Liver diseases and pregnancy

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ABSTRACT

Pregnancy is a time of great maternal physiological and metabolic changes and affects biochemical and hematological parameters used in the assessment of liver disease. Due to the increased physiological and metabolic stress of pregnancy, liver disorders that have previously been subclinical may become symptomatic such as cholestatic diseases. The viral hepatitis constitutes a huge disease burden worldwide and the pregnant state confers particular concerns for the mother and her baby. In particular, hepatitis E has a predilection for the pregnant population and confers a particularly poor prognosis. In addition, certain pregnancy specific disorders such as elevated liver enzymes, low platelets syndrome, acute fatty liver of pregnancy, and obstetric cholestasis-affect primarily the liver. It is important to know how to diagnose and manage these conditions and distinguish them from non-pregnancy specific conditions as this will change the timing and management of affected women and their babies, some of whom can be seriously ill.

Physiological changes in liver during pregnancy

The pregnant woman experiences physiological changes to support fetal growth and development. The levels of estrogens (estradiol) and progesterone increase progressively during pregnancy. These sex hormones have effects on hepatic metabolic, synthesis, and excretory functions. The phenomenon of hemodilution secondary to the increase in plasma volume and the increases in cardiac output, decreases the serum protein concentrations.[1] Liver, in course of pregnancy, reveals no specific structural changes. In spite of this, several changes in values of liver function tests occur during normal pregnancy. Blood flow to the liver remains unchanged, but the percentage of cardiac output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism.[1] Moreover, in pregnancy, gallbladder motility is also decreased for several causes: gallbladder enlargement and incomplete evacuation of bile, increased gallbladder volume during fasting is due to a combination of decreased water absorption by the gallbladder mucosa, enhanced of secretion of cholecystokinin in the response to food intake. All these phenomena can originate to from the high concentration of progesterone.[2] In this paper, we review the liver-related clinical and pathology changes that occur during pregnancy, subdividing these conditions into: i) conditions associated with pregnant status; ii) conditions complicating the pregnancy; iii) liver conditions present at the beginning of pregnancy.

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Conditions associated with pregnant status

Intrahepatic cholestasis

Intrahepatic cholestasis of pregnancy (ICP) usually occurs during the last trimester and has a rapid postnatal resolution.[3] It is characterized by severe pruritus, associated with increase in serum bile acid and aminotransferases (Table 1). The symptoms and biochemical abnormalities resolve rapidly after delivery but may recur in subsequent pregnancies and with the use of hormonal contraception.[4] Genetic variations may implicate heterozygous or homozygous mutations located in different positions of the genes. All the association studies with these candidate genes stress the complex variability of genotypes, the different

penetrance, and the influence of several environmental factors. A recent study demonstrated the presence of up-regulation of *GABRA2* receptor gene (that codes for a subunit of the gamma-aminobutyric acid type A receptor) is potentially correlated to ICP and in particular, GABA may play a role in the pathogenesis of pruritus in this condition.[5] Severe ICP (with serum bile acids >40 µmol/L) is associated with adverse pregnancy outcome.[6] The current medical treatment for ICP is ursodeoxycholic acid (UDCA), which acts as several mechanisms of action: protection of hepatocytes and cholangiocytes by replacing endogenous, cytotoxic bile salts, induction of expression of functional transporters at transcriptional and post-transcriptional level, and enhancing bile flow.[7,8]

