Pregnancy in women with pre-existing chronic liver disease

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INTRODUCTION

Liver disease in pregnant women can be seen in three general settings:

- The patient has liver disease induced by pregnancy, such as:
  - Hyperemesis gravidarum (see "Nausea and vomiting of pregnancy: Clinical findings and evaluation" and "Nausea and vomiting of pregnancy: Treatment and outcome")
  - Preeclampsia or the HELLP syndrome (hemolysis, elevated liver tests, and low platelets) (see "Preeclampsia: Clinical features and diagnosis" and "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)")
  - Intrahepatic cholestasis of pregnancy (see "Intrahepatic cholestasis of pregnancy")
  - Acute fatty liver of pregnancy (see "Acute fatty liver of pregnancy")
- The patient has developed a new liver disease during pregnancy
- The patient has pre-existing chronic liver disease

In order to avoid unintended pregnancy, patients with chronic liver disease should be counseled about contraceptive options, and the method of contraception provided must take the specific liver disease into account. Furthermore, patients contemplating pregnancy should have preconception counseling and disease-specific risk evaluation. (See "The preconception office visit".)

When a woman with chronic liver disease becomes pregnant, two separate issues arise [1,2]:

- What will be the effect of the liver disease or its treatment on the pregnancy and fetus, and
- How will pregnancy affect the health of the patient

This topic will review pregnancy in women with pre-existing chronic liver disease, including the effects on the fetus and on the patient. Pregnancy in women with chronic hepatitis B virus infection, the development of liver disease brought on by pregnancy, and the development of new (not pregnancy-related) liver disease during pregnancy are discussed elsewhere. (See "Hepatitis B and pregnancy" and "Approach to evaluating pregnant patients with elevated liver biochemical and function tests" and "Overview of coincident acute hepatobiliary disease in pregnant women".)

CONTRACEPTION

Contraceptive need — Although patients with decompensated cirrhosis generally have decreased fertility, pregnancy is still possible [1]. While those with chronic liver disease without advanced fibrosis or compensated cirrhosis do not have diminished fertility, such patients may be at risk for complications. Women with chronic medical conditions are less likely to use highly effective contraception, and many pregnancies in women with cirrhosis are unplanned [3,4]. Thus, family planning and contraceptive needs are discussed with all patients of reproductive potential, including transgender and gender nonconforming patients. Further, patients with liver disease may ovulate irregularly or be intermittently anovulatory, which makes fertility difficult to assess [5].

Approach to contraceptive selection — Information to guide the selection of contraception in women with medical disorders is available through the World Health Organization (WHO Medical Eligibility Criteria), the United States Centers for Disease Control (United States Medical Eligibility Criteria for Contraceptive Use), and, in some cases, country-specific medical eligibility criteria. While the guidelines are generally similar, clinicians should use the one that best matches their population. When discussing contraceptive options with a patient who has chronic liver disease, the risks and side effects of the methods below must also be balanced against the risks of pregnancy, should it occur. The American Association for the Study of Liver Disease (AASLD) has developed practice guidance addressing reproductive health and liver disease to assist clinicians in managing this population [6]. In addition, general information on counseling women about contraceptive selection is available elsewhere. (See "Contraception: Counseling and selection".)

Choice of the specific hormonal contraceptive method is guided by patient preferences around dosing schedule, mode of drug delivery, noncontraceptive benefits (eg, menstrual cycle regulation), and side effects.

While the patient ultimately selects the contraceptive method, the following outlines an approach to thinking about contraception in patients with chronic liver disease:

- For patients who desire the most effective contraception or durable contraception, we discuss long-acting reversible contraceptives (LARCs), including the copper intrauterine device (IUD), levonorgestrel-releasing IUDs, and the etonogestrel implant (figure 1). These methods require minimal user action, have failure rates of less than 1 percent, have high continuation rates, and last from 3 to 12 years, depending on the device. Patients with normal liver function can use any of the LARC methods without restriction, including liver transplant recipients [7,8]. However, clinicians should be aware that the manufacturer's inserts for all levonorgestrel-releasing IUDs list acute liver disease or tumor as contraindications to use, but supporting evidence is not provided [9-12]. Both the levonorgestrel-releasing IUDs and the etonogestrel implant can reduce menstrual volume, which can be helpful in women with heavy menstrual bleeding. The copper IUD contains no hormones and thus can also be used by patients with severe liver disease, including decompensated cirrhosis, whereas the levonorgestrel IUDs and etonogestrel implant are avoided in patients with severe disease, Budd-Chiari syndrome, hepatocellular adenomas, and transplant recipients with graft failure [6-8]. However, as the copper IUD can also increase menstrual volume, we prefer to avoid it in patients with thrombocytopenia or heavy menstrual bleeding. The copper IUD is not used in patients with Wilson disease [13].

