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Concise reviews

Pregnancy in Chronic Liver Disease: Before and After Transplantation

Amr Dokmak[a,*], Hirsh D. Trivedi[b], Alan Bonder[c], Jacqueline Wolf[b]

[a] Department of Hospital Medicine, Catholic Medical Center, Manchester, NH, USA
[b] Department of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[c] Liver Center, Department of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Chronic liver disease poses various challenges for women of reproductive age. Cirrhosis, particularly if decompensated, and liver transplantation may impact gestation and perinatal outcomes. Tailored management of underlying liver disease is critical to optimize maternal and fetal wellbeing. Early education, timely intervention, close monitoring, and a multidisciplinary approach are key elements required to minimize complications and increase chances of a safe and successful pregnancy. In this review, we focus on the pregnancy-related implications of chronic liver disease and liver transplantation on women of reproductive age and highlight disease-specific management considerations.

1. Introduction

The prevalence of chronic liver disease among women of young age (15–39 years) has increased from 10.4% in 1994 to 24.9% in 2012 ($p<0.001$). [1] The 2010 United States(US) Census data estimated the number of women with cirrhosis to be 172,897. [2] Chronic liver disease and liver transplantation (LT) directly impact pregnancy-related outcomes. Cirrhosis, with or without portal hypertension, is associated with increased maternal and fetal complications. [3] Due to the rising prevalence of chronic liver disease among young women and the direct effect it has on pregnancy-related outcomes, awareness of pregnancy-specific disease features and tailored management are important to optimize maternal and fetal outcomes.

In this review, we discuss the impact of chronic liver disease in women of reproductive age and emphasize management considerations in pregnancy. We highlight the disease-specific implications of pregnancy and summarize post-LT care in women of childbearing potential.

2. Search strategy

A comprehensive literature search was performed using keywords and index terms in the MEDLINE database. The search was designed to yield potential reports pertaining to the management of chronic liver disease in pregnancy between January 1, 1971 and March 1, 2021. Keywords and index terms for “chronic liver disease”, “cirrhosis”, “pregnancy”, and “liver transplant”, in addition to term variations, without language or study design restrictions were employed. Reference lists of included studies were screened for additional eligible articles that were found to be relevant to the creation of this narrative review article.

3. General considerations

3.1. Impact on fertility

Pregnancy in women with cirrhosis is uncommon, partly due to cirrhosis-induced infertility. 30–71% of women with cirrhosis experience amenorrhea. [4,5] Cirrhosis is present in approximately 1 in 3333 pregnancies. [6] Infertility is proposed to occur due to hypothalamic-pituitary axis dysfunction and abnormal hepatic sex hormone metabolism leading to anovulation and amenorrhea. [7,8] Optimizing synthetic function and maintaining liver health are key measures to enhancing fertility.

3.2. Maternal complications

Pregnancy-related complications in cirrhosis are observed at a higher rate compared to the general population. Reports from the US Nationwide Inpatient Sample (NIS) database reveal an increased maternal complication rate (Odds Ratio [OR]2.03; 95% Confidence Interval [CI] 1.60–2.57) in women with cirrhosis as well as a 6% mortality rate in those with decompensated disease. [3] A study including 339 obstetric hospitalizations in the US between 1993 and 2005

* Corresponding author.
E-mail address: amr.dokmak@cmc-nh.org (A. Dokmak).

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revealed a higher likelihood of antepartum hospitalization (OR 2.97; 95%CI 2.24−3.96) and Caesarean-section (C-section) deliveries (42%vs28%; adjusted OR [aOR]1.41; 95%CI 1.06−1.88) in pregnant women with cirrhosis though specific C-section indications were not reported. [3] Gestational complications were increased in cirrhosis and included placental abruption (7.1%vs1.7%; p<0.0001,95%CI 2.55 −7.60), postpartum uterovaginal bleeding (13.3% vs 3.0%; p<0.0001,95%CI 3.10−7.91), hypertension (14.5%vs9.4%; p = 0.003 95%CI 1.19−2.23), and need for blood transfusion (9.7%vs0.8%; p<0.0001, 95%CI 8.68−21.40). [3] Further studies revealed a higher likelihood of maternal venous thromboembolism (aOR12.3; 95%CI 4.9−31), protein-calorie malnutrition (aOR67.4; 95%CI 11.9 − 29.0), and peripartum infection (aOR3.9; 95%CI 1.2−12.0) in cirrhosis. [9] Comparisons between decompensated and compensated cirrhosis revealed a higher rate of C-section delivery (72%vs47.6%; p = 0.04), preterm delivery (66%vs34.4%; p = 0.004), placenta previa (4.6%vs0%; p = 0.005), and need for blood transfusion (40.9%vs9.3%; p<0.001) in decompensated disease. [9]

