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Drinking During Pregnancy and the Developing Brain: Is Any Amount Safe?

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Abstract

Heavy prenatal alcohol exposure can have lifelong, disabling effects on brain and cognition. Unlike animal studies, research on light-to-moderate drinking in humans demonstrates less consistent impact. Discussions of negative research findings in popular media underestimate potential adverse outcomes and complicate decisions about risks versus benefits of light-to-moderate drinking during pregnancy.

The scientific method is ideally suited to falsifying hypotheses, and we are more confident in rejecting than accepting a null hypothesis. Nowhere is this concept more evident than in the debate over the null hypothesis that light-to-moderate drinking during pregnancy causes no harm to the fetus. Studies that fail to demonstrate harmful effects of light-to-moderate maternal drinking on childhood development, cognition, or behavior [2] have been heralded in the press as proving that light-to-moderate drinking during pregnancy is safe. Here, the media are far more willing to accept the null hypothesis than the authors of the papers they describe. A negative study should always raise questions concerning whether it was underpowered, controlled insufficiently for confounding variables, or examined the wrong outcome measure or developmental epoch [2]. Left in the middle are pregnant women, who

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must evaluate conflicting claims of safety in the media and the US Surgeon General's recommendation that they abstain from drinking while pregnant or trying to conceive.

Alcohol has been ubiquitous since antiquity, and within living memory physicians advised women to drink moderately during pregnancy. It was only in 1973 that Jones and Smith[RS1] published the first English-language description of fetal alcohol syndrome (FAS), a syndrome of facial d[RS2]ysmorphology, growth retardation, and central nervous system dysfunction caused by heavy maternal drinking (reviewed in [5][RS3]). Since then, several facts have emerged. Alcohol is a teratogen in multiple species, including humans [6]. The effects of prenatal alcohol exposure on development vary as a function of timing, frequency, and dose and are modified by maternal age, gravidity, parity, nutrition, socioeconomic status, and genetics [4]. Alcohol exposure during the first trimester may produce the characteristic facial dysmorphology that supports a diagnosis of FAS; however, alcohol exposure has adverse effects on brain development throughout pregnancy, giving rise to a spectrum of abnormalities referred to as fetal alcohol spectrum disorders (FASD) [6]. The most disabling elements of FASD are impairments of neurocognition, self-regulation, and adaptive function [1]. The full characterization of the structural and functional brain abnormalities of FASD remains an area of active research (reviewed in [7]) and a goal of the National Institute on Alcohol Abuse and Alcoholism-funded Collaborative Initiative on Fetal Alcohol Spectrum Disorders.

We lack a complete understanding of the structural and functional brain abnormalities of FASD, and it is difficult to determine whether a specific neurocognitive deficit or behavioral disorder is a consequence of prenatal alcohol exposure or some other factor. Therefore, it may never be possible to know with certainty whether prenatal alcohol exposure has resulted in a minor decrement in intellectual ability, even in the absence of other stigmata of FASD. Hence, the question of the safety of light-to-moderate drinking during pregnancy is not fully informed by available human studies. In contrast, preclinical studies do permit a more systematic evaluation of whether there is a safe threshold for fetal alcohol exposure.

Cellular and animal models enable the study of the teratogenic effects of prenatal alcohol exposure in the absence of the nutritional, environmental, and social variables that confound human studies [8]. Concentrations of alcohol attained after a single drink in pregnant women disrupt the function of the developmentally critical L1 neural cell adhesion molecule [9]. The effects of alcohol on L1 and many other molecules are dose-dependent and within the range of social drinking. Likewise, animal studies demonstrate dose-dependent effects of moderate prenatal alcohol exposure on brain structure and function, including learning and behavior [8]. In general, the dose-response curves do not reveal a threshold below which alcohol has no effects, at least within the range of blood alcohol concentrations attained during social drinking.

