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EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy☆

European Association for the Study of the Liver*

Summary

Liver diseases in pregnancy comprise both gestational liver disorders and acute and chronic hepatic disorders occurring coincidentally in pregnancy. Whether related to pregnancy or pre-existing, liver diseases in pregnancy are associated with a significant risk of maternal and fetal morbidity and mortality. Thus, the European Association for the Study of Liver Disease invited a panel of experts to develop clinical practice guidelines aimed at providing recommendations, based on the best available evidence, for the management of liver disease in pregnancy for hepatologists, gastroenterologists, obstetric physicians, general physicians, obstetricians, specialists in training and other healthcare professionals who provide care for this patient population.

Introduction

Liver diseases in pregnancy comprise both gestational liver disorders and acute and chronic hepatic disorders occurring coincidentally in pregnancy. Whether pregnancy specific or pre-existing, liver diseases in pregnancy are associated with a significant risk of maternal and fetal morbidity and mortality.

Rates of pre-existing liver disorders amongst women of childbearing age are increasing. In a US National Health and Nutrition Examination Survey the prevalence of chronic liver disease (CLD) in women aged between 15- and 39-years old rose from 10.4% between 1988-1994 to 24.9% between 2007-2012.[1] Consequently, increasing numbers of women with pre-existing liver disease are considering pregnancy. To promote the best possible outcomes, these women should be able to access pre-pregnancy counselling to optimise their health and disease management prior to embarking on pregnancy, and to inform them regarding the impact of pregnancy on their disease and the potential risks associated with their disorder for a pregnancy. Many of the drugs used in the management of CLD are safe in pregnancy and should not routinely be stopped as this could cause clinical deterioration. However, some require cessation or substitution, and this should be discussed in advance of pregnancy (Table 1).

Gestational liver disorders affect 3% of the pregnant population and include preeclampsia and HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome; acute fatty liver of pregnancy; hyperemesis gravidarum; and intrahepatic cholestasis of pregnancy. These disorders require prompt investigation and management in order to reduce maternal and fetal morbidity and mortality.

When investigating liver disease in pregnancy one should be aware of the normal physiological and hormonal changes of pregnancy that can mimic those seen in women with CLD. A hyperdynamic circulation is common in pregnancy, owing to increased cardiac output and circulating plasma volume, accompanied by a reduction in peripheral vascular resistance. As such, physical examination may reveal features of this hyperdynamic circulation, as well as clinical signs that are typically associated with hepatic disease, *e.g.* palmar erythema and spider naevi (likely increased due to the hyper-oestrogenic state of pregnancy). Serum biochemistry and haematological normal ranges may also alter in pregnancy (Table 2).

Investigations including imaging, ultrasound, magnetic resonance cholangiopancreaticography, endoscopic retrograde cholangiopancreaticography, oesophago-gastroduodenoscopy and liver biopsy may be performed in pregnancy, where the benefits are thought to outweigh the risks; safety data are outlined in Table 3.

Methods

The European Association for the Study of the Liver (EASL) invited a panel of experts to develop clinical practice guidelines (CPGs) aimed at providing recommendations, based on the best available evidence, for the management of liver disease in pregnancy for hepatologists, gastroenterologists, obstetric physicians, general physicians, obstetricians, specialists in training and other healthcare professionals who provide care for this patient population.

C.W. was invited to chair the CPG and a further eight panellists (including one Governing Board representative (U.B.) and

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° Clinical Practice Guideline Panel: Chair: Catherine Williamson; Secretary, Melanie Nana; Panel members: Liona Poon, Limas Kupcinskas, Rebecca Painter, Gloria Taliani, Michael Heneghan, Hanns-Ulrich Marschall; EASL GB Representative: Ulrich Beuers.

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Table 1. Drug safety table.

Drug	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Antibiotics					
Rifampicin	Limited data	Limited data	Limited data[a]	Limited data	Yes
Antihypertensives					
Labetalol	Yes	Yes	Yes[b]	Yes	Yes
Nifedipine	Yes	Yes	Yes	Yes	Yes
Methyldopa	Yes	Yes	Yes	Yes	Yes
Hydralazine	Yes	Yes	Yes	Yes	Yes
Magnesium sulphate	Yes	Yes	Yes	Yes	Yes
Antivirals					
Tenofovir disoproxil fumarate	Yes	Yes	Yes	Yes	Yes
Tenofovir alafenamide	Yes	Yes	Yes	Yes	Yes
Lamivudine	Yes	Yes	Yes	Yes	Yes
Telbivudine	Yes	Yes	Yes	Yes	Yes
Ledipasvir-sofosbuvir	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Sofosbuvir-velpatasvir	No data	No data	No data	No data	Yes
Glecaprevir-pibrentasvir	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Ribavirin	No	No	No	No	No
Benzodiazepines					
Diazepam	Limited data[c]	Limited data[c]	Limited data[c,d]	Limited data[c]	Yes
Carbamate derivatives					
Disulfiram	No	No	No	No	Yes
Corticosteroids					
Dexamethasone	Yes	No[e]	No[e]	Yes	Yes
Betamethasone	Yes	No[e]	No[e]	Yes	Yes
Prednisolone	Yes	Yes	Yes	Yes	Yes
Budesonide	Yes	Yes	Yes	Yes	Yes
Fibrates					
Bezafibrate	No	No	Very limited data[r]	No	Yes
GABA-B receptor agonists					
Baclofen	Limited data	Limited data	Limited data	No	Yes
Ileal bile acid transporter inhibitors/bile acid sequestrants					
IBAT inhibitors	Limited data	Limited data	Limited data	Limited data	Yes
Cholestyramine	Yes[f]	Yes[f]	Yes[f]	Yes	Yes
Colestipol	Limited data[f]	Limited data[f]	Limited data[f]	Limited data	Yes
Immunomodulators					
Interferon	Limited data[g]	Limited data[g]	Limited data[g]	Limited data[g]	yes
Immunosuppressants					
Tacrolimus	Yes	Yes[h]	Yes[h]	Yes	Yes
Mycophenolate mofetil	Stop 12 weeks in advance	No	No	No	Yes
Sirolimus	Limited data[i]	Limited data[i]	Limited data[i]	Limited data[i]	Yes
Everolimus	Limited data[i]	Limited data[i]	Limited data[i]	Limited data[i]	Yes
Cyclosporin	Yes	Yes[j]	Yes[j]	Yes	Yes
Infusions					
Plasma exchange	Yes	Yes	Yes	Yes	Yes
N-acetylcysteine	Yes	Yes	Yes	Yes	Yes
FFP	Yes	Yes	Yes	Yes	Yes
Platelets	Yes	Yes	Yes	Yes	Yes
Blood	Yes	Yes	Yes	Yes	Yes
Immunoglobulin	Yes	Yes	Yes	Yes	Yes
Opioid agonists					
Naltrexone or nalmefene	Limited data[k]	Limited data[k]	Limited data[k]	Limited data[k]	Yes
N-methyl-D-aspartate agonists					
Acamprosate	Limited data[l]	Limited data[l]	Limited data[l]	Limited data[l]	Yes
Nutrient replacements					
Calcium supplements	Yes	Yes	Yes	Yes	Yes
Pabrinex	Yes	Yes	Yes	Yes	Yes
Vitamin K	Yes	Yes	Yes	Yes	Yes
Salicylates					
Aspirin	Yes	Yes	Yes	Yes	Yes
Thiopurines					
Azathioprine	Yes	Yes	Yes	Yes	Yes
Mercaptopruine	Yes	Yes	Yes	Yes	Yes
ICP drugs					
Ursodeoxycholic acid (UDCA)	Yes	Yes	Yes	Yes	Yes
S-adenosyl methionine (SAMe)	Limited data[m]	Limited data[m]	Limited data[m]	Limited data[m]	Yes
Guar gum	Very limited data	Very limited data	Very limited data	Very limited data	Yes
Activated charcoal	Limited data	Limited data	Limited data	Limited data	Yes
Semisynthetic bile acid obeticholic acid	Very limited data[n]	Very limited data[n]	Very limited data[n]	Very limited data[n]	Yes

(*continued on next page*)

Table 1. (*continued*)

Drug	Compatible peri-conception	Compatible with 1st trimester	Compatible with 2nd/3rd trimester	Compatible with breastfeeding	Compatible with paternal exposure
Portal hypertension					
Carvedilol	Limited data[s]	Limited data[s]	Limited data[b,s]	Yes	Yes
Propanolol	Yes	Yes	Yes	Yes	Yes
Anti-emetics					
First-line recommended treatments for management of Hyperemesis Gravidarum					
Chlorpromazine	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Cyclizine	Yes	Yes	Yes	Yes	Yes
Doxylamine/pyridoxine	Yes	Yes	Yes	Yes	Yes
Prochlorperazine	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Promethazine	Yes	Yes	Yes	Yes	Yes
Second line recommended treatments for management of Hyperemesis Gravidarum					
Domperidone	Yes	Yes	Yes	Yes	Yes
Metoclopramide	Yes[o]	Yes[o]	Yes[o]	Yes[o]	Yes[o]
Ondansetron	Yes[p]	Yes[p]	Yes[p]	Yes[p]	Yes[p]
Third line recommended treatments for management of Hyperemesis Gravidarum					
Corticosteroids	Yes[q]	Yes[q]	Yes[q]	Yes[q]	Yes[q]

UKTIS, UK Teratology Information Service.

[a]Limited data, however, available data do not suggest increased risk, therefore should not be withheld where indicated. Neonatal haemorrhage has been reported following exposure in late pregnancy, therefore both maternal supplementation with vitamin K and neonatal intramuscular vitamin K at birth is recommended when rifampicin is administered in the weeks preceding delivery (UKTIS).

[b]Monitor for rare risk of neonatal bradycardia, hypotension and hypoglycaemia post-delivery.

[c]Limited data. Recent, well-designed studies do not report fetal risk therefore where clinically justifiable can be used in pregnancy, ideally with lowest effective dose. Abrupt withdrawal should be avoided (UKTIS).

[d]Prolonged use near term, particularly in large doses, is associated with risk of neonatal withdrawal syndrome and/or 'floppy infant syndrome' therefore monitoring for neonatal respiratory depression is advised (UKTIS).

[e]Both dexamethasone and betamethasone are fluorinated corticosteroids thus readily cross the placenta. Repeated doses in pregnancy have been associated with neurocognitive and neurosensory disorders in the offspring during childhood.[2] Their use should be avoided where possible in pregnancy where the indication is for treatment of the mother; their use should be reserved for fetal lung maturity in the context of preterm birth.

[f]Cholestyramine and colestipol may cause maternal deficiencies of fat-soluble vitamins which may lead to adverse effects (particular vitamin K deficiency) therefore assessment of maternal prothrombin time, appropriate maternal vitamin K supplementation and administration of vitamin K to the neonate should be considered if given during pregnancy (UKTIS).

[g]Interferon administration is usually not recommended for viral hepatitis.

[h]Monitoring of maternal blood pressure, renal function, blood glucose and drug levels recommended.

[i]Limited data, not routinely recommended.

[j]Monitoring of maternal blood pressure recommended.

[k]Limited published data do not report fetal anomaly. Use in pregnancy should be weighed up against the risk of fetal alcohol syndrome on a case-by-case basis.

[l]Limited published data do not report fetal anomaly. Unpublished data (n = 32) include cases of miscarriage, congenital malformation and adverse neurodevelopmental effects (however, number of exposed pregnancies small and data likely confounded by maternal alcohol use) (UKTIS). Use in pregnancy should be weighed up against the risk of fetal alcohol syndrome on a case-by-case basis.

[m]Data are limited but reassuring.

[n]Too few data to make recommendation; animal data reassuring.

[o]Drug-induced extrapyramidal symptoms and oculogyric crises can occur with the use of phenothiazines and metoclopramide, patients reporting relevant symptoms should have the drug withdrawn and appropriate treatment initiated.

[p]Ondansetron use in pregnancy has been associated with an increased rate of orofacial clefting. However, the absolute risk increases from a background risk of 11 cases per 10, 000 births to 14 cases per 10, 000 births, this risk should be put into context when advising women regarding this medication vs. the risk of untreated disease.

[q]Typical dosing regimen includes intravenous hydrocortisone 100 mg twice daily and following clinical improvement conversion to oral prednisolone 40-50 mg daily with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached.

[r]For women with severe pre-existing cholestasis fibrates may be considered after the first trimester if benefits are likely to exceed perceived risks.

[s]Data is highly limited, however, studies of beta-blockers as a class are reassuring and therefore carvedilol should be initiated or continued as primary prophylaxis for variceal haemorrhage based on a benefit *vs*. theoretical risk basis.

one trainee representative (M.N.)) (Fig. 1) were then selected to comprise the remainder of the CPG panel. The process undertaken is summarised in Fig. 1. The panel initially agreed on the most relevant topics to be addressed in the guideline.

The CPG panel drafted 32 clinically relevant questions using the PICO (population/patient-intervention-comparison-outcome) format. The PICO format represents a standardised method to address the patient population, intervention, comparisons and outcome and ensures consistency across recent EASL guidelines. A Delphi panel, jointly nominated by the CPG group, was formulated of 25 academic experts and other stakeholders (Fig. 1) including obstetricians, hepatologists, obstetric physicians, anaesthetists, midwives and patient groups from Europe, North America and Asia. A simplified Delphi process was undertaken, and the proposed PICO questions reviewed, with feedback incorporated into a finalised draft. Consensus of over 75% of voting members of the Delphi Panel was required for approval.

The CPG panel was divided into subgroups and allocated a proportion of the PICO questions. Recommendations were drafted for each question following unbiased systematic review of the literature and rated based on the OCEBM (Oxford Centre for Evidence-Based Medicine) guidelines (Table 4 and 5). The CPG panel met 12 times during this process to discuss

Table 2. Normal ranges for clinical chemistry and haematology tests that are commonly used to evaluate pregnant women with liver disorders.

		Pregnant		
	Non-pregnant	1st trimester	2nd trimester	3rd trimester
Blood tests				
Full blood count				
Hb (g/L)	120-150	110-140	105-140	
WCC, x10^9/L	4-11			6-16
Platelets, x10^9/L	150-400			150-400
MCV (fl)	80-100			80-100
Lymphocytes, x10^9/L	0.7-4.6	1.1-3.6	0.9-3.9	1-3.6
Urea and electrolytes				
Urea (mmol/L)	2.5-7.5	2.8-4.2	2.5-4.1	2.4-3.8
Creatinine (μmol/L)	65-101	52-76	44-72	55-77
Potassium (mmol/L)	3.5-5.0			3.3-4.1
Sodium (mmol/L)	135-145			130-140
Liver tests				
Bilirubin (μmol/L)	0-17	4-16	3-13	3-14
Albumin (g/L)	35-46	28-37		
AST (IU/L)	7-40	10-28	11-29	11-30
ALT (IU/L)	0-40	6-32		
GGT (IU/L)	11-50	5-37	5-43	3-41
ALP (IU/L)	30-130	32-100	43-135	133-418
Bile acids (μmol/L)	0-6 (fasting) 0-10 (non-fasting)			0-19 (non-fasting)*
Inflammatory markers				
CRP (mg/L)	<10	Unchanged		
Procalcitonin (ng/L)	<0.05	Unchanged		
ESR (mm/hr)	0-20	18-48		30-70
Other				
Arterial blood gas				Expect a mild compensated respiratory alkalosis in pregnancy

*Non-fasting bile acid concentrations preferable in pregnancy (see section on ICP), while fasting measurement is recommended in non-pregnant individuals.

progress. Once the recommendations were drafted and agreed by the CPG panel a further simplified Delphi process was conducted and the recommendations were reviewed; suggested changes were taken into account in a revised draft that was subsequently reviewed and approved by the EASL Governing Board.

Table 3. Data relating to safety of radiological investigations used to assess pregnant women with liver disorders.

Radiological investigations	
Ultrasound	Safe at any gestation in pregnancy
Liver elastography	Safe at any gestation in pregnancy It should be noted that there may be a small increase in liver stiffness and controlled attenuation parameter in the third trimester which reflects the physiology of normal pregnancy[3]
MRCP	Safe at any gestation in pregnancy
ERCP	Fetal radiation estimated between <0.1-0.5 mGy[4] (threshold for malformation = 50 mGy) Can be performed in pregnancy, ideally in the 2nd/3rd trimester
Other	
OGD	Safe in pregnancy, ideally performed in 2nd trimester in left lateral position Midazolam may be used judiciously
Liver biopsy	Can be performed where clinical need/diagnostic uncertainty dictates, and delay in diagnosis would be more dangerous for the pregnant woman Ensure coagulopathy corrected

ERCP, endoscopic retrograde cholangiopancreaticography; MRCP, magnetic resonance cholangiopancreatography; OGD, oesophago-gastroduodenoscopy.

Pre-existing liver disorders

Pre-existing cholestatic liver disease

What advice should be given to women with pre-existing cholestatic liver disease regarding the risk of impaired outcome for the fetus, and for the mother (exacerbated pruritus, elevated serum bile acids and transaminases) in pregnancy?

Recommendations

- Women with pre-existing cholestatic diseases should be advised that approximately 50% will have worsening or *de novo* pruritus during pregnancy, but most women will have stable hepatic function. However, up to 70% have postnatal deterioration of serum liver tests. They should also be informed that preterm birth occurs more commonly, and live birth rates are reduced in primary biliary cholangitis and primary sclerosing cholangitis **(LoE 3; strong recommendation, strong consensus).**
- In the ~50% of pregnant women with worsening or *de novo* pruritus, repeated measurement of total serum bile acids should be performed, as higher serum bile acids are associated with reduced gestation length in pre-existing cholestatic liver disorders **(LoE 5; strong recommendation, strong consensus).**

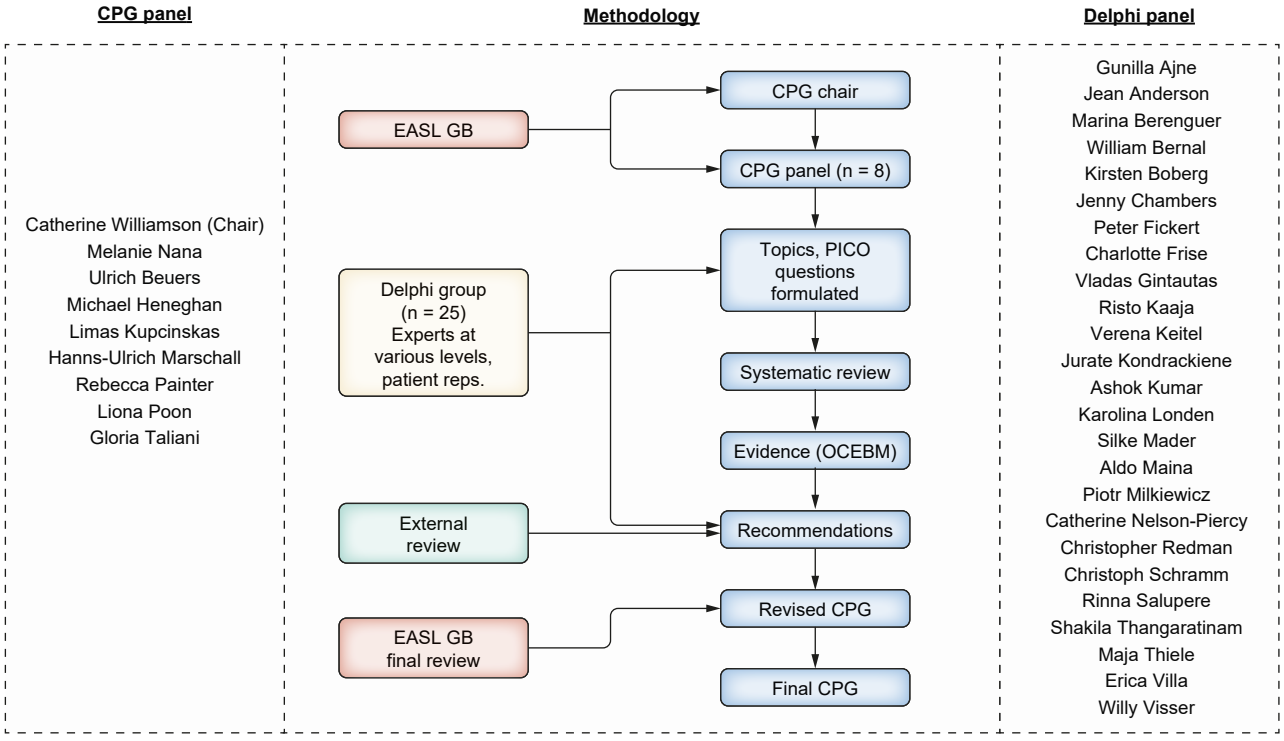

Fig. 1. Summary of the methods used to prepare the clinical practice guidelines. EASL, European Association for the Study of the Liver; GB, Governing body; PICO, Patient problem, the Intervention, the Comparison and the Outcome; OCEBM, Oxford Centre for Evidence-Based Medicine.

Table 4. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than an individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

Pre-existing cholestatic liver diseases include primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and hereditary cholestatic liver disease. Most of the data on outcomes of pregnancy are from women with PBC and PSC. It is likely that guidance relating to pruritus and hypercholanaemia will be relevant to all cholestatic liver disorders.

Primary biliary cholangitis

PBC is an immune-mediated, progressive cholestatic liver disease characterised by biliary epithelial damage and inflammation. The disease predominantly affects women and is typically diagnosed in the 5th and 6th decade, though it is diagnosed at childbearing age in up to 25% of cases.[5] Its stages and severity range from asymptomatic biochemical signs of cholestasis, through symptomatic disease – commonly presenting with fatigue, pruritus, complaints of sicca syndrome ('dry eye, dry mouth') or right upper quadrant abdominal complaints – to liver fibrosis and biliary cirrhosis (and associated complications). The pathogenesis of PBC is complex and involves, among others, environmental, immunogenetic and epigenetic factors, immune response to mitochondrial autoantigens and altered cholangiocyte physiology with impaired defences against toxic bile acids.[6]

It has been reported that up to one third of new diagnoses of PBC are made during pregnancy,[7] particularly when pregnant women develop pruritus and cholestasis that may be misdiagnosed as intrahepatic cholestasis of pregnancy (ICP). No differences in fertility have been reported between women with PBC and non-PBC controls.[8]

Maternal outcome in PBC pregnancies. While an earlier study described severe worsening of liver function during pregnancy

Table 5. Grades of recommendation.

Grade	Wording	Criteria
Strong	Shall, should, is recommended. Shall not, should not, is not recommended.	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested. May not, is not suggested.	

in 6/14 women with PBC,[9] newer studies reported an overall good maternal outcome with no serious hepatic complications. Rather, up to 70% of women with PBC had stable or improved serum liver tests when pregnant, but increased liver disease activity was reported in 60% to 70% postpartum, including one patient who was referred for liver transplantation (LT).[7–11] A reduction in immunoglobulin M levels and anti-mitochondrial-M2 antibody titres has been observed during pregnancy, with a return to baseline levels postpartum.[11] *De novo* onset or worsening of pruritus during pregnancy has been reported in approximately 50% of women with PBC.[7,10]

Fetal outcome in PBC pregnancies is impaired. In the larger series, relatively low rates of live births of 58–76%, as well as increased rates of preterm delivery of 6–33% and other neonatal complications of 3–7% were reported.[7,10,12] A study of pregnancies in women with PBC and PSC reported a negative correlation between the extent of elevation of maternal serum bile acid concentrations and transaminases and the length of gestation.[12]

Primary sclerosing cholangitis

PSC is a chronic cholestatic disease affecting both intra- and extrahepatic bile ducts. Most patients with PSC (60–80%) have inflammatory bowel disease (IBD), predominantly ulcerative colitis. Patients may develop progressive biliary strictures, leading to recurrent bacterial cholangitis, biliary cirrhosis, and end-stage liver disease. There is a substantially increased risk of hepatobiliary and colorectal cancer.[13,14] The male to female ratio is approximately 2:1, and most women are diagnosed at childbearing age.

Fertility is not affected by PSC.[15] Fetal and maternal outcomes in women with PSC depend on the concurrent management of liver and bowel disease that may be independently associated with adverse pregnancy outcomes.[16]

Maternal outcome in PSC pregnancies is impaired. De novo pruritus and abdominal pain are the most frequently reported symptoms during pregnancy.[17] Most women have stable serum liver tests; notably, use of ursodeoxycholic acid (UDCA) during pregnancy was associated with stable serum liver tests in 67% of pregnant women in a German cohort, while only 13% of those who were not on UDCA showed stable serum liver tests during pregnancy. Up to one-third of the mothers had deterioration in serum liver tests postpartum.[15]

For new symptoms or worsening liver tests during pregnancy, the development of relevant bile duct strictures should be considered in PSC. Ultrasound is the initial imaging test of choice. Magnetic resonance cholangiopancreaticography is regarded as safe during pregnancy and can be applied for diagnostic purposes when cholestasis is worsening. Depending on severity of symptoms, stage of pregnancy and presence of relevant bile duct strictures on imaging, endoscopic retrograde cholangiopancreaticography can be performed for therapeutic interventions in the bile ducts during the second or third trimester. While there are concerns about radiation exposure in the first trimester, endoscopic retrograde cholangiopancreaticography may be used in early pregnancy if a woman is acutely unwell; the dose of radiation that the fetus is exposed to[4] is considerably lower than the dose threshold of 50 mGy, above which there is concern about risk to the fetus.[18] Relevant strictures in PSC, defined as high-grade (>75%) biliary strictures on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis, are treated by endoscopic balloon dilatation or, if unsuccessful, short-term bile duct stenting according to existing guidelines, even in pregnancy.[19]

Fetal outcome in PSC pregnancies is impaired. In terms of fetal outcomes, a rate of early fetal loss of 16% was reported in a German cohort[15] and preterm births were reported in 10% to 30%.[12,15,17] A Swedish study confirmed the higher rate of preterm births (16.3% *vs*. 5.1%), about half of them iatrogenic, and also of Caesarean delivery (29.4% *vs.* 13.3%), independently of IBD, but no differences were seen in small size for gestational age, stillbirths, malformations, or neonatal deaths.[20]

Which drugs can be recommended to pregnant women with pre-existing cholestatic liver disease for the treatment of maternal biochemical derangements and pruritus, and how do they impact on pregnancy outcomes and risk of congenital defects, compared to no therapy?

Recommendations

- Ursodeoxycholic acid should be continued during pregnancy in primary biliary cholangitis (and primary sclerosing cholangitis when treated) as it is safe in pregnancy and breastfeeding **(LoE 4; strong recommendation, strong consensus).**
- Obeticholic acid use is currently not recommended in pregnancy or during lactation in women with primary biliary cholangitis or primary sclerosing cholangitis due to a lack of safety data, while fibrates may be used after the first trimester if the clinical team believes that the benefits outweigh the risks (**LoE 5; open recommendation, consensus).**
- Vitamin K deficiency related to cholestasis and/or use of anion exchange resins or rifampicin should be corrected **(LoE 5; strong recommendation, strong consensus).**
- For women with *de novo* or worsening pruritus, suggested treatments include rifampicin (300-600 mg daily) and anion exchange resins (cholestyramine, 4-8 g/day or colestipol, 5–10 g/day), the latter given at least 4 hours after ursodeoxycholic acid **(LoE 4; weak recommendation, consensus).**
- Imaging with ultrasound or magnetic resonance cholangiopancreaticography is recommended in primary sclerosing cholangitis, when cholestasis worsens, to exclude obstruction by gallstones or progress of high-grade strictures that are accessible to endoscopic balloon dilatation **(LoE 4; strong recommendation, strong consensus).**

UDCA is the first-line treatment for PBC. The semisynthetic bile acid obeticholic acid is the only approved second-line therapy (in combination with UDCA) for PBC in patients with an incomplete response, or in very rare cases intolerance, to UDCA.[21] Similar to obeticholic acid, bezafibrate was shown to

improve biochemical parameters in incomplete UDCA responders, but it also ameliorated mild pruritus in the BEZURSO trial in PBC.[22] The FITCH trial demonstrated the improvement of severe to moderate pruritus by bezafibrate in PSC and PBC.[23] Improvement of pruritus, especially in paediatric cholestatic liver disease, but also in PBC, was reported in phase II trials assessing the effect of compounds that inhibit the re-uptake of bile acids from the ileum (IBAT inhibitors); major adverse events included abdominal side effects, such as diarrhoea.[24]

UDCA at doses of 15-20 mg/kg/day can be given in PSC since it may improve serum liver tests and surrogate markers of prognosis. Available data do not allow a firmer recommendation.[25,26] Medium-dose UDCA is regarded as safe during pregnancy.[26]

In pregnant women with PBC (and PSC), treatment with UDCA is recommended or accepted, based on well-documented case series[7,8,10,25] and the documented safety of UDCA in ICP (see below), and also during breastfeeding.[25] In contrast to UDCA, robust data on the use of obeticholic acid in pregnancy and lactation are missing so, at present, obeticholic acid should be discontinued as soon as pregnancy is confirmed and should not be restarted during breastfeeding. Fibrates have been used in pregnant women with hypertriglyceridemia after the first trimester,[27] but there are limited safety data. Thus, decisions about the use of fibrates should be individualised and based upon the severity of maternal disease.

For treatment of cholestasis-associated pruritus in pregnancy, general recommendations include using emollients to prevent dryness of skin, avoiding hot baths or showers, using cooling gels (*e.g.*, menthol gels) for affected skin areas, and keeping nails shortened.[26] An antipruritic effect of UDCA as an anticholestatic secretagogue has never been studied for PBC or PSC during pregnancy, although the antipruritic efficacy in ICP (as shown in meta-analyses)[28,29] may justify an attempt to use UDCA at moderate doses under these circumstances (start with low dose of 10 mg/kg/day and slowly increase the dose up to 20 mg/kg/day). Evidence for anion exchange resins is poor (cholestyramine or colestipol) or non-existent (colesevelam).[26] Rifampicin appears safe and effective in the third trimester.[21] Thus, for the treatment of cholestasis-associated pruritus, in agreement with existing EASL CPGs,[21,30] cholestyramine (or colestipol) and rifampicin are recommended as they are considered safe in pregnancy, although the data are limited.[31,32] UDCA and cholestyramine administration should be separated by at least 4 hours. In rare cases of unbearable itch, usually connected to dominant strictures, biliary drainage[19] or plasmapheresis may provide transient relief.[33,34] Cholestasis and the use of anion exchange resins may exacerbate vitamin K deficiency; replacement should be given in women with steatorrhoea or confirmed vitamin K deficiency. In women treated with these drugs, it is reasonable to monitor coagulation tests, *e.g.*, international normalised ratio (INR). Rifampicin may cause hepatotoxicity in 5%, but this resolves on cessation of treatment.[35] Neonates of women treated with rifampicin should receive vitamin K.

For pregnant women with PBC and PSC who have documented or suspected cirrhosis, the management is not different to any other aetiology of cirrhosis (see below).

Drug-induced liver disease

When should a diagnosis of drug-induced liver disease be considered in pregnancy?

Recommendation

- A careful history of previous or current use of prescribed and over-the-counter medications and herbal products is demanded in any case of unexplained serum liver test elevations **(LoE 5; strong recommendation, consensus).**

A very large number of xenobiotics, including prescribed or over-the-counter medications, herbal products, nutritional supplements, metals, and toxins can provoke idiosyncratic liver injury. The diagnosis of drug-induced liver disease (DILI) is particularly challenging, since it is based largely on exclusion of other causes. Acute hepatocellular hepatitis is the most common form of idiosyncratic drug reaction and is characterised by increased serum transaminases while drug-induced cholestatic liver injury typically presents with pruritus and elevated alkaline phosphatase.[36] In pregnant women, cholestatic features may be accompanied by elevated serum bile acid concentrations, and the extent of the hypercholanaemia is likely to have the same relationship to adverse pregnancy outcomes as in ICP. It is important to distinguish DILI during pregnancy from autoimmune disease, viral hepatitis or ICP.

There is limited evidence suggesting that pregnant women are more susceptible to DILI.[37,38] Information on drugs associated with DILI in pregnant women is mainly restricted to antihypertensive agents (such as methyldopa and hydralazine), antithyroid drugs (propylthiouracil) and antimicrobials (in particular tetracycline and antiretroviral agents). The link between pregnancy and DILI due to methyldopa and hydralazine likely stems from the fact that these drugs are used to treat gestational hypertension. Similar to methyldopa and hydralazine, propylthiouracil is most likely associated with DILI during pregnancy because it is advocated as the treatment of choice for pregnant women with hyperthyroidism during the first trimester. Several studies report antiretroviral hepatotoxicity in pregnant women, although the role of pregnancy as an independent risk factor is debatable.[37] Drugs that typically cause cholestatic liver injury in pregnant women include antibiotics, *e.g.* amoxicillin-clavulanic acid and proton pump inhibitors.[38] Progestogen use in pregnancy for assisted conception or prevention of preterm birth may enhance the risk of cholestasis.[39]

Alcohol-related liver disease

Which drug therapies for pregnant women with alcohol-related liver disease, who are unable to discontinue alcohol use in pregnancy, could help to reduce alcohol-related fetal complications?

