Is prematurity a part of fetal alcohol spectrum disorder?


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Since fetal alcohol syndrome was first reported, studies have demonstrated a range of perinatal/developmental abnormalities that fall under the umbrella term fetal alcohol spectrum disorders. Of these, low birth weight in exposed children is among the most commonly observed and widely accepted. However, in the past, assertion of an association between prenatal alcohol exposure and preterm birth was controversial. Methodological difficulties may have contributed to failure to consistently detect such a relationship. However, new evidence suggests that pregnancy drinking may be a major contributor to extreme, but not mild prematurity. Extreme prematurity is a major cause of severe perinatal morbidity and mortality. If recent findings are confirmed, it suggests that extreme prematurity might be reduced by eliminating prenatal alcohol exposure.

Four decades have passed since the characteristics of children born to women who consumed alcohol during pregnancy were described in the medical literature [1]. The term fetal alcohol syndrome (FAS), which characterizes the growth retardation, CNS/neurodevelopmental delays and facial malformations of affected children, appeared soon after [2]. More recently, the terms alcohol-related neurodevelopmental disorder and fetal alcohol spectrum disorder (FASD) have emerged to characterize a spectrum of problems associated with prenatal alcohol exposure, in addition to classic FAS [3].

Adverse outcomes & prenatal exposure to alcohol

A vast body of research now details outcomes associated with prenatal alcohol exposure. Exposure to alcohol during gestation has been implicated as the most common cause of mental retardation, and the leading preventable cause of birth defects in the USA, accounting for significant public health and educational costs [4]. The national incidence of FAS is approximately 1–4.8 per 1000 or 9.1 per 1000 when those with FASD are included [5].

Individuals with FAS have three primary defining features. First, prenatal or postnatal growth deficiency is evident, particularly in the form of reduced overall height and relative microcephaly [6]. These children are born small for gestational age and typically do not exhibit complete growth catch-up [7]. Consequently, growth curves tend to be somewhat flat. Second, children with FAS have characteristic facial dysmorphology, which includes midfacial hypoplasia, long smooth philtrum, thin upper lip, small eyes (which thus appear to be widely spaced) and inner epicanthal folds [8]. The third feature of FAS is CNS and neurodevelopmental abnormalities. These may be evident in the form of fine and gross motor deficits, hyperactivity, attentional problems, learning difficulties or mental retardation [9].

Even when diagnosable FAS is not evident, alcohol consumption increases the risk of adverse physical, cognitive and behavioral outcomes in exposed children. In addition to continued growth restriction [10–12], delays in motor development have been noted, including fine and gross motor dysfunctions [13,14]. Others have described deficits in grip strength [15] and impairments in visual motor integration [16]. Imaging studies have revealed specific neuroanatomical and neurochemical abnormalities associated with prenatal alcohol exposure [17–19].

Prenatal alcohol exposure has, as noted, been linked to cognitive and behavioral deficits. Decreases in overall cognitive performance and
general IQ scores associated with even moderate levels of prenatal alcohol exposure have been noted in multiple samples of various ages [20-22]. In addition, specific cognitive deficits have been associated with exposure to alcohol during gestation, including slowed mental processing [23-25], problems with receptive language function [26], delayed reading ability [27], planning ability deficits [28], increased errors in encoding verbal information [29], decreased academic achievement and increased learning problems [32]. Most of the behavioral outcomes that have been associated with prenatal alcohol exposure have involved overactivity and poor attention. For example, studies have demonstrated that those with prenatal alcohol exposure had problems in initiating, organizing and maintaining attention, and demonstrated an increase in impulsivity [30]. Similarly, problems with sustained attention have been described [31,32]. However, other studies have detailed school behavioral problems, including hyperactivity and delinquent behavior among children with prenatal alcohol exposure [33,34]. Finally, long-term studies have identified an association between prenatal exposure to alcohol and psychiatric disorders [35].

