Alcohol and fertility: how much is too much?

Kristin Van Heertum* and Brooke Rossi

Abstract: Alcohol use is prevalent in the United States. Given that a substantial portion of the drinking population is of reproductive age, it is not uncommon for couples who are attempting conception, or for women who are already pregnant, to be regularly consuming alcohol. Alcohol use is associated with multiple reproductive risks, including having a child with a Fetal Alcohol Spectrum Disorder, increased risk of fetal loss, and decreased chance of live birth. This review serves to examine the risks of alcohol in the context of reproductive health.

Keywords: Alcohol, Infertility, Fertility, Lifestyle, Fecundability

Background
Approximately 12% of couples in the U.S. experience difficulty conceiving or impaired fecundity, defined as the ability to achieve a live birth in a single menstrual cycle [1]. As alcohol is the most widely used recreational substance, it is important to understand any deleterious effects it has on human reproduction [2]. In this review, we will discuss the prevalence of alcohol use in the U.S.; the health risks and benefits associated with alcohol consumption outside of reproduction; the risks of alcohol use in pregnancy including congenital anomalies and pregnancy loss; the effects of alcohol on fertility in both women and men, such as alcohol’s impact on ovarian reserve, steroid hormone production, sperm quality and fecundability; and finally the impact of alcohol consumption on fertility treatments.

Prevalence of alcohol use and abuse
Alcohol use is common in the United States. The 2015 National Survey on Drug Use and Health (NSDUH) found that 86.4% of people age 18 or older reported alcohol consumption at some point in their lives, and 56% reported drinking in the past month [3]. The survey reported a prevalence of binge drinking, defined as drinking a quantity of alcohol to raise the blood alcohol concentration (BAC) to 0.08 g/dL (typically 4 drinks for women and 5 drinks for men in 2 h), of 26.9% (see Table 1 for alcohol consumption definitions) [4]. Another study performed using data from the Behavioral Risk Factor Surveillance System (BRFSS), a telephone based survey implemented by U.S. state health departments, found that while the overall prevalence of alcohol consumption is not increasing, it appears that the rate of binge drinking is rising across the country [5].

The rates of alcohol use in pregnancy in the U.S. remain surprisingly high. According to a report from the Substance Abuse and Mental Health Services Administration, 8.5% of pregnant women in 2011-2012 reported current alcohol use, 2.7% reported binge drinking, and 0.3% reported heavy drinking, defined as 5 more episodes of binge drinking in the past month [6, 7]. A recent cohort study of over 5000 pregnant women found that women with an intended pregnancy were 31% less likely to consume alcohol in pregnancy than those with unintended pregnancies [8]. This study also found several surprising characteristics associated with drinking in pregnancy, including college-education, white race, older age (particularly over 35 years), higher income, and nulliparity. Factors associated with binge drinking during pregnancy in this study were smoking (past or current), illicit drug use, younger age and being unmarried. Other risk factors for continuation of alcohol use during pregnancy include stressful life events prior to conception and a high level of pre-pregnancy alcohol consumption [9, 10]. Women may be less likely to drink during pregnancy if they have experienced any difficulty conceiving [10].

Rates of alcohol use in women undergoing fertility treatment vary across different studies, but appear to be somewhere between 26 and 41% [11, 12]. However,
Fetal Alcohol Spectrum Disorders (FASD), which are caused by alcohol exposure in utero, include fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND) and alcohol-related birth defects (see Table 2 for summary of characteristics) [18]. FASD represents a continuum of disease characterized by behavioral and cognitive deficits, craniofacial anomalies, and growth retardation. Prevalence of FASD has been estimated at 2-5% in the general U.S. population, with rates of FAS estimated to be 0.2 to 7 per 1,000 children [19]. While studies have shown that the degree of deficits/defects worsens with increasing dose and exposure time, there has been no definitive identification of a safe exposure dose or duration in pregnancy [20, 21]. A recent prospective cohort of 992 women found a strong association between consumption of alcohol in the late first trimester and some characteristic facial anomalies, microcephaly, low birth weight and reduced length [22]. However, alcohol use in the second trimester was also associated with low birth weight and length, while use in the third trimester only affected birth length. Other studies have confirmed that growth deficiency, neurobehavioral issues and microcephaly can occur following alcohol exposure in any trimester, but the characteristic facial features are likely due to first trimester exposure [23]. In many studies, it is often difficult to determine if alcohol was consumed in an isolated trimester or throughout the pregnancy. Therefore, it is not possible, currently, to make a determination regarding the fetal effects of alcohol in women who abstain from use in the first and/or second trimesters and subsequently use alcohol in the third trimester.