Hepatic decompensation in pregnancy, observed in 15% of pregnant women with cirrhosis, can cause ascites and catastrophic bleeding from esophageal varices or splenic artery aneurysmal rupture. [3] Increase in plasma volume worsens portal hypertension. Historical data reports esophageal variceal bleeding in up to a third of pregnant women with cirrhosis and half of those with portal hypertension. [10,11] More recent data demonstrate lower variceal bleeding rates at approximately 5%. [3] Variceal bleeding is associated with an elevated risk of abortion (29.4%vs15.2%; p>0.05) and perinatal death (33.3%vs14.3%; p>0.05). [12]

Measures to decrease hepatic decompensation in pregnancy are crucial. Experts recommend a screening endoscopy during the second trimester given the increased circulating blood volume and fetal compression on the inferior vena cava. [13] Prophylaxis and treatment of bleeding from varices are similar to that in non-pregnant cirrhotics. Nonselective beta blockers can be used although carry a risk of neonatal bradycardia, hypoglycemia, and intrauterine growth retardation (Table 1). The management of variceal bleeding requires endoscopic band ligation. Transjugular intrahepatic portosystemic shunt, which carries a low fetal radiation exposure risk, has been described as salvage therapy. [14]

3.3. Fetal complications

Fetal complications are also higher with liver disease. An NIS database study reveals an increased fetal complication rate (OR3.66; 95%CI 2.74−4.88) and 12% fetal mortality rate in cases of decompensated maternal disease. [3] Cirrhosis is associated with higher rates of preterm birth (38.7% vs 10.3%; CI 4.16%−7.30%, p<0.0001) and fetal intrauterine growth restriction (5.3% vs 2.1%; CI 1.47%−4.96%, p = 0.003). [3] Adequate management of underlying liver pathology and maintenance of hepatic function are essential for a safe and successful pregnancy.

3.4. Mode of delivery

The optimal mode of delivery in women with portal hypertension remains controversial as there are no large randomized studies. Prolonged vaginal deliveries involving augmented intra-abdominal pressures through repetitive Valsalva maneuvers increase portal pressure, but the effect on variceal bleeding remains unclear. [13,15] In women with portal hypertension, C-section delivery may carry a higher risk of hemorrhage via portal hypertensive collaterals. [13] A shortened second stage of delivery, through forceps use, in conjunction with extradural anesthesia has been done. [16] If a C-section delivery is planned for a woman with cirrhosis, adequate vascular surgery support is prudent. [17]

3.5. Prognostication

It is important for providers to educate cirrhotic patients about risks. Model for end-stage liver disease (MELD) can be used in predicting pregnancy outcomes. [18] MELD scores above 10 (83% sensitivity, 83% specificity) strongly correlate with gestational hepatic decompensation. [18]

4. Disease-Specific implications to pregnancy: Hepatitis B virus (HBV)

4.1. Maternal and fetal complications

The worldwide prevalence of chronic HBV is estimated to be 250 million, a quarter of which are estimated to be women of reproductive age who can theoretically transmit the virus to their offspring. [19] Historical studies do not reveal a significant association between maternal HBV and adverse pregnancy outcomes. [20,21] More recent data, however, demonstrate the significant impact maternal HBV imposes on pregnancy. Hepatitis B surface antigen (HBsAg)-positive status is, in fact, associated with increased rates of gestational diabetes mellitus (GDM) (OR2.04; 95%CI 1.21−3.44, p = 0.008) (Table 2), antepartum hemorrhage(OR2.18; 95%CI 1.11 −4.26, p = 0.023), and threatened preterm labor(OR2.007; 95%CI 1.01 −3.97, p = 0.046). [22] There is no increased incidence of preterm labor, preeclampsia, placenta previa, placental abruption, preterm premature rupture of membranes, or birth weight. [22]

