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AISF position paper on liver disease and pregnancy

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ABSTRACT

The relationship between liver disease and pregnancy is of great clinical impact. Severe liver disease in pregnancy is rare; however, pregnancy-related liver disease is the most frequent cause of liver dysfunction during pregnancy and represents a severe threat to foetal and maternal survival. A rapid differential diagnosis between liver disease related or unrelated to pregnancy is required in women who present with liver dysfunction during pregnancy. This report summarizes the recommendation of an expert panel established by the Italian Association for the Study of the Liver (AISF) on the management of liver disease during pregnancy. The article provides an overview of liver disease occurring in pregnancy, an update on the key mechanisms involved in its pathogenesis, and an assessment of the available treatment options.

The report contains in three sections: (1) specific liver diseases of pregnancy; (2) liver disease occurring during pregnancy; and (3) pregnancy in patients with pre-existing chronic liver disease. Each topic is discussed considering the most relevant data available in literature; the final statements are formulated according to both scientific evidence and clinical expertise of the involved physicians, and the AISF expert panel recommendations are reported.

1. Introduction

The relationship between liver disease and pregnancy is a poorly studied topic and specific suggestions for the management of these patients are lacking.

The present document was generated by the Gender Committee of the Italian Association for the Study of the Liver (AISF) to provide an official position paper in a setting characterized by uncertain clinical behaviour and lack of uniform approach.

For this reason, two Expert Opinion Meetings were organized with the aim of fine-tuning recommendations for the management of liver disease in pregnancy. The two meetings were held in Rome during the AISF Annual Meeting in February 2014 and in Naples during the AISF Monothematic Conference in October 2014.

Primary objective of this document is to provide recommendations for clinical practice defining the best management of liver disease in relation with pregnancy. The format of recommendations was chosen to offer a documented approach to pregnant patients with liver disease.
The report is structured in three parts:

1. Specific liver disease of pregnancy.
2. Occurrence of liver disease during pregnancy.
3. Pregnancy in patients with chronic liver disease.

The issues related to liver transplantation and pregnancy were not considered in this report due to space constraints. A publication by the AISF expert panel on this topic will be forthcoming.

The recommendations were drawn using the level of evidence and strength of recommendations graded according to the American College of Cardiology and the American Heart Association Practice Guidelines, listed in Supplementary Table S1.

2. Specific liver diseases of pregnancy

2.1. Physiological changes in liver during pregnancy

In pregnancy, the liver is affected primarily by circulatory and hormonal changes. Pregnancy is associated with a hyperdynamic circulatory status in which cardiac output increases. Blood flow to the liver remains unchanged, but the percentage of cardiac

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output to the liver is reduced, which may impair clearance of substances requiring extensive hepatic metabolism [1]. The physiological changes of normal pregnancy mimic abnormalities that are associated with liver disease in non-pregnant individuals (Supplementary Table S2). Because of the hyperestrogenic state, up to 60% of pregnant women may exhibit spider naevi or palmar erythema. Gall bladder motility is also decreased [2].

2.2. Hyperemesis gravidarum

Hyperemesis gravidarum (HG) occurs in 0.1–2.0% of all pregnancies and presents with ptyalism, spitting, nausea and vomiting leading to dehydration, ketosis and weight loss of 5% or more. It can start as early as week 4 and typically resolves by week 18 [3,4].

Risk factors include increased body mass index (BMI), psychiatric illness, molar pregnancy, pre-existing diabetes, multiple pregnancies and HG in a previous pregnancy. Hyperthyroidism is observed in about 60% of cases likely because of increased thyroid-stimulating activity by human chorionic gonadotropin (HCG).

The pathophysiology appears to have a complex metabolic background [5]. Hormones such as HCG, prolactin and oestradiol have been implicated [6].

Persistent vomiting may lead to postural hypotension, tachycardia, electrolyte disturbances, ketosis, muscle wasting and weight loss [7,8]. Jaundice is uncommon, but indicates liver involvement when present. No single confirmatory test exists, however clinical symptoms and biochemical abnormalities, including raised serum urea and creatinine, hypophosphataemia, hypomagnesiumia and hypokalaemia, are suggestive for HG [9]. Abnormal liver function tests are found in about 50% of patients with HG [4]: mild aminotransferase elevation (up to 200 U/l) is the most common liver laboratory abnormality, while elevation greater than 1600 U/l has been reported rarely; alkaline phosphatase may rise to twice normal values; both indirect and direct hyperbilirubinemia up to 4 mg/dL may also occur; serum amylase and lipase may rise up to 5 times normal values. Interestingly, the severity of nausea and vomiting in patients with liver involvement correlates with the degree of liver enzyme elevation [5].

Treatment is supportive and includes intravenous rehydration, antiemetics, gradual reintroduction of oral intake and vitamins supplementation (vitamin B1 or thiamine, vitamin B6, vitamin B12, vitamin C). Early administration of high-dose thiamine (150 mg daily orally or 100 mg weekly intravenously) to prevent Wernicke's encephalopathy is suggested [7,8]. Among anti-emetics, dopamine agonists (metoclopramide 5–10 mg every 6 hours and domperidone 10–20 mg every 6–8 hours), phenothiazines (prochlorperazine 5–10 mg every 8 hours) and antihistamines (promethazine 12.5–25 mg every 4–6 hours) have all been shown to be safe. H2 receptor antagonists have been used occasionally with some benefit [9].

The use of the 5-hydroxytryptamine (5-HT3) receptor blocker ondansetron (8 mg every 12 hours) has been reported to be safe in intractable hyperemesis.

Most patients usually need 5–8 days of hospital admission with a self-limiting disease but relapse is common. Serious morbidity can result only from inadequate or inappropriate treatment. As HG resolves by 18 weeks, lactation is not contraindicated.

AISF expert panel recommendations:

- **Intravenous rehydration (Class I, Level C), anti-emetics (metoclopramide 5–10 mg every 6 hours, or domperidone 10–20 mg every 6–8 hours, or prochlorperazine 5–10 mg every 8 hours, or promethazine 12.5–25 mg every 4–6 hours), gradual reintroduction of oral intake and vitamins (Class I, Level A) are first line treatments of HG.**
- **High-dose thiamine (150 mg daily orally or 100 mg weekly intravenously) should be given to prevent Wernicke's encephalopathy in women with HG (Class I, Level A).**

2.3. Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) usually occurs during the last trimester and has a rapid post-natal resolution [10]. It is characterized by severe pruritus, associated with increase in serum bile acid and aminotransferases. The symptoms and biochemical abnormalities resolve rapidly after delivery but may recur in subsequent pregnancies and with the use of hormonal contraception [11]. Interestingly, serum autotaxin, a lysophospholipase D essential for angiogenesis and neuronal development during embryogenesis, was found to be a highly sensitive, specific and robust diagnostic marker distinguishing ICP from other pruritic disorders of pregnancy and pregnancy-related liver disease [12]. The incidence of ICP ranges between 0.5% and 1.8% of pregnancies in Europe, but the highest peak of incidence has been reported in Chile (up to 28% in the Araucanic population) and in Scandinavia [13]. Genetic defects in at least 4 canalicular transporters can be found in ICP (Supplementary Table S3). 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 utilizing micro-array technology in 12 women with ICP and in 12 healthy controls, found that twenty genes were potentially correlated to ICP [14]. Among these, an up-regulation of GABRA2 receptor gene (that codes for a subunit of the gamma-aminobutyric acid type A receptor) may indicate that GABA may play a role in the pathogenesis of pruritus in this condition.

Severe ICP (with serum bile acids >40 μmol/L) is associated with adverse pregnancy outcome [15].

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 [16]. A recent meta-analysis including 9 published randomized controlled trials (3 double blind) that compared the effect of UDCA to other drugs, placebo, or no specific treatment in patients with ICP, demonstrated that UDCA is effective in reducing pruritus and improving liver tests in patients with ICP [17].

AISF expert panel recommendations:

- **Management of ICP should be performed by a dedicated team; monitoring of serum bile acids is recommended, although there is no general consensus on a correlation between severe complications and high serum bile acid levels (Class III, Level A).**
- **Ursodeoxycholic acid at a dosage of 15 mg/kg of body weight is safe and effective in the management of symptoms of ICP (Class IIa, Level A).**

2.4. Eclampsia and preeclampsia

Pre-eclampsia occurs after 20 weeks of pregnancy and/or within 24–48 hours after delivery. It affects 5–10% of all pregnancies and can involve the kidney, the liver, the central nervous and haematological system. Pre-eclampsia is characterized by hypertension and proteinuria (greater than 300 mg in 24 h). Presence of seizures differentiates eclampsia from pre-eclampsia [18].

