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Commentary on Day and colleagues (2013): The association between prenatal alcohol exposure and behavior at 22 years of age—Adverse effects of risky patterns of drinking among low to moderate alcohol-using pregnant women

Sandra W. Jacobson, Ph.D, R. Colin Carter, M.D., M.M.Sc., and Joseph L. Jacobson, Ph.D.
Department of Psychiatry and Behavioral Neurosciences (SWJ, JLJ), Wayne State University School of Medicine, Detroit, MI, and the Departments of Human Biology and of Psychiatry and Mental Health (SWJ, JLJ), University of Cape Town, Cape Town, South Africa; and Department of Pediatrics (RCC), Division of Emergency Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Abstract

Day and colleagues have presented the first data showing that the behavioral effects of low to moderate prenatal alcohol exposure seen in childhood and adolescence persist into adulthood. Using the Achenbach Adult Self Report, they found dose-dependent effects of prenatal exposure on Internalizing, Externalizing, and Attention problems that persist in young adults and, thus, appear to be permanent. To date, few studies have attempted to identify thresholds at which prenatal alcohol exposure is harmful, although the animal literature suggests that even 1–2 binge episodes can result in adverse effects in the offspring. Four prospective longitudinal studies have reported adverse effects at what can be characterized as moderate exposure levels based on NIAAA criteria, but moderate drinking women often concentrate their alcohol use on 1–2 days per week, thereby engaging in binge drinking. In this study binge drinking was not a strong predictor of adverse outcome when average daily dose was held constant, a conclusion that the authors note runs “counter to studies that have reported that binge drinking has a greater effect.” This inconsistency may be due to the difficulty of allocating variance that is shared (overlapping) between average daily dose and binge drinking (i.e., dose/occasion). Data from laboratory animal studies, in which dosage can be manipulated experimentally, demonstrate that a higher dose per occasion, the key feature of binge drinking, leads to more severe adverse effects. Day et al.’s findings of adverse effects at low levels of exposure provides clear evidence that there is no safe level of drinking during pregnancy and that, even at low levels, drinking results in irreversible behavioral impairment. On the other hand, given the evidence from the animal and most human studies, it is important for all women who drink during pregnancy, even at light to moderate levels, to recognize that minimizing their intake per occasion and refraining from binge drinking can reduce risk to the fetus.

Keywords

light to moderate prenatal alcohol exposure; fetal alcohol spectrum disorders; binge drinking; adult behavior; prospective longitudinal studies; internalizing and externalizing behavior; attention

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Corresponding author and reprint requests: Sandra W. Jacobson, PhD, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 3901 Chrysler Drive, Suite 2-C, Room 478, Detroit, MI 48201; Tel.: 313-993-5454; Fax: 313-993-3427; sandra.jacobson@wayne.edu.

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Day and colleagues have provided impressive new data from their Pittsburgh study showing that behavioral effects of low to moderate levels of prenatal alcohol exposure extend into adulthood. Although effects of heavy alcohol exposure have been studied extensively and are known to persist through adulthood (e.g., Streissguth et al., 1991), little is known about effects of low or even moderate exposure in young adults and whether deficits seen at these levels in childhood are permanent or, like attention-deficit/hyperactivity disorder (ADHD), may diminish with adult development (Barkley et al., 2002; Biederman et al., 2000). Recent studies from the United Kingdom, Western Australia, and Denmark, have presented data suggesting that children exposed at light and moderate levels may actually do better behaviorally than those born to mothers who abstain, although confounding of lower socioeconomic status with abstinence in those studies suggests that this finding is likely to be spurious (Jacobson and Jacobson, 2010, 2013).

An extensive literature of case-control studies comparing children with known heavy prenatal alcohol exposure to control children has yielded information and insights about fetal alcohol spectrum disorders (FASD; see Mattson et al., 2011). Day et al. have conducted one of the very few prospectively-recruited longitudinal human cohort studies of FASD. One major advantage of the prospective design is the opportunity to assess maternal alcohol exposure with less recall bias, thus improving estimates of fetal exposure. Although the accuracy of maternal self-report has been questioned, reports of maternal alcohol consumption obtained during pregnancy have been validated in relation to infant and child cognitive deficits that were not detected by maternal retrospective report (Jacobson et al., 2002) and in relation to alcohol metabolites measured in meconium samples (Bearer et al. 2003). Prospectively-recruited longitudinal cohorts also avoid selection (or referral) bias inherent in case-control studies, in which the behaviorally most disruptive or difficult children may be over-represented, leading to results that may not be generalizable to the larger population of those with FASD. Longitudinal studies also enable investigators to adjust for serial measurements of potential confounders over time, thus reducing confounding.

