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REVIEW

Alcohol-associated liver disease and pregnancy

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INTRODUCTION

Alcohol use disorder (AUD) affects 1 in 10 women of childbearing age.[1] Women are highly susceptible to the toxic effects of alcohol for several reasons including decreased gastric metabolism of alcohol, higher blood concentrations due to lower effective circulating volume, and increased inflammatory response to alcohol.[2] Recent trends indicate a rapid rise in alcohol-associated liver disease (ALD) in premenopausal women, and thus pregnant patients with ALD will be increasingly encountered in clinical practice.[3] In this article, we will briefly review the effects of alcohol on reproductive and obstetric health and discuss clinical management of women with AUD and/or ALD who experience pregnancy or are interested in family planning.

Alcohol and the reproductive axis

Alcohol is associated with reproductive organ toxicity and dysregulation of the hypothalamic-pituitary-gonadal axis.[4] Though hormonal profiles vary by age, alcohol has been shown to cause hyperprolactinemia and hypothalamic hypogonadism in reproductive-age women.[4] As a result, women with chronic or heavy alcohol use experience anovulation, irregular menstruation, and in advanced disease, secondary amenorrhea.[1,5] Alcohol use is also associated with reduced ovarian volume and a lower number of oocytes, and it lowers the chance of becoming pregnant.[5,6] There is evidence that alcohol impacts fertility independent of underlying hepatic dysfunction including lower rates of success with assisted reproductive technologies in women who use alcohol and lower rates of childbirth in women with ALD compared to women with other forms of chronic liver disease.[1,3]

Alcohol and obstetric outcomes

Alcohol use in pregnancy increases the risk of multiple adverse maternal and fetal outcomes (Table 1).

Fetal outcomes

There is no safe amount of alcohol that can be consumed in the prenatal period for fetal development. Offspring born to women with AUD/ALD experience increased rates of intrauterine growth restriction and low birth weight, and are more likely to be born small for gestational age. They also are at increased risk of having a low appearance, pulse, grimace, activity, respiration score (< 7 points) 5 minutes after delivery.[7] Fetal alcohol syndrome (FAS) affects ~5% of pregnancies complicated by AUD and is arguably the most devastating outcome of alcohol use in pregnancy.[8] FAS is the most common preventable cause of intellectual disability and results from in utero brain tissue damage and volume reduction secondary to fetal alcohol exposure.[9] Children with FAS may have dysmorphic features including short palpebral fissures, a thin vermillion border, and a smooth philtrum. Clinical manifestations range from mild developmental delay to severe intellectual disability. It is estimated that 3

Abbreviations: ACOG, American College of Obstetrics and Gynecology; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; FAS, fetal alcohol syndrome.

TABLE 1 Maternal and fetal outcomes associated with alcohol use during pregnancy

Maternal outcomes	Fetal outcomes
• ↑ Gestational diabetes • ↑ Cesarean section • ↑ Late pregnancy hemorrhage • ↑ Preterm delivery • ↑ Stillbirth • ↑ Miscarriage	• ↑ Preterm birth • ↑ Intrauterine growth restriction • ↑ Low birth weight • ↑ Small for gestational age • ↑Poor APGAR Scores • ↑ Cognitive, behavioral, and social deficits [FAS]

Abbreviations: APGAR, appearance, pulse, grimace, activity, respiration; FAS, fetal alcohol syndrome.

times as many children with FAS have cognitive deficits than physical abnormalities associated with FAS.[9]

Maternal outcomes

Alcohol use during pregnancy increases the risk of gestational diabetes, preterm birth, hemorrhage, and birth by cesarean section.[10] Heavy alcohol use (≥4–5 drinks/week) has also been associated with early pregnancy loss and stillbirth.[1,11] There are relatively limited data regarding maternal outcomes in women with ALD compared to other forms of liver disease. One large cohort study (n = 339, 31% ALD) reported the highest rates of obstetric complications (delivery by cesarean section, preterm labor, premature rupture of membranes, placental abruption, or placenta previa) in women with ALD.[12] Specifically, 58% of women with ALD experienced ≥1 complication compared to 55% of women with viral hepatitis and 42% of women with autoimmune hepatitis or primary biliary cirrhosis. In-hospital mortality rate was second highest in ALD (3%) following viral hepatitis (8%). In a separate study of pregnant women with *a prior* liver disease, decompensated patients were more likely to have ALD than compensated patients (42% vs. 9%, $p < 0.001$). Decompensated patients in this study experienced more liver-related complications in the perinatal period (13% vs. 1%); however, it is unclear if these findings could be attributed to ALD.[3] Ultimately, there are no clear data addressing whether pregnancy affects the natural progression of ALD.