Low birth weight & preterm birth
As described previously, growth restriction is a defining feature of FAS and has also been associated with even moderate levels of prenatal alcohol exposure. Therefore, it should not be surprising that prenatal alcohol exposure is a strong predictor of low birth weight (i.e., weight at birth of less than 2500 g). Numerous reports have described a strong association between pregnancy alcohol consumption and the risk of low birth weight and actual birth weight, with increasing levels of exposure associated with decreased birth weights. Early studies clearly revealed links between decrements in birth weight and both heavy [36] and moderate [37], alcohol consumption during pregnancy. More recently, in a study of over 8500 infants, a strong association was reported between pregnancy alcohol consumption and low birth weight [38]. Other studies have sought to quantify the risks to birth weight attributable to alcohol exposure. For example, a study of over 1000 infants revealed that consumption of three or more drinks per week during pregnancy resulted in an odds ratio (OR) of 2.6, suggesting a more than doubled risk of low birth weight, and a reduction in birth weight of 143 g, associated with that level of gestational exposure [39]. Finally, heavy drinking (defined in one study as one or more drinks per day) was associated with an approximately five-fold increase in the likelihood of a low birth weight delivery (OR: 8.81) [40].

While the link between low birth weight and gestational alcohol exposure has been fairly well established, especially at high levels of consumption, this relationship could be accounted for entirely by the well-recognized association between prenatal alcohol exposure and intrauterine growth restriction (IUGR). However, it should be considered that some of the relation of prenatal alcohol exposure to low birth weight could be accounted for by an increased risk for preterm birth. Low birth weight and preterm birth (delivery occurring before 37 completed weeks of gestation), are together the leading cause of neonatal morbidity and mortality in the USA, and an infant's gestational age and birth weight at delivery are the strongest biological predictors of immediate and long-term developmental outcomes [41]. In addition to the effects for the individuals and families, premature and low-birth-weight infants consume disproportionate amounts of scarce healthcare resources. A national report suggests that in the USA alone, the costs of caring for children born prematurely or with reduced birth weight are US$3.5-6 billion more than normal birth weight children during the first 15 years of life [42]. More recently, the cost for neonates born at different gestational ages was quantified [43]. The average cost of hospital care for a 38-week gestation neonate was $1100. This amount doubled for an infant born at 36 weeks, rose to $7200 and $19,000 for infants born at 34 and 32 weeks, and was $202,000 for infants born at 25 weeks.

The assertion of an association between prenatal alcohol exposure and preterm birth is controversial. As many researchers have pointed out, the findings for an effect of maternal drinking on preterm delivery have been inconsistent [43,44]. Many possible explanations for contradictory results across studies have been proposed. Factors related to the assessment and reporting both of exposure and gestational age, as well as control for confounding and issues of statistical power may all account for differential outcomes. From a more clinical perspective, preterm birth may itself be associated with IUGR homeostatically (i.e., as a way in which the fetus protects itself from an adverse intrauterine environment that is limiting growth) by precipitating an early labor onset. This biologic 'collinearity' complicates definition of IUGR as independent of gestational duration and thereby makes statistical control of confounding problematic.

Issues of study methodology
Accurate and appropriate assessment of pregnancy alcohol consumption is a critical factor when evaluating the validity of a study relating exposure to outcomes. An initial consideration is whether data are obtained prospectively or retrospectively. It has frequently been suggested that prospective ascertainment of alcohol consumption (i.e., queries during pregnancy) is likely to be more accurate than retrospective data collection (i.e., questioning regarding pregnancy drinking at some point after delivery) [45,46]. The reasoning here is that memory is less accurate over time. Additionally, this assumption is also supported by the fact that it is the prospective studies, rather than the retrospective ones, that are more likely to demonstrate associations between prenatal alcohol...
exposure and outcomes, suggesting greater precision in prospective alcohol data [39]. A Danish report revealed that greater levels of consumption were reported retrospectively compared with concurrent reports, and the authors suggested that women may under-report consumption prospectively [43]. However, a research group in the USA that also reported higher levels of consumption from retrospective reports concluded that, while retrospective reports may provide a better indication of mean levels of exposure, they may be less precise in rank ordering among individuals, decreasing their predictive ability [47]. More recently, the same US researchers reported stronger associations between prospective reports of alcohol consumption and outcomes compared with retrospective reports. They concluded that pregnancy interviews provide the most valid information, and that it is important to assess prenatal alcohol use during pregnancy to minimize the risk of failing to detect effects [48].

