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Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases

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Purpose and Scope of the Guidance

This first Practice Guidance on Reproductive Health from the American Association for the Study of Liver Diseases (AASLD) is intended to be a comprehensive reference on adolescents and adults with chronic liver disease. The Guidance specifically (1) addresses management of reproductive health in women and men from puberty to senescence and (2) summarizes the natural history, risk factors, evaluation, and optimal management of liver diseases during pregnancy and after delivery.

Intended for use by health care providers, this Guidance identifies preferred approaches to diagnostic, therapeutic, and preventive aspects of reproductive health. It should not replace clinical judgment for a unique patient, but instead provide general guidance to optimize the care of most patients.

A critical aspect of reproductive care in patients with liver disease is the need for close collaboration among hepatologists, maternal-fetal medicine (MFM) specialists, and pediatricians. Whether for preconception counseling, assisted reproduction, pregnancy, or postpartum care, a multidisciplinary approach is advised to help yield the best outcomes.

This AASLD Guidance provides a data-supported approach to the management of reproductive health in patients with liver disease. It differs from AASLD Guidelines, which are supported by systematic reviews of the literature, formal rating of the quality of the evidence and strength of the recommendations, and, if appropriate, meta-analysis of results using the Grading of Recommendations Assessment, Development, and Evaluation system. In contrast, this Guidance was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of the literature on the topics, with oversight provided by the AASLD Practice Guidelines Committee at all stages of Guidance development. The Committee chose to perform a Guidance on this topic because a sufficient number of randomized controlled trials were not available to support the development of a meaningful Guideline.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ABCB4, adenosine triphosphate–binding cassette subfamily B member 4; ABCB11, adenosine triphosphate–binding cassette subfamily B member 11; AFLP, acute fatty liver of pregnancy; AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, aminophospholipid transporter; ATP7B, aminophospholipid transporter synthase copper transporting beta; ATP8B1, aminophospholipid transporter synthase copper transporting 8B1; BCS, Budd-Chiari syndrome; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CHC, combined hormonal contraception; CI, confidence interval; CNI, calcineurin inhibitor; CT, computed tomography; DAA, direct-acting antiviral; DIC, disseminated intravascular coagulation; DMPA, depot medroxyprogesterone acetate; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; EVL, esophageal variceal ligation; FDA, Food and Drug Administration; FNH, focal nodular hyperplasia; GDM, gestational diabetes mellitus; GEV, gastroesophageal varices; GI, gastrointestinal; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCA, hepatocellular adenoma; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, low platelets; HEV, hepatitis E virus; HSV, herpes simplex virus; IBD, inflammatory bowel disease; ICP, intrahepatic cholestasis of pregnancy; IUD, intrauterine device; IUFD, intrauterine fetal demise; LARC, long-acting reversible contraception; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; LT, liver transplant; MEC, Medical Eligibility Criteria; MELD, Model for End-Stage Liver Disease; MFM, maternal-fetal medicine; MPA, mycophenolic acid; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MTCT, mother-to-child transmission; mTOR, mammalian target

Sexual Function Across Age in Patients with Chronic Liver Disease

In women with advanced liver disease, altered estrogen metabolism and disruption of the hypothalamic-pituitary axis with low follicle-stimulating hormone and luteinizing hormone can lead to anovulation, amenorrhea, and infertility.[1,2] Amenorrhea or oligomenorrhea are seen in more than 25% of women with advanced liver disease[3,4] and nearly three quarters of premenopausal women awaiting liver transplant (LT).[5] Excess alcohol intake can also affect the hypothalamic-pituitary axis or more directly affect ovarian function.[6-8] Although menstrual irregularities are common in cirrhosis,[9] pregnancies occur even in those with decompensated disease, underscoring the need for contraception in women with cirrhosis who wish to avoid pregnancy.

In men with advanced liver disease, low testosterone levels result from hypogonadotropic hypogonadism,[10] with an additional contribution of increased peripheral conversion of androgens to estrogen.[11,12] Free testosterone also declines in part from observed rise in sex hormone–binding globulin (SHBG), although the reasons for SHBG rise in chronic liver disease remain unclear.[13-15] Produced in the liver, SHBG synthesis is stimulated by estrogens, although with further progression from compensated to decompensated cirrhosis, SHBG levels ultimately decline.[16,17] Estrogen levels are also elevated in the setting of portosystemic shunting,[10,18] and increased circulating levels suppress the hypothalamic-pituitary axis,[19] contributing to erectile dysfunction, oligospermia, testicular atrophy, and feminization.[20]

EVALUATION AND MANAGEMENT OF SEXUAL DYSFUNCTION IN CHRONIC LIVER DISEASE

Sexual dysfunction is common in chronic liver disease and may present with erectile dysfunction, dyspareunia, or impaired arousal, lubrication, orgasm or satisfaction.[21,22] Libido can be decreased in the context of chronic illness and hormonal abnormalities.[10,19,23] The differential diagnosis of sexual dysfunction includes psychogenic causes, alcohol use, medication effects (e.g., spironolactone or

of rapamycin; NAFLD, nonalcoholic fatty liver disease; NSBB, nonselective beta-blocker; OR, odds ratio; PBC, primary biliary cholangitis; PCOS, polycystic ovary syndrome; PHT, portal hypertension; PSC, primary sclerosing cholangitis; PT, prothrombin time; SAA, splenic artery aneurysm; SAMe, S-adenosyl-L-methionine; SHBG,, sex hormone–binding globulin; 6-MP, 6-mercaptopurine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UDCA, ursodeoxycholic acid; US, ultrasonography; VTE, venous thromboembolism; WD, Wilson Disease.

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beta-blockers), hypogonadism (including as seen in hemochromatosis), and autonomic dysfunction (as seen in diabetes).[19] Open and directed inquiry in clinic provides an opportunity for patients to identify and disclose sexual dysfunction. A careful history also assesses menstrual patterns and psychosocial health. Laboratory workup may include sex hormone levels and thyroid function, although patients should generally be referred to appropriate specialists for evaluation and management.

GUIDANCE STATEMENT

- Sexual dysfunction is common in chronic liver disease and clinicians should routinely inquire about symptoms. When identified, referral to a specialist may be needed for evaluation and treatment.

PREGNANCY PLANNING IN ADOLESCENTS AND ADULTS WITH LIVER CONDITIONS

Women with chronic liver disease or prior transplant have potential for unique risks in pregnancy, including worsening of underlying liver disease during pregnancy and/or the postpartum period, increased obstetric and/or perinatal complications, as well as potential exposure to liver-related medications that may not be safe for pregnancy or breastfeeding.[24,25] Moreover, because many women with chronic liver disease have impaired fertility,[2,3] the potential for pregnancy may not come to mind for sexually active patients or their clinicians. Thus, reproductive health counseling is critical in this population to ensure the use of safe and effective contraception in those wishing to avoid pregnancy, while ensuring appropriate planning to minimize pregnancy-associated risks in mothers and infants. Clinicians should routinely inquire about family planning, including sexual activity, contraception use, and pregnancy intentions, in all reproductive-aged patients. Pregnancy planning allows clinicians to perform necessary liver-related evaluation before conception, transition the patient from teratogenic medications to regimens that are compatible with pregnancy, and ensure liver disease stability on modified drug regimens. Moreover, pregnancy planning also ensures that patients are informed of the specific risks related to their disease etiology and degree of liver dysfunction, to help guide their decisions on whether to pursue pregnancy.

Unique Aspects in Adolescent Liver Care

Adolescents with chronic illness may struggle with self-management, including acceptance and understanding of their liver disease.[26] Scaffolding support—which may include temporary financial, housing, and emotional support or guidance, with the goal of gradually increasing autonomy of the teenager—is typically provided by family or friends.[27] For those with limited support, health services, including transition coordinators and public health teams, may help with the transition from adolescent to adult care. Approximately 75% of pregnancies among adolescents are unplanned.[28] Long-acting reversible contraception (LARC) has advantages in this setting.[29] Depending on jurisdiction, legal consent for reproductive medical care can vary by age and whether an adolescent is pregnant.[30] Collaboration between pediatric and adult hepatology and MFM specialists is needed to manage pregnant adolescents.[31] Adult providers must recognize the distinct psychosocial needs of most adolescents with chronic liver disease.[32]

Contraceptive Options in Chronic Liver Disease

Contraceptive discussions should incorporate shared decision making with patients to maximize their adherence and satisfaction with selected methods.[33] A common reference for contraceptive safety in women with medical conditions is the Centers for Disease Control and Prevention (CDC) U.S. Medical Eligibility Criteria (MEC).[34] Here we provide recommendations for contraception use in female patients with medical conditions, including those with cirrhosis, hepatocellular adenomas (HCAs), and solid-organ transplant, and note instances in which the AASLD guidance recommendations may differ from the MEC (Table 1).

Combined Hormonal Contraception

Combined hormonal contraception (CHC) medications contain estrogen and progestin. Typical failure rates are approximately 9%.[34,35] General safety

TABLE 1. Contraception in Patients With Liver Disease

	Copper IUD	Hormonal (Progestin) IUD	CHCs (Pill, Patch, Ring)	Progesterone-Only Pills	DMPA Injection	Subcutaneous Implant
Strengths	Failure rate <1%, convenient, does not rely on adherence, no estrogen-associated risks, effective at least 10 years	Failure rate <1%, convenient, does not rely on adherence, no estrogen-associated risks, lightens menses, effective at least 3-5 years	Regular bleeding, lightened menses	No estrogen-associated risks	No estrogen-associated risks, injections every 3 months	Failure rate <1%, convenient, does not rely on adherence, no estrogen-associated risks, effective at least 3 years
Limitations or concerns	Increased menstrual cramping and bleeding (less ideal if anemia or low platelets)	Irregular bleeding common	Typical failure rate 9%, contraindications as denoted subsequently, interacts with P450, associated with hypertension, VTE, and (less commonly) stroke and rare cholestatic liver injury	Typical failure rate 9%, requires strict daily timing, possible conversion of high-dose progestins to small amount of estrogen (unlikely relevant with modern-day, lower-dose progestin preparations), irregular bleeding common	Typical failure rate 6%, irregular bleeding common, can decrease bone density (less favored for liver diseases associated with osteopenia/osteoporosis)	Irregular bleeding common
CDC MEC safety categories/AASLD recommendations						
Cirrhosis						
Compensated	1/Acceptable	1/Acceptable	1/Acceptable	1/Acceptable	1/Acceptable, but less favored	1/Acceptable
Decompensated	1/Acceptable	3/Acceptable	4/Unacceptable	3/Acceptable	3/Acceptable, but less favored	3/Acceptable
BCS	2/Acceptable	2/Acceptable	4/Unacceptable	2/Acceptable	2/Acceptable	2/Acceptable
HCAs	1/Acceptable	3/Acceptable	4/Unacceptable	3/Acceptable	3/Acceptable	3/Acceptable
Posttransplant graft function						
Normal	2/Acceptable	2/Acceptable	2/Acceptable	2/Acceptable	2/Acceptable, but less favored	2/Acceptable
Graft failure	3/Acceptable	3/Acceptable	4/Unacceptable	2/Acceptable	2/Acceptable, but less favored	2/Acceptable

Note: A common reference for contraceptive safety is the 2016 U.S. MEC for Contraceptive Use, developed by the CDC. This reference defines safety categories as follows: 1, no restrictions; 2, benefits generally outweigh theoretical or proven risks; 3, risks may outweigh benefits but safer than pregnancy and may be used if other agents are unavailable or unacceptable to the patient; or 4, unacceptable risk. Here we note contraceptive agents and respective conditions with MEC category 3, which contrasts with the AASLD expert guidance that considers these agents to be acceptable for use: (1) progestin-only contraception, including the progestin IUD in decompensated cirrhosis—historical concerns stem from higher-dose progestins, which may have a small amount of conversion to estrogens, although higher-dose progestins are no longer used in contemporary contraceptive formulations; (2) HCAs—few case reports noted adenoma regression with cessation of agents containing higher-dose progestin, although these formulations are no longer used in contraceptive regimens; (3) IUD use with posttransplant graft failure—few case reports of unplanned pregnancy using older, less effective IUDs (concerns for lower IUD efficacy or increased risk of pelvic inflammatory disease in immunocompromised patients have not been substantiated).

concerns include venous thromboembolism (VTE), hypertension, and rarely stroke, although data in chronic liver disease are limited.[36] CHCs are not advised in Budd-Chiari syndrome (BCS).[34,37-40] Higher-dose CHCs increased the risk of liver enzyme elevations, although current regimens carry no greater risk than placebo.[41-43] Rare cholestatic liver injury has been reported, particularly with higher-dose estrogens.[42,44]

CHCs are considered safe in women with compensated cirrhosis but should be avoided in decompensated cirrhosis due to concerns of impaired estrogen metabolism.[34] Although controlled studies are lacking, these agents are considered acceptable in LT recipients[45] but not in those with graft failure, because of the potential for increased estrogen-associated risks such as VTE. Women with HCAs should also avoid CHCs, as estrogens promote adenoma growth. CHCs affect P450 metabolism; thus, a review for potential drug interactions is warranted. CHCs should be avoided in women with multiple cardiovascular risk factors[34]; therefore, women with nonalcoholic fatty liver disease (NAFLD), in particular, warrant careful review of metabolic profiles. CHCs are acceptable with other chronic liver diseases and are not known to increase liver enzymes or fibrosis progression.[46]

Progestin-Only Agents

Progestin-only pills, depot medroxyprogesterone acetate (DMPA) injections, and the subcutaneous implants do not have estrogen-associated risks.[34] Failure rates with progestin-only pills are approximately 9% and require strict adherence to timing of daily dosing.[34,35] DMPA injections, administered every 12 weeks, have a typical failure rate of approximately 6%[34,35] and delay return to fertility up to 18 months.[47] DMPA has a black box warning for decreased bone density, which normalizes with cessation of use.[48] The subcutaneous implant is considered a LARC agent and has the lowest failure rate (0.05%).[34,35] It is associated with minimal to no bone loss[49] and may be used for up to 3 years. No prospective studies have evaluated HCA growth with progestin-only agents.[50-52]

Intrauterine Devices

Intrauterine devices (IUDs), also considered a form of LARC, have failure rates of less than 1%.[34,35] Effective for at least 10 years, copper IUDs are hormone-free. Progestin-only levonorgestrel IUDs are effective for at least 3 to 5 years. The levonorgestrel IUD lightens or eliminates menstrual bleeding,[53] whereas the copper IUD often increases menstrual bleeding. Data on liver-related risks of levonorgestrel IUD with either decompensated cirrhosis or HCAs are lacking, though none are anticipated given the lack of estrogen.[34] LARC is also favored by adolescents given their convenience and high efficacy, which does not rely on patient adherence.[54] IUD use in solid-organ transplant recipients has been controversial, largely due to early case reports of unplanned pregnancies with older, less effective IUDs. The hypothesis that IUD failures were due to a dampened inflammatory response with immunosuppression[55] has not been substantiated.[56] Initial concern for pelvic inflammatory disease in immunocompromised women using IUDs[55] has been dispelled.[57-60] Thus, IUDs are considered acceptable for use in LT recipients, including those with graft failure.

Perioperative and Emergency Contraception

Contraceptive risk in the perioperative setting is not well studied, although the American College of Obstetricians and Gynecologists does not recommend discontinuation of estrogen-containing contraception following major surgeries in the absence of prolonged immobility and advises that all other agents be continued regardless of postsurgical mobility status.[34,61] This contraceptive strategy is reasonable for LT recipients and living donors.

Emergency contraception can reduce the likelihood of pregnancy in the first 5 days following sexual intercourse. Options include the copper IUD and hormonal contraceptive pills. The copper IUD has the highest efficacy (<1% failure rate).[34] Progestin-only emergency contraception pills should be avoided if body mass index (BMI) is greater than 30 mg/kg^2.[34] There are no data on estrogen-containing emergency contraception in specific liver conditions. Given the short duration of use, these are unlikely to pose harm, although non-estrogen-containing options are preferable in patients with HCAs, BCS, decompensated cirrhosis, or graft failure.