Another challenge is that up to 44% of women with HBV experience a disease flare within 1 month of delivery. [23] Higher rates of flares occur in untreated mothers with increased viremia or positive hepatitis B e antigen(HBeAg). [24] Most flares are self-limited though there have been reported cases of acute liver failure. [25]

4.2. Mother-to-Child transmission

In an attempt to decrease mother-to-child transmission, all women contemplating pregnancy or pregnant should be screened for HBsAg. [26] HBV transmission can occur during gestation, delivery, and breastfeeding with maternal viremia and positive HBeAg status acting as key transmission contributors with rates nearing 90% in untreated HBeAg positive mothers. [27−30] Early infection in life portends an increased risk of chronic infection with rates up to 95% in perinatally acquired infections as compared to 5−10% in adulthood acquired infections. [31]

4.3. Management of HBV in pregnancy

American association for the study of liver diseases(AASLD) guidelines recommend timely antiviral therapy for all women who meet standard HBV treatment criteria. [26] Women who do not meet treatment criteria but carry HBV DNA levels greater than 200,000 IU/mL should be considered for treatment during the second trimester. [27] Women with cirrhosis should be started on tenofovir disoproxil fumarate(TDF) to prevent hepatic decompensation. [27] Entecavir has not been sufficiently studied in pregnant women with HBV and is not currently recommended. [27] TDF is the preferred agent of choice due to increased potency and lower resistance rates(Table 1). It should be initiated with a planned treatment course until delivery or 4 weeks postpartum. [26] Despite the postpartum period being a vulnerable time for mothers with HBV, prolonged treatment beyond 4 weeks does not reduce risk of postpartum flares. [32] Newborns to mothers with chronic HBV should receive hepatitis B immune globulin and HBV vaccine within 12 h of birth. Similar to infants without maternal HBV exposure, exposed infants should receive all 3 doses of the HBV vaccination series. They should also undergo serologic testing of HBV between the age of 9 and 15 months. [26]

Table 1
Pregnancy and lactation risks for medications commonly utilized in several chronic liver disease etiologies.

Etiology	Medication	Present in Human Breast Milk	Pregnancy and Lactation – Compatibility and Risks
Cirrhosis	Propranolol	Yes (low) [96]	• Risk of neonatal hypoglycemia, bradycardia, intrauterine growth retardation • Compatible with breastfeeding [97]
Hepatitis B Virus	Tenofovir disoproxil fumarate	Yes (low) [98]	• Preferred choice in pregnancy due to increased potency & lower resistance [26] • Breastfeeding not contraindicated though unknown risk of exposure to infants should be discussed [26]
	Lamivudine	Yes (low) [99]	• TDF preferred to minimize risk of viral resistance [26] • Breastfeeding not contraindicated though unknown risk of exposure to infants should be discussed [26]
	Entecavir	Unknown	• No adequate or well-controlled studies in pregnant women • Breastfeeding not recommended due to unknown fetal risk
Hepatitis C Virus	Ribavirin	Unknown	• Contraindicated in pregnancy
	Ledipasvir/sofosbuvir	Unknown	• Treatment ideal before conception
	Elbasvir/grazoprevir	Unknown	• Treatment ideal before conception
Autoimmune Hepatitis	Azathioprine*	Yes (low) [94]	• Safely used in pregnancy in IBD [54] • Safely used in maintenance of graft function in pregnancy after LT [63] • Fetal effects include bone marrow suppression, hypogammaglobulinemia, and thymic hypoplasia though effects are reversed within 1 year of birth [57] • Compatible with breastfeeding [94,95]
	Corticosteroids*	Yes (very low) [100]	• Recommended for IBD flares in pregnancy [61] • Safely used for control of graft deterioration in pregnancy post LT [63] • Historically associated with orofacial clefts though more recent data demonstrate no added risk [59,60] • Compatible with breastfeeding [101]
	Mycophenolate mofetil*	Unknown	• Contraindicated in pregnancy due to increased risk of fetal malformations and first trimester pregnancy loss [107] • No adequate or well-controlled studies in lactating women
	Cyclosporine*	Yes [106]	• Increased risk of premature birth and small for gestational age births [102] • Benefits in controlling hepatic disease might outweigh teratogenicity risks • Safely used in maintenance of graft function in pregnancy after LT [63] • Breastfeeding not recommended per FDA though successful outcomes in exposed infants have been reported [89]
Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis	Ursodeoxycholic acid	Yes (low) [103]	• No reported fetal side effects in mothers receiving UDCA throughout gestation [69] • Compatible with breastfeeding [104] • Recommend continuation throughout pregnancy
	Obeticholic acid	Unknown	• No adequate or well-controlled studies in pregnant or lactating women
Liver Transplantation(LT)	Tacrolimus	Yes (low) [105]	• Recommended in pregnancy for maintenance of immunosuppression [87] • Safely used in maintenance of graft function in pregnancy after LT [63] • Compatible with breastfeeding [92]
	Everolimus and sirolimus (mTOR inhibitors)	Yes [108]	• Use in pregnancy not recommended due to reports of miscarriages [109] • Use while breastfeeding not recommended due to scarce data on humans • Successful maternal and fetal outcomes have been reported in case reports [110,111]