Risk factors include extreme maternal age (<16 years and >45 years), primiparity, pre-existing hypertension, family history and occurrence in a previous pregnancy [18].

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 [19].

Clinical features include right upper quadrant pain, headache, nausea and vomiting. 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 [20].

Pre-eclampsia and eclampsia are associated with 3-to-25-fold increased risk of pulmonary oedema, abruption, aspiration pneumonia, renal failure, hepatic failure, disseminated intravascular coagulation (DIC), and stroke. Haemorrhagic stroke is the most common cause of death, vascular disease, renal, and neurological sequelae. Most cases resolves within 12 weeks postpartum [21,22].

Maternal mortality is 15–20% while foetal mortality is 1–2% of live births [23,24].

Close monitoring of blood pressure and proteinuria is necessary during pregnancy. First line of hypertension treatment in pregnant women with pre-eclampsia is labetolol, methyldopa or nifedipine. Treatment is aimed to keep the systolic blood pressure below 150 mmHg and the diastolic between 80 and 100 mmHg. Magnesium sulphate remains the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia. Treatment consists in early delivery whenever possible [23,24]. Breast-feeding is not contraindicated in women on antihypertensive therapy post-partum: nifedipine, labetalol, atenolol, methyldopa, captopril and enalapril have been shown to be safe [25]. Magnesium sulphate is excreted in breast milk but is safe for breastfed infants.

AISF expert panel recommendations:

- **Labetolol, methyldopa or nifedipine are first-line treatments for pre-eclampsia (Class I, Level A).**
- **Magnesium sulphate should be given for seizure prophylaxis in severe pre-eclampsia and for controlling seizures in eclampsia (Class I, Level A).**
- **In pre-eclampsia, early delivery should be performed when gestational age is over 37 weeks or maternal-foetal conditions are deteriorating (Class I, Level A).**
- **Breast-feeding is not contraindicated in pre-eclamptic women on antihypertensive therapy: nifedipine, labetalol, atenolol, methyldopa, captopril, and enalapril can be used safely (Class III, Level B).**

2.5. HELLP syndrome

The haemolysis, 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% of pre-eclampsia [25].

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 [26,27].

Patients may present with right upper quadrant and epigastric pain, nausea, vomiting, and malaise. Hypertension and proteinuria are evident in up to 85% of cases. Because of the haemolysis, high serum unconjugated bilirubin and lactate dehydrogenase are frequent [28,29], as well as a moderate rise in liver enzymes. In later stages, DIC may be present with increased levels of fibrin degradation products and D-dimer, and thrombin–antithrombin complexes. Two recognized classifications of HELLP (known as the Tennessee and the Mississippi systems) are available [30].

Complications include DIC, pulmonary oedema and placental abruption. Perinatal mortality rate is 6–70%, while maternal mortality is 1% [31].

Once HELLP develops, the only definitive treatment is delivery of foetus. If the gestational age is between 24 and 34 weeks, corticosteroids are usually given to promote foetal lung maturity. Delivery should be considered 24 hours after administration. After delivery, close monitoring of the mother should continue, as some women may have worsening thrombocytopenia and increasing LDH levels up to 48 hours postpartum [27,31]. 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 been shown to be safe [32].

AISF expert panel recommendations:

- **Delivery of the foetus is first-line treatment of HELLP syndrome before 24 or after 32 weeks gestation and in presence of maternal-foetal complications (Class I, Level B).**
- **In HELLP syndrome between 24 and 34 weeks' gestation, corticosteroids should be given to promote foetal lung maturity (Class I, Level A) and delivery should be considered 24 hours after corticosteroids administration (Class I, Level A).**
- **Breast-feeding is not contraindicated in women with HELLP syndrome on antihypertensive therapy: nifedipine, labetalol, atenolol, methyldopa, captopril, and enalapril can be used safely (Class III, Level B).**

2.6. Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a microvescicular 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 [33]. Risk factors are nulliparity, preeclampsia, multiple gestation, pregnancies with a male foetus, low BMI [33].

The aetiology is unknown. Defects in intra-mitochondrial fatty acid beta-oxidation (enzymatic mutations), in particular a homozygous foetal deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in a mother carrying a heterozygous LCHAD deficiency can be found [34]. Hepatotoxic metabolites produced by the foetus and/or placenta may cause liver disease in the heterozygous mother when combined with the metabolic stress of the third trimester [34,35]. However, AFLP may occur in the absence of known genetic mutations [36].

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, anaemia, thrombocytopenia and hypoalbuminemia, increased uric acid, renal impairment, metabolic acidosis, hyperammonemia, biochemical pancreatitis. Differential diagnosis is with HELLP syndrome (Table 1) [37,13]. The diagnosis

Table 1
Differential diagnosis between haemolysis, elevated liver enzymes, and low platelets syndrome and acute fatty liver of pregnancy.

	HELLP	AFLP
Prevalence (%)	0.2–0.6	0.005–0.01
Onset	Third trimester or post-partum	Third trimester or post-partum
Family history	No	Occasionally
Onset of preeclampsia (%)	70–80	50
Clinical features	Haemolysis (anaemia) Thrombocytopenia (50,000 platelets)	Liver failure, coagulopathy, encephalopathy hypoglycemia, DIC
Aminotransferases	Mild increase (may be up to 10–20 fold)	300–500 UI/L typically
Bilirubin	<5 mg/dL unless massive necrosis	>5 mg/dL
Liver imaging	Hepatic infarcts, hematomas, rupture	Fatty infiltration
Histology	Patchy/extensive, necrosis, periportal haemorrhage, fibrin deposits	Microvesicular steatosis in zone 3
Maternal mortality (%)	1–25	7–18
Foetal/perinatal mortality (%)	11	9–23
Recurrence in subsequent pregnancy (%)	4–19	25 (fatty acid oxidation defects)

HELLP, haemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DIC, disseminated intravascular coagulation

is based on clinical and laboratory findings. Liver biopsy is the gold standard although rarely necessary [38].

Complications include encephalopathy, thrombocytopenia, DIC and renal failure. Prompt diagnosis and adequate management improve clinical conditions in 1 to 4 weeks postpartum. Maternal mortality ranges from 7% to 18% and foetal mortality from 9% to 23% [13,37,38].

The management of AFLP requires: (i) early recognition and diagnosis, as the best maternal survival rate is when the interval from occurrence of AFLP to delivery is one week; (ii) aggressive maternal stabilization in intensive care setting, adequate supportive therapy (diet low in fat and protein and high in carbohydrates, blood components, plasma exchange and haemodialysis, broad-spectrum antibiotics, correction of dehydration, electrolyte and acid-base balance, treatments to protect the liver, reduce jaundice, and diminish liver enzymes); (iii) rapid delivery: if vaginal delivery cannot be achieved quickly, caesarean section is the preferred method [37,38]. 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.

AISF expert panel recommendations:

- **Interval from AFLP onset to delivery should not exceed one week (Class IIa, Level B), therefore prompt diagnosis is crucial.**
- **In women with AFLP, maternal stabilization should be performed in an intensive care setting with prompt supportive therapy (Class IIa, Level B).**
- **When vaginal delivery cannot be achieved quickly in AFLP, caesarean section should be performed (Class IIa, Level B).**

3. Liver disease occurring during pregnancy

3.1. 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 socio-economic conditions [39].

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. In a recent study of the Korea University, 16,944 pregnant women were reviewed retrospectively and 12 cases of acute HAV infection were identified (0.07%). Among them, 4 patients (30%) developed maternal complications, including cholestatic hepatitis and preterm contraction. In only 1 case it was reported foetal ascites and intra-abdominal calcifications [40].

HAV vaccination should be considered particularly for women living in areas of high endemicity and poor socioeconomic conditions, to avoid maternal and foetal 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 [41]. A recent study involving 22 pregnant patients and 87 matched non-pregnant controls investigated the clinical features and outcome of acute hepatitis B in pregnancy [42]. No difference in mortality or occurrence of fulminant hepatitis was found between the 2 groups. 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 [43]. HBV vaccination and hepatitis B immune globulin administration to newborns of HBsAg-positive mothers represent the main strategy to prevent HBV vertical transmission [44].