There is conflicting data regarding the effects of alcohol exposure in utero when there is no evidence for FASD. Several studies from the Danish National Birth Cohort did not identify any effect on general intelligence, attention or executive function in 5 year old children whose mothers reported low-consumption, moderate-consumption, or binge drinking compared with children whose mothers

| Level of consumption | Definition |
|----------------------|-----------|
| Current use          | ≥ 1 drink in the past 30 days |
| Moderate use         | Up to 1 drink per day for women, up to 2 drinks per day for men |
| Binge drinking       | Drinking a quantity of alcohol to raise the BAC to 0.08 g/dL - typically 4 drinks for women and 5 drinks for men in 2 h |
| Heavy alcohol use    | Binge drinking on 25 days in the past month |

Non-reproductive sequelae of alcohol use
Excessive alcohol intake can lead to multiple chronic diseases including hypertension, heart disease, liver disease, gastrointestinal bleeds, cancer (breast, mouth, throat, esophagus, liver, colon), dementia and other cognitive deficits, anxiety/depression, and social and economic losses, such as damage to relationships and loss of employment [13]. Conversely, moderate alcohol intake, defined as up to 1 drink per day for women and up to 2 drinks per day for men, may offer some health benefits [14, 15]. These benefits include decreased risk of stroke and diabetes, as well as decreased risk of heart disease or mortality from heart disease. In 2005, it was estimated that 26,000 deaths were prevented in the U.S. due to reductions in ischemic heart disease, diabetes and ischemic stroke because of benefits attributed to moderate alcohol consumption [6]. However, care providers must still balance the overall risks and benefits of alcohol use when counseling their patients on their level of alcohol intake.

Alcohol use during pregnancy
The teratogenic effects of alcohol use during pregnancy are well documented [16]. Alcohol readily crosses the placenta to the amniotic fluid and fetus [17]. The fetus will typically be exposed to higher concentrations of alcohol than the mother due to accumulation of alcohol and its metabolites in the amniotic fluid, and comparatively reduced fetal metabolic enzyme activity [17]. Some proposed mechanisms of teratogenicity include impaired anti-oxidant capability, increased free radicals and reactive oxygen species with resultant increased apoptosis in fetal cranial/brain tissue [17].

Table 1 Definitions of Levels of Alcohol Consumption (compiled from [7])

| Level of consumption | Definition |
|----------------------|-----------|
| Current use          | ≥ 1 drink in the past 30 days |
| Moderate use         | Up to 1 drink per day for women, up to 2 drinks per day for men |
| Binge drinking       | Drinking a quantity of alcohol to raise the BAC to 0.08 g/dL - typically 4 drinks for women and 5 drinks for men in 2 h |
| Heavy alcohol use    | Binge drinking on 25 days in the past month |

Alcohol related birth defects
- Fetal alcohol syndrome: Facial dysmorphia, growth deficits, and CNS abnormality
- Partial fetal alcohol syndrome: Facial dysmorphia with growth deficits or CNS abnormality
- Alcohol related neurodevelopmental disorder: CNS abnormality and/or intellectual disabilities without growth deficits or facial dysmorphia
- Alcohol related birth defects: Facial dysmorphia plus additional birth defect(s) without growth deficits or CNS abnormality

