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Strengthening the Case: Prenatal Alcohol Exposure is Associated with Increased Risk for Conduct Disorder

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Abstract

Objective—The purpose of this study was to examine the relationship between alcohol exposure in pregnancy and offspring conduct disorder (CD) symptoms in adolescence, and to examine how much this increasingly well-known association may be mediated by maternal and paternal externalizing diagnoses, including lifetime maternal and paternal alcohol and drug abuse/dependence diagnoses as well as antisocial disorders. Few other studies have examined the contribution of these diagnoses across both parents.

Method—A population sample of 1252 adolescents (53.8% female; drawn from the Minnesota Twin Family Study) as well as both their parents completed structured diagnostic interviews to generate lifetime psychiatric diagnoses; mothers were also retrospectively interviewed about alcohol and nicotine use during pregnancy. Linear regression models were used to test the effects of prenatal alcohol exposure on adolescents' CD symptoms.

Results—Prenatal exposure to alcohol was associated with higher levels of CD symptoms in offspring, even after statistically controlling for the effects of parental externalizing disorders (i.e., illicit substance use disorders, alcohol dependence, and antisocial/behavioral disorders), prenatal nicotine exposure, monozygosity, gestational age, and birth weight.

Conclusions—Prenatal alcohol exposure contributes to increased risk for CD in offspring.

Keywords

conduct disorder; prenatal alcohol exposure; fetal alcohol effects

Introduction

Approximately one in five American women consume alcohol in pregnancy¹, despite increasing recognition of alcohol's adverse effects on fetal development, including Fetal Alcohol Syndrome (FAS). FAS accompanies significant prenatal alcohol exposure, and is characterized by facial dysmorphology, growth restriction and central nervous system abnormalities². However, lesser amounts of prenatal alcohol exposure have also been shown to be associated with adverse psychological and neurodevelopmental outcomes, including deficits in cognitive performance³⁻⁵ and psychosocial functioning.⁶⁻⁸ Fetal Alcohol Spectrum Disorders (FASD) is the umbrella term for this constellation of associated deficits.⁹

While the deficits in psychosocial functioning appear diffuse, one area of particular concern is the increased rates of externalizing behaviors, such as aggressiveness and delinquency, observed among children prenatally exposed to even small amounts of alcohol. This association was first noted in studies using standardized parent questionnaires, such as the Child Behavior Checklist (CBCL), to examine samples of alcohol-exposed children.^{3, 10-12} The pattern of elevated CBCL scores suggested that this population might also be at increased risk of clinically significant impairment, i.e., diagnoses of externalizing disorders. In fact, Langbehn and Cadoret¹³ reported that in a sample of approximately 200 adopted adults, fetal alcohol exposure was associated with increased risk for later Antisocial Personality Disorder (APD). Similarly, Hill et al.¹⁴ reported an association between prenatal alcohol exposure and later CD diagnoses in a sample of 150 youths selected for risk for alcoholism.

However, the authors of these studies, as well as a review by Rutter,¹⁵ have questioned whether the behavioral effects of low levels of prenatal alcohol exposure could be confounded with an inherited vulnerability to disinhibitory behavior. This concern arose from the fact that women who choose to drink in pregnancy are not a randomly selected sample. For instance, women who drink in pregnancy are known to be more likely to have preexisting antisocial or alcohol use disorders¹⁶⁻¹⁸ as well as indicators of adverse environments such as physical abuse¹⁹ or high levels of psychosocial stress and low social support.²⁰ Additionally, women with antisociality or alcohol use disorders may be more likely to select antisocial or alcoholic mates.²¹⁻²² Both genetic and environmental risks are associated with having antisocial or alcoholic parents, and are known to lead to higher prevalence of offspring antisocial disorders.²³⁻²⁶

To address these potentially confounding factors, some investigators who examined the effects of prenatal alcohol exposure on externalizing diagnoses in offspring examined the possible mediating role of familial alcoholism. Langbehn and Cadoret¹³ assessed parental diagnosis, and Hill et al.¹⁴ familial risk. Langbehn and Cadoret reported that the effect of prenatal alcohol was still significant even after accounting for parental alcoholism, while Hill found the effect was no longer significant after accounting for familial alcoholism. It should be noted that Hill employed an extensive accounting of familial alcoholism diagnoses, including both first- and second-degree relatives, which may have more fully accounted for familial risks. Additionally, Hill was able to assess alcohol use in pregnancy by direct interviews with mothers. In contrast, Langbehn and Cadoret had to rely on a review of adoption clinic records, which may have focused the sample on particularly heavy drinkers who would be most likely to be recognized. Neither of these studies investigated the role of parental antisocial diagnoses.