  Detailed descriptions of the IUDs and implant are presented separately.

  - (See "Intrauterine contraception: Background and device types".)
  - (See "Intrauterine contraception: Candidates and device selection".)
  - (See "Contraception: Etonogestrel implant".)

- For patients who do not find LARC methods acceptable or who desire contraception for only a short timeframe, and who have normal hepatic function, we discuss short-acting hormonal contraception. These methods include combined estrogen-progestin products (oral pills, transdermal patch, and vaginal rings) and progestin-only methods (depot medroxyprogesterone acetate injections and progestin-only oral pills). These methods are highly effective when used correctly and consistently, although they are less effective than LARC methods (figure 1). Although estrogens and progestins are metabolized by the liver, use of these products in patients with chronic liver disease has not been associated

with worsening of the underlying disease or supratherapeutic levels of hormones [14]. However, these products are not advised for patients with decompensated cirrhosis, and initiation of estrogen-containing contraception is avoided in patients with increased risk of thromboembolism [7,8,14]. Women with hepatocellular adenoma (HCA) are cautioned about the use of estrogen-containing contraception, and this is discussed separately [15]. (See "Hepatocellular adenoma".)

Detailed descriptions of the hormone-containing short-acting contraceptives are presented in other topics.

- (See "Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use".)
- (See "Combined estrogen-progestin contraception: Side effects and health concerns".)
- (See "Contraception: Hormonal contraceptive vaginal rings".)
- (See "Contraception: Transdermal contraceptive patches".)
- (See "Depot medroxyprogesterone acetate (DMPA): Efficacy, side effects, metabolic impact, and benefits".)
- (See "Depot medroxyprogesterone acetate (DMPA): Formulations, patient selection and drug administration".)
- (See "Contraception: Progestin-only pills (POPs)".)

- Patients at risk of sexually transmitted infection are advised about consistent condom use (male or female) even if other contraceptive methods are being used. (See "External (formerly male) condoms" and "Internal (formerly female) condoms".)

CIRRHOSIS AND PORTAL HYPERTENSION

Management of pregnant women with cirrhosis and portal hypertension involves a multidisciplinary team (maternal-fetal medicine, hepatology). Preconception counseling is advised for all women with cirrhosis who are contemplating pregnancy. Assisted reproduction in women with cirrhosis is not contraindicated, but Child-Pugh class B or C cirrhosis has been associated with higher risk of complications. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Child-Pugh classification' and "In vitro fertilization: Overview of clinical issues and questions".)

While pregnancy is generally uncommon in women with cirrhosis, pregnancy rates in such patients have been increasing [16-18]. In a database study including 339 pregnant women with cirrhosis who were admitted to the hospital, the mean number of deliveries increased annually

from 68 (1993 to 1999) to 106 (2000 to 2005) [17]. In a cohort study including 2022 women with cirrhosis, the incidence of childbirth increased from 2.0 to 14.9 births per 100,000 person-years from the year 2000 to 2016 [16]. This trend is expected to continue with the increasing incidence of cirrhosis in women of childbearing age in the North America and Europe [18,19].

Maternal complications — Maternal complications in pregnant women with cirrhosis include liver-related events and pregnancy-related events (see 'Pregnancy outcomes' below):

- Pregnancy related complications – Pregnancy in women with cirrhosis has been associated with higher risk of pregnancy-related complications. In a cohort study of 2022 pregnant women with compensated cirrhosis (median maternal age at conception: 31 years), the most common etiology of cirrhosis was nonalcohol-associated fatty liver disease (NAFLD), and women with NAFLD were more likely to have baseline metabolic complications (pre-pregnancy diabetes, hypertension, obesity, dyslipidemia). Women with compensated cirrhosis were more likely to have complications such as hypertension, intrahepatic cholestasis of pregnancy (ICP), antepartum and postpartum hemorrhage, preterm birth, and puerperal infections compared with women in the general population [16]. For example, after adjusting for demographic and metabolic factors, cirrhosis was associated with a higher risk of intrahepatic cholestasis of pregnancy (ICP) (risk ratio [RR] 10.64, 95% CI 7.49-15.12). (See "Intrahepatic cholestasis of pregnancy".)