Eclampsia and preeclampsia

Pre-eclampsia is a condition that occurs after 20 weeks of pregnancy and/or within 24-48 h after delivery. It affects 5-10% of all pregnancies and can involve the kidney, the liver, the central nervous and hematological system. Pre-eclampsia is characterized by hypertension and proteinuria (greater than 300 mg in 24 h), right upper quadrant pain, headache, nausea and vomiting. Presence of seizures differentiates eclampsia from pre-eclampsia.[9] Abnormal liver tests, secondary to vasoconstriction of the hepatic vascular bed, occur in 20-30% of patients and include 10-to-20-fold elevation in aminotransferases, elevations in alkaline phosphatase and bilirubin increase of less than 5 mg/dL[10] (Table 1). Risk factors include extreme maternal age (<16 years and >45 years), primiparity, pre-existing hypertension, family history and occurrence in a previous pregnancy. The pathophysiology involves suboptimal utero-placental perfusion associated with systemic inflammatory response and vascular endothelial dysfunction. Genetic predisposition and imbalance of prostacyclin and thromboxane have also been implicated in the pathogenesis of this disturbance.[11] Pre-eclampsia and eclampsia are associated with 3-to-25-fold increased risk of pulmonary edemas, abruption, aspiration pneumonia, renal failure, hepatic failure, disseminated intravascular coagulation (DIC), and stroke. Hemorrhagic stroke is the most common cause of death, vascular disease, renal, and neurological sequelae. Treatment is aimed to keep the systolic blood pressure below 150 mmHg and the diastolic between 80 and 100 mmHg. First line of hypertension treatment in pregnant women with pre-eclampsia is labetolol, methyldopa or nifedipine. Magnesium sulfate remains the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia. Treatment consists in early delivery whenever possible.[12,13]

Hemolysis, elevated liver enzymes, and low platelets syndrome

The hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is associated with endothelial cell injury and microangiopathic platelet activation and consumption. It occurs in 4-20% cases of pre-eclampsia.[14] The disorder can be diagnosed antepartum (in 70% of cases between 27 and 30 weeks) or postpartum. Risk factors are advanced maternal age, multiparity and Caucasian ethnicity. The pathophysiology remains unknown: activation endothelial cells may lead to release of Von Willebrand factor multimers which are highly reactive with platelets. The syndrome seems to be the final manifestation of some insult that leads to microvascular endothelial damage and intravascular platelet activation.[15,16] Patients may present with right upper quadrant and epigastric pain, nausea, vomiting, and malaise. Hypertension and proteinuria are ev-

Table 1. Conditions associated with pregnant status.

Conditions associated with pregnant status	Biochemical modifications and clinical manifestation	Period of pregnancy
Intrahepatic cholestasis	It is characterized by severe pruritus, associated with increase in serum bile acid and aminotransferases	Last trimester
Eclampsia and preeclampsia	Pre-eclampsia is characterized by hypertension and proteinuria (greater than 300 mg in 24 h), right upper quadrant pain, headache, nausea and vomiting. Presence of seizures differentiates eclampsia from pre-eclampsia. Abnormal liver tests include 10-to-20-fold elevation in aminotransferases, elevations in alkaline phosphatase and bilirubin increase of less than 5 mg/dL	After 20 weeks of pregnancy and/or within 24-48 h after delivery
Hemolysis, elevated liver enzymes, and low platelets syndrome	Biochemical findings include elevated aminotransferases levels (from mild elevation to 1000 IU/L, usually 300-500), elevated bilirubin (frequently >5 mg/dL), leukocytosis, anemia, thrombocytopenia and hypoalbuminemia, increased uric acid, renal impairment, metabolic acidosis, hyperammonemia, biochemical pancreatitis	It can occur antepartum between 27 and 30 week) or postpartum

ident in up to 85% of cases. Because of the hemolysis, high serum unconjugated bilirubin and lactate dehydrogenase are frequent.[17,18] Complications include DIC, pulmonary edema and placental abruption. Perinatal mortality rate is 6-70%, while maternal mortality is 1%.[19] Once HELLP develops, the only definitive treatment is delivery. As in pre-eclampsia, breast-feeding is not contraindicated in HELLP syndrome and for women receiving antihypertensive therapy; nifedipine, labetalol, atenolol, methyldopa, captopril and enalapril have shown to be safe.[20]

