in the third trimester, when estrogen levels peak [5,6,10], and occurs five times more frequently in multiple gestations, a condition in which estrogen levels are elevated [15]. Cholestasis can be induced experimentally by administration of estrogens, particularly ethinylestradiol, in nonpregnant women who previously had ICP [16,17].

The liver is important in steroid metabolism. Some individuals may be more susceptible to the cholestatic effects of estrogens or may have specific defects in estrogen metabolism. Women with ICP or administered contraceptives may have impaired sulfation. Sulfation is an important physiologic metabolic pathway in the detoxification of endogenous and exogenous compounds [18]. Impaired sulfation favors formation of glucuronide conjugates, which can promote cholestasis [18].

### *Progesterone*

Progesterone also may play a pathogenetic role [19–21]. Patients with ICP may have abnormal progesterone metabolism, with elevated serum levels of sulfated metabolites [20]. These metabolites could saturate the hepatic transport systems for biliary excretion. Oral administration of micronized natural progesterone (900–1200 mg/d) during the third trimester was associated with elevated serum bile acid concentration and serum ALT activity [22].

In a prospective study, 62% of patients with ICP received oral micronized natural progesterone [19]. These patients developed pruritis from ICP earlier during pregnancy than patients who had not received exogenous progesterone. The pruritis disappeared and the liver function improved after withdrawal of progesterone therapy in approximately half of these patients. Progesterone should not be prescribed in pregnant women with a history of ICP and should be withdrawn immediately if cholestasis occurs during pregnancy.

### *Exogenous factors*

Environmental factors also may play a pathogenetic role. Evidence supporting this role includes a recurrence rate of only 45% to 70% in subsequent pregnancies in multiparous women [19,23], seasonal variations in the incidence of ICP in Finland [24] and Sweden [7], and a recently decreasing disease incidence in Sweden [7] and Chile [23].

### *Clinical course*

The primary symptom is pruritus. The pruritis involves mostly the hands and feet, but may extend to the trunk, extremities, eyelids, and even the oral cavity in severe cases [25]. The pruritus is worse at night and may cause sleep deprivation, which can contribute to psychologic distress [15,26–28]. Pruritus usually develops in the third trimester, after 30 weeks of gestation, but can occur as early as the sixth week [19,29–31].

Jaundice occurs in 10% to 15% of cases [15,19]. It develops 2 to 34 weeks after the onset of pruritus and resolves rapidly by 1 to 40 days postpartum. Jaundice without pruritis is rare [19,32]. The jaundice is mild: the serum bilirubin level is less than six times the upper limits of the normal (ULN), and the bilirubin is predominantly conjugated. In most patients, serum levels of AST and ALT are elevated two to ten fold above the ULN [33]. Rare instances with ALT values over 500 times the ULN have been reported [34]. Serum levels of alkaline phosphatase are difficult to interpret because of the physiologic increase during pregnancy as a result of placental production. The prothrombin time may become abnormal in severe cholestasis with jaundice or with long-term administration of cholestyramine; hence, vitamin K deficiency should be anticipated and treated adequately before delivery [35].

The fasting serum concentrations of bile acids in a normal pregnancy are similar to the concentrations in nonpregnant women when measured by an enzymatic method [19], but are increased in ICP [36]. Conjugated primary bile acids, especially cholic acid, are predominantly elevated [30,37,38]. Indeed, the most sensitive predictors of ICP before the onset of symptoms are an increased serum cholic acid level or a ratio of the cholic acid to chenodeoxycholic acid level greater than 1 [39]. These abnormalities persist with established ICP. Measurement of fasting serum total bile acid

concentration is, therefore, a valuable diagnostic test [23,40]. This test is valuable particularly when a pregnant patient experiences pruritis with normal aminotransferase levels.

### *Pathology*

Liver biopsy rarely is necessary for the diagnosis. Histopathology reveals cholestasis, with bile plugs in hepatocytes and canaliculi, which occur predominantly in the centrilobular regions. No inflammation or necrosis is observed and the portal tracts are normal [41].

### *Maternal outcome*

Intense pruritis can lead to severe fatigue and psychologic distress. Anorexia, nausea, vomiting, and poor weight gain can occur [6,25]. Postpartum, the risk of cholelithiasis increases 2.7-fold in a primigravida who had ICP [4,6,25]. The stones are composed predominantly of cholesterol. The risk of postpartum hemorrhage increases as a result of vitamin K malabsorption [1]. There are no long-term clinically significant sequelae.

### *Fetal outcome*

ICP is associated with an increased risk of fetal prematurity, stillbirth, meconium-stained amniotic fluid, and abnormal fetal heart rate patterns [1–3,7,12,25,37,42,43]. The high rate of multiple pregnancies in patients with ICP may contribute to the observed fetal prematurity [19]. Fetal mortality may not be correlated with the severity of maternal symptoms, traditional signs of intrauterine hypoxia, or chronic impaired placental perfusion, because the birth weights of the infants are appropriate for gestational age [3]. Two series note that decreasing fetal mortality is attributed to antenatal testing, including nonstress testing (NST), amniocentesis, and induction of labor when fetal lung maturity is achieved [8,44].