- Liver related complications – Although women with cirrhosis can sustain pregnancy without worsening of hepatic function [20], some women develop liver-related complications, with ascites reported in 10 to 25 percent and variceal bleeding in 7 to 42 percent of women [4,20-22]. In a study of 29 women and a total of 62 pregnancies, liver-related complications occurred in 10 percent of patients and were associated with higher Model for End-stage Liver Disease (MELD) scores at the time of conception [4]. A preconception MELD score of ≥10 was a risk factor for hepatic decompensation during pregnancy. The MELD scoring system is a prognostic model for estimating disease severity and survival in patients with chronic liver disease. (See "Model for End-stage Liver Disease (MELD)".)

  In a cohort study including 2022 pregnant women with compensated cirrhosis, 34 patients (2 percent) experienced hepatic decompensation, and the majority of decompensating events occurred prior to delivery [16]. Variceal hemorrhage was the most commonly reported event (21 women [62 percent]), followed by ascites, hepatic failure, hepatic encephalopathy and hepatorenal syndrome. Six women (0.3 percent) died. This has been a significant improvement over historical cohorts where mortality of up to 10 percent was reported, possibly reflecting improvements in recognizing and managing complications of

cirrhosis. However, early studies generally captured data from referral centers which may have included more women with decompensated liver disease.

As the increase in total blood volume associated with pregnancy may worsen portal hypertension, rates of variceal hemorrhage are higher after the second trimester. Compression from the gravid uterus combined with repeated Valsalva maneuvers further increase bleeding risk during the second stage of labor [4,23-26]. Variceal bleeding during pregnancy should be managed similarly to nonpregnant patients, and management of variceal bleeding including pharmacologic and endoscopic therapy is discussed separately. (See "Overview of the management of patients with variceal bleeding" and "Methods to achieve hemostasis in patients with acute variceal hemorrhage".).

Measures to control increased pressure transmitted to collateral vessels during labor can be helpful. One method to avoid straining during delivery is to place an epidural early in labor and allow the infant to descend with uterine contractions alone. Delivery is then assisted using low forceps or vacuum extraction. (See "Assisted vaginal birth".)

Spontaneous rupture of a splenic artery aneurysm is a rare complication of pregnancy in women with portal hypertension and is also a known complication of pregnancy in patients without portal hypertension [27]. (See "Approach to acute abdominal/pelvic pain in pregnant and postpartum patients", section on 'Visceral artery aneurysm rupture' and "Splenomegaly and other splenic disorders in adults", section on 'Splenic artery aneurysm'.)

Assessing risk for variceal bleeding — The bleeding risk for women with portal hypertension is ideally evaluated prior to conception [28]. Women with cirrhosis or portal hypertension who desire pregnancy should have an upper endoscopy to look for varices before pregnancy. If present, patients should be informed of the increased risk of gastrointestinal hemorrhage with pregnancy. If not previously done, upper endoscopy should be performed in the second trimester. (See "Pathogenesis of variceal bleeding in patients with cirrhosis".)

Patients at high risk for variceal hemorrhage should receive primary prophylaxis with nonselective beta blockers or undergo endoscopic variceal ligation. Carvedilol is a nonselective betablocker with mild anti-alpha 1 adrenergic activity that results in greater reduction in portal pressure [29]. Selecting a preventive strategy, including contraindications to beta blocker use, are discussed in detail separately. (See "Primary prevention of bleeding from esophageal varices in patients with cirrhosis".)

Prophylaxis with beta blockers should be continued during pregnancy, but newborns should be monitored during the first days of life because of risks of hypoglycemia and bradycardia. Both

salvage and preventive transjugular intrahepatic portosystemic shunt (TIPS) placement has been reported during pregnancy [30]. In addition, all patients should be monitored by a maternal fetal medicine specialist. (See "Overview of transjugular intrahepatic portosystemic shunts (TIPS)".)

Pregnancy outcomes — Data have suggested that cirrhosis was associated with higher rates of adverse maternal and infant outcomes [4,17,20,31,32]. The incidence of stillbirths and premature delivery was increased in women with cirrhosis or portal hypertension [4,20,31]. In a retrospective cohort study of 31 women with cirrhosis, the rate of at least one obstetrical complication (ie, preterm delivery, preeclampsia, placental abruption, small for gestational age, and fetal or neonatal death) was higher in women with cirrhosis compared with a control group without cirrhosis, matched for maternal age, parity, and body mass index (61 versus 12 percent, odds ratio [OR] 11.5, 95% CI 4.7-28.4) [31]. There were three cases of fetal or neonatal deaths in women with cirrhosis compared with none in the control group [31]. In a study of 29 women with a total of 62 pregnancies, the live birth rate was 58 percent, with a median gestational age of 36 weeks. Higher MELD/MELD-Na scores and higher Child-Pugh scores were associated with preterm delivery [4]. (See "Model for End-stage Liver Disease (MELD)" and "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Child-Pugh classification'.)