Acute fatty liver of pregnancy (AFLP) is a microvesicular fatty infiltration of hepatocytes and a common cause of liver failure in pregnancy. It is a late-gestational complication, often occurring at week 28-40. It is a rare disorder affecting from 1:7000 to 1:16,000 pregnancies, but it is a medical and obstetrics emergency.[21] Risk factors are nulliparity, preeclampsia, multiple gestation, pregnancies with a male fetus, low body mass index (BMI).[22] The etiology is unknown. Defects in intra-mitochondrial fatty acid β-oxidation (enzymatic mutations), in particular a homozygous fetal deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in a mother carrying a heterozygous LCHAD deficiency can be found.[22] However, AFLP may occur in the absence of known genetic mutations.[23] The initial manifestations of AFLP include headache, fatigue, nausea and vomiting. Clinical presentation may vary from abdominal pain, jaundice, signs of preeclampsia (50%), hypoglycemia, hepatic encephalopathy, coagulopathy (DIC). Biochemical findings include elevated aminotransferases levels (from mild elevation to 1000 IU/L, usually 300-500), elevated bilirubin (frequently >5 mg/dL), leukocytosis, anemia, thrombocytopenia and hypoalbuminemia, increased uric acid, renal impairment, metabolic acidosis, hyperammonemia, biochemical pancreatitis (Table 1).[3,9,14] The diagnosis is based on clinical and laboratory findings. Liver biopsy is the gold standard although rarely necessary.[24] Maternal mortality ranges from 7% to 18% and fetal mortality from 9% to 23%.[25-27] The management of AFLP requires supportive therapy (diet low in fat and protein and high in carbohydrates, blood components, plasma exchange and hemodialysis, broad-spectrum antibiotics, correction of dehydration, electrolyte and acid-base balance, treatments to protect the liver, reduce jaundice, and diminish liver enzymes); rapid delivery: if vaginal delivery cannot be achieved quickly, Cesarean section is the preferred method.[25,27] Breast-feeding is not contraindicated by AFLP itself, however this should be evaluated on the basis of the supportive therapy needed for maternal stabilization in the intensive care setting.

Liver disease occurring during pregnancy

Acute viral hepatitis

The most common cause of jaundice in pregnancy is acute viral hepatitis. The incidence of hepatitis in pregnancy varies greatly throughout the world according to hygiene, sanitation and socioeconomic conditions.[28]

Hepatitis A virus (HAV) is the most common cause of acute viral hepatitis in the general population but its occurrence during pregnancy has been scarcely reported. Hepatitis A is not associated with a severe outcome during pregnancy and vertical transmission is very rare. HAV vaccination should be considered particularly for women living in areas of high endemicity and poor socioeconomic conditions, to avoid maternal and fetal complications associated with HAV infection in pregnancy. Since there is no evidence of HAV vertical transmission with lactation, breast-feeding appears to be safe.

Acute hepatitis B virus (HBV) infection is not associated with an increased mortality or congenital malformations, although it can cause spontaneous abortion in the first weeks of pregnancy.[29] No difference in mortality or occurrence of fulminant hepatitis was found between the pregnant or not pregnant women. Clinical recovery was also similar between pregnant and non-pregnant women. However, significantly higher levels of hepatitis B surface antigen (HBsAg) and lower ant-HBs seroconversion rates were found in pregnant patients than in non-pregnant patients, indicating that pregnancy could be a risk factor for chronicity following acute HBV infection. Acute HBV infection in pregnancy has a higher rate of vertical transmission than that usually occurring during delivery, due to newborn exposure to cervical secretions and maternal blood.[30] HBV vaccination and hepatitis B immune globulin administration to newborns of HBsAg-positive mothers represent the main strategy to prevent HBV vertical transmission.[31]

Acute hepatitis C virus (HCV) infection has been rarely reported during pregnancy and is limited to high-risk groups, such as intravenous drug users. Frequency of acute hepatitis C during pregnancy is estimated between 0.4% and 6%.[32] HCV infection can be vertically transmitted (risk from 3% to 5%), but there is no evidence of increased transmission through breast-feeding.[33] However antiviral treatment is contraindicated due to the teratogenic effect of drugs available until recently[34] while no data are available for the new interferon-free regimens in this setting.

Hepatitis D virus (HDV) can be acquired by co-infection with HBV or by super-infection of a HBV carrier.[35] Data regarding acute hepatitis D and pregnancy are scant. Considering the availability of HBV vaccination and the change in HDV epidemiology, acute hepatitis D in pregnancy appears to be only sporadic.