Table 2 Fetal Alcohol Spectrum Disorders – all diagnoses require documented prenatal alcohol exposure (compiled from [19])

| Disorder                              | Features                                      |
|---------------------------------------|-----------------------------------------------|
| Fetal alcohol syndrome                | Facial dysmorphia, growth deficits, and CNS abnormality |
| Partial fetal alcohol syndrome        | Facial dysmorphia with growth deficits or CNS abnormality |
| Alcohol related neurodevelopmental disorder | CNS abnormality and/or intellectual disabilities without growth deficits or facial dysmorphia |
| Alcohol related birth defects         | Facial dysmorphia plus additional birth defect(s) without growth deficits or CNS abnormality |
reported no alcohol use in pregnancy [24, 25]. However, there are weaknesses to these studies, as they did not include any diagnostic evaluation for FASD in their cohort, and 5 years of age may be too young to make a true assessment on any neuropsychological effects of alcohol, as the brain is still developing at this age [26].

The findings of studies examining the effects of alcohol intake on the risks of pregnancy loss have been variable [27]. This, in part, can be attributed to the inconsistency of classification of alcohol consumption: some studies report on a dichotomous categorization of use or no use, while others include information on specifics of amount or type of alcohol used. Additionally, given the clear documentation of the teratogenicity of alcohol, this is not a subject that allows for a robust study such as a randomized controlled trial. Finally, as mentioned previously, if women think it is socially unacceptable to drink alcohol while pregnant, they may underreport or not report use.

There is some consensus that at a threshold of 2 to 4 drinks per week the risk of miscarriage begins to increase, particularly in early pregnancy, though there have been several studies that did not document any increased risk of fetal loss with any level of alcohol consumption [28–30]. Table 3 provides a summary of notable findings on fetal loss. It has been theorized that an increase in reactive oxygen species plays a significant role in the pathogenesis of fetal loss due to alcohol exposure [31]. Avalos et al., in a prospective cohort study in the Kaiser Permanente system, found that women who consumed 4 or more alcoholic beverages per week were more than twice as likely to experience a miscarriage as those who did not drink any alcohol (HR 2.65, 95% CI 1.38-5.10) [27]. The study did not find any increased risk of miscarriage in those women who drank less than 4 drinks per week, or in women who drank only beer or wine, compared to those who abstained. The study did, however, document a significantly increased risk of fetal loss in women who only drank liquor compared to those who did not drink at all (HR 2.24, 95% CI 1.32-3.80). Another study from the Danish health registry had similar findings, with the risk of first trimester loss in those women who drank 4 or more drinks per week being more than double the risk of those who abstained (HR 2.82, 95% CI 2.27-3.49) [28]. This study also found that women who consumed 2-3.5 drinks per week had an increased risk of miscarriage in the first trimester (HR 1.66, 95% CI 2.27–3.49) as well as fetal loss at 13–16 weeks (1.57, 95% CI 1.30-1.90). A different Danish cohort study also documented an increase in the risk of stillbirth in those who consumed 5 or more drinks per week in pregnancy, versus those who drank less than one drink per week on average (OR 2.65, 95% CI 1.18-5.97) [32]. The study did not find any increase in the risk of neonatal death with any amount of alcohol consumption in pregnancy. On the other hand, pre-pregnancy alcohol consumption, at least in low to moderate amounts, does not appear to increase the risk of miscarriage or stillbirth [33]. The recommendation, therefore, should be for pregnant women to abstain from any alcohol use in pregnancy, as even those women who drink less than moderately are at an increased risk for loss, in addition to the risk of FASD with even low doses of alcohol exposure.

**Effects of alcohol on female reproduction**

The physiologic effects of alcohol consumption on female reproductive physiology have not been well delineated due to a paucity of high quality studies in this area. Table 4 summarizes several of the studies reviewed below. Studies in humans and animal models have found alterations in ovulation and menstrual cycle regularity with chronic/prolonged alcohol intake, though amount consumed is often not specified [34]. Schliep et al. found that acute alcohol use increased estradiol, testosterone and LH levels, with greater increases seen in women who reported recent binge drinking, though with no associated menstrual cycle dysfunction [35]. While acute alcohol consumption may have little or no associated effect on the menstrual cycle, there does appear to be a negative effect on fertility treatment outcomes, as will be discussed later.