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% [45]. Several case reports can be found in literature and none of them reported relevant adverse clinical outcome in pregnancy [46]. HCV infection can be vertically transmitted (risk from 3% to 5%), but there is no evidence of increased transmission through breast-feeding [47]. However antiviral treatment is contraindicated due to the teratogenic effect of drugs available until recently [48] 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 [49]. Data regarding acute hepatitis D and pregnancy are scant. Krajden et al. described a case in a 18-year-old pregnant woman (intravenous drug user) who developed fatal fulminant hepatitis with massive hepatic necrosis due to HBV and HDV co-infection [50]. 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) [51]. A recent study compared maternal and foetal outcomes in pregnant women with acute viral hepatitis caused by HEV and other hepatitis viruses. Authors found that fulminant hepatic failure was more common (relative risk, 2.7 [95% CI, 1.7–4.2]; $p = 0.001$) and maternal

Table 2
Clinical features of acute viral hepatitis in pregnancy.

	Maternal complications	Foetal complications	Vertical transmission	Prevention and treatment
HAV	Mild gestational complications	Rare	Probable in perinatal period	Vaccination
HBV	Same as general population	Rare, preterm delivery	50–70% in III trimester	Vaccination and prophylaxis
HCV	No	No	3–5%	Peg-IFN + RBV contraindicated
HDV	Same as general population	n.a.	n.a.	HBV vaccination
HEV	Lethal (up to 25%)	Preterm labour and stillbirth	~50%	No FDA-approved vaccine

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; n.a., not available; Peg-IFN, pegylated interferon; RBV, ribavirin.

mortality was greater (relative risk, 6.0 [95% CI, 2.7–13.3]; $p < 0.001$) in HEV-infected women than in non-HEV-infected women. Moreover, women with HEV infection had a higher risk of intrauterine foetal death [52]. Vertical transmission rates are reported between 33.3% and 78.9% [53,54]. There is currently no evidence of HEV transmission through breast-milk. Table 2 summarizes the clinical features of acute viral hepatitis and pregnancy.

AISF expert panel recommendations:

- **Vaccination is the most effective strategy for prevention of HAV and HBV transmission (Class I, Level A). In addition, hepatitis B immune globulin must be administered to newborns from HBsAg-positive mothers to prevent HBV vertical transmission (Class I, Level A).**
- **Currently, there is no FDA-approved vaccine to prevent HEV infection. Considering the severe course of hepatitis E in pregnancy, particularly in countries with poor sanitation, early delivery of the foetus should be considered to avoid maternal complications (Class I, Level C).**
- **Breast-feeding is not contra-indicated in case of maternal acute viral hepatitis (Class I, Level B).**

3.2. Gallstone disease

Gallstones are common during pregnancy. The prevalence ranges between 2.5% and 11% of cases [45]. During pregnancy, female sex hormones are endogenously increased, and biliary sludge (composed of cholesterol, calcium bilirubinate and mucin) appears in 5–30% of women [55]. 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 [56,57]. Additional risk factors include obesity, reduced high-density lipoprotein cholesterol and metabolic syndrome [55]. Another often underdiagnosed condition may be the low-phospholipid-associated cholelithiasis, which is associated to a genetic defect in the *ABCB4* gene with loss of canalicular MDR3 protein and/or loss of protein function [58]. Most women with this genetic variant develop intrahepatic cholestasis of pregnancy and eventually cholelithiasis.

Acute biliary colic or uncomplicated cholecystitis can be treated conservatively with bed rest, intravenous fluids, and antibiotics. Conservative treatment of cholelithiasis and its complications during pregnancy is associated with recurrent biliary symptoms and frequent emergency department visits; thus ERCP and laparoscopic cholecystectomy should be considered [59]. The use of drugs such as UDCA and the lipid-lowering compound ezetimibe could also be considered [60]. ERCP can be performed safely during pregnancy and remains the first-line modality for the management of choledocolithiasis and its associated complications. While newer techniques focus on avoiding the use of fluoroscopy, their benefits over traditional techniques employing minimal fluoroscopy are unclear [61]. Cholecystectomy during pregnancy is not entirely safe because of the abortion risk with anaesthesia. In a retrospective study, however, surgical management of symptomatic cholelithiasis in pregnancy was found to be safe and more useful than conservative management in reducing the rate of labour induction and preterm deliveries [62]. Laparoscopic cholecystectomy, when indicated, should be performed in the second trimester to avoid serious complications.

AISF expert panel recommendations:

- **Biliary colic and acute cholecystitis during pregnancy should be treated conservatively. ERCP should be considered in case of choledocolithiasis and its complications (Class III, Level A).**
- **Laparoscopic cholecystectomy should be considered in selected cases as second-line management in case of failure of conservative management; when indicated, it should be performed in the second trimester to avoid serious complications (Class III, Level A).**

3.3. 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 haemostatic balance towards hypercoagulability, which persists up to 8 weeks after delivery [63]. Therefore, it is not surprising that the vascular liver diseases, in which thrombophilia often plays a major role, can occur or worsen during pregnancy.

3.3.1. 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, ischaemic liver damage and portal hypertension [64,65].

One or more risk factors for venous thromboembolism are usually present in BCS patients. Pregnancy, as well as oral contraception or oestrogen-replacement therapy, may precipitate BCS [66–70].

BCS occurring in pregnancy accounts for about 15% of all women with BCS [71]. Symptoms include fever, abdominal pain, ascites, lower limb oedema, 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 [72]. Computed tomography (CT) scan is contraindicated. The safety of gadolinium-based contrast agents is controversial; therefore magnetic resonance imaging (MRI) should be used if the diagnosis of BCS cannot be otherwise excluded (Class IIb, Level C).

Besides few reports of BCS in pregnancy [66,68,73], a recent study [74] investigated the maternal and foetal outcome of 43 women with BCS, seven of them with the disease presenting in pregnancy. In these 7 women there were 3 miscarriages, 1 early

preterm delivery, and 3 healthy newborns. Two women received tranjugular porto-systemic shunt (TIPS) and one underwent orthotopic liver transplantation (OLT) within two months postpartum. All were alive after 57 ± 46 months from delivery.

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 foetal haemorrhage and teratogenicity [72]. A stepwise treatment, starting with a twice-daily low molecular weight heparin (LMWH), followed by TIPS in failures or relapses, is recommended (Class IIa, Level C). Liver transplantation is possible [75]. Anticoagulation, with LMWH or VKA, can be restarted 12 hours after delivery (or 24 hours after caesarean 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).

AISF expert panel recommendations:

- **Pregnancy may precipitate BCS. The clinical presentation is often fulminant. The treatment of BCS during pregnancy is the same as in non-pregnant women except for the contraindication of VKA (Class I, Level C).**
- **Management of women with BCS during pregnancy requires a multidisciplinary team in tertiary referral centres (Class I, Level C). Maternal outcome may be good provided a stepwise treatment is adopted (Class IIa, Level C). Foetal outcome, although a matter of concern, can be good (Class II, Level C). Due to the rarity of the disease, there is no data to support further recommendations.**
- **Breast-feeding is contraindicated in women taking LMWH and allowed in women taking VKA (Class I, Level C).**

3.3.2. 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. However, and in contrast to BCS, pregnancy rarely triggers EHPVO. Indeed, in three European series, pregnant women accounted for only 0–2% of patients [76–78].

Acute EHPVO often presents with abdominal pain, ascites or fever. However, symptoms vary from almost asymptomatic to intestinal infarction, depending on the extension of the involvement of the spleno-portal axis, particularly of the proximal roots of the superior mesenteric vein.

As for BCS, Doppler ultrasound is the procedure of choice in pregnancy.

No data on maternal and foetal morbidity and prognosis in acute EHPVO are available. In acute EHPVO not occurring in pregnancy, if early recognized and treated, a 75% rate of complete or partial recanalization is expected [79].

As in non-pregnant women, the treatment is based on anticoagulation with LMWH. Anticoagulation can be restarted 12 hours after delivery (or 24 hours after caesarean section) with VKA if breast-feeding is desired (*Class I, Level C*).

AISF expert panel recommendations:

- **Pregnancy rarely triggers EHPVO. The treatment of EHPVO occurring in pregnancy, is the same as in non-pregnant women, except for the contraindication of VKA (Class I, Level C). Due to the rarity of the disease, there is no data to support further recommendations.**
- **Breast-feeding is contraindicated in women taking LMWH, and allowed in women taking VKA, (Class I, Level C).**

4. Pregnancy in patients with pre-existing chronic liver disease

4.1. Chronic hepatitis B

In women with chronic HBV infection, immunological changes typical of pregnancy may cause an increase in HBV DNA levels while alanine aminotransferase (ALT) remain normal or near normal. Mild exacerbations may occur after delivery [80,81]. 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 [82]. 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 hours after delivery [83]. This strategy is cost-effective [84]. However, newborns to HBeAg-positive mothers retain a 6–10% risk of acquiring HBV infection, despite prophylaxis [83]. There is general agreement that risk of immunoprophylaxis failure increases with increasing maternal viral load. Most studies set the risk threshold at a HBV DNA level of 10^7 IU/mL, although there is no consensus on this point [85].