Abbreviations: FDA, Food and Drug Administration; TDF, Tenofovir disoproxil fumarate; UDCA, Ursodeoxycholic acid, LT, Liver Transplantation, mTOR, Mammalian target of rapamycin.
*Also used in LT.

C-section delivery has not been shown to reduce vertical transmission and is not recommended. [33,34] Similarly, breastfeeding does not increase vertical transmission of HBV and is encouraged as long as appropriate immunoprophylaxis takes place. [34,35] HBV vaccination is safe in pregnancy and is recommended for women are not immune or infected. [27]

5. Hepatitis C virus (HCV)

5.1. Maternal and fetal complications

Chronic HCV infection has the potential to negatively impact pregnancy outcomes and increase the probability of complications for mother and fetus. [36,37] HCV's effects can be seen as early as conception with decreased chances of successful implantation and pregnancy occurring in women with active viral replication. [38] Maternal HCV is further associated with an increased incidence of preterm delivery(OR1.34; 95%CI 1.060–1.690), GDM (OR1.24; 95%CI 1.020–1.510), preeclampsia (OR1.206; 95%CI 0.935–1.556), and lower incidence of live birth(OR0.754; 95%CI 0.622–0.913)(Table 2). [36] Furthermore, there is a greater risk of fetal growth restriction (OR1.53; 95%CI 1.40–1.68) and low birth weight (OR1.97; 95%CI 1.43–2.71). [39] There is no association between worse outcomes and levels of maternal viremia, which implies that isolated chronic HCV might not be the main culprit, but rather alternative factors such as advanced maternal liver disease, inadequate perinatal care, poor nutrition, and ongoing drug abuse may potentially contribute to poor outcomes. [40]

5.2. Mother-to-Child transmission

The US HCV prevalence rate noted in a 2011–2014 report increased 22%, among women of childbearing age. [41] Curative treatment prior to conception and achievement of a sustained

Table 2
Pregnancy-related complication risk profile for various chronic liver disease etiologies.

OutcomesChronicLiverDisease	Maternal Mortality	Live Birth Rate	Preterm Delivery	fetal intra-uterine growth restriction	cesarian section	Preeclampsia	Gestational Diabetes Mellitus
Cirrhosis [3,18]	6% in decompensated cirrhosis	58%	OR 1.51; 95% CI 4.16−7.30	OR 2.70; 95% CI 1.47−4.96	OR 1.41; 95% CI 1.06−1.88	OR 1.78; 95% CI 1.15−2.78	N/A
Hepatitis B[22]	No Significant Difference	OR 2.04; 95% CI 1.21−3.44					
Hepatitis C[36,39]	N/A	OR 0.754; 95% CI 0.622−0.913	OR 1.336; 95% CI 1.059−1.685	OR 1.53; 95% CI 1.40−1.68	N/A	N/A	OR 1.24; 95% CI 1.020−1.510
Autoimmune Hepatitis [51]	N/A	73%	20%	N/A	N/A	N/A	N/A
Primary Biliary Cirrhosis [68−70]	N/A	58%	16%	N/A	OR 0.52; 95% CI 0.29−0.94	N/A	N/A
Primary Sclerosing Cholangitis [71,72]	N/A	88%	OR 3.63; 95% CI 2.35−5.61	N/A	OR 2.18; 95% CI 1.50−3.17	OR 1.33; 95% CI 0.62−2.83	N/A
NAFLD [48]	N/A	N/A	aRR 2.50; 95% CI 1.38−4.55	aRR 2.40; 95% CI 1.21−4.78	aRR 1.52; 95% CI 1.19−1.94	aRR 1.95; 95% CI 1.03−3.70	aRR 2.78; 95% CI 1.25−6.15
Liver Transplantation(LT) [78,80]	N/A	76.9%	39.4%; 95% CI 33.1%−46.0%	OR 4.1, 95% CI 2.1−7.7	44.6%; 95% CI 39.2%−50.1%	21.9%; 95% CI 17.7%−26.4%	OR 1.9, 95% CI 1.0−3.5