## **Management**

### *Medical treatment*

The goal of pharmacologic treatment is amelioration of maternal symptoms and improving the fetal outcome. Antihistamines, benzodiazepines, and other tranquilizers have been used to treat pruritis, with minimal success in alleviating maternal symptoms and with no improvement in the biochemical status or fetal outcomes. Low doses (2–5 mg/kg) of phenobarbital have been shown to improve the pruritis in 50% of patients, but do not improve the biochemical indices of cholestasis [5]. Other studies, however, have not confirmed this finding [6,45]. Dexamethasone treatment suppressed fetoplacental estrogen production, decreased bile acid levels, and ameliorated the pruritis in a study of 10 patients [45]. The safety and risk of

dexamethasone therapy requires further study. Cholestyramine, an anion exchange resin, binds bile acids in the intestine and increases bile acid excretion in feces. It improves maternal pruritis, but does not improve biochemical parameters or fetal outcome [6,46]. Cholestyramine paradoxically may worsen maternal and fetal outcomes by intensifying maternal vitamin K malabsorption, leading to a coagulopathy and, in case reports, fetal cerebral hemorrhage [47,48]. Maternal coagulation status determination and administration of parenteral vitamin K is recommended, as needed, when cholestyramine is administered long term [6,47,48].

Intravenous administration of S-adenosyl methionine (SAME) at 800 mg/d for 20 days has been shown to decrease pruritis, bile acid levels, and aminotransferase levels [6]. It reduces the inhibition by ethinyl estradiol of bile flow and increases the sulphation of bile acids for bile acid detoxification [6,49]. These beneficial results could not, however, be duplicated by Ribalta et al [43]. More studies of SAME are needed.

Ursodeoxycholic acid (UDCA), a naturally occurring tertiary bile acid, modifies the bile acid pool composition by replacing lithocholic acid, which is mildly cytotoxic to the hepatocyte membrane [6,50], and by decreasing the absorption of cholic acid and chenodeoxycholic acid [37]. UDCA improves ethinyl estradiol-induced cholestasis in the rat [51]. In ICP, UDCA improved pruritis and liver function tests without maternal or fetal toxicity [52–56]. In a randomized, double-blind, placebo-controlled study, administration of 14 mg/kg/d of UDCA improved maternal pruritus and fetal outcome in ICP [31]. In a controlled study of 20 patients with ICP in the last trimester, 450 mg/d of oral UDCA was more effective than 1000 mg of SAME intramuscularly in controlling pruritis and reducing serum total bile acid concentrations [57]. UDCA also improves the maternal bile acid concentration profile and decreases the percentage of cholic acid [21,30], improves progesterone metabolism, and markedly decreases the serum levels and urinary excretion of sulfated steroids [21]. UDCA is not known to be teratogenic.

### *Obstetric management*

Fetal outcome is improved by early diagnosis and aggressive management, including intense fetal surveillance, delivery after fetal lung maturity, and administration of pharmacologic agents that decrease bile salts [8,44]. In one study, perinatal mortality decreased when an aggressive approach was compared to routine care [32].

An obstetric decision to terminate pregnancy should be made after weighing the risk of prematurity resulting from early delivery versus the risk of intrauterine death. Rioseco et al proposed that patients without jaundice should be delivered at 38 weeks of gestation provided that pulmonary maturity has been achieved and the serum bilirubin is greater than 1.8 mg/dL [8]. Perinatal outcome with this intervention was better than

previously reported and approximated that of controls [8]. Sudden fetal death can occur. This death is difficult to predict by conventional fetal surveillance, including weekly NST and amniotic fluid assessment, probably because it is the result of acute fetal hypoxia [42].

### **Acute fatty liver of pregnancy**

Acute fatty liver of pregnancy (AFLP) was first identified by Sheehan in 1940 [58]. It is a rare and potentially fatal disease, complicating a normal pregnancy in the third trimester. The name AFLP has replaced earlier terminologies, “acute yellow atrophy of pregnancy” and “acute obstetric fatty metamorphosis of liver” [59–66].

#### *Incidence and characteristics*

AFLP is rare, occurring once in every 7,000 to 14,000 deliveries [67,68]. It has a worldwide distribution with no distinctive epidemiologic feature related to geography or ethnicity. AFLP affects pregnant women mostly in the third decade, but has been diagnosed in women from 16 to 39 years of age [59,63]. The frequency is higher in primiparous women, but it can occur after multiple uneventful pregnancies [59,63]. It occurs more frequently in pregnant women carrying a male fetus or more than one fetus [69,70]. AFLP occurs usually between weeks 30 and 38 of gestation, but can occur as early as 26 weeks of gestation or immediately postpartum [62,71]. Maternal and fetal mortality as high as 70% and 90%, respectively, were reported in older series, but recently the rates have diminished substantially because of greater disease awareness, earlier diagnosis, and improved intensive care support [63,68,72–74].

#### *Pathogenesis*

The etiology is not known precisely. AFLP causes microvesicular steatosis and mitochondrial dysfunction. A genetic component has been suggested, although no familial cases (ie, in mother and daughter) have been reported [75,76]. Recent research suggests that AFLP is associated with a Glu474Gln mutation in the long-chain 3-hydroxy acyl-coenzyme A dehydrogenase (LCHAD), a fatty acid  $\beta$  oxidation enzyme [75,76]. Short chain acyl-coenzyme A dehydrogenase deficiency (SCHAD) in an infant also has been reported to be associated with AFLP [77]. Women with LCHAD deficiency, however, do not always have liver disease [78–80]. Liver disease in pregnancy occurs most often when the fetal deficiency of enzymatic activity is severe with fetal-maternal transfer of accumulated metabolites. Two women with AFLP had healthy children in subsequent pregnancies without developing recurrent AFLP [81].