Administration of antiviral nucleos(t)ide analogues (NUCs) active against HBV to mothers with high viral load has been examined in some studies, in order to establish the safety and efficacy in preventing vertical transmission.

4.1.1. Safety of NUCs in pregnancy

The Food and Drug Administration (FDA) recently released rules that replace the current product letter categories – A, B, C, D and X – to indicate the potential of a drug to cause birth defects if used during pregnancy [86]. The new labelling system entails the use of three subsections in the labelling, titled “Pregnancy”, “Breast-feeding” and “Females and Males of Reproductive Potential” that provide a summary of the risks of using a drug during pregnancy and breast-feeding and a discussion of the supporting data.

Lamivudine, tenofovir and telbivudine have been administered in pregnancy. Lamivudine was previously listed in class C; however, it was used extensively in human immunodeficiency virus (HIV)-positive mothers as part of their antiretroviral treatment, with no excess in reported birth defect rates [87]; tenofovir and telbivudine were listed in class B. In 6 studies of HIV type 1 and/or HBV-infected women receiving tenofovir during pregnancy, adverse events were mild to moderate; none were considered to be tenofovir-related. Five studies that followed in utero tenofovir-exposed infants showed no increased risk of growth or bone abnormalities [88]. A long-term follow-up of babies born to mothers treated with telbivudine confirmed safety [89].

4.1.2. NUCs in preventing mother-to-child transmission from highly viremic women

Lamivudine given from week 32 of pregnancy to mothers with serum HBV DNA $\geq 10^9$ IU/mL reduced the incidence of newborn infection in a placebo-controlled trial [90]; however not all newborns received complete prophylaxis. A further meta-analysis of six studies confirmed the efficacy of lamivudine [91]. One study showed a rapid emergence of resistant variants [92].

Telbivudine was administered to 135 HBeAg-positive women starting from week 20 to week 32 of gestation; 94 women served

as control. All newborns received active and passive immunoprophylaxis. The incidence of perinatal transmission was 0% in the treatment group vs. 8% in controls ($p = 0.002$) [93]. No serious adverse events were reported. A meta-analysis of six studies confirmed the efficacy of telbivudine in this context; however, the quality of the studies was poor [94]. A further study in 648 mothers receiving telbivudine or lamivudine or no drug ($n = 252/51/345$) from week 28 of pregnancy showed that both regimens were safe and superior to no drug [95].

Tenofovir was evaluated in three non-randomized, small-sized studies, both showing efficacy in preventing newborn infection [96–98]. In a non-randomized study tenofovir given for 58 ± 19 days before delivery was more potent than lamivudine [99].

Of note, the labels of NUCs recommend against their use during breast-feeding. A recent paper reviewed the data on lamivudine and tenofovir and found that the exposure to the drugs is lower during breast-feeding than in utero [100].

Amniocentesis performed on HBsAg-positive mothers with serum HBV DNA $\geq 10^7$ copies/mL significantly increased the frequency of vertical transmission [101].

AISF expert panel recommendations:

- **All pregnant women must be tested for HBsAg (Class I, Level A) and if positive tested for HBeAg/antiHBe and HBV-DNA (Class I, Level B). Early testing may allow a better management of HBsAg-positive women (Class I, Level C). Early antiviral treatment must be considered in the presence of advanced liver fibrosis (F3-F4); tenofovir is the preferred drug due to its high genetic barrier, safety and potency; treatment must be continued after delivery (Class I, Level A).**
- **Pregnant women with serum HBV DNA $\geq 10^7$ IU/mL should receive antiviral treatment with a NUC to minimize the risk of vertical transmission (Class II, Level B). Tenofovir or telbivudine are the drugs of choice and should be started no later than week 32 of gestation (Class I, Level B); lamivudine is also allowed (Class II, Level B); treatment is stopped at week 0–4 after delivery. During breast-feeding, the safety of continuing treatment is uncertain (Class II, Level C).**
- **All newborns from HBsAg-positive mothers must receive standard prophylaxis with vaccine against HBV and antiHBs immunoglobulins within 12 hours after delivery (Class I, Level A).**

4.2. Chronic hepatitis C

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% [45,102,103], 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. However, in different studies, which monitored viral load by monthly testing, HCV RNA was stable during pregnancy in chronic HCV carriers without biochemical activity, whereas viremic flares occurred in pregnant women with biochemical activity [46,104].

Few data are available about the impact of HCV infection on fertility or pregnancy. 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 [105,106]. Moreover, retrospective data suggests 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% [107], in infants born from HCV-positive mothers. Some studies suggest that perinatal transmission is limited to viremic women, particularly if maternal viral load is higher than 100,000 UI/mL during delivery. Besides viral load, the risk of vertical transmission increases in women co-infected with HIV, in those abusing alcohol or drugs and after invasive procedures such as amniocentesis, instrumented vaginal delivery and prolonged ruptures of membranes (>6 hours). Delivery modalities do not influence transmission, and caesarean section does not decrease perinatal HCV transmission. Breast-feeding should not be discouraged, as transmission of HCV by breast-feeding has not been demonstrated [108].

HCV-infected pregnant women do not need specific monitoring; 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 (Table 3). Treatment options should be offered before pregnancy [109,110].

AISF expert panel recommendations:

- **Pregnancy does not seem to modify the natural course of HCV disease and chronic hepatitis C only rarely influences the course of pregnancy (Class I, level B).**
- **The risk of vertical transmission increases in highly viremic HCV-infected women, in those co-infected with HIV, or abusing alcohol or drugs, or after invasive procedures (amniocentesis, instrumented vaginal delivery, prolonged ruptures of membranes) (Class II, level A).**
- **Antiviral therapy for HCV is contraindicated during pregnancy due to the potential teratogenic effects of ribavirin and the side effects of PEG-IFN (Class I, level A). No data are available about interferon-free regimens.**

4.3. Autoimmune hepatitis

Autoimmune hepatitis (AIH) usually affects women in fertile age, thus pregnancy is rather common in those patients. In a retrospective German study the outcome of pregnancy was assayed by a questionnaire obtained by 22 AIH patients with 42 pregnancies [111]. Seven pregnancies (17%) were delivered pre-term before week 36 of gestation, and the rate of adverse pregnancy outcome was 26%. Of the 35 live births, 30 children showed a completely normal development over a median observation of 56 months. One child was born with Smith-Lemli-Opitz syndrome, a rare autosomal recessive disorder of cholesterol metabolism, and another developed tetraparesis after pre-term delivery. The cause of adverse pregnancy outcome could be elucidated in 4 of 11 cases: one septic abortion occurred in the week 19 of gestation. Another pregnancy loss occurred in the week 18 of gestation, due to maternal fulminant hepatic failure. One child was delivered by emergency caesarean section at week 32 and died for congenital heart block. The same mother delivered a second baby at week 24 and the baby had Edward's syndrome (trisomy 18) and died shortly thereafter [111].

Table 3
Pharmacotherapy for hepatitis C virus infection during pregnancy and breast-feeding.

