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Increased Vulnerability to Alcohol-Related Birth Defects in the Offspring of Mothers Over 30

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The risk of fetal alcohol syndrome (FAS) is known to increase with increased maternal age and parity. This study investigated the hypothesis that the deficits in growth and intellectual function seen in non-FAS infants exposed to alcohol at moderate-to-heavy levels are also found disproportionately in the offspring of older mothers. Mothers of 480 African-American, inner-city infants were interviewed at each prenatal clinic visit regarding their use of alcohol during pregnancy. Infants were assessed for physical growth and cognitive development repeatedly through age 13 months. In analyses run separately for the infants of younger and older mothers, alcohol-related deficits were seen most strongly in the offspring of women over 30 years of age. This pattern was not caused by lower levels of drinking by the younger mothers. Age-related increases in maternal body fat-to-water ratio and a faster rate of alcohol metabolism in chronic drinking women may account for the greater vulnerability of the offspring of the older mothers. These data suggest that physiological changes associated with aging and/or chronic drinking may play an important role in the alcohol-related birth defects seen in infants exposed at moderate-to-heavy levels.

Key Words: Fetal Alcohol Syndrome, Alcohol-Related Birth Defects, Maternal Age, Intellectual Function, Physical Growth.

FETAL ALCOHOL syndrome (FAS) is characterized by a distinctive pattern of craniofacial dysmorphology, growth retardation, and central nervous system (CNS) impairment, including mental retardation and/or hyperactivity.[1] Less severe deficits in somatic growth and CNS function are found in the offspring of nonalcoholic women who drink at moderate-to-heavy levels during pregnancy (≥7 drinks/week).[2–4] Only a small proportion of heavy drinking mothers give birth to children with full FAS. According to one recent estimate, the full syndrome occurs in only 4.3% of the offspring of heavy drinkers,[5] although heavily exposed infants are likely to exhibit at least one dimension of the syndrome. The incidence and severity of alcohol-related birth defects (ARBDs) in the offspring of moderate-to-heavy drinking mothers also varies considerably among infants receiving equivalent prenatal exposures. Despite extensive speculation attributing this differential susceptibility to differences ranging from genetic predisposition to nutritional inadequacy, there has been relatively little systematic empirical investigation of its determinants, particularly in human infants.

Case reports of both Caucasian[6] and Native American[7] multiparous women indicate that the incidence of FAS increases with maternal age and parity, a pattern confirmed statistically by Sokol et al.[8] In virtually every reported case, each successive child born to an alcoholic mother is more severely impaired than the previous one. Because maternal age and parity are necessarily confounded in human studies, this increased vulnerability has been examined experimentally in laboratory animals. In one study in which primiparous rat dams were exposed to equal amounts of alcohol at three ages, alcohol was more likely to be associated with spontaneous abortion and lower birthweight, wherein the pup was born to an older exposed mother[9] (see also Vorhees[10]). By contrast, where dams of the same age but different parities (first versus fourth pregnancy) were exposed to the same level of alcohol, ARBDs were as evident in the offspring of primiparous as later parity dams.[11] Thus, the increased risk of impairment seems to be associated with aging rather than number of pregnancies. This study investigated the degree to which the risk of ARBDs in non-FAS children exposed at moderate-to-heavy levels is also increased where the infant is born to an older drinking mother.

METHODS

The sample consisted of 480 African-American infants (275 male, 205 female) whose mothers were recruited during their initial visit to the prenatal clinic of a large urban maternity hospital. Each mother was interviewed regarding her drinking on a day-by-day basis during the preceding 2 weeks and during a "typical" week near the time of conception, with recall linked to specific times of day and activities. All women reporting alcohol consumption at conception of at least 0.5 oz absolute alcohol/day (AA/day; 7 drinks/week) were invited to participate in the study, together with a 5% random sample of lower level drinkers and abstainers. Thirty of the 239 mothers reporting at least 0.5 oz AA/day also used cocaine regularly (at least once/week) during pregnancy. To reduce the risk that the effects of alcohol would be confounded with those associated with crack/cocaine, 78 high-cocaine (≥2 days/week), low-alcohol (<0.5 oz AA/day) users were also included in the sample.

Two-week drinking histories were obtained at all prenatal clinic visits (median = 5.0 visits; range = 1–14), converted to oz AA/day,[12] and averaged to provide a composite measure of fetal alcohol exposure. Three types of developmental assessments were administered by psychology doctoral students trained in our laboratory: physical growth; the Bayley Scales, which is the most widely used standardized assessment of infant development; and four experimental cognitive processing tasks (Table 1).