Abbreviations: NAFLD, Non-alcoholic Fatty Liver Disease; OR, Odds Ratio; aRR, adjusted Relative Risk; CI, Confidence Interval, N/A Not available.

virologic response(SVR) is the ideal transmission prevention strategy. Unfortunately, a mere 16% of individuals with HCV infection receive treatment and 9% achieve SVR. [42] Factors contributing to low treatment rates include lack of diagnosis awareness, inadequate access to healthcare, and poor compliance.

HCV mother-to-child transmission is approximately 5.8%(95% CI 4.2%−7.8%) with the risk of transmission increasing to 10.8%(95%CI 7.6%−15.2%) in women with human immunodeficiency virus coinfection. [43] AASLD and Infectious Diseases Society of America(IDSA) currently recommend HCV screening for all pregnant women. [44] Among children vertically infected with HCV, 31% of infections are acquired intrauterine and 50% are acquired intrapartum. [45] Nevertheless, there is no evidence to suggest benefit with C-section delivery unless prolonged rupture of membranes or invasive monitoring are anticipated. [46]

Breastfeeding in HCV is safe as disease transmission is rare unless there are bleeding or cracked nipples. [46,47] Safety data on direct-acting antiviral therapy use in pregnancy is yet to be elucidated and society recommendations favor treatment either prior to conception or postpartum (after lactation). [46]

6. Non-alcoholic fatty liver disease (NAFLD)

Given the escalating worldwide prevalence of NAFLD, understanding its effect on pregnancy outcomes is essential. Maternal NAFLD is associated with multiple pregnancy-related complications for both mother and fetus. Maternal NAFLD is associated with increased incidences of GDM (adjusted relative risk [aRR]2.78; 95%CI 1.25−6.15), preeclampsia (aRR1.95; 95%CI 1.03−3.70), C-section delivery (aRR1.52; 95%CI 1.19−1.94), preterm birth (aRR 2.50; 95%CI 1.38−4.55), and low birth weight (aRR2.40; 95% CI 1.21−4.78). [48] The management of NAFLD in pregnancy is similar to that in the non-pregnant patient and is centered around lifestyle modifications. Weight loss and a Mediterranean diet can decrease the incidence of GDM (OR0.67; 95%CI 0.53−0.84). [49] Mothers with NAFLD are encouraged to breastfeed. Data show an association of breastfeeding with decreased rates of nonalcoholic steatohepatitis (OR0.04; 95%CI 0.01−0.10) and hepatic fibrosis (OR0.32; 95%CI 0.16−0.65) in infants independent of maternal NASH presence. [50]

7. Autoimmune hepatitis (AIH)

AIH directly impacts pregnancy with up to 38% of pregnancies leading to maternal complications and 33% of women experiencing disease flares. [51] Flares mostly occur after delivery. [52] AIH flares are more likely to occur in women who do not achieve remission for more than 1 year prior to conception (48.27%vs23.07%; p = 0.03), are older (29vs26 years; p = 0.047), or are not on treatment (50%vs26.22%; p = 0.048). [51] Disease flares are associated with hepatic decompensation (19.23%vs1.81%; p = 0.01) and increased incidence of neonatal intensive care admissions (50%vs7.27%; p = 0.047). Women with cirrhosis from AIH have a higher incidence of spontaneous abortion, preterm deliveries, hepatic decompensation, requirement for LT and mortality compared to women without cirrhosis. [51] Continuation of immunosuppressive therapy throughout the gestational and postpartum period is imperative to mitigate complications and ensure successful outcomes. [51−53]