A second consideration related to the assessment of alcohol exposure is the use and format of self-report data. Biological ascertainment of alcohol consumption is limited, largely due to rapid clearance of alcohol from the body [46]. Thus, interview data are most often relied upon, with under-reporting being common due to stigma associated with pregnancy alcohol consumption [46]. If under-reporting occurs at all levels of consumption, then this would simply mean that absolute levels are higher than data indicate. However, if the extent of under-reporting differs at different levels of consumption, the actual nature of the association between exposure and outcomes may not be the same as the study results suggest. For example, if only women at higher levels of consumption under-report (as might be expected), a finding of no significant association between exposure and outcome may be solely a result of the under-reporting and resulting restricted range of exposure, rather than the true absence of an association. Thus, asking questions in a way to minimize social desirability responding and consequent under-reporting is essential. Concrete and specific questions that include detailed alcohol-use histories, sensitively asked, can significantly increase the likelihood of obtaining accurate consumption data. This was evident in a study that found disclosure rates in a structured research interview were twice as high as those obtained in more informal clinical encounters [49]. A specific way of querying for alcohol use, known as the Timeline Followback Method, has been demonstrated to be particularly reliable [50]. Participants are asked to recall how much alcohol was consumed on each day during a specified period (often the prior 2 weeks). This method captures all drinking, including sporadic heavy days and unpatrolled drinking (compared to asking about a 'typical day'), and allows an examination of quantity, frequency and pattern of consumption [51]. This Timeline Followback method was validated with pregnant women nearly 30 years ago [52], and has been widely accepted and used since.

A third consideration in the collection of prenatal alcohol exposure data is how to represent amount or level of consumption [53]. While many investigations simply compared outcomes of those exposed to alcohol prenatally with those not exposed, a dose-response relation or possible threshold effect has been of interest for some time. Thus, accurate assessment of amount of exposure is critical. Most studies convert consumption to number of drinks, number of standardized drinks or ounces of absolute alcohol. Less standardized, however, is how to convert that to a 'typical amount' of exposure. Many studies calculate an average amount in ounces of absolute alcohol per day to represent exposure across pregnancy. Others have looked at the average number of days per week on which drinking occurred (or some similar variation on this), which minimizes effects of under-reporting of amount [54]. In addition, the harmful effects of pregnancy binge drinking on outcomes have been highlighted [55], with researchers examining ounces of absolute alcohol per drinking day (i.e., how much are they consuming each day that they do drink), or classifying women as binge drinkers (typically five or more drinks per occasion with some degree of regularity). Longitudinal studies that have included assessment of binge drinking patterns have revealed that in many cases binge drinking, but not high frequency drinking in lesser amounts per occasion, strongly predicted deficits in cognitive and behavioral outcomes [55,56,57]. Various reports have included discussion of which method is likely to yield the most reliable data, both in terms of accuracy and with respect to associations with outcomes. Failing the availability of a reliable validated biomarker for moderate alcohol intake (but at levels considered at-risk during pregnancy), it appears that prospectively obtained timeline follow-back information regarding alcohol intake, expressed as quantity-frequency data represents the current state of the art in assessing prenatal alcohol exposure against perinatal and long-term outcomes.

A further consideration in the assessment of pregnancy alcohol consumption is the point during gestation at which exposure occurred [56]. Many studies have revealed differential effects associated with alcohol exposure during different periods of gestation. For example, late pregnancy (month 7) drinking, but not early pregnancy (month 1) drinking was significantly associated with preterm delivery, revealing substantial differences in risk based on period of exposure [57]. However, very early pregnancy drinking has been more strongly associated with specific brain dysfunctions, due to the rapid brain development early in gestation [58]. In fact, an early study noted that the most critical exposure period for the formation of craniofacial and other anatomic congenital anatomic abnormalities is around the time of conception [56]. Many studies have demonstrated effects of first- and second-trimester alcohol exposure and cognitive outcomes in particular [58,59], while physical outcomes, such as size, have been more often found to be associated with third-trimester exposure [61]. It may be that early exposure is more predictive of higher level deficits, while later pregnancy exposure is more likely to increase the risk of adverse physical outcomes, although results are certainly equivocal. Definitive findings here are complicated by the fact that exposure at one point in gestation is often highly associated with exposure at other points, making conclusions
about timing of exposure difficult. However, it is evident that research in this area should involve assessment of alcohol consumption at multiple points during pregnancy, including at around the time of conception.