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Table 1. Developmental Outcomes Assessed

Assessments and measures	Age (mos.)
Weight, length, and head circumference	Birth, 6.5 & 13
Bayley Scales of Infant Development	13
Mental Development Index	
Psychomotor Development Index	
Fagan Test of Infant Intelligence[13]	6.5 and 12
Recognition memory (novelty preference)	
Processing speed (duration visual fixations)	
Cross-modal Transfer Test[14]	12
Cross-modal transfer (novelty preference)	
Processing speed (duration visual fixations)	
Manipulative play[17]	12
Spontaneous play	
Elicited play	
Visual Expectancy Paradigm[18]	6.5
Reaction time	
Percentage of fast responses (201–300 msec)	
Percentage of anticipations	

Table 2. Pregnancy Drinking Levels in the Younger and Older Mothers

		Mother's age		
	oz AA/day	≤30 yr	>30 yr	Total
Abstainer	0	67	13	80
		(19.1)	(10.0)	(16.7)
Light	0.01–0.49	253	93	346
		(72.3)	(71.5)	(72.1)
Moderate	0.5–0.99	15	15	30
		(4.2)	(11.5)	(6.3)
Heavy	1.0–1.99	10	6	16
		(2.9)	(4.7)	(3.3)
Very heavy	2.0+	5	3	8
		(1.4)	(2.3)	(1.7)
Total	—	350	130	480
		(100.0)	(100.0)	(100.0)

Values are numbers of women in each category. Column percentages are shown in parentheses.

At the age at which it was administered in this study, the Bayley Mental Development Index assesses simple fine motor and prehensile coordination, imitation of a model, and, to a limited degree, receptive and productive language; the Psychomotor Development Index assesses walking and balance. The Fagan Test of Infant Intelligence (FTII)[13] uses the infant's propensity to fixate novel stimuli to assess visual recognition memory; cross-modal transfer[14] uses preference for novelty to assess the ability to transfer information from the tactual to the visual mode. Cognitive processing speed was assessed on the FTII and the Cross-modal Transfer Test in terms of the average duration of visual fixations directed at the stimuli.[15] Shorter fixations have been shown to indicate faster, more efficient processing of information.[16]

The infant's manipulative play was assessed by observing 10 min of spontaneous play with toys, which was rated for complexity on an ordinal scale.[17] The examiner then modeled progressively more complex levels of toy manipulation than those exhibited spontaneously by the infant and rated the infant for complexity of elicited play. The Visual Expectancy Paradigm (VExP)[18] was administered to a subsample of the infants. In the VExP, visual stimuli are displayed alternatively in the infant's left and right visual fields. Reaction time in shifting gaze and anticipatory glances are used to assess the infant's ability to form expectations for the location of the stimuli.

Fourteen control variables known to affect somatic growth were assessed, including maternal age, parity, prepregnancy weight, height, years of education, and marital status; whether the family was on welfare; number of prenatal clinic visits; infant sex and age at assessment; and pregnancy smoking (cigarettes/day) and use of cocaine, opiates, and marijuana. Drug use was reported by maternal interview at each prenatal clinic visit (except the initial recruitment visit) and confirmed by urine screen. Because of wide variability in the dosage and degree of purity of illicit drugs, exposure was summarized in terms of the average number of days per month each of the following were used: cocaine, marijuana, opiates (heroin, methadone, or codeine), depressants, and other stimulants. Cocaine, marijuana, and opiate use was estimated for 54 mothers who tested positive, but denied using one or more of these drugs during pregnancy[19] by assigning them the median values reported by those who also tested positive but did not deny use of these drugs.

The drug use variables were also estimated for 63 mothers with only one prenatal visit. Women for whom there was no evidence of a given category of drug use—from hospital medical records, the urine screen, or a 13-month retrospective interview—were assigned a frequency of 0. Those with positive urine screens were estimated as previously indicated; the others were estimated by multiple regression based on 13-month recall of pregnancy drug use and/or prospectively ascertained alcohol consumption data. Because use of depressants and other stimulants was rare and not hypothesized to affect these developmental outcomes, these two variables were not routinely included in multivariate analyses. Instead, their influence was assessed by rerunning analyses yielding significant effects for the sample as a whole, omitting infants whose mothers reported using them at least once per week during pregnancy.[3,4,17,19,20] Sixteen variables known to influence cognitive development were assessed, including 12 of the 14 control variables listed herein (all except maternal prepregnancy weight and height) plus examiner and three measures of quality of maternal intellectual stimulation: Home Observation for Measurement of the Environment (HOME Inventory), Peabody Picture Vocabulary Test–Revised, and Sentence Completion Test of Ego Development. The latter were administered by the infant examiners upon completion of the infant assessments. The alcohol and drug use variables were normalized by means of $\log X + 1$ transformation.