Recommendations

- Pregnant women should be screened for alcohol use and referred for management when appropriate **(LoE 4; strong recommendation, strong consensus).**

- For women with alcohol-related liver disease, delaying conception is recommended until abstinence is achieved **(LoE 4; strong recommendation, strong consensus).**
- Medication use to treat alcohol use disorder during pregnancy should be individualised; disulfiram should be avoided, and consideration of other drugs, *e.g.* naltrexone or acamprosate, should include careful weighing of the risks of alcohol use *vs.* those of medication exposure **(LoE 5; open recommendation, strong consensus).**

Alcohol use among women of childbearing age has increased in recent years.[40] A large study from the US, comparing the periods of 2001–2002 and 2012–2013, found increases of any alcohol use in both women of childbearing age (from 66% to 75%) and pregnant and postpartum women (from 58% to 66%), and also of heavy episodic drinking in these populations (from 23% to 36%, and from 18% to 28%, respectively).[41] In a study from Norway, any pre-pregnancy alcohol use and binge drinking was reported by 89% and 59% of women, respectively; 85% of women changed their drinking behaviour after becoming pregnant, with alcohol use reported by 23% at 12 weeks' gestation, and binge drinking by 25% at 0–6 weeks' gestation.[42]

The effect of alcohol on fertility seems to be unclear, indicating reduced fecundity[43] but no association with recurrent pregnancy loss.[44] In women with compensated cirrhosis due to alcohol-related liver disease (ALD), birth rates were significantly lower compared to a matched non-cirrhotic population (27.2 *vs.* 45.8 per 1,000 person-years).[45]

Alcohol use in pregnancy is strongly associated with increased risk of preterm birth and small for gestational age infants.[46–48] In addition, long-lasting impairments of the offspring due to alcohol exposure during pregnancy are well documented and include fetal alcohol spectrum disorder and its most severe form, fetal alcohol syndrome.[49] These studies underline the importance of inquiring about alcohol use in all women of childbearing age, both at preconception counselling and during pregnancy management.

All women should be screened for alcohol use in pregnancy.[50] ALD in females is usually suspected upon documentation of regular alcohol consumption >20 g/day together with the presence of clinical and/or biological abnormalities suggestive of liver injury (alcoholic steatohepatitis). Investigations should not only include serum liver tests but also a test to detect liver fibrosis (*e.g.* transient elastography) since advanced liver fibrosis may present with normal serum liver tests (ALD fibrosis/cirrhosis).[40] Alcohol use disorder (defined by DSM-5 criteria) should be evaluated with the AUDIT (alcohol use disorders identification test) questionnaire.[40] For women with ALD and alcohol use disorder, the achievement of alcohol abstinence is the most important aspect of preconception and pregnancy management.

Psychosocial treatment is first-line intervention in alcohol use disorder that, outside pregnancy, may be complemented by drugs such as disulfiram, opioid antagonists naltrexone or nalmefene, N-methyl-D-aspartate agonist acamprosate, and the GABA-B receptor agonist baclofen.[40] Disulfiram is associated with fetal abnormalities[51,52] while baclofen may accumulate and potentially cause neonatal withdrawal syndrome;[53] disulfiram is therefore contraindicated and baclofen should be used with caution. Limited available data for the use of naltrexone and acamprosate during human pregnancy did not show fetal abnormalities.[54,55] The decision to continue these medications must be taken on an individual basis, weighing their risks against the risks connected to alcohol withdrawal syndrome.[56] Withdrawal syndrome otherwise should be treated with benzodiazepines.[37]

No cases of pregnancy in alcohol-related hepatitis have been published; hence it is not possible to give evidence-based advice on whether women with alcohol-related hepatitis should be treated in a similar way to a non-pregnant population, *i.e.* by administration of prednisolone in severe life-threatening alcohol-related hepatitis with Maddrey's discriminant function ≥32[38].

Hepatic tumours and pregnancy

Liver masses are being increasingly detected in pregnancy as a consequence of widespread use of abdominal ultrasound. The majority are benign (haemangiomas, focal nodular hyperplasia [FNH] and hepatocellular adenomas [HCAs]) and can usually be managed conservatively, although in rare cases they can cause significant haemorrhage. Malignant tumours include hepatocellular carcinoma (HCC), cholangiocarcinoma and metastatic lesions; the diagnosis of these aggressive tumours can be difficult in pregnancy due to an overlap in symptomatology with other more common conditions. To facilitate prompt diagnosis and early management, investigations should reflect those conducted outside pregnancy, where indicated.

For women with hepatic tumours, what is the impact of pregnancy on tumour size and rate of maternal and fetal complications?

Hepatocellular adenoma

Recommendations

- For women with hepatocellular adenomas with a diameter <5 cm diameter, pregnancy does not increase the risk of complications related to the tumour and therefore no additional interventions are recommended. However, some tumours may increase in size and therefore ultrasound assessment is recommended **(LoE 1; strong recommendation, strong consensus).**
- Women planning pregnancy with a hepatocellular adenoma that has a diameter >5 cm should, where possible, have treatment prior to pregnancy. These tumours are associated with an increased risk of enlargement and haemorrhage **(LoE 2; strong recommendation, consensus).**

HCAs are benign liver tumours that affect 3-4 per 100,000 women.[57] There is a genetic component to the aetiology of HCA, with mutations reported in *HNF1α* (35%), β-catenin (15%) and in several genes resulting in reduced activation of STAT3 (50%).[58] In the context of pregnancy, women with HNF1α mutations are at an increased risk of gestational diabetes mellitus (GDM) and should be screened using local protocols. HCAs rarely undergo malignant transformation, but specific mutations increase the risk; an exon 3 mutation in β-catenin is more likely to result in malignant transformation than mutations in exons 7/8.[59] There is a strong association between HCA and ingestion of the oral

contraceptive pill or the presence of maternal cardiometabolic disorders, including obesity, type 2 diabetes mellitus, hypertriglyceridaemia and hypertension.[60,61]

The most common complication of HCA relates to bleeding (25-30% cases) and clearly has implications in pregnancy.[62] A single-centre, retrospective study of 261 HCA cases reported haemorrhage in 32%; multivariate analysis demonstrated that risk factors include tumour size, presence of a β-catenin mutation on exons 7/8, evidence of activation of sonic hedgehog signalling and alcohol consumption.[62] Tumour size was also shown to be associated with haemorrhage in a large US cohort of 184 cases.[63]

In the context of pregnancy, a prospective study of 48 women (51 pregnancies) with HCA <5 cm in diameter reported growth of HCA (increase in size ≥20%) in 13 pregnancies (25.5%); the median increase was 14 mm (IQR 8-19). One woman underwent successful transarterial embolisation at 26 weeks' gestation when the HCA grew to >7 cm, the other pregnancies proceeded without any complication.[64] These reassuring data suggesting good maternal and fetal outcomes in women with HCA <5 cm diameter are supported by a systematic review of the literature that reported outcomes of 73 pregnancies without prior HCA-related intervention; 39 remained stable (53.4%), 11 regressed (15.1%), and 23 (31.5%) progressed.[65] Whilst acknowledging the limitation of using historical data, this study provided clinically valuable risk estimates of haemorrhage based on tumour size and the time of tumour presentation. HCA-related haemorrhages occurred in 15 women with larger tumours (6.5-17.0 cm), and eight patients experienced bleeding during pregnancy; in seven women, bleeding occurred in the third trimester, two during labour and five postpartum. A case series of 17 pregnancies in 12 women from a tertiary centre that advised active treatment of HCA >5 cm diameter prior to pregnancy, and close monitoring of tumour size during pregnancy, reported good outcomes despite five women becoming pregnant with HCA >5 cm[64]. There was tumour enlargement in four cases; two were managed with elective caesarean section, one with radiofrequency ablation in the first trimester and one conservatively, with good maternal and fetal outcomes.[66] Regular assessment of HCA size is therefore recommended in pregnancy, as tumours that enlarge are more likely to bleed and may require intervention. Close surveillance is also recommended in women with adenomas that have previously been complicated by haemorrhage. For women where tumour size increases to ≥5 cm, although there are limited data, it is likely that prevention of a prolonged second stage of labour and consideration of assisted delivery (to avoid excessive Valsalva) may reduce the risk of haemorrhage.

Haemangioma

Recommendations

- Women with haemangiomas, even giant ones, should be advised that they do not preclude pregnancy **(LoE 4; strong recommendation, strong consensus).**
- Imaging is recommended during each trimester of pregnancy to monitor haemangioma size in those at higher risk of rupture (large or exophytic) **(LoE 4; strong recommendation, strong consensus).**

Haemangiomas are the most common benign liver tumour, with prevalence ranging from 0.4% to 7.3% (female:male ratio of up to 5:1).[67] They can increase in size during pregnancy but, unlike HCA, the role of female sex hormones and the effect of pregnancy on the evolution of haemangiomas is uncertain. The majority of pregnancies in individuals with haemangioma do not develop complications. However, accelerated growth, increased intra-abdominal pressure and direct contact with the gravid uterus are all plausible mechanisms for spontaneous rupture or worsening symptoms during pregnancy.[68]

In a retrospective cross-sectional study of 2,071 patients, the risk of hepatic rupture in a giant (>4 cm) liver haemangioma was 3.2%, with increased risk in peripherally located and exophytic lesions.[69] In lesions >10 cm, the risk increases to 5%; in these relatively higher risk cases, discussion of the merits of treatment prior to conception should be considered.[70]

Haemangiomas can usually be managed conservatively. Resection is rarely required, but it can be performed during pregnancy in case of rapidly enlarging cases or in those complicated by rupture.[68] Thus, haemangiomas do not preclude pregnancy, but close monitoring is recommended.

Focal nodular hyperplasia

Recommendations

- Women with focal nodular hyperplasia should be advised that pregnancy is not contraindicated and vaginal delivery is not associated with increased risks **(LoE 4; strong recommendation, strong consensus).**
- Imaging is not routinely recommended to monitor focal nodular hyperplasia during pregnancy **(LoE 4; open recommendation, n.a.).**

FNH, the second most common benign liver tumour after liver haemangioma, is characterised by the presence of focal hyperplasia within normal liver tissue. It occurs more frequently in females than males (estimated sex ratio of 26:1)[65]. FNH development and growth may be influenced by steroid hormones; the relationship between FNH and oestrogen exposure is controversial. A benign course of FNH can be expected during pregnancy.[71] In a study of 20 pregnant women with FNH, size remained constant in seven patients, reduced in 10 patients and three had non-significant growth; there were no FNH-related complications.[72] The heterogeneity of oestrogen receptor expression between different patients in the context of the benign lesion may explain the observed differences in behaviour of the tumour during pregnancy. The benign course described in pregnancy indicates that pregnancy should not be discouraged. The management of benign liver tumours is summarised in Fig. 2.

Hepatocellular carcinoma

Recommendations

- Maintain ultrasound surveillance for hepatocellular carcinoma in patients with cirrhosis, in accordance with screening outside of pregnancy **(LoE 4; strong recommendation, n.a.).**

- Perform close surveillance with abdominal ultrasound or MRI each trimester to enable detection of focal lesions in pregnant women considered to be at risk of recurrent hepatocellular carcinoma development **(LoE 4; strong recommendation, consensus).**
- In women with hepatocellular carcinoma, treatment with surgery, radiofrequency ablation or other potentially curative treatment should be individualised according to stage of pregnancy, location and size of the tumour **(LoE 4; intermediate recommendation, strong consensus).**
- Women with hepatocellular carcinoma should be advised that spontaneous and induced vaginal delivery are not contraindicated **(LoE 4; strong recommendation, strong consensus).**

HCC is rarely observed among women of childbearing age, therefore it is an infrequent finding during pregnancy. HCC in pregnancy is most commonly reported in China and Korea, likely a consequence of the endemic hepatitis B virus (HBV) infection.[73] Overall, fewer than 65 cases have been reported worldwide over the past 60 years.[74] However, HCC is important because it is generally associated with poor obstetric outcomes; with a 12.5% risk of spontaneous hepatic rupture[73] and shorter median survival of pregnant compared to non-pregnant women.[75,76] Cobey *et al.* reported that 20 out of 33 mothers who presented with HCC in pregnancy died within a few days of the initial presentation, indicating that pregnancy may have an adverse effect on HCC prognosis; the rise in oestrogen and gestational immune suppression have been described as possible implicating factors.[77] A large propensity score-matched study performed in Taiwan confirmed overall low survival in women of reproductive age with primary liver cancer (HCC and cholangiocarcinoma); 40 peripartum women, who were diagnosed with primary liver cancer between 10 months prior to and 6 months postpartum, had similar risk of death (adjusted hazard ratio 1.40; 95% CI 0.89–2.20; $p = 0.149$) as 160 women diagnosed outside of the pregnancy period, with follow-up for 0.5-5 years.[74] The study showed that the risk of death was significantly higher only among pregnant patients with cholangitis (adjusted hazard ratio 3.34, 95% CI 1.49–7.47, $p = 0.003$).[74] Although these findings may not generalise to Western populations, it is reassuring that the results of this study did not confirm worse outcomes in pregnant compared to non-pregnant women and are consistent with a study by Choi *et al.*, which demonstrated improving survival rates over time in 48 pregnant women with HCC. In particular, the median survival of the group of pregnant women diagnosed after 1995 was significantly longer (25.5 months) compared to the survival observed among pregnant women diagnosed during or before 1995 (18 months, p <0.001).[73] It is reasonable to assume that improved timing of diagnosis and tumour management may have favourably impacted outcomes.

Early diagnosis is of paramount importance, but it may be delayed by the low specificity of symptoms such as nausea, vomiting, right upper quadrant and epigastric pain with possible weight loss, that may be attributed to the pregnancy itself, and by the limited knowledge of risk factors for development of HCC during pregnancy. Screening and diagnosis mostly rely on abdominal ultrasound,[77] especially with contrast[78] showing a sensitivity of 90%, and on MRI without contrast, which can be performed safely during pregnancy.[79] Percutaneous liver biopsy is indicated for investigation of HCC in pregnant women, with the aim of avoiding unnecessary surgery in cases where imaging studies are ambiguous.[73]

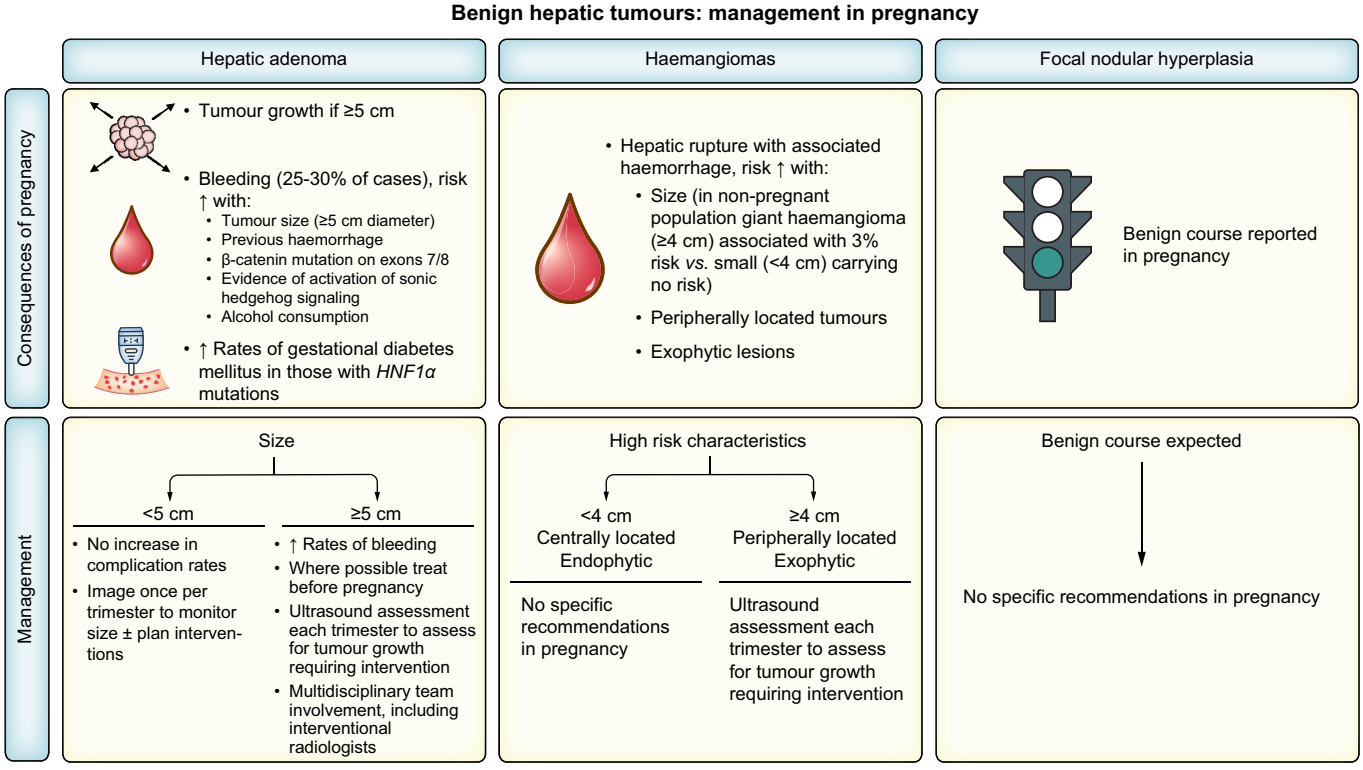

Fig. 2. Management of benign hepatic tumours in pregnancy.

Radical surgery is the best potentially curative therapy for HCC during pregnancy and can be safely performed from the second trimester onward. During the first trimester, pregnancy termination is probably the best option before any intervention on the tumour, or it may spontaneously occur as consequence of treatment. Management may be complicated by mother's concerns about surgery, although multidisciplinary team input should enable reassurance and evidence-based approaches. Another possible strategy is radical local radiofrequency ablation if the HCC is less than 2 cm size[80] or radiofrequency ablation followed by surgery after delivery to prevent local recurrence in the case of larger HCC nodules.[75] Spontaneous or induced vaginal delivery is not contraindicated, although caesarean section may be necessary in a small proportion of women dependent upon the HCC presentation.[73] Decisions should be made on an individualised basis with the support of the multidisciplinary team.

Cholangiocarcinoma

Recommendation

- Women with cholangiocarcinoma in pregnancy should have a case-by-case evaluation by a multidisciplinary team to consider diagnostic and therapeutic strategies based on symptoms and prognosis **(LoE 4; strong recommendation, n.a.).**

Cholangiocarcinoma is a rare condition representing approximately 3% of all gastrointestinal malignancies, with an incidence of two cases per 100,000.[81] Only nine cases of cholangiocarcinoma during pregnancy were reported in the literature between 1975 and 2015, and characteristically the signs and symptoms overlapped with more common pregnancy disorders, such as ICP or HELLP syndrome.[82]

A case of metastatic cholangiocarcinoma diagnosed in the postpartum period was reported in a patient with cystic fibrosis,[83] which is associated with an increased risk of biliary tract cancer compared to the age-adjusted general population (standardised incidence ratio 11.4; 95% CI 3.6 to 27.4).[84] Pregnancy may preclude the early identification of cholangiocarcinoma owing to a reluctance to use radiologic diagnostic modalities because of concerns about the safety of the fetus. This is unwarranted (see Table 3) and may lead to delayed diagnosis and potentially worse outcomes. The prognosis of women with cholangiocarcinoma in pregnancy is generally poor; the seven cases reported so far died within 6-10 months after diagnosis.[82]

Metastatic lesions of the liver

Recommendation

- In pregnant patients with a history of extrahepatic cancers known to metastasise to the liver, ultrasound surveillance is recommended and, if metastases are identified, careful multidisciplinary follow-up is recommended including adherence to recommended oncological management for non-pregnant people if metastases are identified **(LoE 4; strong recommendation, consensus).**

It has been postulated that the weaning-induced liver involution after pregnancy establishes a pro-metastatic microenvironment that may facilitate the occurrence of metastatic growth.[85] Several case reports support this suggestion. Examples include a young woman with very long-term (6 years) stabilisation of a G2 pancreatic neuroendocrine tumour metastasis that progressed 2 months after a normal delivery.[86] Another recent report described the occurrence of rectal cancer in a multiparous pregnant woman in whom, despite pregnancy termination at week 20 and administration of neoadjuvant therapies, CT scan performed 2 weeks after completion of chemoradiation showed marked regression of the rectal tumour while liver metastasis showed progression and required curative surgical resection.[87] A case of metastatic lesion of the liver was reported in a 35-year-old woman after removal of ovarian follicular carcinoma arising in a teratoma at 10 weeks of gestation and without evidence of metastasis until after delivery. Another report described extraovarian spread in malignant struma ovarii in <5% of patients, raising the possibility of a link between pregnancy and liver metastasis.[88] Thus, it appears that the liver may be a preferred target for at least some metastatic lesions developing after delivery.

Pregnancy in autoimmune hepatitis

For pregnant women with pre-existing or new-onset autoimmune hepatitis (AIH), does treatment with immunosuppressive drugs reduce the rate of adverse maternal or fetal outcomes?

Recommendation

- Therapy with prednis(ol)one, budesonide and thiopurines should be continued in pregnancy and should be given for *de novo* AIH as in non-pregnant women, as treatment is associated with better maternal and fetal outcomes **(LoE 3; strong recommendation, strong consensus).**

AIH is an inflammatory liver disease that may present in an acute, fulminating or chronic form, with a female predominance of 4:1 affecting all age groups.[89–91] Women present with elevated globulins, arthralgia, skin rashes and CLD and may have subfertility and amenorrhea. Typically, AIH is a disease of remission and relapse and for most patients (other than those with cirrhosis) fertility is maintained and successful pregnancy a realistic proposition. Ideally, this should be planned, since complications may be anticipated and prevented with appropriate counselling. This provides an opportunity to optimise remission and obtain disease stability, review medication, and institute screening if appropriate in addition to generating a delivery plan.

Reduced fertility is associated with poorly controlled AIH which is reversed with disease control and stable effective immunosuppression.[92] Amenorrhoea related to hypothalamic-pituitary dysfunction and nutritional status still impacts as many as 30-50% of women with cirrhosis and therefore women may still experience subfertility.[45,93] AIH may present with index presentations during pregnancy or postpartum including presentations with acute liver failure. The diagnosis of AIH in pregnancy is akin to the non-pregnant state and is based on the exclusion of other liver disorders, characteristic liver biochemistry and serology with the exclusion of other

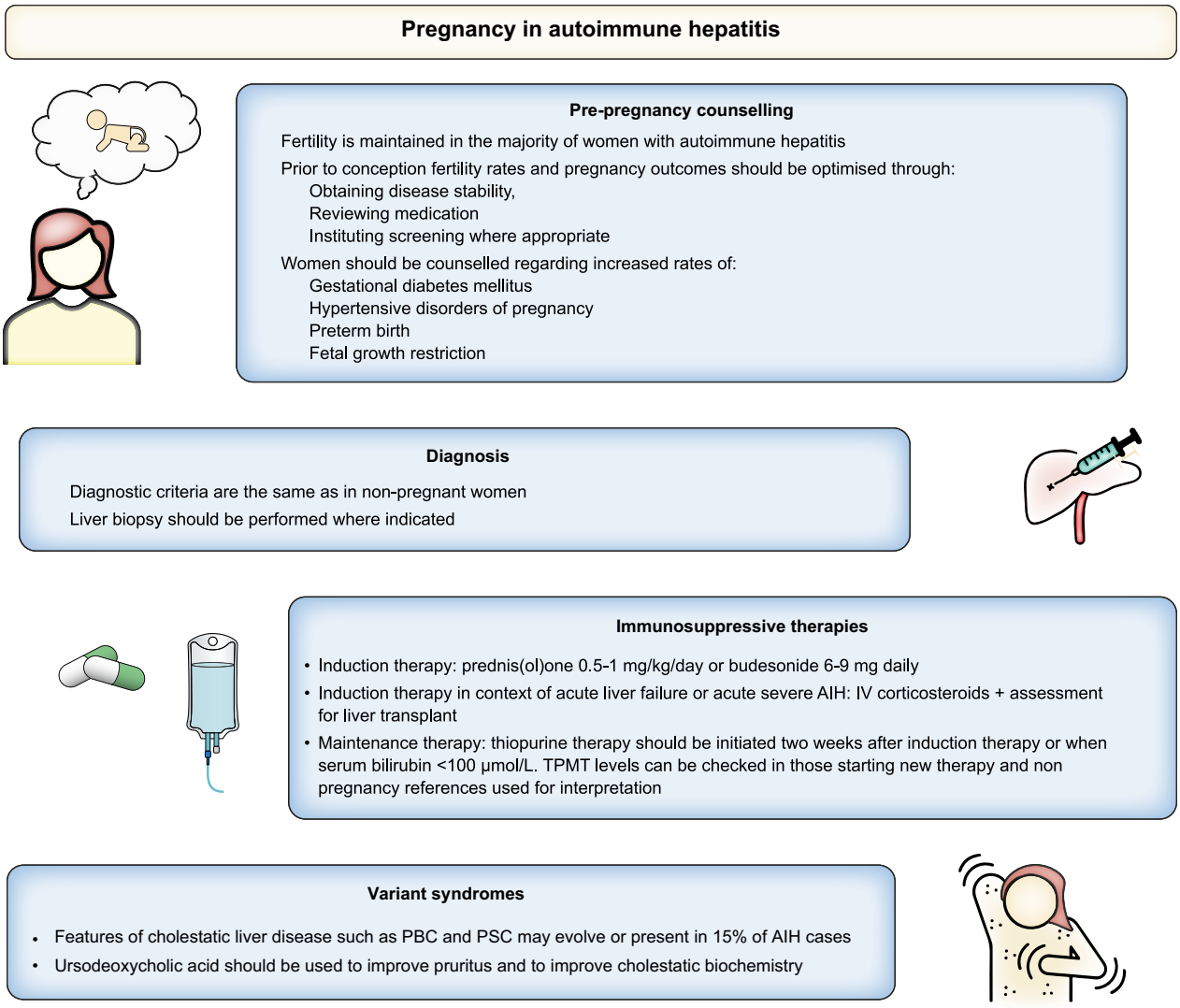

Fig. 3. Management strategies for autoimmune hepatitis before and during pregnancy. AIH, autoimmune hepatitis; IV, intravenous; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TPMT, thiopurine methyl transferase.

pathologies such as viral hepatitis.[94] Liver biopsy should be predicated on clinical need and diagnostic uncertainty, although biopsy in pregnancy has not been shown to increase preterm birth or stillbirth when compared to pregnancies with CLD.[95] See Fig. 3 for summary of management.

Management of new-onset AIH in pregnancy is similar to the non-pregnant state with high dose prednis(ol)one as induction therapy.[96,97] Current EASL CPGs advise prednis(ol)one 0.5-1 mg/kg/day.[97] In more severe disease, such as in the context of acute liver failure or acute severe AIH, intravenous corticosteroids may be used in parallel with assessment for LT. Whilst older data suggested a risk of oral-facial clefts and increased preterm birth, preeclampsia and low birth weight, recent evidence has not supported this (Table 1).[98] Budesonide (6–9 mg daily) may also be considered as first-line induction therapy in women without cirrhosis, portal hypertension or advanced disease, with the potential advantage being its localised effect and improved tolerability, as reported in a recent cases series of five women with eight pregnancies in the context of AIH.[99] Standard paradigms of management should include the initiation of appropriate thiopurine therapy, such as azathioprine or mercaptopurine, as corticosteroid-sparing maintenance therapy, typically 2 weeks after induction therapy[96] or when serum bilirubin levels are less than 100 μmol/L. The reassuring safety data for thiopurines in pregnancy and breastfeeding are summarised in the post-transplant section and in Table 1.

Does pregnancy cause deterioration of underlying liver disease in women with autoimmune hepatitis?

Recommendations

- Immunosuppressive drugs with good safety data should be continued throughout pregnancy. Autoimmune hepatitis may deteriorate postpartum and therefore immunosuppressive therapy should be continued and an increase in dose considered postpartum due to the risk of flares **(LoE 5; strong recommendation, strong consensus).**

- Women with AIH should be advised that they have increased rates of gestational diabetes mellitus, hypertensive disorders of pregnancy, preterm birth and fetal growth restriction (often associated with preterm birth) and need close obstetric surveillance with screening to predict and manage these disorders **(LoE 2; strong recommendation, strong consensus).**

AIH is associated with both GDM and the umbrella term of hypertensive complications in pregnancy (gestational hypertension, eclampsia, preeclampsia and HELLP syndrome).[91,100–102] A 4.7% prevalence of GDM was identified in AIH compared with a 1.1% rate in non-AIH pregnancies, with a relative risk (RR) of 4.35 (95% CI 2.21-8.57).[91] This differential in risk was also evident in patients with AIH not receiving immunosuppression (6.1% AIH *vs.* 1.1% non-AIH, RR 5.094 95% CI 2.18-11.88). This suggests that GDM risk may not be exclusively explained by corticosteroid therapy. Other studies demonstrated a non-statistically increased risk of GDM in AIH, which could be explained by small sample sizes.[102] A recent large US population study reviewed 935 AIH pregnancies (60 with cirrhosis) with 120,100 CLD pregnancies of other aetiologies (845 cirrhosis) and 18,474,310 non-CLD pregnancies.[100] GDM occurred in 17% of patients with AIH compared to 9% and 7% of CLD and non-CLD pregnancies, respectively (p <0.001). Women with AIH undergoing pregnancy should therefore be closely monitored and screened for GDM. With regard to the prevalence of hypertension in pregnancy, this large US-based study demonstrated hypertensive complications in 9% compared to 4% of pregnant women with and without CLD, respectively.[100] Whilst the original Swedish cohort study reported no increased risk of preeclampsia in AIH, a more recent study has reported a 3.65-fold increased risk.[91,102]

Pregnancy in AIH is associated with a preterm birth (before 37 weeks gestation) rate between 6-20%.[92,103–107] Compared to women without CLD, a 9% *vs.* 5% differential exists (p = 0.01) but compared to pregnancies in women with CLD of other aetiologies, no statistically significant difference in preterm birth rates (9% AIH *vs*. 7% CLD, p = 0.39) was observed. A population-based study reported a preterm birth rate of 13.5% (RR 3.21), which is similar to rates in other conditions such as rheumatoid arthritis, IBD and ALD.[91] A German study reported increased fetal loss and preterm births with positive anti-Ro/SSA and anti-soluble liver antigen/liver pancreas antibodies.[106] Finally, a retrospective study reported increased risk of preterm birth in patients with type-2 AIH compared to type-1 AIH (67% *vs*. 19%, p = 0.044).[108]

An early Swedish study reported a rate of low birth weight infants (<2,500 g) of 9.9% in AIH pregnancies *vs*. 3.2% in non-AIH patients (RR 2.51),[91] while an updated Swedish report showed that the association with low birth weight in AIH pregnancies diminished when restricted to term births.[102] There was also no association with small for gestational age (SGA) infants. In contrast, a Danish registry study, reported a three-fold higher risk of infants being SGA in pregnant women with AIH (2/70 [2.9%] in AIH *vs.* 4/661 [0.6%] in non-AIH).[109] The larger US population-based study found no apparent difference in rates of fetal growth restriction.[100]

Loss of biochemical remission during pregnancy was associated with an increased risk of admission to neonatal care units, which supports the concept of maintaining biochemical remission in pregnancy. The same cohort reported one neonatal death due to sepsis in a mother who was not on azathioprine therapy. Regarding increased risk of congenital malformations, neonatal mortality and stillbirth, neither population studies nor single-centre studies have demonstrated significantly increased rates, irrespective of the presence or absence of immunosuppression.[90,92,94,95,100]

Variant syndromes

Features of cholestatic liver disease such as PBC and PSC may evolve or be present in 15% of AIH cases.[110] There are case reports of pregnancies in variant syndromes of PBC with features of AIH (formerly 'overlap syndromes'), but data are lacking in variant syndromes of PSC with features of AIH ('autoimmune sclerosing cholangitis').[7] UDCA therapy in cholestatic liver disease and in ICP is well established. Current recommendations would advocate continued UDCA use in variant syndromes to alleviate pruritus if pregnant and improve the degree of cholestasis as determined by biochemical markers of cholestasis.

Metabolic dysfunction-associated steatotic liver disease

What is the optimal management of women with pre-existing metabolic dysfunction-associated steatotic liver disease to optimise maternal and fetal outcomes?