Clinical considerations in reproductive-age patients with AUD and ALD

Preconception

Reproductive health and family planning should be routinely discussed in women with AUD and ALD.[13] These conversations should address menstrual health, sexual activity, and contraception. Addressing each of these components is crucial as irregular menses can limit insight into reproductive capacity and reduce the use of appropriate contraception.[3] With patients who express a desire to become pregnant, clinicians should counsel delaying conception attempts until achieving abstinence.[13] It should be explained that abstinence maximizes the likelihood of achieving and maintaining pregnancy and that abstinence is crucial for normal fetal development.[1] This should be further emphasized in the context of liver transplantation, given the potential for brisk return of normal menses and fertility after transplant.[14] Further, women with young children may be at increased risk of alcohol relapse and may require extra support in the post-transplant and postpartum periods.[15]

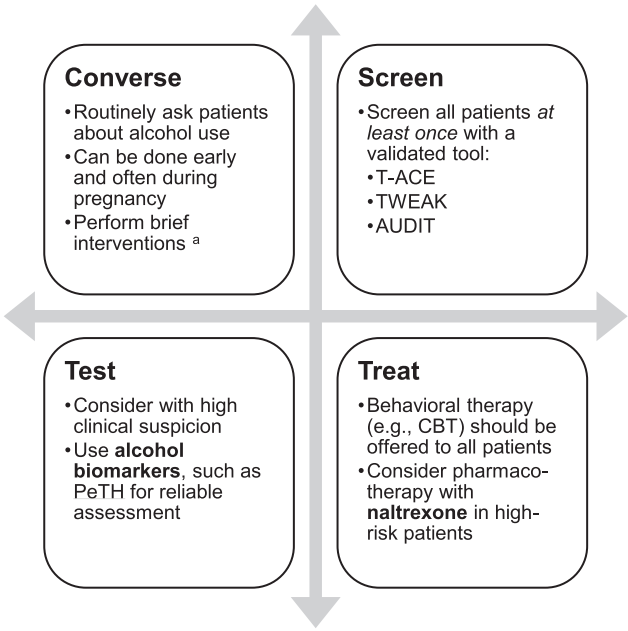

FIGURE 1 General management principles of alcohol use disorder in pregnancy. Managing alcohol use in pregnancy requires multidisciplinary care. Clinicians (obstetricians, hepatology, and primary care) should routinely address alcohol use and consider the 4 key components of care when approaching care to pregnant women with alcohol use disorder: Converse, Screen, Test, and Treat. [a]For detailed information and example brief interventions, refer to the "At-Risk Drinking and Alcohol Dependence: Obstetric and Gynecologic Implications."[17] Referenced screening questionnaires (T-ACE, TWEAK, AUDIT) are routinely available online through the National Institutes of Health and the National Institute of Alcohol Abuse and Alcoholism and are summarized in Table 3. Abbreviations: AUDIT, Alcohol Use Disorder Identification Test; CBT, cognitive behavioral therapy; PeTH, phosphatidylethanol; T-ACE, tolerance, annoyed, cut down, eye-opener; TWEAK, tolerance, worrisome, eye-opener, amnesia, cut down.

Postconception

All individuals should be evaluated for alcohol use during pregnancy. There are multiple steps to consider when evaluating for alcohol use in this setting. In short, these steps include: Converse, Screen, Test, and Treat[16] (Figure 1). Clinicians should ask patients about alcohol

TABLE 2 Pharmacologic treatment of alcohol use disorder in the perinatal patient

Medication	Clinical data and use
Acamprosate	• Mechanism: Not fully elucidated • Teratogenicity: fetal malformations observed in animal models; data in humans are limited. • AASLD Reproductive Guidance: risk-benefit discussion during pregnancy
Disulfiram	• Mechanism: inhibits aldehyde dehydrogenase → ↑ blood acetaldehyde → ↑ unpleasant side effects of alcohol • Teratogenicity: multiple reports of fetal malformation in humans • AASLD Reproductive Guidance: avoid use in pregnancy
Naltrexone	• Mechanism: binds to opioid receptors → blocks pleasurable effects of alcohol → reduces cravings • Teratogenicity: shown to be safe in human studies of opioid use disorder • AASLD Reproductive Guidance: Compatible with pregnancy and lactation • Other: may reduce anovulatory cycles pregestation; safe in breastfeeding patients

Abbreviation: AASLD, American Association for the Study of Liver Diseases.

and other substance use early and often during pregnancy. Conversations regarding alcohol should be used as an opportunity to conduct brief interventions such as motivational interviewing and education. Additionally, all patients should complete a screening questionnaire at least once during pregnancy. There are three alcohol-