### *Clinical course*

AFLP presents with sudden onset of nausea and vomiting in 70% of cases, right upper quadrant or epigastric pain in 50% to 80%, or a flulike syndrome with malaise, headache, and anorexia [64,69,82]. Typically, the pregnancy is considered normal until the disease occurs. Jaundice usually occurs one to two weeks after the onset of these nonspecific symptoms, but pruritis is rare [60,64], except for a high incidence of pruritis reported in one series [63]. One half of patients develop preeclampsia [69]. Physical findings are typically minimal and the liver edge is rarely palpable [59,63,64,73,83].

Most patients improve one to four weeks postpartum. The delivery may be spontaneous or induced. A cesarean section may be performed. Rarely, the disease may worsen postpartum [63,73,84,85]. If not terminated promptly, pregnancy may culminate in fulminant hepatic failure with its attendant complications and a high maternal and fetal mortality. Some authorities, however, favor expectant management of mild cases [69]. Maternal and fetal mortality has decreased from 85% before 1980 to less than 20% in 2000 [60,63,64,82].

### *Laboratory findings*

Leukocytosis occurs commonly. Coagulation disorders, including thrombocytopenia, decreased clotting factors, and disseminated intravascular coagulopathy (DIC) are common. Liver test abnormalities include serum conjugated hyperbilirubinemia (usually between 5 and 15 mg/dL), increased alkaline phosphatase, and modest increases in serum aminotransferases (usually < 1000 IU/L). Hypoglycemia and renal dysfunction can occur. Ultrasound, CT, and MRI scans may suggest a fatty liver [63,86,87].

### *Histopathology*

Although not required, a liver biopsy is helpful diagnostically. The hepatic architecture is intact and the lobules are swollen with compressed sinusoids. Centrilobular microvesicular fatty infiltration of hepatocytes is diagnostic. Subtle signs of inflammation or hepatocyte necrosis may be present. One fourth of patients have substantial inflammatory cell infiltration of the lobules and portal tracts [64,68,88].

### *Complications*

Complications include cerebral edema, gastrointestinal hemorrhage (33%), renal failure (60%), coagulopathy (30%), hypoglycemia (53%), and infections (45%) [63,73]. Once severe liver dysfunction develops, spontaneous labor or fetal death can occur and the delivery often is complicated by severe postpartum hemorrhage. Maternal DIC can cause placental infarcts, placental insufficiency, and fetal asphyxiation [89]. Liver function

often returns spontaneously to normal postpartum, without demonstrable chronic liver disease [90,91].

### *Treatment*

There is no specific therapy. Early recognition and prompt delivery are recommended to improve maternal and fetal survival. Severely affected patients (encephalopathy, severe jaundice, and prothrombin time < 40 percent of the control value) or patients with extrahepatic complications should be attended in intensive care units with aggressive treatment of complications [63,73,84,92,93]. Liver transplantation is a therapeutic alternative for patients who deteriorate or do not improve postpartum. It has been performed successfully in anecdotal cases [94,95].

### **Hemolysis, elevated liver enzymes, and low platelets syndrome**

Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is a form of pre-eclampsia that threatens the gravida and fetus; its features are listed in the Box 1. Weinstein originally described this condition in 29 patients [96,97]. Goodlin et al divided the severe forms of edema proteinuria hypertension (EPH) into two entities, one group at risk of seizures and another at risk of multiorgan failure, including significant liver abnormalities and thrombocytopenia [98,99]. Patients with a history of HELLP have an increased risk of developing HELLP and preeclampsia during subsequent pregnancies [100,101].

### *Pathology*

The peripheral smear characteristically reveals a microangiopathic hemolytic anemia. The liver histology shows periportal hemorrhage and periportal or focal parenchymal necrosis with hyaline deposits. Fibrin microthrombi and fibrinogen deposition in sinusoids may occur. Steatosis occurs in one third of patients [102–105]. Hepatic infarction has been reported. The liver capsule occasionally can rupture from an underlying hematoma.

### *Clinical presentation*

Nausea and epigastric or right upper quadrant pain are the most frequent symptoms. They occur in 36% to 86% of patients [97,106]. Nearly one third of patients experience headaches, and approximately 10% experience visual changes [97]. Most patients have significant proteinuria and hypertension. Hypertension is mild in approximately 16% of patients and is absent in

**Box 1. Diagnostic features of HELLP syndrome***Hemolytic anemia*

Abnormal peripheral smear  
Total bilirubin >1.2 mg/dL  
Lactic dehydrogenase >600 U/L

*Elevated liver enzymes*

Serum aspartate aminotransferase >70 U/L or >2 times  
upper normal limit

*Thrombocytopenia*

Platelet count < 100,000/mL

another 15% of patients [107]. The degree of proteinuria may not reflect disease severity. Physical signs include right upper quadrant tenderness, nondependent edema, and hyperreflexia.

HELLP occurs preterm in more than 80% of cases, with 11% of cases occurring before 27 weeks. Approximately 20% of cases develop postpartum. HELLP occurs in 20% of cases of severe preeclampsia [106]. Most patients worsen initially postpartum, followed by recovery within 72 hours [108,109].