Recommendations

- In women of reproductive age with metabolic dysfunction-associated steatotic liver disease, preconception counselling should include a review of maternal and fetal risks associated with being overweight/obese and/or having diabetes. Pre-pregnancy non-invasive screening for liver fibrosis is advised using the most reliable tests available for women of reproductive age **(LoE 3; open recommendation, consensus).**
- Treatment of metabolic comorbidities should be optimised for women with metabolic dysfunction-associated steatotic liver disease before conception and should be implemented during pregnancy **(LoE 3; strong recommendation, strong consensus).**
- In pregnant women with metabolic dysfunction-associated steatotic liver disease, lifestyle modifications, including dietary advice, are advised as for the non-pregnant population **(LoE 3; strong recommendation, strong consensus).**
- Women with known metabolic dysfunction-associated steatotic liver disease should be managed as a group with increased risk of gestational diabetes mellitus and hypertensive disease in pregnancy with the use of appropriate national screening protocols, including monitoring of tests of liver function **(LoE 3; open recommendation, n.a.).**
- Breastfeeding is encouraged in women with metabolic dysfunction-associated steatotic liver disease **(LoE 3; strong recommendation, strong consensus).**

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a major cause of CLD worldwide,[111,112] and can progress to metabolic dysfunction-

associated steatohepatitis (MASH), fibrosis and cirrhosis (and its complications).[113] The incidence of MASLD in women of childbearing age is at least 10%.[114] However, available literature usually does not give specific information on the precise diagnosis *i.e.* MASLD/MASH or presence of liver fibrosis. MASLD is the most common cause of CLD in the US, with the largest rise in incidence amongst those under 40 years of age.[115]

Maternal obesity and diabetes have been associated with a higher risk of MASLD in infants and adolescents,[116–118] and a recent Swedish nationwide study found a strong association between maternal overweight/obesity and future biopsy-proven MASLD in offspring.[119] Another study from Sweden evaluated changes in obesity rates in two generations of mothers entering pregnancy, assessing body mass index in mothers and the risk of their adult daughters being overweight/obese. In 25,561 Swedish mothers and daughters who were first born, there was a fourfold increase in obesity rates that rose from 3.1% among women entering pregnancy between 1982-1988 to 12.3% amongst their daughters when entering pregnancy in 2000-2008. The greater the maternal BMI, the greater the risk of their daughters being overweight or obese. It was almost four-fold more likely that obese mothers would have obese daughters.[120] Mitochondrial dysfunction, epigenetic reprogramming, immune dysregulation and dysbiosis are discussed as underlying mechanisms.[121] MASLD is more prevalent in women with polycystic ovary syndrome (PCOS) which is associated with irregular menstruation and elevated androgens.[122,123] A meta-analysis of 17 studies reported MASLD in 42% of women with PCOS compared to 16% of controls without PCOS.[122] PCOS also appears to be associated with more severe histologic features of MASH.[124]

MASLD *per se* has not been associated with infertility. In women with compensated cirrhosis due to MASLD, birth rates were significantly higher compared to a matched non-cirrhotic population (57.6 *vs.* 45.8 per 1,000 person-years).[45]

Sonographic evidence of hepatic steatosis has been associated with higher likelihood of GDM, independent of BMI and age (17-20), and also of preeclampsia.[125] Conversely, GDM is associated with increased odds of subsequent MASLD development in middle age.[126]

Adverse obstetric outcomes in women with MASLD were shown in two population-based cohort studies. A study from Sweden reported approximately three-fold higher rates of GDM, caesarean delivery, preterm births, and SGA births and a two-fold increased risk of preeclampsia[127] in mothers with MASLD, even after adjustment for BMI and diabetes.[127] A recent US-based study derived from the US National Inpatient Sample evaluated 5,640 pregnancies in patients with MASLD.[128] This study demonstrated that pregnancies with MASLD increased from 10.5/100,000 pregnancies in 2007 to 28.9/100,000 pregnancies in 2015. Unsurprisingly, the rates of pre-existing comorbidity were higher in patients with MASLD including obesity (39.6%), dyslipidaemia (7.4%), hypertension (15.5%), and diabetes (11.3%).[128] These pregnancies were associated with higher rates of gestational diabetes when compared to non-MASLD CLD pregnancies or women without any known underlying CLD (23% *vs.* 8% *vs*. 7%, respectively). Similarly, rates of hypertension in pregnancy were 5.9% amongst women with MASLD compared to 3.4% and 3.9% in women with other CLDs or without any known diseases, respectively. The prevalence of hypertensive complications such as preeclampsia, eclampsia or HELLP syndrome were approximately fourfold higher in women with MASLD (16% *vs*. 3.8%-3.9%). Rates of postpartum haemorrhage were higher in women with MASLD than in those with other CLDs or without any known liver disease. Maternal death rate was higher (p <0.00, 5/5,640 *vs*. 920/18,453,375 women without any liver disease) and the adjusted odds ratio (OR) for risk of maternal death was 17.9, although this is limited by low event numbers. Perinatal adverse outcomes including preterm birth and large for gestation age were higher in MASLD pregnancies. Rates of fetal death were similar between groups.[128]

Breastfeeding and duration of lactation have been associated with a lower incidence of the metabolic syndrome and MASLD in the mother.[129,130] Furthermore, breastfeeding may have a protective effect on development and severity of MASLD in the offspring.[117,131,132]

The management of MASLD in pregnancy is not different from non-pregnant women as no MASLD-specific medications are approved and management is based on lifestyle modifications, in particular in weight reduction by up to 10% in women who are overweight/obese.[133] Excessive gestational weight gain should be avoided owing to its association with poorer maternal and fetal outcomes.[134,135]

Wilson's disease

Should medical treatment be continued to optimise maternal and fetal outcomes in women with Wilson's disease?

Recommendation

- Women with Wilson's disease should continue therapy with zinc, D-penicillamine and trientine with dose reduction of chelators in the second and third trimesters **(LoE 4; strong recommendation, n.a.).**

Wilson's disease (WD) is an autosomal recessive genetic liver disorder which results from mutations in the ATP7B copper transporter protein, resulting in excessive deposition of copper, most commonly in the liver and brain. This may result in acute liver failure or CLD with or without neuropsychiatric symptoms. Women with WD should receive pre-pregnancy counselling and be informed that they have increased risk of miscarriage[136] and infertility.[137] The mainstay of treatment includes the use of copper chelating agents, including D-penicillamine and trientine, and zinc salts to reduce the absorption of intestinal copper.

In a systematic review, 822 pregnancies in 449 women with WD are described. Spontaneous miscarriage occurred in 21.7% of pregnancies. In total, 2.2% of pregnancies were associated with exacerbation of neurological symptoms. Symptoms of hepatic deterioration were observed in 4.6% of cases with the majority of women experiencing transient deterioration with recovery postpartum; death due to liver failure was rare (0.2%). Importantly, anti-copper treatment was associated with positive maternal and fetal outcomes.[138]

Zinc is considered safe in pregnancy and can be continued throughout pregnancy. In a retrospective study of 136 women with WD, which recorded 282 pregnancies,[136] 118 were taking

D-penicillamine and 36 trientine, the birth defects in this study were comparable to the background population. In a further study, women maintained on therapy have been demonstrated to be less likely to suffer fetal loss and there have been reports of hepatic deterioration and death in women who have stopped treatment in pregnancy.[139–141] Therefore, therapy should be continued with dose reduction in the second and third trimester to avoid the risk of over-chelation which may adversely affect the fetus.[142] Post-delivery doses should be up-titrated to reflect those prior to pregnancy. A prospective study of 18 women with WD treated with D-penicillamine, trientine or zinc reported normal concentrations of copper and zinc in the breastmilk with no differences compared to controls.[143] Therefore, women with WD receiving treatment should not be discouraged from breastfeeding.

Cirrhosis and portal hypertension

In women with portal hypertension that would like to pursue pregnancy, are there clinical or biochemical parameters that can be used to predict poor maternal outcomes (e.g. death, bleeding from varices or intensive care unit admission)?

Recommendation

- Patients should undergo pre-pregnancy counselling and risk scores should be calculated to characterise their risk profile and determine the likelihood of complications prior to pregnancy **(LoE 3; strong recommendation, strong consensus).**

Rates of pregnancy in women with cirrhosis have risen over time in both single-centre and population-based studies.[144,145] Maternal mortality has also fallen with rates decreasing from as high as 14% in the 1980s,[146] to less than 2% in recent series.[45,144,146] Indeed, some case series report no maternal mortality.[147] Therefore, with careful assessment, stratification, and management, it is possible to plan and optimise outcomes.

Live birth rates in pregnancies of women with cirrhosis are poorly reported, with rates varying between 58% and 100%.[93,148,149] Rates of neonatal death are reported between 0-8.3%. Composite data from these series suggest stillbirth rates of between 1% and 8%.[93,145,147,150–152] A recent large registry study reported that pregnancies in women with cirrhosis are independently associated with a need for induction of labour, increased risk of puerperal infections, preterm delivery, large for gestational age infants and neonatal respiratory distress, all of which contribute to poorer outcomes.[45] A summary of the recommended management of cirrhosis with and without portal hypertension is provided in Fig. 4. Since pregnancy-related outcomes are correlated with severity of underlying maternal liver disease, it is critical to stratify patients according to their risk of decompensation and likelihood of obtaining a good outcome in pregnancy. A model for end-stage liver disease (MELD) score of <6 pre-conception predicts excellent pregnancy outcomes, whereas a MELD score >10 is predictive of decompensation in pregnancy.[93] Such patients should be counselled in relation to the risks of decompensation, need for LT and death during pregnancy. A later study from the same institution confirmed the importance of pre-conception MELD score but further reported that a pre-conception albumin-bilirubin (ALBI) score of ≤2.7 (ALBI grade 1) was even more predictive of a live birth.[144] Moreover, a pre-conception aspartate aminotransferase (AST)-to-platelet ratio index (APRI) of 0.84 (APRI grade 1) was predictive of having a pregnancy that proceeded to term (≥37 weeks).[144] In contrast, higher ALBI grade (a surrogate marker of higher bilirubin and lower albumin levels) was associated with shorter gestation and preterm birth in the same report.

For women with oesophageal varices, are maternal and fetal outcomes improved in those that have treatment of varices with banding or other therapies?

Recommendations

- Beta-blockers should either be initiated or continued during pregnancy for primary or secondary prophylaxis of variceal bleeding, provided there are no contraindications **(LoE 2; strong recommendation, n.a.).**
- Patients with established cirrhosis or known portal hypertension should undergo a screening endoscopy within 1 year prior to conception to assess for the presence of clinically significant varices and for primary prophylaxis to be instituted as appropriate **(LoE 4; strong recommendation, strong consensus).**
- Appropriate endoscopic management of women at risk of clinically significant varices should be undertaken during pregnancy and high-risk varices should undergo endoscopic band ligation **(LoE 4; strong recommendation, strong consensus).**

Variceal bleeding has been reported in up to 33% of pregnant women with cirrhosis and up to 50% of women with portal hypertension.[146–148,152] Associated mortality was up to 50% in older studies,[153] although recent series suggest rates <20%.[93,147,148] For women with non-cirrhotic portal hypertension, although variceal haemorrhage can occur during pregnancy, mortality rates are lower (2%–6%), which is likely attributable to more stable liver synthetic function.[154]

Timing and need for endoscopy during pregnancy is predicated on several factors, including stage of pregnancy, whether an endoscopy has been performed within 1 year of pregnancy and whether that or previous endoscopic examination demonstrated varices. We recommend that an endoscopy is performed within 1 year of a planned pregnancy, particularly in patients with a history of portal hypertension, decompensation or previous bleeding, so that variceal management can be optimised. Although Baveno VI recommendations advised to risk stratify patients with gastro-oesophageal varices, these criteria have not been tested in pregnant cohorts.[155] A combination of a liver stiffness measurement (Fibroscan reading) <20 kPa and platelet count >150 × 10^9 cells/L predicts patients with a low likelihood of having high-risk varices, but small varices may be missed.

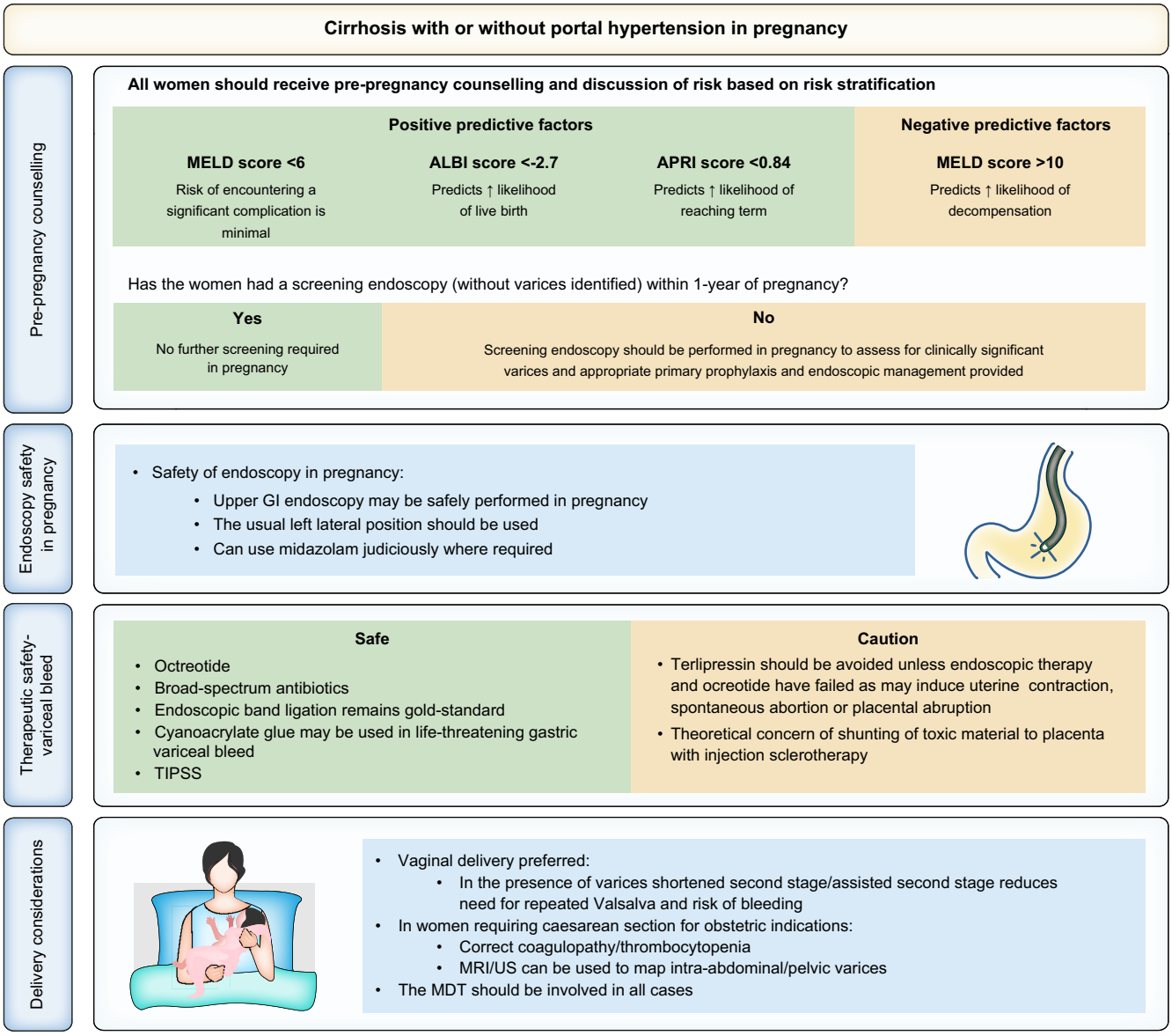

Fig. 4. Cirrhosis with and without portal hypertension and pregnancy. ALBI, albumin-bilirubin; APRI, AST-to-platelet ratio index; GI, gastrointestinal; MELD, model for end-stage liver disease; TIPSS, transjugular intrahepatic portosystemic shunt; US, ultrasound.

Data from a single centre showed that a platelet count <110 × 10^9 cells/L may predict the presence of varices in the second trimester. In patients who have not had a screening endoscopy prior to pregnancy, an endoscopy should be undertaken preferably in the second trimester and findings dealt with appropriately through beta blocker initiation/optimisation and endoscopic management of high-risk varices (large or with red signs) (endoscopic band ligation). For primary or secondary prophylaxis of variceal bleeding, beta-blockers (including carvedilol which is often the preferred agent) may be either initiated or continued during pregnancy, since benefits outweigh the risks of fetal growth restriction or hypoglycaemia. A study in women with established cardiovascular disease who received beta blockade throughout pregnancy demonstrated that carvedilol may be preferable to propranolol as the former was not associated with fetal growth restriction.[156]

Upper gastrointestinal endoscopy may be safely performed in pregnancy; although there is a slightly increased risk of premature delivery, this is likely to relate to underlying disease rather than the procedure.[157] In later pregnancy, compression of the aorta and vena cava in the supine position may reduce venous return, reduce cardiac output and placental blood flow, so placement in the left lateral position avoids this issue. In practice, midazolam is used widely during endoscopy in pregnant women and, if used judiciously, is not associated with significant complications.[157] The risk of over-sedation from benzodiazepines and opiates may cause hypotension and hypoxia for mother and fetus. Meperidine (pethidine) and propofol have both been used safely in pregnancy.[157]

Standard paradigms of management of acute variceal bleeding should be applied to the pregnant patient with cirrhosis with modifications. In acute haemorrhage, octreotide and broad-spectrum antibiotics should be initiated. Use of

terlipressin should be avoided since its vasoconstrictive properties may induce uterine contraction, decrease uterine blood flow and cause ischaemia, resulting in fetal loss and placental abruption.[158] It should only be used in cases when endoscopic therapy and octreotide have failed. Endoscopic band ligation remains the endoscopic gold-standard for the management of acute variceal bleeding.[159] Although injection sclerotherapy has been successfully used in the past, shunting of toxic material to the placenta remains a theoretical concern.[152] For gastric variceal bleeding, injection of cyanoacrylate glue has been life-saving.[160] In patients with refractory bleeding despite optimal endoscopic therapy, transjugular intrahepatic portosystemic shunts can be deployed to successfully control bleeding and have been used to facilitate caesarean delivery in the context of abdominal wall varices.[161,162] However, a risk-benefit analysis should be performed in a multidisciplinary manner before proceeding with transjugular intrahepatic portosystemic shunt placement.

Spontaneous rupture of a splenic artery aneurysm (SAA) is rare; the greatest risk in pregnancy is in the context of cirrhosis in the third trimester when increased splenic blood flow from a hyperdynamic circulation is maximal.[163,164] It typically presents with abdominal pain and syncope. Approximately a quarter of patients present with 'double rupture phenomenon' with warning symptoms from an initial small herald bleed that is self-contained. This is followed sometime later by a major rupture with rapid intra-abdominal bleeding and haemorrhagic shock. Both maternal and fetal mortality rates have been reported to reach 70%–95% in these more advanced cases.[164]

Interventional radiology with trans-catheter embolisation is the mainstay of treatment in cases of rupture, with surgical arterial ligation and splenectomy reserved for failed therapy. Prophylactic intervention may be appropriate if a known SAA has previously ruptured or if a large aneurysm (>2–3 cm) has been identified pre-conception. However, since up to 50% of SAA may rupture at sizes of less than 2 cm, it is difficult to make definitive recommendations on these smaller dilatations. Therefore, attention to the presence of SAA in women with severe splenomegaly is appropriate.

In pregnant women with oesophageal varices grade ≥2, which mode of delivery (planned caesarean section or vaginal delivery) is advised?

Recommendation

- Delivery should be performed for obstetric indications, taking into consideration the severity and distribution of portal hypertension including size/severity of oesophageal, gastric and pelvic varices **(LoE 5; strong recommendation, strong consensus).**

The optimal delivery strategy in women with cirrhosis or non-cirrhotic hypertension is yet to be defined. Excessive pushing and repeated Valsalva manoeuvres during the second stage of labour, which changes intraabdominal and therefore portal pressures, may precipitate variceal bleeding. In general, vaginal delivery is preferred where possible with a shortened second stage of labour; an assisted second stage will reduce the need for pushing. Caesarean section should be performed for obstetric indications. Caesarean section rates vary from 12%–81% among reported series with patient choice, centre experience and obstetric trends influencing decisions about mode of delivery.[144,145,148–152] Planning for surgery involves correction of coagulopathy and platelet transfusion and, where appropriate, MRI or ultrasound imaging to map intra-abdominal/pelvic varices and multidisciplinary team discussions about the optimal approach to delivery. Post-partum haemorrhage occurs in 5%–45% of women with cirrhosis related to a combination of factors including coagulopathy, ectopic varices, and thrombocytopenia.[145,147–149,152] Management strategies include transfusion with fresh frozen plasma, blood, platelets, uterine contractile agents, and surgical intervention.

Vascular liver disease

How should women with vascular liver disease be counselled regarding maternal and fetal outcomes?

Recommendation

- Women with vascular liver disease can be counselled that the condition is associated with preterm birth and operative delivery **(LoE 4; weak recommendation, consensus).**

Vascular liver disease may affect the intrahepatic blood vessels both small and large, the portal vein, hepatic veins and the terminal portion of the inferior vena cava. This category of disorders often manifests either during or after pregnancy. Pregnancy is known to be associated with increased activity of procoagulant factors and a decrease in certain anticoagulant factors and fibrinolysis. Moreover, the antiphospholipid syndrome may be present in some women who develop vascular liver disease around pregnancy.[165] A more comprehensive review of these changes can be obtained elsewhere.[165]

Approximately 6-16% of female patients with Budd-Chiari syndrome (occlusion of the hepatic veins), are diagnosed within 3 months of pregnancy.[166–168] Many women will have other risk factors for developing Budd-Chiari syndrome including protein S deficiency or antiphospholipid syndrome. Other risk factors including the presence of myeloproliferative disease are associated with vascular disorders, and 5% of 237 pregnancies in women with essential thrombocytosis were associated with the development of splanchnic vein thrombosis in the weeks and months after delivery.[169] Thus, thromboprophylaxis with low molecular weight heparin is advisable in most cases throughout pregnancy. A multidisciplinary team should consider this to enable individualised management strategies using national guidelines; these should consider the pregnancy-associated thrombosis risk in women with likely thrombophilia, alongside the potential for variceal bleeding.

The outcomes of pregnancy in individuals with previously diagnosed well-controlled Budd-Chiari syndrome are encouraging. In 24 pregnancies in 16 patients (from three European centres) with stable disease at the time of conception, no death occurred during pregnancy, although there were three

thrombotic events, including two related to obstruction of two pre-existing shunts.[170] However, in this report, premature birth occurred in 76% of patients, Caesarean sections were performed in 47% of patients and the stillbirth rate was 6%.[170] Similarly, a retrospective cohort study in the Netherlands did not report any maternal deaths, but one woman had a pulmonary embolism and two had variceal bleeds; of the 34 (76%) live births, 27 were born at term.[171] Higher rates of adverse pregnancy outcomes were also reported in a single-site cohort of 16 pregnancies in seven women; there were six fetal losses before 20 weeks' gestation. In the 10 ongoing pregnancies, six were complicated by preterm birth, there was one pregnancy complicated by preeclampsia, four had ICP and two had confirmed/suspected placental abruption.[172] In a larger study of 45 pregnancies in 24 women with portal vein thrombosis (PVT), 62% of whom were treated with low molecular weight heparin, 20% of pregnancies were lost before the 20th gestational week and preterm birth occurred in 38% of deliveries. Only 26% of births progressed to term; the caesarean section rate was 53% and two patients developed HELLP syndrome. Oesophageal variceal bleeding occurred in three women during pregnancy and none had received appropriate primary prophylaxis. There were no maternal deaths.[173]

PVT may also be associated with pregnancy and in the largest series, up to 4% of PVT presented during pregnancy or postpartum.[174–176] Protein S deficiency may also predispose to PVT and, in contrast to Budd-Chiari syndrome, myeloproliferative disorders are rare.[177] A recent study of 76 pregnancies in 45 women (12 Budd-Chiari syndrome, 33 PVT) described the use of low molecular weight heparin throughout the majority of pregnancies. Of 45 first pregnancies, there were nine fetal losses (25%) and 34 (76%) live births, of which 79% were at term. No maternal deaths were observed but one woman had a pulmonary embolism during pregnancy and two women had variceal bleeding requiring intervention.[171] In this dual report, a term birth rate of 79% suggests that, although high-risk, a reasonable outcome could be achieved for many patients.[171]

For women with oesophageal varices, the second stage of labour may need to be expedited by operative vaginal delivery in order to reduce the impact of the Valsalva manoeuvre. Otherwise, decisions about mode of delivery should be based primarily on obstetric indications.

Post-transplant management

What should women with a liver transplant be advised regarding the risk of rejection or deterioration in pregnancy?

Recommendations

- Female liver transplant recipients should be advised that delaying pregnancy for at least 1 year after transplant is associated with improved maternal and fetal outcomes **(LoE 3; strong recommendation, strong consensus).**
- Blood markers of rejection should be checked regularly during pregnancy, and immunosuppression titrated appropriately **(LoE 4; strong recommendation, n.a.).**
- Clinicians should ensure increased frequency of review of pregnant liver transplant recipients, as they are also at risk of gestational maternal disorders including gestational hypertension, preeclampsia, gestational diabetes, cholestasis and acute kidney injury, and low-dose aspirin therapy should be initiated in the first trimester for preeclampsia prophylaxis **(LoE 1; strong recommendation, n.a.).**
- Antenatal care providers should ensure increased surveillance for adverse pregnancy outcomes, including preterm birth and fetal growth restriction, in pregnant liver transplant recipients **(LoE 2; strong recommendation, consensus).**

The return of menstrual function can occur as early as 1 month after successful LT with up to 95% of recipients experiencing complete normalisation within the first year.[178–181] Re-balance of sex hormones, including alterations in pituitary function through improved hormonal feedback loops also contribute to this return of function. Age, social circumstance, medication side effects and libido can all reduce sexual activity and whilst many of these factors improve post-transplant, there are still a proportion of patients who experience problems following transplant.[182,183] Female recipients who failed to recover sexual function post-transplant had issues with self-worth related to factors such as depression, unemployment, ongoing health issues and body dysmorphia.[183]

Once fertility is restored, it is suggested that patients delay pregnancy for at least 1 year following LT.[184,185] Having more predictable/stable graft function, complete wound-healing, reduced immunosuppression burden, reduced infection risk and reduced susceptibility to acute cellular rejection during this phase of transplantation means that a successful outcome is more likely to occur.

The National Transplantation Pregnancy Registry (NTPR) has derived data that suggest that a transplant-to-conception interval of >2 years is associated with reduced rates of low birth weight, rejection and graft loss; women who conceived within 6 months of LT were at the greatest risk of these outcomes.[186] These data are supported by single-centre studies in which one successful live birth occurred in 7/38 pregnancies conceived within 12 months of LT.[187] Another study of 71 pregnancies demonstrated no difference in rates of low birth weight between women who conceived within the first year of liver transplant compared to those who conceived >1-year after LT. However, increased rates of prematurity, low birth weight and rejection were observed in the 'early group'.[188]

Focusing on maternal outcomes, death rates have not been reported to be higher in pregnant LT recipients, with maternal death rates during pregnancy and postpartum reported to be 0-1%.[189–192] In older studies where higher rates of maternal death were reported (5%-17%), the majority of deaths occurred more than a year post-partum.[187,188,193] One study reported rates of pregnancy-induced hypertension of 30% in LT recipients compared to 9% in controls.[189] A meta-analysis reported largely similar findings and it is notable that rates of pregnancy-induced hypertension are almost two-fold lower in liver compared to kidney transplant recipients (54%).[194] Rates

of hypertension vary according to immunosuppressive therapy utilised, with reported rates of 22-29% with corticosteroids, 63-73% with cyclosporine and 47-54% with tacrolimus-based immunosuppression.[187,193,195,196]

Older studies in pregnant LT recipients reported pre-eclampsia rates of 21-26%,[187,193,194] whereas rates of 7-12% have been reported in more recent studies.[192,197–200] Greater understanding of the disease process has probably resulted in this reduction. Preeclampsia is the dominant contributing factor for preterm delivery in LT recipients.[186,192] Daily aspirin should be initiated ≤16 weeks' gestation since it improves placental haemodynamics and reduces the risk of preterm (<37 weeks) preeclampsia.[201,202] Our recommendation is to commence aspirin at a dose of 150 mg in the evening from the first trimester.[203] Where this dose is not available, a dose of 162 mg once a day (81 mg tablets x 2) is also suitable. Aspirin can be discontinued at 36 weeks' gestation.

Rates of rejection in pregnant LT recipients are variable at between 0-20%.[187–189,195,198,199,204–209] Postpartum, reported rejection rates vary from 3-12%.[187,188,191–193,210] Rejection during pregnancy is often multifactorial, relating to deliberate or inadvertent discontinuation/reduction of immunosuppression, partly owing to the dilutive effect of increased plasma volume. Patients that experience acute rejection during pregnancy usually respond to standard pulse steroids or augmentation of immunosuppression.[188,191,193] In a recent report, 9% of the cohort (8/93 patients) required re-transplantation at a median of 42 months postpartum for indications as varied as chronic rejection, recurrent disease and late hepatic artery thrombosis. In all cases, graft loss was not felt to be specifically related to pregnancy.[192]

Increasing renal impairment in pregnancy is recognised as a key outcome predictor and it is notable that *de novo* renal impairment occurs in 11-25% of pregnant LT recipients.[187,188] Recent data suggest that preconception estimated glomerular filtration rate of <90 ml/minute in LT recipients was associated with preterm delivery and that a progressive decline in estimated glomerular filtration rate during pregnancy predicted gestational length and outcome.[192]

The rate of GDM in pregnant LT recipients varies between 0-11%.[188,190,194,197,198,208,209] Discrepancies in rates likely relate to type-II error in reporting, ethnicity and inclusion of pre-existing diabetes. In a US-based study, the rate of GDM in LT recipients was 8.6% *vs*. 5.4% in a non-transplant group.[190]

The frequency of infections acquired during pregnancy has been reported to be largely similar between LT recipients and the general population[189,211] although rates reached up to 11% (including viral-related).[188] Genito-urinary tract infection has been reported to be more frequent (5.3% *vs.* 1.4%, respectively).[190]

Fetal outcomes

In the largest meta-analysis to date, a live birth rate of 77% was reported in 346/450 LT pregnancies. Indeed, it is notable that during the same time period, the live birth rate in the general US population was lower at 67%.[194] However, Lim *et al.* demonstrated that live birth rates have improved sequentially over the last three decades in their cohort of LT recipients, from 60% pre-1997, to 70% between 1997-2006, and to 84% from 2007-2016.[192] Deshpande *et al.*, in the large meta-analysis, reported a miscarriage rate of 16% *vs.* 17% in the general population.[194] Stillbirth rates of 0-1.2% are typically reported in pregnant LT recipients,[187,192,194] although rates as high as 12% have been reported.[197,204] NTPR data suggest that cholestasis development is sixfold more likely during pregnancy in LT recipients than the general population (37). Preterm birth rates in LT recipients range between 14-53%,[187,188,193,197,198,204–206,209,210,212] with a rate of 39%, 2.5-fold higher than in the general population (14%), reported in the study by Deshpande *et al.*[194] A recent systematic review reported a preterm birth rate of 32% in 1,079 pregnancies.[213] Rates of 5-20% have been reported for fetal growth restriction (FGR).[187,198,204,210]

Rates of delivery by caesarean section in pregnant LT recipients vary between 20-63%.[187–189,191,193,197,204–207,209,210,212] In a meta-analysis, Deshpande *et al.* reported a rate of 45%, compared to 32% in a comparative US population.[194] Mode of delivery should be predicated by obstetric indications. There are no specific contraindications to vaginal delivery in LT recipients whilst delivery in a transplant centre does not appear to alter obstetric outcomes.[189] Rates of antepartum haemorrhage are similar between LT recipients and the general population, although postpartum haemorrhage is more common in LT recipients compared to controls (8% *vs.* 3%, respectively).[189,190]

For pregnant LT recipients, is the use of specific immunosuppressive drugs associated with an increased risk of adverse maternal or fetal outcomes?