Drug	FDA class	Pregnancy	Breast-feeding
Peg-Interferon α	C	There are no adequate and well-controlled studies of PEG-IFN in pregnant women. PEG-IFN is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.	No data available. Because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue nursing or discontinue PEG-IFN treatment.
Ribavirin	X	There are no controlled data in human pregnancies. Ribavirin-containing regimens are contraindicated in pregnant women and in male partners of women who are pregnant. Effective contraception (at least 2 reliable forms) is required during ribavirin therapy and for at least 6 months after therapy.	No data available. Because of the potential for adverse reactions from the drugs in nursing infants, a decision must be made whether to discontinue nursing or discontinue Ribavirin treatment.
Telaprevir	X	Telaprevir combination therapy is contraindicated in women who are or may become pregnant and in the male partners of women who are pregnant.	Nursing should be discontinued before starting therapy.
Boceprevir	X	Boceprevir combination therapy is contraindicated in women who are or may become pregnant and in the male partners of women who are pregnant.	Nursing should be discontinued before starting therapy.
Sofosbuvir	B[a]	Use should be avoided.	Use should be avoided.
Simeprevir	X	Use should be avoided.	Use should be avoided.
Daclatasvir	X	Use should be avoided. There are no data from the use of daclatasvir in pregnant women therefore daclatasvir is not recommended during pregnancy.	Use should be avoided. It is not known whether daclatasvir is excreted in human milk. Mothers should be instructed not to breastfeed if they are taking daclatasvir.
Ledipasvir	B[a]	Use should be avoided. This drug should be used during pregnancy only if the benefit outweighs the risk to the foetus. Effective	Use should be avoided. It is not known whether ledipasvir is excreted in human milk. Developmental and health benefits of breast-feeding should be considered as well as the mother's clinical need for the drug; potential side effects in the breastfed child due to the drug or the mother's underlying condition should be considered.
Viekira Pack[b]	B[a]	Not recommended for use during pregnancy.	Use should be avoided. It is not known whether Viekira Pack drugs are excreted in human milk. Mothers should be instructed not to breastfeed if they are taking dasabuvir.

PEG-IFN, peginterferon.
[a] In association with ribavirin, to be considered FDA class X.
[b] Ombitasvir, paritaprevir, and ritonavir plus dasabuvir.

An English study reported the outcome of pregnancy in 53 women with 81 pregnancies [112]. Six pregnancies were conceived by in vitro fertilization; 20% of pregnancies were delivered preterm. The live birth rate was 73% (59/81). Of the remaining 22 conceptions, there were 8 spontaneous miscarriages (10%), 12 terminations of pregnancy, 1 stillbirth and 1 foetal death due to an unexpected maternal death. Two of the live birth children had abnormalities: one had cerebral palsy and the other developed Perthes' disease of the hip. The presence of maternal cirrhosis impacted on foetal outcome, and the live birth rate was lower in mothers with liver cirrhosis at the time of conception ($p = 0.002$).

A Brazilian study reported a retrospective analysis of 54 pregnancies in 39 AIH patients [113]. The rate of pre-term delivery was 11.8% and the foetal loss rate was 29.4%. One woman experienced a tubal ectopic pregnancy. One twin pregnancy and one full-term pregnancy were delivered via emergency caesarean section because of acute foetal distress without neonatal death. One pregnancy resulted in a stillbirth secondary to an anencephalic foetus; another women delivered a baby with uretral stenosis.

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 foetus has a low chance of survival [114]. In general, women who reach disease remission and do not have cirrhosis with portal hypertension, have a high chance of a favourable pregnancy outcome [115]. 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 [116,117]. 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 (Supplementary table S4), whereas the probability of fares is highest after delivery with an incidence as high as 40% [118]. Table 4 reports the recommendations of pharmacotherapy for AIH during pregnancy and breast-feeding.

AISF expert panel recommendations:

- **Treatment options should be discussed before pregnancy in patients with AIH. If the patient is receiving steroid monotherapy the dosage needed to maintain remission will likely be lower. As pregnancy-related flare may occur, a reasonable recommendation is to increase the steroid dose shortly before the expected date of delivery, and to monitor liver enzymes and IgG closely in the weeks following delivery (Class II-III, Level A).**
- **In case of combined treatment with steroids and azathioprine, azathioprine can be discontinued although the risk of stillbirth and/or foetal malformation is negligible. In case of azathioprine monotherapy there is a risk of flare after therapy withdrawal; thus maintenance therapy with azathioprine should be continued strictly monitoring liver enzymes (Class III, Level A).**
- **During the breast-feeding period only steroids can be used (Class III, Level A).**

4.4. 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. There is only one report dealing on the onset of PBC during pregnancy

Table 4
Pharmacotherapy for autoimmune hepatitis during pregnancy and breast-feeding.

Drug	FDA class	Pregnancy	Breast-feeding
Prednisone or Prednisolone	C	Should be used monitoring the dosage	Excreted into the breast milk but in such low doses that no effect to the child can be expected
Budesonide	C	Clinical experience is scant, should only be used under strict indication	No data available
Azathioprine	D	Should be used under strict indication and monitoring the dosage	Use should be avoided
Tacrolimus		Should not be used without special risk evaluation, little clinical experience	Use should be avoided
Cyclosporine	C	Clinical experience is scant, but animal studies indicate that is safe, could be used if the advantage to the mother is greater than the risk to the offspring	Excreted into breast milk, risk of adverse effects on the newborn cannot be excluded
Mycophenolate Mofetil	C	Use should be avoided	Use should be avoided
Metothrexate	X	Use should be avoided	Use should be avoided

[119], in a 47 year-old Japanese woman who developed jaundice at the 24th week of pregnancy. Information on PBC and pregnancy in the literature have been obtained by a questionnaire methodology. In particular, the National Health and Nutrition in the USA administered a standardized questionnaire to 182 PBC patients and 225 age- and sex-matched controls [120]. The results of this study showed that there were significantly more pregnancies among the PBC cases than among controls. This study, however, presented several limitations: there was no confirmation of the self-reported data, nor information on the timing of pregnancies, and bias in the selection of the control group. A recent retrospective study identified 32 women (50 pregnancies) who either became pregnant after PBC diagnosis or in whom pregnancy led to diagnosis [121]. Liver biochemistry remained stable in 70% of patients throughout pregnancy, no adverse maternal events were observed during pregnancy or post-partum, and only 6% developed progressive disease following delivery [121]. 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 [122]. 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, involving 11 babies (2.7%, $p < 0.05$). Eight pregnancies occurred after PBC was diagnosed in 6 patients, all of whom had a favourable course at term, with no complications at childbirth.

UDCA is safe and well tolerated during pregnancy. A report from a French group described 6 patients with PBC having 9 pregnancies: their UDCA treatment was withdrawn in the first trimester and restored during the second and third [123]. All the women remained asymptomatic and their liver function tests fell within normal range for a normal pregnancy, and there were no delivery issues or childbirth complications [123]. UDCA treatment with increasing doses up to 25 mg/kg/day during breast-feeding has been shown to be safe, and no adverse effects were observed in either infants or mothers [124].

AISF expert panel recommendations:

- **Pregnancy in PBC patients in the pre-cirrhotic stage (histological stage I-III) has a favourable outcome and there is no contraindication for pregnancy continuation (Class III, Level A).**
- **In patients with PBC in the cirrhotic stage pregnancy and delivery must be monitored for the potentially higher than normal risk of complications both due to portal hypertension and child birth complications (Class III, Level A).**
- **UDCA should be continued at standard dosage during pregnancy and breast-feeding (Class III, Level A).**

4.5. *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 [125]. Up to 80% of PSC patients have concurrent inflammatory bowel disease (IBD) [125]. 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 [126].

Thirteen pregnancies in 10 patients with PSC were observed in Sweden [127]. Seven patients had PSC before pregnancy, 2 developed PSC during pregnancy, and one patient developed PSC 2 months after a normal pregnancy with a normal delivery. No foetal loss occurred, the outcome of all neonates was normal and liver tests did not change during pregnancy. However, the symptoms related to PSC, and in particular pruritus and abdominal pain, worsened in several affected women, and in one case this brought to preterm birth [127].

A case report described a 36-year-old woman with PSC who became pregnant after developing dominant stricture [128]. A healthy baby boy was delivered at 33.5 weeks. The mother required cholangiography and stent placement immediately after delivery, but her post-partum course was otherwise unremarkable.

Another case report showed an improvement in liver function during pregnancy and deterioration after pregnancy, suggestive of autoimmune aetiology [129].

The largest series of patients ($n = 17$) with PSC having at least one pregnancy was reported in Germany [130]. Despite a frequent rise in serum liver tests, no serious maternal complications were observed. Two pregnancies were delivered pre-term and 4 foetal losses occurred early in pregnancy. 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 [127]. PSC also carries a risk of biliary sludge and stones; nevertheless, the risk of biliary colic and/or complications of gallstones is very low.

AISF expert panel recommendations:

- **Pregnancy is not contraindicated in patients with PSC; the risk of unfavourable course, is correlated with the degree of portal hypertension. The increased risk of preterm birth and foetal demise associated with high foetal bile acid levels suggests the need for close foetal monitoring (Class II-III, Level A).**

- **UDCA should be continued at a standard dose during pregnancy, steroids can be used for management of both PSC and IBD, if present (Class II, Level A). UDCA should also be continued during breast-feeding (Class II, Level A).**
- **Possibly avoid azathioprine, although the risk of stillbirth and/or foetal malformation is negligible (Class III, Level A).**

4.6. Genetic disorders

4.6.1. Hereditary hemochromatosis

Hereditary hemochromatosis (HH) is a recessive disease (prevalence 2–5/1000) due in most of the 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 [131].