Heavy alcohol use may diminish ovarian reserve and fecundability in women. Ovarian reserve, a measure of a woman’s reproductive potential determined by her remaining oocytes, can be measured in a variety of ways, including serum follicle stimulating hormone (FSH) and anti-Müllerian hormone (AMH) levels as well as antral

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**Table 3** Summary of study findings on alcohol and pregnancy loss

| Level of alcohol consumption in pregnancy | Effects on pregnancy loss | Reference |
|------------------------------------------|--------------------------|-----------|
| Any alcohol consumption vs. abstaining   | No increased risk of miscarriage (RR 1.1, 95% CI 0.9 - 1.4) | Parazzini, et al. 1994 |
| ≥ 4 drinks per week vs. abstaining       | Increased risk of miscarriage (HR 2.65, 95% CI 1.38 - 5.10) | Avalos, et al. 2014 |
|                                          | Increased risk of miscarriage (HR 1.66, 95% CI 2.27 - 3.49) | Andersen, et al. 2012 |
|                                          | Increased risk of 13-16 week loss (HR 1.57, 95% CI 1.30 - 1.90) | Kesmodel, et al. 2002 |
folicle count [36]. A study of African American women in Michigan found that women who regularly binge drink two or more times a week had a 26% lower AMH level than current drinkers who do not binge after age-adjustment [37]. There is also evidence that women who suffer from alcoholism may experience menopause at an earlier age than their non-alcoholic counterparts [38]. On the other hand, the relationship between light to moderate alcohol use and female infertility has yet to be fully characterized [39]. An 8-year cohort study of 18,555 women without a history of infertility who were attempting to conceive found no relationship between alcohol consumption and ovulatory dysfunction [40]. Multiple other studies have found no relationship between moderate alcohol consumption and fecundability [41–43]. A retrospective study of almost 40,000 pregnant women actually reported a shortened time to pregnancy in women who consumed a moderate amount of alcohol compared with those who did not drink at all [44]. However, a Danish cohort study found that, compared with women who drank no alcohol, women who reported consuming 1–5 drinks per week, in addition to those who consumed more than 10 drinks per week, had a decreased chance of clinical pregnancy (OR 0.61, 95% CI 0.40 - 0.93) [47]. Though the findings are inconsistent, women who are already seeking treatment for infertility should be encouraged to minimize alcohol consumption, as even moderate levels could negatively impact their ability to conceive.

### Effects of alcohol on male reproduction

Alcohol consumption in men can also cause difficulties with fertility. Some studies on long-term, heavy alcohol use have reported reduced gonadotropin release, testicular atrophy, and decreased testosterone and sperm production [48]. Other studies of men who drink heavily have documented increases in gonadotropins and estradiol, independent of liver disease, with decreased testosterone as a consistent finding [49]. Alcoholism is also associated with liver dysfunction, which can result in hormonal disturbances due to the inability to metabolize estrogens. A decrease in the quality of semen parameters has also been consistently documented in heavy consumers of alcohol, even with occasional azoospermia [50]. Furthermore, it has been well documented that alcohol abuse and acute intoxication are associated with sexual dysfunction, including issues with arousal and desire, as well as erectile and ejaculatory dysfunction, all of which could lead to difficulties conceiving if men are unable to have effective intercourse [48, 49, 51].