Human studies are by nature less definitive. Drinking during pregnancy is stigmatized, and reporting of alcohol consumption during pregnancy is never fully reliable [4]. Studies differ in their definitions of mild, moderate, and heavy drinking and set different thresholds for each [3]. Some studies focus on drinking in the first trimester, whereas others evaluate the effects of drinking throughout pregnancy. Social factors associated with light-to-moderate

alcohol consumption, such as maternal affluence, also impact child development; hence, an enriched postnatal environment may mitigate the adverse effects of an affluent mother's moderate drinking [10]. These experimental challenges make it difficult to comprehensively evaluate the effects of maternal drinking on development across a range of alcohol exposures.

Despite these complexities, an emerging consensus from human studies also suggests that there is no safe level of maternal drinking during pregnancy. A sibling comparison study showed a linear correlation between the number of days of light-to-moderate drinking during pregnancy and the number of childhood externalizing problems; attention and impulsivity were not similarly correlated [11]. A recent meta-analysis of 34 published cohort studies showed associations between light-to-moderate levels of prenatal alcohol exposure – less than daily drinking - and behavioral problems during childhood [3]. The affected behaviors included social interaction, conduct, and affect. The authors did not find associations between light-to-moderate maternal drinking and childhood cognition, attention, language skills, or visual or motor development. In contrast, maternal binge drinking was clearly associated with impaired cognition in the offspring. Flak *et al*. [3] concluded that "there is no known safe amount of alcohol to consume while pregnant."

The choices for pregnant women are further complicated by the role of genetics in the susceptibility to FASD. Susceptibility to alcohol teratogenesis differs markedly in different mouse strains (e.g. [9]), and a number of FASD susceptibility genes have been identified [12]. In humans, there is greater concordance for the diagnosis of FAS and for IQ in monozygotic twins than in dizygotic twins, despite the fact that twin pairs are exposed to identical concentrations of alcohol *in utero* [13]. Mendelian randomization, a technique that is minimally influenced by confounding variables, such as socioeconomic status, was used to show that four variants in genes involved in alcohol metabolism were related to reduced IQ at age 8, but only among children of light-to-moderate drinkers [10]. No comparable effect was found in children of abstainers. Because the genetics of the mother and the child may separately influence alcohol metabolism, light-to-moderate levels of alcohol consumption might be "safe" for one mother and her child, but not for her next child or for another maternal-child pair.

Preclinical and clinical studies have failed to establish a threshold for safe drinking during pregnancy. These studies reject the null hypothesis that light-to-moderate drinking during pregnancy causes no harm, and accordingly, most study authors endorse the recommendation for abstinence during pregnancy. Informed by various negative studies, others find daylight between the failure to establish a safe level of drinking and the hypothesis that some level of light drinking during pregnancy causes no harm [14, 15]. If one drink three times per week produces inconsistent evidence of harm, then can one say that lower levels of consumption (e.g., one drink per month) are not safe?

Recommendations for maternal abstinence during pregnancy have been characterized as medical paternalism [14] and maternal blame [15]. Some argue that true respect for informed decision-making and maternal autonomy requires informing pregnant women that light drinking may or may not be harmful to their babies, rather than universally advocating

abstinence [14]. The arguments for and against abstinence during pregnancy can be cast in terms of relative risk and benefit or from an ethical standpoint, beneficence or non-maleficence [14]. The risks of light-to-moderate drinking during pregnancy are readily demonstrable in preclinical studies and some clinical studies. In contrast, the benefits of light-to-moderate drinking during pregnancy - the pleasure and relaxation afforded by alcohol - are modest. As clinical evidence accrues for the risks of light-to-moderate maternal drinking, its modest benefits are rendered less salient in a risk-benefit analysis.