*Maternal and fetal outcomes*

The most important cause of maternal morbidity is the development of DIC and spontaneous or postpartum hemorrhage [106]. Patients may require blood transfusion. Hypertension, eclampsia, pulmonary edema, acute renal failure, and abruptio placentae can occur. Hepatic rupture occurs rarely [106]. Maternal mortality ranges from 0% to 24% [97, 106,110]. More than one third of fetuses are born premature or exhibit intrauterine growth retardation. Prematurity increases the risk of perinatal mortality, which ranges from 7.7% to 60% in different series [97,107, 111–113].

*Management*

Several other conditions mimic this syndrome, as indicated in Box 2. HELLP usually is differentiated by considering the timing of the illness and the clinical findings. The specific management of HELLP is expeditious delivery, if the baby is viable. The detailed management of preeclampsia is

**Box 2. Differential diagnosis of HELLP syndrome***Hyperemesis gravidarum*

Gastritis

Pancreatitis

Cholecystitis

Appendicitis

Glomerulonephritis

Pyelonephritis

Hemolytic uremic syndrome

Thrombotic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura

Systemic lupus erythematosus

beyond the scope of this article, and the interested reader is referred to several reviews on the subject [114–116].

**Pregnancy and portal hypertension**

Pregnancy in a cirrhotic patient is rare because of reduced fertility and the older age of cirrhotic patients [117–121]. In patients with noncirrhotic portal hypertension (NCPH), including extrahepatic portal vein obstruction (EHPVO) and noncirrhotic portal fibrosis (NCPF), liver function and fertility are relatively well preserved [122–124]. Certain liver diseases, such as primary biliary cirrhosis, biliary atresia, and primary sclerosing cholangitis, progress slowly and have relatively well-preserved fertility until hepatic failure develops [125–129]. Pregnancy affects the splanchnic circulation and portal hypertension, and cirrhosis or portal hypertension affects the pregnancy and increases maternal and fetal morbidity.

*Hemodynamic changes in pregnancy*

Pregnancy profoundly affects systemic hemodynamics, as indicated in Box 3 [130], and may contribute to rapid deterioration of portal hypertension, including increasing the risk of variceal hemorrhage [118,123,131]. The effects on systemic hemodynamics begin early in the first trimester in response to markedly increased oxygen and nutrient demands by the growing fetus and also serve to maintain an adequate reserve for the mother during pregnancy, delivery, and the puerperium.

To achieve adequate tissue perfusion, a normal blood volume, relatively normal hematocrit, and adequate perfusion pressure are required. Blood pressure is directly related to the cardiac output and systemic vascular resistance (SVR). The SVR is determined by the arteriolar tone across all vascular beds,

**Box 3. Physiologic changes in systemic hemodynamics during pregnancy***Increased blood volume*

Sodium and water retention  
Increased erythrocyte volume

*Changes in venous return*

Increase secondary to increased blood volume  
Decrease as a result of vena cava compression by gravid uterus

*Increased cardiac output*

Increased heart rate  
Increased stroke volume

*Decreased blood pressure*

Decreased systemic vascular resistance  
Systemic vasodilatation  
Placental circulation

and, in turn, determines the intravascular space of the blood. A critical balance between the circulating blood volume and the available intravascular space determines the adequacy of tissue perfusion. To maintain adequate perfusion of all organs, including the growing fetus, changes occur in all hemodynamic parameters, including increased blood volume, changes in venous return, increased cardiac output, and decreased arterial blood pressure.

The plasma volume rises progressively from approximately the sixth week of gestation to the 32nd week of gestation, with a total increase of 40% to 50% [132]. An early change in volume homeostasis is an increase in sodium retention, despite an increase in the glomerular filtration rate (GFR), resulting in overall net retention of approximately 1000 mEq of sodium [133]. Increased tubular reabsorption is promoted by increased plasma aldosterone levels and increases in estrogen, deoxycortisone, and placental lactogen levels. The renin-angiotensin-aldosterone system (RAAS) changes dramatically, with an up to tenfold increase in plasma renin activity (PRA), and a two to three fold increase in plasma aldosterone levels [134,135]. The increase in PRA results from the vasodilated state, elevated progesterone levels [136], and activation of the macula densa resulting from increased sodium delivery [136,137].

Pregnancy induces water retention beyond that expected from the sodium retention [138,139]. The precise molecular mechanism is unknown. Water retention may involve activation of specific water channels (aquaporins) in the distal nephron, which permits water to move from the hypo-osmolar

lumen to the hyperosmolar interstitium in order to return to the systemic circulation [140].

Sodium and water retention produce an increase in maternal blood volume. The total erythrocyte mass increases by approximately 20% to 30% and contributes to the increase in blood volume [141]. The plasma volume increases more than the erythrocyte volume, resulting in a significant decrease in maternal hematocrit [141,142]. The effect on venous return depends not only on the volume, but also on the distribution of blood. Late in pregnancy, the gravid uterus compresses the inferior vena cava and reduces venous return in the supine position [143]. The net effect usually is an increased venous return.

Maternal cardiac output increases by 30% to 50% during pregnancy to 6.0 L/min, from a nonpregnant level of 4.5 L/min [133,144]. Cardiac output is the product of heart rate and stroke volume, both of which increase during pregnancy. The stroke volume increases by up to 75 ml per stroke [133,145] and the heart rate by 15 to 20 beats per minute [127]. Peripheral vascular resistance falls during pregnancy because of endothelial muscle relaxation, mediated by elevated progesterone levels. This leads to a progressive decline in systemic arterial blood pressure during the first 24 weeks. The placental circulation adds to the decline in arterial blood pressure. Decreased SVR and increased cardiac output produce a hyperdynamic circulatory state with an increased pulse pressure [133]. After 24 weeks, systolic and diastolic pressures slowly rise to return to nonpregnant levels by term.