Recommendations

- The immunosuppressive drugs azathioprine, cyclosporine, tacrolimus and prednisolone should not be stopped in pregnant women **(LoE 3; strong recommendation, strong consensus).**
- Mycophenolate mofetil is teratogenic and should be stopped at least 12 weeks before conception **(LoE 3; strong recommendation, strong consensus).**
- Women taking cyclosporine and tacrolimus should be closely monitored for hypertension and preeclampsia throughout pregnancy **(LoE 3; strong recommendation, strong consensus).**
- Women taking glucocorticoid treatment should be screened for gestational diabetes mellitus **(LoE 2; strong recommendation, strong consensus).**
- Clinicians should be aware that women taking >5 mg prednisolone per day for more than 3 weeks are at increased risk of adrenal suppression and there should be consideration of increased glucocorticoid dose at the time of delivery, and if there is intercurrent infection, vomiting or hyperemesis gravidarum **(LoE 2; strong recommendation, strong consensus).**

Congenital abnormalities are rare in offspring of LT recipients. Rates of 0-4% have been reported,[186,189,193,205,207,208,210] with older data suggesting incidences of up to 17%.[187,206] Coffin *et al.* reported a congenital malformation rate of 1.4% in 206 LT pregnancies (*vs*. 0.6% in the non-transplanted group),[189] however, it is notable that in 2006, the NTPR database reported a 3-5% malformation rate in a comparative general population.[209] Documented congenital anomalies in the neonates of female LT recipients include cleft defects, tracheoesophageal fistula, pyloric stenosis, ventricular septal defects, Tetralogy of Fallot, valvular disease, total anomalous pulmonary venous defect, cystic kidney, hydrocoeles, and hypospadias.[186,187,193,199,210,214] With regard to specific immunosuppression, 10% of the maternal corticosteroid dose reaches the developing baby; while older data suggest an association between use in the first trimester and cleft lip/palate abnormalities,[215,216] this has not been supported by more recent studies.[217–219] However, women taking high doses have increased risks of GDM and prolonged use (*i.e*. >5 mg prednisolone per day for more than 3 weeks) is associated with adrenal suppression and the need for glucocorticoid replacement at the time of labour.[220] Intramuscular or parenteral glucocorticoid replacement may be needed if women have severe hyperemesis gravidarum or intercurrent infection. Azathioprine has an excellent safety profile;[221] it has been associated with myelosuppression in the fetus in one study,[222] but other studies are reassuring.[217] Cyclosporine crosses the placenta with concentrations in the fetus reported to be between 30-60% of maternal concentration.[222,223] There is no significant malformation risk with either cyclosporine or tacrolimus. Tacrolimus use in pregnancy has been shown to lower incidences of hypertension and preeclampsia when compared to cyclosporine[193,207] whilst renal toxicity and glucose intolerance during pregnancy may also be prevalent. In a literature review of 83 pregnant liver/kidney transplant recipients treated with tacrolimus, the incidence of fetal malformations was 6%.[214] Other data have reported rates of 4-5% in liver/kidney transplant recipients, which is comparable to the general population.[186,193] Mycophenolate mofetil (MMF) is contraindicated in pregnancy and patients should use two reliable forms of contraception. Risk associated with its use include miscarriage rates of 49%, stillbirth rates of 2% and structural anomaly rates of 23%.[186] One study reported nine conceptions in 77 LT recipients, with 66% live births, two early miscarriages and one maternal death in the first trimester of pregnancy from known chronic rejection.[224] Sifontis *et al.* reported 33 pregnancies in a range of organ transplant recipients with early exposure to MMF, demonstrating a high incidence of hypoplastic nails, shortened fifth fingers, microtia and cleft lip/palate abnormalities.[225] Other reported malformations include the absence of auditory canals, Tetralogy of Fallot and total anomalous pulmonary venous return. Patients should have a washout period of 12 weeks from the last MMF dose before attempting pregnancy. Limited data exist on the effects of sirolimus or everolimus during pregnancy, so it is not possible to exclude the possibility that these drugs could affect fetal development through their anti-proliferative effects.

Viral disorders

To reduce the risk of perinatal transmission of hepatitis viruses (HAV, HBV, HCV, HDV, HEV), should pregnant women avoid vaginal delivery and breastfeeding?

HAV

Recommendations

- In pregnant women with acute hepatitis A, caesarean section is not recommended unless there is an obstetric indication **(LoE 4; strong recommendation, strong consensus).**
- Breastfeeding should not be discouraged in women with acute hepatitis A **(LoE 4; strong recommendation, strong consensus).**
- Active or passive immunisation of newborns of mothers with acute hepatitis A is not routinely suggested **(LoE 5; weak recommendation, consensus).**

Careful consideration must be paid to viral hepatitis in pregnancy, particularly with regard to epidemiology, tendency to chronicity and the consequences for the health of the mother and fetus. Beyond management during pregnancy, this period represents an opportunity to identify women with chronic infection and thus initiate appropriate ongoing management and surveillance.

Mother-to-child transmission (MTCT) in women with hepatitis A virus (HAV) is a rare occurrence,[226] and has only been reported in a few cases.[227,228] Transient cholestatic jaundice has been reported in two full-term infants born to jaundiced mothers with detectable anti-HAV IgM. Anti-HAV IgM was detected in both babies on day 6 and 7 after delivery.[229] Thus, caesarean section should not be routinely recommended in women with acute HAV infection unless there is an obstetric indication.[230,231] There is no evidence to support HAV transmission to breastfeeding infants despite detection of very low or fluctuating levels of HAV RNA in breastmilk.[232] Therefore, breastfeeding should not be discouraged. Administration of either immunoglobulin or the inactivated HAV vaccine to newborns of mothers with acute HAV infection is not routinely indicated,[233,234] although administration of passive IgG immunisation to the neonate may be considered if the mother has acute hepatitis A just prior to delivery.

HBV

Recommendations

- Caesarean section is not recommended to reduce the risk of HBV mother-to-child transmission in HBsAg-positive women **(LoE 1; strong recommendation, n.a.).**

- Caesarean section may be recommended only in Asian HBeAg-positive women with high HBV DNA titre (>7 log_{10} copies/ml; 6.14 log_{10} IU/ml) who have not received antiviral therapy during pregnancy **(LoE 1; open recommendation, n.a.).**
- Breastfeeding of infants born to HBsAg-positive mothers should not be discouraged (unless mothers with detectable HBV DNA present with cracked nipples and/or the infant has oral ulcers) **(LoE 1; strong recommendation, n.a.).**

The risk of MTCT is negligible (0.04%, 95% CI 0.00–0.25) when the maternal level of hepatitis B virus (HBV) DNA is <5.30 log_{10} IU/ml (200,000 IU/ml), while it increases when the HBV DNA level is above this threshold, regardless of infant immunoprophylaxis.[235] The rate of hepatitis B MTCT from high-titre HBV DNA (>7 log_{10} copies/ml; 6.14 log_{10} IU/ml) and hepatitis B e-antigen (HBeAg)-positive mothers can be reduced from >90% to 5%–10% with the administration of HBV vaccine and hepatitis B immunoglobulin (HBIG) to infants within 24 hours of birth.[236] Since HBV DNA may be difficult to detect in some areas of the world, HBeAg can be used as an accurate surrogate marker to identify women with HBV DNA levels above this threshold, with a pooled sensitivity of 88.2% (95% CI 83.9–91.5) and a pooled specificity of 92.6% (90.0–94.5); thus, enabling prediction of cases of immunoprophylaxis failure.[235] Hepatitis B core-related antigen may be a useful serological marker to indicate clinically important high viremia in treatment-naïve HBV-infected patients; a value of 5.3 log U/ml predicts HBV DNA level ≥200,000 IU/ml with an area under the receiver-operating characteristic curve of 0.96 (0.94-0.98).[237]

A meta-analysis including 19 studies (18 from China) and 11,144 HBV-positive pregnant women, of whom 5,251 underwent vaginal delivery and 5,893 caesarean section, showed that caesarean section reduces the risk of MTCT of HBV in pregnant Chinese women. Based on a random effect model, the pooled OR for MTCT at birth was 0.42 (95% CI 0.23–0.76), while in a fixed effect model, the pooled OR for MTCT was 0.62 (95% CI: 0.48–0.81).[238] The same protective evidence of caesarean section, even after vaccine and immunoglobulin administration, was obtained in a study of 196 high-risk newborns born to untreated HBeAg-positive mothers, but only when hepatitis B surface antigen (HBsAg) carriers were compared with children who had recovered from HBV infection.[239] In a prospective cohort study of 852 mothers who did not receive antiviral therapy during pregnancy, 56% of whom had HBV DNA serum level >8 log_{10} IU/ml, caesarean section showed a tendency to reduce the risk of infection, while a meta-analysis of 13 studies (12 from China) showed that caesarean section (3,429 participants) reduced the risk of MTCT compared with vaginal delivery (RR 0.58, 95% CI 0.46-0.74), but the administration of immunoglobulins to newborns did not alter the results.[240] However, the benefit of caesarean section seems to be limited based on the analysis of this study. This meta-analysis has several flaws[241] and, even among pregnant women with high HBV DNA titres, the benefit of caesarean section seem to be limited: 23 women would need to undergo caesarean section to prevent one case of MTCT, and caesarean section carries risks[242] especially in low- and middle-income countries.[243] The beneficial effect of maternal antiviral therapy in terms of almost complete abrogation of MTCT should be emphasised[244] and antiviral treatment of pregnant women with high viral load implemented whenever it is possible.[235]

Breastfeeding. Overall concentration of HBV DNA in both colostrum and mature breastmilk are significantly lower than that in serum. The likelihood of detecting HBV DNA in breast milk is associated with serum HBV DNA concentration. It has been reported that for negative serum HBV DNA, HBV DNA levels between $5x10^2$-10^9 copies/ml (low viral load), or levels >10^6 copies/ml (high viral load), the positive rates of HBV DNA in colostrum were 0%, 6% and 78.6%, respectively, while the positive rates of HBV DNA in mature milk were 0%, 0%, and 15.4%.[245] Thus, HBV DNA presence in breast milk may cast some doubts about the possible risk of HBV transmission via breastfeeding from mothers with high viral load. However, a study demonstrated that the HBV infection rate of breast-fed infants was not significantly different compared to formula-fed infants (11.1% and 2.2%, respectively, p >0.05) among children who received active and passive immunisation.[245] In addition, no significant difference in anti-HBs positivity rate was observed between breastfeeding and formula-feeding groups, irrespective of the HBV DNA level of the mother, indicating that breastfeeding does not interfere with the humoral immune response to active-passive immunisation of newborns.[245] A recent prospective cohort study on 852 mothers (56% of whom had HBV DNA serum level >8 log_{10} IU/ml), showed that among pregnant women with high viral load, non-breastfeeding (RR 0.88) showed a tendency to reduce the risk of infection, while a meta-analysis of 12 studies concerning the feeding mode (2,443 infants) showed that formula feeding reduced the risk of MTCT (RR 0.74, 95% CI 0.56-0.98).[240] However, this meta-analysis has several flaws[241] and further analysis of these data showed 65 women would need to avoid breastfeeding to prevent one case of MTCT.[231] Furthermore, the economic, immunological and developmental benefits of breastfeeding far outweigh the limited risk of MTCT. In addition, it should be underlined that the association between breastfeeding and MTCT is confounded by mode of delivery and receipt of infant prophylaxis. A study on infants who had been vaccinated against hepatitis B, 53.3% of whom received HBIG, showed that HBV infection in children was not associated with breastfeeding by logistic regression analysis, adjusting for the effect of maternal HBeAg status.[246] Therefore, even when the recommended prophylaxis is not strictly performed, breastfeeding does not represent a key risk factor for MTCT of HBV. Besides, before HBIG and vaccine administration became mandatory for infants born to HBsAg-positive mothers, there were no reported differences in the rate of HBsAg or anti-HBs between breastfeeding and formula-feeding infants.[247] In conclusion, breastfeeding is safe for infants who receive active/passive immunisation, although some caution should be applied to mothers with high serum HBV DNA load if the nipples are cracked and the infants have oral ulcers.

HBV/HDV

Recommendations

- As HDV mother-to-child transmission is rare and prevention of HBV infection is effective at preventing HDV infection, recommendations for the management of delivery in HBV/HDV-coinfected pregnant women should be the same as for HBV-infected women **(LoE 5; strong recommendation, n.a.).**
- Breastfeeding should not be discouraged in infants born to HBV/HDV-coinfected mothers as it is safe **(LoE 1; strong recommendation, consensus).**

HBV/hepatitis D virus (HDV) MTC co-transmission has previously been described in case reports, but the chances of co-transmission of HBV/HDV seem to be exceptional.[248,249] Measures to prevent perinatal infection with HBV are uniformly effective in preventing infection by hepatitis D.

HCV

Recommendations

- HCV testing of pregnant women is recommended as part of antenatal care **(LoE 2; strong recommendation, consensus).**
- Caesarean section should not be recommended to reduce mother-to-child transmission in women with isolated HCV infection as it does not decrease perinatal transmission of HCV **(LoE 3; strong recommendation, strong consensus).**
- For HCV/HIV-coinfected women, decisions about mode of delivery can be individualised dependent upon whether there is detectable HIV RNA and HCV RNA **(LoE 3; weak recommendation, strong consensus).**
- In women with HCV infection, amniocentesis can be performed as an invasive prenatal diagnostic procedure if the option of non-invasive prenatal testing has been ruled out, while chorionic villus sampling should be avoided, as should episiotomy during labour **(LoE 4; strong recommendation, consensus).**
- Breastfeeding should not be discouraged in HCV-infected mothers, nor in women with HCV/HIV coinfection on antiretroviral treatment **(LoE 3; strong recommendation, strong consensus).**

Testing all pregnant women for hepatitis C virus (HCV) has been shown to be cost-effective if the prevalence among them is 0.03% or above and should be recommended.[250] American[251] and European[252] guidelines recommend HCV screening for all pregnant women, ideally at the time of presentation for prenatal care.

HCV RNA-positive women are at risk of MTCT,[251] especially if the mother has a high viral load and is human immunodeficiency virus (HIV) positive; transmission may occur before, during or after delivery.[253]

Randomised trials on the effect of elective caesarean delivery *vs.* vaginal birth are not available, due to the ethical challenges related to randomisation to each mode of delivery. A systematic review of 18 observational studies reported that 14 studies found no clear association between vaginal *vs.* caesarean delivery and risk of transmission, and two studies reported an association between prolonged duration of ruptured membranes and increased risk of transmission.[254] A systematic Cochrane review including seven observational studies, mostly underpowered, in which maternal HCV viremia was not always available, stated that even if the intervention prevented all HCV transmission, 20 caesarean sections would be needed to prevent one MTCT.[255] A meta-analysis including eight studies that involved 641 unique HCV RNA-positive mothers, comparing rates of perinatal transmission of HCV between elective or emergency caesarean section and vaginal delivery, suggested that caesarean section does not decrease perinatal HCV (pooled OR 1.1 (95% CI 0.45–2.67).[256] All studies concluded that no good evidence exists to support using caesarean section to reduce MTCT of hepatitis C[247].

Prolonged rupture of membranes (>6 hours) shows inconsistent risk.[230,257] Amniocentesis can be carried out in selected cases if an invasive prenatal diagnostic procedure is necessary. Chorionic villus sampling should not be carried out.[258] Episiotomy is possibly associated with increased risk of vertical transmission and should be avoided in HCV RNA-positive mothers.[230,257,259]

Concerning HIV/HCV-coinfected mothers, in a recent meta-analysis the risk of vertical HCV infection was 5.8% (95% CI 4.2%-7.8%) (17 studies) for children of HCV RNA-positive women and 10.8% (95% CI 7.6%-15.2%) (eight studies) for children of HIV/HCV-coinfected women.[253] These results confirmed the findings of a previous meta-analysis that included one retrospective observational and nine prospective studies, all with high potential for selection bias, and none of which was conducted in a developing country, examining 4,424 mother-infant pairs, including 858 (19.39%) HIV/HCV-coinfected women. When the analysis was restricted to the five studies that had sample sizes of >50 individuals and were of better overall quality, HIV/HCV coinfection increased the risk of HCV vertical transmission by approximately 90% (OR 1.9; 95% CI 1.36-2.67) compared with maternal HCV infection alone, with low heterogeneity.[260] A lower mean HCV viraemia seems to be sufficient for transmission in HIV/HCV-coinfected women compared to non-HIV-coinfected women, although the difference was not statistically significant.[261] A study including 214 mother-and-child pairs, 55 of whom (26%) were HIV/HCV coinfected, showed that for HCV RNA values of at least 6 log IU/ml the risk of transmission was independent of maternal HIV status, whereas for lower levels, the probability of HCV transmission was higher among HCV/HIV-coinfected women (OR 8.3, 95% CI 1.4–47.5; $p = 0.01$). However, caesarean section before membrane rupture did not appear to protect against MTCT of HCV.[262] Similarly, no significant difference in rate of transmission was observed between vaginal

or caesarean delivery if caesarean section is performed after membrane rupture.[263]

A study that examined costs, and cost-effectiveness of elective caesarean delivery to prevent perinatal transmission of HCV in HIV/HCV-coinfected women with suppressed HIV RNA but detectable HCV RNA, showed that elective caesarean section would avoid 45 vertical HCV transmissions/1,000 deliveries with increased maternal mortality of 1/100,000 deliveries, with an overall estimated one maternal death per 1,000 transmissions avoided.[264]

Finally, although HCV can occasionally be found in breast milk, a meta-analysis of 14 cohort studies (total of 2,971 mother-infant pairs) found no association between breastfeeding and transmission risk. Therefore, breastfeeding should not be restricted,[254] unless the nipples are cracked or bleeding.[230]

HEV

Recommendations

- Vaginal delivery should not be discouraged in women with HEV infection **(LoE 4; strong recommendation, strong consensus).**
- Breastfeeding of infants born to HEV-infected asymptomatic mothers should not be discouraged **(LoE 4; strong recommendation, strong consensus).**

A high burden of HEV infection in pregnancy in high endemic countries is usually reported, although prevalence has been reducing over time. HEV prevalence is usually higher in symptomatic pregnant women, *i.e.* with nausea, anorexia, or jaundice, compared to asymptomatic pregnant women (adjusted prevalence OR 1.76; 95% CI 1.61–1.91), and it decreases with increasing year of publication.[265] Acute liver failure following acute infection may occur more often during the third trimester and this phenomenon seems to particularly occur with HEV genotype 1 infection. In particular, HEV genotype 1 has been shown to efficiently replicate in decidua and placenta tissues, causing severe tissue alterations and altering their secretion profile.[266] In addition, genotype 1 is the exclusive cause of HEV acute hepatitis in India[267] and this finding may provide a plausible explanation for the discrepant pregnancy outcomes observed in this area compared to areas where other HEV genotypes are prevalent.[268–270]

Data on vertical transmission of HEV from infected mothers to their infants are limited. Vertical transmission does not occur from HEV RNA-negative mothers, but intrauterine transmission of HEV infection can occur in newborns by women with acute HEV infection with detectable serum HEV RNA.[271] According to a recent meta-analysis of three studies (155 pregnant women), the proportion of HEV vertical transmission was 36.9% (13.3–64.2)[256] and the risk was associated with a maternal viral load higher than 13,266 copies/ml.[272]

Most pregnant women with acute HEV hepatitis examined in these studies had spontaneous onset of labour and vaginal delivery and no studies specifically evaluated the effect of mode of delivery on HEV MTCT.

In women with acute HEV infection, HEV RNA has been isolated from colostrum and breastmilk.[273] In the study of Chibber *et al.*, the level of HEV RNA in colostrum correlated well with that of the corresponding maternal serum, albeit lower. Although HEV is present in maternal milk, infection through breastfeeding was not observed in any of the 86 breast-fed infants. Moreover, breastfeeding appeared to be safe for infants breast-fed by clinically asymptomatic mothers.[273] In a more recent case report, HEV RNA was found in breastmilk at a level similar to that of the serum.[274] Breastfeeding was interrupted, albeit no transmission had occurred in the 18-month-old child.

In pregnant women with HBV infection with/without HDV infection, can perinatal HBV transmission be reduced by a) antepartum hepatitis B immunoglobulin administration; b) antiviral prophylaxis administration during pregnancy; c) performing diagnostic amniocentesis; or d) scaling up HBV testing of pregnant women (and their partners) in areas of intermediate endemicity of HBV?

Recommendations

- Antepartum administration of hepatitis B immunoglobulin to HBV-infected pregnant women is not recommended as it is not effective at reducing mother-to-child transmission of HBV irrespective of maternal HBV DNA titre **(LoE 2; strong recommendation, strong consensus).**
- Pregnant women with HBV DNA levels higher than 200,000 IU/ml or HBeAg-positive pregnant women, should start antiviral prophylaxis with tenofovir disoproxil fumarate at week 24–28 of gestation and continue up to 12 weeks after delivery **(LoE 1; strong recommendation, strong consensus).**
- In pregnant women with chronic HBV infection and advanced fibrosis or cirrhosis, therapy with tenofovir is recommended **(LoE 2; strong recommendation, strong consensus)**, and those on antiviral treatment with tenofovir should continue the treatment **(LoE 2; strong recommendation, strong consensus).**
- Breastfeeding of infants born to mothers treated with tenofovir is safe and should not be discouraged **(LoE 1; strong recommendation, strong consensus).**
- HBeAg-positive pregnant women, or those with high HBV DNA levels (>5.3 $\log_{10}$ IU/ml), should be counselled about the high risk of HBV transmission associated with amniocentesis and that non-invasive prenatal testing is preferred **(LoE 2; strong recommendation, strong consensus).**
- Screening for HBsAg in the first trimester of pregnancy is recommended, as this is important for recognising and reducing the risk of HBV MTCT **(LoE 1; strong recommendation, strong consensus)**, and HBsAg quantitation can be an accurate predictor of HBV DNA level **(LoE 2; strong recommendation, strong consensus).**

Hepatitis B immunoglobulin

In spite of passive-active immunisation of newborns, 5%-10% of those born to HBsAg-positive mothers can still be infected with HBV.[275] Therefore, it was proposed that administration of HBIG

to the mother in the third trimester of pregnancy might reduce MTCT of HBV.[276] However, a randomised-controlled trial showed no benefit of antepartum HBIG administration in preventing MTCT in 117 cases *vs.* 133 untreated controls. In particular, neither the maternal HBV DNA levels nor the HBsAg levels were significantly reduced by the antepartum administration of HBIG. In addition, mothers who received antepartum HBIG delivered anti-HBs-negative newborns at birth, challenging the hypothesis that HBIG would confer passive immunity to the newborn.[277] Moreover, a recent study on mothers with higher than 6 $\log_{10}$ copies/ml of HBV DNA showed that antepartum administration of HBIG did not prevent MTCT of HBV; there were no differences in HBsAg-positive rates between the control group (5.3%) and the women that received 200 IU or 400 IU HBIG intramuscularly once a month for 3 months before delivery (5.1%).[278] This study confirmed the results of a previous prospective cohort study that did not find a significant difference in the HBV infection rate of infants between the groups of mothers who received 200 IU HBIG/monthly for 3 months antepartum (4.5%) and those who did not (3.1%).[279] Finally, there is a safety concern regarding antepartum HBIG use, as there is a potential risk that HBIG binding with HBsAg could induce immune complex disease.[280] Therefore, the administration of HBIG during pregnancy to HBsAg-positive mothers is not considered useful and is not recommended.

Antiviral prophylaxis administration during pregnancy

Maternal antiviral prophylaxis during pregnancy should be considered in the context of the WHO position papers[281] on immunisation that recommend all infants receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours and that HBIG, which contains high levels of purified HBsAg-specific antibodies from plasma donors, is given simultaneously at different sites intramuscularly. The birth vaccine dose should be followed by two or three doses of hepatitis B vaccine to complete the primary series. The estimated transmission rates without vaccination, with vaccination, and with vaccination plus HBIG, were 75%, 21%, and 6% in HBeAg-positive women and 10%, 3%, and 1% in HBeAg-negative ones, respectively.[244] Therefore, the combination is superior to vaccine alone and the benefit of active/passive immunisation has been confirmed independently of the methodological quality of the trials, the mother's HBeAg status or the time of immunisation.[280] However, HBIG costs are high, supply may be limited, a cold chain is required and therefore coverage may be not appropriate in every country.

Infants born to mothers with HBV DNA levels above 1,000,000 copies (or 200,000 IU/ml) are at risk of failure of immunoprophylaxis, resulting in chronic HBV infection – the maternal serum concentration of HBV DNA has been identified as the single most important predictor and independent risk factor for MTCT.[275] A large study that enrolled 1,043 mother-infant pairs reported a linear correlation between rates of immunoprophylaxis failure and maternal HBV DNA levels.[282] The reasons for failure could be due to intrauterine transmission, which is likely not prevented by HBIG and HBV vaccination. This may occur via maternal oocytes in the early embryonic stage, via infected male germline, by HBV circulating to the fetus via maternal peripheral blood mononuclear cells during placental contraction or secondary to microvascular tearing.[275] Moreover, data from epidemiological studies and modelling suggest that infant vaccination alone would not guarantee achievement of the 0.1% HBsAg prevalence goal in children by 2030, and that peripartum antiviral prophylaxis may also be needed for all pregnant women with high viral load.

Antiviral treatment of HBV pregnant women could be an effective strategy to reduce HBV MTCT. All pregnant women should first be assessed for eligibility for long-term treatment based on their own health needs in accordance with the indications for treatment of chronic HBV infection. This will include consideration of serologic status, HBV DNA level and evidence of liver injury to avoid exacerbation or postpartum flare after cessation of prophylaxis. Pregnancy is also a possible cause of progression of underlying liver disease, with a variable presentation ranging from mild hepatitis flare to acute hepatic decompensation, which suggests that HBsAg-positive mothers should be evaluated to identify those with advanced liver disease who are at high risk for maternal and perinatal complications.[145,283,284] It is noteworthy that there is limited understanding of the natural history of chronic HBV infection during pregnancy and nearly 10% of HBeAg-positive mothers who continued antiviral treatment up to postpartum week 110 had HBeAg seroconversion.[285]

A seminal randomised-controlled trial demonstrated that tenofovir disoproxil fumarate (TDF) administered from week 30 of gestation is safe and effective in preventing HBV transmission in mothers with high viral load.[286] In the same year, the American Association for the Study of Liver Diseases recommended antiviral therapy in HBsAg-positive pregnant women who had an HBV DNA level of more than 200,000 IU/ml[287].

A recent large meta-analysis that included 129 studies, 33 randomised controlled trials and 96 non-randomised studies, evaluated the effect of TDF 300 mg (19 studies), lamivudine 100–150 mg (40 studies), and telbivudine 600 mg (83 studies), on reducing the risk of HBV MTCT, and showed similar efficacy for all drugs.[244] This analysis confirmed that peripartum antiviral prophylaxis is highly effective at reducing the risk of HBV MTCT. The pooled ORs for randomised controlled trials were 0.10 (95% CI 0.03–0.35) for TDF, 0.16 (0.10–0.26) for lamivudine, and 0.14 (0.09–0.21) for telbivudine. All studies in the meta-analysis included HBIG in both trial arms, with the exception of six studies, in which the use of HBIG was not reported. Thus, large studies on the efficacy of peripartum antiviral prophylaxis without HBIG are urgently needed, given that access to HBIG is restricted in many low- and middle-income countries. A previous meta-analysis that included 26 studies enrolling 3,622 pregnant women, found a reduction of MTCT at 6-12 months of life by employing lamivudine or telbivudine or tenofovir in infants who also received hepatitis B vaccine at birth, with a RR of HBsAg seropositivity of 0.3 (95% CI 0.2-0.4) and of HBV DNA seropositivity of 0.3 (95% CI 0.2-0.5) at 6-12 months after birth.[288] Thus, antiviral prophylaxis during pregnancy in women with high HBV DNA viral load was confirmed to significantly decrease the risk of HBV MTCT.

Evaluation of the timing of antiviral initiation has shown that treatment has a similar efficacy at preventing MTCT whether started in the first or second trimester. When antiviral treatment is initiated during the third trimester, a higher rate of MTCT occurred compared to earlier administration (RR = 0.045, 95% CI 0.0053 to 0.20).[289]

On the other hand, the benefit of TDF treatment, when newborns receive hepatitis B vaccine at birth and at 1, 2, 4, and 6 months and HBIG at birth, was challenged in some geographic areas. A randomised clinical trial performed in Thailand examined HBeAg-positive pregnant women with mildly elevated alanine aminotransferase (ALT) levels (≤60 IU/L), 168 of whom were randomly assigned to the TDF group and 163 to the placebo group from 28 weeks of gestation to 2 months postpartum.[290] No significant difference in the newborn infection rate was observed between treated and untreated[244] pregnant women (0/147 infants (0%; 95% CI 0-2) in the TDF group *vs.* 3/147 (2%; 95% CI 0-6) in the placebo group (p = 0.12). The authors concluded that in areas where the rate of HBV MTCT is low, maternal use of TDF during pregnancy does not improve the protection offered by administration of HBV vaccine and HBIG at birth.[290]

All HBV antiviral drugs are category C, except for TDF and telbivudine, which are category B drugs. The occurrence of antiviral resistance to lamivudine or telbivudine in treatment-naïve pregnant mothers is uncommon due to the short duration of drug exposure; however, in treatment-experienced patients, TDF is recommended because of its favourable resistance profile.[283] In addition, TDF has shown long-term safety for the fetus.[291]

HBV DNA should be tested in all HBsAg-positive pregnant women or, if HBV DNA testing is not available, HBeAg testing should be performed. The WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥5.3 $\log_{10}$ IU/ml (≥200,000 IU/ml) should receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent MTCT of HBV, in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose**.** It should be noted that most clinical trials that examined the efficacy of TDF were performed in settings where HBIG was administered at birth. However, it is reasonable to assume that recommendations about the efficacy of antiviral prophylaxis may be extended to settings where HBIG is not administered.[281] Six studies that reported the risk of maternal HBV flare after TDF discontinuation were included in a meta-analysis.[244] In these studies, 35 of 418 mothers (8%) who received TDF experienced a flare after discontinuation, compared with 23 of 382 control mothers (6%) at a matched time-point. No significant differences were observed between the two groups, suggesting that discontinuation of tenofovir prophylaxis might not increase the risk of flare (weighted pooled risk difference in the meta-analysis: 0.00; 95% CI 0.04–0.04).[244]

Therefore, if the maternal HBV DNA is >200,000 IU/ml, antiviral prophylaxis is recommended to minimise vertical HBV transmission.[230,292] Antiviral treatment can be discontinued 12 weeks after delivery in women without clinical indications for long-term therapy and if infants received HBIG and vaccination.

Finally, the safety of breastfeeding during tenofovir administration is still debated. Breast milk levels of tenofovir are lower than levels in the blood of mothers taking TDF and tenofovir is unlikely to have biological effects in the nursing infant.[293] Although small differences in tenofovir plasma concentrations occurred with tenofovir alafenamide (TAF) compared to TDF, the concentrations of tenofovir in the breast milk were significantly higher in mothers receiving TAF than in the TDF group, despite the lower dosage of TAF, but a gradual decline in the levels of tenofovir in the milk was observed in the following days postpartum.[294] In addition, TDF absorption by infants through oral breast milk is low because breast milk is expected to contain TDF almost exclusively in an unesterified anionic form, which has low oral bioavailability; in a recent study its concentrations were undetectable (<4 ng/ml) in all of the infant plasma samples examined.[295]

In terms of maternal and infant bone mineralisation, TDF prophylaxis in HBV-monoinfected women in Asia appeared safe and maternal and infant bone mineral density 1 year after delivery/birth was not affected by maternal TDF use. In particular, no differences were reported between 62 infants in the prophylaxis group and 53 infants in the placebo group in terms of lumbar spine bone mineral density (mean: 0.324 (SD ± 0.036) and 0.330 (SD ± 0.036), respectively).[296]

Conclusively, TDF toxicity is unlikely to occur and breastfeeding should be regarded as safe for infants born to HBV mothers treated with tenofovir. Nevertheless, large-scale prospective cohort studies are needed to confirm these results.