Hepatitis E virus (HEV) is responsible for major outbreaks of acute hepatitis in developing countries. HEV is enterally transmitted and clinical manifestations are similar to other forms of viral hepatitis, except in pregnant women that are at greater risk of developing fulminant hepatitis (25% mortality rate).[36] Authors found that fulminant hepatic failure was more common and maternal mortality was greater in HEV-infected women than in non-HEV-infected women. Moreover, women with HEV infection had a higher risk of intrauterine fetal death.[37] Vertical transmission rates are reported between 33.3% and 78.9%.[38,39] There is currently no evidence of HEV transmission through breast-milk.

Gallstone disease

Gallstones are common during pregnancy. The prevalence ranges between 2.5% and 11% of cases.[32] During pregnancy, female sex hormones are endogenously increased, and biliary sludge (composed of cholesterol, calcium bilirubinate and mucin) appears in 5-30% of women.[40] In the post-partum period sludge resolution develops in two-third of cases, small gallstones (microlithiasis) disappear in one-third, but definite gallstones become established in approximately 5% of cases.[41,42] Additional risk factors include obesity, reduced high-density lipoprotein cholesterol and metabolic syndrome.[40] Acute biliary colic or uncomplicated cholecystitis can be treated conservatively but endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy should be considered in cases of multiple relapse of the disease.[43] The use of drugs such as UDCA and the lipid-lowering compound ezetimibe could also be considered.[44] Cholecystectomy during pregnancy is not entirely safe because of the abortion risk with anesthesia and for this reason, laparoscopic cholecystectomy, when indicated, should be performed in the second trimester to avoid serious complications.

Vascular liver diseases

In pregnancy, the levels of coagulation factors VII and VIII, von Willebrand factor and fibrinogen are increased, while free protein S levels are reduced. Moreover, increased plasminogen activator inhibitor-1 and 2 (the latter synthesized by the placenta) decrease fibrinolytic activity. Such changes shift the hemostatic balance towards hypercoagulability, which persists up to 8 weeks after delivery.[45] Therefore, vascular liver diseases, can occur and worsen the normal course of pregnancy.

Budd-Chiari syndrome

Budd-Chiari syndrome (BCS) is a rare disease caused by the obstruction of the hepatic venous outflow, due to thrombosis of the hepatic veins or of the suprahepatic portion of the inferior vena cava, leading to sinusoidal congestion, ischemic liver damage and portal hypertension.[46,47] One or more risk factors for venous thromboembolism are usually present in BCS patients. Pregnancy, as well as oral contraception or estrogen-replacement therapy, may precipitate BCS.[48-52] BCS occurring in pregnancy accounts for about 15% of all women with BCS.[53] Symptoms include fever, abdominal pain, ascites, lower limb edema, jaundice, gastrointestinal bleeding and hepatic encephalopathy. In pregnancy, the clinical presentation is frequently fulminant, with a high mortality. Ultrasound is the imaging technique of choice in pregnancy as there is no ionizing radiation exposure associated with it.[54] The safety of gadolinium-based contrast agents is controversial; therefore, magnetic resonance imaging should be used if the diagnosis of BCS cannot be otherwise excluded. The management of BCS occurring in pregnancy differs from that in non-pregnant women as vitamin K antagonists (VKA) are contraindicated due to risk of fetal hemorrhage and teratogenicity.[54] A stepwise treatment, starting with a twice-daily low molecular weight heparin (LMWH), followed by transjugular intrahepatic portosystemic shunt (TIPS) in failures or relapses, is recommended. Liver transplantation is possible.[55] Anticoagulation, with LMWH or VKA, can be restarted 12 h after delivery (or 24 h after Cesarean section). Breast-feeding is contraindicated in women taking LMWH, but not in those taking VKA, which are excreted inactive in maternal milk (Class I, Level C).