### *Hemodynamics of portal hypertension and pregnancy*

Portal hypertension is defined as a portal pressure in excess of 5 mm Hg [137] as measured by the hepatic venous pressure gradient (HVPG):  $HVPG = WHVP - FHVP$ , where WHVP is the wedged hepatic venous pressure and reflects the portal pressure in the absence of obstruction in the pre-sinusoidal vascular tree and FHVP is the free hepatic venous pressure that corrects for intra-abdominal pressures [146]. As in any vascular system, the pressure gradient along the portal venous system is the product of portal blood flow and vascular resistance, defined according to Ohm's law as: pressure = flow (Q)  $\times$  resistance (R).

Inflow of blood to the portal venous bed depends on the delivery of blood from the splanchnic bed and the resistance of the splanchnic arterioles (Fig. 1). The former depends on the presence of an effective circulating blood volume and a normal cardiac output. Portal inflow is critically dependent on the tone of the splanchnic arterioles, which are susceptible to pharmacologic manipulation.

Portal hypertension usually is initiated by increased resistance within the portal venous bed, which can occur at a presinusoidal, sinusoidal, or post-sinusoidal level. Portal hypertension usually is associated with a paradoxical increase in portal venous inflow, caused by mesenteric arteriolar dilatation,

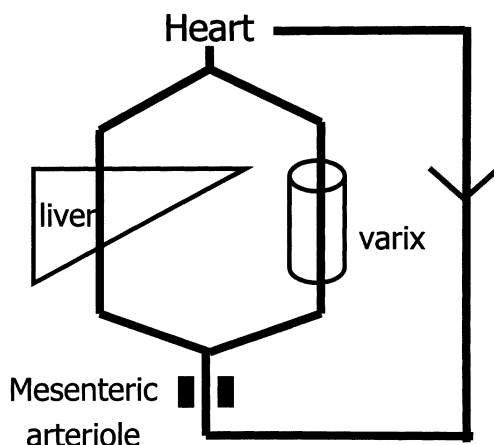
**Pressure= flow x resistance**

Fig. 1. A diagram of the splanchnic circulation and its relationship to the systemic circulation.

which aggravates the portal hypertension [146]. Although portal pressure has not been directly measured in pregnant humans, indirect evidence suggests portal pressure increases during pregnancy. Indeed, transient portal hypertension and development of varices have been described as rare physiologic accompaniments of late pregnancy [147]. This mainly is the result of, presumably, increased portal venous inflow from increased blood volume or increased cardiac output, mesenteric vasodilatation, or increased resistance from increased inferior vena cava pressure. Increased intra-abdominal pressure in the second and third trimesters also contributes a postsinusoidal component to the portal hypertension by increasing inferior vena cava pressure. Rerouting of blood via gastroesophageal collaterals occurs as a result of the increase in inferior vena cava and portal vein pressures [148].

The hemodynamic effects of portal hypertension do not become clinically significant until the HVPG exceeds 12 mm Hg [137]. At this pressure, the vessels in the collateral circulation enlarge and become tortuous, forming varices. Such varices occur mainly in the esophagus and stomach. They come to clinical attention when they rupture and bleed. The risk of bleeding from varices depends on their mural tension, as mathematically defined from Laplace's principle as:  $tension = (P_1 - P_2) \times r/w$ , where  $P_1 - P_2$  is the transmural pressure gradient,  $r$  is the radius of the varix, and  $w$  is the variceal wall thickness. The pressure gradient primarily reflects intravariceal pressure, which obeys Ohm's law and is related to flow and resistance. Wall tension can thus be redefined as:  $tension = (variceal\ flow \times collateral\ resistance) \times r/w$ .

Varices with a high pressure, large radius, and thin wall are, therefore, most likely to rupture. During pregnancy, increased portal pressure drives

additional blood into the portosystemic collateral circulation and the varices. Variceal wall tension is increased from increased portal pressure, increased collateral inflow caused by increased intra-abdominal pressure, or Valsalva's maneuver during the second stage of labor; these increase the tendency for hemorrhage. The changes in the systemic and portal circulation are maximal in the second trimester; consequently, the risk of hemorrhage is greatest during this period. Furthermore, during labor, collateral resistance rises sharply because of increased systemic venous pressure from use of Valsalva's maneuver to push the fetus through the birth canal [147].

### *Clinical considerations*

Pregnancy in a patient with cirrhosis or portal hypertension is challenging for the obstetrician and hepatologist. If she conceives, what would be the fetal and maternal outcome? What would be the best obstetric management during pregnancy, labor, and puerperium? What may happen to the underlying liver disease? These are important questions to address.

### *Effect of cirrhosis or portal hypertension on pregnancy outcome*

Because of few data on pregnancy outcome, the effects of cirrhosis on pregnancy complications and outcome are controversial (see Box 4). Cirrhotic patients have a high incidence of fetal wastage, ranging from 9.6% to 66% [118,149,150,151]. Fetal wastage in patients with NCPH ranges from 7.9% to 20% [122,149,150].