Spontaneous fetal loss occurred in 26 percent of pregnancies (19 percent were miscarriages prior to 20 weeks gestation, and 6 percent were stillbirths after 20 weeks gestation). It should be noted that published reports may be biased toward complications, leading to an overestimation of the risk. Although maternal and infant outcomes were substantially better in a subsequent cohort study including 2022 pregnant women with compensated cirrhosis, infant mortality was higher for mothers with cirrhosis compared with the general population (0.7 versus 0.3 percent) [16]. Infants born to mothers with compensated cirrhosis were more likely to be large for gestational age. In addition, the risk of stillbirth, respiratory distress, or death within one year of birth was higher in women with cirrhosis compared with the general population.

CHRONIC VIRAL HEPATITIS

Chronic hepatitis B virus — Chronic hepatitis B virus infection in pregnancy is discussed separately. (See "Hepatitis B and pregnancy".)

Chronic hepatitis C virus — Hepatitis C virus (HCV) infection rates in women of reproductive age have been increasing [33]. We agree with recommendations from the CDC and other

professional societies to screen pregnant individuals for HCV during each pregnancy [34-37]. (See "Screening and diagnosis of chronic hepatitis C virus infection".)

Most women chronically infected with HCV will have an uneventful pregnancy without worsening of liver disease or other adverse effects on the mother or fetus [38]. However, some studies evaluating the impact of chronic HCV on hepatic, maternal, and fetal outcomes have suggested potential harms. In a population-based cohort study, infants of HCV-positive mothers were more likely to be of low birth weight (odds ratio [OR] 2.2, 95% CI 1.2-3.8), small for gestational age (OR 1.5, 95% CI 1.0-2.1), need assisted ventilation (OR 2.4, 95% CI 1.4-3.9), or require neonatal intensive care (OR 2.9, 95% CI 1.9-4.6) [39]. There were nonsignificant trends for low APGAR scores (OR 1.5, 95% CI 0.9-2.5), prematurity (OR 1.5, 95% CI 1.0-2.4), and neonatal jaundice (OR 1.3, 95% CI 0.8-1.9) being associated with HCV.

In addition, studies have confirmed that maternal HCV infection is associated with an increased risk for intrahepatic cholestasis of pregnancy [40]. (See "Intrahepatic cholestasis of pregnancy".)

An improvement in serum aminotransferase concentrations in pregnant women with chronic HCV has been observed in some reports, possibly related to the immune suppressive state during pregnancy [41-43]. Aminotransferase levels typically return to baseline postpartum.

Studies have had conflicting results regarding the effect of pregnancy on histologic progression in women with chronic HCV, but most suggest minimal impact. Still, at least one study suggested that pregnancy may be associated with worsening histology on liver biopsy [44]. Twelve HCV-positive women who underwent liver biopsies before and after pregnancy were compared with 12 matched HCV positive controls who underwent paired liver biopsies but did not have an intervening pregnancy. Women who had been pregnant were more likely to have worsening of the necroinflammatory and fibrosis scores on liver biopsy compared with women who had not been pregnant. By contrast, another study found that pregnancy was associated with improvement in long-term progression of fibrosis [45].

Transmission of HCV from the mother to the newborn can occur, with estimated rates of transmission between 3 and 10 percent [40,46]. Some studies have suggested that viral load was associated with increased risk of mother to child transmission [40]. Issues surrounding vertical transmission of HCV including risk factors, management of HCV-infected women, labor and delivery management, neonatal diagnosis, and breastfeeding are discussed in detail separately. (See "Vertical transmission of hepatitis C virus".)

HCV exposure with resolved infection does not appear to impact pregnancy outcomes [40].

Hepatitis E — Issues related to hepatitis E in a woman who is pregnant are discussed in detail elsewhere. (See "Hepatitis E virus infection", section on 'Pregnant women'.)

NONVIRAL LIVER DISEASES

Autoimmune hepatitis — Pregnancy in women with autoimmune hepatitis is discussed separately [47]. (See "Management of autoimmune hepatitis", section on 'Pregnancy'.)

Primary biliary cholangitis — The course of primary biliary cholangitis (PBC) during pregnancy is uncertain. Case reports have demonstrated that the disease may remain quiescent, improve, or worsen during pregnancy [48-50]. Treatment of PBC most commonly involves ursodeoxycholic acid (UDCA), which studies have suggested is safe during pregnancy [51]. (See "Intrahepatic cholestasis of pregnancy", section on 'Ursodeoxycholic acid'.) Obeticholic acid and fibrates are not used during pregnancy due to lack of safety data [6]. (See "Overview of the management of primary biliary cholangitis".)