GUIDANCE STATEMENTS

- Clinicians should routinely inquire about sexual activity and pregnancy intentions in all

reproductive-aged adolescents and women with chronic liver disease or liver transplant.
- Adolescents have an increased risk of unplanned pregnancy. Long-acting reversible contraceptives have advantages in this population.
- Pregnant adolescents with chronic liver disease require increased psychosocial support, necessitating close collaborations between pediatric and adult hepatologists, patient support (e.g., social workers), and maternal-fetal medicine specialists.
- Estrogen-containing agents should be avoided in patients with decompensated cirrhosis, BCS, hepatocellular adenomas, and transplant recipients with graft failure.
- Patients using agents other than long-acting reversible contraceptives are encouraged to combine these with a barrier method given their higher failure rates; this is particularly important for women taking teratogenic medications, such as mycophenolic acid (MPA) products.
- All forms of emergency contraception may be used in the setting of chronic liver disease.

ASSISTED REPRODUCTION AND LIVER DISEASE

Although liver disease may be associated with impaired fertility,[62,63] assisted conception in this population is understudied. Infertility is defined as the failure to achieve pregnancy within 12 months of unprotected intercourse or donor insemination in women younger than 35 years of age or within 6 months in women older than 35 years of age.[64] Fertility rates are similar in patients with compensated cirrhosis and the general population but are 40% lower in women with a history of decompensation.[65] Hypothalamic–pituitary dysfunction is associated with an inadequate response to gonadotropic-releasing hormone agonists and clomiphene citrate as well as diminished gonadotrophin release relative to the reduced levels of circulating sex steroids.[7] In the post-LT literature, several case reports describe pregnancies with successful births after assisted reproduction.[66-68] One retrospective review included 18 women with liver disease: 7 who were post-LT patients, 6 with autoimmune hepatitis (AIH), 2 with primary biliary cholangitis (PBC), 1 with hepatitis B, 1 with BCS, and 1 with noncirrhotic portal hypertension (PHT).[69] Of the 18 women, 7 had cirrhosis, and 16 underwent *in vitro* fertilization, of which 3 (18%) failed to conceive after three cycles. In addition, 2 women experienced no liver-related adverse events, and 1 (after LT) developed severe worsening of graft function with hormonal treatment, with improvement in liver graft function with administration of steroids. The remaining 13 women had 16 conceptions. The live birth rate was 50% in patients with cirrhosis and 67% in patients with noncirrhotic liver disease. Data informing the risk of hepatic decompensation are lacking.

GUIDANCE STATEMENTS

- There is no absolute contraindication to assisted reproduction in women with cirrhosis or prior transplant. Preconception counseling for risk stratification is recommended.
- For patients with cirrhosis, the degree of hepatic decompensation is important when considering assisted reproduction, with caution used in Child-Turcotte-Pugh B or C cirrhosis.
- For liver transplant recipients, stability of graft function should be assessed when considering assisted reproduction.

MENOPAUSE, ANDROPAUSE, AND HORMONE THERAPY

Menopause is the process of reproductive aging, characterized by ovarian senescence, hormonal changes, and cessation of menses.[70] Estrogen levels begin to fluctuate during perimenopause, with irregularity of menses. Age-related biochemical and immunologic transitions in combination with hormonal changes influence liver-related health. The benefits of estrogen include inhibition of hepatic stellate cell activity and fibrogenesis[71-73] as well as broader benefits on metabolic health. Hormonal therapy is effective for menopausal symptoms and prevention of bone loss and fractures.[74,75] Patients with advanced liver disease have decreased bone synthesis; increased bone resorption, poor nutritional status, and reduced muscle mass and immobility further increase this risk.[76-80] Hormone replacement therapy is used in the management of menopausal symptoms and bone health. There is concern about cholestatic effects of estrogens, particularly in women with existing cholestatic liver disease. However, topical, oral, and parenteral forms of estrogen-containing hormone therapy appear to be safe in women with PBC.[81,82] Estrogen-containing

menopausal hormone therapy can promote HCA growth.[42] Non-liver-related considerations include risk of VTE, ischemic stroke, and potentially breast cancer,[74,75] and treatment decisions must consider personalized risk-benefit ratios.

In men, testosterone levels gradually decline but may remain within age-appropriate normal range.[83] If testosterone declines below normal levels, symptoms consistent with hypogonadism ensue, an age-related clinical presentation referred to as andropause, late-onset hypogonadism, or testosterone deficiency syndrome. Clinical signs and symptoms of andropause include sexual dysfunction, mood changes, fatigue, and loss of bone mass that warrant treatment with testosterone replacement therapy.[84] Low testosterone levels are also observed in men with advanced liver disease and are associated with sarcopenia, which is a predictor of mortality in patients with cirrhosis.[85,86] Benefits of testosterone therapy in men with cirrhosis, including those with decompensated disease, include significant increases in muscle and bone mass, with a trend toward lowering mortality.[87] However, testosterone repletion may be associated with myocardial infarction or stroke,[88] and testosterone levels that prompt replacement vary by clinical symptoms.[89,90] Testosterone replacement therapy may be associated with transient elevations in liver enzymes that are usually self-limited.[42]

An emerging area of clinical importance is transgender health, including the interplay of sex hormones and liver disease in this population. Clinicians should be prepared to support or refer transgender patients and to eliminate barriers to care. Limited data suggest effects of hormonal alterations on risk of hepatic steatosis and metabolic health in transgender patients.[91,92] Female-to-male transgender patients should be screened for liver abnormalities and polycythemia before initiation of high-dose androgen therapy.[93] Male-to-female transgender patients receiving estrogen therapy should work in coordination with their hepatologist during transition. A welcoming and supportive environment for transsexual individuals seeking hepatology care is important.[94]

GUIDANCE STATEMENTS

- Menopausal hormone therapy should not be used in women with decompensated liver function, BCS, or hepatocellular adenomas.
- Testosterone replacement may be used in hypogonadal men with chronic liver disease.

Evaluation of Liver Disease in Pregnancy

INITIAL EVALUATION OF A PREGNANT PATIENT WITH LIVER DISEASE

Normal Physiologic and Biochemical Changes in Pregnancy

Many physiological and hormonal changes occur in pregnancy, and these changes can mimic those seen in chronic liver disease. Pregnancy is associated with increased circulating plasma volume, heart rate, and cardiac output as well as decreased systemic and splanchnic vascular resistance (Fig. 1). Blood volume and red blood cell mass increase gradually during pregnancy. Cardiac output increases up to 50% in the third trimester,[95] although absolute hepatic blood flow remains unchanged, as the liver receives a lower percentage of the cardiac output.[96] This resultant hyperdynamic state is similar to the systemic changes seen in decompensated cirrhosis. These physiological changes may impair clearance of substances with hepatic metabolism[97,98] and lead to decreased gallbladder motility with an increased risk of developing gallstones.[99] In pregnant women without underlying liver disease, clinically insignificant esophageal varices can occur in the latter part of pregnancy due to compression of the inferior vena cava by the gravid uterus and a reduction in venous return.[100] Spider angiomas and palmar erythema, presumably related to the hyperestrogenic state, can also develop.[101] The liver is generally not palpable but can be displaced upward as the gravid uterus enlarges.

Liver Biochemistry Changes During Normal Pregnancy

Normal changes include an increase in alkaline phosphatase of placental origin and an increase in alpha-fetoprotein of fetal liver origin (Table 2). Albumin levels decrease during the second half of pregnancy due to hemodilution. However, serum aminotransferases,

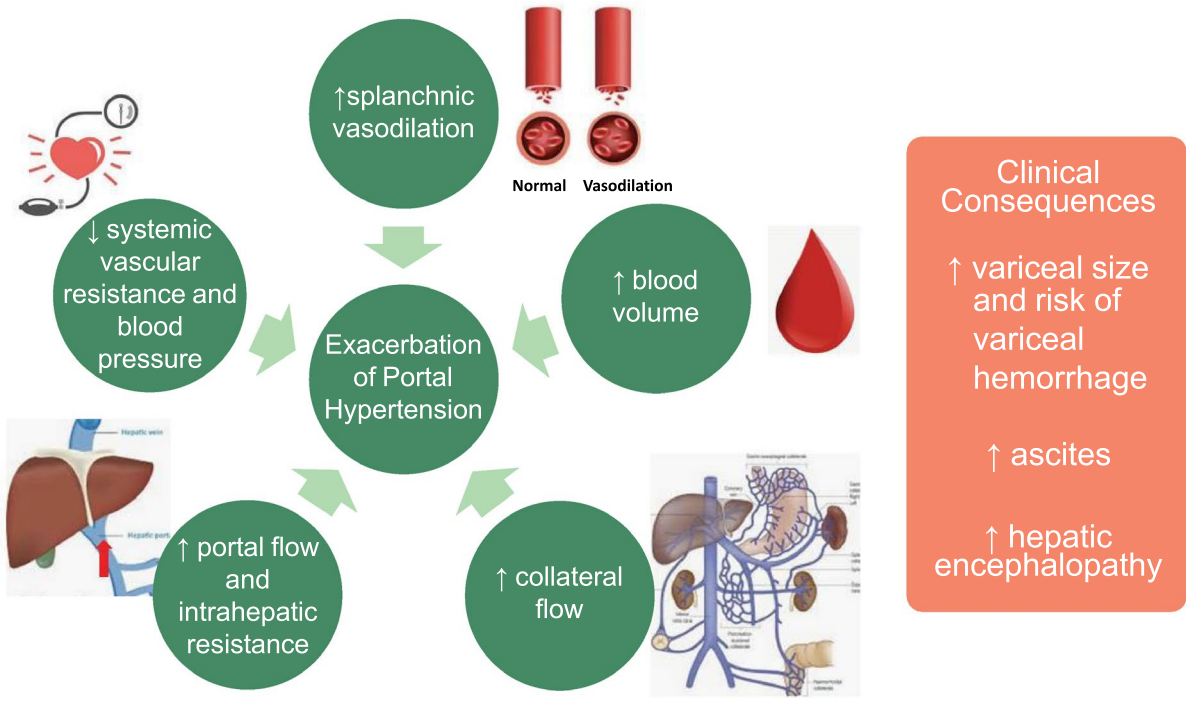

FIG. 1. Physiologic changes and resultant portal hypertensive complications in pregnant patients with chronic liver disease. Many of the physiological and hormonal changes that occur in pregnancy mimic those seen in patients with cirrhosis and PHT. The clinical consequences of these changes are the development of *de novo* or worsening varices, ascites, or hepatic encephalopathy.

TABLE 2. Liver-Related Biochemistry in Normal Pregnancy

Liver Biochemistry	1st Trimester	2nd Trimester	3rd Trimester
ALT and AST	Normal	Normal	Normal
Gamma-glutamyl transferase			
Bilirubin			
Bile acids			
Alkaline phosphatase		Increased	Increased
Albumin	Normal/decreased	Normal/decreased	Normal/decreased
AFP	Normal/increased	Increased	Increased

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase.

bilirubin level, prothrombin time (PT), gamma-glutamyltransferase, and total bile acid levels remain normal throughout pregnancy, and any elevation should be evaluated. Clotting factors II, V, VII, X, XII, and fibrinogen are increased, increasing hypercoagulability.

Liver dysfunction in pregnancy is best categorized as diseases unique to pregnancy, exacerbated by pregnancy, or coincidental to pregnancy. Diseases unique to pregnancy include hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (ICP), acute fatty liver of pregnancy (AFLP), and the spectrum of hypertensive disorders, including preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome (Fig. 2). Each disorder typically occurs within a specific trimester, but overlap does occur.[102] Diseases exacerbated by pregnancy

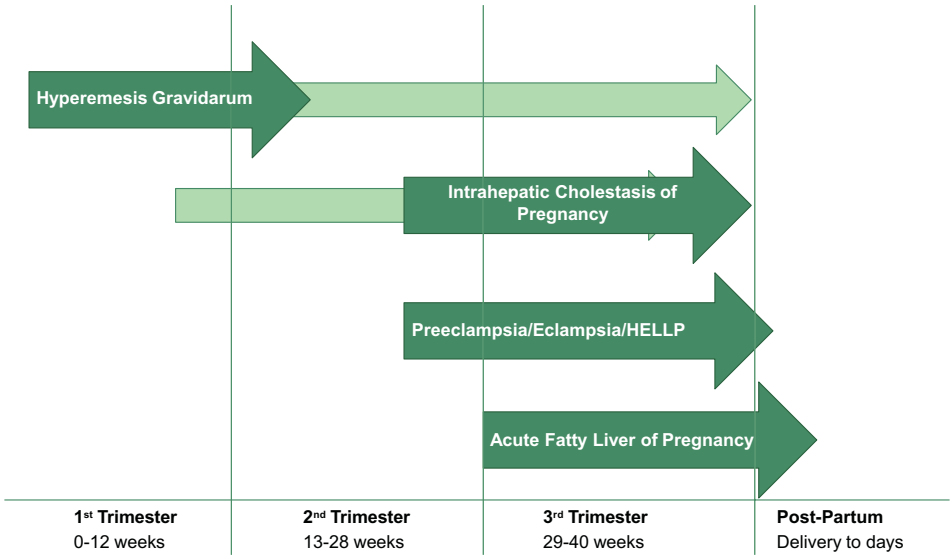

FIG. 2. Typical time of onset for diseases unique to pregnancy. Hyperemesis gravidarum typically occurs in the first trimester; rarely, symptoms can persist throughout the pregnancy. ICP typically presents after 30 weeks of gestation but has been reported in the first trimester. Preeclampsia by definition occurs after the 20th week of gestation, and HELLP between weeks 27 and 37. AFLP occurs in the third trimester (week 29 and beyond) and, rarely, postpartum.

include gallstones, vascular diseases, and cirrhosis. Additionally, the natural history of chronic liver diseases may be affected by pregnancy or require unique management during pregnancy or lactation, as discussed in subsequent sections.

Evaluation is similar to nonpregnant patients (Fig. 3) and must include a thorough history (including travel, environmental, and drug exposures), physical examination, and focused serologic testing. Hepatic ultrasonography (US) is the favored initial imaging modality. Diagnosis can usually be determined without liver biopsy.

GUIDANCE STATEMENT

- Elevation in aminotransferases, bilirubin, or bile acids in pregnancy is abnormal and requires investigation.

Abdominal Imaging in Pregnancy

Abdominal US without Doppler is the imaging modality of choice given the lack of ionizing radiation and absence of known fetal risks.[103,104] Doppler interrogation of the hepatic vasculature can be safely conducted in all trimesters of pregnancy, but exposure time should be minimized. Use of US contrast agents is not widely accepted because lung hemorrhage has been seen in some animal models.[105] If further imaging is needed, computed tomography (CT) or magnetic resonance imaging (MRI) without gadolinium can be used, but MRI is the preferred modality in all trimesters. Magnetic resonance cholangiopancreatography (MRCP) without contrast can provide additional benefit for suspected choledocholithiasis not visualized on US.[106] MRI with gadolinium should be avoided throughout pregnancy, because gadolinium crosses the placenta and can accumulate in the fetal urinary tract where it is later excreted in amniotic fluid, thereby increasing fetal exposure.[107]

The deleterious effects of fetal radiation are dependent on the radiation dose and the stage of fetal development at the time of exposure.[108] Radiation of less than 50 mGy in the first 2 weeks of gestation may have an "all-or-none" effect before implantation. The risk of teratogenicity occurs between weeks 2 and 8. There is an association with intellectual deficit between weeks 8 and 25, but this is considered a lower risk after week 15. After week 25, the risks are minimal.[109,110] The currently accepted cumulative dose of ionizing radiation to the fetus is less than 50 mGy (Table 3).[111,112]

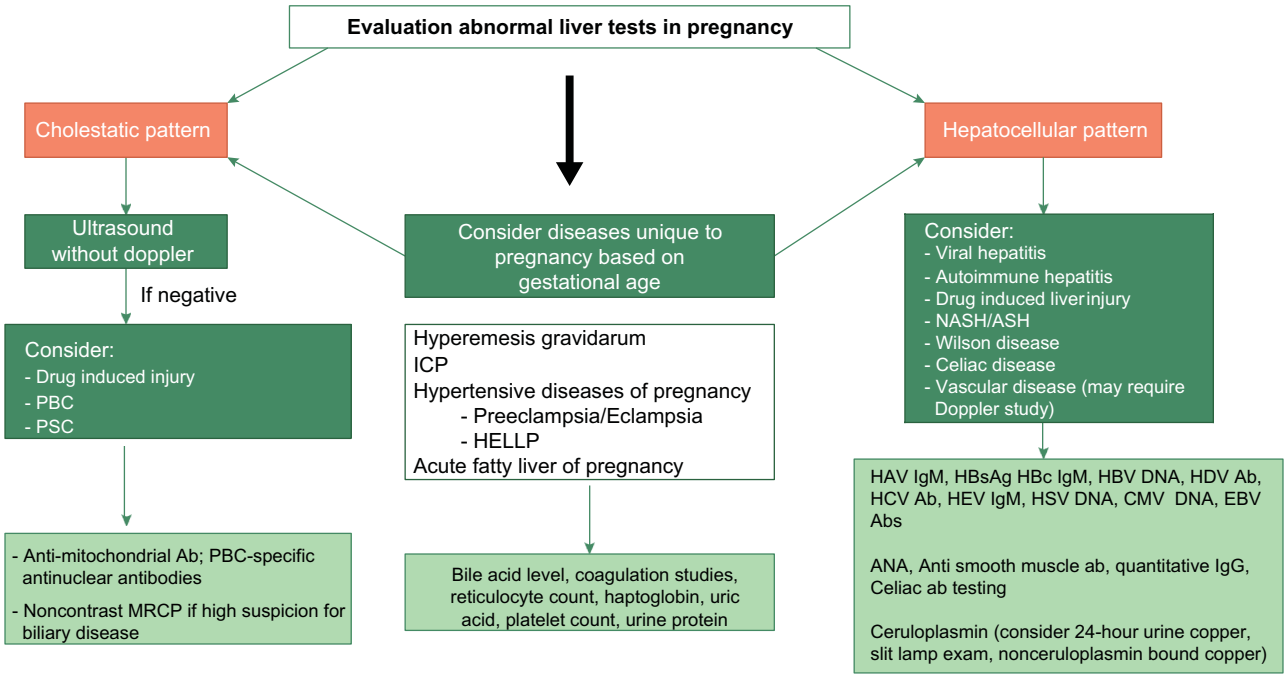

FIG. 3. Evaluation of abnormal liver tests in pregnancy. The approach to abnormal liver tests in pregnant patients is similar to nonpregnant patients. The pattern of liver test abnormality guides the diagnostic workup with concurrent consideration of diseases unique to pregnancy that may present during a given trimester. Abbreviations: Ab, antibody; ANA, anti-nuclear antibody; ASH, alcohol-associated steatohepatitis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HDV, hepatitis D virus; IgG, immunoglobulin G; IgM, immunoglobulin M; NASH, nonalcoholic steatohepatitis.