Performing diagnostic amniocentesis

Theoretically, amniocentesis might result in antepartum transmission of HBV due to the introduction of maternal infected blood into amniotic fluid or the fetal circulation. Although older studies did not report an increase in MTCT following amniocentesis,[297,298] these studies were mainly based on detection of the infants' HBsAg without HBV DNA testing and some of them had relevant flaws such as small sample sizes or poorly defined study populations. More recently, in infants who completed appropriate immunisation, born to mothers without antiviral treatment, amniocentesis has been found to be associated with a non-significant overall increase in HBV transmission rate (6.35%) compared to newborns without amniocentesis (2.53%; p = 0.226) born to young, HBeAg-positive mothers with high levels of HBV DNA, in spite of the higher rate of caesarean section in the amniocentesis group compared with the control group.[299] This study, which enrolled 63 infants in the amniocentesis group compared with 198 matched infants where amniocentesis was not performed, concluded that in mothers with HBV DNA levels ≥7.0 $\log_{10}$ copies/ml the rate of HBV MTCT was significantly higher among infants following amniocentesis (50% *vs.* 4.5%, respectively, p = 0.006) and amniocentesis in these mothers is a significant risk factor for HBV transmission (OR 21.3, 95% CI 2.960–153.775). A more recent retrospective cohort study enrolled 143 HBsAg-positive women undergoing amniocentesis and compared them to 605 women who did not, matched for maternal viral loads, antiviral therapy regimens and delivery dates.[300] Significant risk of MTCT emerged for infants born to mothers who underwent amniocentesis (2.80% *vs.* 0.50%; RR 5.64, 95% CI 1.28-24.93). Furthermore, maternal HBV DNA ≥7.0 $\log_{10}$ IU/ml and HBeAg positivity were associated with higher MTCT rates.[300]

Performing a randomised study that includes mothers who undergo amniocentesis *vs.* controls is deemed difficult, because indications for performing the procedure are not subjected to a randomisation design, and thus the best available evidence may originate only from observational studies. HBsAg-positive women with a high level of HBV viremia (≥7 $\log_{10}$ copies/ml) who are planning to undergo amniocentesis should be counselled about the risk of vertical transmission due to their HBV DNA level. Further studies are needed to explore

the potential benefit of antiviral treatment before the procedure with the aim of reducing MTCT.

Scaling up HBV testing of pregnant women (and their partners) in areas of intermediate endemicity of HBV

The main hepatological societies recommend screening for HBsAg in all pregnant women to enable recognition, diagnosis and reduction of the risk of HBV MTCT.[236,292,301] Examining only individuals at risk because of intravenous drug use, promiscuous sex, work in sex industry, sexual contact with HBsAg carriers, will leave up to 50% of pregnant women without a diagnosis of HBV infection.[302] Currently available studies indicate that the level of HBsAg is stable during pregnancy, is positively correlated with maternal viral load ($r = 0.69$; $p < 0.001$) and accurately predicts maternal viral load above 6, 7, and 8 $\log_{10}$ IU/ml with an area under the receiver-operating characteristic curve (AUC) of 0.97, 0.98, and 0.95[303]. Therefore, HBsAg quantitation in areas of limited resource should be encouraged.

Should antiviral treatment for HCV infection be offered to pregnant women or to women of childbearing age planning a pregnancy in the near future?

Recommendations

- Women of reproductive age with HCV infection should be screened and counselled to undergo antiviral treatment before pregnancy or after delivery and breastfeeding **(LoE 1; strong recommendation, strong consensus).**
- If necessary, antiviral therapy with directly acting agents can be considered during pregnancy after a thorough discussion about the potential risks and benefits of treatment with the pregnant woman that includes advice from the multidisciplinary team (including hepatology and obstetric specialists) **(LoE 4; weak recommendation, consensus).**

It has been estimated that 25% of the 15.6 million people who inject drugs worldwide are 25 years or younger and the highest proportion of young drug users reside in eastern Europe, where interventions to prevent the spread of bloodborne viruses are few.[304] Overall, an increasing number of young adults, including women of childbearing age and pregnant women, are infected by HCV via intravenous drug use.[305] This trend is particularly evident in the US, where people of reproductive age born between 1975 and 2000 are responsible for 60% of the new HCV infections. HCV infections among women of childbearing age are surpassing infections among older women. HCV prevalence in pregnant women varies in Europe between 0.06% and 3.9%, and in the rest of the world it ranges from 0.24 to 7%.[305] Therefore, it has been recommended to broaden the HCV screening to all childbearing age and pregnant women. Currently, only a few countries, including Italy, France, Poland, Taiwan, Pakistan[305] and the US[250] recommend universal screening during pregnancy, which is the most effective measure to increase the uptake of HCV testing during pregnancy and promote linked care with a hepatologist to start antiviral treatment after delivery and completion of breastfeeding.[251] However, treatment deferral until after giving birth will capture only a small fraction of those who could benefit.[306] Current guidelines recommend that women of reproductive age should be screened for HCV[233,252,307,308] and those that are positive should be counselled to undergo antiviral treatment before pregnancy to improve health and eliminate the risk of vertical transmission. Women becoming pregnant while on directly acting antiviral therapy with ribavirin should discontinue the treatment or at least discontinue ribavirin.[234]

Although there is no approved HCV treatment for pregnant women, directly acting antiviral administration during pregnancy could theoretically limit the risk of perinatal transmission, since MTCT is probably an early event during pregnancy.[309] In addition, the odds of developing gestational cholestasis with pruritus are 20-fold higher in HCV-infected pregnant women,[310] and antiviral treatment could limit this risk.

Currently, AASLD/IDSA guidelines state "treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits"[305] and pregnancy allows HCV screening and treatment because of increased maternal engagement in the healthcare system and expectations about neonatal health outcomes. Similarly, EASL guidelines state that "treatment can be considered during pregnancy only on a case-by-case basis after a thorough discussion with the patient about the potential risks and benefits".[252]

Concerning the effects of pregnancy on maternal viral load, a case-control study of 26 HCV-infected pregnant women compared with 12 HCV-infected non-pregnant women demonstrated an increase in HCV RNA among the pregnant women during the second and third trimesters,[311] while in an observational study of 65 HCV-positive women followed through pregnancy and after delivery, there were no changes in viral load.[312]

HCV transmission to the newborn is an understandable concern in women of childbearing age and a recent survey reported that 60% would take antepartum directly acting antiviral therapy to lower the risk of perinatal transmission and 21% for self-cure.[313] Among currently available therapies, the combination of sofosbuvir/ledipasvir[314] did not show any evidence of fetal harm in animal reproduction studies employing doses significantly higher than those recommended in humans.

Recently, an open-label, phase I study has enrolled nine pregnant women with HCV genotype 1 infection between 23 and 24 weeks of gestation for a 12-week course of oral ledipasvir-sofosbuvir. Pharmacokinetic analysis did not show significant differences in drug exposure among pregnant *vs.* non-pregnant women,[315] although the primary inactive circulating metabolite GS-331007, which has a half-life of 27 hours, had a serum level 38% lower in pregnant women than in non-pregnant women.[315] All the participants achieved a sustained virological response 12 weeks after completion of treatment and no discontinuation of the treatment due to any adverse event occurred. All newborns had normal weight, one was delivered at 36 weeks and 6 days for gestational hypertension. None of them was infected by HCV and none had adverse events related to ledipasvir-sofosbuvir exposure during the 12 months of follow-up.[315] All women stated that cure from HCV would be "life-changing" and "treatment during pregnancy was convenient, adherence to daily pill was feasible, and was facilitated by non-judgmental interactions with providers and researchers".[316]

Trials of treatment of pregnant women with sofosbuvir/velpatasvir are still in progress (ClinicalTrials.gov Identifier: NCT04382404).

MTCT is probably an early event during pregnancy[309] and it is believed to occur *in utero* in up to 40% of cases,[317] with the remaining cases likely occurring at birth.[318] Consequently, initiation of antiviral treatment during the second trimester could prevent antenatal as well as the intrapartum HCV transmission. This strategy would be particularly important in pregnant women with HIV/HCV coinfection, who have a doubled risk of HCV transmission to the fetus.[253] The final benefit of antenatal HCV treatment relies on viral eradication and prevention of disease progression in the mother, prevention of cholestasis in pregnancy and related complications, and prevention of viral transmission to the fetus in the current and future pregnancies. Moreover, in countries where screening of pregnant women is recommended, an increase in the demand for infection management during pregnancy can be expected and directly acting antiviral therapy administration will be a key aspect to address when counselling mothers.[313]

Should acute HAV infection in low-intermediate risk regions be prevented by vaccination of childbearing age women or pregnant women to prevent adverse pregnancy outcomes, or should prophylaxis be administered after HAV exposure in non-immune pregnant women?

Recommendations

- Vaccination of pregnant women identified to be at risk for HAV infection during pregnancy is recommended **(LoE 3; strong recommendation, strong consensus).**
- Both hepatitis A vaccine and immunoglobulin for post-exposure prophylaxis can be used in pregnancy **(LoE 2; strong recommendation, strong consensus).**

Although maternal-fetal transmission of HAV is exceedingly rare, HAV infection during the second and third trimester of pregnancy can cause a high rate of gestational complications and preterm labour. Specifically, a study of 13 women acutely infected with HAV during pregnancy found that 69% had placental separation, uterine bleeding and premature contractions that may lead to preterm delivery.[319] The paucity of reported HAV cases in pregnant females is probably because many of the studies evaluating acute viral hepatitis in pregnancy have been conducted in hyperendemic areas, where acute HAV infections in adults are extremely rare. However, in countries where early life exposure to HAV has decreased due to improvement in sanitation, incident HAV infections among women has dramatically increased.[320] In these regions, broader use of vaccines among women of childbearing age, as well as children and adolescents, would be appropriate. Inactivated vaccines are available as monovalent HAV single antigen vaccines (HAVRIX or VAQTA, administered as two doses) or dual antigen vaccines in combination with the HBV vaccine (TWINRIX—administered as three doses at 0, 1, and 6 months).

By comparing 1,140 women that received one of the three inactivated HAV vaccines (51% of whom received the vaccine within the first 6 weeks of pregnancy; Vaccine Safety Datalink data) with 652,684 pregnant women who were not vaccinated, no significant associations between HAV vaccine exposure and gestational complications were reported, although a statistically significant association between vaccine exposure and SGA infants was observed (adjusted OR 1.32; 95% CI 1.09–1.60; $p = 0.004$).[321] However, the biological plausibility of the hepatitis A vaccine causing SGA is lacking and SGA in this population was associated with age younger than 26 years and non-white race, as previously observed.[322] Besides, the presence of other maternal risk factors for SGA could not be examined, thus limiting the interpretation of such a result.

The safety of the inactivated HAV vaccine used in this study confirmed a previous study on 139 cases observed over a 17-year period and referred to the Vaccine Adverse Event Reporting System, a spontaneous reporting system co-administered by the CDC (Centres for Disease Control and Prevention) and the FDA (Food and Drug Administration). The study, which collated the adverse events occurring after the single HAV vaccine or dual HAV-HBV vaccine, did not find any concerning adverse events in either pregnant women or their infants.[323]

The Center for Disease Control and Prevention (CDC) recommends consideration of inactivated HAV vaccine administration in pregnant women with any risk factor for this disease, since the occurrence of such infections in pregnant women outweighs the risk of receiving the vaccine, which has not been shown to be harmful during pregnancy.[324] The risk relates to type of occupation, homelessness, drug use, travel to regions with intermediate or high HAV endemicity, HIV, and CLD.[325]

Immunoglobulin is used for both preexposure and post-exposure prophylaxis of HAV. Due to the declining prevalence of HAV antibodies in the donors, the recommended doses for preexposure and postexposure prophylaxis were changed in 2017.[326] HAV postexposure prophylaxis with immunoglobulins, administering as a single weight-based intramuscular injection (0.1 ml/kg), is recommended in pregnancy and is 80% to 90% effective when administered within 14 days of exposure,[325] although specific data concerning pregnant women are scarce.[230,234] Vaccine administration is also recommended.[327]

A non-inferiority, randomised clinical trial compared the efficacy of hepatitis A vaccine and immunoglobulin for post-exposure prophylaxis given to 568 and 522 contacts, respectively.[328] The study found that both provided adequate protection with a rate of acute HAV infection of less than 5% if administered less than 14 days after exposure, although a slightly higher rate of hepatitis A was observed after vaccination compared with immunoglobulin administration. This difference might be clinically meaningful in some settings, including pregnant women, especially if affected by any form of CLD. Therefore, immunoglobulin continues to be recommended in clinical practice; however, if immunoglobulin is not readily available, the hepatitis A vaccine can be administered

alone. It is important to underline that administration of immunoglobulin more than 2 weeks after exposure is not effective in preventing or ameliorating the severity of hepatitis A.

To ensure the best outcome of the pregnant woman and the fetus, can optimal management of hepatitis E be achieved by recommending early delivery in severe cases and active vaccination against HEV for women of childbearing age living in settings of endemic HEV or settings of high risk of HEV outbreak?

Recommendation

- Delivery of the fetus (either preterm birth or therapeutic termination of pregnancy) can be considered to reduce maternal morbidity and mortality in mothers with acute severe hepatitis E and encephalopathy grade I-III **(LoE 4; weak recommendation, strong consensus).**

Pregnant women may be more vulnerable to HEV infection, but the reasons for increased susceptibility to HEV infection during pregnancy and the occurrence of severe disease are still unclear.[284] Overall, the odds of maternal death during pregnancy are seven times higher in the presence of HEV infection, while fetal growth and maturity may be significantly impaired, likely in association with preterm delivery.[265] HEV viral load in pregnant patients with acute liver failure is usually higher compared with pregnant patients with acute viral hepatitis alone. Furthermore, babies born to mothers with HEV-related acute liver failure are more often infected with HEV.[329] It has been postulated that severe fetal disease is the likely cause of increased severity of HEV infection in the mother.[329] Thus, acute liver failure in pregnant women has been suggested to be an example of mirror syndrome.[329]

Therapeutic termination of pregnancy, although not universally recommended, deserves careful evaluation.[271] A study examining 42 pregnant women with HEV infection, showed a beneficial effect in patients with encephalopathy grade I-III.[330] Therefore, early delivery of the baby in the context of severe maternal liver disease has been proposed as an option to reduce the risk of maternal mortality.[271] However, no consensus exists and in HEV-associated acute liver failure in pregnancy, the rationale for actively terminating a pregnancy with the aim of improving the outcome of the mother has been questioned.[284]

Strategies to curb HEV burden mainly rely on prevention and, at present, no specific antiviral agents exist, particularly for pregnant women.[331] Thus, provided it becomes available, HEV vaccination should be recommended in women of childbearing age living in endemic areas or in countries where HEV outbreaks are likely to occur. A phase IV trial is ongoing in Bangladesh to assess the effectiveness, safety, and immunogenicity of a vaccine named HEV 329 among women of childbearing age[332] since its safety and efficacy in pregnant women remains to be proven.[289] A recent trial aimed at evaluating efficacy and safety of a recombinant hepatitis E vaccine in healthy adults which enrolled 48,693 (86%) participants in the vaccine group and 48,663 participants (86%) in the placebo group showed that efficacy after three doses was 100.0% (95% CI 72.1-100.0). Adverse effects attributable to the vaccine were few and mild.[333] Interestingly, the trial also included 37 pregnant women who were inadvertently vaccinated. No changes in tolerability or fetal outcome were seen.

Gestational liver disorders

Preeclampsia and HELLP syndrome

For pregnant women with preeclampsia or HELLP syndrome, is derangement of serum transaminases, or other clinical/biochemical determinants, of prognostic value in predicting the course of disease as well as maternal and fetal complications?

Recommendations

- HELLP syndrome should be considered a manifestation of severe preeclampsia **(LoE 3; strong recommendation, strong consensus).**
- Evaluation of serum liver tests is recommended as abnormalities are frequently associated with an adverse maternal outcome in HELLP syndrome, but they should not be used in isolation to guide care **(LoE 3; strong recommendation, strong consensus).**
- Platelet transfusion should be considered in pregnant women with a platelet count $<100\times10^9$/L, as this is associated with increased risk of abnormal coagulation and adverse maternal outcomes associated with preeclampsia **(LoE 2; strong recommendation, strong consensus).**
- For women with preeclampsia, maternal assessment should include clinical features (blood pressure and proteinuria), as well as biochemical tests as components of multivariate models, *e.g.*, fullPIERS model or the PREP model as recommended by obstetric guidelines **(LoE 1; strong recommendation, strong consensus).**
- It is advisable for women with a history of prior HELLP syndrome to undergo first-trimester screening to assess the risk of early-onset preeclampsia, as this is likely to result in preterm delivery **(LoE 4; weak recommendation, n.a.).**

Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide. Each year, preeclampsia is responsible for over 500,000 fetal and neonatal deaths and over 70,000 maternal deaths. It has previously been defined as the onset of hypertension accompanied by significant proteinuria after 20 weeks' gestation. Recently, the definition of preeclampsia has broadened; the internationally agreed definition is now the one proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP).[334]

According to the ISSHP,[334] preeclampsia is defined as:

- Systolic blood pressure (BP) at ≥140 mmHg and/or the diastolic BP at ≥90 mmHg on at least two occasions measured 4 hours apart in previously normotensive women and is accompanied by ≥1 of the following new-onset conditions at or after 20 weeks' gestation:
  a. proteinuria (*i.e.*, ≥30 mg/mol protein:creatinine ratio; ≥300 mg/24 hour; or ≥2+ dipstick);

b. other maternal end-organ dysfunction, including: neurological complications (*e.g.*, eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata), pulmonary oedema, haematological complications (thrombocytopenia–platelet count <150,000/μl, disseminated intravascular coagulation (DIC), haemolysis), acute kidney injury (*e.g.* creatinine ≥90 μmol/L; 1 mg/dl), liver involvement (elevated transaminases, ALT or AST >40 IU/L, with or without right upper quadrant or epigastric abdominal pain, or;
c. uteroplacental dysfunction (*e.g.* placental abruption, angiogenic imbalance, FGR, abnormal umbilical artery Doppler wave form analysis, or intrauterine fetal death).

HELLP syndrome (full or partial, with only some manifestations, such as elevated liver enzymes and low platelets), is considered to belong to the disease spectrum of preeclampsia, and occurs in 0.5-0.9% of all pregnancies and in 10-20% of those with severe preeclampsia.[335] It is generally accepted that preeclampsia, particularly early-onset disease, results from impaired placentation in early gestation and HELLP syndrome has been shown to share histopathological, placental morphological alterations and changes in gene expression with early-onset preeclampsia.[336–338] HELLP syndrome may be difficult to distinguish from acute fatty liver of pregnancy (AFLP); clinical and biochemical features that typically characterise each condition are summarised in Table 6. A summary of the recommended management of HELLP syndrome is provided in Fig. 5.

Serum liver enzymes

The PIERS (Preeclampsia Integrated Estimate of Risk) prospective multicentre cohort study of 2,008 women with preeclampsia demonstrated that the absolute levels of AST, ALT, and lactate dehydrogenase (LDH) predicted adverse maternal outcomes (AUCs for AST: 0.73, 95% CI 0.67–0.97; ALT: 0.73, 95% CI 0.67–0.79; LDH: 0.74, 95% CI 0.68–0.81).[339] A systematic review[340] evaluating the accuracy of measurement of liver enzymes for predicting adverse maternal (eclampsia, pulmonary oedema, maternal death, abruption, DIC, renal failure, intracerebral haemorrhage, adult respiratory distress syndrome, or retinal detachment) and fetal (neonatal deaths, fetal distress, FGR, intraventricular haemorrhage, respiratory distress syndrome, mechanical ventilation, necrotising enterocolitis, or bronchopulmonary dysplasia) outcomes in women with preeclampsia, including 13 primary articles (a total of 3,497 women) demonstrated that for predicting any adverse maternal outcome, raised liver enzymes had an AUC of 0.79 (95% CI 0.51–0.93) while the sensitivity ranged from 0.04 (95% CI 0–0.34) to 0.95 (95% CI 0.63–1) and specificity from 0.17 (95% CI 0.14–0.20) to 0.97 (95% CI 0.93–0.99). For predicting adverse fetal outcomes, based on five primary studies, the sensitivity and specificity of raised liver enzymes ranged from 0.11 (95% CI 0–0.67) to 0.86 (95% CI 0.23–1) and from 0.66 (95% CI 0.59–0.73) to 0.88 (95% CI 0.83–0.92), respectively. In women with preeclampsia, liver enzyme tests performed better in predicting adverse maternal than fetal outcomes. While the presence of increased liver enzymes was associated with an increased probability of maternal and fetal complications, they should not be used in isolation to guide care due to poor sensitivity.

Table 6. Clinical and laboratory features of HELLP *vs.* AFLP.

Clinical/laboratory feature	HELLP	AFLP
Clinical		
Altered sensorium	Late feature	+
Hypertension	++	+/-
Polyuria and polydipsia	—	+
Laboratory		
Thrombocytopenia	Early feature	Late feature
Coagulopathy	Late feature	+
Acidosis	—	+
Acute kidney injury	+/-	++
Abnormal serum liver tests Low fibrinogen Prolonged aPTT (disproportionate to platelet fall)	+	++
Hyperbilirubinemia	+/-	++
Hypoglycaemia	—	++

AFLP, acute fatty liver of pregnancy; HELLP, haemolysis, elevated liver enzymes, and low platelets.

Liver function tests

The PIERS Canadian cohort study found that, in comparison to abnormal serum liver enzymes, evidence of liver function abnormality (*e.g.* elevated serum bilirubin or INR) was less common among women with preeclampsia, but was associated with increased ORs of adverse maternal outcomes.[339] For example, INR in the top quartile affected 3% of those with preeclampsia, of whom 30.2% had an adverse maternal outcome. Similarly, serum bilirubin in the top quartile affected 2.9% of those with preeclampsia, of whom 35.7% had an adverse maternal outcome. Therefore, compared to serum liver enzyme abnormalities, which are common in preeclampsia (up to 55%), liver *function* abnormalities should be interpreted as markers of more concerning maternal prognosis.

Platelet count

There are contradictory results from retrospective and case-control studies with regard to the utility of a low platelet count to predict adverse outcomes associated with HELLP syndrome. One study showed that HELLP syndrome (n = 44) with a very low platelet count (<50×10^9/L) was associated with higher rates of DIC and acute kidney injury;[341] one study of 292 HELLP syndrome cases showed that very low platelet count (≤40×10^9/L) was associated with a higher rate of postpartum haemorrhagic complications;[342] however, another study of 119 preeclamptic cases and 165 healthy controls showed that a low platelet count was not predictive of the severity of preeclampsia.[343] Data from women in the PIERS database were utilised to determine the relationship between platelet counts and the risk of abnormal coagulation and adverse maternal outcomes in women with preeclampsia. The odds of having abnormal coagulation (105 of 1,405, 7.5%), defined as either an INR greater than and/or a serum fibrinogen level less than the local hospital laboratory's pregnancy-specific normal range, were increased for women with platelet counts <50×10^9/L (OR 7.78; 95% CI 3.36–18.03) and between 50 and 99×10^9/L (OR 2.69; 95% CI 1.44–5.01), compared with women who had platelet counts >150×10^9/L (11). Thus, a platelet count <100×10^9/L is highly specific and is associated with significantly increased risk of abnormal coagulation and adverse maternal outcomes associated with preeclampsia, most specifically the need for blood transfusion. However, the platelet count should not be used in isolation to guide care because of its poor sensitivity.

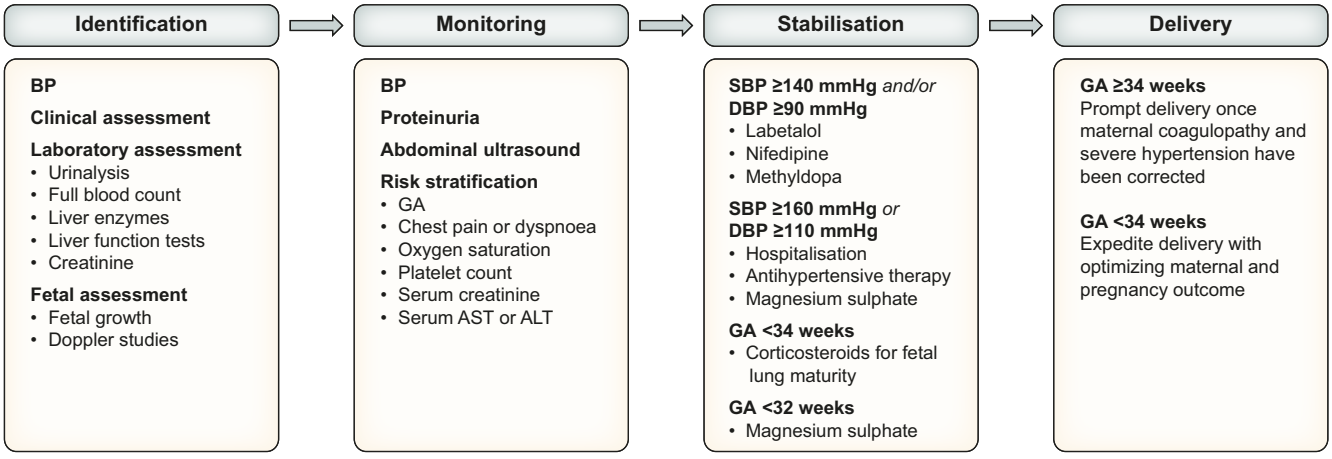

Fig. 5. Management of HELLP syndrome or preeclampsia with liver derangement. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; DBP, diastolic blood pressure; GA, gestational age; SBP, systolic blood pressure.

Uric acid

A meta-analysis[344] of 196 studies comprising 39,540 women has demonstrated that preeclampsia is associated with elevated uric acid levels. Diagnostic accuracy analysis has demonstrated that serum uric acid concentrations during the second and third trimester can be used to detect preeclampsia with estimated sensitivities of 0.79 (95% CI 0.52-0.92) and 0.77 (95% CI 0.71-0.82), respectively, and specificities of 0.62 (95% CI 0.57-0.66) and 0.80 (95% CI 0.74-0.84), respectively. For the prediction of adverse perinatal outcomes, the mean sensitivity of the marker ranges from 0.67 to 0.83 and its specificity from 0.48 to 0.71. It is suggested that increased serum uric acid levels can be used to predict disease severity, and pregnancy complications; however, the optimal cut-offs for the prediction of maternal and perinatal outcomes remain to be determined. Further, it has been determined that serum uric acid is not independently predictive of adverse maternal outcomes in the fullPIERS study (see below).[345]

Proteinuria

A systematic review of 16 primary articles, including a total of 6,749 women, demonstrated that summary likelihood ratios of positive and negative tests for a threshold proteinuria level of 5 g/24 hours were 2.0 (95% CI 1.5, 2.7) and 0.53 (95% CI 0.27-1) for stillbirths, 1.5 (95% CI 0.94-2.4) and 0.73 (95% CI 0.39-1.4) for neonatal deaths and 1.5 (95% 1, 2) and 0.78 (95% 0.64, 0.95) for neonatal intensive care unit admission.[346]

Multivariate models including clinical and/or laboratory parameters

A systematic review and meta-analysis, including six primary articles and 2,573 women, demonstrated that individual symptoms of preeclampsia, such as headache, epigastric pain and visual disturbances, have poor predictive ability for adverse maternal outcomes.[347] Meanwhile, a systematic review of symptoms, signs, laboratory tests and biomarkers, including 32 studies, has demonstrated that the most promising prediction for adverse maternal outcomes is achieved with multivariable models, especially when oxygen saturation, or chest pain/dyspnoea are included.

PIERS cohort. To facilitate risk stratification and improve the management of hypertensive disorders of pregnancy, the fullPIERS model was developed and internally validated to predict adverse maternal outcomes occurring within 48 hours after hospital admission for preeclampsia or in women who developed preeclampsia after admission in a prospective study including tertiary obstetric centres in Canada, the UK, New Zealand and Australia. The adverse outcomes predicted by the model included major organ dysfunction and death.[348] Of 2,023 women with preeclampsia, 261 had adverse outcomes at any time after hospital admission (106 (5%) within 48 hours of admission). The fullPIERS model was based on maternal demographics, signs, symptoms, and laboratory tests, with the final model consisting of six predictor variables: gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, serum creatinine, and serum AST or ALT. On internal validation, the fullPIERS model predicted an adverse maternal outcome within 48 hours of hospital admission with an AUC of 0.88 (95% CI 0.84–0.92).[349,350]

PREP (prediction of complications in early-onset preeclampsia) models. The PREP-L model includes: maternal age, gestational age at diagnosis, medical history, systolic BP, urine protein-to-creatinine ratio, platelet count, serum urea concentration, oxygen saturation, baseline treatment with antihypertensive drugs and administration of magnesium sulphate.[351,352] The PREP-S model additionally includes exaggerated tendon reflexes and serum ALT and creatinine concentrations. For the prediction of maternal complications, the reduced PREP-L has been externally validated, demonstrating good performance with c-statistics of 0.81 (95% CI 0.77 to 0.85) in PIERS and 0.75 (95% CI 0.64 to 0.86) in PETRA (a Dutch intervention trial) cohorts[353] and calibrated well with slopes of 0.93 (95% CI 0.72-1.10) and 0.90 (95% CI 0.48-1.32), respectively. Whilst the reduced PREP-S model achieved a c-statistic of 0.71 (95% CI 0.67 to 0.75) and a calibration slope of 0.67 (95% CI 0.56 to 0.79) in the PIERS cohort.

PIERS (preeclampsia integrated estimation of risk) models. An online calculator is available for the fullPIERS model (https://preempt.bcchr.ca/evidence/fullpiers). Without ready access to laboratory results, the miniPIERS model can be used, which includes: systolic BP, dipstick proteinuria, parity, gestational age, and symptoms (headache/visual symptoms, chest pain/dyspnoea, abdominal pain with vaginal bleeding); model performance

is improved with the addition of pulse oximetry; an online calculator is available (https://pre-empt.bcchr.ca/evidence/minipiers). External validation studies have demonstrated that the fullPIERS model has good predictability for adverse maternal outcomes within 48 hours of admission (AUC >0.8) as well as up to 7 days before complications arise (AUC >0.7).[349,350,354,355] The miniPIERS model achieves an AUC >0.7, showing reasonable ability to identify women at increased risk of adverse maternal outcomes associated with preeclampsia.[356]

For women with preeclampsia, maternal assessment should include BP and proteinuria, as well as the components of the multivariate models, *e.g*. the fullPIERS model. With regard to the PREP models, which include the administration of magnesium sulphate as a predictor, these may have limited value in predicting adverse maternal outcomes, as this medication is routinely administered when there is severe preeclampsia.

Angiogenic markers

Angiogenic imbalance, as assessed by reduced PlGF (<5th centile for gestational age) or increased sFlt-1/PlGF ratio (*e.g*., >38 by the Roche assay), has been evaluated for its role in making an earlier diagnosis of preeclampsia based on the presence of uteroplacental dysfunction. Systematic review of 33 studies, including 9,426 women, has demonstrated that angiogenic imbalance shows promise for the prediction of adverse maternal and perinatal outcomes, although there is significant between-study heterogeneity.[357] Among women with suspected preeclampsia, angiogenic imbalance has high negative predictive value in ruling out the development of proteinuric preeclampsia within 7 days, adverse maternal outcomes within 14 days,[358] or delivery with preeclampsia within 14 days, when suspected preeclampsia is primarily related to hypertension.[359–362] Use of angiogenic markers to guide management may reduce adverse maternal outcomes (from 5% to 4%), time-to-diagnosis of preeclampsia (by an average of 2 days)[361,363] and identify women at increased risk of peripartum severe maternal morbidity (including postnatal hypertension).[364] Prediction of adverse outcomes may be improved by combining angiogenic markers with other clinical, routine laboratory, and ultrasonographic data. The ISSHP has moved to incorporate angiogenic markers, where available, into investigations as another marker of uteroplacental dysfunction, but not as a sole criterion for diagnosing preeclampsia.[334] Angiogenic markers may be particularly useful in the face of pre-existing proteinuria, chronic hypertension, or chronic kidney disease.

For pregnant women with a prior history of HELLP syndrome, does prophylaxis with aspirin reduce the risk of recurrence?

Recommendations

- In the absence of contraindications, following first trimester screening for preterm preeclampsia, women identified at high-risk should receive aspirin prophylaxis commencing before 16+0 weeks' gestation at a dose of 150 mg to be taken every night until either 36 weeks' gestation, when delivery occurs, or when preeclampsia/HELLP syndrome is diagnosed **(LoE 1; strong recommendation, strong consensus).**
- In women with low calcium intake (<800 mg/day), either calcium replacement (≤1 g elemental calcium/day) or calcium supplementation (1.5–2 g elemental calcium/day) is suggested as it may reduce the burden of both early- and late-onset preeclampsia **(LoE 2; weak recommendation, strong consensus).**

There are no specific studies evaluating whether aspirin prophylaxis reduces the approximately 25% risk of recurrence of HELLP syndrome.[365] Therefore, considering HELLP syndrome as a serious manifestation of preeclampsia, we describe existing guidance for the prevention of recurrence of preeclampsia. The argument for first trimester screening is given above.