A normal pregnancy usually mobilizes about 1 g of iron from the mother's body to allow expansion of the blood volume and provide iron to the foetus, thus mild anaemia is frequent in pregnancy, and iron supplementation is frequently prescribed. 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 [132].

AISF expert panel recommendations:

- **No special care for pregnant women with hereditary hemochromatosis is needed, except for cases of juvenile hemochromatosis or in women who developed cirrhosis. Phlebotomies in pregnant women with hereditary hemochromatosis should be delayed to the end of pregnancy (Class III, Level A).**

4.6.2. 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 haemolysis.

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% [133].

Maintaining therapy during pregnancy is essential because interrupting the drugs has been associated with haemolytic 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 foetal risks. The ideal regimen is 750 mg to 1 g of either D-penicillamine or trientine during the first two trimesters and 0.5 g in the last trimester. There is no evidence that zinc sulfate or acetate increases the risk of foetal abnormalities. Therefore, therapy should be continued at regular doses. All patients with Wilson disease should be offered genetic counselling when considering pregnancy and offspring should always be screened for the disease [133–135].

AISF expert panel recommendations:

- **All patients with Wilson disease should be offered genetic counselling when considering pregnancy and offspring should always be screened for the disease. Copper status should be optimized before pregnancy. Maintaining therapy during pregnancy is essential with reduced doses of chelators compared to the pre-pregnancy period (Class II-III, Level B).**

4.6.3. Porphyrias

Porphyrias 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. Prevalence ranges from 0.5 to 10/100,000 for acute porphyrias (acute intermittent porphyria, variegate porphyria and hereditary coproporphyria), with polymorphous clinical presentation that can be life-threatening. A prevalence of 1/25,000 is known for porphyria cutanea tarda. This is the most frequent of chronic porphyrias and usually presents with cutaneous symptoms, while porphyria variegata and hereditary coproporphyria may also present neuropsychiatric symptoms.

Acute porphyrias usually manifest after puberty, more frequently in women with a peak in the third decade [136]. 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 foetal 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 [136]. Most commonly no specific therapy for acute porphyrias 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. The list of potentially safe and unsafe drugs is reported at: www.drugs-porphyria.org.

AISF expert panel recommendations:

- **In women with acute porphyrias pregnancy is not contraindicated although attacks may exacerbate in periods of hormonal changes, Pregnant patients with acute porphyrias should be referred to a porphyria reference Centre for follow up (Class III, Level A).**

4.6.4. Glycogen storage diseases

Glycogen storage diseases (GSD) are very rare inherited recessive metabolic diseases (prevalence 3–6/100,000) caused by defects of enzymes involved in glycogen storage and disposal. Al least 15 types have been identified with some involving primarily the liver and others the skeletal muscle. Initially considered an almost universally fatal disease, nowadays GSD are conditions, which allow women to grow into adulthood and potentially become pregnant.

Presentation is strongly dependent on the type of disease, and is characterized by severe hypoglicemia, and/or muscle symptoms. Long-term complications (hepatic adenoma often correlated to polycystic ovaries, nephropathy, and cardiomyopathy) can be delayed or prevented with optimal metabolic control.

Despite high prevalence of irregular menstrual cycles and polycystic ovaries, no fertility impairment was detected in women with GSD type Ia/Ib, and IIIa/IIIb, the two more prevalent GSD, which involve the liver. Hepatic adenomas and nephropathy (in particular in women with albuminuria) are the main risks of pregnancy.

Good metabolic control prior to conception and maintained throughout gestation directly correlates with successful outcome in women with GSD [137,138].

AISF expert panel recommendations:

- **In women with glycogen storage diseases good metabolic control prior to conception and throughout gestation is essential since directly correlates with successful outcome (Class III, Level B).**

4.7. Metabolic disorders

4.7.1. 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 [139].

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 cirrhosis.

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 oestrogen and endocrine metabolism [140]. When pregnancy is successful in a cirrhotic woman, spontaneous abortion rate, risk of prematurity, and perinatal death rate are all increased [141].

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 [141,142]. Maternal prognosis depends on the degree of hepatic dysfunction during pregnancy rather than its cause [143]. 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. Up to 25% of patients with varices have a bleeding episode during pregnancy [45]. The greatest risk is in the second trimester, when portal pressures peak [142]. 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 caesarean section to avoid increased straining [144]. Caesarean section is more common in women with ALD, but one cannot rule out that the liver disease contributed to the choice (very low evidence; weakly negative recommendation).

Concerning the effects of alcohol on other organs, is important to mark that during pregnancy maternal heart rate and cardiac output increase, while blood pressure and systemic vascular resistance decrease. These alterations mimic physiological changes in patients with decompensated chronic liver disease. Blood volume increases by about 50%, peaking in the second trimester. However, blood flow to the liver remains constant during pregnancy.

Alcohol consumption during pregnancy has been linked to poor-birth outcomes and long-term cognitive and behavioural deficits [145]. Abusive and heavy drinking are associated with foetal alcohol syndrome (FAS), which includes growth retardation, central nervous system damage, neurodevelopmental delays and facial malformations [146]. Epilepsy is often reported in children with FAS [147]. 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 [148].

Data on disease frequencies in children born to mothers with ALD do not exist, although prenatal alcohol exposure may negatively affect the foetus [147]. However, convincing evidence of adverse effects related to low to moderate prenatal exposure to alcohol is lacking [149]. Studying amount and timing of alcohol intake during pregnancy is complicated by recall bias and by socio-economic and life-style confounding such as cigarette smoking and underreporting of drinking during pregnancy.

Women hospitalized with ALD have an increased risk of adverse pregnancy outcomes, including preterm and SGA birth. The increased risk of preterm birth could be attributed to alcohol intake during pregnancy, but also to chronic liver disease per se. Chronic liver disease is associated with increased levels of inflammatory cytokines, which may increase the risk of preterm birth [150]. A Danish study found that alcohol consumption below four drinks per week did not increase the risk of preterm birth. Women in that study, who consumed 2–3.5 drinks per week, had a 20% reduction in risk [151]. Several recent studies found that alcohol is a risk factor for preterm birth [152,153] (moderate evidence; weakly positive recommendation).

There is a nearly 40% increase in risk of stillbirth for women with ALD diagnosed before pregnancy. However, the numbers of stillbirth were few and did not reach statistical significance in the adjusted models. Data should therefore be interpreted with caution (very low evidence; weakly negative recommendation).

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 [154] (low evidence; weakly positive recommendation).

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 [155] (moderate evidence; weakly positive recommendation).

AISF expert panel recommendations:

- **ALD was associated with adverse pregnancy outcomes, especially among women diagnosed before delivery (Class III, Level A).**
- **Screening for alcohol use in antenatal care could identify high-risk women and thereby prevent pregnancy and birth complications (Class III, Level A).**
- **Alcohol consumption during pregnancy is contraindicated; breast-feeding in women with or without pre-existing liver disease is contraindicated (Class III, Level B).**

4.7.2. 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 (MS) and shares the risks associated with its components. However, very few studies have addressed the concerns related to pregnancy in NAFLD. It is difficult to ascertain from available data whether pregnancy may play a role in presentation or deterioration of pre-existing NAFLD. In a small series from UK [156], pregnant women with chronic (at least 29 weeks) abnormal liver function tests during pregnancy were screened for potential hepatic disorders, both related and unrelated to pregnancy. In 5 women all known aetiologies were excluded; further evaluation by liver ultrasound showed a variable degree of fatty liver and confirmed the diagnosis of NAFLD, associated with increased BMI. None of them had pre-eclampsia nor gestational diabetes (GDM)

during pregnancy. The presence of NAFLD did not affect the maternal and neonatal outcomes. However, liver function tests usually deteriorated after delivery. Pregnancy is associated with a 50–60% decrease in insulin sensitivity during physiological gestation [157] 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. However, with the increase in age and BMI observed in pregnancy [158,159], this association may be casual rather than causal. Although there are no specific studies considering the impact of NAFLD on maternal and foetal 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.