The purpose of the present investigation was to address the role of both parental substance use diagnoses as well as parental antisocial diagnoses in the relationship between low levels of prenatal alcohol intake and later offspring CD symptoms. Also addressed was the role of prenatal tobacco exposure. Risk for drinking in pregnancy is often correlated with risk for smoking in pregnancy.^{1, 27-28} There is also increasing evidence of an association between prenatal tobacco exposure and later development of offspring externalizing disorders²⁹⁻³² although this association is similarly confounded by issues discussed above.³³⁻³⁴ Therefore, we also investigated the role of prenatal nicotine exposure on the association between alcohol exposure and conduct disorder.

Method

Participants

Participants in this study were drawn from the Minnesota Twin Family Study (MTFS) and included 674 girls and 578 boys (from 626 same-gender twin pairs, 65.8% monozygotic) and their parents. The MTFS is designed to identify genetic and environmental factors influencing the development of substance abuse and associated psychological disorders. A full description

can be found in Iacono et al.³⁵ The study used a population-based twin ascertainment method in which all twins born in Minnesota were identified by public birth records. Male twins were identified from records for 1972-1978, and female twins from 1975-1979. Over 90% of all pairs in which both members were still living were located. Excluded were families in which the twins were adopted or had a disability which precluded completing our assessment. Of eligible twin families, 17% declined participation. After a description of the study, written informed consent or assent was obtained from parents and twins. All assessments were conducted when the twins turned age 17 (mean age= 17.48, SD=0.46). MTFs family demographics approximate those for Minnesota families in the 1990 U.S. Census for urban/rural split (.66/.34), mean parental age (42 years), percent Caucasian (98%), and percent married (85%), indicating participants were broadly representative of families in this state.³⁶

Mean years of education was 13.7 (SD=1.9) for mothers and 14.2 (SD=2.3) for fathers. Mean occupational status, as assessed on the Hollingshead system, was 3.7 (SD=1.6) for mothers and 3.9 (SD=1.8) for fathers. The Hollingshead scale runs from 1 (executives) to 7 (unskilled employees), with a code of 4 denoting jobs such as data entry operator or bank teller. Consistent with Minnesota demographics for birth years sampled, the majority of parents (98%) were Caucasian. There were no differences on maternal or paternal Hollingshead scores between parents reporting maternal alcohol use in pregnancy and those not reporting use.

Clinical Assessments

All twins and their parents were interviewed separately by different interviewers who underwent extensive training and had at least a B.A. in psychology. Both the mother and each twin provided documentation of each youth's CD symptoms. Maternal reports of CD symptoms were obtained using a modified parent version of the Diagnostic Interview for Children and Adolescents-Revised (DICA-R).³⁷ CD was assessed in twins using the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II).³⁸ DSM-III-R was the reigning diagnostic classification system at the time of this assessment.

To assess alcohol dependence, nicotine dependence, and illicit drug disorders in biological parents, the expanded substance abuse module (SAM) of the World Health Organization's Composite International Diagnostic Interview³⁹ was used. Assessment of the DSM-III-R antisocial personality disorder (ASPD) criteria was obtained with the SCID-II. Adult antisocial behavior (AAB) was additionally assessed; this designation derived from DSM-III-R criteria for antisocial personality disorder, which requires the presence of conduct disorder before age 15 as well as four symptoms of "irresponsible and antisocial behavior since the age of 15." Participants with AAB satisfy the second requirement, but do not satisfy the criteria for conduct disorder before age 15. Various reports substantiate the construct validity of AAB, showing that its correlates mirror those of ASPD.^{13, 40}

Data from interviews was used to diagnose lifetime DSM-III-R disorders by teams of two advanced clinical psychology Ph.D. students who reviewed audiotaped interviews to arrive at a consensus on each clinically significant diagnostic symptom. For adolescents, mother and child reports were independently reviewed, and any CD symptom reported by either informant was counted as present. Previous reports have shown that each informant contributes valuable information not contributed by other informants.^{41,42} A computer algorithm, based on DSM-III-R, was then used to assign diagnoses. To estimate the reliability of the consensus process, interviews of over 600 subjects from the MTFs were independently re-evaluated by a second team. Inter-team agreement, assessed with the kappa statistic, was .89 or higher for adult diagnoses and .75 for CD.