It has been hypothesised that the effect of aspirin on the inhibition of inflammation and platelet aggregation could be useful to prevent or treat preeclampsia.[366] In the first randomised trial evaluating the effect of aspirin on placenta-mediated complications, Beaufils *et al.* randomised 102 women at high risk of preeclampsia and FGR, mainly based on their obstetric history, to receive daily aspirin at 150 mg and dipyridamole at 300 mg from 12 weeks of gestational age, or usual care.[367] There were six cases of preeclampsia, five of perinatal death and another four of FGR in the control arm, none of these events occurred in the treatment arm. Numerous randomised trials followed in the next few decades, with inconsistent results and conclusions, largely explained by a high degree of heterogeneity regarding the selection of trial participants, baseline risk of the included women, dose of aspirin, gestational age of prophylaxis initiation and definition of preeclampsia. In 2007, Askie *et al.* published an individual patient data meta-analysis on the effect of antiplatelet agents (including 24 randomised-controlled trials with aspirin alone) on the incidence of preeclampsia. A 10% risk reduction (RR 0.90, 95% CI 0.84-0.97) was identified.[368] A series of subsequent meta-analyses of aggregate data have demonstrated that aspirin is highly effective in reducing preeclampsia rates if initiated before 16 weeks' gestation (RR 0.47, 95% CI 0.34-0.65) but confers no beneficial effect when started after 16 weeks (RR 0.81, 95% CI 0.63-1.03)[369] and the effect on preeclampsia rates is mainly due to a reduction of the severe and preterm forms of the disorder (RR 0.11, 95% CI 0.04 to 0.33), with no significant beneficial effect on term preeclampsia (RR 0.98, 95% CI 0.42 to 2.33).[369,370]

Due to the conflicting results and significant heterogeneity of previous studies, and informed by the results of the aforementioned meta-analyses demonstrating that aspirin is highly effective in reducing preeclampsia rates if initiated before 16 weeks' gestation, the ASPRE trial was proposed.[371] High-risk women were randomly and blindly allocated to receive 150 mg of the trial drug daily, or placebo, from 11-14 weeks' gestation until 36 weeks' gestation or delivery, whichever occurred first. Aspirin was given at night, based on a previous chronotherapy trial suggesting that the beneficial effects are dependent on the time of administration, with better regulation of ambulatory blood pressure when taken at night.[372] 1,776 high-risk women were recruited, and treatment with aspirin was demonstrated to reduce the rate of preterm preeclampsia by 62% (1.6% *vs.* 4.3%, OR in the aspirin group 0.38, 95% CI 0.20–0.74; $p = 0.004$). The effect of aspirin on the rate of preterm preeclampsia was subsequently confirmed by an updated meta-analysis.[201]

In a Cochrane review, preeclampsia rates were reduced consistently with low-dose calcium with or without co-supplements (nine trials, 2,234 women; RR 0.38, 95% CI 0.28–0.52), as well as for subgroups: low-dose calcium alone (four trials, 980 women; RR 0.36, 95% CI 0.23–0.57); low-dose calcium plus linoleic acid (two trials, 134 women; RR 0.23, 95% CI 0.09–0.60); low-dose calcium plus vitamin D (two trials, 1,060 women; RR 0.49, 0.31–0.78) and a trend for low-dose calcium plus antioxidants (one trial, 60 women; RR 0.24, 95% CI 0.06–1.01). Overall results were consistent with the single quality trial of low-dose calcium alone (171 women, RR 0.30, 95% CI 0.06–1.38). For high-dose calcium, the average risk of high blood pressure was reduced with calcium supplementation *vs*. placebo (12 trials, 15,470 women: RR 0.65, 95% CI 0.53-0.81). There was a reduction in the average risk of preeclampsia associated with calcium supplementation (13 trials, 15,730 women: RR 0.45, 95% CI 0.31-0.65). The effect was greatest for women with low baseline calcium intake (eight trials, 10,678 women: RR 0.36, 95% CI 0.20-0.65) and those selected as being at high-risk (five trials, 587 women: RR 0.22, 95% CI 0.12-0.42). The variable methods of selecting women as being at high risk limit the clinical usefulness of these pooled results.[373]

For pregnant women with HELLP syndrome, does treatment with corticosteroids, antihypertensive agents, magnesium sulphate improve maternal disease severity and reduce perinatal morbidity and mortality?

Recommendations

- For women with HELLP syndrome that have non-severe hypertension (systolic blood pressure 140-159 mmHg and/or a diastolic blood pressure 90-109 mmHg), treatment should be initiated using oral labetalol, nifedipine, or methyldopa **(LoE 1; strong recommendation, strong consensus).**
- Women with HELLP syndrome that have severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg) should be treated urgently in a monitored setting with antihypertensive therapy using oral labetalol, nifedipine or methyldopa. Intravenous therapy with labetalol or hydralazine may be required **(LoE 2; strong recommendation, strong consensus).**
- Magnesium sulphate should be given to women with HELLP syndrome with co-existing severe hypertension to prevent eclamptic seizures **(LoE 1; strong recommendation, strong consensus)**, and also as a neuroprotective agent for preterm preeclampsia if delivery is required before 32 weeks' gestation. Dose should be as per local/national guidance **(LoE 2; strong recommendation, strong consensus).**
- Corticosteroid treatment should not be given to improve maternal outcomes in HELLP syndrome **(LoE 1; strong recommendation, strong consensus).**
- High-dose dexamethasone or betamethasone should be given as per national guidance to improve fetal lung maturity if a pregnancy complicated by HELLP syndrome is to be delivered before 35 weeks' gestation **(LoE 1; strong recommendation, strong consensus).**

There are no studies that specifically evaluate whether magnesium sulphate and antihypertensive agents improve maternal and perinatal outcomes associated with HELLP syndrome. However, there are valuable data from studies of severe preeclampsia that can be extrapolated as the basis of advice for management of pregnancies complicated by HELLP syndrome. Not all women with HELLP syndrome have hypertension, but when this is present (systolic BP ≥140 mmHg and/or a diastolic BP ≥90 mmHg), it should be treated with antihypertensive therapy.

The CHIPS Trial (Control of Hypertension in Pregnancy Study) was designed to evaluate the impact of BP control on pregnancy outcomes, for 987 women with chronic (n = 736, 75%) or gestational (n = 251, 25%) hypertension at 14-33 weeks' gestation. Women were randomised to "tight" BP control (target diastolic BP ≤85 mmHg) or "less tight" control (target diastolic BP of 100 mmHg), preferentially using labetolol as the antihypertensive of first choice, but with the flexibility to use other medications if desired. In the mother, "tight" (*vs*. "less tight") control reduced the incidence of severe hypertension (27.5% *vs.* 40.6%; adjusted OR 0.56, 95% CI 0.42-0.74), thrombocytopaenia (1.6% *vs.* 4.3%; adjusted OR 0.38, 95% CI 0.17-0.87) and elevated liver enzymes with abdominal symptoms (1.8% *vs.* 4.3%; adjusted OR 0.43, 95% CI 0.19-0.95), without having adverse effects on the fetus or newborn.[374] These findings were true regardless of the gestational age at which BP control was instituted. No antihypertensive agent has been shown to be superior to others for the treatment of non-essential hypertension, but oral labetolol, nifedipine and methyldopa are recommended by most clinical practice guidelines.[375–377] For treatment of severe hypertension (systolic BP ≥160 mmHg or a diastolic BP ≥110 mmHg), most guidelines recommend intravenous labetolol, oral nifedipine, or intravenous hydralazine.[375] In a network meta-analysis (51 trials), these medications were similarly effective in achieving target BP (32 trials, 3,236 women), although target BP was achieved more quickly with nifedipine than intravenous hydralazine.[378] In another network meta-analysis restricted to first-line agents (17 trials, 1,591 women), oral nifedipine was more effective at reducing severe hypertension than intravenous hydralazine.[379] Therefore, the evidence currently favours intravenous labetolol or oral nifedipine over intravenous hydralazine.

With regard to the use of magnesium sulphate and antihypertensive agents for patients with HELLP syndrome, recommendations for the management of women with preeclampsia and eclampsia should be followed. Based on the clear evidence from large, multicentre placebo-controlled trials that magnesium sulphate halves both the incidence and recurrence of eclampsia, women with preeclampsia who have proteinuria and severe hypertension, or hypertension with neurological signs or symptoms, should receive magnesium sulphate for eclampsia prevention, while women with eclampsia should receive magnesium sulphate to prevent recurrent seizures.[380–383] Magnesium sulphate is also recommended as a neuroprotective agent to prevent perinatal morbidity in preterm preeclampsia requiring delivery at <34 weeks.[384] Standard dosage of magnesium sulphate is usually a 4 g intravenous loading dose followed by maintenance of either 5 g intramuscularly to each buttock every 4 hours or 1 g/hour intravenously for 24 hours after the last eclamptic seizure or birth, whichever occurs later.[380]

Respiratory morbidity including respiratory distress syndrome is a serious complication of preterm birth and the primary cause of early neonatal mortality and disability. Evidence from a Cochrane review of 27 studies (11,272 randomised women and 11,925 neonates) has demonstrated that antenatal corticosteroids reduce the risk of perinatal death (RR 0.85, 95% CI 0.77-0.93; 9,833 infants; 14 studies), neonatal death (RR 0.78, 95% CI 0.70-0.87; 10,609 infants, 22 studies) and respiratory distress syndrome (RR 0.71, 95% CI 0.65-0.78; 11,183 infants; 26 studies). Antenatal corticosteroids probably reduce the risk of intraventricular haemorrhage (RR 0.58, 95% CI 0.45-0.75; 8,475 infants; 12 studies) and probably lead to a reduction in developmental delay in childhood (RR 0.51, 95% CI 0.27 to 0.97; 600 children; three studies).[385–387]

Evidence from a meta-analysis of 15 randomised-controlled trials of 675 cases with antepartum and postnatal administration of corticosteroids *vs.* 787 control cases has demonstrated that corticosteroid administration to patients with HELLP syndrome improves platelet count, serum levels of LDH and liver transaminases, reduces hospital/intensive care unit stay and blood transfusion rate but is not significantly associated with better maternal mortality and overall morbidity.[388] Therefore, corticosteroids should not be specifically administered for HELLP syndrome to hasten the resolution of the disorder.

For pregnant women with HELLP syndrome, does prompt delivery irrespective of gestational age improve maternal outcomes and fetal/neonatal outcomes?

Recommendations

- Women with HELLP syndrome should be delivered promptly once maternal coagulopathy and severe hypertension have been corrected, as there is evidence for worse maternal outcomes if this is not done **(LoE 2; strong recommendation, consensus).**
- In women with HELLP syndrome, if there are signs of hepatic failure that may require transplantation, early referral to a transplant centre should be made **(LoE 5; strong recommendation, n.a.).**

An open-label randomised-controlled trial of temporising management (n = 30) *vs.* immediate delivery (n = 26) in early-onset severe preeclampsia with or without HELLP syndrome between 28 and 34 weeks' gestation (the TOTEM study) demonstrated a lack of difference in maternal and perinatal outcomes between the management groups, and no conclusions could be drawn as to which management option provided a better balance of maternal complications *vs.* infant outcomes.[389] Retrospective studies comparing expectant and active management (*i.e.* delivery within 48 hours following diagnosis) have provided limited evidence suggesting that expectant management might be beneficial for patients with HELLP syndrome through the reduction of prematurity and associated complications, such as respiratory distress syndrome.[390,391] However, this management option cannot be considered for all patients with HELLP syndrome. Future research is needed to identify parameters predictive of disease evolution in order to identify patients for whom expectant management is suitable.

A randomised clinical trial of expectant management (n = 134) *vs.* prompt delivery (n = 133) performed in eight tertiary hospitals in Latin America (MEXPRE Latin Study) did not demonstrate neonatal benefit with expectant management of severe preeclampsia diagnosed at 28-34 weeks' gestation, though there was prolongation of pregnancy (2.2 days for prompt delivery group *vs*. 10.3 days for the expectant management group; $p = 0.0001$).[392] In addition, a conservative approach increased the risk of abruption (RR 5.07; 95% CI 1.13-22.7; $p = 0.01$) and SGA infants (RR 2.27; 95% CI 1.21-4.14; $p = 0.005$). Meanwhile preliminary results of the prospective observational study "International HELLP-Multicenter-Study" conducted in 12 hospitals in Germany, Austria, Belgium and the Netherlands showed that expectant management (n = 34) was associated with a higher incidence of severe maternal complications than aggressive management (n = 95) (23.5% *vs.* 9.5%; $p < 0.05$).[393] Nonetheless, the investigators concluded that expectant management of women with HELLP syndrome might be useful in well-selected patients (stable maternal and fetal condition) to enhance fetal lung maturity and to improve neonatal outcome before 34 weeks' gestation.

To date, there is limited evidence to support temporising management for women with severe preeclampsia, including HELLP syndrome. Current recommendations regarding the indications for planned birth for preeclampsia, regardless of gestational age, apply to 'complicated' preeclampsia (*i.e.* involving end-organ complications that are associated with a heightened risk of maternal or perinatal death). Indications include abnormal and rising liver transaminases, hepatic dysfunction (INR >2 in absence of DIC or warfarin, haematoma or rupture), progressive thrombocytopenia or platelet count <50 $\times 10^9$/L, transfusion of any blood product, abnormal neurological features (such as eclampsia, severe intractable headache or repeated visual scotomata), repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents, pulmonary oedema, abnormal and rising serum creatinine, placental abruption with evidence of maternal or fetal compromise or non-reassuring fetal status (including intrauterine death). If timing allows, delivery should occur in a tertiary centre capable of caring for critically ill mothers and newborns.

Women with HELLP syndrome fulfil the criteria for timed birth, and delivery should be expedited with the aim of optimising maternal and pregnancy outcomes. If the gestation is pre-viable, termination of pregnancy should be discussed and patient values considered, along with transfer of care to a tertiary referral hospital as expectant care is associated with very high perinatal mortality (>80%), as well as frequent maternal complications (in 27-71% of cases) that may include death. From viability to 33+6 weeks, delivery will be planned following a course of corticosteroids as the clinical situation allows. Clinicians should be aware that HELLP syndrome may occur *de novo* up to 2 weeks postpartum.

For pregnant women with HELLP syndrome or deranged serum liver transaminases, does liver imaging inform differential diagnosis, reduce maternal complications (seizures, hepatic haemorrhage, hepatic rupture, intensive care unit admissions) and/or impact on fetal/neonatal complications?

Recommendations

- Abdominal ultrasound should be performed in women with severe preeclampsia or HELLP syndrome if there are symptoms suggestive of hepatic haematoma, *e.g.*, abdominal, epigastric or right shoulder pain **(LoE 4; strong recommendation, strong consensus).**
- Clinicians may be alert to the higher prevalence of hepatic haemorrhage or haematoma in women with HELLP syndrome and markedly reduced platelet count ($\leq 20\times10^9$/L) **(LoE 4; weak recommendation, strong consensus).**

There is no evidence from randomised-controlled trials to answer this question, as current evidence comprises retrospective observational or case-control studies.

The prevalence of intrahepatic haematoma in women with HELLP syndrome has been reported to be as high as 39%.[394] Hepatic infarction is less frequent than hepatic haematoma. Capsular rupture occurs in 0.5–2% of women with preeclampsia and/or HELLP syndrome, which is associated with 17% and 38% maternal and fetal mortality, respectively.[395] In women with hepatic haematoma, the incidence of hepatic capsular rupture can reach up to 12%. Presenting clinical symptoms are often non-specific, including abdominal pain, epigastric pain, anaemia, right shoulder pain. The reported overall mortality rate of women with HELLP syndrome is 1% and this rate is greater when complications are present. It is therefore critical to identify hepatic complications of HELLP syndrome at an early stage. In this regard, the use of ultrasound is recommended to identify any hepatic abnormalities that may precede capsular rupture, including hepatic haematoma, especially in patients with abdominal symptoms, hypotension, anaemia or referred shoulder pain.

In an early observational study evaluating the role of hepatic imaging (CT, MRI and ultrasound) in 34 patients with HELLP syndrome with complaints of severe right upper quadrant abdominal pain in association with either shoulder pain, neck pain, or relapsing hypotension, the CT results were abnormal in 15/34 (45%).[394] The most frequent abnormal hepatic imaging findings were subcapsular haematoma (n = 13) and intraparenchymal haemorrhage (n = 6). There was no statistically significant correlation between the presence of an abnormal hepatic imaging finding and the severity of liver function test abnormalities. However, an abnormal hepatic imaging finding was noted for 10/13 (77%) with a platelet count of $\leq 20\times10^9$/L. The investigators concluded that abnormalities in liver function test results did not accurately reflect the presence of abnormal hepatic imaging findings in HELLP syndrome and that patients with symptomatic HELLP syndrome should undergo imaging of the liver. In contrast, in a retrospective series involving 586 women with HELLP syndrome or preeclampsia, only 0.53% of cases had positive imaging findings for hepatic rupture or haemorrhage.

In a longitudinal observational study, serial liver sonographic examinations were performed on 32 pregnant women with severe preeclampsia and acute right upper quadrant and epigastric pain.[396] Initial sonograms showed liver abnormalities in 28/32 (87.5%) patients. Abnormalities consisted of liver hypertrophy (n = 24), hyperechoic thickening of the periportal area (periportal halo sign; n = 23), striated thickening of the gallbladder wall (n = 27), hyperechoic thickening of the Glisson capsule (n = 11), liver areas of increased echogenicity (n = 11), subcapsular haematoma (n = 1), and subcapsular calcification (n = 1). Ascites (n = 16) and pleural effusion (n = 11) were also present. All patients eventually developed HELLP syndrome. This study demonstrated that in women with severe preeclampsia who subsequently developed HELLP syndrome, liver ultrasound showed sonographic abnormalities before biological abnormalities. Thus, serial liver sonographic examinations may play a role in the evaluation of severe preeclamptic women with acute right upper quadrant and epigastric pain and should be further investigated in future studies.

Acute fatty liver of pregnancy

AFLP represents both a medical and obstetric emergency that can cause maternal or fetal mortality if not identified early and managed promptly. The incidence is between 1:10,000-1:20,000 births.[397,398] AFLP typically presents in the third trimester of pregnancy and, for those who present antenatally, the mean time of diagnosis is 35.25 ± 5.80 weeks' gestation.[399] Between 5-25% present postnatally.[398–400] Risk factors include extremes of maternal age, low BMI, pregnancy-induced hypertension, multifetal pregnancy, FGR and male fetus.[397–399,401]

Symptoms may be non-specific and most commonly include nausea and vomiting, abdominal pain, anorexia and fatigue.[397–399,401] Polyuria and polydipsia are common features and affected women may also present with signs of liver decompensation (jaundice, encephalopathy, abdominal distension).[397,400,401] The pathogenesis of AFLP is not well understood, although there is evidence for maternal and/or fetal disorders of fatty acid metabolism in a small proportion of cases.[402] Short-, medium- and long-chain fatty acid oxidation disorders can result in accumulation of fatty acid metabolites in maternal hepatocytes, which in turn may overwhelm mitochondrial capacity, resulting in mitochondrial dysfunction and subsequent acute liver failure.[403]

Adverse maternal outcomes include haemorrhage secondary to coagulopathy (52%), ascites (48%), acute liver failure (47.3%), acute renal failure (80%), encephalopathy (18%), hepatorenal syndrome (4%), pancreatitis (16%) and multiorgan failure (2%).[397–399,401] Diabetes insipidus can result from impaired hepatic degradation of placental vasopressin. Approximately 60% of women with AFLP will require admission to an intensive care unit and 20% to a specialist liver unit.[398,399] Maternal mortality has improved over the last few decades and is reported to be between 2-18%.[398,401] Obstetric complications include hypertension/preeclampsia (typically 25-50%),[404] placental abruption (13%), meconium-stained amniotic fluid (40%) and postpartum haemorrhage (53%).[399] There are higher rates of preterm delivery (48%). In terms of fetal/infant outcomes there are increased rates of fetal distress (46%),

asphyxia of the newborn (25%) and neonatal intensive care unit admission (20%).[399] Fetal/infant death rates of 7-11% have been reported.[398,399,401]

Are certain biochemical markers or clinical features in women with AFLP able to predict risk of deterioration or need for intensive care unit admission?

Recommendation

- Women with acute fatty liver of pregnancy who develop encephalopathy, elevated serum lactate (>2.8 mg/dl), a model for end-stage liver disease score ≥30 or who score >7 on the 'Swansea criteria' should be considered for level 2 or 3 care (intensive care admission) **(LoE 3; intermediate recommendation, strong consensus).**

Systematic review of the literature revealed increased ALT, higher total bilirubin and lower mean value of prothrombin activity as prognostic markers for negative outcomes (placental abruption, oligohydramnios, meconium staining, postpartum haemorrhage, poor wound healing, liver failure, renal failure, coagulation disorders, shock and infection in one study;[399] and abnormal prothrombin time with severe maternal complications ICU hospitalisation, long ICU stay, disseminated intravascular coagulation, pleural effusion, ascites, haemorrhage and acute kidney injury) in another.[405] Women with elevated serum creatinine levels, lactate, prolonged prothrombin time or activated partial thromboplastin times and presence of encephalopathy were at increased risk of death.[400,406] Prolonged prothrombin time was also associated with severe maternal complications.[405] Lower platelet counts, reduced total protein and elevated total bilirubin concentrations were correlated with longer postpartum recovery times.[401] Table 6 summarises biochemical markers that may be useful to distinguish AFLP from HELLP syndrome.

In a retrospective analysis of 76 patients, univariate analysis revealed hepatic encephalopathy as a predictor of poor prognosis.[407] Similarly, a series of 54 women admitted to a tertiary liver unit with AFLP or HELLP syndrome reported that elevated serum lactate (>2.8 mg/dl) and the presence of encephalopathy were the most useful predictors of maternal death or liver transplant.[406]

In a retrospective single-centre study including 52 women, those who scored >7 on the Swansea criteria (Box 1) had increased risk of stillbirth, requirement for continuous blood purification treatment and postpartum haemorrhage.[408] In another single-centre retrospective study of 44 women, the MELD score showed good performance in predicting most of the perinatal complications of AFLP including ascites, wound seroma, hepatic encephalopathy, disseminated intravascular coagulopathy, sepsis, renal insufficiency and stillbirth. In addition, maternal complications (jaundice, severe renal failure, coagulation abnormalities) were more frequent in women with a MELD score ≥30 (p <0.05).[409] In a retrospective single-centre study of 44 cases, the development of pancreatitis was considered to be indicative of poor prognosis, both in terms of maternal and fetal death.[401]

Box 1. Swansea criteria for acute fatty liver of pregnancy.

Six or more of the following in the absence of another explanation:

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Bilirubin >0.8 mg/dl (14 μmol/L)
- Hypoglycaemia <2 mg/dl (<4 mmol/L)
- Uric acid >5.7 mg/dl (>340 μmol/L)
- Leukocytosis (>11x10^6/L), ascites or bright liver on sonogram
- ALT or AST >42 IU/L
- Ammonia >27.5 mg/dl (>47 μmol/L)
- Creatinine >1.7 mg/dl (>150 μmol/L)
- Coagulopathy (prothrombin time >14s or activated partial thromboplastin time >34 s)
- Microvesicular steatosis on liver biopsy

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

For women with AFLP, are interventions, e.g. plasma exchange, N-acetylcysteine or delivery associated with improved maternal disease severity or reduced perinatal mortality?

Recommendations

- Delivery should be expedited once coagulopathy and remediable metabolic derangements have been treated, and decisions about mode of delivery should be made jointly by obstetricians, hepatologists and the multidisciplinary team **(LoE 5; strong recommendation, strong consensus).**
- Based on limited data from small case series, the use of plasma exchange post-delivery may be considered to improve maternal disease severity and decrease the time to recovery in women with acute fatty liver of pregnancy and severe hepatic impairment. There are currently insufficient data to recommend therapy outside clinical centres with expertise in plasma exchange in high-dependency settings or intensive care units **(LoE 4; weak recommendation, strong consensus).**
- There are no existing data to support or refute the benefit of N-acetylcysteine treatment in the management of acute fatty liver of pregnancy. However, benefits have been demonstrated in other causes of non-paracetamol-induced liver failure and it can be considered in women requiring admission to intensive care units **(LoE 5; weak recommendation, strong consensus).**
- In the subset of women with acute fatty liver of pregnancy who have severe hepatic impairment and may require transplantation, early referral to a transplant centre should be made **(LoE 5; strong recommendation, strong consensus).**

Plasma exchange

Four studies (including a total of 149 patients) have reported the outcomes of women with AFLP treated with plasma exchange. These include one prospective study and three retrospective studies. In a case-control study of 13 women treated with plasma exchange *vs.* 15 who refused plasma exchange, there was no significant difference in mortality rate between the two groups, but the plasma exchange group had shorter intervals of hepatic function recovery, ICU stay and hospitalisation (p <0.05).[410] In an observational study of 39 cases, 37/39 (95%) were cured.[411] In this study, the sooner the patient received plasma exchange the faster the recovery time (p <0.01). Adverse reactions were reported in three studies and included pulmonary oedema, hypocalcaemia, metabolic alkalosis, hypernatremia, itch, lower limb convulsions, and fever. In all studies they were reported as mild and all improved after treatment.[410,412]

Small case series have reported outcomes for patients treated with plasma exchange in combination with plasma perfusion[413] or continuous haemofiltration in patients with AFLP complicated by acute kidney injury[414,415] or multiorgan failure. Six patients treated with plasma exchange and plasma perfusion had improved liver and kidney function and survival compared to 16 patients treated with conventional treatment only (p <0.05).[413] In 17 patients treated with plasma exchange and continuous haemofiltration, most biochemical indices improved within one week; one patient died and the other 16 recovered (all clinical parameters) within 4 weeks.[414] In these patients, the rates of acute pulmonary oedema (p = 0.007) and hypocalcaemia (p = 0.039) were significantly higher in the plasma exchange sessions compared to the haemofiltration sessions.[414] In a series of five patients with AFLP, with hepatic encephalopathy and renal failure, plasma exchange and continuous renal replacement therapy were well tolerated by all; four responded and showed improvement in clinical state and laboratory results, and one was successfully bridged to transplant.[415] In the context of AFLP and multiorgan failure, 11 patients had combined therapy with plasma exchange and continuous haemofiltration; 10 survived and one died of septic shock in the ICU.[416]

Use of N-acetylcysteine

There are no data to support the use of N-acetylcysteine to treat AFLP, but benefits have been demonstrated for other causes of non-paracetamol-induced acute liver failure.[417]

Liver transplantation

A small proportion of women can progress to acute liver failure despite delivery, necessitating LT. In a retrospective review of a national Scientific Registry of Transplant Recipients in the US, there were 39 women requiring LT for AFLP between 1991 and 2015. The outcomes of this group were compared to outcomes of women of childbearing age requiring LT for acute liver failure from acetaminophen and 'other causes'.[418] Of the 39 patients with AFLP; 18 underwent LT; three died on the waiting list; and 18 were delisted as liver function improved. When compared to women who required transplant for acetaminophen poisoning or 'other causes', women with AFLP had lower degrees of coagulopathy, bilirubin levels equivalent to the 'other causes' group but higher than the acetaminophen group, and median creatinine concentrations that were equivalent or higher, respectively. In terms of outcomes, the AFLP group had the longest number of days from LT to hospital discharge and similar 5-year survival.

Delivery

Current recommended practice is to ensure coagulopathy, hypoglycaemia and metabolic acidosis are stabilised/corrected and then to expedite delivery of the fetus in women diagnosed with AFLP antenatally. In a study that aimed to characterise the duration of recovery of multiorgan dysfunction in women with AFLP, recovery from hepatic, renal and haemostatic dysfunction was estimated after delivery.[397] Hepatocellular necrosis was demonstrated to peak at the time of delivery and showed prompt recovery with reduction of liver transaminase measurements to <100 IU/L by the second or third day postpartum. In a similar fashion, recovery of renal function was prompt after delivery. Haemostatic dysfunction was treated intensively to facilitate safe delivery, and reassuringly even those women with profound coagulopathy who were treated intensively had sufficient procoagulant synthesis to allow for adequate haemostasis post-delivery. This supports both the benefits and safety of delivery in such cases.

A systematic review and meta-analysis that included 78 cohort studies and 2 case-control studies (1,350 patients) explored the effect of caesarean section on maternal and fetal outcomes and compared caesarean section with vaginal delivery; two out of three primary outcomes in the caesarean section group exhibited positive effects; the maternal mortality rate was 44% lower (RR 0.56; 95% 0.41–0.76) compared to those that had vaginal delivery, and the perinatal mortality rate was also reduced (RR 0.52; 95% CI 0.38–0.71).[419] However, reverse causation cannot be excluded here, *i.e.* that intrauterine demise may be the reason for choosing vaginal delivery. There was no association between caesarean section and other poor maternal or perinatal outcomes in AFLP.

Hyperemesis gravidarum

Nausea and vomiting of pregnancy are common, affecting up to 80% of pregnant women. Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting of pregnancy that affects 1-3% of all pregnancies.[420] The Windsor definition of HG consists of: start of symptoms in early pregnancy (before 16 weeks' gestation); nausea and vomiting, at least one of which is severe; inability to eat and/or drink normally; symptoms strongly limit daily living activities.[421] The presence of a biochemical abnormality is not required for the diagnosis. For the majority, symptoms improve as gestation advances beyond 20 weeks; in around 20% symptoms persist throughout gestation.[422]

The aetiology of HG is poorly understood, but likely multifactorial, with genetic, endocrine, gastrointestinal, psychiatric and infectious mechanisms. Recently, GDF-15, a protein produced by the trophoblast with direct effects in the brain's area postrema, has been suggested to play an important role.[423]

HG commonly results in poor nutritional intake, weight loss, dehydration and electrolyte imbalance. Rare but serious complications include cardiac arrhythmia related to electrolyte imbalance, thrombosis secondary to dehydration, thiamine deficiency leading to Wernicke's encephalopathy, sodium abnormalities resulting in central pontine myelinolysis and vitamin K deficiency resulting in coagulopathy.[424] The physical and mental distress caused by the condition results in 4.9% of women terminating a wanted pregnancy and 6.6% suffering suicidal ideation.[425] Fetal complications include increased rates of SGA infants and preterm birth.[426,427] Offspring health outcomes in the long term may also be affected by HG, with

increases in neurodevelopmental disorders including autism spectrum disorder.[428,429] A summary of the recommended management of HG is provided in Fig. 6.

Does the presence of abnormal serum liver tests predict more severe disease/complications in women with hyperemesis gravidarum?

Recommendations

- Serum liver tests may be measured in women with hyperemesis gravidarum as they are elevated in 40-50% of severe cases; hyperemesis gravidarum-associated abnormalities are usually mild and self-limiting **(LoE 4; weak recommendation, strong consensus).**
- Women with hyperemesis gravidarum who have markedly raised serum liver tests should be screened for a primary liver disease **(LoE 5; strong recommendation, consensus).**

Serum liver test disturbances occur in 40-50% of all women with HG.[430,431] In one series, HG accounted for 32% and 94% of all serum liver test abnormalities among pregnant women of all gestations and those in the first trimester, respectively.[432] The pathogenesis for hepatic dysfunction is not entirely understood; proposed mechanisms include starvation injury with subsequent slow bile flow and transient reversible liver cell damage (as has been reported in rapid weight loss following bariatric surgery).[433] Alternative potential mechanisms include dehydration resulting in reduced hepatic blood flow, placental release of inflammatory cytokines and impairment of fatty acid oxidation.[434,435]

Mild aminotransferase elevation (up to 200 IU/L) is the most common liver test disturbance encountered.[436] There are rare cases in which aminotransferase levels >1600 IU/L are described but fulminant liver failure has not been reported in HG.[437,438] A two-fold increase in alkaline phosphatase, mild hyperbilirubinaemia and mild elevation in amylase levels may also be encountered.[436] In very rare cases the hyperbilirubinaemia may result in jaundice, but otherwise the clinical presentation of HG with and without liver involvement is the same.[438] No long-term sequalae of liver dysfunction in this context have been reported.

Imaging studies in women with serum liver test abnormalities secondary to HG are typically unremarkable. Liver biopsies have shown histopathological changes in keeping with necrosis, steatosis and bile plugs.[439] Neither imaging nor biopsy is routinely recommended based on abnormal liver tests in the context of HG, unless another primary liver pathology is suspected. Ultrasound should be considered to rule out multifetal pregnancy or trophoblastic disease. In women with HG associated with liver test abnormalities the management should be the same as for those without liver test abnormalities and includes supportive management with anti-emetics, rehydration, vitamin supplementation and venous thromboprophylaxis. Serum liver test abnormalities typically return to baseline following rehydration and cessation of vomiting. Further investigations should be initiated if this does not happen.