The spontaneous abortion rate in cirrhotic patients is approximately 15% to 20% [118,120,151,152], a rate higher than in patients with EHPVO (3% to 6%) [121,123,153]. In the latter group [123], the overall spontaneous abortion rates are comparable with the general population. In a study from India, patients with NCPH had nearly the same pregnancy outcome as the general population, except for an increased incidence of abortion of 20% [122]. Interestingly, cirrhotic patients with well-preserved liver function who underwent a portal decompressive operation before conception have abortion rates similar to those with EHPVO [118,120]. Most spontaneous abortions occur in the first trimester, regardless of the cause of portal hypertension [118,149], except in the Indian series of patients with NCPH, in which 60% of the abortions were midtrimester [122]. The rate of premature termination of pregnancy is similar among patients with cirrhotic and noncirrhotic portal hypertension [123].

Perinatal mortality is increased in patients with cirrhosis or portal hypertension, with a rate ranging from 11% to 18% [120,151,152,154]. A higher perinatal mortality of 33.3% was reported from India for patients with NCPH resulting from the occurrence of variceal hemorrhage during pregnancy [122]. Patients with portal hypertension diagnosed before pregnancy

**Box 4. Causes of premature termination of pregnancy and fetal demise in patients with liver disease***Causes of termination of pregnancy before 20 weeks of gestation*

Spontaneous abortion (10% to 18%)  
Therapeutic abortion  
Hysterotomy

*Causes of termination of pregnancy from 20 to 37 weeks of gestation*

Maternal death  
Variceal hemorrhage  
Therapeutic abortion

*Causes of perinatal mortality*

Stillbirth  
Prematurity  
Intrauterine growth retardation  
Maternal complications during labor and delivery

fared better than patients who were diagnosed during pregnancy. Fetal outcome was improved in patients who underwent endoscopic obliteration of varices or decompressive shunt surgery prior to conception [30,118,122,123,150,155].

*Effect of pregnancy on portal hypertensive mother*

Various maternal complications occur in 30% to 50% of women who conceive in the presence of portal hypertension, including variceal hemorrhage, hepatic failure, hepatic encephalopathy, postpartum hemorrhage, rupture of splenic artery aneurysm, rupture of splenorenal shunts, spontaneous bacterial peritonitis, and maternal death [118,120,122,123,149,150]. Women with cirrhotic portal hypertension develop maternal complications more frequently than women with NCPH [118].

Toxemia of pregnancy is not more frequent in women with portal hypertension [118]. Variceal hemorrhage occurs in 19% to 45% of patients. It is most common in the second trimester and during labor [118,120,155]. Up to 78% of patients with varices bleed during pregnancy [118,120,121]. Maternal mortality associated with variceal bleeding in the perinatal period in patients with varices and cirrhosis ranges from 18% to 59%, whereas the mortality in noncirrhotic patients is only 2% to 6% [149,156,157]. Although one review reported that variceal bleeding is not predicted by a prior history

of variceal bleeding [149], other data support that prior variceal hemorrhage is a risk factor for rebleeding during pregnancy [120].

Postpartum hemorrhage occurs in 7% to 26% of cases and is more common in cirrhotic patients because of a higher likelihood of coagulopathy and thrombocytopenia [118,152,155,158]. Postpartum hemorrhage has been reported even in patients status post a portocaval shunt [151]. Hepatic decompensation, usually secondary to variceal hemorrhage, is an important cause of maternal mortality. Acute-on-chronic hepatic failure occurs in up to 24% of cirrhotic patients during pregnancy and nearly one third of these patients die within the first 48 hours [121,159]. Jaundice and hepatic encephalopathy often are precipitated by hemorrhage and hypotension [120,121,155,160]. Ascites and peritonitis occur rarely, for unknown reasons. Pregnant patients with portal hypertension have a 2.6% risk of rupturing a splenic artery aneurysm; this should be suspected in patients presenting with sudden abdominal pain and hemodynamic collapse [161–163]. During pregnancy, 69% of these aneurysms rupture in the third trimester, with a fetal mortality of nearly 80% and a maternal mortality of up to 70% [164–166]. The overall maternal mortality ranges from 4% to 7% in patients with EHPVO [121,123,149] and from 10% to 18% in patients with cirrhosis [121,153]. Portal decompression before pregnancy decreases mortality [118,157].

### *Management of pregnancy with portal hypertension*

The optimal management of pregnancy in a cirrhotic patient requires a coordinated approach by a team including an obstetrician, hepatologist, neonatologist, and anesthesiologist. The patient and the immediate family should be informed of the possible complications and probable outcome in the context of the facilities available. Such patients ideally should be managed at centers with facilities for high-risk obstetric care, perinatal intensive care, and expertise with endoscopy and portal-vascular decompressive surgery.

### *Preconception counseling*

Preconception counseling should focus on assessing the risks of pregnancy, the patient's psychologic status, and the parents' desire for children. The potential risks to the mother and fetus should be explained to the prospective parents [165]. The initial evaluation should include a complete history, physical examination, and laboratory studies of liver, renal, and coagulation function. The risks of transmitting genetic hepatic diseases, such as  $\alpha$ -antitrypsin deficiency and hemochromatosis, or of transmitting infectious diseases, such as hepatitis B and C, to the offspring should be explained. Pregnancy should be planned when the liver disease is stable and reliable contraception encouraged until conception is desired. If liver transplantation is contemplated, pregnancy should be delayed until after the transplantation.

Medical regimens must be tailored to optimize maternal and fetal outcome. Immunosuppressive drugs, such as prednisone and azathioprine, used frequently in patients with autoimmune hepatitis, and cyclosporine, used in liver transplant recipients, should be used at the lowest effective dosage, because they are associated with intrauterine growth retardation and neonatal immunosuppression [167–169].