In addition to the assessment of alcohol, accurate and appropriate assessment of gestational age is also crucial when exploring associations between prenatal alcohol exposure and preterm delivery. Unreliable and inaccurate dating of gestational age is likely to have contributed to failure to find an effect of maternal alcohol consumption on the risk of preterm delivery in previous studies [54]. Many studies have relied upon self-report of last menstrual period as the indicator of gestational age at delivery. However, this estimate may be incorrect owing to inaccurate recall and delayed or early ovulation [61]. Comparisons of dating from last menstrual period and from ultrasound scan reveal that the latter estimate is a significantly better predictor of day of delivery than the former [62]. Additionally, it has been shown that inaccuracies associated with using last menstrual period estimates tend to be overestimates [61]. That is, a delivery date arrived at through ultrasound examination is likely to be later than that suggested using last menstrual period dating. Thus, dating based on self-report of last menstrual period is likely to be less accurate and to result in fewer births being classified as preterm. Consequently, studies that use ultrasound dating to estimate gestational age at delivery are likely to produce more accurate findings regarding the association between prenatal alcohol exposure and preterm delivery than those relying on date of last menstrual period.

From a clinical perspective, preterm delivery/prematurity is not a monolith. Infants born at just less than 37 weeks may have slightly rockier neonatal courses than full-term infants, (e.g., slightly longer nursery stays due to 'wet lung,' or other typically short-term conditions). However, birth at approximately 26 weeks is associated both with prolonged nursery stays and a range of severe and long-term morbidities, such as respiratory distress syndrome (RDS) and necrotizing enterocolitis (NEC), as well as increased risks of neurobehavioral abnormality, such as cerebral palsy and perinatal mortality. Thus, it is becoming a clinical and research standard to divide prematurity into severe or extreme, defined as less than 32 completed weeks' gestation, and mild, defined as 32–37 weeks' gestation, with term defined as delivery at or after 37 weeks of gestation. Making such a division can allow separation of factors that might prove to be a risk for one, but not the other.

Another methodological consideration for studies examining the association between prenatal alcohol exposure and preterm delivery is the identification of potentially confounding factors. An identified association between prenatal alcohol exposure and prematurity could be attributed to many factors. For example, a large percentage of women who drink during pregnancy also smoke. Dozens of studies have reported a link between pregnancy smoking and preterm birth [62]. Thus, it could just be that alcohol appears to be related to prematurity because those who drank also smoked or vice versa. In order to address this issue, all factors that may lead to preterm birth that might also be associated with pregnancy alcohol use need to be measured and controlled for statistically. Such factors include not only tobacco and other substance use, but inadequate prenatal care, socioeconomic status, and older maternal age to name a few. Care must be taken, however, not to overadjust for confounding factors, increasing the likelihood that an association that does in fact exist is not identified (i.e., Type II error). This could occur, for example, when almost all women who consume alcohol also smoke. Statistical adjustment for confounding would eliminate almost all unique variance attributable to alcohol consumption, making it next to impossible to identify an independent effect. Thus, care must be taken to obtain a sample without significant overlap of factors that cause preterm birth, and to be sure that the sample is large enough to make up for any such overlap statistically. In the case of smoking and alcohol, for example, this would mean ensuring that the sample contained a significant number of women who drank but did not also smoke. Unfortunately, many studies are not designed with this in mind, and suffer from problems with Type II error. Thus, investigators may conclude that alcohol is not independently associated with preterm birth as there is not enough unique variance in alcohol consumption to truly perform such an analysis.

A final methodological consideration is sample size and resultant statistical power. In order to have adequate statistical power to find effects of prenatal alcohol exposure on preterm delivery after control for the multitude of confounding factors, the number of participants must be quite large. Reports on such studies should include a detailing of the power analyses performed to assure the reader that the study had adequate power to detect effects should they be present. Additionally, a large sample size does not necessarily ensure sufficient numbers of those with alcohol exposure or those with preterm birth, especially extreme preterm delivery. Investigations of low incidence behaviors and outcomes such as these may need to rely on over-sampling. For example, prospective studies may need to over sample women who consume alcohol during pregnancy in order to obtain adequate numbers of exposed children for study, while retrospective studies may need to rely on over sampling of extreme preterm deliveries.