The Day et al. study is the first to extend findings of behavior problems seen in children and adolescents at low to moderate levels (e.g., Carmichael-Olson et al., 1997; Jacobson et al., 2006; Larkby et al., 2011) to adulthood. Using the 126-item Achenbach Adult Self Report (ASR), the authors found dose-dependent effects on Internalizing, Externalizing, and Attention problems, after control for critical confounders. Although effects of exposure on behavior were seen for each trimester, duration across pregnancy was a better predictor than drinking during the first trimester only. The authors conclude that even at low levels, effects of exposure extend into young adulthood and, thus, appear to be permanent. These findings represent the culmination of their large longitudinal cohort study, which incorporated prospective ascertainment of prenatal alcohol and drug use, serial sociodemographic factors, and a broad range of developmental outcomes from infancy into young adulthood. This longitudinal design is the gold standard for examining long-term effects of prenatal exposure and, in FASD, is a rare feat.

Indeed, only three other prenatally recruited human cohorts examining the long-term teratogenic effects of prenatal alcohol exposure have been followed through adulthood. The first, Streissguth's Seattle 500 Study, was comprised of heavy drinkers and a sampling of women across the continuum of alcohol use from total abstinence through heavy drinking, resulting in a cohort characterized as moderate drinkers based on their mean oz absolute alcohol (AA) per day = 0.7 prior to pregnancy recognition and 0.3 averaged across pregnancy. Participants followed through young adulthood (mean age = 20 years) exhibited deficits in attention and executive function (Connor et al. 2000). In their mid-20s, prenatal exposure to one or more episodes of maternal binge drinking doubled the risk of six

psychiatric diagnoses assessed on the Structured Clinical Interview for DSM Disorders (Barr et al., 2006).

Coles and colleagues have found long-term neuroanatomical changes in adults with FASD exposed at moderate-to-heavy levels in their predominantly African American, low-income Atlanta cohort, in which alcohol consumers averaged 1.7 oz AA per day (range = 0.1–7.0). In their fMRI study conducted on participants in their early 20s, those with alcohol-related dysmorphic features exhibited poorer arithmetic performance and less activation in regions known to be associated with arithmetic processing when compared with exposed non-dysmorphic subjects and controls (Santhanam et al. 2009). Other studies by this group have demonstrated hippocampal-mediated memory deficits, visual attention and reaction time deficits, and brain, occipital, and temporal region size reductions in the dysmorphic adults (e.g., Coles et al., 2011).

Jacobson and colleagues recruited a large prospective cohort of pregnant African American women in inner-city Detroit designed to over-represent moderate-to-heavy use of alcohol during pregnancy, including a 5% random sample of low-level drinkers and abstainers. Average maternal alcohol consumption among drinkers was 0.3 oz AA per day (mean oz AA per occasion = 1.9). Longitudinal analyses of serial anthropometric measurements obtained from birth through age 19 years demonstrated that alcohol-related growth restriction seen in infancy persisted through adulthood among those whose mothers drank at least monthly or consumed 2 or more oz AA per day on average (Carter et al., 2013), which is consistent with basic principles in behavioral teratology, that higher levels of exposure may be needed to impact physical growth than behavior (Vorhees, 1986). Behaviorally, prenatal alcohol exposure was related to poorer interhemispheric transfer of tactile information in young adulthood at lower levels and in a linear, dose-response fashion, with stronger effects among adults whose mothers binge drank during pregnancy (Dodge et al. 2009). In a recent study on young adults from this cohort, Eckstrand et al. (2012) reported reduced gray matter volume in multiple brain regions even at low levels of exposure. Thus, the new Day et al. and Eckstrand et al. studies appear to be the first to document that long-term effects on behavior and the brain persist into adulthood even at prenatal exposure levels at or below 1 drink/day on average.

Because the body has the ability to tolerate low doses of most toxic substances, adverse effects are generally seen only when exposure exceeds a certain minimum threshold dose. However, toxic substances are usually more harmful during early development, and levels that may be tolerated by an adult may be harmful to the more vulnerable fetus. To date, few studies have attempted to identify thresholds at which prenatal alcohol exposure is harmful, although the animal literature suggests that even 1–2 maternal binge episodes of ethanol exposure can result in detectable effects in the offspring (e.g., Bonthius and West, 1990). Given that almost half of all pregnancies are not planned, with many women consuming alcohol unaware that they are pregnant, alcohol exposure in the first trimester of pregnancy is likely to be common. Studies that have examined pattern of pregnancy drinking in humans and laboratory animals have found that dose per occasion is often more important than drinking frequency in determining adverse effect (e.g., Streissguth et al., 1994).