Obesity, metabolic syndrome and pregnancy. Obesity affects nearly one-third of women at the child-bearing age in Western countries [159]. Obesity and pregnancy are independently associated with insulin resistance and inflammatory changes, which may be exacerbated when these two conditions are combined [157]. Consequently, overweight and obese women are at increased risk of metabolic dysfunctions during pregnancy. Indeed, obese women have a 10–15% increased risk for pre-eclampsia [160] and are at higher risk to develop GDM [161]. Furthermore, basal triglycerides and cholesterol concentrations increase two to three-fold with advancing gestation along with an increase in free fatty acid levels related to the decreased ability of insulin to suppress lipolysis. Notably, these elevations are more pronounced in pregnant women with GDM [157]. These alterations in glucose and lipid metabolism play a major role in excessive foetal growth and adiposity [162].

As described above, pregnancy can be considered a metabolic stress test for the future risk of the MS. Indeed, although these pregnancy-related dysmetabolic conditions most likely resolve after delivery, these women still have a subclinical metabolic disorder and are at increased risk for the development of MS later in life, particularly when associated with an increased post-partum weight [163]. Since women with a history of GDM are at higher risk of developing type 2 diabetes and NAFLD, a recent English study [164] evaluated the prevalence of ultrasound-diagnosed NAFLD after 10 years from delivery in a cohort of 110 non-diabetic women with previous GDM, compared with 113 women without previous GDM. There was no significant difference in BMI in women with previous GDM compared with those without (28.9 ± 0.6 vs. 27.9 ± 0.6 kg/m^2, respectively; $p = 0.12$), however women with previous GDM showed higher waist circumference (89 ± 1 vs. 84 ± 1 in controls, $p = 0.002$). The prevalence of metabolic dysfunctions (i.e. higher fasting and 2 h glucose concentrations following a 75 g oral glucose tolerance test, dyslipidemia, insulin resistance-HOMA index), was higher in women with previous GDM. Not surprisingly, also the prevalence of NAFLD was greater in women with previous GDM compared with those without (38% vs 17%, respectively, $p = 0.001$), with an odd ratio (OR) of 2.77 (95% CI 1.43–5.37, $p = 0.002$), after adjustment for BMI. These results may be consistent with NAFLD preceding type 2 diabetes. However, long-term prospective studies are required to confirm these data.

As a result of increasing maternal age, a higher proportion of women older than 40 years of age may start pregnancy with central fat accumulation. Although lean and obese pregnant women gain similar fat mass, in the latter there is a preference to store fat in ectopic sites, particularly in the visceral area [165], with concomitant lipotoxicity. Lipotoxic effects in pregnancy include maternal endothelial dysfunction, decreased trophoblast invasion and negative influences on placental metabolism and function, leading to potential miscarriages and adverse pregnancy outcomes, such as preeclampsia, preterm delivery and neonatal morbidity [166].

Obesity, metabolic syndrome and neonatal outcomes. There is now growing evidence that maternal obesity, GDM and the foetal nutritional environment may contribute to the offspring's risk of developing juvenile obesity and metabolic disorders. Foetal and neonatal life are characterized by extraordinary plasticity and ability to respond to environmental stimuli by altering gene expression via epigenetic modifications, i.e. covalent modifications to DNA and chromatin that alter gene transcription independently of DNA base sequence. The foetal exposure to excess lipids or to GDM determines epigenetic modifications of genes involved in glucose and lipid metabolism, leading to multiple metabolic alterations in the foetus, newborn and possibly in the adult offspring [167,168]. Moreover, excess maternal lipid supply in utero, coupled with the reduced oxidative capacity of the foetal 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 (NASH) [169,170]. Similarly, elevated maternal consumption of fructose-sweetened beverages seems to potentiate the susceptibility of the offspring to develop future metabolic disturbances and hepatic steatosis [171]. Whether these alterations could be further promoted in the setting of an obesogenic environment (i.e. chronic intake of high-fat/high-sucrose diets and sedentary habits), or whether they could be reverted by a healthy lifestyle is of great importance, but has to be ascertained.

Very recently, the results of a multicentre randomized trial, aimed to determine the effect of antenatal dietary and lifestyle interventions on neonatal outcomes in overweight and obese pregnant women, have been published. A cohort of 2152 pregnant women and 2142 liveborn infants were included: although there were no differences in pregnancy, infants born to women following lifestyle advice were significantly less likely to have birth weight above 4.5 kg or respiratory distress syndrome and showed a shorter length of postnatal hospital stay, compared to infant born to women who received standard care [172]. The prolonged and constant follow-up on this population will clarify the long-term benefits on the risk of child obesity and metabolic derangements.

NAFLD and the polycystic ovary syndrome. Among the conditions associated with NAFLD, the polycystic ovary syndrome (PCOS) deserves particular attention. PCOS affects 6–25% of reproductive-aged women and is associated with reproductive complications, including oligo/amenorrhea and sub-fertility, and metabolic derangements, such as insulin resistance, diabetes, hypertension, dyslipidemia [173]. PCOS has recently been recognized as a potential risk factor for NAFLD [174]. Although screening has not been recommended, clinicians should be aware that female patients with PCOS may develop NAFLD and its progressive form, NASH, even at younger age; childbearing NAFLD women with reproductive problems may have an underlying PCOS [175].

Early diagnosis of these two associated conditions, is mandatory to ensure a multidisciplinary approach.

AISF expert panel recommendations:

- **NAFLD should be considered in the differential diagnosis of abnormal liver function tests during pregnancy. Pregnant women with NAFLD should undergo screening for GDM and should be carefully monitored for the development of gestational hypertension, especially those who are overweight/obese. After delivery, these women should be referred to a hepatologist for management of their liver disease (Class IIa, Level C).**
- **Women with a history of GDM should be clinically monitored because of their increased risk to develop NAFLD, in addition to metabolic derangements (Class IIb, Level C).**
- **Women with NAFLD, especially those who are overweight/obese or have features of the metabolic syndrome, should receive antenatal lifestyle counselling to reduce the**

risk of adverse maternal and neonatal outcomes and of future metabolic alterations in the offspring (Class IIb, Level C).
- **Clinicians should be aware of the association between PCOS and NAFLD and should consider performing liver ultrasound and liver function tests in women with PCOS, particularly in those with features of the metabolic syndrome (Class IIa, Level C).**

4.8. Vascular disorders

4.8.1. Budd–Chiari syndrome (BCS)

Recent data [176] refer to sixteen women (24 pregnancies) with compensated BCS at conception, followed at three European centres. Anticoagulation was administered during 17 pregnancies. Foetal loss before week 20 occurred in seven of 24 pregnancies (29%). Two pregnancies resulted in very preterm births (between weeks 20 and 31) of one stillbirth and one infant with low birth weight. Eleven pregnancies resulted in moderately preterm births (between weeks 32 and 36) of 11 infants with a favourable outcome, although 3 were small for gestational age and 1 had severe respiratory distress syndrome. Finally, four pregnancies resulted in four infants at 37 or more gestation weeks, all with a favourable outcome. Out of the 17 pregnancies reaching gestation week 20, there were nine vaginal deliveries and eight caesarean sections.

Bleeding at delivery occurred in six women who were on anticoagulant treatment. Ascites recurred in two, because of portal thrombosis and TIPS occlusion, respectively, despite anticoagulation. Other maternal complications, unlikely related to BCS, including intrahepatic cholestasis, intrauterine haematoma, preeclampsia and placenta praevia, occurred in 9 of 16 women.

A favourable pregnancy outcome, defined as live birth at 32 or more weeks of gestation, with a healthy infant and no serious obstetrical complication, occurred in half of the 24 pregnancies. All women were alive after a median follow-up of 34 months.

AISF expert panel recommendations:

- **Pregnancy is not contraindicated in women with BCS in stable condition, since maternal and foetal outcome (beyond week 20 of gestation) are good (Class IIa, Level C). However, maternal morbidity is increased (Class I, Level C). The risk-benefit ratio of anticoagulation is unclear.**
- **Breast-feeding is contraindicated in women taking LMWH, but not in women taking VKA, which are excreted inactive in maternal milk (Class I, Level C).**

4.8.2. Chronic-extra hepatic portal vein obstruction

In chronic extra-hepatic portal vein obstruction (EHPVO), the portal vein trunk is replaced by a cavernoma, a network of hepatopetal, small venous vessels bypassing the obstructed portal vein and variably extending into the liver.

Main features of chronic EHPVO are recurrent bleeding from oesophago-gastric varices, splenomegaly with hypersplenism and, rarely, jaundice due to portal hypertensive biliopathy, or ascites. Chronic EHPVO can be asymptomatic. Liver function is normal or slightly altered. Ultrasound is adequate to identify the cavernoma, portal vein collaterals and splenomegaly.