As can be easily discerned, there are a large number of considerations which could adversely affect our ability to discern real and clinically relevant prenatal alcohol effects on preterm delivery. As we will now see, it is likely that a combination of these factors has been at work in the available literature, probably accounting for the contradictory results that have been reported.

Overview of the evidence
A review of the medical literature turned up nearly two dozen reports that examined the potential association between alcohol consumption during pregnancy and preterm birth (nine key studies are summarized in Table 1 and described later). The vast majority of the studies reported suffered from methodological weaknesses including small sample size (and/or small numbers of
Table 1. Nine key studies examining the association between pregnancy alcohol consumption and preterm birth.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Alcohol assessment</th>
<th>Gestational age assessment</th>
<th>Primary preterm birth findings</th>
<th>Limitations</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Marbury et al. (1983)</td>
<td>12,440 largely Caucasian and college-educated American women</td>
<td>Retrospective self-report after delivery; Averaged number of drinks/week in each trimester; Analyzed dichotomously at 2 or more drinks/week vs rest for first trimester only; Also looked at those reporting 14 or more drinks/week</td>
<td>Data extracted from the medical records – method of dating unknown; used continuous number of weeks and preterm (&lt;37 weeks) vs rest</td>
<td>Pregnancy alcohol not associated with prematurity after control for confounding</td>
<td>Homogeneous, low-risk sample; Retrospective alcohol assessment using ‘typical’ amount; Unknown method of gestational dating (likely not ultrasound); Level of prematurity not examined</td>
<td>[66]</td>
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<td>Shiono et al. (1986)</td>
<td>28,513 American women</td>
<td>Self-report once at initiation of prenatal care (asked about 1st trimester only); Reported in terms of typical daily amount of &lt;1, 1-2, 3-5, or 6 or more drinks</td>
<td>No ultrasound dating – based on best clinical estimate using odds ratio and exam at first prenatal visit; Categorized for analysis as preterm (&lt;37 weeks) or very preterm (&lt;33 weeks)</td>
<td>No level of alcohol consumption was significantly associated with either level of prematurity after control for confounding</td>
<td>Alcohol use assessed only once at beginning of pregnancy; Asked regarding ‘typical’ amount of alcohol consumption; Ultrasound dating not used; Little demographic information given on sample</td>
<td>[68]</td>
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<td>Bada et al. (2005)</td>
<td>8637 women from four urban research network centers</td>
<td>Self-report once during pregnancy; Reported in terms of typical amount of &lt;1 drink/month, 1-3/month, ≥1/week (i.e., ‘heavy’); Also reported if binge episodes occurred</td>
<td>Based on ‘best obstetric estimate’ from medical charts; Categorized for analysis as preterm (&lt;37 weeks) vs term</td>
<td>Alcohol exposure at any level did not increase the risk of prematurity after control for confounding</td>
<td>Alcohol use assessed only once during pregnancy; Asked about ‘typical’ amount of alcohol consumption; Gestational age estimation not based exclusively on ultrasound (unknown method of dating); Level of prematurity not examined</td>
<td>[38]</td>
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<td>Verkerk et al. (1993)</td>
<td>3447 low-risk Dutch women</td>
<td>Assessed at mid-pregnancy and after delivery to get self-report retrospective consumption data for each trimester; Asked about average or typical amount in g/week</td>
<td>Based on last menstrual period for 99% of sample; Categorized for analysis as preterm (&lt;37 weeks) vs term</td>
<td>No association between alcohol use at any point during pregnancy and preterm birth after control for confounding</td>
<td>Asked about ‘typical’ amount of alcohol consumption; Gestational age estimation not based on ultrasound; Level of prematurity not examined</td>
<td>[70]</td>
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<td>Albertson et al. (2004)</td>
<td>40,892 Danish women from a national registry</td>
<td>Asked about typical amount per week at multiple points during pregnancy; Amount categorized as none, 0.5, 1-1.5, 2-3.5, 4-6.5 or 7 or more drinks/week</td>
<td>Based on either ultrasound or last menstrual period, Categorized for analysis as moderate preterm (32-37 weeks) or very preterm (&lt;32 weeks)</td>