Diagnoses were assigned at two levels of certainty: definite = all diagnostic criteria satisfied, and probable = one symptom short of definite diagnosis. Probable diagnoses were included to

help identify lifetime disorder in currently asymptomatic subjects who must rely on memory to recall symptoms. This approach was introduced as part of the Research Diagnostic Criteria to increase diagnostic sensitivity of lifetime diagnoses and is particularly appropriate for nonclinical population samples.⁴³ Using these criteria, 35.8% of the boys (N=207, 79 probable) and 10.4% of the girls (N=70, 46 probable) exhibited enough symptoms to qualify them for definite or probable diagnoses of CD. Significantly more adolescents of mothers who drank during pregnancy (30.5%) were diagnosed with CD than adolescents whose mothers did not drink during pregnancy (20.9%; $X^2=4.19$, $p=.04$).

Alcohol dependence (at any point in a lifetime) was diagnosed in 43.0% of fathers and 11.1% of mothers. Rates of paternal and maternal lifetime illicit drug disorder were 15.7% for fathers and 8.8% for mothers. Lifetime nicotine dependence was diagnosed in 52.0% of fathers and 38.8% of mothers. Antisocial spectrum diagnosis (i.e., lifetime CD, ASPD, or AAB) was present in 40.3% of fathers and 9.4% of mothers. When data for one parent were missing, only diagnosis positive cases were included.

Maternal prenatal alcohol and tobacco use

Maternal prenatal alcohol use was assessed by the following interview questions: "As you know, it was very common in the past for women to drink during pregnancy. During your pregnancy with the twins, how much did you drink during an average week?" Mothers endorsing 1 or more drinks per week were coded positive as drinking during pregnancy. Maternal prenatal tobacco use was assessed by the following interview question on the SAM: "During your pregnancy with the twins, how much did you usually smoke/use tobacco per day?"

Statistical Analyses

The number of DSM-III-R CD symptoms was chosen as the outcome variable, rather than categorical diagnosis, for several reasons. First, there is ample evidence supporting the dimensional nature of CD⁴⁴⁻⁴⁶ and the construct validity of measuring this dimension using CD symptom counts.^{47,48} Second, symptom counts provide increased statistical power, especially important in a community-based sample where CD rates are lower than in clinical samples. To reduce skewness, the symptom count was log transformed.

In all analyses, data were clustered within twin pairs to account for nonindependence. This was done using generalized estimating equations⁴⁹ in PROC GENMOD and PROC MIXED, procedures in the Statistical Analysis Software (SAS) package. First, we used logistic regression (in PROC GENMOD) to test the extent to which characteristics of families, specifically children's gender, rates of mothers' and fathers' psychopathology, and maternal smoking during pregnancy, differed by maternal alcohol use groups. Second, we used multiple regression (in PROC MIXED) to test the effect of prenatal alcohol exposure on offspring CD symptoms, and in separate models included covariates that are likely associated with mothers' use of alcohol during pregnancy as well as with CD symptoms in offspring. To determine whether the effect of prenatal alcohol exposure remained once parental psychopathology and prenatal nicotine exposure were statistically controlled, three separate regression models were fit. The Base Model included prenatal alcohol exposure (yes/no), offspring gender, and their interaction, with the latter included because the symptom counts varied by gender. The Parental Psychopathology Model examined whether prenatal alcohol exposure predicted adolescent CD after adjusting for parental DSM-III-R diagnosis (either parent affected) of alcohol dependence, illicit drug disorder, and antisocial spectrum diagnosis. This model also included all the terms of the base model. The Prenatal Nicotine Exposure Model examined the effect of prenatal alcohol exposure after accounting for the possible contribution of maternal smoking in addition to all the other variables in the first two models.

Results

Eighty-two of 626 mothers (13.1%) reported drinking during pregnancy, averaging 2.9 (SD=3.1) drinks per week. Mean non-log transformed symptom counts for CD were 1.95 (SD= 2.35) for boys with prenatal alcohol exposure (N=92) versus 1.42 (SD= 1.75) for boys without prenatal alcohol exposure (N=486). For girls, the mean symptom count for CD was 0.74 (SD= 0.93) for those with prenatal alcohol exposure (N=72), versus 0.42 (SD= 0.96) for those without prenatal alcohol exposure (N=602). There were no significant differences between pregnancy drinkers and nondrinkers on length of gestation in weeks (nondrinkers, 38.0 SD=6.09, drinkers, 37.7, SD=3.21; $X^2=.78$, $p=.38$), or in offspring birth weight in ounces (nondrinkers, 92.7, SD=19.5, drinkers 88.8, SD=19.3, $X^2=2.91$, $p=.09$).