The question of whether abnormal liver tests can assist clinicians in assessing the prognosis or severity of HG was addressed in a systematic search of the literature. The search yielded 123 papers; raised liver enzymes were reported in 16-60% of included patients with HG. Elevation of liver enzymes was usually described as mild. Only one study[440] reported a prognostic outcome; in this study, Tan *et al.* found that raised liver enzymes, in particular AST, were associated with a decreased chance of hospital readmission. A small retrospective series of 15 women with HG-associated Wernicke's encephalopathy reported elevated AST concentrations >100 IU/L in 40%, likely related to prolonged vomiting. This indicates the importance of considering thiamine replacement in women with sufficiently severe disease to cause hepatic impairment.[441]

Intrahepatic cholestasis of pregnancy

ICP is characterised by (i) pruritus in pregnancy, (ii) elevated serum ALT activities and serum bile acid concentrations (hypercholanaemia), and (iii) exclusion of other causes of liver dysfunction or itching.[21] ICP is confirmed when serum liver tests completely normalise after delivery.[21] ICP is the commonest gestational liver disorder, affecting approximately 0.7% women of European ancestry and double this proportion of women of Asian origin.[442] The condition occurs more commonly in women from Latin America, particularly those from the Andean nations where 4% of the indigenous population develop ICP when pregnant.[443] Approximately 25% of women affected by ICP have heterozygous mutations in the biliary transporters *ABCB4, ABCB11* and *ATP8B1*,[444] and a smaller proportion have mutations in other genes implicated in cholestasis.[445]

Gestational cholestasis can develop as the clinical endpoint of a variety of pathological processes and should not be considered as a single diagnostic entity. While elucidating the underlying maternal pathology is important to optimise subsequent maternal health, consideration of the severity of maternal hypercholanaemia is most likely of relevance to the risk of adverse pregnancy outcomes regardless of the aetiology of maternal cholestasis. Gestational cholestasis is associated with undiagnosed autoimmune and cholestatic liver disorders[446] and positive hepatitis C serology[446,447], and also occurs in women known to have these disorders. Consistent with this, women with gestational cholestasis are at increased risk of being diagnosed with hepatobiliary disorders subsequent to pregnancy.[446] The cholestatic impact of elevated concentrations of reproductive hormones, *e.g.* 17β-estradiol or progesterone sulphates, are likely to unmask symptoms and biochemical features of ICP in genetically susceptible individuals, and also of women with previously asymptomatic underlying liver diseases, *e.g.* PBC, PSC or chronic hepatitis C.[448]

Women with ICP typically present with pruritus in the third trimester, but first symptoms and clinical features may occur in

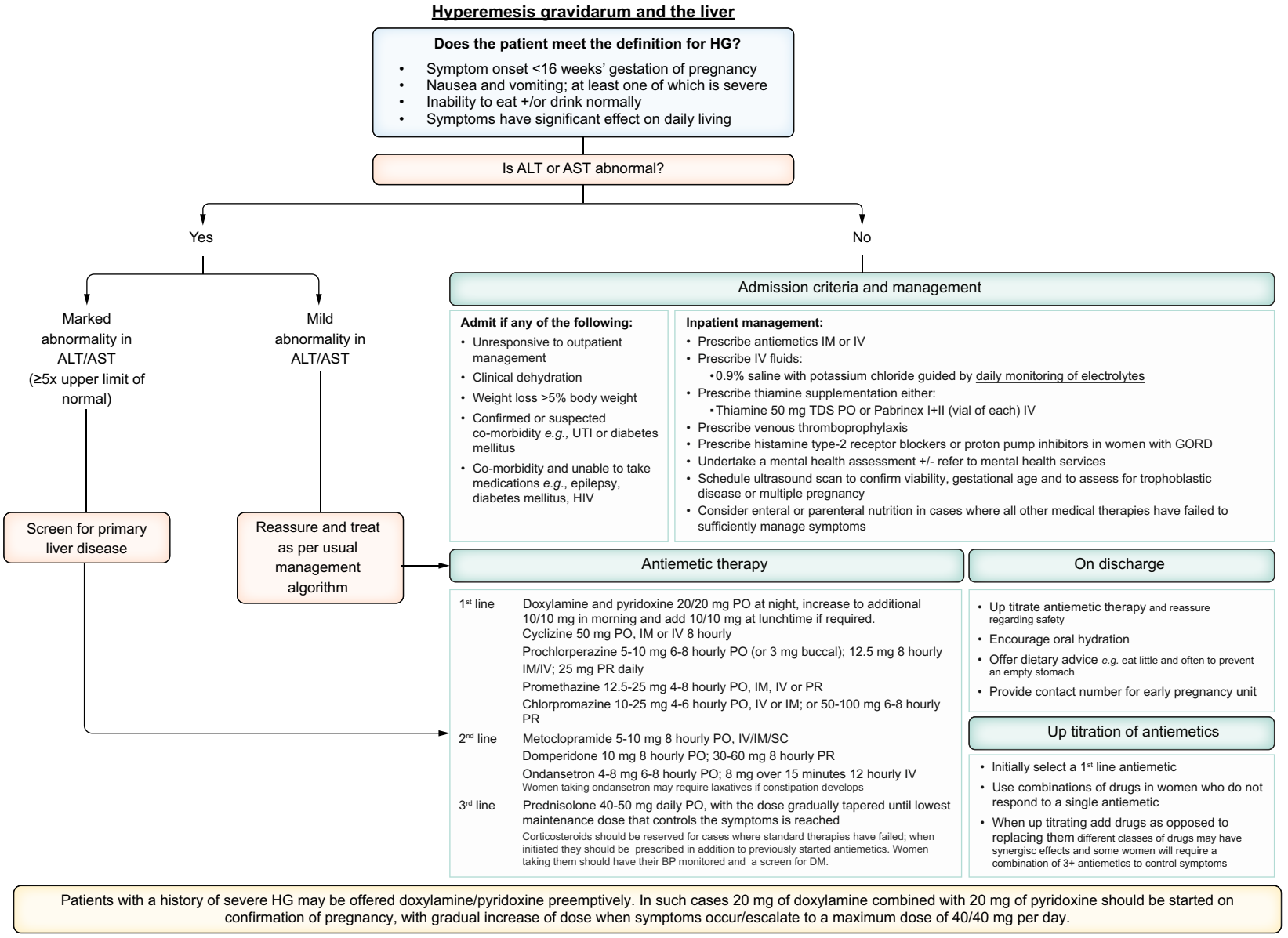

Fig. 6. Management summary for hyperemesis gravidarum. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GORD, gastroesophageal reflux disease; HG, hyperemesis gravidarum; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; PO, orally; PR, per rectum; SC, subcutaneous; TDS, three times a day; UTI, urinary tract infection. [A downloadable version of this figure is available in the supplementary material]

the first trimester of pregnancy. Affected women have variable degrees of elevated serum transaminase activities in addition to increased serum bile acid concentrations; hyperbilirubinaemia affects up to 30% women with ICP and is usually relatively mild.[449,450] In women with ICP, serum concentrations of bile acids, transaminases and bilirubin may continue to rise with advancing gestational week. Biochemical derangements usually resolve within 3 months of parturition; if persistent, investigations should be performed to exclude underlying liver disease.[21] In particular, it is important to consider whether women have autoimmune liver disease, pathogenic mutations in biliary transporters or positive hepatitis C serology, all of which can be screened for. ICP can be complicated by adverse pregnancy outcomes, including stillbirth, preterm birth, meconium-stained amniotic fluid and prolonged admission to the neonatal intensive care unit.[451–453] The children of affected women have increased rates of adiposity and dyslipidaemia in later life.[454] A summary of the recommended management of ICP is provided in Fig. 7.

For pregnant women with intrahepatic cholestasis of pregnancy, are measurements of serum transaminases or bilirubin better tests than measurement of serum bile acid concentrations to identify women with increased risk of fetal complications?

Recommendations

- Women with intrahepatic cholestasis of pregnancy should be tested for serum bile acid concentrations to identify pregnancies at risk of stillbirth, spontaneous preterm birth, fetal anoxia or meconium-stained amniotic fluid **(LoE 1; strong recommendation, strong consensus).**
- In women with confirmed intrahepatic cholestasis of pregnancy, serum bile acids should be measured at least weekly from 32 weeks' gestation to identify those with concentrations ≥40 μmol/L who are at an increased risk of adverse pregnancy outcomes **(LoE 1; strong recommendation, strong consensus).**
- In women with post-prandial serum bile acid concentrations ≥100 μmol/L, the risk of stillbirth increases after 35 weeks' gestation, and elective early delivery should be planned at this stage of pregnancy to reduce the risk of fetal death **(LoE 1; strong recommendation, strong consensus).**

Two large cohort studies,[451,452] several smaller studies,[455–457] and an individual participant data (IPD) meta-analysis that included 5,269 cases of gestational cholestasis[453] evaluated the relationship between adverse pregnancy outcomes and the serum levels of bile acids, transaminases and bilirubin. The IPD meta-analysis showed that serum bile acid concentrations are a more valuable serum biomarker to predict pregnancies at risk of ICP-associated stillbirth, with an AUC of 0.83 (95% CI 0.74-0.92), compared to ALT, AST and bilirubin (AUC and 95% CI 0·46 (0·35–0·57) 0·49 (0·36–0·62) and 0·57 (0·42–0·72), respectively.[453] The threshold concentration of non-fasting serum bile acids above which stillbirth risk increases significantly is 100 μmol/L, which occurs in 10% of women diagnosed with ICP. When the stillbirth rate was plotted according to number of fetuses remaining *in utero*, the risk increased markedly between 35 to 36 weeks' gestation, and thus consideration of delivery at this stage of pregnancy is a reasonable option with the aim of avoiding stillbirth in this high-risk subgroup of women with ICP. The data from the IPD meta-analysis[453] were consistent with the results of a subsequent systematic review that included data from six articles, including 1,280 singleton ICP pregnancies, and evaluated the association between elevated serum bile acid concentrations and perinatal death.[458] In women with serum bile acids ≥40 μmol/L, the risk of spontaneous preterm birth, meconium-stained amniotic fluid and fetal anoxia are increased.[451,452] Prospective cohort studies in Sweden[451] and the UK[452] and the IPD meta-analysis that included international data[453] did not demonstrate an association between elevated serum transaminases or bilirubin and these adverse pregnancy outcomes.

Serum concentrations of bile acids increase about two-to three-fold post-prandially in non-pregnant individuals,[459,460] and therefore it is recommended that fasting serum bile acid measurement is used in this group. Postprandial bile acid measurement shows a similar increase in pregnant individuals.[461,462] However, the peak concentrations of serum bile acids are of clinical importance for prediction of adverse pregnancy outcomes, and one study that evaluated the impact of feeding on bile acid concentrations in pregnant women demonstrated that the majority (9/10) of women whose serum bile acids rise to ≥40 μmol/L or ≥100 μmol/L postprandially will not be identified if only fasting serum bile acids are measured.[462] Two recent studies proposed the use of a new reference range for non-fasting serum bile acid concentrations of ≥20 μmol/L[462,463] and one demonstrated, using data from the IPD meta-analysis, that this would not result in increased perinatal morbidity or mortality.[462] In terms of the frequency of testing, if the serum bile acid concentration is ≥100 μmol/L at any stage of the pregnancy, it is not necessary to continue testing as the increased risk of stillbirth has been established. However, in women with established cholestasis, but with serum bile acids below this threshold, it is justifiable to measure more frequently from 32 weeks' gestation as serum bile acids may increase with advancing gestation, and it is important to identify pregnancies at risk of fetal demise to enable decisions about early delivery in this group where the risk increases markedly from 35 weeks' gestation.[453]

While measurement of serum transaminases and bilirubin is not of proven value for prediction of adverse pregnancy outcomes in ICP, they may be valuable for the differential diagnosis of the underlying hepatic pathology. A recent study also demonstrated that combined measurement of ALT, bilirubin, gamma-glutamyltransferase and alkaline phosphatase can be used to generate a combined laboratory score that can reliably

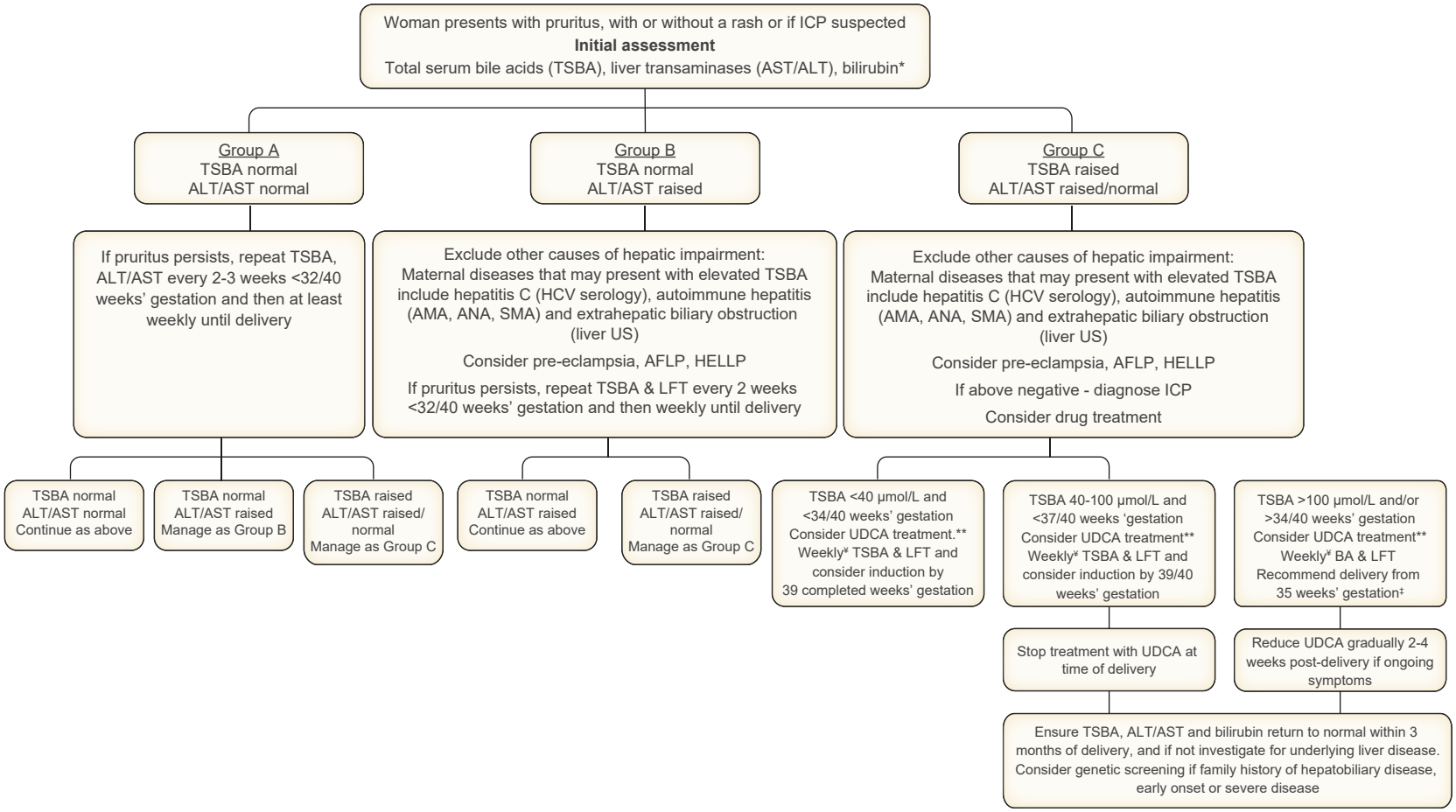

Fig. 7. Intrahepatic cholestasis of pregnancy management algorithm. *Bilirubin concentrations are rarely raised in ICP and if marked or persistent investigations should be performed to identify the cause. ¥TSBA (non-fasting) should be checked at least weekly as they may continue to rise with advancing gestation. **UDCA protects against spontaneous preterm birth in singleton pregnancy and may also protect against stillbirth ‡The risk of stillbirth rises markedly from 35 weeks' gestation in women with TSBA ≥100 µmol/L. AFLP, acute fatty liver of pregnancy; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; HCV, hepatitis C virus; HELLP, haemolysis elevated liver enzymes and low platelets; ICP; intrahepatic cholestasis of pregnancy; SMA, smooth muscle antibody; TSBA, total serum bile acids; US, ultrasound; UDCA, ursodeoxycholic acid. [A downloadable version of this figure is available in the supplementary material]

exclude ICP,[464] a test that may be of value in settings where serum bile acid measurement is not possible.

For pregnant women with intrahepatic cholestasis of pregnancy, is the use of ursodeoxycholic acid (or other therapies for cholestatic disease, e.g., rifampicin) more effective than no treatment to improve a) maternal symptoms, b) maternal hepatic dysfunction, c) adverse pregnancy outcomes?

Recommendations

- Ursodeoxycholic acid should be considered for treatment of maternal pruritus in intrahepatic cholestasis of pregnancy, despite having a relatively small effect on symptoms **(LoE 2; strong recommendation, strong consensus).**
- Additional therapies that may improve maternal pruritus can be considered, *e.g.* rifampicin, cholestyramine, guar gum and activated charcoal, but current evidence to support their use is limited **(LoE 4; weak recommendation, consensus).**
- In women with intrahepatic cholestasis of pregnancy and serum bile acid concentrations ≥40 μmol/L, ursodeoxycholic acid should be offered as a treatment to reduce the risk of spontaneous preterm birth and it may also be protective against stillbirth **(LoE 2; strong recommendation, consensus).**

Pharmacological therapies used to treat ICP aim to relieve maternal pruritus, improve maternal biochemical derangements and reduce the rate of adverse pregnancy outcomes.

UDCA is the most studied drug and has several mechanisms of action that improve the severity of hypercholanaemia, reviewed in.[465] In brief, UDCA increases the secretory capacity of hepatocytes, mostly via post-transcriptional mechanisms that stimulate vesicular exocytosis and the insertion of transporters/channels into the canalicular membrane,[465] and enhances chloride and bicarbonate excretion by the cholangiocyte,[466] thereby enhancing bile formation. UDCA strengthens the 'biliary bicarbonate umbrella' that protects hepatocytes and cholangiocytes from biliary bile acid-mediated damage.[467] In the intestine in ICP, the UDCA-induced stimulation of impaired bile acid secretion together with microbial deconjugation and modification of UDCA results in increased luminal concentrations of lithocholic acid, which may contribute to increased secretion of ileal fibroblast-growth factor 19 and, thereby, reduced synthesis of primary bile acids.[468] In terms of protection against adverse fetal outcomes, UDCA protects against cholic acid-induced arrhythmia in human and murine cultures of fetal cardiac myocytes,[469] and in UDCA-treated pregnancies, the fetuses were protected against abnormal heart rate variability and elevated umbilical venous N-terminal pro B-type natriuretic peptide compared to ICP pregnancies that were not treated.[470] UDCA has been studied in three placebo-controlled blinded trials,[451] and compared with cholestyramine and S-adenosyl methionine (SAMe) in unblinded trials.[31,471] Most clinical trials reported a reduction in maternal pruritus as confirmed in a meta-analysis.[28] The magnitude of itch reduction was limited in the largest placebo-controlled trial,[472] which included pregnant women with itch and postprandial serum bile acids ≥10 μmol/L thus not only ICP patients, but also pregnant women with other causes of pruritus. A Cochrane review concluded that the UDCA-mediated reduction in pruritus may fall below the minimum clinically worthwhile effect,[473] although for women with severe pruritus even a mild improvement may be clinically and psychologically beneficial.

In the majority of trials, maternal ALT and bilirubin concentrations were significantly reduced[451,472,474–477] following UDCA treatment, while total serum bile acid concentrations (including UDCA) were reduced in some studies,[475,477] but not all.[472,474,476] In one trial, the maternal serum bile acid concentration was only reduced in pregnancies where the concentration had been elevated to ≥40 μmol/L[439].

Many studies have had too few participants to be able to reach definitive conclusions about relatively rare adverse pregnancy outcomes such as stillbirth, although some have indicated a reduction in meconium-stained amniotic fluid[472,474,477] or preterm birth[475–477] following the use of UDCA during pregnancy. The largest placebo-controlled trial that evaluated the impact of UDCA on a composite outcome of stillbirth, preterm birth, neonatal death and neonatal unit admission did not show an impact of UDCA treatment, but it should be noted that approximately 75% of participants had serum bile acids <40 μmol/L at randomisation.[474] A subsequent IPD meta-analysis that obtained data from 6,974 women with ICP in 34 studies, 4,726 of whom were treated with UDCA, demonstrated that when only randomised-controlled trials were studied, UDCA protected against a composite outcome that included stillbirth and preterm birth with a number needed to treat of 15.[478] Furthermore, in pregnancies where the maternal maximal serum bile acid concentration was ≥40 μmol/L, UDCA treatment was associated with a significant reduction in spontaneous preterm birth,[478] while no effect of UDCA treatment on the rate of preterm birth was observed in pregnancies where the maternal serum bile acid concentration was <40 μmol/L.

There have been fewer studies of other potential drug treatments for ICP. SAMe increases hepatic excretion of bilirubin glucuronides by increasing hepatic expression of the transporter MRP2. Two small studies have reported improvements in maternal pruritus and serum bile acid, ALT and bilirubin concentrations following SAMe treatment,[479,480] but the number of participants was only 21 in both studies combined. Another small study did not report any impact of SAMe on maternal biochemical derangements or pruritus.[481] Cholestyramine[31] and activated charcoal[482] have each been reported to improve maternal biochemical abnormalities in one study, and guar gum[481] improved maternal pruritus, as did cholestyramine, although cholestyramine had a less marked impact on pruritus than UDCA.[31] In a retrospective, observational study, rifampicin improved maternal serum bile acid concentrations and pruritus in a subgroup of women who had a suboptimal response to UDCA,[31] and this is now being evaluated in the TURRIFIC randomised-controlled trial.[483] The number of participants in each study was small; a recent Cochrane review concluded that there was insufficient evidence that these drugs are efficient therapies for ICP and that more research is needed.[473] Dexamethasone treatment did not have a

significant impact on maternal pruritus or biochemical abnormalities in a randomised-controlled trial.[451] Fibrates may be considered after the first trimester for treatment of pruritus (as for women with pre-existing cholestasis).

For ursodeoxycholic acid-treated pregnant women with intrahepatic cholestasis of pregnancy, can total serum bile acid concentrations be used to predict adverse pregnancy outcomes?

Recommendation

- Alterations in total serum bile acid concentrations should be monitored after ursodeoxycholic acid treatment has been commenced as this helps with evaluation of risk of adverse pregnancy outcomes in intrahepatic cholestasis of pregnancy, but clinicians should be aware that ursodeoxycholic acid is also measured by enzymatic total serum bile acid assays **(LoE 2; strong recommendation, consensus).**

Commercially available enzymic diagnostic kits for total serum bile acids (TSBAs) typically utilise 3-beta-hydroxysteroid dehydrogenase, and therefore measure UDCA in addition to other primary and secondary bile acid species.[484] A study that evaluated individual bile acid species in serum samples from women with ICP showed that UDCA comprises 50-70% of all bile acids measured using an enzymatic assay, but that the pathologically elevated cholic acid and chenodeoxycholic acid are reduced in women treated with UDCA.[485] Thus, an adjustment can be made when considering TSBAs in treated women to enable bile acid measurement to be informative for clinical management. The IPD meta-analyses that considered TSBAs and risk of adverse pregnancy outcomes included UDCA-treated and untreated women,[453,478] so it is reasonable to use these thresholds (*i.e.*, TSBA concentrations of ≥40 μmol/L or ≥100 μmol/L in women receiving UDCA treatment).

Role of the multidisciplinary team

Should women with liver disease in pregnancy receive input from a multidisciplinary team?

Recommendation

- Women with liver diseases of pregnancy that are associated with an increased risk of maternal or fetal morbidity or mortality are suggested to be managed by a multidisciplinary team that should, at a minimum, include a physician, obstetrician and midwife, all of whom should have expertise in the field. If not available locally, patients should be referred to a centre where this multidisciplinary approach can be implemented **(LoE 5; weak recommendation, strong consensus).**

The UK confidential enquiry into maternal death and morbidity consistently reports that deaths from indirect causes are the leading cause of maternal mortality in the UK (accounting for 59% of all deaths).[486] Approximately 3% of all pregnant women are affected by liver disease during pregnancy;[487] when severe, liver diseases are associated with significant maternal and fetal morbidity and mortality. The management of liver diseases in pregnancy commonly requires a holistic approach with input from multiple disciplines including physicians, obstetricians, general practitioners, midwives, dieticians, pharmacists, and the mental health team.

This multidisciplinary team approach is recommended in several national and international guidelines[488,489] and publications.[194] To date, no studies have specifically assessed the benefits of this approach in women with liver diseases in pregnancy, thus highlighting a research gap, but improved clinical outcomes are reported when a multidisciplinary team approach is used for other chronic medical conditions and high-risk obstetric conditions.[490,491] Beyond clinical outcomes, a multidisciplinary team approach has been demonstrated, outside of pregnancy, to be positively associated with patient satisfaction.[492,493] Although a multidisciplinary team approach to patient care is universally recommended, little is known about the optimal structure or working models,[494] hence there is variability in practice globally[495] and models for best practice do not exist.

Preconception counselling

Women with advanced CLD or liver transplant are at increased risk during pregnancy compared to the background population,[93,192] and their babies have increased risk of preterm delivery, low birth weight, intrauterine growth restriction and neonatal distress syndrome.[45,496,497] With an increasing number of women with these conditions undergoing pregnancy, it is important that these women are given specialist advice to enable their health to be optimised prior to pregnancy, and risks of pregnancy discussed. Pre-pregnancy counselling offers the opportunity to do this.

In women with pre-existing liver disease, does preconception counselling improve maternal or fetal outcomes?

Recommendation

- All women with chronic liver disease or a history of gestational liver disease should be offered pre-pregnancy counselling from a team with expertise in management of these disorders **(LoE 4; strong recommendation, strong consensus).**

A study of 58 women with CLD attending a pre-pregnancy counselling clinic reported that, when embarking on pregnancy, women had concerns regarding deterioration, risk of maternal death, pregnancy loss, the effects of their medications on their pregnancy and the risk of genetic inheritance/transmission of their disease to their newborn.[498] Following clinic attendance, 98% of the women felt better informed. Similar levels of satisfaction have been reported in women with other chronic health conditions following attendance at a pre-pregnancy counselling clinic.[499,500] A subgroup of 24 patients were compared to a control group of 75 patients; there were no major differences in pregnancy outcomes (gestational diabetes/hypertension, preeclampsia, FGR [<10th centile for gestational age], preterm delivery [<37 weeks gestation] and

Table 7. Contraception considerations for women with pre-existing and gestational liver disorders.

Condition	Contraception method					
	Copper-bearing intrauterine device (Cu-IUD)	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Progestogen-only implant	Progestogen-only injectable: depot medroxyprogesterone acetate (DMPA)	Progestogen-only pill (POP)	Combined hormonal contraception (CHC)
Pre-existing liver disorders						
Cholestatic disease	Yes	Yes	Yes	Yes	Yes	Yes[a]
Autoimmune hepatitis	Yes	Yes	Yes	Yes	Yes	Yes[a]
Cirrhosis, portal hypertension, vascular liver disease	Yes	Yes	Yes	Yes	Yes	No[b]
Transplant	Yes	Yes	Yes	Yes	Yes	Yes[a]
Viral disorders in pregnancy	Yes	Yes	Yes	Yes	Yes	Yes
MASLD	Yes	Yes	Yes	Yes	Yes	Yes
Alcohol-related liver disease	Yes	Yes	Yes	Yes	Yes[c]	Yes[c]
Tumours	Yes	Yes	Yes	Yes	Yes	No
Gestational liver disorders						
Preeclampsia and HELLP syndrome	Yes	Yes	Yes	Yes	Yes	Use with caution if pre-existing hypertension
AFLP	Yes	Yes	Yes	Yes	Yes	Yes
HG	Yes	Yes	Yes	Yes	Yes	Yes
ICP	Yes	Yes	Yes	Yes	Yes	Use with caution[a]

AFLP, acute fatty liver of pregnancy; HELLP, haemolysis, elevated liver enzymes and low platelets; HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; MASLD, metabolic dysfunction-associated steatotic liver disease.
[a]Approximately 10% women with ICP have cholestatic liver injury when taking the combined oral contraceptive.
[b]In cases with adequate anticoagulation, there is no contraindication to CHC.
[c]Consider compliance problems to daily oral medication in alcohol abuse/addiction.

intrauterine death [>24 weeks gestation]) between those that received pre-pregnancy counselling and those that did not.

A systematic review of the literature did not identify any additional studies reporting pregnancy outcomes for women with CLD who received pre-pregnancy counselling. However, a study in women with inflammatory bowel disease compared those who had received pre-pregnancy counselling to those who had not, and reported that the pre-pregnancy counselling group were more adherent to medication during pregnancy, more compliant with adequate folic acid intake and smoking cessation, had reduced disease relapse during pregnancy (independent of parity, disease duration or activity before conception), and were less likely to deliver babies of low birth weight.[501] Similar positive outcomes have been reported in women with other chronic medical conditions.[502,503]

In vitro fertilisation in women with CLD or liver transplant recipients

Subfertility is more common in women with many CLDs than healthy counterparts, and although subfertility tends to improve post liver transplant for those with persistent subfertility, women in both groups may require *in vitro* fertilisation (IVF). In a retrospective review of 42 women undergoing IVF therapy due to liver-related subfertility, outcome data was available for 57 IVF cycles.[504] The study demonstrated that IVF is both feasible and can be successful in selected patients. Such women, however, have an increased likelihood of developing ovarian hyperstimulation syndrome, reversible deranged liver enzymes, ICP and erratic tacrolimus levels and this requires close monitoring. We also recommend caution when transferring more than a single embryo as the severity of many gestational hepatic disorders is worse in the presence of multifetal pregnancy.

Contraception considerations

Healthcare providers should actively seek to discuss family planning options with patients with underlying liver disorders in their reproductive years. Their ability to safely time pregnancy can enable treatment choices that optimise both liver disease and pregnancy outcomes. Most liver disorders do not impact contraceptive choices (see Table 7), but in specific diseases, the underlying disorder will influence contraceptive choice.

Effects of contraceptives on underlying liver disorder

Approximately 10% women with a history of ICP experience cholestatic liver injury when taking combined hormonal contraception (CHC).[505] Where possible, other forms of contraception should be used.[506] If a woman chooses to take CHC, liver function and serum bile acids should be checked 4 weeks after commencing therapy and treatment should be stopped if concerns arise. The same approach should be used for women with pre-existing cholestatic liver disease, although the risk of hepatic impairment is lower.

Mild active liver disease (*e.g.*, hepatitis or cirrhosis) should not affect the choice of contraceptive. However, in severe hepatitis or decompensated cirrhosis the risks of CHC may outweigh the benefits. Progestin only methods and intrauterine devices can be safe alternatives.

In women with a history of thrombosis (*e.g.*, of the portal venous system) CHC, when used in the absence of adequate

Table 8. Delivery considerations for women with pre-existing and gestational liver disorders.

Condition	Timing of delivery	Mode of delivery					
			Vaginal delivery precautions				
		Neuroaxonal anaesthesia	Induction of labour	Instrumental delivery	Normal vaginal delivery	C-section precautions	Immediate postpartum care
Pre-existing liver disorders							
Cholestatic disease	Planned	Yes	Yes	Yes	Yes	No	Rapid improvement in majority of cases
Autoimmune hepatitis	Planned	Yes	Yes	Yes	Yes	No	May worsen in postpartum period
Cirrhosis, portal hypertension, vascular liver disease	Planned	Yes	Yes	Yes	Yes, aim for short second stage	Haemorrhage precautions	Care with thromboprophylaxis
Transplant	Should not progress post-dates	Yes	Yes	Yes	Yes	Yes	Slight increased risk of infection
Viral disorders in pregnancy	Usually end of pregnancy	Yes	Yes	Yes	Indicated in all viral infections apart from HEV genotype 1 acute hepatitis (if severely ill) and HIV coinfected women (if not virologically suppressed)	Yes	HBV: Neonatal immunoprophylaxis with immune globulins anti-HBs and vaccine administration within 24 hrs
MASLD	Normal	Yes	Yes	Yes	Yes	No	No
Alcohol-related liver disease	Planned	Yes	Yes	Yes	Yes	No	No
Tumours	Normal with exception of adenomas >5 cm, haemangioma >4 cm or malignant tumours which should be discussed with MDT	Yes	Yes	Yes	Yes	Yes	No
Gestational liver disorders							
Preeclampsia and HELLP syndrome	Planned	Yes	Yes	Yes	Yes	Yes	Monitor blood pressure, some women transiently worsen; down titrate antihypertensive drugs
AFLP	Planned	Yes	Yes	Yes	Yes	Yes	May worsen in 20% for 2-3 days postpartum
HG	Normal	Yes	Yes	Yes	Yes	No	No specific needs
ICP	Planned between 35-36 weeks if serum bile acids ≥100 μmol/L	Yes	Yes	Yes	Yes	No	Ensure liver function tests return to normal by 3 months postpartum

AFLP, acute fatty liver of pregnancy; HELLP, haemolysis, elevated liver enzymes and low platelets; HG, hyperemesis gravidarum; ICP, intrahepatic cholestasis of pregnancy; MDT, multidisciplinary team; MASLD, metabolic dysfunction-associated steatotic liver disease.

anticoagulative drugs, can increase the chance of recurrent thrombosis.[506]

Liver adenomas can demonstrate growth under oestrogen exposure, making non-hormonal choices preferable.[506] If a woman is diagnosed with HCA and is using CHC, this should be discontinued.