Zero-order correlations of the control variables with each of the outcome measures were used to determine inclusion in multivariate analyses to control for confounding. Each outcome was evaluated in a multiple regression analysis based on AA/day during pregnancy and all control variables even weakly ($p < 0.10$) related to it. This approach is based on the premise that a control variable cannot be the true cause of an observed relation between alcohol exposure and a developmental outcome unless it is related to the outcome in question.[21] In the analyses of each of the 6.5- and 13-month size measures, the corresponding birth size measure and its covariates were also included in the regressions to provide an assessment of the effect of alcohol on postpartum growth. An alcohol-related deficit was inferred only if the effect of exposure was significant after adjustment for the effects of the relevant control variables.

RESULTS

Although half of the mothers recruited for the study reported averaging at least 0.5 oz AA/day at conception, by mid-to-late pregnancy, only 54 women (11.3%) were continuing to drink at moderate-to-heavy levels (Table 2). Because a large majority of these women (79.6%) drank no more than 3 or 4 days/week, the average daily volume measure understates the dose received by the fetus on the days when the women drank. Twenty-four percent of the moderate-to-heavy drinking mothers averaged 2–4 standard drinks/drinking occasion; 48% averaged 4.1–6 drinks; and 28%, >6 drinks. Among the 480 mothers in the sample, the majority (62.5%) smoked during pregnancy; 15.4% used cocaine, 5.2% used marijuana, and 1.7% used opiates at least once per week.

In multiple regressions for the sample as a whole, pre-

Table 3. Effects of Pregnancy Drinking on Somatic Growth and Cognitive Development in the Infants of Younger and Older Mothers and Pregnancy Drinking by Maternal Age Interactions for the Complete Sample

	Mother's age ≤ 30 yr			Mother's age > 30 yr			Drinking × age interaction
	n	*r*	β	*n*	*r*	β	
Somatic growth							
Birthweight	349	−0.14	−0.02	130	−0.32	−0.22*	−0.48*
Birth length	342	−0.18	−0.09	128	−0.21	−0.14†	−0.23
Birth head circumference	341	−0.10	−0.01	127	−0.35	−0.24**	−0.70**
Weight—6 months	327	−0.16	−0.18**	114	−0.14	−0.06	0.10
Length—6 months	320	−0.10	−0.01	111	−0.09	−0.20*	−0.27
Length—13 months	260	−0.05	0.03	98	−0.26	−0.24*	−0.41
Cognitive development							
Bayley—mental development	274	−0.02	0.01	101	−0.29	−0.21*	−0.54*
Bayley—psychomotor development	267	−0.04	−0.02	101	−0.21	−0.17†	−0.36
Cognitive processing speed	239	0.11	0.09	72	0.26	0.24*	−0.37
Elicited play	228	−0.06	−0.05	82	−0.23	−0.31**	−0.85**
Visual expectation							
Reaction time	73	0.19	0.21†	30	0.50	0.48**	−0.31
Percentage of fast responses	72	−0.22	−0.28*	30	−0.57	−0.54**	0.04

r's are zero-order correlation coefficients and β's are standardized regression coefficients (after control for potential confounders) for drinking during pregnancy measured as a continuous variable (AA/day). Values for interaction terms are β's for pregnancy drinking by maternal age (both measured as continuous variables) from regression analyses for the complete sample. *p* values are as follows: * $p < 0.05$, ** $p < 0.01$, † $p < 0.10$.

natal alcohol exposure was associated with smaller weight, length, and head circumference at birth[19]; slower postpartum growth[20]; and poorer cognitive performance on the outcome measures listed in Table 3.[3,4,17] The cognitive deficits included poorer performance on the Bayley Mental Development Index; slower, less efficient processing of visual information (indicated by slower cognitive processing speed and visual expectation reaction time); and developmental delay in the ability to imitate novel behavior (indicated by poorer elicited play). To evaluate the impact of maternal age on vulnerability to these effects of prenatal alcohol exposure, each regression was rerun to include maternal age and a pregnancy drinking by maternal age interaction term (Table 3). The interaction term was statistically significant in 4 of the 12 regressions, indicating stronger effects of alcohol on the offspring of the older mothers.