The effects of low to moderate consumption of alcohol, however, do not appear to be clinically significant [21, 52]. Table 5 provides a summary of several of

| Level of alcohol consumption | Effects on female reproduction | Reference |
|-------------------------------|-------------------------------|-----------|
| > 1 drink per day vs. abstaining | No increased risk of ovulatory infertility (after controlling for confounders) | Chavarro, et al. 2009 |
| 1-3 drinks per week vs. abstaining | No difference in adjusted fecundability | Mikkelsen, et al. 2016 |
| 4-7 drinks per week vs. abstaining | Decreased chance of clinical pregnancy (OR 0.61, 95% CI 0.4 - 0.93) | Jensen, et al. 1998 |
| 8-13 drinks per week vs. abstaining | Decreased chance of clinical pregnancy (OR 0.34, 95% CI 0.22 - 0.52) | Jensen, et al. 1998 |
| ≥ 14 drinks per week vs. abstaining | Increased risk of seeking fertility treatment with increasing alcohol intake: High vs. moderate RR 1.58 (95% CI 1.07 - 2.34) Low vs. high RR 0.64 (95% CI 0.46 - 0.90) | Eggert, et al. 2004 |
| Low consumers (< 50 g per week) vs. Moderate consumers (50 - 140 g per week) vs. High consumers (> 140 g per week)a | Increased incidence of infertility (Adjusted HR 1.95, 95% CI 1.04 - 3.66) | Tolstrup, et al. 2003 |
| 1-6 drinks per week vs. < 1 drink per week (in women over age 30) | 26% lower AMH level (p < 0.04) | Hawkins, et al. 2016 |

*aOne standard drink in the U.S. has roughly 14 g of alcohol [65]
Table 5  Summary of study findings on alcohol and male reproductive function

| Level of alcohol consumption | Effects on male reproduction | Reference |
|-----------------------------|-----------------------------|-----------|
| Any alcohol consumption     | No effect on fecundability  | Curtis, et al. 1997 |
|                            | No increased subfecundity   | Olsen, et al. 1997 |
|                            | No effect on any semen parameters or pregnancy rate | de Jong, et al. 2014 |
|                            | No difference in any semen parameters | Jensen, et al. 2014 |
| > 20 drinks per week vs. 1-10 drinks per week | Increased serum free testosterone (19.7-24.6 pmo/l higher) and total testosterone (0.9-1.0 nmol/l higher) | |

The effects of alcohol on other forms of fertility treatments have not been well studied. One trial of 932 couples randomized to natural cycle with intracervical insemination (ICI), controlled ovarian stimulation (COS) with ICI, natural cycle with intrauterine insemination (IUI) or COS with IUI examined the effects of multiple lifestyle factors [61]. The study found that across all treatment groups, the pregnancy and live birth rates were higher in women who reported past alcohol usage (previously consumed at least one alcoholic beverage per week more than a month ago) than in current users or those that reported never consuming alcohol. However, this study did not further stratify alcohol usage by amount, and therefore it is difficult to extrapolate this data to form any recommendations.

Conclusion

Given the potentially devastating consequence of FASD, women who are pregnant, attempting to conceive, or at risk for unintended pregnancy should be screened for alcohol use. The women should also be advised against consuming any amount of alcohol, as no “safe dose” has been identified, and effects to the fetus may begin as early as immediately after implantation [2, 62]. Furthermore, ART should not be provided for women who are unwilling or unable to minimize their consumption of alcohol [63]. Women are more likely to abuse alcohol if...
they are unsuccessful in conceiving after initial infertility evaluation, so continued screening for alcohol use should be performed throughout treatment [64]. Those women who do undergo ART should be advised to minimize their alcohol consumption prior to initiating treatment, as even moderate amounts of alcohol may decrease their chances of a successful live birth. While a moderate level of drinking does not appear to alter outcomes in men, male partners should be advised to at least avoid alcohol the week before they provide a semen sample for IVF.

Abbreviations
AMH: Anti-Müllerian hormone; ARND: Alcohol-related neurodevelopmental disorder; ART: Assisted reproductive technology; BAC: Blood alcohol concentration; BRFS5: Behavioral Risk Factor Surveillance System; COS: Controlled ovarian stimulation; FAS: Fetal alcohol syndrome; FASD: Fetal alcohol spectrum disorders; FSH: Follicle stimulating hormone; GIFT: Gamete intrafallopian transfer; ICI: Intracervical insemination; IUI: Intrauterine insemination; IVF: In vitro fertilization; NSDUH: National Survey on Drug Use and Health; PFAS: Partial fetal alcohol syndrome

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