We believe that the message that there is no known safe level of alcohol consumption during pregnancy is critical for society at large. FASD, a major cause of intellectual disability, is completely preventable with abstinence from alcohol from conception to birth. Awareness of these risks will empower women to help their children achieve their full potential. However, many women drink before pregnancy recognition, and approximately 10–16% continue to drink after pregnancy recognition [4], despite widespread government efforts to educate the US population about the risks involved. The current uncertainty over the effects of very low concentrations of alcohol on the developing fetus should be a source of reassurance for those women who have consumed a few drinks during pregnancy. At the same time, this uncertainty should be an impetus for women to refrain from any drinking while pregnant or trying to conceive. How the message is delivered is important. Women should be encouraged and not stigmatized in their efforts to reduce behaviors that might adversely influence pregnancy outcomes.

References

1. Kable JA, et al. Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE): Proposed DSM-5 Diagnosis. Child Psychiatry Hum Dev. 2015
2. Kesmodel US, et al. The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function. Bjog. 2012; 119:1180–1190. [PubMed: 22712700]
3. Flak AL, et al. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. Alcoholism, clinical and experimental research. 2014; 38:214–226.
4. May PA, Gossage JP. Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. Alcohol Res Health. 2011; 34:15–26. [PubMed: 23580036]
5. Warren KR, Hewitt BG. Fetal alcohol spectrum disorders: when science, medicine, public policy, and laws collide. Dev Disabil Res Rev. 2009; 15:170–175. [PubMed: 19731390]
6. Riley EP, et al. Fetal alcohol spectrum disorders: an overview. Neuropsychology review. 2011; 21:73–80. [PubMed: 21499711]
7. Lebel C, et al. Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain. Neuropsychology review. 2011; 21:102–118. [PubMed: 21369875]
8. Valenzuela CF, et al. Does moderate drinking harm the fetal brain? Insights from animal models. Trends Neurosci. 2012; 35:284–292. [PubMed: 22402065]
9. Dou X, et al. Mitogen-activated protein kinase modulates ethanol inhibition of cell adhesion mediated by the L1 neural cell adhesion molecule. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:5683–5688. [PubMed: 23431142]
10. Zuccolo L, et al. Prenatal alcohol exposure and offspring cognition and school performance. A 'Mendelian randomization' natural experiment. Int J Epidemiol. 2013; 42:1358–1370. [PubMed: 24065783]

11. D'Onofrio BM, et al. Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems. Archives of general psychiatry. 2007; 64:1296–1304. [PubMed: 17984398]
12. McCarthy N, Eberhart JK. Gene-ethanol interactions underlying fetal alcohol spectrum disorders. Cell Mol Life Sci. 2014; 71:2699–2706. [PubMed: 24554057]
13. Streissguth AP, Dehaene P. Fetal alcohol syndrome in twins of alcoholic mothers: concordance of diagnosis and IQ. Am J Med Genet. 1993; 47:857–861. [PubMed: 8279483]
14. Gavaghan C. "You can't handle the truth"; medical paternalism and prenatal alcohol use. J Med Ethics. 2009; 35:300–303. [PubMed: 19407034]
15. Richardson SS, et al. Society: Don't blame the mothers. Nature. 2014; 512:131–132. [PubMed: 25119222]

Text Box

What is a Drink?

One challenge in interpreting studies of light-to-moderate drinking is the lack of consistency in the definition of a standard drink or the definition of light, moderate, and heavy drinking. The definition of a standard drink ranges internationally from 6 g (Austria) to 14 g (U.S.) to 20 g (Japan) of absolute alcohol. Light drinking has been defined as 1 to 13 drinks per month with no more than two in one session of drinking (cited in [1]). A meta-analysis [3] used more specific ranges for mild (up to 3 drinks per week), mild-to-moderate (up to 6 drinks per week), moderate (3 to 6 drinks per week), and heavy (>6 drinks per week) drinking, with a standard drink defined as 13.7 g of absolute alcohol. Compounding the challenges of experimental definitions is the inconsistency in reporting among subjects [4]. For the purposes of this commentary, we combine the terms “light” and “moderate” drinking into a single designation of “light-to-moderate” drinking.