Acute extra hepatic portal vein obstruction

Acute extra hepatic portal vein obstruction (EHPVO) is the sudden, usually thrombotic, occlusion of the portal vein, variably involving its intrahepatic branches or tributaries, mesenteric and splenic veins. Thrombophilia and abdominal precipitating factors often coexist. Acute EHPVO often presents with abdominal pain, ascites or fever. As for BCS, Doppler ultrasound is the procedure of choice in pregnancy. In acute EHPVO not occurring in pregnancy, if early recognized and treated, a 75% rate of complete or partial recanalization is expected.[56] As in non-pregnant women, the treatment is based on anticoagulation with LMWH. Anticoagulation can be restarted 12 h after delivery (or 24 h after Cesarean section) with VKA if breast-feeding is desired.

Pregnancy in patients with pre-existing chronic liver disease

Chronic viral hepatitis

In women with chronic HBV infection, immunological changes typical of pregnancy may cause an in-

crease in HBV DNA levels while alanine aminotransferase (ALT) remain normal or near normal. Mild exacerbations may occur after delivery.[57,58] In clinical practice, women who are HBV-positive carriers should be counselled regarding pregnancy both on and off treatment. In all cases, indication to treatment according to current recommendations should be considered and discussed with the patient.[59] When fibrosis is mild or absent, treatment can be delayed; stopping antiviral drugs may be considered in women currently receiving treatment. Pegylated interferon (PEG-IFN) is contraindicated during pregnancy. When treatment is indicated, tenofovir is the drug of choice (see below); women who become pregnant while receiving entecavir, adefovir or PEG-IFN, should be switched to tenofovir, if treatment is indicated. Vertical transmission of HBV infection is prevented by vaccine and anti-HBs immunoglobulin administration to newborns within 12 h after delivery.[60] A long-term follow-up of babies born to mothers treated with telbivudine confirmed safety.[61] Lamivudine given from week 32 of pregnancy to mothers with serum HBV DNA ≥109 IU/mL reduced the incidence of newborn infection in a placebo-controlled trial;[62] however not all newborns received complete prophylaxis.

Hepatitis C is a major public health problem: worldwide more than 200 million people are infected with HCV, with an overall prevalence of 3.3%. The epidemiology of HCV varies among countries and its prevalence in pregnant women has not been extensively studied. The prevalence of anti-HCV positivity among pregnant women in Europe is estimated between 1.7% and 2.5%,[32,63,64] but increases to 8% in some developing countries. The natural history of liver disease in pregnant women and their offspring is not fully understood. Pregnancy does not seem to modify the natural course of HCV disease: pregnant women are generally asymptomatic and during pregnancy a significant reduction in ALT levels has been reported, with a rebound during the postpartum period, accompanied by HCV RNA increase towards the end of pregnancy in the majority of HCV-infected pregnant women. Preliminary data suggest no increase in spontaneous miscarriage rate or in obstetric complications in HCV-infected women compared to controls. However, some studies reported a decrease in newborn weight, an increase in congenital abnormalities and in preterm delivery rate.[65,66] Moreover, retrospective data suggest a significantly higher incidence of intrahepatic cholestasis of pregnancy in HCV-infected pregnant women compared with controls. Chronic hepatitis C can lead to vertical transmission of HCV, while it only marginally influences the course of pregnancy and seldom induces spontaneous abortion. The global rate of vertical transmission of HCV is relatively low; it has been estimated between 3% and 5%,[67] in infants born from HCV-positive mothers. Delivery modalities do not influence transmission, and Cesarean section does not decrease perinatal HCV transmission. Breast-feeding should not be discouraged, as transmission of HCV by breast-feeding has not been demonstrated.[68] Antiviral therapy for HCV is contraindicated during pregnancy due to the potential teratogenic effects of ribavirin and the side effects of PEG-IFN. No data are available regarding new interferon-free regimens. Treatment options should be offered before pregnancy.[69,70]