In the presence of portal hypertension, endoscopic evaluation for esophago-gastric varices is mandatory [120,165]. The absence of varices does not preclude possible variceal hemorrhage during pregnancy, but renders it unlikely [156]. When varices are present, management is affected strongly by whether or not the varices previously bled (Fig. 2). Patients who never have bled from varices but have medium- or large-sized varices are at high risk of variceal hemorrhage during pregnancy [123,170,171]. A nonselective  $\beta$ -adrenergic receptor antagonist is the therapy of choice for primary prophylaxis of variceal bleeding. The role of endoscopic band ligation for primary prophylaxis of high-risk varices is debatable; only anecdotal data supports their use during pregnancy [172–175]. The principal risks of  $\beta$ -adrenergic receptor antagonists are fetal bradycardia and growth retardation. Therefore, close fetal monitoring is required during therapy.

Patients with prior variceal hemorrhage and borderline liver function are considered at high risk for recurrent variceal bleeding, which could lead to hepatic decompensation. Such patients should be advised against conception. Endoscopic sclerotherapy (EST) has been used routinely to treat active variceal hemorrhage during pregnancy with a favorable outcome [176–178]. During the last decade, however, endoscopic variceal band ligation (EVL) has emerged as the preferred method of treatment, with a meta-analysis showing its superiority over EST [179]. EVL currently is considered safe and efficacious in pregnant patients with portal hypertension [180,181].

### *Antenatal management*

Once pregnancy is established, the expectant mother ideally should be monitored by a hepatologist and an obstetrician. Routine antenatal care with vitamin, trace elements, and mineral supplementation must be provided. Fetal development and maternal adaptation should be monitored closely. An ultrasound and Doppler examination for portosplenic vessels should be performed to screen for a splenic artery aneurysm. Sodium restriction may be imposed in selected patients early during pregnancy to prevent volume overload. As soon as the fetus becomes potentially viable, a perinatologist should become involved, as premature termination of pregnancy may be required in the event of a complication.

If the risks of variceal hemorrhage have not been assessed previously, an endoscopic examination is indicated along with laboratory tests of liver function. The management of varices proceeds as discussed previously. Nonselective  $\beta$ -adrenergic receptor antagonists may be used for primary

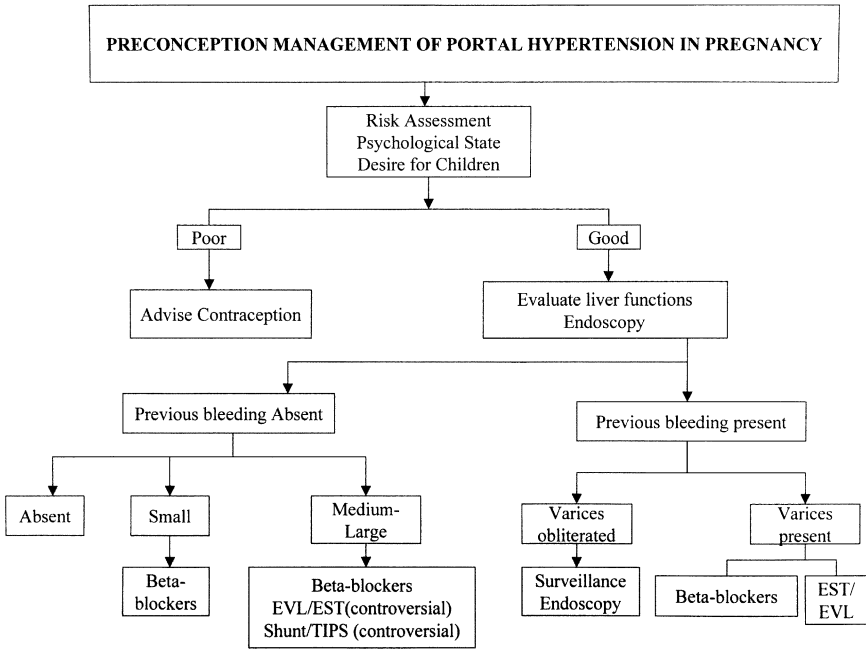


Fig. 2. Preconception management of portal hypertension.

prophylaxis in those patients with high-risk varices. In those patients unable to tolerate these drugs, EVL is a reasonable alternative.

In the event of variceal hemorrhage, the first line of management is endoscopic therapy with EVL or EST, with concomitant use of vasopressors, such as octreotide in a dose of 50 µg intravenously followed by 50 µg/h by continuous infusion for five days [153,182,183]. If the bleeding subsides, additional sessions of EVL should be performed at one- to two-week intervals until the varices are completely obliterated [184]. Failure of endoscopic therapy is a medical and surgical emergency [185]. Performance of transjugular intrahepatic portosystemic shunt (TIPS) exposes the fetus to considerable radiation, and the decision to use this procedure as a salvage therapy should be made considering the risks of exsanguination to the mother and fetus versus the risks of radiation to the fetus.

The underlying cause of portal hypertension should be treated. Patients with immunologically-mediated disease usually do not experience flares during pregnancy, as a result of the immunosuppressive effects of pregnancy. Pruritis, in those with underlying cholestatic liver disease, may worsen. The treatment options for this pruritis include UDCA, mild antihistamines, ultraviolet radiation, and phenobarbital. In patients with hepatitis B or C, interferon treatment should be postponed because of the toxicity and possible teratogenicity. Lamivudine, a nucleoside analog, has been used in mothers with replicating hepatitis B (hepatitis B eAg positive) to

prevent transmission to the fetus and has been shown safe and effective [186]. Currently, lamivudine is recommended as a first-line therapy for chronic hepatitis B [187–191]. In patients who conceive while taking ribavirin, the risk of teratogenicity should be explained and termination of pregnancy advised.