Moderate drinking has been defined by the National Institute on Alcohol Abuse and Alcoholism as 0.5–.99 oz AA per day or the equivalent of $\approx$ 1.0–1.9 standard drinks per day. Most women, however, do not drink daily but concentrate their drinking on 1–2 days per week (Fig. 1). Thus, even women whose average drinks per week is low often engage in a pattern of binge drinking ($\geq$ 2.0 AA per occasion or $\geq$ 4 standard drinks per occasion), unknowingly exposing the fetus to concentrated levels that have been found to be harmful. Willford et al. (2004) noted that, although effects on learning and memory were seen in

adolescents born to light to moderate drinkers in the Pittsburgh cohort, “even low to moderate drinkers engage[d] in binge drinking.” In that paper, when the authors tabulated binge drinking among light, moderate, and heavy drinkers, they found that a substantial number of light and moderate drinkers actually engaged in a pattern of binge drinking (Fig. 2).

Given these considerations, it is surprising that in this new adult study, binge drinking was not a strong predictor of adverse outcome. The authors report that, “when the level of exposure was held constant, at the lower levels of exposure, the effects of binge and nonbinge exposures on the Total Score of the ASR were similar.” They note that average daily volume (ADV) and binge drinking are correlated and suggest that, because “the average ADV of binge drinkers is usually higher, ...binge drinking is a significant predictor when level of exposure is not controlled.” They also note that their failure to find a stronger effect of binge compared to nonbinge drinking runs “counter to studies that have reported that binge drinking has a greater effect,” including Streissguth et al. (1994), Carmichael-Olson et al. (1997), and Dodge et al. (2009). This inconsistency across studies may be due to the difficulty of determining how to allocate variance that is shared (overlapping) between these two correlated predictors in a multivariate analysis. When binge drinking is entered after holding the level of exposure (ADV) constant, the shared variance is automatically allocated to ADV and the degree to which the outcome is related to binge drinking may be systematically understated. How the shared variance is apportioned between these predictors is likely to vary considerably among human studies depending on the distributions of each of these measures in any particular sample.

One major advantage of laboratory animal studies is that they make it possible to experimentally manipulate dosage to clarify the relative contributions of ADV and quantity per occasion. Rat studies by West and colleagues have documented the critical role of peak blood alcohol concentration (BAC) in determining extent of fetal alcohol damage. As noted earlier, these authors have demonstrated in several studies that ingestion of a given dose of alcohol over a short time period generates a higher peak BAC and greater neuronal (e.g., Bonthius and West, 1990) and behavioral impairment (Goodlett et al., 1987) than a larger dose ingested more gradually over several days. These data demonstrate that a higher dose per occasion, the key feature of binge drinking, leads to more severe adverse effects.

Day et al. suggest that their finding that the effects of binge drinking are attributable to ADV rather than bingeing bolsters the conclusion that “there is no safe level...during pregnancy for women to drink.” However, the data from the animal and other human studies suggesting that higher doses per occasion are more deleterious do not suggest that no adverse effects occur from low level exposure. On the contrary, the authors’ findings of adverse effects at low levels of exposure in this and other studies and our own recent finding of reduced gray matter volume at low levels of exposure (Eckstrand et al., 2012) provide clear and compelling evidence that any alcohol consumption during pregnancy entails some degree of risk, particularly since even low and moderate level drinkers often unknowingly engage in binge drinking patterns that place their fetus at risk. On the other hand, if, as the animal studies show and most of the human data suggest, binge drinking during pregnancy entails the most serious risk to the fetus, it is important for all women who drink during pregnancy, including even those who are characterized as light or moderate drinkers, to recognize that minimizing their intake per occasion and refraining from binge drinking can reduce degree of risk to the fetus. Moreover, we and others have identified moderator variables, including maternal age at delivery (May et al., 2011), history of alcohol abuse (Jacobson et al., 2004), body mass index (May et al., 2011; Carter et al., 2013), and genetic differences (e.g., McCarver et al., 1997; Jacobson et al., 2006), that can interact with drinking pattern to increase the risk to the fetus even at relatively low levels of exposure.

Conclusions

A critical area of scientific and public health concern is the need to assess the long-term health risks to the fetus associated with exposure to alcohol at low to moderate levels. As Day et al. have noted, despite numerous advisories, drinking during pregnancy continues to be prevalent—10% of pregnant women report drinking alcohol and as many as 4.4% report binge drinking, a problem of particular concern among college students. The new findings by Day et al. provide important and convincing evidence that adverse effects of low to moderate exposure are permanent and continue to affect adults whose mothers drank during pregnancy.

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Figure 1. The majority of alcohol consuming pregnant women in both the moderate drinking Detroit (A) and heavy drinking Cape Town (B) cohorts concentrated their drinking on 1–2 days per week.

Figure 2.

Number of participants reporting binge drinking by dose of alcohol during the first trimester of pregnancy (Abstain = 0 drinks/day, Light = ≥ 0 drinks and < 0.4 drinks/day, Moderate = > 0.4 and < 0.89 drinks/day, and Heavy = ≥ 0.89 drinks/day). From Willford et al., 2004 (Fig 2B).