Autoimmune hepatitis

Autoimmune hepatitis (AIH) usually affects women in fertile age, thus pregnancy is rather common in those patients. The presence of maternal cirrhosis impacted on fetal outcome, and the live birth rate was lower in mothers with liver cirrhosis at the time of conception (P=0.002). The maternal course is highly variable. In case of pregnancy occurring at presentation of AIH with *acute* onset, liver disease may have a fulminant course and the fetus has a low chance of survival.[71] In general, women who reach disease remission and do not have cirrhosis with portal hypertension, have a high chance of a favorable pregnancy outcome.[72] In general, pregnancy confers a beneficial effect on immunosuppression with a reduction in maintenance therapy. This is due to several factors, including the physiological increase of serum cortisol.[73,74] In clinical practice the dosage of steroids to maintain remission should be reduced in case of pregnancy. However, pregnancy-related flares may occur in up to 21% of cases, whereas the probability of fares is higher after delivery with an incidence as high as 40%.[75]

Primary biliary cholangitis

Primary biliary cholangitis (PBC) generally develops near menopausal age, with a broad range that includes both the fertile and the geriatric ages. Pregnancies are rather uncommon after PBC has been diagnosed, and there are limited reports in the literature specifically focusing on the outcome of pregnancy in PBC patients, as well as on the effect of pregnancy on PBC course. Finally, the outcome of pregnancy and the influence of pregnancy on the course of PBC were analyzed in a case–control study including 186 consecutive patients with PBC who had at least one conception and a 1:2 control group of 367 healthy women.[76] The two groups' history was similar in terms of miscarriages, voluntary interruption of pregnancy, and term and pre-term deliveries. Pruritus during pregnancy was recorded in 15 pregnancies involving 13 PBC patients (3%) and in none of controls. Perinatal and postnatal deaths and complications at childbirth were only recorded in the PBC patients, in-

volving 11 babies (2.7%, P<0.05). Eight pregnancies occurred after PBC was diagnosed in 6 patients, all of whom had a favorable course at term, with no complications at childbirth. UDCA is safe and well tolerated during pregnancy. UDCA treatment with increasing doses up to 25 mg/kg/day during breast-feeding has shown to be safe, and no adverse effects were observed in either infants or mothers.[77]

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) has an incidence around 0.9-1.3 per 100,000 per year and a prevalence around 8.5-14.2 per 100,000 in Northern Europe and in the United States.[78] Up to 80% of PSC patients have concurrent inflammatory bowel disease (IBD).[78] Fertility does not seem to be reduced in patients with PSC, and in young female patients, pregnancy is possible. No strong association has been found between the development of PSC and previous perinatal events including birth length, breast-feeding and the majority of maternal medical complications.[79] Continuation of treatment with UDCA or azathioprine had no negative effects on pregnancy outcome. The exacerbation of IBD during pregnancies complicated by PSC is described in 25-30% of cases.[80] PSC also carries a risk of biliary sludge and stones; nevertheless, the risk of biliary colic and/or complications of gallstones is very low.

Hemochromatosis

Hemochromatosis (HH) is a recessive disease (prevalence 2-5/1000) due in most cases to homozygosity for the C282Y mutation of *HFE* gene, which confers a genetic predisposition to progressive body iron overload. Host-related and acquired factors are needed for the phenotypic expression of the disease. Fertility is impaired only if diagnosis and treatment are late, when women have developed gonadal dysfunction. Given the recessive pattern of inheritance, there is no need for prenatal diagnosis for pregnant women with HH.[81] Iron should not be prescribed routinely to pregnant women with HH unless clearly iron deficient, and ferritin should be frequently checked. In the presence of iron overload, iron depletion by phlebotomy or chelators should be delayed to the end of pregnancy, unless evident cardiac involvement is present. Gestational diabetes seems to be more frequent in pregnant women heterozygous for the C282Y mutation.[82]

Wilson's disease

Wilson's disease is a recessive disease (prevalence 1/30,000) characterized by defective biliary excretion of copper and consequent accumulation in liver and brain, due to rare mutations of *ATP7B* gene, which encodes a copper transporting protein. Clinical presentation, which can occur at any age, may be very different including acute and chronic liver disease, cirrhosis, neuropsychiatric disorders, and acute hemolysis. Women are frequently non-ovulatory, but treatment can restore fertility when started in an early stage of the disease. Successful treatment allows pregnancy but copper status should be optimized before pregnancy. Likelihood of delivering a homozygote, without knowledge of the paternal status, is 0.05%.[83] Maintaining therapy during pregnancy is essential because interrupting the drugs has been associated with hemolytic episodes, hepatic insufficiency and maternal death. d-Penicillamine is safe, although the drug is teratogenic in animal studies, and there are reports of neonates with cutaneous abnormalities. In patients on D-penicillamine therapy, the dose should be reduced by 25-50% of the pre-pregnancy dose to reduce fetal risks.