TABLE 3 Alcohol use questionnaires approved for use in pregnancy

T-ACE Questionnaire		
Questions: • T—tolerance: how many drinks does it take to make you feel high? (> 2 drinks = 2 points) • A—annoyed: have people annoyed you by criticizing your drinking? (yes = 1 point) • C—cut down: Have you ever felt you ought to cut down on your drinking? (yes = 1 point) • E—eye-opener: have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (yes = 1 point) Scoring • A total score of 2 points or more indicates a positive screening for at-risk drinking.	Pros Cons Sensitivity Specificity	• Identifies heavy drinking • May predict sequelae of prenatal alcohol use in offspring • May not detect low levels of alcohol use • 69%–100% • 19%–89%
TWEAK Questionnaire		
Questions • T—tolerance: how many drinks can you hold? (5+ drinks = 2 points) • W—worried: Have close friends or relatives worried or complained about your drinking in the past year? (yes = 1 point) • E—eye-opener: do you sometimes take a drink in the morning when you first get up? (yes = 1 point) • A—amnesia: Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? (yes = 1 point) • K—K/cut down: Do you sometimes feel the need to cut down on your drinking? (yes = 1 point) Scoring • A total score of 2 points or more indicates a positive screening for at-risk drinking.	Pros Cons Sensitivity Specificity	• Validated in pregnant women with known AUD • Identifies heavy drinking • May not detect low levels of alcohol use. • 59%–100% • 36%–89%
Alcohol Use Disorder Identification Test (AUDIT-C)		
Questions • How often did you have a drink containing alcohol in the past year? Never (0 pt); monthly or less = 1 pt; 2–4 times a month = 2 pt; 2–3 times a week = 3 pt; four or more times a week = 4 pt) • How many drinks did you have on a typical day when you were drinking in the past year? (0–2 = 0 pt; 3–4 = 1 pt; 5–6 = 2 pt; 7–9 = 3 pt; ≥ 10 = 4 pt) • How often did you have 6 or more drinks on 1 occasion in the past year? Never (0 pt); Less than monthly (1 pt); monthly (2 pt); weekly (3 pt); Daily or almost daily (4 pt) Scoring • A total score of 5 or more points is a positive screen clinician should consider administering complete 10-question AUDIT.	Pros Cons Sensitivity Specificity	• Commonly used across health care settings • Some studies show unreliable results in pregnant populations • 18%–100% • 71%–100%

Abbreviations: AUD, alcohol use disorder; AUDIT-C, Alcohol Use Disorder Identification Test; T-ACE, tolerance, annoyed, cut down, eye-opener; TWEAK, tolerance, worrisome, eye-opener, amnesia, cut down. The tolerance question in the TWEAK may alternatively be asked as "How many drinks can you hold without falling or passing out?"

specific screening tools developed and/or validated for use in this population: tolerance, annoyed, cut down, eye-opener, tolerance, worrisome, eye-opener, amnesia, cut down, and Alcohol Use Disorder Identification Test (Tables 2 and 3).[16] The American College of Obstetrics and Gynecology (ACOG) recommends the use of the "tolerance, annoyed, cut down, eye-opener" questionnaire, which can be administered via paper or verbally by a clinician.[17] Brief interventions at the time of screening have been shown to reduce alcohol use in a sustainable manner. Of note, the significant stigma associated with alcohol use during pregnancy may reduce self-report and in some cases, laboratory evaluation may be warranted. Because elevated liver enzymes are neither sensitive nor specific to alcohol-mediated liver injury in pregnancy, alcohol-specific biomarkers (eg, ethyl glucuronide, phosphatidylethanol) should be used when there is suspicion of ongoing alcohol use. Phosphatidylethanol should be considered in particular, given its utility in detecting alcohol use in both early and late pregnancy.[18]

Treatment

One in 3 pregnant women report using alcohol during pregnancy. Historically, treatment for AUD during pregnancy has been limited to behavioral therapies due to the lack of clear data demonstrating the safety of routinely used pharmacologic agents (disulfiram and acamprosate).[13] However, this has changed with the development of naltrexone. Studies in women with opioid use disorder have shown no association between naltrexone and adverse fetal outcomes.[19] Thus, naltrexone therapy has been increasingly considered in high-risk pregnant women with AUD, given the risk-benefit profile relative to the profoundly negative impacts of alcohol on fetal development. In 2021, the American Association for the Study of Liver Disease (AASLD) released new practice guidance that support the use of naltrexone in women with ALD and confirmed or desired pregnancy.[13]

Summary

Alcohol has well-documented negative impacts on reproductive health and pregnancy. Preconception alcohol abstinence is the main priority in the management of women with AUD and ALD, and multidisciplinary care involving obstetric, hepatology, and primary care providers is crucial for patient outcomes. It is important to note that the historic epidemiology of ALD limits the amount of literature regarding the effect of ALD on pregnancy and the effect of pregnancy on the progression of ALD, and studies comparing hormonal profiles across cirrhosis etiologies are lacking. Further research is needed to answer these questions and bolster understanding of reproductive health in women with ALD.

CONFLICTS OF INTEREST

Deepika Devuni receives grants from Sequana Medical unrelated to the present work. The remaining authors have no conflicts to report.

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