TABLE 3. Radiation Exposures With Common Procedures

Modality	Fetal Dose (mGy)	Maternal Dose (mSv)
CT abdomen/pelvis (no contrast)	13-25	3-45
Chest, two views	0.0005-0.01	0.06-0.29
Abdominal radiography	0.1-0.3	0.01-1.1
Double-contrast barium enema	1.0-20	2.0-18.0
Small-bowel examination	7	3.0-7.8
Endoscopic retrograde cholangiopancreatiography*	0.1-0.3	2-6

*Varies widely depending on duration of fluoroscopy.

Iodinated contrast can potentially cause neonatal hypothyroidism, but most CT studies now use non-ionic contrast, which has no effect on the thyroid gland. There is not an absolute contraindication to the use of iodinated contrast agents in pregnancy, but their use is recommended only if absolutely required to obtain diagnostic information that would affect the care of the fetus or mother. Breastfeeding after iodinated contrast (or gadolinium) is considered safe, because less than 0.01% of CT contrast (<0.04% of gadolinium) is present in breast milk, and even less is absorbed by the infant's gastrointestinal (GI) tract.[107,113]

Elastography has not yet been approved by the Food and Drug Administration (FDA) in pregnancy, and changes related to pregnancy may affect liver stiffness[114] and confound interpretation of results.

GUIDANCE STATEMENTS

- Abdominal US without contrast is the preferred imaging modality throughout pregnancy. Limited Doppler study of hepatic vasculature can be used, but exposure time should be minimized.
- MRI/MRCP without gadolinium is preferred over CT imaging. Gadolinium is contraindicated in pregnancy.
- Abdominal CT without contrast is generally safe, but the cumulative ionizing radiation exposure should be as low as possible and less than 50 mGy.
- Use of iodinated contrast is recommended only if essential.

- There are insufficient data to recommend use of elastography during pregnancy.
- Breastfeeding is safe after iodinated or gadolinium contrast.

Management of Chronic Liver Diseases During Pregnancy and Lactation

Pregnancies in women with liver disease should be comanaged by hepatologists, MFM specialists, and pediatricians as needed.

HEPATITIS B

Pregnancy provides an important opportunity to identify hepatitis B virus (HBV)-infected women and implement measures to prevent mother-to-child transmission (MTCT). All women should be tested for hepatitis B surface antigen (HBsAg) with prenatal labs,[115] with HBV-DNA testing performed if positive.[116] For women negative for HBV markers, vaccination should be considered and is safe in pregnancy.[117]

Regarding antiviral safety, lamivudine, telbivudine, and tenofovir disoproxil fumarate (TDF) have been studied extensively, with no associated teratogenicity, even in the first trimester,[118] and no increased risk of congenital malformations, prematurity, or low Apgar scores (Table 4).[119] Lamivudine and telbivudine have higher rates of resistance than TDF; thus, TDF is preferred in pregnancy. There are insufficient data on the other preferred HBV antivirals, entecavir and tenofovir alafenamide (TAF), to recommend their use in pregnancy.[116] For women with active chronic hepatitis B who wish to complete a finite course of treatment before conceiving, peginterferon for 12 months may be considered.[116]

Women on antiviral therapy who become pregnant must decide whether to continue antiviral therapy or stop and, if continued, whether to change antivirals if not currently on TDF. Although there are no identified teratogenic effects of non-TDF antivirals, most experts recommend switching to TDF if treatment is continued during pregnancy. Stopping treatment depends on the likelihood and consequences of relapse. Women with advanced fibrosis should not stop therapy, given concerns for decompensation with a clinically significant flare.

Chronic hepatitis B has little influence on the course of pregnancy. Alanine aminotransferase (ALT) flares, variably defined, have been reported during pregnancy and postpartum periods, with greater frequency following discontinuation of antivirals. Most ALT flares are asymptomatic, although underlying advanced fibrosis may lead to clinically severe flares.[120] Hepatic flares occur in 3.5% to 25% of women within the first 3 months after delivery or cessation of antiviral treatment; therefore, monitoring is recommended.[121,122]

Prevention of MTCT of HBV is important. Although infant vaccination and hepatitis B immunoglobulin (HBIG) are highly effective, prophylaxis failure occurs in up to 15% of pregnancies.[123-126] Timeliness of HBV vaccine and HBIG affects success, with vaccination within 12 hours of birth recommended.[127] HBV viral load at delivery is an additional risk factor for prophylaxis failure, and risk of MTCT is extremely rare if HBV DNA is below 200,000 IU/mL. Antiviral therapy in the third trimester is associated with a 70% reduction in MTCT compared with no antiviral therapy (7.5% vs. 27%).[119] The preferred drug is TDF, starting at 28 to 32 weeks' gestation, with reductions in MTCT from 18% to 5%.[123] Earlier initiation of antiviral treatment should be considered for HBV-DNA levels of 7-log IU/mL or greater, to ensure sufficient time to achieve HBV-DNA levels of less than 200,000 IU/mL at delivery.[126] Treatment can be stopped after delivery, with no clear benefit on ALT flares if the antiviral is stopped at delivery versus 1 to 3 months postpartum.[122,128]

Cesarean delivery has not been shown to reduce risk of MTCT[129] and should be used for obstetrical indications only. Theoretically, prolonged rupture of membranes or labor may expose infants to HBV, particularly in mothers with high-level viremia. However, appropriately administered infant immunoprophylaxis appears to negate this risk. Amniocentesis may increase MTCT risk, particularly in highly viremic women (i.e., ≥7 $\log_{10}$ IU/mL).[130-132] The potential risk should be disclosed to parents. In high-risk pregnancies in which invasive procedures are anticipated, earlier use of antiviral therapy may be considered, although data to support this practice are limited.[124]

TABLE 4. Reproductive Considerations for Medications Commonly Used in Patients With Liver Disease

Medication	Pregnancy	Lactation	Fertility	Historical FDA Classification
Acamprosate	Animal data suggest risk of fetal abnormalities; human data are limited; decision about use involves careful consideration of risks of continued alcohol use versus medication exposure	Limited human data Careful consideration of risks of continued maternal alcohol use vs. medication exposure	No human data	C
Acyclovir	Compatible	Compatible	Animal data demonstrated testicular atrophy and aspermatogenesis; human data do not demonstrate this	B
Antihistamines (chlorpheniramine, diphenhydramine, hydroxyzine)	Compatible	Compatible in low doses High doses may be associated with sedation in infants or decreases in breast milk supply Hydroxyzine is less preferred due to limited data reporting adverse reactions (mostly sedation) in infants	No human data	Chlorpheniramine: B Diphenhydramine: B Hydroxyzine: C
Beta-blockers (carvedilol, nadolol, propranolol)	Carvedilol: no data	Carvedilol: no data	Carvedilol: Animal studies suggest protection from diabetes mellitus–induced testicular damage; no human data	Carvedilol: C
	Nadolol, propranolol: overall compatible despite reports of intrauterine growth restriction, neonatal respiratory depression, and infant hypoglycemia	Nadolol: less preferred due to extensive level of excretion into breast milk and its renal excretion	Nadolol: no adverse effects on fertility in animals; no human data	Nadolol: C
	Propranolol is preferred; shorter half-life and less protein-bound than nadolol	Propranolol: compatible; highly protein bound and excreted in milk in small amounts	Propranolol: associated with impotence in men; no data in women	Propranolol: C
Cephalosporins (cefotaxime, ceftriaxone)	Compatible	Compatible	Cefotaxime: animal data showed no adverse effect on fertility; no human data available Ceftriaxone: animal data are mixed, showing decreased sperm concentration and motility in some studies and no effect on fertility in other studies; no human data available	B
Cholestyramine	Compatible High doses can lead to vitamin K deficiency and increased risk of fetal hemorrhage	Compatible	No human data	C
D-penicillamine	Teratogenicity has been documented, but discontinuation in pregnancy may also have deleterious maternal effects May continue with dose adjustments made across pregnancy	Limited data suggest that it is not detectable in human breast milk and that it is compatible with breastfeeding Copper and zinc levels are reduced in the breast milk of women taking D-penicillamine	No data	D

TABLE 4. *Continued*

Medication	Pregnancy	Lactation	Fertility	Historical FDA Classification
DAA agents for HCV (glecaprevir/pibrentasvir, ledipasvir/sofosbuvir, sofosbuvir/velpatasvir)	Glecaprevir/pibrentasvir, ledipasvir/sofosbuvir: no birth defects reported in animal data	Detected in rat milk	No effect on fertility in rats	Glecaprevir/pibrentasvir, sofosbuvi/velpatasvir: none assigned
	Increase in visceral malformations with exposure of velpatasvir alone in rabbits	No human data	No human data	Ledipasvir/sofosbuvir: B
Disulfiram	Associated with fetal malformations	Avoid	No data	None assigned
	Decision about use involves careful consideration of risks of continued alcohol use versus medication exposure			
Entecavir	Avoid due to insufficient data	Avoid due to insufficient data	No human data	C
Fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin)	Avoid due to toxic effects on developing cartilage in animal studies and reports of arthralgias and tendonitis in adolescents	Compatible with monitoring for infant GI infections (*Clostridioides difficile, Candida*) that have been reported with use in lactating women	Animal data are mixed, showing sperm DNA impairment and impaired sperm motility in some studies and no effect on fertility in other animal studies; limited human data available	C
Heparin (low-molecular-weight heparin)	Compatible	Compatible	Animal studies indicated no effect on fertility; no human data	B
Lamivudine	Compatible	Compatible	No adverse effect on fertility in animal studies; no human data	C
Naltrexone	Compatible	Compatible	Limited data suggest possible restoration of ovulation in patients with ovulation disorders	C
Obeticholic acid	Avoid due to lack of data.	Avoid due to lack of data.	No data	None assigned
Octreotide	Careful consideration for use; advise use in setting of acute variceal bleed, as benefits outweigh risks	Limited human data suggest compatibility	No increased adverse effects on fertility in females; no human data in men	B
	Limited human data (reports of fetal growth restriction but no congenital malformations)	Poor excretion into breast milk due to its high molecular weight		
Pegylated interferon alpha	Human data report successful use of interferon alpha; animal data report abortifacient potential	Unlikely to pose risk due to low levels in milk and poor absorption by infant	Animal data suggest association with impaired fertility	C
	Use if potential benefit outweighs potential risk			
Ribavirin	Avoid due to teratogenicity and embryocidal effects observed in multiple animal studies	No data in lactating mothers treated for hepatitis C infection	Avoid use in women and men for 6 months before conception	X
Rifampin	Compatible	Compatible	May decrease effectiveness of some oral contraceptives due to hepatic enzyme induction	C
	Due to induction of P450 hepatic enzymes, it may be associated with vitamin degradation and subsequent hemorrhage in neonates (prophylactic vitamin K has been recommended)	Detectable in breast milk at low levels	No other fertility data available	

TABLE 4. *Continued*

Medication	Pregnancy	Lactation	Fertility	Historical FDA Classification
S-adenosylmethionine	Compatible	No data	Insufficient data Single study reported increase in sperm motility	None assigned
Tenofovir (tenofovir disoproxil fumarate; TAF)	Tenofovir disoproxil fumarate: compatible	Tenofovir disoproxil fumarate: no contraindication for use	Tenofovir disoproxil fumarate: limited human data suggest no adverse effect on fertility in men	Tenofovir disoproxil fumarate: C
	TAF: no human data	TAF: no human data	TAF: no data	TAF: none assigned
Terlipressin	Avoid: data demonstrate that it can cause uterine contractions and decreased uterine blood flow	No data: unknown if terlipressin is excreted into breast milk	No data	Currently not FDA approved
Trientine	Compatible with dose adjustments made across pregnancy	Limited data suggest that it is not detectable in human milk and compatible with breastfeeding Conflicting data on whether copper and zinc levels are reduced in the breast milk of women taking trientine	No data	C
UDCA	Compatible	Compatible	Limited animal data suggest no adverse effects on fertility	B
Zinc	Compatible	Maternal zinc supplementation does not alter zinc concentrations in breast milk	No adverse effect on fertility in men	C

Note: These FDA classifications are no longer used to guide medication safety in pregnancy. Instead, the specific risks and benefits should be interpreted within the clinical context for an individual patient. Historical FDA classifications: A, adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, with no evidence of risk in later trimesters; B, animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; C, Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; and X, studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh the potential benefits.

Breastfeeding is not contraindicated,[133] even in the presence of cracked or bleeding nipples, as infants are protected by vaccination and HBIG. Antiviral therapy with lactation is also not contraindicated, because studies have shown low levels of TDF and lamivudine in breast milk and substantially lower drug exposures than in utero.[134]

GUIDANCE STATEMENTS

- All pregnant women should be tested for HBsAg. Women newly identified as HBsAg-positive should be linked with a clinician knowledgeable in the long-term management of HBV.

HBsAg-positive pregnant women:

- Should be informed of the increased risk of MTCT with invasive pregnancy procedures, such as amniocentesis.
- Require quantification of HBV DNA in the second trimester, and if maternal HBV DNA is greater than 200,000 IU/mL, antiviral therapy should be started between gestational weeks 28 and 32, to reduce the risk of MTCT. Antiviral therapy can be stopped at delivery or up to 3 months postpartum.
- If antiviral therapy is required, TDF is preferred. There are insufficient safety data to recommend entecavir or tenofovir AF.
- Monitoring of ALT and HBV DNA for 6 months postpartum or after cessation of antivirals is recommended.
- Breastfeeding is not contraindicated, even in women who continue on antiviral therapy.

HEPATITIS C

The prevalence of hepatitis C virus (HCV) infection among reproductive-aged women has doubled in recent years, reflecting higher rates of injection drug use.[135] Identification of HCV-infected women of reproductive age is important in order to prioritize HCV treatment before conception. Limitations of risk-based screening are well recognized,[136] and universal screening is recommended[137,138] and cost-effective.[139,140] Women screening positive for HCV during pregnancy should be linked with a clinician who can address the timing of antiviral therapy postpartum.[138]

HCV is not thought to directly affect fertility or fertility interventions, although data are limited.[141,142] Adverse pregnancy outcomes are reported more frequently in antibody to HCV (anti-HCV)-positive versus anti-HCV-negative women, with a meta-analysis of 5,218 women showing a 1.6-fold higher odds of preterm birth, even after adjustment for age, parity, and tobacco and alcohol use.[143] Because HCV-positive women often have higher rates of substance abuse and medical comorbidities as well as lower socioeconomic status, these and other unmeasured factors may account for observed differences. HCV-infected women have a higher incidence of ICP, with a pooled odds ratio (OR) of 20.4 (95% confidence interval [CI], 9.4-44.3).[144] Although the mechanism is unclear, a direct cytopathic effect on biliary epithelial cells has been proposed. The course of HCV infection is not affected by pregnancy, and no specific monitoring is needed. Spontaneous clearance of HCV postpartum has been reported in up to 25% of women, typically within 12 months.[145] Thus, confirmation of HCV-RNA status before postpartum treatment is prudent.