Porphyria

Porphyria can present as acute or chronic disease. The inheritance pattern is usually autosomal dominant, with low penetrance, and trigger factors are needed for the disease to become apparent. Acute porphyria usually manifests after puberty, more frequently in women with a peak in the third decade.[84] Attacks occur particularly during periods of hormonal change (*e.g.*, luteal phase of the menstrual cycle, and during oral contraceptive use). Pregnancy is not contraindicated, although attacks are more frequent during early weeks of gestation, potentially causing maternal and fetal problems, and in the immediate postpartum period. Recurrent attacks may occur during pregnancy in patients with acute intermittent porphyria, variegate porphyria, or hereditary coproporphyria. Porphyria cutanea tarda may present for the first time during pregnancy. In a population-based study, pregnant women with the heritable form of porphyria cutanea tarda or with active acute porphyria had a significant excess risk of prenatal death, low birth weight and premature delivery.[84] Most commonly no specific therapy for acute porphyria is required during pregnancy. In case of acute attacks, standard therapy with glucose infusion (200-500 g/day) and heme arginate (4 mg/kg/day) is recommended for 3-4 days.

Alcoholic liver disease

Pregnancy in alcoholic liver disease (ALD) presents two main problems: liver damage and alcohol intake, including the effects of alcohol on other organs and alcohol dependence, itself.[85] ALD comprises a large spectrum of alcohol-related liver diseases, ranging from fatty liver or simple steatosis to alcoholic hepatitis, chronic hepatitis with hepatic fibrosis or cir-

rhosis. Pregnancy data are scarce in women with ALD, as women with ALD are often infertile. ALD leads to anovulation and amenorrhea due to many factors including disturbed estrogen and endocrine metabolism.[86] When pregnancy is successful in a cirrhotic woman, spontaneous abortion rate, risk of prematurity, and perinatal death rate are all increased.[87] Alcoholic cirrhotic patients have a high risk of liver decompensation because of worsening synthetic liver function, development of ascites, and hepatic encephalopathy with high maternal mortality.[87,88] Maternal prognosis depends on the degree of hepatic dysfunction during pregnancy rather than its cause.[89] Portal hypertension worsens during pregnancy because of increased blood volume and flow. Portal pressures can also increase because of an increased vascular resistance due to external compression of the inferior vena cava by the gravid uterus. All patients with cirrhosis should undergo variceal screening. Banding before pregnancy, although not proven, is appropriate for high-risk varices (moderate evidence; weakly positive recommendation). Finally, although there are no good studies evaluating the impact of vaginal delivery on the risk of variceal bleeding, it is recommended that patients have Cesarean section to avoid increased straining.[90] Abusive and heavy drinking are associated with fetal alcohol syndrome (FAS), which includes growth retardation, central nervous system damage, neurodevelopmental delays and facial malformations.[91] Epilepsy is often reported in children with FAS.[92] Even in the absence of FAS, heavy alcohol consumption during pregnancy is correlated with adverse outcomes, including miscarriage, stillbirth, preterm delivery and small-for-gestational age (SGA) birth.[93] Chronic liver disease is associated with increased levels of inflammatory cytokines, which may increase the risk of preterm birth.[94] A Danish study found that alcohol consumption below four drinks per week did not increase the risk of preterm birth. Several studies have been conducted to investigate whether alcohol intake during breast-feeding can cause damage to the baby. In fact, there was no difference in the scores of cognitive development, while a small but significant difference, was detected in motor development of children.[95] Benzodiazepines seem the most recommendable option for managing alcohol withdrawal, and psychosocial interventions succeed in reducing alcohol consumption or in maintaining abstinence in alcohol-dependent pregnant women.[96]