Management of AIH commonly includes the use of immunosuppressive agents such as prednisone and azathioprine(Table 1). In inflammatory bowel disease (IBD), azathioprine use in pregnancy was demonstrated to be safe with no added risk of maternal or fetal complications, [54,55] although another meta-analysis, potentially confounded by concurrent medications and underlying disease activity, revealed an increased risk of preterm birth (OR1.67; 95%CI 1.26 −2.20). [56] Fetal effects of azathioprine include bone marrow suppression, hygogammaglobulinemia, and thymic hypoplasia though

these effects abate within 1 year of birth (Table 1). [57] Maternal 6-Thioguanine nucleotide (6-TGN), a metabolite of azathioprine, has been shown to decrease during pregnancy. [58] Despite historical data linking its use in pregnancy to an increased risk of fetal orofacial clefts, corticosteroids remain safe and are recommended to maintain immunosuppression and optimize maternal and fetal outcomes. [59,60]

For women with IBD, the Canadian Association of Gastroenterology in 2015 recommended continuation of azathioprine in pregnancy as studies demonstrated no increased teratogenicity risk. [61,62] Similarly, corticosteroids were also recommended for IBD flares. [61] The safe use of azathioprine, cyclosporine, corticosteroids, and tacrolimus in pregnancy has been demonstrated in post LT pregnancies with favorable neonatal outcomes. [63] Mycophenolate mofetil (MMF) should not be used in pregnancy as it increases risk of fetal malformations and first-trimester loss (Table 1). [64,65]

8. Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC)

Appreciating the implications of PBC in pregnancy is especially important as 25% of those diagnosed are women of childbearing age. [66] Although data from 1968 reported a 75% rate of stillbirth or miscarriage, [67] recent data report 70–73% of women with stable liver function throughout pregnancy. [68,69] A case-control study comparing 186 women with PBC and 367 healthy women revealed a lower pregnancy rate (mean 1.91vs2.73; $p<0.05$) and an increased incidence of perinatal and postnatal deaths and complications at childbirth (2.7%; $p<0.05$) in PBC. [70] Another case-series involving 32 women with 50 pregnancies reported at least 1 live birth for 91% of women with no reports of maternal complications, hepatic decompensation, or death. [68] The reported live birth rate in PBC is 58%, which is lower than reported live birth rates for women with AIH (73%) and PSC (88%) (Table 2). [51,68,71]

Miscarriage in PBC occurs in 24%–40% of pregnancies. [68,69] Its probability has not been shown to be significantly impacted by degree of hepatic fibrosis or ursodeoxycholic acid (UDCA) use during pregnancy. Notably, 60–72% of women with PBC experience postpartum disease flares with more than half developing *de novo* pruritis requiring symptomatic treatment. [68,69] In a study comparing women with PBC and healthy matched-controls, those with PBC had higher rates of pruritis during pregnancy. [70] There are no clear risk factors for postpartum flares with no significant differences in women receiving UDCA and biochemical disease activity. [68] The majority of flares are mild and present as a transient elevation in serum alkaline phosphatase. [68,69]

Maternal PSC is associated with a 3.63-fold (95%CI 2.35–5.61) increase in preterm deliveries and a 2.18-fold (95%CI 1.50–3.17) increase in C-section delivery with no increased risks of small for gestational age, stillbirths, or neonatal deaths. [72] A recent study involving pregnant women with PBC (n = 27) and PSC (n = 34) revealed no maternal complications throughout pregnancy including 59% receiving UDCA throughout gestation. Maternal PSC was associated with a 47% C-section delivery rate, although specific indications were not reported. [73] Preterm delivery was 27% for both PBC and PSC compared to the 2013 reported European average of 5.5–11%, though overall neonatal outcomes were favorable with a single stillbirth. [73,74] Gestational age was inversely proportional to early maternal serum alanine aminotransferase level (R = 0.34, p = 0.017) and late gestational bile acid level (R = 0.351, p = 0.033). [73]

Society recommendations support continuing UDCA throughout pregnancy. [13] Its use throughout gestation and breastfeeding has been associated with a favorable drug safety profile. [69,75] Pregnant women with PBC can develop portal hypertension from cirrhosis or nodular regenerative hyperplasia precirrhosis. [76] They should therefore undergo a screening endoscopy during the second trimester to evaluate for esophageal varices. [76]

9. Liver transplantation (LT)

Approximately, 1 in 12 women undergoing LT are of reproductive age. [77] The number of reproductive age women who have undergone LT in the US is estimated to be 14,000 with 500 additional women undergoing LT every year. [78] Pre-LT infertility rates are high due to underlying cirrhosis. LT reverses cirrhosis-induced infertility and improves chances of conception.