Because the power of an interaction term to detect a synergistic effect in a correlational field study is usually very low,[22]* the regression analyses were rerun separately for the infants of older and younger mothers (Table 3). The effect of prenatal alcohol exposure was significant on 9 of the 12 outcomes, with effects just short of conventional levels of statistical significance on two additional outcomes. By contrast, there were no discernible effects of alcohol on the offspring of the younger mothers for 9 of the 12 outcomes, and the effects on 2 of the 3 outcomes that were significant were markedly weaker than in the infants born to older mothers. Thus, even though the younger mothers constituted 72.9% of the sample, the alcohol effects were seen more strongly and in most cases only in the offspring of the older mothers.

Although the younger mothers drank less during pregnancy on the average [mean ± SD = 0.19 ± 0.02 oz AA/day, compared with 0.36 ± 0.07 oz for the older mothers; $t(478) = 2.98, p < 0.01$], the general lack of effects on their offspring cannot be attributed to a restricted range of exposure. We have reported elsewhere[23] that the effects on these outcomes are seen primarily where pregnancy drinking exceeds a threshold of 0.5 oz AA/day (i.e., in the offspring of moderate-to-heavy drinking women). Moderate-to-heavy drinking was as frequent among the younger mothers as among those over age 30 (Table 2). The mean age difference in drinking levels is caused primarily by the lower number of abstainers among the older mothers [$\chi^2(1) = 5.71, p < 0.025$]. There was no significant difference in alcohol intake among the 54 mothers who drank above the 0.5 oz threshold [mean ± SD = 1.23 ± 0.98 oz AA/day for the younger mothers; 1.35 ± 1.41 oz for the older; $t(52) = 0.39, p = 0.70$]. These two groups also did not differ in terms of average number of drinks ingested per occasion during pregnancy [mean ± SD = 3.8 ± 4.4 oz AA/day for the younger mothers; 4.1 ± 2.6 oz for the older; $t(52) = 0.30$, $p = 0.77$] or oz of AA/day at conception [mean ± SD = 3.2 ± 4.4 oz AA/day for the younger mothers; 3.8 ± 4.0 oz for the older; $t(52) = 0.52, p = 0.60$].

With regard to other prenatal exposures, the older mothers smoked more [$t(478) = 4.90$; $p < 0.001$] and used opiates more frequently [$t(478) = 2.19, p < 0.05$] during pregnancy, but did not differ significantly (at $p < 0.10$) from the younger mothers in terms of frequency of cocaine or marijuana use. When an alcohol-by-smoking interaction term was added to regressions of the 12 developmental

* *McClelland and Judd[22] have devised a procedure to evaluate the efficiency of the joint distribution of an independent and moderator variable in a correlational field study for detecting a statistical interaction. Based on five levels of prenatal alcohol exposure (Table 2) and five levels of maternal age (<21 years, 21–25, 25.1–30, 30.1–35, >35.1), McClelland and Judd's test indicates that the distribution of the variables in this sample is only 16% as efficient as in an optimally designed experimental study. Given this limitation, the interaction term regressions were supplemented with the separate regression analyses examining differences in vulnerability in younger and older mothers.*

Table 4. Percentage of Infants of Younger and Older Mothers Performing Poorly on Four Cognitive Outcomes (Moderate-to-Heavy Drinkers Only)

	Mother's age		
	≤30 yr	>30 yr	χ^2
Bayley—mental development	9.1% (2/22)	34.8% (8/23)	4.29*
Bayley—psychomotor development	4.5% (1/22)	52.2% (12/23)	12.42**
Cognitive processing speed	22.7% (5/22)	28.6% (4/14)	0.69
Elicited play	15.0% (3/20)	40.0% (6/15)	2.80†

Values are percentage of infants born to moderate-to-heavy drinking mothers performing >1 SD below the mean (for cognitive speed, >1 SD above the mean). ("Number performing poorly/number with mothers in the designated age group" is given in parentheses.) p values are as follows: * $p < 0.05$, ** $p < 0.001$, † $p < 0.10$.

outcomes in Table 3 for the sample as a whole, there was no evidence of any synergistic effect of alcohol with smoking. Regressions run separately for abstainers and light smokers (≤0.5 packs/day), on the one hand, and heavier smokers, on the other, showed similar effects of alcohol regardless of level of fetal exposure to smoking. Regular opiate use was too rare in this sample to examine its potential for moderating the effects of alcohol.