MTCT can occur intrapartum, peripartum, or postpartum. The risk of MTCT is 5.8% (95% CI, 4.2-7.8) in mothers with HCV viremia and 10.8% (95% CI, 7.6-15.2) in HCV–human immunodeficiency virus coinfection.[146] Although some studies have found an association with level of viremia, a precise threshold has not been identified.[146] Available data suggest intrapartum transmission may account for up to 40% of MTCT events,[147] but peripartum is the highest risk period. If invasive prenatal testing is necessary, amniocentesis with avoidance of placental contact is favored over chorionic villus sampling and fetal blood sampling.[148] However, these recommendations reflect the goal of avoiding maternal–fetal blood contact and lack empiric evidence. Mode of delivery does not influence risk of MTCT, but the avoidance of invasive fetal monitoring and episiotomy is recommended, as well as avoiding prolonged rupture of membranes.[148,149] The best quality study suggests MTCT risk increases with ruptured membranes beyond 6 hours (adjusted OR, 9.3; 95% CI, 1.5-180).[150]

HCV-infected women may breastfeed, as postpartum risk of HCV transmission is negligible. HCV can be detected in the breast milk in 0% to 20% of viremic women but at low titers.[151,152] A systematic review

performed for the U.S. Preventive Services Task Force analyzed 14 cohort studies that included 2,971 participants and found no significant association between breastfeeding and HCV transmission.[149] Nonetheless, most clinicians recommend temporary discontinuation of breastfeeding if skin breakdown with associated bleeding is present.

The safety of current direct-acting antivirals (DAAs) has not been studied extensively in pregnant women. Data from one small safety study[153] and from unplanned pregnancies in women on therapy[154] found no increase in congenital or newborn complications among exposed women. However, the number of DAA-exposed women is small, and treatment during pregnancy is not currently routinely recommended. For women on therapy who become pregnant, the decision to continue therapy requires careful consideration of (1) risk for virologic relapse; (2) risk of MTCT; (3) access and financial concerns; (4) patient and clinician preferences; and (5) limited safety data on DAAs in pregnancy. Ribavirin has embryocidal and teratogenic effects and is contraindicated during pregnancy. Both women and men taking ribavirin as part of their DAA regimen must use highly effective contraception and defer conception for at least 6 months after the last ribavirin dose.

Passive transfer of HCV antibody from mother to child occurs and can persist for up to 18 months of age.[155] In a study of 29 babies born to HCV-viremic mothers who tested positive for anti-HCV after birth, 10% were still anti-HCV-positive at 12 to 18 months of age, but only 5% were still HCV-RNA-positive beyond 12 months.[155] Thus, children born to HCV-infected mothers should be tested for anti-HCV after 18 months of age.[138,156] Infants who test positive for anti-HCV require HCV-RNA testing to confirm viremia and referral to a pediatrician with expertise in HCV care if infected. Until the infant's HCV status is known, parents should be educated about HCV and the precautions needed to prevent transmission to others.[156]

GUIDANCE STATEMENTS

- Pregnant women should be tested for HCV during each pregnancy, and those testing positive should be evaluated for antiviral therapy after completion of pregnancy and breastfeeding.
- Preconception antiviral therapy should be prioritized for HCV-infected women of childbearing age, to eliminate the risk of MTCT during pregnancy.
- For women or men whose HCV therapy includes ribavirin, highly effective contraception is required, and conception should be deferred for at least 6 months following last ribavirin use.
- There are insufficient safety data on DAAs to recommend their use in pregnancy as a means of reducing MTCT.
- HCV-infected women requiring invasive pregnancy procedures, such as amniocentesis, should be informed of the possible risk of MTCT.
- To reduce MTCT in HCV-infected women, prolonged rupture of membranes, invasive fetal monitoring, and episiotomies should be avoided.
- Monitoring for ALT flares in HCV-infected women is not required during pregnancy and postpartum.
- Breastfeeding is not contraindicated in HCV-infected women, but not recommended during antiviral therapy. In addition, caution is needed if skin breakdown occurs with associated bleeding of nipples.

WILSON DISEASE

Wilson disease (WD) is associated with mutation on the aminophospholipid transporter (ATP) synthase (ATPase) copper transporting beta (*ATP7B*) gene, which encodes for the copper transporting P-type ATPase or copper translocase ATP7B. ATP7B is expressed on the ovaries, uterus, and placenta, with possible direct effects of copper on pregnancy outcomes. Women with WD have higher rates of infertility and spontaneous abortion.[157] Although not well studied, oligomenorrhea and amenorrhea may indicate some degree of hormonal dysregulation.

Preconception counseling is desirable to optimize pregnancy outcomes. Treatment of WD includes use of chelating agents, trientine and D-penicillamine, to increase urinary copper excretion or zinc salts to reduce intestinal copper absorption (Table 4). D-penicillamine is associated with teratogenicity in humans,[158] trientine is associated with teratogenicity in nonhuman animals, and zinc is not teratogenic.[159] The limited data on pregnancy outcomes in WD make it difficult to ascertain whether the risks of birth defects are increased. In a large cohort of 282 pregnant women with WD, 162 of whom were on chelating agents (118

on D-penicillamine, 36 on trientine, and 8 on chelator plus zinc), birth defects occurred in 3%, similar to the general population.[160] Smaller series reported no birth defects among women on chelating agents.[161,162] Spontaneous abortion occurred in 10% treated with zinc and D-penicillamine compared with 17% in undiagnosed women and 36% of those who stopped treatment.[160] Women maintained on WD therapy appear less likely to spontaneously abort.[161,163]

Overchelation and copper deficiency may adversely affect the fetus; thus, dose adjustments are necessary during pregnancy. The AASLD WD guidance recommends dose reduction of chelator therapy in pregnancy but no dose adjustment for zinc.[164] Chelating agents should be reduced to the minimum necessary during pregnancy, typically 25% to 50% of the prepregnancy dose.

Postpartum, chelating agents should be up-titrated to prepregnancy levels with adjustments guided by 24-hour urine copper and serum-free copper levels. All medications for WD are excreted in breast milk and may cause infantile copper deficiency. Additionally, ATP7B is expressed in the mammary tissue and influences delivery of copper into breast milk[165] and may lead to inadequate copper for the newborn's metabolic and developmental needs. Therefore, breastfeeding is not generally recommended. Regarding contraception, copper IUDs were historically avoided, but absorption of copper is minimal and should not influence contraception selection.

GUIDANCE STATEMENTS

In women with WD:

- Preconception counseling should include genetic counseling and discussion of medication safety in pregnancy.
- Use of zinc is safe in pregnancy and delaying conception until the patient is on zinc monotherapy should be encouraged.
- Chelating agents should be continued during pregnancy due to the high risk of spontaneous abortion if withdrawn. Dose reductions in the second and third trimesters are required.
- Close monitoring of copper balance is necessary to avoid overchelation during pregnancy. Chelating agents require up-titration to prepregnancy doses after delivery.
- Breastfeeding is associated with infant risks, as all WD drugs are excreted in breast milk, and there is risk for copper deficiency in the infant.

AUTOIMMUNE HEPATITIS

In the absence of cirrhosis, women with AIH do not have reduced fertility.[166] Serum aminotransferase levels tend to improve during pregnancy, with spontaneous remissions reported.[167-169] Flares can occur at any time during and after pregnancy, with rare cases of urgent LT reported.[170] The highest risk period for ALT flares is postpartum, typically within the first 3 months after delivery, with rates of 13% to 55% (median, 27%) reported.[170-175] Risk factors for flares include lack of immunosuppressive therapy and shorter duration of remission before conception (less than 1 year).[170,173] *De novo* AIH has been reported in the postpartum period.[176,177]

Maternal risks are primarily related to risk of flares with worsening of liver function, which are particularly serious in women with cirrhosis. Decompensation during and within 3 months of delivery, need for LT intrapartum or within 12 months of delivery, or death occurred in 11% of pregnancies, with a higher risk of serious events in women with cirrhosis (21% vs. 4%).[170] Women with AIH have higher rates of preterm birth, small for gestational age infants, and fetal losses. Fetal losses are reported in up to 29%, although some reports include early miscarriages and terminations.[171,174,175]

Minimal immunosuppression adjustment during pregnancy reduces the risk of flare during pregnancy and postpartum. An increased risk of early postpartum flare should be anticipated. For women whose immunosuppression was reduced in pregnancy, a preemptive increase in immunosuppression back to prepregnancy levels is advised, with close liver-enzyme monitoring during this period.

Azathioprine has been associated with congenital malformations in pregnant mice,[178] but an increased risk of teratogenicity is not established in humans (Table 5).[166,171,174] Thus, thiopurines may be used in pregnancy. Small amounts of thiopurine metabolite can be detected in breast milk,[179] but this has not been associated with significant adverse infant outcomes. Prednisone[180] is considered low risk in pregnancy and may be considered as monotherapy in women with well-controlled disease; fewer data

TABLE 5. Reproductive Considerations for Immunosuppression Therapy

Medication	Pregnancy	Lactation	Fertility	Historical FDA Classification
6-MP, Azathioprine	Compatible 6-MP: no increased risk of birth defects Azathioprine: associated with low birth weight and preterm birth	Compatible Some reports of self-limited neutropenia	6-MP: normal ovarian function; mixed data in men, with reports of birth defects in children fathered by men taking 6-MP and other data showing no increased rates of birth defects Azathioprine: no increased likelihood of adverse effects on fertility in females and males	D
CNIs (cyclosporine, tacrolimus)	Compatible Cyclosporine: reports of association with low birth weight Tacrolimus: reports of association with hypertension, preeclampsia, and preterm birth	Compatible	No known risk to fertility in females and males	C
Glucocorticoids (budesonide, prednisone)	Compatible Prednisone: possible association with oral clefting Budesonide: may lower fetal exposure	Compatible	Budesonide: no effect on fertility in rats; no human data Prednisone: no increased likelihood of adverse pregnancy outcomes when used in males of reproductive potential	C
mTOR inhibitors (sirolimus, everolimus)	Not recommended due to limited human data	Not recommended due to limited human data	Sirolimus: reports of irregular ovulation and ovarian cysts; reports of decreased sperm counts and decreased male fertility Everolimus: rare reports of reduced sperm count and decreased male fertility	Sirolimus: C Everolimus: not assigned
MPA products (mycophenolate mofetil, mycophenolate sodium)	Contraindicated High risk of miscarriage and birth defects	No reported adverse events Use not advised, given the adverse outcomes observed in pregnancy	No known risk to fertility in females and males In women, discontinue use at least 6 weeks before conception	D

Note: Historical FDA classifications: A, adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, with no evidence of risk in later trimesters; B, animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; C, animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; D, there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; and X, studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh the potential benefits.

are available on the safety of oral budesonide.[181] Although older literature reported a 3.4-fold increased risk of orofacial clefts with first-trimester corticosteroid exposure,[182] a more recent nationwide cohort study of nearly 52,000 pregnancies with first-trimester exposure showed no increased risk.[183] As with all medications used in pregnancy, the lowest effective dose should be used. In contrast, MPA products are associated with a high risk of congenital malformations and spontaneous abortions and are contraindicated in pregnancy. Due to these detrimental effects, the FDA issued a Risk Evaluation and Mitigation Strategies program for MPAs,[184,185] to educate clinicians and patients on fetal risks of MPA products and to collect data on pregnancies conceived with MPA exposure. Prescribing clinicians should document a negative pregnancy test within 1 week of starting MPA products and ensure adequate contraception use. MPAs should be discontinued at least 6 weeks before attempting conception.

GUIDANCE STATEMENTS

In women with AIH:

- Preconception counseling should include discussion of medication safety in pregnancy and potential for

disease exacerbation, including decompensation. Delaying conception until liver disease is well controlled on stable doses of immunosuppressants for at least 1 year is suggested.
- Counseling regarding the potential risks of azathioprine and 6-mercaptopurine (6-MP) is recommended, although these drugs are considered safe in pregnancy and lactation.
- Prednisone and budesonide are considered low risk in pregnancy and lactation.
- MPA products are contraindicated in pregnancy and lactation.
- Liver test monitoring during each trimester is suggested. More frequent monitoring (every 2-4 weeks) is advised for the first 6 months postpartum.
- Breastfeeding is not contraindicated.

CHRONIC CHOLESTATIC LIVER DISEASES

Primary Biliary Cholangitis

Approximately one third of new diagnoses of PBC are made during pregnancy.[186] Because PBC may be associated with elevated total serum bile acids, measurement in the first trimester can help with interpretation of bile acid levels later when superimposed ICP may be a concern. Data regarding fertility and maternal pregnancy outcomes are limited, with no differences compared with non-PBC controls.[187,188] During pregnancy, up to 70% of women with PBC have stable or improved liver tests, but increased liver disease activity occurs in 60% to 70% postpartum.[186,188] Immunoglobulin M levels and M2 antibody titers may decline in pregnancy but return to baseline levels postpartum.[189] *De novo* onset or worsening of pruritus during pregnancy occurs in approximately 50% of women.[186,188] For management of pruritus, cholestyramine, rifampin, or S-adenosyl-L-methionine (SAMe) may be added to ursodeoxycholic acid (UDCA) (Table 4).[190,191] Cholestasis may lead to vitamin K deficiency and increased risk of bleeding.[192] Cholestyramine may exacerbate vitamin K deficiency[193] in persons with cholestasis, with rare case reports of associated hypoprothrombinemia and even hemorrhage.[194-196] Onset varied from 2 weeks to 8 months and responded promptly to parental vitamin K supplementation.[193-196]

Rates of fetal or neonatal complications may be higher in women with PBC compared to healthy controls, although the presence of cirrhosis confounds interpretation of available data.[187,188] UDCA in pregnancy and breastfeeding is not associated with adverse effects.[186-188] Obeticholic acid is not associated with teratogenicity or postnatal abnormalities in animal studies, but human data are lacking. Fibrates were not associated with teratogenic or embryonic risks in animals but adversely affected maternal reproductive outcomes at high doses.[197,198] Whether obeticholic acid and fibrates are excreted in breast milk is unknown.[198,199] Due to the lack of sufficient safety data, neither obeticholic acid nor fibrates are recommended during pregnancy and lactation.

Primary Sclerosing Cholangitis

Women with primary sclerosing cholangitis (PSC) often have inflammatory bowel disease (IBD), and many women will need concurrent management of liver and bowel disease during pregnancy. Published experience with PSC in pregnancy is limited, and interpretation of outcomes is complicated by a lack of adjustment for IBD. Fertility is not affected by PSC.[200] A Swedish study comparing 229 pregnant women with PSC to 2.3 million non-PSC controls identified higher rates of preterm births (16.3% vs. 5.1%) and cesarean delivery (29.4% vs. 13.3%), but no differences were seen in small for gestational age, stillbirths, or neonatal deaths.[201] Smaller studies reported preterm births in 10% to 30%.[200,202,203] IBD, especially if active at the time of conception or during pregnancy, contributes to higher rates of fetal and neonatal complications.[204]

De novo pruritus and abdominal pain are the most frequently reported symptoms during pregnancy.[202] Most women have stable liver tests, but up to one-third have increased liver tests postpartum, although without clinical consequences.[200] Pregnant women on UDCA appear more likely to have stable liver enzymes than those who are not on UDCA (13% vs. 67%),[200] although UDCA is not FDA-approved for PSC treatment due to unconfirmed efficacy.[205]

For new symptoms or worsening liver tests during pregnancy, the development of a dominant stricture should be considered. US is the initial imaging test of choice, with use of cross-sectional studies or

endoscopic retrograde cholangiopancreatography (ERCP) guided by severity of symptoms and stage of pregnancy. Cholestasis may lead to vitamin K deficiency and increased risk of bleeding.[192] Treatment of pruritus is multifaceted: lifestyle measures, antihistamines, cholestyramine, rifampin, and UDCA may be recommended, often requiring combination therapy.[190] Cholestyramine may exacerbate vitamin K deficiency in persons with cholestasis (as previously for PBC), and monitoring of PT during pregnancy may be considered in patients with cholestasis.