Recommendations for management of PBC during pregnancy have been proposed in practice guidance issued by the American Association for the Study of Liver Diseases [52]. The guidance statement advises screening for varices in the second trimester and treating with nonselective beta blockers if indicated.

Primary sclerosing cholangitis — Data are limited with regard to pregnancy in women with primary sclerosing cholangitis (PSC). One series from Germany compared 229 patients with PSC with 569 healthy controls [53]. Patients with PSC did not differ significantly from healthy controls with regard to the number who had children or the mean number of children per person (53 versus 53 percent and 1.06 versus 1.01, respectively). In a population-based study from Sweden, 229 singleton births from women with PSC were compared with over two million births from mothers without PSC [54]. PSC was associated with increases in the risks of preterm birth and need for cesarean delivery (adjusted prevalence odds ratios [OR] of 3.6 and 2.2, respectively) independent of coexisting inflammatory bowel disease, but it was not associated with small for gestational age, congenital anomalies, stillbirth, or neonatal death. According to the results of this study, pregnancy should not be discouraged in women with PSC [54].

Wilson disease — Women who have been anovulatory because of Wilson disease can regain their fertility when treated, often quite promptly. Maintaining therapy during pregnancy is important because interrupting therapy has been associated with hemolytic episodes with hepatic insufficiency and maternal death. The treatment of pregnant women with Wilson disease is discussed elsewhere [55]. (See "Wilson disease: Treatment and prognosis".)

Patients with Wilson disease and cirrhosis may be at increased risk for obstetrical complications such as intrauterine growth restriction and preeclampsia, and they should be referred to a maternal-fetal medicine specialist.

Hepatocellular adenoma — Hepatocellular adenoma (HCA) has been associated with estrogen use (eg, oral contraceptives), and HCA may grow during pregnancy [56]. For pregnant women with HCA, surveillance imaging is performed, and if the lesion becomes symptomatic or large, patients are evaluated for intervention (eg, surgical resection) [57]. Management of patients with HCA is discussed separately. (See "Hepatocellular adenoma".)

Other solid liver lesions — Women with asymptomatic focal nodular hyperplasia (FNH) do not require monitoring during pregnancy because this liver lesion is not hormone sensitive [58]. (See "Focal nodular hyperplasia".)

Women with hepatic hemangioma who are asymptomatic do not routinely require monitoring during pregnancy, and this is discussed separately. (See "Hepatic hemangioma", section on 'Pregnancy'.)

Familial hyperbilirubinemia — The unconjugated hyperbilirubinemia of Gilbert syndrome is not exacerbated by pregnancy [59]. By comparison, the conjugated hyperbilirubinemia of Dubin-Johnson syndrome may worsen during gestation but returns to baseline levels after delivery [60]. (See "Gilbert syndrome" and "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Dubin-Johnson syndrome'.)

Familial intrahepatic cholestatic syndromes — Examples of these rare diseases include Alagille syndrome and Byler syndrome (progressive familial intrahepatic cholestasis). Reports of pregnancy in such patients are infrequent but, if pregnancy occurs, the underlying cholestasis may worsen [61]. (See "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Alagille syndrome' and "Inherited disorders associated with conjugated hyperbilirubinemia", section on 'Progressive familial intrahepatic cholestasis'.)

Porphyria — These genetic disorders of heme metabolism can be exacerbated by estrogenic hormones and may cause maternal and fetal problems during pregnancy. Porphyria cutanea tarda, which is often associated with chronic hepatitis C, has rarely been reported to have its initial presentation during pregnancy [62]. (See "Porphyrias: An overview" and "Extrahepatic manifestations of hepatitis C virus infection", section on 'Porphyria cutanea tarda'.)

Recurrent attacks may occur during pregnancy in patients with acute intermittent porphyria, variegate porphyria, or hereditary coproporphyria and may be associated with intrauterine growth restriction or, rarely, maternal death [63-65].

In a population-based study, women with the heritable form of porphyria cutanea tarda or with active acute porphyria during pregnancy had an excess risk of perinatal death (adjusted odds ratio [AOR] 4.9) [65]. Sporadic porphyria cutanea tarda was associated with an excess risk of small for gestational age (AOR 2.0), and for first-time mothers, low birth weight (AOR 3.4) and premature delivery (AOR 3.5).