Non-alcoholic liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. It is the hepatic expression of the metabolic syndrome and shares the risks associated with its components. Further evaluation by liver ultrasound showed a variable degree of fatty liver and confirmed the diagnosis of NAFLD, associated with increased BMI. The presence of NAFLD did not affect the maternal and neonatal outcomes. Pregnancy is associated with a 50-60% decrease in insulin sensitivity during physiological gestation[97] and NAFLD is driven by insulin resistance. The duration of the pregnancy-related insulin resistance, albeit very short, could have a clinical impact on NAFLD in susceptible individuals. Although there are no specific studies considering the impact of NAFLD on maternal and fetal outcomes, some data can be inferred from the literature on obese and diabetic pregnant women, given the extremely high prevalence of NAFLD in obesity and type 2 diabetes. Consequently, overweight and obese women are at increased risk of metabolic dysfunctions during pregnancy. Indeed, obese women have a 10-15% increased risk for preeclampsia[98] and are at higher risk to develop gestational diabetes mellitus (GDM).[99] There is now growing evidence that maternal obesity, GDM and the fetal nutritional environment may contribute to the offspring's risk of developing juvenile obesity and metabolic disorders. Moreover, excessive maternal lipid supply in utero, coupled with the reduced oxidative capacity of the fetal liver, can promote hepatic steatosis, mitochondrial dysfunction, oxidative damage and inflammation, perhaps priming the liver to a later development of NAFLD and to its progression to non-alcoholic steatohepatitis.[100,101] Among the conditions associated with NAFLD, the polycystic ovary syndrome (PCOS) deserves particular attention. PCOS has recently been recognized as a potential risk factor for NAFLD.[102] Early diagnosis of these two associated conditions, is mandatory to ensure a multidisciplinary approach. Screening has not been recommended.

Cirrhosis and portal hypertension

Pregnancy is uncommon in women with liver cirrhosis, because they tend to be past childbearing age or infertile due to the condition. Cirrhosis leads to anovulation and amenorrhea because of many factors including disturbed of estrogen and endocrine metabolism. When pregnancy is successful in a cirrhotic woman, spontaneous abortion rate, risk of prematurity, and perinatal death rate are all increased.[4] Unfortunately, the outcomes and the optimal management of pregnancy with cirrhosis and portal hypertension in the modern era of obstetrics is still undefined.[32] Portal hypertension worsens during pregnancy because of increased blood volume and flow, and further increased vascular resistance due to external compression of the inferior vena cava by the gravid uterus. Indeed, up to 25% of patients with varices have a bleeding episode during pregnancy. The greatest risk is seen in the second trimester (when portal pressures peak), and during delivery, because of the repeated use of the Valsalva maneuver during ex-

pulsion. However, there are no clear recommendation regarding mode of delivery,[88,103] even if Cesarean section is recommended in patients with large esophageal or gastric varices. Regarding the treatment of variceal bleeding during pregnancy, all cirrhotic patients should undergo variceal screening by upper endoscopy. Banding before pregnancy is appropriate for high-risk varices, although official guidelines are lacking. TIPS can be considered in extreme cases of variceal bleeding, although there is risk of radiation exposure to the fetus. Propranolol has also been used safely in pregnancy. Side effects include fetal growth retardation, neonatal bradycardia and hypoglycemia. Propranolol does not appear to be teratogenic, but maternal and fetal propranolol toxicity may occur. Since data on safety of breast-feeding in cirrhosis are scarce, all medications used during breast-feeding should be checked for infant exposure risk. The outcome of pregnancy in patients with non-cirrhotic portal hypertension (NCPH) is more favorable. Recent studies in women with NCPH show near normal fertility with comparable incidences of spontaneous abortions and stillbirths. No increase in the incidence of hematemesis during pregnancy has been observed. In this setting, a higher risk of SGA babies has been reported.[104]

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