GUIDANCE STATEMENTS

In women with PBC and PSC:

- Measurement of total serum bile acids may be considered in the first trimester to aid in excluding ICP in the setting of new-onset or worsening pruritus during pregnancy.
- UDCA is safe in pregnancy and lactation, although no data support a therapeutic benefit in primary sclerosing cholangitis.
- Obeticholic acid and fibrate use cannot be recommended in pregnancy or lactation in women with PBC due to lack of safety data.
- Clinically significant pruritus typically requires a multifaceted approach with cholestyramine (4-16 g daily, divided dose and separated from other medications by at least 2 hours), rifampin (300-600 mg daily), SAMe (1,000-1,200 mg daily), and antihistamines considered, although evidence is low.
- Vitamin K deficiency related to cholestasis should be corrected, and regular monitoring of PT is recommended.

NONALCOHOLIC FATTY LIVER DISEASE

NAFLD *per se* has not been linked with infertility. Infertility rates are higher in some women with NAFLD due to the presence of polycystic ovary syndrome (PCOS), obesity, or underlying cirrhosis. In a meta-analysis of 17 studies, NAFLD was reported in 42% of women with PCOS compared with 16% of non-PCOS controls.[206] Among women of Hispanic ethnicity, the prevalence of NAFLD is up to 70% of women with PCOS.[207] Thus, young women with NAFLD should be queried for PCOS symptoms[208] (e.g., menstrual irregularities, hirsutism, infertility), as PCOS requires specific therapeutic approaches. PCOS also appears to be associated with more severe histologic disease.[209]

Pregnancy is associated with specific metabolic changes necessary to promote fetal growth and development, including increased adipose tissue, decreased insulin sensitivity, and increased lipolysis. These changes can negatively affect intrapartum and subsequent metabolic risks for women with NAFLD. A large U.S. study using discharge diagnoses reported higher rates of hypertensive complications (OR, 3.1; 95% CI, 2.6-3.8), preterm births (OR, 1.6; 95% CI, 1.3-2.0), and postpartum hemorrhage (OR, 1.7; 95% CI, 1.3-2.2) in mothers with NAFLD compared to those without liver disease.[210] Fatty liver based on US findings has been associated with higher likelihood of gestational diabetes mellitus (GDM), independent of BMI and age.[211-213] A population-based cohort study also reported higher rates of cesarean delivery (64.2% vs. 16.8%), preterm births (16.4% vs. 5.1%), and small for gestational age births (5.8% vs. 2.8%)[214] in patients with NAFLD compared with non-NAFLD controls, even after adjustment for BMI and pre-GDM.[214] However, NAFLD was only associated with increased risk in women with BMI less than 30 kg/m^2 at conception.[214] A study of first pregnancies in 200 women with imaging-confirmed NAFLD and 200 non-NAFLD controls with strict exclusions of diabetes, PCOS, and other prosteatotic conditions found rates of GDM, gestational hypertension, and preeclampsia to be significantly higher in women with NAFLD.[215] Most studies have been limited by reliance on diagnostic codes and/or US to identify women with NAFLD, resulting in underreporting of NAFLD and an inability to distinguish nonalcoholic steatohepatitis from simple steatosis.

Maternal obesity and diabetes have been associated with higher risk of NAFLD in infants and adolescents.[216-218] Proposed underlying mechanisms include epigenetic reprograming, mitochondrial dysfunction, dysbiosis, and immune dysregulation with a more proinflammatory state.[219] Breastfeeding and duration of lactation have been associated with a lower incidence of future metabolic complications, including NAFLD, presumably related to postpartum weight loss and return of blood glucose, lipid, and insulin concentrations to prepregnancy levels.[220,221]

Breastfeeding may have a protective effect on development and severity of NAFLD in children.[222-224]

The cornerstones of NAFLD management are lifestyle modification to achieve optimal weight and treatment of metabolic comorbidities. These measures should also be the focus of pregnant women with NAFLD, for whom prevention of excessive gestational weight gain is the goal.[225,226] For women wishing to or gaining less than the recommended weight during pregnancy (Table 6), guidance needs to be individualized with close monitoring of fetal growth.[227] No NAFLD-specific medications are approved for use in pregnancy.

GUIDANCE STATEMENTS

In reproductive-aged patients with NAFLD:

- Evaluation for symptoms associated with polycystic ovary syndrome is recommended.
- Preconception counseling should include review of maternal and fetal risks associated with obesity and diabetes and the benefits of optimizing weight and metabolic comorbidities before conception.
- Optimal gestational weight gain through healthy diet and appropriate exercise should be emphasized.
- Monitoring of liver tests should be similar to nonpregnant women.

In pregnant patients with NAFLD:

- Breastfeeding is encouraged, and longer duration of lactation is associated with lower rates of future NAFLD among offspring and reduced maternal metabolic complications, including NAFLD.

ALCOHOL-ASSOCIATED LIVER DISEASE

Alcohol use among reproductive-aged women has increased in recent years. In 2012-2013, any alcohol use in the preceding 12 months was reported in 75% of pregnant women, whereas heavy, episodic use was reported in 36%, reflecting increases of 66% and 23%, respectively, in 2001-2002.[228] Alcohol use in pregnant women is lower than in nonpregnant women, with lower rates reported in second and third trimesters versus first trimester.[228,229] Studies show a strong association between alcohol use in pregnancy and risk of preterm births and small for gestational age,[230-232] although the reasons are likely multifactorial, including genetics, environment, and patterns of alcohol use. Effects of the fetus are well recognized, and the complications of fetal alcohol spectrum disorder are long-lasting.[233,234] These statistics highlight the importance of inquiring about alcohol use in all women, especially as a component of preconception and pregnancy management. For women with alcohol-associated liver disease (ALD), the achievement of alcohol abstinence is the most important aspect of preconception management. All women, including those with liver disease of any etiology, should be screened for alcohol use in pregnancy.[235] Interventions may include consideration of medications, although data on the safety of drugs approved for treatment of alcohol use disorder in pregnancy are very limited (Table 4). Disulfiram may be associated with fetal abnormalities.[236-238] Naltrexone has been used in the treatment of women with opiate use disorder without any fetal abnormalities noted.[239] Acamprosate is associated with fetal abnormalities in animals,[240] but limited human data do not show this.[241] Thus, for women who are stable on these medications and become pregnant, the decision to continue needs to be individualized and balance the harms of alcohol use with those of the medications.[242]

GUIDANCE STATEMENTS

- Pregnant women should be screened for alcohol use and referred for management when appropriate.

TABLE 6. Weight Gain During Pregnancy*

Baseline Pregnancy Weight Category	BMI Prepregnancy	Weight Gain During Pregnancy (lb)	Rate of Weight Gain During Second and Third Trimesters
Underweight	<18.5	28-40	1-1.13
Normal	18.5-24.9	25-35	0.8-1
Overweight	25-28.9	15-25	0.5-0.7
Obese	≥30	11-20	0.4-0.6

*Per Institute of Medicine guidelines and American College of Obstetricians and Gynecologists.[227]

- For women with ALD, counseling should include delaying of conception until abstinence is achieved.
- Medication use to treat alcohol use disorder during pregnancy should be individualized, with careful weighing of the risks of alcohol use versus those of medication exposure.

Liver Conditions Requiring Special Management in Pregnancy

BENIGN HEPATIC LESIONS IN PREGNANCY

Hepatocellular Adenomas

HCAs are benign hepatic lesions occurring predominantly in reproductive-aged women. The association of estrogens with HCAs is well established.[243] Estrogen receptors have been found in up to one-third of HCAs,[244] and cessation of estrogen-containing hormonal contraception is associated with regression of HCAs.[245,246] The risk of HCA with hormonal contraception has significantly declined with use of lower doses of estrogen in contemporary contraceptive methods.[245,247]

Given the estrogenic state of pregnancy, HCAs deserve attention in this setting. In a cohort study from 1970, 6 of 88 (6.8%) women with well-characterized HCAs were followed during pregnancy or the postpartum period, and 5 (83%) experienced tumor rupture and hemorrhage, with 1 maternal death.[243] In contrast, less than 30% of nonpregnant women experienced intraperitoneal bleeding. In another report from 2004 of 26 cases of HCAs in pregnancy, 16 had rupture, all with HCAs greater than 6.5 cm in diameter, with maternal and fetal deaths occurring in 44% and 38% of cases, respectively.[248] However, a more contemporary study, published in 2011, supports more favorable pregnancy outcomes with HCAs, including experience from 17 pregnancies during which HCAs enlarged in four cases, none of which experienced rupture.[249] In a recent cohort of 51 pregnancies with confirmed HCAs less than 5 cm in diameter, only 25.5% grew by greater than 20% (median increase, 14 mm) and none with maternal or fetal complications.[250] Improvement in clinical outcomes in contemporary studies may relate to more aggressive management of HCAs found incidentally or during prior pregnancies and fewer delays in diagnosis.[249] For HCAs greater than 5 cm in diameter before pregnancy, bland embolization or segmental hepatectomy can be considered to mitigate risk during pregnancy (Fig. 4).[250-252] Size, location, presence of hemorrhage, and other factors are relevant in deciding the best therapeutic approach. Consultation with a hepatobiliary surgeon and interventional radiology should be considered.

HCA surveillance with US during pregnancy is indicated (Fig. 4) and should be continued postpartum, as HCAs continue to pose a risk during this period of rapid normalization of sex hormone levels.[248] Although MRI with gadolinium is the imaging modality of choice for diagnosis of HCAs in nonpregnant patients,[253] gadolinium is contraindicated in pregnancy. MRI without gadolinium, performed in the second or third trimester, is the preferred study in pregnancy if there is need to diagnose HCA.[254]

Hepatic Hemangioma

Hepatic hemangiomas are the most common benign liver lesion, with prevalence estimates of 0.4% to 8%[255,256]; a contemporary study reported 2.5%.[257] Lesions are usually asymptomatic,[256-258] with intervention limited to large lesions complicated by abdominal pain, bleeding, or rupture (<1%).[257] Prevalence is higher in women,[256-259] although an association with estrogens is not well established,[259] and use of CHC or pregnancy is considered safe with no monitoring required.

The caveat to this approach is for cavernous hemangiomas, variably defined by size greater than 5 cm to greater than 10 cm, for which the increased intra-abdominal pressure of the expanding uterus, increase in blood volume, and up-regulation of cytokines predisposes to continued expansion and potential rupture, although rupture is quite rare.[260,261] Resection of giant cavernous hemangiomas, although rarely used, has been safely reported in three cases during the second trimester of pregnancy, without maternal or fetal death.[261-263] New onset of symptoms should prompt investigation, and the decision to intervene should be approached with caution and be determined on a case-by-case basis, guided by symptoms and risk to maternal and fetal outcomes.

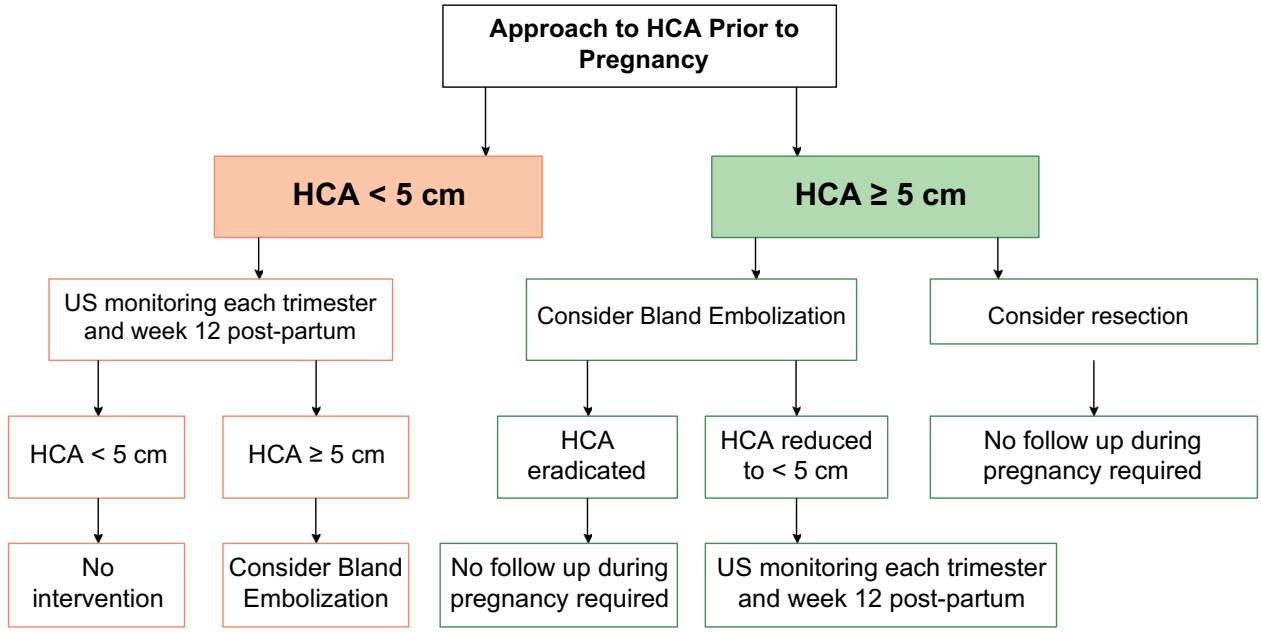

FIG. 4. Management approach to HCAs before and during pregnancy. This algorithm includes considerations for preconception management of HCAs based on size as well as surveillance intervals during and after pregnancy. For women with multiple HCAs, surveillance of <5 cm is advised during pregnancy even if a dominant lesion ≥5 cm is treated.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the second most common benign liver lesion, with a prevalence of 0.3% to 3%, and is commonly diagnosed in reproductive-aged women.[255,264] Given its vascular nature, FNH may coexist with other vascular hepatic lesions, such as hepatic hemangiomas, in up to 20% of cases.[265]

The association of FNH with estrogen is not well established. One case-control study found that history of any or prolonged CHC use was associated with prevalent FNH,[266] whereas another study found no association between size or number of lesions.[265] Moreover, of the 12 pregnancies that occurred in the latter study, no significant change in the size of lesions was observed, with no instances of maternal or fetal mortality.[267] These data have been replicated in contemporary cohorts, with only one case of hepatic rupture reported in the literature.[268,269] Thus, both CHC use and pregnancy are considered safe, with no monitoring required.

GUIDANCE STATEMENTS

- Reproductive-aged women with HCAs should be counseled about the possibility of adenoma growth and rupture in pregnancy.
- US monitoring of HCAs during each trimester of pregnancy and up to 3 months postpartum is reasonable.
- Pregnancy in women with HCAs less than 5 cm in diameter is not contraindicated.
- For HCAs greater than 5 cm in diameter, prophylactic treatment with embolization or resection should be considered before conception to reduce the risk of rupture during pregnancy.
- Hepatic hemangiomas, regardless of size, do not require monitoring during pregnancy, but new onset of symptoms should prompt investigation.
- Focal nodular hyperplasia, regardless of size, does not require monitoring.

BUDD-CHIARI SYNDROME

Pregnancy shifts the hemostatic balance toward hypercoagulability that lasts up to 8 weeks postpartum.[270] Pregnancy alone is unlikely to cause BCS but often unmasks an underlying clotting disorder, which warrants investigation.[271] A Doppler study is sufficient in most cases to establish the diagnosis. Presenting symptoms include abdominal pain and ascites, reflecting outflow obstruction and associated sinusoidal hypertension.

Therapeutic options include anticoagulation, thrombolysis, transjugular intrahepatic portosystemic shunt, and LT.[272,273] Treatment choices in pregnancy are more limited, as vitamin K antagonists are contraindicated in pregnancy due to the risk of fetal hemorrhage and teratogenicity.[274,275] Thrombolytic therapy may be acceptable, but data are limited. Low-molecular-weight heparin is the anticoagulant of choice during pregnancy. Breastfeeding is acceptable with vitamin K antagonists and low-molecular-weight heparin.

GUIDANCE STATEMENTS

- Doppler US is the imaging modality of choice for diagnosing BCS.
- Treatment of acute BCS is the same as in nonpregnant patients with the exception of more limited choices of anticoagulation and insufficient safety data to endorse thrombolytic therapy in pregnancy.
- Low-molecular-weight heparin is the anticoagulant of choice during pregnancy and lactation in women with BCS.
- Vitamin K antagonists are contraindicated during pregnancy but acceptable during breastfeeding.