The older and younger mothers did not differ (at $p < 0.10$) in terms of number of prenatal visits, an indicator of quality of prenatal care; welfare status; graduation from high school; maternal vocabulary score; home environment; or sex of infant. They were higher in parity [$t(478) = 9.61, p < 0.001$], somewhat more likely to be married [$\chi^2 = 2.93, p < 0.10$), and weighed more before pregnancy [$t(477) = 2.19$, $p < 0.05$] but did not differ in height. We ran regressions for the 12 outcomes in Table 3 separately for lower and higher parity pregnancies, comparing first and second borns versus third or later borns and then first through third borns versus fourth or later borns. The effects of prenatal alcohol exposure were consistently stronger and in most cases seen only in the children from later pregnancies. Because 68.5% of the infants of the older mothers were also from high parity pregnancies (third born or later), it is not possible to evaluate in these human correlational data whether this pattern is because of maternal aging or pregnancy history.

In an effort to evaluate the functional significance of these findings, analyses were performed on the incidence of "poor performance" on the four cognitive outcomes on which most of the infants were assessed. Poor performance was defined as >1 SD below the sample mean for the Bayley Scales and elicited play, >1 SD above the mean for cognitive processing speed. The incidence of poor performance in the offspring of older versus younger moderate-to-heavy drinking mothers was compared in contingency table analyses. For three of these outcomes, the incidence of poor performance was substantially higher in the exposed infants born to older mothers (Table 4). Of the 10 infants of moderate-to-heavy drinking mothers who performed poorly on the Bayley Mental Scale, eight were born to older mothers, and of the 13 who performed poorly on the Bayley Psychomotor Scale, 12 were born to older mothers.

DISCUSSION

This study demonstrates that maternal age is an important moderator of vulnerability not only to FAS, but also of the alcohol-related deficits in physical growth, mental development, and information processing speed associated with prenatal alcohol exposure in non-FAS infants. It should be noted that maternal age was controlled statistically in the analysis of all outcomes even weakly related to it. The deficits shown in Table 3 are, therefore, attributable to the alcohol exposure of the offspring of the older mothers and not to maternal aging per se. Nor is this pattern attributable to heavier drinking among the older mothers. There was no age difference in either average oz AA/day or volume per occasion among the mothers who drank in the moderate-to-heavy range[23] at which fetal alcohol effects are found. It was not possible to determine whether the differential vulnerability was associated more directly with maternal age or parity in this correlational study, but the experimental rat studies cited herein suggest that maternal age is the more relevant factor.

This increased vulnerability may be attributable to physiological changes relating to the aging process or to consequences of chronic drinking over a more prolonged period. Age-related increases in the ratio of maternal body fat to water lead to higher peak blood alcohol concentrations (BACs) per unit dose of ethanol consumed,[24] exposing the fetus of the older mother longer to heavier doses. In an experimental rat study, Church et al.[25] confirmed that the higher BACs in older dams were attributable, in part, to age-related changes in body water content. However, BACs remained somewhat higher in the older dams even when alcohol doses were administered on the basis of body water content, leading the authors to suggest that age-related changes in rates of alcohol absorption and/or elimination may also play a role. It has also been suggested that the higher uterine and placental collagen and elastin content found in women in the 30- to 49-year age range[26] could exacerbate fetal hypoxia in the alcohol-exposed infant.[27]

With regard to chronic drinking, Majewski[28] evaluated mothers of 72 FAS children for severity of alcohol illness using Jellinek's[29] stages. In the prodromal stage, alcohol intake is excessive, but there is no loss of control. The critical stage is marked by psychological and physical dependence; the chronical stage, by compulsive drinking and severe loss of control. Majewski found only one case of FAS in a child with a mother in the prodromal stage, and it was described as mild. The remaining 71 FAS children were born to women in the critical or chronical stages, with most of the severe cases in children born to women in the chronic stage. Although few, if any of the mothers in our sample were in advanced stages of alcoholism, long-term chronic

drinking, even at moderate-to-heavy levels, could impact significantly on physiological function.

Few studies have directly investigated mechanisms linking prolonged chronic maternal drinking to effects on fetal development. It has been shown, however, that long-term alcohol-abusing women without severe liver damage metabolize alcohol faster, potentially exposing the fetus to higher levels of acetaldehyde, the highly toxic metabolite of alcohol.[30,31] Chronic maternal drinking could also affect fetal development by reducing the availability of critical nutrients. In laboratory animals, chronic alcohol exposure diminishes activity in enzymes involved in placental transport of amino acids essential to fetal growth and metabolism.[32] Effects of aging and long-term chronic drinking on physiological function have been examined in older alcoholics (e.g., after age 60), but rarely in women during the later child-bearing years. Data in this study suggest that research on the effects of aging and chronicity on alcohol metabolism and physiology in older mothers could shed important new light on mechanisms responsible for the deleterious effects of prenatal alcohol exposure on fetal development.

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