<td>Risk estimates for very preterm were higher than for moderate preterm; however, the association between even the highest level of alcohol consumption and preterm birth was nonsignificant after control for confounding</td>
<td>Asked about ‘typical’ amount of alcohol consumption; Gestational age estimation not based exclusively on ultrasound (% unknown); Low preterm birth rate</td>
<td>[71]</td>
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<tr>
<td>Study</td>
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<td>Sulaiman et al. (1988)</td>
<td>952 British women</td>
<td>Assessed by self-report twice during pregnancy; Quantity and frequency assessed and converted to average amount of absolute alcohol in grams consumed daily; Binge drinking also assessed</td>
<td>Ultrasound exam used for gestational age dating for all women; Gestational age at birth analyzed as continuous number of weeks</td>
<td>Very heavy pregnancy drinking (≥120 g/week) was significantly associated with continuous gestational age at birth after control for confounding</td>
<td>Gestational age not categorized into preterm birth categories; Comparatively smaller sample; however acceptable power analysis reported</td>
<td>[72]</td>
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<td>Jaddoe et al. (2007)</td>
<td>7141 Dutch women</td>
<td>Assessed by self-report three times during pregnancy; Typical amount of consumption categorized as none, &lt;1 drink/week, 1–6 drink/week, ≥1 drink/day</td>
<td>Ultrasound exam used for gestational age dating for all women Categorized a preterm (&lt;37 weeks) vs full term</td>
<td>Early pregnancy consumption at high levels (≥1 drink/day) resulted in slight increased risk of preterm birth; Later pregnancy consumption at any level not significantly associated with preterm birth</td>
<td>Asked about 'typical' amount of alcohol consumption; Level of prematurity not examined</td>
<td>[46]</td>
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<td>Adams et al. (1995)</td>
<td>1825 enlisted US servicewomen</td>
<td>Drinking at entry to prenatal care abstracted from medical records; Alcohol consumption classified as any vs none</td>
<td>Ultrasound exam used for gestational age dating for 65% of sample (last menstrual period used for rest); Categorized prematurity at &lt;29 weeks, 29–32 weeks, and ≥33–36 weeks</td>
<td>Alcohol consumption at entry to prenatal care associated with a significant increase in severe preterm delivery (29–32 weeks), but not delivery at 33–36 weeks</td>
<td>Alcohol data not collected through pregnancy or specifically for research purposes; Amount not assessed; Gestational age estimation not based exclusively on ultrasound</td>
<td>[73]</td>
</tr>
<tr>
<td>Sokol et al. (2007)</td>
<td>3130 urban African–American women</td>
<td>Drinking assessed prospectively throughout pregnancy; Amount and timing of exposure assessed; Alcohol exposure represented as proportion of drinking days/week averaged across pregnancy</td>
<td>Ultrasound exam used for gestational age dating for all women; Categorized prematurity as mild (32–36 weeks) and extreme (&lt;32 weeks)</td>
<td>Prenatal alcohol exposure associated with increased risk for extreme preterm delivery; associated with mild preterm delivery only for women over 30 years old; No significant effects were found when sample doubled by using women who did not have ultrasound dating (i.e., last menstrual period used); Alcohol abstinence would have decreased extreme prematurity by 41%</td>
<td>Homogeneous minority sample; Trimester specific consumption not analyzed; Needs replication for validation</td>
<td>[54]</td>
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exposed or preterm births) and failure to adequately control for confounding or extremely high associations between alcohol and other exposures [63,64], retrospective or other inadequate assessment of alcohol exposure [37,65-68], and unreliable gestational dating [38,57,69,70]. For example, in a sample of over 12,000 women, Marbury et al. reported no association between pregnancy alcohol consumption and preterm delivery, even when high levels of consumption were considered [64]. However, alcohol use was assessed retrospectively at delivery. The effect of alcohol consumption and other factors on prematurity was also examined by Stinson et al. in a sample of over 20,000 women [68]. They reported no association between either light or heavy alcohol use and either mild or severe preterm delivery. In this study, while level of prematurity was examined, alcohol use was assessed once at initiation of prenatal care rather than through ongoing assessment of exposure.