GALLSTONE DISEASE IN PREGNANCY

Hormonal changes in pregnancy lead to decreased gallbladder motility and lithogenic bile.[276] The strongest risk factors are high prepregnancy BMI and high serum leptin level.[277] Although gallstones may occur in up to 10% of pregnancies, the estimated incidence of gallstone-related disease complicating pregnancy is 0.5% to 0.8%.[278,279] US is the diagnostic imaging of choice.

Symptomatic biliary colic is the most common presentation, although pancreatitis, cholangitis, or acute cholecystitis may occur. Management is similar to the nonpregnant patient, with supportive care as the first-line treatment. If recurrent or persistent episodes or other complications occur, ERCP or cholecystectomy should be considered.

Cholecystitis has high recurrence rates if treated conservatively[280,281] and is associated with prolonged hospitalization, preterm delivery, and spontaneous abortions. Gallstone pancreatitis is associated with increased risk of fetal death.[282]

Laparoscopic cholecystectomy and ERCP are safest if performed in the second trimester. When possible, nonoperative management is preferred in the third trimester.[283] However, emergent surgery should be performed regardless of trimester. Fetal radiation risk is the main concern with ERCP during pregnancy (Table 3). Radiation risks during ERCP can be minimized by directing the x-ray beam on the treatment area, limiting procedure duration, and using lead shields on the pelvis and lower abdomen. If technically feasible, an ERCP without fluoroscopy can also be considered.

There is no role for UDCA therapy. Biliary sludge may resolve postpartum, although gallstones often persist.[284]

GUIDANCE STATEMENTS

- US is the imaging modality of choice for suspected gallstone disease in pregnancy.
- Initial management of gallstone disease in pregnancy is supportive, although ERCP and laparoscopic cholecystectomy can be considered, ideally in the second trimester.
- If ERCP is required, fetal radiation should be minimized by reducing fluoroscopy time and shielding the fetus with lead shields placed on the pelvis and lower abdomen.

ACUTE VIRAL HEPATITIS

Pregnancy is not associated with a higher incidence of acute or severe viral hepatitis, except for hepatitis E virus (HEV) and herpes simplex virus (HSV) infections. For acute hepatitis unrelated to HEV or HSV, management is similar to nonpregnant women, with supportive care being the mainstay. For treatment of acute HBV, TDF is the antiviral drug of choice during pregnancy.[116] For symptomatic acute viral hepatitis, potential adverse outcomes include spontaneous abortion,[285] preterm labor,[285-288] and MTCT of viruses, although risks are poorly quantified due to the rarity of reported cases.

Hepatitis E

Typically, HEV infection is a mild self-limiting disease with low case fatality rate, but pregnant women, particularly in the second and third trimester, are more susceptible to HEV and severe clinical

outcomes.[289] Proposed factors contributing to risk in pregnancy include HEV genotype 1 (with varying replication efficiency at the maternal–fetal placenta interface),[290,291] folate or other nutritional deficiencies,[292] and immunologic changes in pregnancy.[293] Acute HEV is responsible for an estimated 3,000 stillbirths worldwide annually,[294] with fetal and neonatal mortality rates likely influenced by the severity of maternal illness. A systematic review reported the median fetal and neonatal case fatality rate of 33% (interquartile range [IQR], 19%-37%) and 8% (IQR, 3%-20%), respectively.[295] Adverse pregnancy outcomes are reported in countries where genotype 1 predominates, although there is no clear explanation for the apparent geographic variation in clinical outcome.[296,297] MTCT of HEV can occur (in utero or peripartum), but rates of transmission vary from 33% to 100%.[296,298] Ribavirin and interferon alpha, although effective therapy for HEV, are contraindicated in pregnancy.[299]

Herpes Simplex Virus

HSV hepatitis is a rare cause of acute viral hepatitis, and pregnancy increases risk for disseminated infection,[300] accounting for approximately 25% of reported cases.[301] The most common symptoms are fever (98%), coagulopathy (84%), and encephalopathy (80%).[301] Laboratory features of elevated aminotransferase levels (up to several thousand units per liter), leukopenia, thrombocytopenia, and acute renal failure can mimic features of preeclampsia/HELLP/AFLP and contribute to delays in diagnosis. Herpetic rash is seen in approximately 20% of pregnant patients.[302] Diagnosis is often delayed, owing to its rarity and nonspecific symptoms.[301] Because the disease can worsen rapidly and has high mortality, empiric therapy with intravenous acyclovir is warranted while awaiting diagnostic testing. Early use of intravenous acyclovir is associated with improved outcomes,[303] and acyclovir is not associated with an increased rate of birth defects.[304,305] For patients progressing to acute liver failure (ALF), LT should be considered.[306,307]

GUIDANCE STATEMENTS

- Acute viral hepatitis in pregnancy warrants closer monitoring for maternal and fetal complications, especially for acute HEV and HSV infections.
- Management is supportive, and use of specific antiviral therapy should be guided by safety of the drugs in pregnancy.
- A high index of suspicion is needed to identify HSV hepatitis, and intravenous acyclovir should be initiated while awaiting diagnostic studies. Acyclovir is safe in pregnancy and lactation.

Pregnancy in the Patient With Cirrhosis

Pregnancy is less common in cirrhosis, with an estimated frequency of approximately 1 per 3,000-6,000 pregnancies.[308,309] Maternal mortality in women with cirrhosis was initially reported as 20%,[1] although more recent data report mortality rates of less than 2%.[69,310,311] Given improved maternal outcomes, cirrhosis and PHT are no longer considered absolute contraindications to pregnancy. The Model for End-Stage Liver Disease (MELD) score can be a helpful prognostic tool. A recent study showed preconception MELD scores greater than or equal to 10 have 83% sensitivity and specificity for predicting hepatic decompensation during pregnancy.[69] In a population-based study of 2,106 women with cirrhosis, liver-related complications during and up to 1 year postpartum were seen in 1.2% with compensated cirrhosis and 13% with a history of prior decompensation.[65] Therefore, all women with cirrhosis, particularly those with prior hepatic decompensation or MELD scores greater than or equal to 10, should be counseled on the risk of worsening liver disease during pregnancy.

MATERNAL AND FETAL OUTCOMES

A California-based registry from 2016 identified 37 cases of cirrhosis in more than 2.2 million pregnancies, with no maternal deaths reported.[312] However, data from tertiary centers demonstrate increased risks of preeclampsia and preterm birth with worsening severity of cirrhosis.[69,308,313] In data from the U.S. Nationwide Inpatient Sample, cirrhosis in pregnancy conferred increased maternal (1.8% vs. 0%; $P < 0.0001$) and fetal mortality (5.2% vs. 2.1%; $P < 0.0001$) compared with controls.[310] Among

pregnant women with cirrhosis, hepatic decompensation occurred in 15%; 11% developed ascites, and 5% had variceal hemorrhage, and, in this group, maternal and fetal mortality were 6% and 12%, respectively.[310] Cesarean delivery, placental abruption, uterovaginal hemorrhage, and gestational hypertension were also more common with cirrhosis, and infants had higher rates of prematurity and growth restriction.[310] A Canadian population-based cohort study of pregnant women with and without cirrhosis reported higher rates of hypertensive complications (11% vs. 9%), preterm delivery (11% vs. 7%), antenatal hemorrhage (10% vs. 8%), ICP (5% vs. 0.5%) as well as higher infant mortality (0.7% vs. 0.3%).[65] Similar findings were reported in a Swedish registry comparing women with and without cirrhosis, with higher risks of cesarean delivery (36% vs. 16%), low birth weight (15% vs. 3%), preterm delivery (19% vs. 5%), and neonatal death (1% vs. 0.2%).[314] However, rates of GDM, preeclampsia, small for gestational age, congenital malformations, maternal death, and stillbirth were similar between groups.[314]

MANAGEMENT OF PHT IN PREGNANCY

Prophylactic Management

Bleeding from gastroesophageal varices (GEV) is the most feared complication among pregnant women with cirrhosis and PHT, with an 18%-20% maternal mortality rate.[310,315] The incidence of variceal bleeding has fallen from a range of 18% to 33% to range of 5% to 8.5%, likely due to effective variceal bleeding prophylaxis before conception and during pregnancy.[309,310,316,317] Risk is greatest in the second trimester when intravascular volume increases and during delivery due to compression of the inferior vena cava by the gravid uterus and repeated Valsalva maneuvers. Variceal bleeding risk is determined by the presence of clinically significant PHT. Based on expert AASLD guidance, variceal screening is recommended for all women with cirrhosis within 12 months of conception. Women with noncirrhotic liver disease, such as Fontan-associated liver disease,[318] but evidence of PHT should undergo similar variceal screening.

Noninvasive tests have been shown to reliably risk stratify patients with GEV.[319,320] Liver stiffness measurement less than 20 kPa and platelet count greater than 150×10^9 cells/L identify those with a low likelihood of high-risk GEV, defined as greater than 5 mm in diameter and/or with high-risk bleeding stigmata, in whom esophagogastroduodenoscopy (EGD) could be safely avoided. However, these criteria, which were not developed to exclude the presence of small varices, miss up to 30% of small varices in patients with Child-Turcotte-Pugh A cirrhosis.[321] Because the preconception goal in surveilling women with cirrhosis is to detect varices of any size, screening EGD is the test of choice (Fig. 5). If EGD is not performed before pregnancy, it is recommended early in the second trimester. Repeat EGD in the second trimester is not required if the patient has been screened and has no varices preconception or is already on primary prophylactic therapy, unless there is ongoing liver injury (active alcohol use, untreated HCV infection) or new symptoms of decompensation (e.g., ascites).

Primary prophylaxis can consist of nonselective beta-blockers (NSBBs) or esophageal variceal ligation (EVL) if medium or large esophageal varices are identified. Given the hemodynamic changes in later pregnancy (Fig. 1) that may potentially increase variceal size and risk of bleeding, NSBBs may be considered for small esophageal varices, although evidence to support this practice is lacking. Treatment selection should be based on expected complications or adverse events, comorbid conditions that preclude the use of NSBBs, severity of liver disease, and patient's preference. EVL is preferred if high-risk bleeding stigmata are found (e.g., cherry red spots, red wale signs).

EGD appears safe in pregnancy, with 95% of patients undergoing EGD delivering healthy infants.[310,322-324] If possible, all endoscopic procedures should be deferred until the second trimester of pregnancy. For endoscopic procedures, midazolam, meperidine, fentanyl, and propofol are acceptable for use in pregnancy. The FDA released a warning in 2017 about the possible risk of fetal brain damage and subsequent impairment of neurocognitive function after prolonged (>3 hours) or frequent exposure to general anesthetics and sedatives, including midazolam and propofol, during the third trimester of pregnancy[325]; minimizing fetal exposure to anesthetic agents during pregnancy should be the goal.[326] Preoperative evaluation by a MFM specialist is recommended.

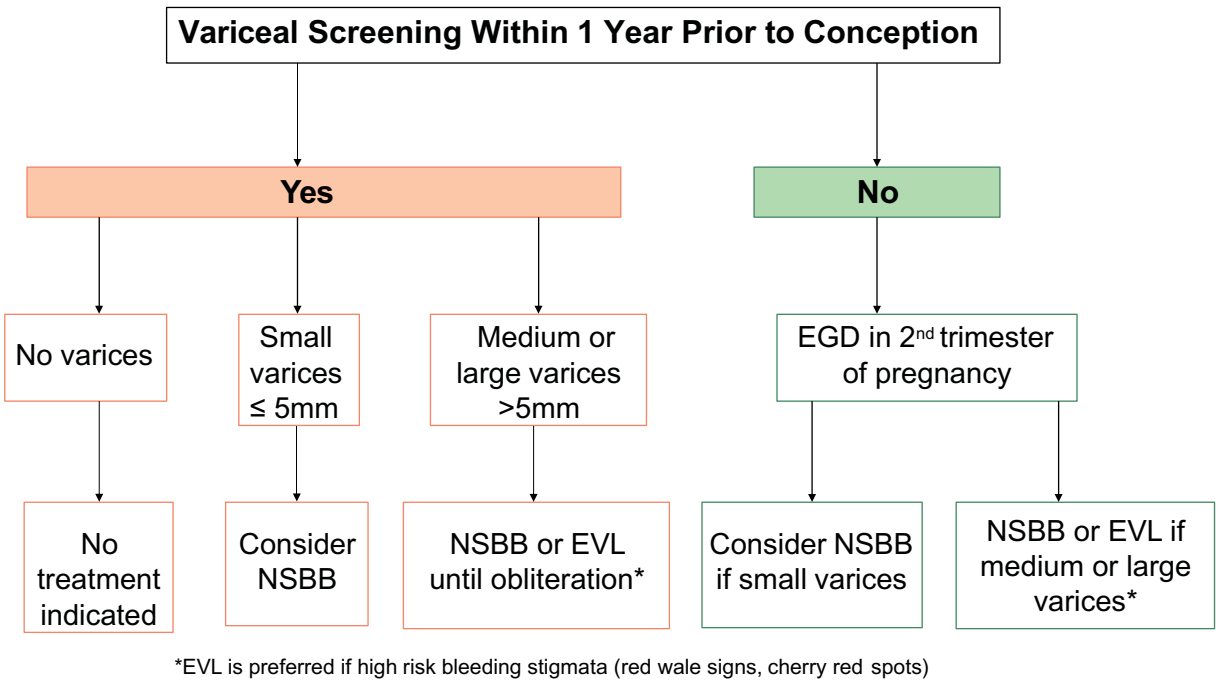

FIG. 5. Variceal surveillance in pregnancy. Endoscopic variceal screening within 12 months before conception is indicated for all women with cirrhosis. The circulatory changes normally occurring during pregnancy might increase variceal size and risk of bleeding. Risk is highest in the second trimester of pregnancy. EGD is recommended early in the second trimester of pregnancy if variceal screening was not done before conception, if there is ongoing liver injury, or in the setting of new symptoms of hepatic decompensation. Prophylactic therapy is advised if varices of any size are detected. NSBBs should be considered if small varices are identified. NSBBs or EVL are recommended for medium and large esophageal varices (do not flatten with insufflation), with EVL preferred if high-risk bleeding stigmata is present. If variceal screening algorithm is followed preconception, EGD is only indicated during pregnancy if there is ongoing liver injury or hepatic decompensation occurs. *EVL is preferred if high-risk bleeding stigmata (red wale signs, cherry red spots) are present.

Management of Gastroesophageal Variceal Bleeding

Management of GEV bleeding during pregnancy is extrapolated from nonpregnant patients. NSBBs may be used for primary or secondary variceal bleeding prophylaxis, with propranolol favored in pregnancy (Table 4). EVL is preferred for medium or large esophageal varices and should continue until obliteration of varices (Fig. 5). For active variceal hemorrhage, immediate resuscitation and stabilization of the mother and emergent endoscopic therapy are req uired.[114,201,327-329] Octreotide or somatostatin should also be initiated, but terlipressin should be avoided because it can cause uterine contractions and reduce uterine blood flow (Table 4). Although splanchnic vasoconstriction could reduce placental perfusion and increase risk of placental abruption,[330] comprehensive management of life-threatening variceal bleeding outweighs this theoretical risk. For antibiotic prophylaxis in acute variceal bleeding, cephalosporins are preferred due to favorable pregnancy and lactation safety data.[331]

Data on treatment of pregnant women with recurrent esophageal bleeding or bleeding from gastric varices are limited. Cyanoacrylate with or without coiling are options, depending on center expertise.[332-336] A transjugular intrahepatic portosystemic shunt has been used with success as rescue therapy for uncontrolled GEV bleeding and for decompression of abdominal wall varices before cesarean section when vaginal delivery was contraindicated.[334,335,337] Secondary prophylaxis for variceal bleeding includes use of NSBBs and EVL, with the combination preferred.[337]

Management of Lower GI Bleeding Due to PHT

Clinically significant PHT can manifest as hemorrhoids, anorectal varices, and portal hypertensive colopathy.[338] The prevalence of portal hypertensive colopathy is 23%, and rectal varices is as high as 56%,

but severe rectal variceal bleed occurs in only 0.5% to 5%.[338,339] The management approach should mirror that of nonpregnant patients.[340] Prophylaxis with NSBBs can be used in portal hypertensive colopathy, as 90% of patients concomitantly have GEV.[341] If lower endoscopy is indicated, sigmoidoscopy with tap water enemas are preferred. The safety of polyethylene glycol has not been adequately studied in pregnancy.[342]

Management of Splenic Artery Aneurysm

Splenic artery aneurysm (SAA) is a rare condition that affects patients with PHT and can present with rupture during pregnancy. SAA rupture is associated with a high fetal and maternal mortality of 15.6% to 90% and 21.9% to 70%, respectively. Limited data support treatment of SAA to prevent rupture. There is no established consensus for SAA therapy based on diameter, as risk appears to be highest when SAA is greater than or equal to 2 cm, but 50% of lesions presenting with rupture during pregnancy are smaller than 2 cm. More data are needed to make recommendations on treatment approaches to SAA based on size.