### *Perinatal care*

The management of a portal hypertensive patient near term depends on the status of the liver disease and the size of esophageal varices. The delivery should be monitored closely and adequate sedation administered to avoid premature exertion, while avoiding oversedation. The second stage of labor should be kept short using appropriate obstetric techniques. Overzealous administration of intravenous fluids is not recommended because of the risk of volume overload and variceal bleeding. Coagulation parameters should be monitored closely and a coagulopathy corrected. If cesarean section is planned, a vascular surgeon with expertise in portal decompressive surgery ideally should be available in case of variceal bleeding or ectopic varices in the operative field.

### **Viral hepatitis in pregnancy**

Viral hepatitis may affect women of child-bearing age and their infants. All the hepatotropic viruses can infect a pregnant woman. Viral hepatitis A (HAV) has the same course during pregnancy as in the nonpregnant patient [192]. Intrauterine [193] and perinatal maternal-fetal transmission has been reported, but maternal HAV infection during pregnancy rarely is associated with fetal loss or developmental anomalies. Passive immunization with pooled human serum immunoglobulin, three to six months before, or within two weeks after exposure to HAV, attenuates or prevents HAV in 85% to 95% of cases. Pregnant women traveling to endemic areas may receive safely the HAV vaccine and HAV immunoglobulin for urgent post-exposure prophylaxis [194]. Mothers with HAV have no restrictions concerning breast-feeding.

Hepatitis B virus (HBV), another hepatotropic virus, is known for its risks of vertical transmission to the child, who subsequently can develop chronic liver disease. Ninety-five percent of perinatal transmission occurs intrapartum. The risk of transmission from mother to child is 10% to 40% in mothers who are hepatitis B-e-antigen (HBeAg) negative, but 90% in mothers who are HBeAg positive, in the absence of appropriate prophylaxis [195,196]. Acute HBV infection usually is not severe during pregnancy. Ten percent of infants born to mothers infected during the first trimester are hepatitis B surface antigen (HBsAg) positive at birth [197], whereas 80% to 90% of infants born to mothers infected during the third trimester are HBsAg positive at birth [198]. Thus, antepartum HBsAg testing is mandatory. HBV vaccine is safe and effective in seronegative mothers. Infants born to infected

mothers should receive HBV human hyperimmune globulin (HBIG) at delivery along with the first dose of HBV vaccine [194]. Because HBsAg also is secreted in milk, administration of active and passive immunization at birth reduces the possibility of viral transmission by breast-feeding [199]. Recently, lamivudine, a nucleoside analog, has been used with good safety and efficacy in the last four weeks of pregnancy to decrease the risks of vertical transmission [186].

Hepatitis C virus (HCV) infection during pregnancy does not interfere with normal pregnancy, unless the patient has cirrhosis. Pregnancy, moreover, does not alter the natural course of the infection. Vertical transmission of HCV is possible with a calculated risk of 0% to 36%, depending on the population studied, the diagnostic tests used, and the duration of follow-up. Risk factors for vertical transmission include HIV co-infection and high maternal HCV RNA levels of more than 1 million copies/mL [200–204]. HCV has been isolated from breast milk, but the risk of transmission during breast-feeding is unknown. Breast-feeding was not found to be a risk factor for transmission in a multicenter European trial, however; hence, avoidance of breast-feeding is not recommended. The risks of transmission by breast-feeding were significant only when HIV co-infection was present [205].

Hepatitis E virus (HEV) is rare in the United States and occurs mainly in developing countries. Females in the child-bearing age group commonly are infected. HEV hepatitis generally is mild and self-limited, but commonly (up to a rate of 58%) causes fulminant hepatic failure during pregnancy [206]. The mortality is 1.5% during the first trimester, 8.5% during the second trimester, and 21% during the third trimester [207]. HEV infection during the third trimester is associated with increased fetal complications and fetal death [195,207]. There are no contraindications to breast-feeding, although scrupulous hand washing is essential.

Hepatitis D virus (HDV) occurs in conjunction with HBV and no cases of vertical transmission have been reported. Recommendations regarding breast-feeding are unknown because of the paucity of data on HDV [208].

### **Pregnancy after liver transplantation**

Pregnancy in a liver transplant recipient is considered a high-risk pregnancy [209]. The recommendation is to delay conception until six months after transplantation because of the potential for CMV infection and acute cellular rejection in the first six months after transplantation [210]. Pregnancy after liver transplantation also has a high risk of preeclampsia and worsening hypertension, although the risk of pre-eclampsia has decreased with tacrolimus therapy [109]. Pregnancy is well tolerated provided graft function and renal function are stable. Those patients with recurrent liver disease, especially viral hepatitis or CMV infection, appear to be at greater risk to the mother and the fetus. Immunosuppressive therapy may increase the risk of maternal and fetal infections; antibiotic prophylaxis usually is

recommended during delivery [109]. When managed by expert obstetricians, perinatologists, and transplant surgeons, pregnancy after transplant has a favorable outcome without evidence of congenital malformations, unusual infections, physical impairment, or developmental problems. Breast-feeding generally has been discouraged, but is becoming popular among transplant recipients [210].

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