Budd-Chiari syndrome — Women with known Budd-Chiari syndrome (BCS) have become pregnant after the BCS has been treated and is well controlled. However, fetal outcomes remain relatively poor, possibly because of underlying prothrombotic disorders, and patients are counseled regarding fetal and maternal risk. In one study of 24 pregnancies, seven were lost prior to week 20, and there was one stillbirth [66]. In addition, two patients delivered between weeks 20 and 31, and 11 patients delivered between weeks 32 and 36. Finally, two patients developed symptomatic thrombotic complications. In another study including 80 women with BCS with >8 year follow-up, 60 women (75 percent) conceived before symptom onset, and live birth rates were higher for women during treatment for BCS compared with prior to treatment (18 versus 0 percent) [67]. (See "Budd-Chiari syndrome: Management".)

Treatment for BCS typically includes anticoagulation; however, warfarin is avoided during pregnancy. Thus, pregnant women are treated with low molecular weight heparin (LMWH) [68]. Multidisciplinary care is usually required for these patients, including the involvement of a hepatologist, hematologist, obstetrician, and maternal-fetal medicine specialist.

Nonalcohol-associated fatty liver disease — Nonalcohol-associated fatty liver disease (NAFLD) is characterized by hepatic steatosis in the absence of excessive alcohol use. In women of reproductive age, estimated NAFLD rates up to 18 percent have been reported [69-71]. However, rates may be much higher. In a cohort study using hospital discharge data, pregnancies impacted by NAFLD tripled from 2007 to 2015 [72]. Subsequent data from the United States National Health and Nutrition Examination Surveys (NHANES) found that 40 percent of the population between the ages of 15 and 39 had NAFLD as defined by vibration-controlled transient elastography (VCTE), and 20 percent of those with NAFLD had significant fibrosis (ie, F3 or greater) [71]. In a study using national administrative health care data, NAFLD was the most common etiology for cirrhosis during pregnancy (accounting for 72.5 percent of pregnancies with cirrhosis) [73]. The epidemiology and clinical features of NAFLD in the general population and the association of NAFLD with other disorders (eg, polycystic ovarian syndrome) are discussed separately [74]. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults" and "Clinical manifestations of polycystic ovary syndrome in adults".)

Data have suggested that gestational diabetes mellitus (GDM) is associated with NAFLD [69,72,75]. In a study including 608 pregnant women who had a liver ultrasound during the first trimester, women with hepatic steatosis had higher rates of GDM during the second trimester compared with women without steatosis (56 versus 16 percent) [69]. In addition, GDM was associated with development of NAFLD postpartum. In a large cohort study with 25 year follow-up, women with a history of GDM had higher rates of NAFLD compared with no GDM (14 versus 6 percent, OR 2.56, 95% CI: 1.44–4.55) [72]. (See "Gestational diabetes mellitus: Glucose management and maternal prognosis".)

Specific outcomes include:

- Maternal outcome – Hepatic steatosis has been linked to several negative pregnancy outcomes, including preeclampsia and gestational hypertension [76]. Some studies have also found higher rates of caesarean section and preterm delivery (<32 weeks) [70,77]. In addition, in a nationwide cohort study, maternal NAFLD was a risk factor for preeclampsia and GDM in mothers with a body mass index less than 30 kg/m^2 [77].

- Fetal outcomes – The impact of maternal steatosis on the infant is largely uncertain. However, in a study including 25 infants, neonatal intrahepatic fat (assessed by magnetic resonance imaging) was increased by 68 percent in the offspring of women with obesity and GDM compared with offspring of mothers without obesity [78]. Another study found that grade 2 to 3 steatosis by ultrasound in early pregnancy was a risk factor for large for gestational age (LGA) birth weight, even after adjusting for GDM [79].

LIVER TRANSPLANTATION

Patients who undergo orthotopic liver transplantation often regain their fertility [80]. Delaying conception until at least 24 months after transplantation is advised to allow for stabilization of the immunosuppressive regimen and to assure that the transplanted organ is functioning well [81]. Preconception care after liver transplantation is coordinated by clinicians from high-risk obstetrics and the liver transplant center. (See "The preconception office visit".)

Pregnancy outcomes for both the mother and infant in liver transplant recipients are generally good, but there is an increased incidence of preterm delivery, hypertension/preeclampsia, fetal growth restriction, and gestational diabetes [81-90]. The higher risk of preterm birth appears to be due in part to episodes of graft rejection and early onset preeclampsia [81]. Pregnancy-induced hypertension and preeclampsia may be related to an increased incidence of baseline renal dysfunction in these women and use of immunosuppressive therapy. The risk appears to

be higher with use of cyclosporine A than with tacrolimus, but the number of reported patients is small [81,91]. Gestational diabetes is likely provoked by chronic prednisone administration, thus these patients may benefit from diabetes screening in the first trimester, as well as between 24 and 28 weeks of gestation. (See "Gestational diabetes mellitus: Screening, diagnosis, and prevention".)