MANAGEMENT OF PHT AT DELIVERY AND POSTPARTUM

The increase in intra-abdominal pressure during vaginal delivery might increase portal pressure and risk of variceal rupture.[313,343,344] Assisted vaginal delivery to minimize straining and shorten the second stage of labor can reduce this risk. Cesarean delivery may increase risk of bleeding from direct injury to abdominal wall varices and increase risk for postpartum ascites.[336] For cesarean delivery, platelet counts should generally be greater than 50,000/mL. Ultimately, mode of delivery should be guided by obstetric indications.[345,346] Postpartum hemorrhage risk is increased in women with cirrhosis, which may be related to underlying thrombocytopenia or higher rate of cesarean deliveries.[310] Prevention by active management of the third stage of labor is the mainstay of therapy.

GUIDANCE STATEMENTS

- Endoscopic procedures require preoperative consultation with MFM specialists to coordinate fetal monitoring and maternal sedation.
- In women with cirrhosis, prepregnancy endoscopic variceal screening is recommended. Screening in the early second trimester is indicated if not performed within 1 year before conception or if there is ongoing liver injury or decompensation occurs.
- Meperidine, midazolam, propofol, and fentanyl may be used in pregnancy, with efforts to minimize the duration of anesthesia.
- For pregnant women with small GEV, primary prophylaxis using NSBBs should be considered.
- For pregnant women with medium or large GEV, primary prophylaxis using band ligation or NSBBs is recommended. Propranolol is the preferred NSBB.
- For pregnant women with acute variceal hemorrhage, standard therapy with octreotide or somatostatin, proton pump inhibitors, antibiotic therapy with cephalosporins, and endoscopy are recommended. Terlipressin should be avoided.
- Mode of delivery should be guided only by obstetric indications.

Liver Diseases Unique to Pregnancy and Their Management

HYPEREMESIS GRAVIDARUM

Hyperemesis gravidarum occurs in 0.35% to 2.0% of pregnancies.[347] It typically occurs in the first trimester and is characterized by persistent vomiting with weight loss greater than or equal to 5% of prepregnancy body weight, dehydration, and ketonuria (Table 7). Rarely, symptoms persist throughout the pregnancy. Abnormal liver enzymes occur in approximately 50% and are rarely greater than 1,000 IU/mL.[348,349] In general, ALT is greater than aspartate aminotransferase (AST), and jaundice rarely occurs. Biochemical abnormalities typically resolve with hydration and resolution of vomiting. Liver biopsy is rarely indicated, but, when performed, reveals normal parenchyma, mild fatty change, or bland cholestasis.[350]

Treatment includes rehydration, correction of electrolyte abnormalities, nutrition, thiamine supplementation to prevent Wernicke's encephalopathy,[351,352] and anti-emetic therapy. Anti-emetic agents with favorable pregnancy safety include ondansetron,

TABLE 7. Liver Diseases Unique to Pregnancy

	Hyperemesis Gravidarum	ICP	HELLP	AFLP
Trimester	First (rare second/third)	Second or third	Second or third	Third or postpartum
Prevalence	0.35%-2.0%	0.4%-10%	0.2%-0.6% (preeclampsia affects 3%-5%)	0.005%-0.010%
Risk factors	Prior history	Multiparous, metabolic syndrome, HCV infection, personal or family history of ICP, ABCB11, ABCB4, and ATP8B1 mutations	Preexisting hypertension, DM, advanced maternal age, multiple gestations, previous history of preeclampsia	Primiparous, multiple gestations, male fetus
Clinical findings	Vomiting with weight loss ≥5% of prepregnancy body weight, dehydration	Generalized pruritus, especially palms and soles, without rash	Abdominal pain, nausea/vomiting; commonly have preeclampsia	Abdominal pain, nausea/vomiting, jaundice, hypoglycemia If hepatic failure, will have encephalopathy
Laboratory findings	Abnormal AST and ALT seen in ~ 50% but rarely >1,000 U/L and typically improve with hydration	AST and ALT 2-30 times the ULN	AST and ALT typically >500 units/L	AST and ALT 300-1,000 U/L
	Jaundice rare	Total bile acids >10 μmol/L	Platelets <50 L to 150 × 10^9/L Bilirubin <5 mg/dL	Low antithrombin III, elevated PT, low fibrinogen, elevated bilirubin, elevated LDH
	Ketonuria		Hemolysis (schistocytes, spherocytes, reticulocytes); hyperuricemia, markedly elevated LDH >600 units/L	Platelets <100,000 × 10^9/L
	Electrolyte abnormalities			If ALF, will have coagulopathy, hypoglycemia, hyperuricemia, and DIC
Diagnosis	Clinical	Clinical plus elevated bile acids >10 μmol/L are sufficient for diagnosis	Clinical + maternal organ dysfunction, including renal, hepatic, neurologic, or hematologic complications, uteroplacental dysfunction, or fetal growth restriction	Clinical
	Upper endoscopy rarely indicated	Elevated AST and ALT are frequent but not necessary for diagnosis US may exclude biliary causes if needed		Swansea criteria can be used (high sensitivity but low specificity if acute liver failure)

Abbreviations: DM, diabetes mellitus; LDH, lactate dehydrogenase; ULN, upper limit of normal.

metoclopramide, and promethazine (Table 4). Oral prednisolone therapy has no proven benefit; data for intravenous corticosteroids are conflicting but can be considered for severe disease.[353] If treated early, hyperemesis gravidarum is not usually associated with any major adverse maternal or fetal outcomes[354]; low birth weight and premature delivery have been associated, although long-term health effects are unknown.[355] Recurrence is high with subsequent pregnancies, although there is no association with chronic liver disease.

GUIDANCE STATEMENTS

- Treatment of hyperemesis gravidarum is supportive with rehydration, correction of electrolyte abnormalities, thiamine supplementation, and anti-emetic therapy.
- Liver chemistry abnormalities typically resolve with hydration and resolution of vomiting. Persistent liver chemistry abnormalities, despite symptom resolution, should prompt investigation for another etiology.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Epidemiology, Clinical Presentation, and Diagnosis

ICP is a common pregnancy-associated liver disease, affecting 0.4%-10% of pregnancies. The prevalence varies by geography and ethnicity,[356] with the highest rates initially reported in South America, particularly in Chile, in women of Araucanian admixture, as well as in Sweden and Baltic countries.[357] In the United States, prevalence of ICP is as high as 5.6% among Latina women.[358,359] Genetic, hormonal (estrogen and sulphated progesterone), and environmental factors have been linked with risk.[360] Maternal factors include advanced maternal age, multiparity, metabolic syndrome, and HCV infection. A personal or family history of ICP is a risk factor, with recurrent ICP reported in 40%-92% of these women.[361,362] Multiple gene mutations help explain the ethnic and familial clustering of ICP,[363] with the hepatic phospholipid transporter (adenosine triphosphate–binding cassette subfamily B member 4 [ABCB4]), the bile salt export pump (ABCB11), and ATP8B1 most frequently cited. Genetic testing should be considered in women with severe ICP (total bile acids >100 μmol), recurrent ICP, or early-onset ICP, given the increased likelihood of ABCB11, ABCB4, or ATP8B1 variants. Identification of these women is relevant to pregnancy and postpartum management, as some may have risk for progressive liver disease, gallstones and cholangitis,[364] and possibly even liver cancer.[365]

The classic symptom is generalized pruritus, most severe in the palms and soles without an accompanying rash, with typical onset in the second or third trimester; 80% of women present after 30 weeks of gestation, but ICP in the first trimester has been reported.[356] AST and ALT levels may be elevated, varying from 2-fold to 30-fold higher. It is important to consider other causes of pruritus and elevated liver tests in women with suspected ICP. Because pruritus can precede laboratory abnormalities, if initial testing of total bile acids is normal, repeat testing is indicated. Symptoms and laboratory tests are sufficient to make the diagnosis, with US used to exclude biliary causes in select cases (Table 7).

In a healthy pregnancy, a mild increase in total bile acids occurs, but levels remain within the reference range. Because most women without ICP have total bile acids less than 10 μmol, this threshold is frequently considered the upper limit of normal.[361] There is no consensus on whether to measure as fasting or postprandial, but in women with ICP, higher levels are detected postprandially.[366] The prevalence of intrauterine fetal demise (IUFD) is 0.1%, 0.3%, and 3.4% in women with serum total bile acids of >40, 40 to 99, and ≥100 μmol/L, respectively.[367] In a population-based study from Sweden, 20% of pregnant women with ICP had total bile acids ≥40 μmol/L and 80% between 10 and 40 μmol/L; the latter group had similar fetal outcomes as women without ICP.[368]

Maternal and Fetal Risks

Maternal complications of ICP are minimal, and serum aminotransferase elevations do not appear to influence maternal symptoms or fetal outcomes. Although symptomatic pruritus can reduce quality of life, this typically resolves within days to weeks postpartum. Pruritus management includes lifestyle measures and UDCA as first-line therapy,[369] with antihistamines, cholestyramine, rifampicin, and SAMe added for refractory symptoms. All appear safe in pregnancy (Table 4). ICP may increase risk for future gallstones and biliary fibrosis/cirrhosis.[364] These associations may be due to underlying chronic liver disease being misdiagnosed as ICP. Alternatively, women with genetic variants, including ABCB11, ABCB4 or ATP8B1, have a different risk profile than nongenetic variants and may have benign recurrent intrahepatic cholestasis or progressive familial intrahepatic cholestasis. Thus, follow-up of women with ICP postpartum is recommended to confirm resolution of liver test abnormalities, with further evaluation reserved for those with persistent symptoms or liver test abnormalities.

The main risks of ICP are to the fetus, with increased risk of preterm birth, meconium-stained amniotic fluid, neonatal respiratory depression and asphyxia, and IUFD. These adverse consequences are poorly understood. Proposed mechanisms include toxicity of bile acids on cardiomyocytes,[370] vasoconstrictive effect of bile acids on placental chorionic veins,[371] reduced lung surfactant and altered macrophage activity leading to respiratory distress syndrome,[372,373] and higher rates of intrauterine meconium passage due to bile acid–induced increase in fetal gut motility.[374]

The highest risk group is women with total bile acids ≥100 μmol/L.[359,367,375,376] Levels of bile acids in mother and fetus are correlated, supporting a causal relationship between bile acid levels and fetal complications.[359,375,377] IUFD appears to develop suddenly, and this contributes to the lack of specific recommendations on antenatal monitoring.

Pregnancy Management

No method of fetal monitoring has been shown either to predict those at risk of adverse perinatal outcomes or to reduce the risk of IUFD. Thus, monitoring should be guided by best obstetrical practice. The American College of Obstetricians and Gynecologists recommends delivery at 36-37 weeks or at diagnosis if diagnosed after 37 weeks.[378] Concerns regarding preterm deliveries have led some to recommend a more individualized approach, considering the known risks of iatrogenic preterm delivery (e.g., respiratory distress)[359] versus the small but less well-characterized risk of IUFD.[379]

UDCA reduces maternal and fetal bile acid levels.[380] A meta-analysis of nine randomized controlled studies, including 173 women with ICP and 303 non-ICP controls, showed UDCA (doses 450-1,000 mg per day) was associated with improved pruritus, serum ALT levels, and bile acid levels.[381] Although meta-analyses suggest that UDCA may reduce risk of fetal complications, differential use of early delivery based on bile acid levels and maternal symptoms confounds interpretation.[381] In the largest randomized, placebo-controlled study of UDCA in women with ICP (24% with baseline total serum bile acids ≥40 μmol/L) (n = 306 UDCA and 300 placebo), there was no difference between groups in the primary composite outcome of perinatal death, preterm delivery, and neonatal intensive care unit stay for greater than or equal to 4 hours: 23% in the UDCA group versus 27% in the placebo group (adjusted risk ratio, 0.85; P = 0.28).[382] Subgroup analyses limited to women with baseline total bile acids ≥40 showed no difference (18% in both groups),[382] but whether women with bile acids ≥100 μmol/L may benefit remains an open question, even though a *post hoc* analysis of this subgroup also found no difference. Thus, UDCA is regarded as a safe first-line therapy for management of pruritus and liver test abnormalities but has not been shown to reduce fetal complications. For refractory pruritus, rifampicin, cholestyramine, and SAMe have been suggested, but there is no evidence of benefit.[383-385] Cholestyramine, especially at high doses, can exacerbate vitamin K deficiency and the risk of fetal intracranial hemorrhage. Additionally, increased risk of postpartum hemorrhage related to vitamin K deficiency in women with ICP has led to the recommendation to monitor PT and treat mothers with vitamin K if the PT is elevated, although data are limited.[386,387]

GUIDANCE STATEMENTS

- Pruritus presenting in the second or third trimester plus total bile acids >10 μmol/L without other causes of pruritus is diagnostic for ICP. Elevation of AST and ALT are frequent but not required for the diagnosis.
- Women with ICP should be tested for HCV, if not previously performed.
- Pruritus management is multifaceted and includes UDCA (10-15 mg/kg) as first-line therapy. For refractory symptoms, antihistamines, cholestyramine, rifampin, and SAMe may be considered, although the evidence is scant.
- UDCA is safe in pregnancy and reduces serum bile acid levels, although data supporting a benefit in reducing fetal risks, including IUFD, are lacking.
- Vitamin K should be supplemented when PT is prolonged. More frequent monitoring of PT may be considered for women on cholestyramine.
- Women with persistent symptoms or elevated liver tests or total bile acids postpartum should be evaluated for other causes of chronic liver diseases, including genetic variants associated with cholestasis.

HYPERTENSIVE DISEASES OF PREGNANCY

Preeclampsia/Eclampsia

Preeclampsia-related liver disease is unique to pregnancy and is usually seen in the third trimester or immediately postpartum, but may occur earlier. It is a multisystem disorder defined as *de novo* hypertension after the 20th week of gestation with additional maternal organ dysfunction, including renal, hepatic, neurologic, or hematologic complications. Although proteinuria is often present, it is not required for

diagnosis (Table 7). Preeclampsia affects 3%-8% of pregnancies[388,389] and may be diagnosed in patients with preexisting hypertension (superimposed preeclampsia) if additional findings of worsening blood pressures, maternal organ dysfunction, or proteinuria are present.[24,390] Preeclampsia with severe features involves extreme elevations in systemic blood pressure and organ compromise. Eclampsia includes seizures in addition to the findings of preeclampsia. For preeclampsia without severe features, delivery is recommended at 37 weeks; however, delivery at 34 weeks is recommended with preeclampsia with severe features. Delivery for patients with eclampsia is as soon as possible after maternal stabilization, regardless of gestational age. Overlapping clinical features of preeclampsia are present in many patients with HELLP syndrome.

HELLP Syndrome

HELLP syndrome is present in 0.2%-0.6% of pregnancies and can occur in patients with normal blood pressure.[391] Most cases occur between weeks 27 and 37, with 20% occurring within 48 hours of delivery. The pathophysiology of HELLP syndrome involves inadequate placental perfusion, progressing to endothelial dysfunction and subsequent multisystem involvement with defective arterial placental perfusion.[392] The placenta releases nitric oxide, prostaglandins, and endothelin, which induce platelet aggregation, endothelial dysfunction, and arterial hypertension. In turn, fibrin is released from endothelial damage and forms cross-linked networks in small blood vessels, causing a microangiopathic hemolytic anemia. Hepatic involvement is thought to be secondary to fibrin deposition within the hepatic sinusoids, resulting in sinusoidal obstruction and subsequent hepatic ischemia, which can result in subcapsular hematomas, parenchymal hemorrhage, and hepatic rupture.[393]

HELLP syndrome is diagnosed clinically, and liver biopsy is not advised (Table 7). Patients may present with preeclampsia and HELLP syndrome asymptomatically. When symptoms are present, 65% of patients have weight gain and right upper quadrant pain or epigastric pain, 35% have nausea or vomiting, and 30% have headache as well as malaise. Jaundice is noted in up to 40% of patients.[391] Hypertension is present in 85% of cases, and proteinuria is commonly noted. Disseminated intravascular coagulation (DIC) can occur. Microangiopathic hemolytic anemia is the hallmark of the disorder.[394] The only treatment available for HELLP is delivery, which should occur as soon as maternal stabilization is achieved.