The way gestational age at birth is determined and how preterm birth is classified is also an important consideration. For example, a large study (n = 8637) by Bada et al. that included prospective alcohol consumption data and controlled for confounding resulted in no significant association between pregnancy alcohol consumption at any level and risk of preterm birth [98]. However, gestational age at birth was based on the 'best obstetric estimate,' and did not include a breakdown by prematurity level. Similarly, in another large study (n = 3447), which involved detailed prospective alcohol use data (including amount and timing of exposure) and controlled for confounding factors, no association was found between gestational alcohol exposure and preterm birth [70]. However, as in the Bada et al. study, gestational age at birth was not based on ultrasound dating, but on date of last menstrual period, and did not include examination of level of prematurity [98]. Finally, in a study reported by Albertson et al., a nonsignificant association between alcohol exposure and severe prematurity was reported [97]. In that study, alcohol use was assessed prospectively at four points during pregnancy, and level of prematurity was considered. However, ultrasound dating was not a criterion for inclusion, probably producing less reliable gestational age estimates among women for whom ultrasound dating was unavailable. Additionally, the overall preterm birth rate was quite low at 4.2%.

A handful of large-scale studies that included ongoing prospective alcohol assessment and ultrasound dating of gestational age, have revealed associations between pregnancy alcohol consumption and preterm delivery. In a sample of almost 1000 women, Sulaiman et al. found that heavy pregnancy alcohol use (12 or more drinks per week) was associated with reduced gestational age at birth after control for confounding [72]. In a more recent report, Jadad et al. describe a significant effect of heavy pregnancy drinking (one or more drinks per day) on the risk of preterm birth (adjusted OR: 2.51) [98]. However, while the Jadad et al. study included an assessment of timing of alcohol exposure, neither examined impact of exposure on level of prematurity.

We were able to identify only two reports that detailed studies with large samples, adequate control for confounding, adequate assessment of alcohol exposure and relatively reliable gestational dating examined at different levels of prematurity. Adams et al. examined preterm delivery risk factors among a cohort of army service women [73]. Alcohol consumption at entry into prenatal care was associated with a significant increase in severe preterm delivery (29–32 weeks’ gestation, OR: 2.9), but not at 33–36 weeks’ (OR: 1.6). While gestational age at birth was not universally obtained through ultrasound examination, it was the method available for most women (65%). Thus, the Adams et al. study was the first to detect the association between alcohol consumption and reliably measured extreme preterm delivery.

Perhaps the most definitive study to date is that conducted by Sokol et al. [54]. Over 3000 women were followed prospectively for pregnancy substance use (alcohol users were oversampled) and had ultrasound confirmed pregnancy dating. Prenatal Alcohol Exposure was associated with significantly increased risk of extreme preterm delivery (less than 32 weeks’ gestation) after control for potential confounders, including the use of other substances and demographic and clinical factors. Specifically, based on risk estimates, if all women in this sample had abstained from alcohol consumption during pregnancy, more than two out of every five preterm births would have been avoided. Prenatal alcohol consumption was also associated with mild prematurity, but only for women over 30 years of age. Why prenatal alcohol exposure might be associated with extreme but not mild prematurity for most pregnancies is unclear, and future research is needed to elucidate a biological explanation. The Sokol et al. report also included a repeat analysis using the Ballard estimate of gestational age in patients for whom ultrasound dating was unavailable. In this study and others, the Ballard estimate has been found to be a reliable tool for estimating gestational age in different populations.

Expert commentary

While the Sokol et al. study [54] is an important step in answering the question regarding the association between prenatal alcohol exposure and preterm birth, future work is clearly needed to further explore the relationship between prenatal alcohol exposure and preterm birth. How much is too much drinking? How big can the resulting risk for preterm delivery be confirmed to be? Are different population samples at the same or different risk?