Liver transplant patients require life-long immunosuppression. A slightly increased risk of teratogenicity has been suggested with standard immunosuppressive regimens that include glucocorticoids, tacrolimus, and azathioprine, but the magnitude of the risk is uncertain [81,91]. Increased monitoring of blood levels of cyclosporine is needed because of increased hepatic clearance of cyclosporine during pregnancy [92,93]. Mycophenolate mofetil (MMF) use during pregnancy should be avoided as MMF has been associated with increased risk of fetal malformations and first-trimester pregnancy loss [94,95]. Pregnancies in women who have undergone liver transplantation should be managed together with a maternal-fetal medicine specialist. (See "Safety of rheumatic disease medication use during pregnancy and lactation".)

Although pregnancy does not increase the risk of maternal mortality in liver transplant recipients, these women should be aware of their prognosis for long-term survival and ability to care for a child. In one series of women who underwent liver transplantation from 1992 to 2002, 5 of 29 died between 10 and 54 months postpartum [81].

Both fetus and mother have survived liver transplantation performed during pregnancy [92,96-99]. Obviously, such heroic surgery must be considered with extreme care. If the condition prompting transplantation is caused by the pregnancy (eg, acute fatty liver of pregnancy), then prompt diagnosis followed by interruption of the pregnancy with maximal support of the mother is the treatment of choice.

SUMMARY AND RECOMMENDATIONS

- **Cirrhosis and portal hypertension** – Pregnancy has a variable effect in women with cirrhosis and portal hypertension. Worsening jaundice with progressive liver failure, ascites, and hepatic encephalopathy can occur, but some women with cirrhosis can sustain pregnancy without any worsening of hepatic function. In addition, the incidence of stillbirths and premature deliveries may be increased. (See 'Cirrhosis and portal hypertension' above.)

  The increase in total blood volume associated with pregnancy may worsen pre-existing portal hypertension. One approach to women with known cirrhosis who desire pregnancy

is to perform an upper endoscopy to screen for varices before pregnancy (or during the second trimester if not performed prior to pregnancy). If present, patients should be informed of the increased risk of upper gastrointestinal hemorrhage with pregnancy. Patients at high risk for variceal hemorrhage should receive primary prophylaxis with nonselective beta blockers or endoscopic variceal ligation. Newborns whose mothers were receiving beta blockers should be monitored during the first days of life because of risks of hypoglycemia and bradycardia. (See 'Assessing risk for variceal bleeding' above.).

- **Viral hepatitis** – Women chronically infected with hepatitis C virus (HCV) can have an uneventful pregnancy without worsening of liver disease or other adverse effects on the mother or fetus, although some studies have suggested potential harms. HCV is associated with an increased risk for intrahepatic cholestasis of pregnancy (ICP). Transmission of the virus from mother to the newborn occurs, but appears to be much less efficient than for hepatitis B virus infection. (See 'Chronic hepatitis C virus' above.)

  Pregnancy in women with chronic hepatitis B virus is discussed in detail elsewhere. (See "Hepatitis B and pregnancy".)

- **Nonalcohol-associated fatty liver disease (NAFLD)** – Rates of NAFLD are increasing in females of childbearing age. NAFLD is now the leading cause for cirrhosis in the pregnant population. NAFLD during pregnancy increases the risk for complications including pregnancy-associated hypertensive disorders, gestational diabetes, and infants large for gestational age.

- **Liver transplant recipients** – Patients who have undergone orthotopic liver transplantation often regain their fertility. Delaying conception until at least 24 months after transplantation is advised to allow for stabilization of the immunosuppressive regimen and to assure that the transplanted organ is functioning well. Pregnancy outcomes for both the mother and infant in liver transplant recipients are generally good, but there is an increased incidence of preterm delivery, hypertension/preeclampsia, fetal growth restriction, and gestational diabetes. In addition, there may be a slightly increased risk of teratogenicity with standard immunosuppressive regimens, but the magnitude of the risk is uncertain. (See 'Liver transplantation' above.)