If abdominal pain, shoulder pain, or hypotension develop, imaging must be performed to rule out hepatic hemorrhage, rupture, or infarction, which can occur in up to 45% of patients.[395] Hepatic hemorrhage or rupture is associated with increased mortality. Management includes coagulation support, antibiotics, and transfusion. Urgent angiography and hepatic artery embolization or surgical intervention (packing of the liver, hepatic artery ligation, or resection) is indicated if supportive measures are unsuccessful.

GUIDANCE STATEMENTS

- In women with preeclampsia, delivery by 37 weeks is advised, with close monitoring for the development of eclampsia and HELLP syndrome.
- When HELLP syndrome or eclampsia are suspected, expeditious delivery is recommended after maternal stabilization.
- Abdominal imaging should be performed in suspected HELLP to rule out hepatic hemorrhage, infarct, or rupture.
- HELLP complicated by hepatic rupture or ALF should prompt transfer to a transplant center for evaluation.

ACUTE FATTY LIVER OF PREGNANCY

AFLP is a rare medical and obstetric emergency, occurring in the third trimester of pregnancy or postpartum, and described in 0.005%-0.010% of pregnancies.[396] AFLP is associated with significant perinatal and maternal mortality, and established risk factors include primiparous births, male infants, and twin pregnancies.[396] There is a strong association between AFLP and mitochondrial long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency in the fetus, although other fetal fatty acid oxidation disorders can be associated with maternal liver disease.[397] LCHAD deficiency in the fetus causes accumulation of hepatotoxic long-chain 3-hydroxy-fatty acyl metabolites that pass from the fetal to maternal circulation. Newborns of mothers with AFLP should be screened for LCHAD deficiency, given the risk of metabolic

crises and death within the first year of life. Genetic counseling is also indicated for affected mothers and their newborns. Newborns with LCHAD deficiency can be treated with dietary modifications with reduced morbidity and mortality.[398]

The clinical presentation of AFLP can sometimes be similar to preeclampsia and includes headache, malaise, nausea, vomiting, right upper quadrant or epigastric pain, and jaundice. Maternal consequences include hypoglycemia, renal failure, coagulopathy, hypertension, edema, and ascites, with hepatic encephalopathy occurring later in the disease. If hepatic encephalopathy occurs, there should be a high suspicion for AFLP. PT is prolonged, fibrinogen levels are reduced, and lactate dehydrogenase is elevated. DIC is noted in 10% of patients. These laboratory abnormalities help differentiate preeclampsia from AFLP. Infections, vaginal bleeding, or bleeding from cesarean delivery wounds are common. Although AFLP typically resolves on delivery, progression to ALF will require LT.[399] Intrahepatic hemorrhage or hepatic rupture can occur at a rate of less than 2%.[395,400]

The Swansea criteria have been used to bring uniformity to the diagnosis of AFLP across studies.[396,401-403] The presence of six or more of the following findings, in the absence of another cause, are highly correlated with a clinical diagnosis of AFLP: vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, elevated transaminases (AST or ALT >42 IU/L, elevated bilirubin (>0.8 mg/dL), hypoglycemia (<72 mg/dL), leukocytosis (>11 × 10^6/L), elevated uric acid (>5.7 mg/dL), elevated ammonia (>42 IU/L), ascites or bright liver on ultrasound, renal impairment (creatinine >1.7 mg/dL), coagulopathy (PT >14 seconds or partial thromboplastin time >34 seconds), or microvesicular steatosis on biopsy.[396] However, in women with severe AFLP with features of ALF, the Swansea criteria have high sensitivity, but low specificity.[404] AFLP is characterized histologically by microvesicular hepatic steatosis, although liver biopsy is not indicated unless the diagnosis is in doubt and/or the results of the biopsy would influence management. If done, tissue should be reserved for special stains (e.g., Oil Red O) or electron microscopy to confirm the presence of fat.

Early recognition of AFLP and rapid delivery are critical. Maternal mortality rates were as high as 92% before 1970, but have improved to less than 10% in recent years.[405,406] Outcomes of women with ALF undergoing LT due to AFLP are comparable to those of other indications.[407]

GUIDANCE STATEMENTS

- When AFLP is suspected, expeditious delivery is recommended after maternal stabilization.
- Diagnosis of AFLP can be made on clinical and laboratory parameters, and liver biopsy is rarely required.
- Abdominal imaging should be performed in AFLP to rule out hepatic hemorrhage, infarct or rupture, and presence of hepatic rupture or ALF should prompt transfer to a transplant center for evaluation.
- All newborns of mothers with AFLP should be screened at birth for long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency or other fatty acid oxidation defects; referral to genetic counseling is indicated for affected families.

Reproductive Health and Pregnancy in Transplant Recipients

The number of pregnancies in LT recipients is rising, and reproductive health is a central issue among recipients of childbearing age.[408-411] To best support reproductive intentions and to help prevent unintentional pregnancies, transplant providers should discuss family planning with patients, ideally pre-LT and in the early postoperative period. Of the 543 pregnancies reported to the Transplant Pregnancy Registry International from November 1985 through May 2018, 40% were unplanned.[412] Unplanned pregnancies were more frequent among younger patients and those with shorter time from transplant to conception, highlighting the importance of pregnancy planning and a more proactive approach to contraceptive counseling.[413-416]

MALE REPRODUCTIVE CONSIDERATIONS

Sex hormone levels in men with cirrhosis often normalize after LT,[417] which can lead to improved libido, reduced erectile dysfunction, and overall sexual

satisfaction. However, nearly 50% of men may have persistent erectile dysfunction after LT, and 20%-30% may develop *de novo* symptoms of sexual dysfunction.[418,419] Immunosuppressive medications can affect male fertility through effects on the hypothalamic-pituitary-gonadal axis and the testes. Calcineurin inhibitors (CNIs) decrease sperm counts and motility in animal models.[420] There are no clear effects of CNIs on circulating levels of follicle-stimulating hormone, luteinizing hormone, and testosterone.[421] In human studies, sirolimus causes seminiferous tubule dystrophy, decreased sperm counts and motility, altered testosterone synthesis in Leydig cells, impaired spermatogenesis,[420] and increases in gonadotropic-releasing hormone, luteinizing hormone, and follicle-stimulating hormone with lower free testosterone levels.[422-424] Limited data exist on gonadal function and fertility with everolimus.

The FDA recommends that sexually active male patients and/or their female partners use effective contraception while using MPA products and for at least 90 days after discontinuation, and that men avoid sperm donation for at least 90 days after discontinuation.[425] However, there are no clear human data of a negative effect of mycophenolate on gonadal function or fertility. Favorable outcomes are seen in pregnancies fathered by men who underwent transplantation and are taking MPA-inclusive immunosuppressants,[426,427] although more data are needed.

PREGNANCY CONSIDERATIONS

Most women resume regular menses within a year of LT, although ovulation may resume as early as the first month.[4,428] Pregnancy is associated with higher risk of maternal and fetal complications in transplant recipients, particularly if unplanned or occurring within the first year.[415,429,430] The American Society of Transplantation suggests that LT recipients wait at least 1 year after LT before conceiving, with consideration of recent rejection, infections (such as cytomegalovirus), stability of graft function, and immunosuppressive regimen when planning pregnancy.[431]

CNIs (cyclosporine and tacrolimus) are the mainstay of immunosuppression for LT patients. Established CNI side effects could influence pregnancy outcomes.[429,430] Earlier data reported intrauterine growth restriction and hypertension, preeclampsia, and premature rupture of membranes leading to premature delivery in transplant recipients on tacrolimus.[432,433] However, the largest data derive from the Transplant Pregnancy Registry International and demonstrate favorable pregnancy outcomes with CNI use, and CNIs are considered compatible with pregnancy (Table 5).[412,434]

Optimal dosing of CNIs in pregnant LT patients is unknown. Multiple physiologic changes in pregnancy influence the metabolism of tacrolimus, including increased cytochrome P450 3A (CYP3A) activity, increased glomerular filtration rate, increased renal transporter activity (such as P-glycoprotein), altered CNI volume of distribution due to weight gain and increased total body water, and decreases in hemoglobin and albumin levels that affect tacrolimus binding and reduce whole-blood concentrations of tacrolimus trough levels.[435] Importantly, the unbound concentration of tacrolimus, the active form of the drug, remains unchanged despite decreased hemoglobin and albumin levels. Thus, goals for target tacrolimus trough levels in pregnancy should be established based on the patient's medical history, history of allograft function, and the potential impact of the unbound concentration on the patient's health and course of pregnancy. Given the need to balance these issues, close monitoring should occur, with measurement of trough levels every 2-4 weeks.

As discussed earlier, MPAs are contraindicated in pregnancy,[436-440] and, given their higher failure rates, contraceptive agents other than the subcutaneous implant or IUDs should be combined with a barrier method in patients on MPAs. Azathioprine was used widely in the early era of solid-organ transplantation, but its use has been replaced by CNIs and mycophenolate. The use of azathioprine and its metabolite, 6-mercaptopurine (6-MP), in pregnancy were reviewed earlier. Substitution of MPA with either of these agents in LT recipients seeking pregnancy is a reasonable immunosuppression strategy, with or without dose up-titration or addition of prednisone.

Data on mammalian target of rapamycin (mTOR) inhibitors in pregnancies are limited (Table 5). Transplant Pregnancy Registry International data identified a miscarriage rate of 31% (18) of 57 pregnancies in transplant recipients with sirolimus exposure, but 19 of those 57 pregnancies also had concomitant MPA exposure.[412] The reported miscarriage rate with everolimus exposure was 17%, with no MPA

exposures reported.[412] Birth defects were seen in 5 infants (2 with concomitant MPA).[412] Given the limited safety data, mTOR inhibitor use in pregnancy is not recommended.

LACTATION CONSIDERATIONS

Available data indicate that the average daily ingestion of tacrolimus through breast milk is minimal: between 0.06% and 0.5% of the mother's weight-adjusted dose.[441-443] Breastfed infants of mothers on cyclosporine with whole-blood trough levels of 55-130 ng/mL all had undetectable cyclosporine levels.[444] Corticosteroids, azathioprine, cyclosporine, and tacrolimus are considered safe for breastfeeding.[445] Mycophenolate, sirolimus, and everolimus in lactation are not recommended due to paucity of data. LactMed, an online medical reference, provides up-to-date information on the safety of medications in lactation.[445]

MATERNAL, FETAL, AND GRAFT OUTCOMES

Maternal mortality and fetal/neonatal survival do not differ significantly between LT recipients and the U.S. general population, but maternal and fetal complications are higher.[408,446] Maternal complications, including hypertensive diseases of pregnancy, postpartum hemorrhage, placental abruption, cesarean delivery, preterm delivery and coagulopathy, are found at a higher rate in pregnant LT recipients. Additionally, LT recipients are 4-fold (95% CI: 5.6-12.8) more likely to have severe maternal morbidity, as determined by CDC criteria, during the delivery hospitalization compared with their non-LT counterparts.[408]

Maternal and Graft Complications

Preconception diabetes is common among LT recipients, and pregnant LT recipients have an approximately two-fold higher risk of GDM than nontransplant patients.[447] GDM incidence rates are approximately 10%,[430,434,448] with numerically higher rates with tacrolimus-based versus cyclosporine-based immunosuppression.[430,434] Earlier glucose tolerance tests in the first trimester have been advocated,[449,450] with aggressive glycemic control to attenuate gestational diabetes-associated risks.[451-453]

Hypertensive disorders, including preeclampsia,[447] are more frequent in LT recipients. Preeclampsia incidence varies by immunosuppressive regimen: 22%-29% with corticosteroids, 68%-73% with cyclosporine, and 47%-54% with tacrolimus.[439] The continuum of hypertensive disorders includes chronic hypertension, gestational hypertension, and preeclampsia, with many studies failing to distinguish these disorders. In a meta-analysis of eight studies, inclusive of 450 pregnancies in 306 LT recipients, the pooled rate of preeclampsia was 21.9% (95% CI, 17.7-26.4).[416] In the 2018 Transplant Pregnancy Registry International report, 20% of pregnant LT recipients experienced preeclampsia.[412] This increased incidence likely relates to the vasoconstrictive effects of CNIs and altered renal function. Hypertension and preeclampsia are associated with preterm delivery and intrauterine growth restriction[430,434]; thus, blood pressure control before conception and during pregnancy is paramount.[454]

Most studies have not found higher rates of graft loss attributable to pregnancy.[409,416,430] The Transplant Pregnancy Registry International reports rejection episodes in 4.4% of pregnant women (acute or chronic), with 3.0% of women experiencing graft loss within 2 years of delivery.[412] A prospective study of 139 pregnancies from the United Kingdom found rejection requiring treatment in 7.7% during pregnancy and 1.4% within 3 months of delivery.[429] Across studies, postpartum rejection is reported in less than or equal to 10%, with estimates influenced by presence of biopsy-proven rejection.[409,430,455] Rates of acute cellular rejection are higher in women conceiving at less than 12 months versus greater than 12 months following LT (46% vs. 11%, respectively; $P = 0.001$),[430] highlighting the importance of graft stability before conception.[415,430,456]

Fetal Complications

In general, fetal outcomes are favorable. Pooled estimates indicate a live birth rate of approximately 75%, which is greater than observed in the general population (67%).[416] Stillbirths and ectopic pregnancy rates are low. Preterm birth is more common in LT recipients than the general population (27% vs. 11%; $P < 0.001$) as well as lower-birth-weight infants and intrauterine growth restriction (5% vs. 2%; $P = 0.05$).[446]

Infant outcomes are affected by pregnancy planning. Termination rates are lower with planned (0.9%) versus unplanned (approximately 6%) pregnancies.[412] Data on unplanned pregnancies found no maternal deaths in the first month postpartum, although 2.5% of infants died during this period.[412] Notably, there were no infant deaths among those born from planned pregnancies during follow-up. In the absence of MPAs, birth defects in infants born to LT recipients is low, with a numerically higher number reported in the Transplant Pregnancy Registry International born from unplanned versus planned pregnancies (7.7% vs. 4.0%).[412]

GUIDANCE STATEMENTS

In liver transplant recipients:

- Mycophenolic acid products are contraindicated in pregnancy and lactation, and contraceptive agents with low failure rates should be used.
- Pregnancy should be delayed until at least 1 year after transplant and with greater than or equal to 6 months of stable graft function.
- CNIs, azathioprine/6-MP, and corticosteroids are acceptable for use in pregnancy and lactation.
- mTORs are not recommended in pregnancy or lactation due to lack of safety data.
- CNI trough levels should be obtained every 2-4 weeks during pregnancy, with dosing guided by levels and liver tests.
- More frequent monitoring of graft function during pregnancy and in the postpartum period is recommended.
- Mode of delivery should be guided only by obstetric indications.

Future Directions and Areas of Additional Research

Additional research is needed in several important areas in reproductive health and liver diseases, including the following:

1. A prospective, multicenter pregnancy registry for adolescents and adults with chronic liver disease to comprehensively define incidence, natural history, and long-term outcomes of mothers and their children.
2. Clinical studies to determine the safety of medications to treat sexual dysfunction in the setting of liver disease and the effects of hormonal therapies on liver-related health, including transgender populations.
3. Evaluation of systems-level interventions to help improve transition from adolescent to adult care, with specific focus on evaluating and managing reproductive health in teens and young adults with chronic liver disease.
4. Prospective, controlled studies to evaluate the safety of hormonal contraception in the setting of chronic liver disease and LT, including whether dose and type of hormonal agents confer differential risks.
5. Larger-scale clinical trials of DAA therapy in pregnant women with chronic hepatitis C.
6. Clinical studies to determine safety and efficacy of TAF in pregnant women with chronic hepatitis B.
7. Longitudinal studies of pregnancy outcomes among patients with fatty liver, with specific attention to long-term cardiometabolic and liver-related risks to mothers and children.
8. Additional studies to define risk groups and efficacy of UDCA in patients with ICP.
9. Studies on HCAs in pregnancy, particularly for adenomas greater than 5 cm in diameter, to define the risk of complications and need for adenoma treatment before or during pregnancy.
10. Studies to determine the best timing for preconception variceal screening among patients with cirrhosis (6 vs. 12 months before conception) and whether primary prophylaxis of variceal hemorrhage among pregnant patients should differ from nonpregnant patients.

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