Post-LT pregnancy is associated with increased rates of hypertension, preeclampsia, preterm delivery, low birth weight, postpartum hemorrhage and requirement for C-section. [77–82] Renal function impacts pregnancy outcomes with declining glomerular filtration rates correlating with shorter gestational periods. [83] The most common indications for C-section delivery are gestational hypertension, preeclampsia, placental abruption, breech presentation, failure to progress, and threatening intrauterine asphyxia. [84,85] There is no evidence of increased fetal or maternal mortality or allograft loss in pregnant post-LT recipients when conception occurs beyond 6 months of transplantation. Women are advised to delay conception by one year after undergoing LT due to increased risk of unstable immunosuppression and infection in the first year after transplantation which increases the risk of acute rejection. [79,86] Westbrook et al. revealed that women who conceived within 1 year of transplantation experienced higher rates of rejection. [79] Those with acute cellular rejection or poor graft function tend to fare worse and are advised to delay conception until 6–12 months after stability is reached. [79,86]

Optimal pregnancy outcomes occur with adequate immunosuppression, stable allograft function, and sufficient control of underlying medical comorbidities. Tacrolimus is considered the ideal immunosuppressive agent of choice in pregnancy given its combined efficacy and safety (Table 1). [87] As the maternal plasma volume increases throughout gestation, tacrolimus levels should be monitored and dosages adjusted accordingly. [88] Cyclosporine, azathioprine, and prednisone have been successfully used in pregnancy post transplantation (Table 1). [63,89] The use of MMF is contraindicated in pregnancy and should be discontinued pre-conception. Instances of acute rejection should be managed similar to the non-pregnant patient. [87] Mammalian target of rapamycin inhibitors (mTOR) such as everolimus are increasingly used in post-LT patients particularly as a means to mitigate calcineurin inhibitor(CNI)-associated chronic kidney disease (Table 1). [90] Early conversion from CNIs to mTORs has been shown to improve glomerular filtration rate but to date there is minimal information on pregnancy outcome. [90]

Historically, breastfeeding has been discouraged due to lack of safety data. [91] Recent data have demonstrated no adverse events on breastfed infants of mothers receiving tacrolimus post transplantation. [92,93] Similarly, azathioprine use is safe given negligible concentrations of its metabolites, 6-mercaptopurine (6-MP) and 6-TGN, in breast milk. [94,95]

10. Conclusion

Chronic liver disease carries significant pregnancy-related implications for women. Pregnancy in women with cirrhosis is uncommon and when present, portends increased gestational and perinatal risks for mother and child. With improvement in cirrhosis management pre-conception, fertility and improved outcomes are expected to follow suit. Appropriate counseling, adequate awareness of increased risks, and disease-specific management are key factors for success. Improvement in chronic liver disease management and post-LT care over the years has enhanced maternal and fetal outcomes. Table 1 summarizes pregnancy and lactation risks of specific medications

commonly used in chronic liver disease. [91,96–107] Table 2 displays the gestational and postpartum risk profile of several chronic liver diseases. Pregnancy in women with cirrhosis is plausible though remains high-risk. Appropriate management compels a multidisciplinary approach involving high-risk obstetricians, hepatologists, anesthesiologists, and pediatricians.

Abbreviations

LT	liver transplantation
NIS	nationwide inpatient sample
OR	odds ratio
CI	confidence interval
aOR	adjusted OR
AASLD	american association for the study of liver diseases
GDM	gestational diabetes mellitus
MELD	model for end stage liver disease
HBV	hepatitis B virus
TDF	tenofovir disoproxil fumarate
HCV	hepatitis C virus
SVR	Sustained Virologic Response
IDSA	Infectious Disease Society of America
NAFLD	non-alcoholic fatty liver disease
aRR	adjusted relative risk
AIH	autoimmune hepatitis
6-TGN	6-thioguanine nucleotide
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis
MMF	mycophenolate mofetil
UDCA	ursodeoxycholic acid
mTOR	mammalian target of rapamycin receptor
CNI	calcineurin inhibitor
6-MP	6-mercaptopurine

Conflicts of interest

The authors declare that they have no conflict of interest.

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