- **Other liver conditions** – Other liver diseases that may have an effect on or be affected by pregnancy include:

  - Autoimmune hepatitis (see 'Autoimmune hepatitis' above)
  - Primary biliary cholangitis (PBC) (see 'Primary biliary cholangitis' above)
    Primary sclerosing cholangitis (PSC) (see 'Primary sclerosing cholangitis' above)

- Wilson disease (see 'Wilson disease' above)
- Hepatocellular adenoma (HCA) (see 'Hepatocellular adenoma' above)
- Familial hyperbilirubinemia (see 'Familial hyperbilirubinemia' above)
- Familial intrahepatic cholestatic syndromes (Alagille syndrome and progressive familial intrahepatic cholestasis) (see 'Familial intrahepatic cholestatic syndromes' above)
- Porphyria (see 'Porphyria' above)
- Budd-Chiari syndrome (BCS) (see 'Budd-Chiari syndrome' above)

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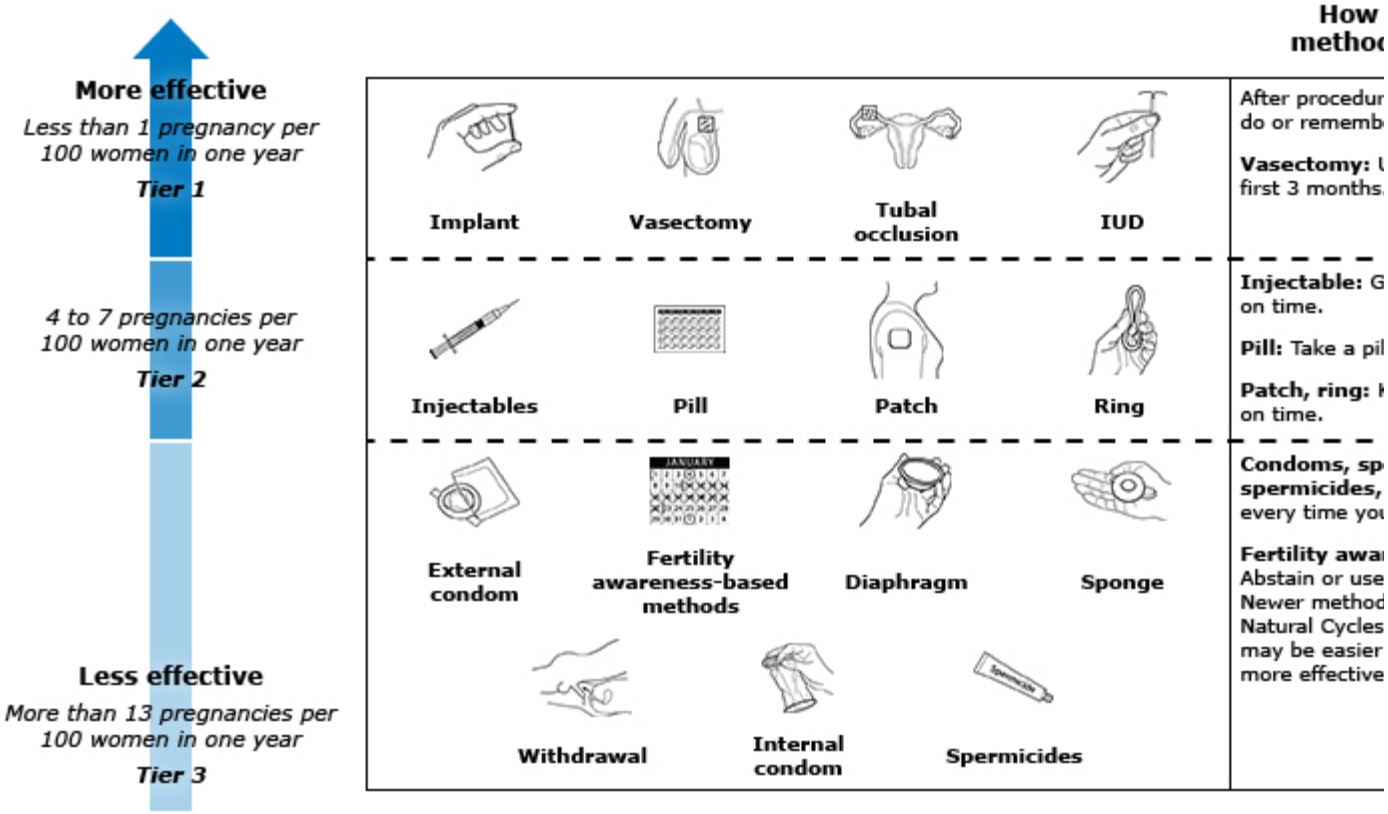
GRAPHICS

Contraceptive methods and comparison of typical effectiveness



IUD: intrauterine device.

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Graphic 119765 Version 5.0

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