Portal hypertension increases in pregnancy. Variceal bleeding is reported in 15% of pregnant women with chronic EHPVO [177–179]. Frequently the foetal outcome is poor. Mortality, mainly due to bleeding and preeclampsia, occurs in 4–10% of cases. Upper endoscopy, before pregnancy and at the end of the second trimester, even in women without varices before, is recommended [45] (Class I, Level C). Non-selective beta-blockers, albeit with the sporadic risk of intrauterine growth retardation and foetal bradycardia, or endoscopic variceal band ligation, are recommended for large-sized varices [180,181]. If anticoagulation is required (persistent thrombotic risk), LMWH at therapeutic dose must replace VKA and anti-platelet agents, before conception or as soon as possible. Because of placental heparinase and the increased glomerular filtration rate and distribution volume in pregnancy, anti-Xa activity should be checked once a month [182]. Anticoagulation, with LMWH or VKA, can be restarted 12 hours after delivery (or 24 hours after caesarean section). Breast-feeding is contraindicated in women taking LMWH, but not in women taking VKA, which are excreted inactive in maternal milk (Class I, Level C).

Miscarriage, prematurity, small for gestational age infants and perinatal death are increased in women with chronic EHPVO [183]. Caesarean section is hazardous for possible pelvic varices, and should be restricted to obstetric indications (*Class I, Level C*).

In a recent multicentre study [184] evaluating the maternal and foetal outcome of 45 pregnancies in 24 women with chronic EHPVO, miscarriage occurred in 20% and preterm birth in 38% of pregnancies. Variceal bleeding occurred in three patients, all without prophylaxis. HELLP syndrome occurred in two. Genital or parietal bleeding occurred postpartum in four patients, of which only one was on anticoagulants. Thrombotic events occurred in two patients. There were no maternal deaths. Overall, a favourable outcome (live birth at 32 or more weeks of gestation, with a healthy infant and no serious obstetrical complication) occurred in 64% of pregnancies.

AISF expert panel recommendations:

- **Pregnancy is not absolutely contraindicated in women with stable chronic EHPVO. However, maternal morbidity is increased. Anticoagulation, with LMWH is indicated in permanent pro-thrombotic disorders. Prophylaxis of variceal bleeding is mandatory (Class I, Level C).**
- **Breast-feeding is contraindicated in women taking LMWH, but not in women taking VKA (Class I, Level C).**

4.8.3. Idiopathic non-cirrhotic portal hypertension

Portal hypertension with patent portal and hepatic veins, absence of cirrhosis, and exclusion of other common causes of liver disease defines idiopathic non-cirrhotic portal hypertension (INCPH). This term has been proposed instead of hepatoportal sclerosis, non-cirrhotic portal fibrosis or idiopathic portal hypertension, which indicate, apparently distinct although overlapping features of a unique vascular disorder. INCPH accounts for about 25% of patients with portal hypertension in developing countries. Thrombophilia may have a role, at least in the West [185].

Main features of INCPH include splenomegaly, portal hypertension with repeated variceal bleeds. Liver function is usually preserved. Rare complications include jaundice, ascites and encephalopathy.

Complications during pregnancy include variceal bleeding, anaemia, and thrombocytopenia due to hypersplenism. A recent study in pregnant women with INCPH suggests normal fertility, non-increased incidences of miscarriages and stillbirths, but a higher risk of small for gestational age infants [186]. As in EHPVO, there is no role of elective caesarean section, apart from obstetric indications (*Class I, Level C*).

AISF expert panel recommendations:

- **Pregnancy is not absolutely contraindicated in women with INCPH. However, maternal morbidity is increased. Anticoagulation is currently not indicated. Prophylaxis of variceal bleeding is mandatory (Class I, Level C).**

- **In women with INCPH breast-feeding is not contraindicated.**

4.8.4. Hereditary haemorrhagic telangiectasia

Hereditary haemorrhagic telangiectasia (HHT) is an inherited autosomal dominant disease featuring abnormal blood vessels and arteriovenous fistulas in multiple organs.

HHT worsens in pregnancy, mainly in pulmonary or cerebral localizations, and improves postpartum.

Among 47 women and 161 pregnancies, worsening of intrapulmonary shunts occurred in six, with fatal pulmonary haemorrhage in two, and stroke in 3 [187].

Hepatic vascular malformations, often formerly unrecognized, may become symptomatic in pregnancy [188]. Anecdotal cases of congestive heart failure from hepatic arteriovenous fistulas with spontaneous improvement after delivery [189], as well as cases of biliary necrosis are reported [190,191].

AISF expert panel recommendations:

- **Maternal morbidity and mortality are increased in HHT. Women must be counselled on the risks associated with pregnancy (Class I, Level C).**
- **In women with HHT breast-feeding is not contraindicated.**

4.9. 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 oestrogen and endocrine metabolism. When pregnancy is successful in a cirrhotic woman, spontaneous abortion rate, risk of prematurity, and perinatal death rate are all increased [13]. Unfortunately, the outcomes and the optimal management of pregnancy with cirrhosis and portal hypertension in the modern era of obstetrics is still undefined [45]. Further, a rate of maternal mortality up to 5–10% has been described in this group of patients. Maternal prognosis depends on the degree of hepatic dysfunction during pregnancy rather than its cause [13,142].

Recently, Westbrook et al. demonstrated that Model for end-stage liver disease (MELD) score is useful to predict liver decompensation in pregnant women with cirrhosis. Indeed, no patient with MELD score ≤6 developed any significant liver complications [192].

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 manoeuvre during expulsion. However, there are no clear recommendation regarding mode of delivery [142,193], even if caesarean section is recommended in patients with large oesophageal or gastric varices; risk of vaginal delivery in patients with small varices is unknown [193,194].

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 foetus. Propranolol has also been used safely in pregnancy. Side effects include foetal growth retardation, neonatal bradycardia and hypoglycaemia. Propranolol does not appear to be teratogenic, but maternal and foetal propranolol toxicity may occur. Terlipressin has not been studied in pregnancy. Many concerns exist about decreased placental perfusion and increased risk of placental abruption (Table 5) [142,194].

Table 5
Safety pharmacotherapy and procedures for portal hypertension during pregnancy.

Drug	FDA class	Used and safety
Beta-blockers		
1st trimester	C	Close foetal monitoring needed to avoid foetal bradycardia and intrauterine growth retardation.
2nd/3rd trimester	D	
Octreotide	B	Use is controversial, limited by splanchnic vasoconstriction precipitating placental ischaemia and abruption.
Vasopressin	X	Absolutely contraindicated due to uterine ischaemia.
Band ligation		Safe and effective from the 2nd trimester of pregnancy.
TIPS		Use is controversial due to exposure of the foetus to radiation.

TIPS, transjugular intrahepatic porto-systemic shunt.

Pregnant patients with cirrhosis have an increased risk of splenic artery aneurysm rupture, which occurs in 2.6% of patients. More than 20% of all splenic artery aneurysm ruptures occurs during the third trimester, and may be related to increased splenic flow from both pregnancy and portal hypertension [195]. Therefore, an ultrasound examination of the splenic artery should be performed in early pregnancy, to exclude pre-existing splenic artery aneurysm. Furthermore, dietary sodium restriction to reduce fluid retention and portal pressure is recommended [142].

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 favourable. 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 [196].

AISF expert panel recommendations:

- **Pregnancy is uncommon in women with liver cirrhosis. When it occurs, spontaneous abortion rates (15–20%), risk of prematurity (26–64%) and perinatal death rate are increased compared to general population. Maternal prognosis of patients with portal hypertension depends on the degree of hepatic dysfunction assessed by MELD score and maternal mortality is 5–10% (Class III, Level A).**
- **Oesophageal variceal bleeding rate is high in pregnant cirrhotic women with varices (up to 25%). A screening endoscopy is recommended before or early in the second trimester of gestation (Class III, Level A). Pregnant patients with medium-to-large varices must be treated with non-selective β-blockers or band ligation (Class III, Level B).**
- **Caesarean section is recommended in pregnant women with cirrhosis with large oesophageal or gastric varices (Class III, Level A); risk of vaginal delivery in patients with small varices is unknown (Class III, Level C).**
- **Since data on safety of breast-feeding in cirrhosis are scarce, all medications used during breast-feeding should be checked for infant exposure risk.**

Conflict of interest
None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.11.004.

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