It is now evident that any research in this area should use prospective collection of alcohol consumption data, accurate dating of gestational age through the use of ultrasound, and should delineate extreme prematurity. In addition to the need for confirmatory studies, future work in this area should address additional questions. For example, the Sokol et al. study suggested that women over 30 years of age are at increased risk for alcohol-related preterm birth, with effects seen for this group of
women even for mild prematurity [54]. Work by other researchers has revealed that women over 30 years of age who consume alcohol during pregnancy are at an increased risk of having a child with FAS/FASD compared with those under 30 years [74]. Further work is needed to confirm that this is also the case for preterm birth outcomes as well. Additional work is also needed to address the question of whether prenatal alcohol exposure is associated with prematurity in middle class, Caucasian samples or in samples including large numbers of minorities besides African-Americans. The Sokol et al. study included only urban African-American women, most of whom were of lower socioeconomic status. Effects may be more or less pronounced in different populations. Finally, it is important to use what we know about the role of pregnancy alcohol consumption in preterm birth rates to affect change. The implementation and evaluation of interventions to decrease alcohol use during pregnancy would go a long way toward reducing preterm birth rates and the associated deleterious outcomes, and should be a focus of future work in this area. Data from the Sokol et al. study show that if all women in their study had abstained from alcohol use, extreme prematurity would have decreased by 41%. This would have occurred even if these women continued to smoke and use illicit drugs at the same rate. Thus, it is clear that finding a way to get women to abstain from alcohol consumption during pregnancy would have important personal and public health implications.

**Five-year view**
The authors of this review believe that if appropriate databases are examined using the rigorous methodologic techniques specified previously, that the strong relationship of risky prenatal alcohol consumption to extreme prematurity and possibly also to mild prematurity as well in susceptible individuals, such as older mothers, will be confirmed. The next steps then will include evaluations of the potential for prevention by decreasing alcohol exposures. Review of documented effective prevention strategies is beyond the scope of the current review. Suffice to say that evidence-based prevention strategies have been reported and are currently being tested by several investigative groups. Adding preterm delivery as a primary or secondary outcome in clinical trials would be reasonable, given the observed high OR. Extreme prematurity is also an outcome of great clinical importance, as well, and decreased rates of preterm birth would be a more convincing outcome than just reported decreased intake. Against achieving a convincing demonstration is one of the same factors that has made detecting extreme prematurity as an alcohol-related adverse pregnancy outcome — its low frequency. Thus, a randomized clinical trial would need to be very large in order to include a substantial number of extreme preterm births, unless rather than just adding extreme preterm delivery as a secondary outcome, the trial was designed to include both an increased frequency of heavy drinkers who also have other risk factors for preterm delivery. Future well-designed, large-scale studies are clearly needed in order for us to better understand the link between prenatal alcohol exposure and preterm delivery, and it is our hope that researchers in this field heed the call.

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**Key issues**

- Fetal alcohol spectrum disorder includes a range of problems associated with prenatal alcohol exposure.
- Problems known to be linked to fetal alcohol spectrum disorder include adverse physical, cognitive and behavioral outcomes.
- Prenatal alcohol exposure is a strong predictor of low birth weight.
- The link between prenatal alcohol exposure and another newborn outcome, preterm birth, has also been studied but findings have been inconsistent.
- Failure to find a consistent association between drinking and prematurity is probably due to methodological weaknesses and differences across studies.
- Pregnancy alcohol consumption data should be prospectively collected, sensitively elicited and involve validated measures that assess quantity and timing; ultrasound dating should be used for the most accurate assessment of gestational age at delivery and data should be analyzed to examine level of prematurity; additional confounding factors must be appropriately considered and the sample size must be adequate when examining the association between prenatal alcohol exposure and preterm birth.
- While studies with methodological concerns have often resulted in no significant association being found between pregnancy drinking and prematurity, two recent studies have identified such an association.
- When alcohol consumption and gestational age are reliably and validly measured using a large sample with appropriate control for confounding, a link between prenatal alcohol exposure and extreme prematurity specifically is evident.
- A recent definitive study needs to be replicated and expanded upon. Interventions to reduce or eliminate pregnancy alcohol consumption could lead to significant reductions in the rates of preterm births, and extreme preterm births in particular, and should be investigated.
References

Papers of special note have been highlighted as:

• of interest
•• of considerable interest

• Clinically oriented and relatively current overview of fetal alcohol spectrum disorder (FASD), including some information regarding prevention.


55 Methodologically rigorous evaluation of prenatal alcohol exposure and risk for preterm delivery.


63 Provides a good understanding of the importance of using ultrasound dating to produce valid estimates of gestational age.


Is prematurity a part of the fetal alcohol spectrum disorders?

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- First published study to report an association between pregnancy alcohol consumption and reliably measured extreme preterm delivery.