Effects of liver disorders on contraceptive failure or side effects

A summary of contraceptive recommendations is provided in Table 7.

Women with a history of HELLP syndrome should be screened for the presence of chronic hypertension after delivery. In most cases there is no pre-existing hypertension or persistent hypertension beyond the postpartum period. If this is the case and in women with well-controlled and monitored hypertension who are ≤35 years old, a trial of CHC may be appropriate as long as the patient is otherwise healthy, shows no signs of end-organ vascular disease, and does not smoke. If blood pressure remains well controlled several months after the trial is started, combination contraceptives may be continued.

Alcohol or other substance use can be more prevalent in women with ALD, and viral hepatitis. Substance use is associated with non-compliance and contraceptive failure. Long-acting reversible alternatives (*e.g.*, implant of an intrauterine device) could provide a method at lower risk of failure in such cases.

Delivery considerations

Liver disease in pregnancy can result in specific choices regarding timing, precautions and mode of delivery, as summarised in Table 8.

Liver disorders and timing of delivery

HELLP syndrome, AFLP, decompensated cirrhosis or any other rapid maternal deterioration should trigger delivery after diagnosis and stabilisation, regardless of the gestational age.

In AFLP, there is no reason to delay delivery after diagnosis: there is little to gain in terms of fetal-neonatal outcome as perinatal mortality is high and maternal outcomes may be severely impacted by delayed delivery. However, when fetal demise has occurred, expedited vaginal induction could be considered (instead of caesarean section).

When HELLP is diagnosed at very early gestational ages (<32 weeks), in order to improve the fetal-neonatal prognosis, and only in the absence of severe symptoms, some clinicians may opt for expectant management with close monitoring, although this practice may lead to an increased risk of adverse maternal outcomes.

ICP with high bile acids (≥100 μmol/L), based on the highest level measured in pregnancy, regardless of decreases at later terms) should trigger delivery between 35-36 weeks due to the increased risk of sudden fetal demise. In cases with lower bile acid levels, delivery can be delayed until >37 weeks.

In most pre-existing liver disorders, delivery can be planned in early term (*e.g.*, 38-39 weeks).

Considerations regarding liver disorders and specific maternal delivery risks

Haemorrhage can be a major concern in those with portal hypertension (low platelets and oesophageal variceal bleeding), cirrhosis (due to coagulopathy), HELLP syndrome (associated with thrombocytopenia and less frequently coagulopathy due to diffuse intravascular coagulation), AFLP (coagulopathy due to hepatic failure), and women on anticoagulation due to vascular liver disease. Correction of coagulopathy, access to cross-matched blood products and intravenous access for rapid fluid resuscitation when needed can be important precautions preceding delivery.

In portal hypertension, with abdominal wall variceal vessels, a median low abdominal skin incision at caesarean may afford lower risks of haemorrhage than a low transverse skin incision in selected cases.

Both maternal thrombocytopenia or coagulopathy can limit the safe regional anaesthetic options (spinal or epidural), leaving general anaesthetic the only option for caesarean section, and systemic opiates (*e.g.*, remifentanil, patient-controlled administration) the only safe alternative for pain relief during vaginal delivery.

In HELLP syndrome, marked maternal hypertension can also require the attention of the multidisciplinary team

Box 2. Research recommendations.

Pre-existing cholestasis and ICP

Can we quantify the risk of fibrates in the second and third trimester and their role in the relief of pruritus for the management of primary biliary cholangitis, primary sclerosing cholangitis and ICP?

What is the role of vitamin D in the management of ICP?

The role of new therapies to treat maternal pruritus and reduce the rate of adverse pregnancy outcomes in intrahepatic cholestasis of pregnancy.

The role of genomic testing in women with ICP for optimisation of future health.

For women with intrahepatic cholestasis of pregnancy what is the optimal postpartum strategy for monitoring and interventions to improve maternal health?

Preeclampsia and HELLP syndrome

Can we identify specific first trimester biomarkers for the prediction of HELLP syndrome?

Can we identify first trimester prediction algorithms for HELLP syndrome?

To evaluate the role of angiogenic markers for the short-term prediction of HELLP syndrome and associated maternal and perinatal morbidity and mortality.

To identify specific biomarkers for the short-term prediction of HELLP syndrome and associated maternal and perinatal morbidity and mortality.

To evaluate whether magnesium sulphate and or antihypertensive agents (when there is associated hypertension) would improve maternal and perinatal outcomes associated with HELLP syndrome.

Acute fatty liver of pregnancy

What is the role of N-acetylcysteine in the management of acute fatty liver of pregnancy?

What is the role of plasma exchange in the management of acute fatty liver of pregnancy?

Evaluation of genetic factors and underlying metabolic disorders in the aetiology of AFLP.

Hyperemesis gravidarum

Does nutrient status in women with hyperemesis gravidarum contribute towards maternal and fetal outcomes, including hepatic injury?

Evaluation of the genetic aetiology of hyperemesis gravidarum.

The role of novel therapies to improve outcomes in hyperemesis gravidarum.

General

The effectiveness of pre-pregnancy counselling at improving maternal and pregnancy outcomes for liver disease in pregnancy.

Accurate evaluation and communication of the risks and benefits for mother and fetus/child of continuation or commencement of specific drug therapies in liver disorders of pregnancy

HELLP, haemolysis, elevated liver enzymes, and low platelets; ICP, intrahepatic cholestasis of pregnancy.

(obstetrician, obstetric anaesthetist, hepatologist, obstetric physician) at the time of delivery and in the direct postpartum period. General anaesthesia can precipitate uncontrolled hypertension in women with preeclampsia. Generally, strict fluid balance to avoid pulmonary oedema and magnesium sulphate (to lower the risk of eclamptic seizures, in cases where eclampsia is thought likely) are continued for 24 hours after delivery.

Overall, input from the multidisciplinary team including obstetric anaesthetic expertise can be of value in developing a delivery plan.

Considerations regarding liver disorders and choice of mode of delivery

In HELLP syndrome, mode of delivery is dependent on gestational age, fetal condition, severity of the maternal condition and cervical status.

When vaginal delivery is being considered for women with (low grade) oesophageal varices, the focus should be on limiting bleeding risk in the pre-pregnancy/early pregnancy period, *e.g.*, establishing women on primary prevention with beta blockade or banding. Contingency plans, including consideration of a short second stage of labour, access to an acute endoscopic team, octreotide, and emergency theatre, should be considered in the delivery plans to address to possibility of acute oesophageal haemorrhage. For pregnant women with high-grade (untreated) oesophageal varices, bleeding risks may be considered unacceptably high during vaginal delivery, warranting consideration of planned caesarean delivery.

In AFLP, small observational studies found that caesarean section is associated with improved maternal and perinatal outcomes compared to vaginal delivery. Bias by indication may have affected these findings. Nonetheless, generally rapid delivery after stabilisation of hypoglycaemia, acid-base balance and coagulopathy is recommended.

It is important to note that some medications often used to induce labour may be less suitable for women with hepatic failure: misoprostol (E1 prostaglandin) is metabolised to its active substance (E2 prostaglandin) in the liver. Other methods of labour induction may be more suitable for women with advanced liver failure when aiming for vaginal delivery or drug-induced termination of pregnancy.

Effects of liver disorders on fetal-neonatal outcomes around delivery

In cases of hepatitis C, especially when there is high viral load, invasive procedures (*e.g.*, internal cardiotocographic monitoring, fetal scalp sampling or vacuum extraction) should be avoided to lower the risk of vertical transmission. Caesarean section could be a safe alternative in cases of suspected fetal distress or failure to progress.

General considerations in anticipated preterm delivery

Fetal lung maturation in cases when preterm delivery is anticipated within 10-14 days can be improved by administering a 2-day course of betamethasone or dexamethasone and should be considered when delivery is imminent (<34 weeks). Intravenous magnesium sulphate should be administered in anticipated early preterm delivery (<30 weeks) to decrease the risk of neonatal cerebral palsy, and can be considered up to gestational ages of 34 weeks.

Conclusions and research recommendations

Hepatic disorders are increasing in frequency in women of reproductive age and there is a clinical need for guidelines based on robust, well-powered research data. While the evidence base for some recommendations in this CPG is excellent, there are limited data to support others. Box 2 summarises recommendations for new research to improve the evidence available to enable clinicians to change practice and optimise maternal and fetal outcomes for women with pre-existing and gestational liver disorders.

Appendix. Delphi round consensus on the statements and recommendations of the present CPGs.

Recommendations	Consensus
Women with pre-existing cholestatic diseases should be advised that approximately 50% will have worsening or *de novo* pruritus during pregnancy, but most women will have stable hepatic function. However, up to 70% have postnatal deterioration of serum liver tests. They should also be informed that preterm birth occurs more commonly, and live birth rates are reduced in primary biliary cholangitis and primary sclerosing cholangitis **(LoE 3; strong recommendation).**	100%
In the ~50% of pregnant women with worsening or *de novo* pruritus, repeated measurement of total serum bile acids should be performed, as higher serum bile acids are associated with reduced gestation length in pre-existing cholestatic liver disorders **(LoE 5; strong recommendation).**	100%
Ursodeoxycholic acid should be continued during pregnancy in primary biliary cholangitis (and primary sclerosing cholangitis when treated) as it is safe in pregnancy and breastfeeding **(LoE 4; strong recommendation).**	100%
Obeticholic acid use is currently not recommended in pregnancy or during lactation in women with primary biliary cholangitis or primary sclerosing cholangitis due to a lack of safety data, while fibrates may be used after the first trimester if the clinical team believes that the benefits outweigh the risks **(LoE 5; open recommendation).**	85%
Vitamin K deficiency related to cholestasis and/or use of anion exchange resins or rifampicin should be corrected **(LoE 5; strong recommendation).**	100%
For women with *de novo* or worsening pruritus, suggested treatments include rifampicin (300-600 mg daily) and anion exchange resins (cholestyramine, 4-8 g/day or colestipol, 5–10 g/day), the latter given at least 4 hours after ursodeoxycholic acid **(LoE 4; weak recommendation).**	86%

(*continued on next page*)

(*continued*)

Recommendations	Consensus
Imaging with ultrasound or magnetic resonance cholangiopancreaticography is recommended in primary sclerosing cholangitis, when cholestasis worsens, to exclude obstruction by gallstones or progress of high-grade strictures that are accessible to endoscopic balloon dilatation **(LoE 4; strong recommendation).**	100%
A careful history of previous or current use of prescribed and over-the-counter medications and herbal products is demanded in any case of unexplained serum liver test elevations **(LoE 5; strong recommendation).**	94%
Pregnant women should be screened for alcohol use and referred for management when appropriate **(LoE 4; strong recommendation).**	100%
For women with alcohol-related liver disease, delaying conception is recommended until abstinence is achieved **(LoE 4; strong recommendation).**	100%
Medication use to treat alcohol use disorder during pregnancy should be individualised; disulfiram should be avoided, and consideration of other drugs, *e.g.* naltrexone or acamprosate, should include careful weighing of the risks of alcohol use *vs.* those of medication exposure **(LoE 5; open recommendation).**	100%
For women with hepatocellular adenomas with a diameter <5 cm diameter, pregnancy does not increase the risk of complications related to the tumour and therefore no additional interventions are recommended. However, some tumours may increase in size and therefore ultrasound assessment is recommended **(LoE 1; strong recommendation).**	100%
Women planning pregnancy with a hepatocellular adenoma that has a diameter >5 cm should, where possible, have treatment prior to pregnancy. These tumours are associated with an increased risk of enlargement and haemorrhage **(LoE 2; strong recommendation).**	94%
Women with haemangiomas, even giant ones, should be advised that they do not preclude pregnancy **(LoE 4; strong recommendation).**	100%
Imaging is recommended during each trimester of pregnancy to monitor haemangioma size in those at higher risk of rupture (large or exophytic) **(LoE 4; strong recommendation).**	100%
Women with focal nodular hyperplasia should be advised that pregnancy is not contraindicated and vaginal delivery is not associated with increased risks **(LoE 4; strong recommendation).**	100%
Imaging is not routinely recommended to monitor focal nodular hyperplasia during pregnancy **(LoE 4; open recommendation).**	n.a.
Maintain ultrasound surveillance for hepatocellular carcinoma in patients with cirrhosis, in accordance with screening outside of pregnancy **(LoE 4; strong recommendation).**	n.a.
Perform close surveillance with abdominal ultrasound or MRI each trimester to enable detection of focal lesions in pregnant women considered to be at risk of recurrent hepatocellular carcinoma development **(LoE 4; strong recommendation).**	88%
In women with hepatocellular carcinoma, treatment with surgery, radiofrequency ablation or other potentially curative treatment should be individualised according to stage of pregnancy, location and size of the tumour **(LoE 4; strong recommendation).**	100%
Women with hepatocellular carcinoma should be advised that spontaneous and induced vaginal delivery are not contraindicated **(LoE 4; strong recommendation).**	100%
Women with cholangiocarcinoma in pregnancy should have a case-by-case evaluation by a multidisciplinary team to consider diagnostic and therapeutic strategies based on symptoms and prognosis **(LoE 4; strong recommendation).**	n.a.
In pregnant patients with a history of extrahepatic cancers known to metastasise to the liver, ultrasound surveillance is recommended and, if metastases are identified, careful multidisciplinary follow-up is recommended including adherence to recommended oncological management for non-pregnant people if metastases are identified **(LoE 4; strong recommendation).**	94%
Therapy with prednis(ol)one, budesonide and thiopurines should be continued in pregnancy and should be given for de novo AIH as in non-pregnant women, as treatment is associated with better maternal and fetal outcomes **(LoE 3; strong recommendation).**	100%
Immunosuppressive drugs with good safety data should be continued throughout pregnancy. Autoimmune hepatitis may deteriorate postpartum and therefore immunosuppressive therapy should be continued and an increase in dose considered postpartum due to the risk of flares **(LoE 5; strong recommendation).**	100%
Women with AIH should be advised that they have increased rates of gestational diabetes mellitus, hypertensive disorders of pregnancy, preterm birth and fetal growth restriction (often associated with preterm birth) and need close obstetric surveillance with screening to predict and manage these disorders **(LoE 2; strong recommendation).**	100%
In women of reproductive age with metabolic dysfunction-associated steatotic liver disease, preconception counselling should include a review of maternal and fetal risks associated with being overweight/obese and/or having diabetes. Pre-pregnancy non-invasive screening for liver fibrosis is advised using the most reliable tests available for women of reproductive age **(LoE 3; open recommendation).**	88%
Treatment of metabolic comorbidities should be optimised for women with metabolic dysfunction-associated steatotic liver disease before conception and should be implemented during pregnancy **(LoE 3; strong recommendation).**	100%
In pregnant women with metabolic dysfunction-associated steatotic liver disease, lifestyle modifications, including dietary advice, are advised as for the non-pregnant population **(LoE 3; strong recommendation).**	100%
Women with known metabolic dysfunction-associated steatotic liver disease should be managed as a group with increased risk of gestational diabetes mellitus and hypertensive disease in pregnancy with the use of appropriate national screening protocols, including monitoring of tests of liver function **(LoE 3; open recommendation).**	n.a.
Breastfeeding is encouraged in women with metabolic dysfunction-associated steatotic liver disease **(LoE 3; strong recommendation).**	100%
Women with Wilson's disease should continue therapy with zinc, D- penicillamine and trientine with dose reduction of chelators in the second and third trimesters **(LoE 4; strong recommendation).**	n.a.
Patients should undergo pre-pregnancy counselling and risk scores should be calculated to characterise their risk profile and determine the likelihood of complications prior to pregnancy **(LoE 3; strong recommendation).**	100%
Beta-blockers should either be initiated or continued during pregnancy for primary or secondary prophylaxis of variceal bleeding, provided there are no contraindications **(LoE 2; strong recommendation).**	n.a.
Patients with established cirrhosis or known portal hypertension should undergo a screening endoscopy within 1 year prior to conception to assess for the presence of clinically significant varices and for primary prophylaxis to be instituted as appropriate **(LoE 4; strong recommendation).**	100%
Appropriate endoscopic management of women at risk of clinically significant varices should be undertaken during pregnancy and high-risk varices should undergo endoscopic band ligation **(LoE 4; strong recommendation).**	100%
Delivery should be performed for obstetric indications, taking into consideration the severity and distribution of portal hypertension including size/severity of oesophageal, gastric and pelvic varices **(LoE 5; strong recommendation).**	100%
Women with vascular liver disease can be counselled that the condition is associated with preterm birth and operative delivery **(LoE 4; weak recommendation).**	93%

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Recommendations	Consensus
Female liver transplant recipients should be advised that delaying pregnancy for at least 1 year after transplant is associated with improved maternal and fetal outcomes **(LoE 3; strong recommendation).**	100%
Blood markers of rejection should be checked regularly during pregnancy, and immunosuppression titrated appropriately **(LoE 4; strong recommendation).**	n.a.
Clinicians should ensure increased frequency of review of pregnant liver transplant recipients, as they are also at risk of gestational maternal disorders including gestational hypertension, preeclampsia, gestational diabetes, cholestasis and acute kidney injury, and low-dose aspirin therapy should be initiated in the first trimester for preeclampsia prophylaxis **(LoE 1; strong recommendation).**	n.a.
Antenatal care providers should ensure increased surveillance for adverse pregnancy outcomes, including preterm birth and fetal growth restriction, in pregnant liver transplant recipients **(LoE 2; strong recommendation).**	94%
The immunosuppressive drugs azathioprine, cyclosporine, tacrolimus and prednisolone should not be stopped in pregnant women **(LoE 3; strong recommendation).**	100%
Mycophenolate mofetil is teratogenic and should be stopped at least 12 weeks before conception **(LoE 3; strong recommendation).**	100%
Women taking cyclosporine and tacrolimus should be closely monitored for hypertension and preeclampsia throughout pregnancy **(LoE 3; strong recommendation).**	100%
Women taking glucocorticoid treatment should be screened for gestational diabetes mellitus **(LoE 2; strong recommendation).**	95%
Clinicians should be aware that women taking >5 mg prednisolone per day for more than 3 weeks are at increased risk of adrenal suppression and there should be consideration of increased glucocorticoid dose at the time of delivery, and if there is intercurrent infection, vomiting or hyperemesis gravidarum **(LoE 2; strong recommendation).**	95%
In pregnant women with acute hepatitis A, caesarean section is not recommended unless there is an obstetric indication **(LoE 4; strong recommendation).**	100%
Breastfeeding should not be discouraged in women with acute hepatitis A **(LoE 4; strong recommendation).**	100%
Active or passive immunisation of newborns of mothers with acute hepatitis A is not routinely suggested **(LoE 5; weak recommendation).**	93%
Caesarean section is not recommended to reduce the risk of HBV mother-to-child transmission in HBsAg-positive women **(LoE 1; strong recommendation).**	n.a.
Caesarean section may be recommended only in Asian HBeAg-positive women with high HBV DNA titre (>7 $\log_{10}$ copies/ml; 6.14 $\log_{10}$ IU/ml) who have not received antiviral therapy during pregnancy **(LoE 1; open recommendation).**	n.a.
Breastfeeding of infants born to HBsAg-positive mothers should not be discouraged (unless mothers with detectable HBV DNA present with cracked nipples and/or the infant has oral ulcers) **(LoE 1; strong recommendation).**	n.a.
As HDV mother-to-child transmission is rare and prevention of HBV infection is effective at preventing HDV infection, recommendations for the management of delivery in HBV/HDV-coinfected pregnant women should be the same as for HBV-infected women **(LoE 5; strong recommendation).**	n.a.
Breastfeeding should not be discouraged in infants born to HBV/HDV-coinfected mothers as it is safe **(LoE 1; strong recommendation).**	94%
HCV testing of pregnant women is recommended as part of antenatal care **(LoE 2; strong recommendation).**	84%
Caesarean section should not be recommended to reduce mother-to-child transmission in women with isolated HCV infection as it does not decrease perinatal transmission of HCV **(LoE 3; strong recommendation).**	100%
For HCV/HIV-coinfected women, decisions about mode of delivery can be individualised dependent upon whether there is detectable HIV RNA and HCV RNA **(LoE 3; weak recommendation).**	100%
In women with HCV infection, amniocentesis can be performed as an invasive prenatal diagnostic procedure if the option of non-invasive prenatal testing has been ruled out, while chorionic villus sampling should be avoided, as should episiotomy during labour **(LoE 4; strong recommendation).**	92%
Breastfeeding should not be discouraged in HCV-infected mothers, nor in women with HCV/HIV coinfection on antiretroviral treatment **(LoE 3; strong recommendation).**	100%
Vaginal delivery should not be discouraged in women with HEV infection **(LoE 4; strong recommendation).**	100%
Breastfeeding of infants born to HEV-infected asymptomatic mothers should not be discouraged **(LoE 4; strong recommendation).**	100%
Antepartum administration of hepatitis B immunoglobulin to HBV-infected pregnant women is not recommended as it is not effective at reducing mother-to-child transmission of HBV irrespective of maternal HBV DNA titre **(LoE 2; strong recommendation).**	100%
Pregnant women with HBV DNA levels higher than 200,000 IU/ml or HBeAg-positive pregnant women, should start antiviral prophylaxis with tenofovir disoproxil fumarate at week 24–28 of gestation and continue up to 12 weeks after delivery **(LoE 1; strong recommendation).**	100%
In pregnant women with chronic HBV infection and advanced fibrosis or cirrhosis, therapy with tenofovir is recommended **(LoE 2; strong recommendation)**, and those on antiviral treatment with tenofovir should continue the treatment **(LoE 2; strong recommendation).**	100%
Breastfeeding of infants born to mothers treated with tenofovir is safe and should not be discouraged **(LoE 1; strong recommendation).**	100%
HBeAg-positive pregnant women, or those with high HBV DNA levels (>5.3 $\log_{10}$ IU/ml), should be counselled about the high risk of HBV transmission associated with amniocentesis and that non-invasive prenatal testing is preferred **(LoE 2; strong recommendation).**	100%
Screening for HBsAg in the first trimester of pregnancy is recommended, as this is important for recognising and reducing the risk of HBV MTCT **(LoE 1; strong recommendation)**, and HBsAg quantitation can be an accurate predictor of HBV DNA level **(LoE 2; strong recommendation).**	100%
Women of reproductive age with HCV infection should be screened and counselled to undergo antiviral treatment before pregnancy or after delivery and breastfeeding **(LoE 1; strong recommendation).**	100%
If necessary, antiviral therapy with directly acting agents can be considered during pregnancy after a thorough discussion about the potential risks and benefits of treatment with the pregnant woman that includes advice from the multidisciplinary team (including hepatology and obstetric specialists) **(LoE 4; weak recommendation).**	94%
Vaccination of pregnant women identified to be at risk for HAV infection during pregnancy is recommended **(LoE 3; strong recommendation).**	100%
Both hepatitis A vaccine and immunoglobulin for postexposure prophylaxis can be used in pregnancy **(LoE 2; strong recommendation).**	100%
Delivery of the fetus (either preterm birth or therapeutic termination of pregnancy) can be considered to reduce maternal morbidity and mortality in mothers with acute severe hepatitis E and encephalopathy grade I-III **(LoE 4; weak recommendation).**	100%
HELLP syndrome should be considered a manifestation of severe preeclampsia **(LoE 3; strong recommendation).**	95%
Evaluation of serum liver tests is recommended as abnormalities are frequently associated with an adverse maternal outcome in HELLP syndrome, but they should not be used in isolation to guide care **(LoE 3; strong recommendation).**	100%
Platelet transfusion should be considered in pregnant women with a platelet count $<100\times10^9$/L, as this is associated with increased risk of abnormal coagulation and adverse maternal outcomes associated with preeclampsia **(LoE 2; strong recommendation).**	100%

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Recommendations	Consensus
For women with preeclampsia, maternal assessment should include clinical features (blood pressure and proteinuria), as well as biochemical tests as components of multivariate models, *e.g.* fullPIERS model or the PREP model as recommended by obstetric guidelines **(LoE 1; strong recommendation).**	100%
It is advisable for women with a history of prior HELLP syndrome to undergo first-trimester screening to assess the risk of early-onset pre-eclampsia, as this is likely to result in preterm delivery **(LoE 4; weak recommendation).**	n.a.
In the absence of contraindications, following first trimester screening for preterm preeclampsia, women identified at high-risk should receive aspirin prophylaxis commencing before 16+0 weeks' gestation at a dose of 150 mg to be taken every night until either 36 weeks' gestation, when delivery occurs, or when preeclampsia/HELLP syndrome is diagnosed **(LoE 1; strong recommendation).**	100%
In women with low calcium intake (<800 mg/day), either calcium replacement (≤1 g elemental calcium/day) or calcium supplementation (1.5–2 g elemental calcium/day) is suggested as it may reduce the burden of both early- and late-onset preeclampsia **(LoE 2; weak recommendation).**	100%
For women with HELLP syndrome that have non-severe hypertension (systolic blood pressure 140-159 mmHg and/or a diastolic blood pressure 90-109 mmHg), treatment should be initiated using oral labetalol, nifedipine, or methyldopa **(LoE 1; strong recommendation).**	100%
Women with HELLP syndrome that have severe hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg) should be treated urgently in a monitored setting with antihypertensive therapy using oral labetalol, nifedipine or methyldopa. Intravenous therapy with labetalol or hydralazine may be required **(LoE 2; strong recommendation).**	100%
Magnesium sulphate should be given to women with HELLP syndrome with co-existing severe hypertension to prevent eclamptic seizures **(LoE 1; strong recommendation)**, and also as a neuroprotective agent for preterm preeclampsia if delivery is required before 32 weeks' gestation. Dose should be as per local/national guidance **(LoE 2; strong recommendation).**	100%
Corticosteroid treatment should not be given to improve maternal outcomes in HELLP syndrome **(LoE 1; strong recommendation).**	100%
High-dose dexamethasone or betamethasone should be given as per national guidance to improve fetal lung maturity if a pregnancy complicated by HELLP syndrome is to be delivered before 35 weeks' gestation **(LoE 1; strong recommendation).**	100%
Women with HELLP syndrome should be delivered promptly once maternal coagulopathy and severe hypertension have been corrected, as there is evidence for worse maternal outcomes if this is not done **(LoE 2; strong recommendation).**	94%
In women with HELLP syndrome, if there are signs of hepatic failure that may require transplantation, early referral to a transplant centre should be made **(LoE 5; strong recommendation).**	n.a.
Abdominal ultrasound should be performed in women with severe preeclampsia or HELLP syndrome if there are symptoms suggestive of hepatic haematoma, *e.g.*, abdominal, epigastric or right shoulder pain **(LoE 4; strong recommendation).**	100%
Clinicians may be alert to the higher prevalence of hepatic haemorrhage or haematoma in women with HELLP syndrome and markedly reduced platelet count (≤20×10^9/L) **(LoE 4; weak recommendation).**	100%
Women with acute fatty liver of pregnancy who develop encephalopathy, elevated serum lactate (>2.8 mg/dl), a model for end-stage liver disease score ≥30 or who score >7 on the 'Swansea criteria' should be considered for level 2 or 3 care (intensive care admission) **(LoE 3; intermediate recommendation).**	100%
Delivery should be expedited once coagulopathy and remediable metabolic derangements have been treated, and decisions about mode of delivery should be made jointly by obstetricians, hepatologists and the multidisciplinary team **(LoE 5; strong recommendation).**	100%
Based on limited data from small case series, the use of plasma exchange post-delivery may be considered to improve maternal disease severity and decrease the time to recovery in women with acute fatty liver of pregnancy and severe hepatic impairment. There are currently insufficient data to recommend therapy outside clinical centres with expertise in plasma exchange in high-dependency settings or intensive care units **(LoE 4; weak recommendation).**	100%
There are no existing data to support or refute the benefit of N-acetylcysteine treatment in the management of acute fatty liver of pregnancy. However, benefits have been demonstrated in other causes of non-paracetamol-induced liver failure and it can be considered in women requiring admission to intensive care units **(LoE 5; weak recommendation).**	100%
In the subset of women with acute fatty liver of pregnancy who have severe hepatic impairment and may require transplantation, early referral to a transplant centre should be made **(LoE 5; strong recommendation).**	100%
Serum liver tests may be measured in women with hyperemesis gravidarum as they are elevated in 40-50% of severe cases; hyperemesis gravidarum-associated abnormalities are usually mild and self-limiting **(LoE 4; weak recommendation).**	100%
Women with hyperemesis gravidarum who have markedly raised serum liver tests should be screened for a primary liver disease **(LoE 5; strong recommendation).**	94%
Women with intrahepatic cholestasis of pregnancy should be tested for serum bile acid concentrations to identify pregnancies at risk of stillbirth, spontaneous preterm birth, fetal anoxia or meconium-stained amniotic fluid **(LoE 1; strong recommendation).**	100%
In women with confirmed intrahepatic cholestasis of pregnancy, serum bile acids should be measured at least weekly from 32 weeks' gestation to identify those with concentrations ≥40 μmol/L who are at an increased risk of adverse pregnancy outcomes **(LoE 1; strong recommendation).**	100%
In women with post-prandial serum bile acid concentrations ≥100 μmol/L, the risk of stillbirth increases after 35 weeks' gestation, and elective early delivery should be planned at this stage of pregnancy to reduce the risk of fetal death **(LoE 1; strong recommendation).**	100%
Ursodeoxycholic acid should be considered for treatment of maternal pruritus in intrahepatic cholestasis of pregnancy, despite having a relatively small effect on symptoms **(LoE 2; strong recommendation).**	100%
Additional therapies that may improve maternal pruritus can be considered, *e.g.* rifampicin, cholestyramine, guar gum and activated charcoal, but current evidence to support their use is limited **(LoE 4; weak recommendation).**	94%
In women with intrahepatic cholestasis of pregnancy and serum bile acid concentrations ≥40 μmol/L, ursodeoxycholic acid should be offered as a treatment to reduce the risk of spontaneous preterm birth and it may also be protective against stillbirth **(LoE 2; strong recommendation).**	94%
Alterations in total serum bile acid concentrations should be monitored after ursodeoxycholic acid treatment has been commenced as this helps with evaluation of risk of adverse pregnancy outcomes in intrahepatic cholestasis of pregnancy, but clinicians should be aware that ursodeoxycholic acid is also measured by enzymatic total serum bile acid assays **(LoE 2; intermediate recommendation).**	87%
Women with liver diseases of pregnancy that are associated with an increased risk of maternal or fetal morbidity or mortality are suggested to be managed by a multidisciplinary team that should, at a minimum, include a physician, obstetrician and midwife, all of whom should have expertise in the field. If not available locally, patients should be referred to a centre where this multidisciplinary approach can be implemented **(LoE 5; weak recommendation).**	100%
All women with chronic liver disease or a history of gestational liver disease should be offered pre-pregnancy counselling from a team with expertise in management of these disorders **(LoE 4; strong recommendation).**	100%

Abbreviations

AFLP, acute fatty liver of pregnancy; AIH, autoimmune hepatitis; ALBI, albumin-bilirubin; ALD, alcohol-related liver disease; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BP, blood pressure; CHC, combined hormonal contraception; CLD, chronic liver disease; CPGs, Clinical Practice Guidelines; DIC, disseminated intravascular coagulation; EASL, the European Association for the Study of Liver; FGR, fetal growth restriction; FNH, focal nodular hyperplasia; GDM, gestational diabetes mellitus; HAV, hepatitis A virus; HBeAg, hepatitis B e-antigen; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HELLP, haemolysis, elevated liver enzymes, and low platelets; HEV, hepatitis E virus; HG, hyperemesis gravidarum; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; INR, international normalised ratio; IPD, individual participant data; ISSHP, International Society for the Study of Hypertension in Pregnancy; IVF, *in vitro* fertilisation; LT, liver transplant(ation); MELD, model for end-stage liver disease; MTCT, mother-to-child transmission; MASLD, metabolic dysfunction-associated steatotic liver disease; NTPR, National Transplantation Pregnancy Registry; OR, odds ratio; PBC, primary biliary cholangitis; PCOS, polycystic ovary syndrome; PIERS, preeclampsia integrated estimate of risk; RR, relative risk; SAA, splenic artery aneurysm, SGA, small for gestational age; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TSBAs, total serum bile acids; WD, Wilson disease.

Conflict of interest

Please refer to the accompanying EASL disclosure forms for further details.

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Supplementary data

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