Characteristics of families by maternal alcohol use groups are presented in Table 1. Families in which the offspring were exposed to maternal alcohol use during pregnancy generally had higher rates of maternal and paternal externalizing psychopathology, although only a few of these differences were significant at $p < .05$. Families with maternal prenatal alcohol use had higher rates of maternal alcohol dependence, maternal nicotine dependence, and maternal smoking during pregnancy. However, only a small proportion of the women who used alcohol in pregnancy were judged to have a lifetime diagnosis of alcohol dependence (20.7%). Mothers who drank prenatally were more than twice as likely (32.4% versus 15.5%) to smoke during pregnancy than nondrinking mothers, reporting an average number of 13.8 (SD=9.5) cigarettes per day.

Table 2 presents the results of the three regression models, with the first two columns indicating the effects for the Base Model in the absence of covariates. Results for the Base Model indicate that, as expected, male gender and prenatal alcohol exposure were associated with higher levels of CD symptoms. The interaction between gender and prenatal alcohol exposure was not significant. In the Parental Psychopathology Model, parental substance use and antisocial disorders were added as covariates. Although many of the parental disorders significantly predicted offspring CD symptoms, the effect of prenatal alcohol exposure remained statistically significant. The Prenatal Nicotine Exposure Model, which accounted for mother's smoking during pregnancy and all the other covariates, similarly showed that the effect of prenatal alcohol exposure remained significant. In other words, all three models consistently found that after accounting for the effects of important possible confounds, prenatal alcohol exposure was associated with elevated levels offspring CD symptom counts. Drinking alcohol during pregnancy had a significant, independent impact on the prediction of offspring CD, even after the impact of parental alcoholism, illicit drug disorder, antisociality, and pregnancy smoking were taken into account.

Because other factors in addition to parental substance use and antisociality might affect the likelihood of offspring CD outcomes, we re-ran the above analyses while adjusting for monozygosity, gestational age and birth weight. When these factors were included as simultaneous, additional covariates, the effects of prenatal alcohol exposure on CD symptoms remained significant.

Discussion

In this report, we showed that drinking during pregnancy plays a strong and significant role on offspring development. Prenatal alcohol exposure raised rates of offspring CD symptoms in this population sample, even after the effects of parental alcoholism, parental drug abuse/dependence, and externalizing disorders had been taken into account. We arrived at these results using a sophisticated statistical technique, hierarchical linear modeling, which corrected for the correlated observations found in twin samples and also adjusted for potentially

confounding covariates, including parental psychopathology and prenatal nicotine exposure. We were also able demonstrate that these differences were not accounted for by zygosity, gestational age or birth weight.

We chose to focus on rates of CD symptoms, rather than diagnoses, in order to strengthen the statistical power needed to make multiple statistical adjustments for potentially confounding effects, as well as to take into account the nonclinical nature of our sample. However, analyses using diagnoses of CD in adolescents and diagnoses of alcoholism in mothers suggested similar patterns. When mothers who had lifetime diagnoses of alcoholism (N=69) were divided into those who reported drinking while pregnant (N=17), and those who did not (N=69), rates of CD in offspring were higher among the pregnancy-drinkers (44.1% of whose offspring had CD) in contrast to the nonpregnancy-drinkers (20.2%; $p<.05$), corroborating our finding that the alcohol exposure played a unique role.

These findings build on earlier literature that observed this relationship using questionnaire-based outcome measures.^{3,10,12,50} It is also consistent with reports of CD and CD-related behaviors in FAS samples, such as Streissguth's studies, which have yielded results suggestive of increased rates of CD.⁵¹ Moreover, these findings are congruent with recent work suggesting that even low levels of alcohol exposure in pregnancy can be harmful.^{11,52-53} In this general population sample, reporting a very low average alcohol consumption of just three drinks per week in pregnancy, adverse developmental outcomes were still observed.

One methodological limitation is the 17-year period between pregnancy and the interviews for this study. This is longer than most studies and raises the concern of under-reporting of alcohol use in pregnancy. However, some previous reports suggest that accuracy of reporting (as indexed by correlations with alcohol-related physical anomalies) may be increased by gathering reports of mothers' pregnancy alcohol use one to ten years after birth, when presumably anxiety about pregnancy behaviors has subsided.⁵⁴⁻⁵⁶ Concern about the effects of this time lapse on our reports on pregnancy drinking behaviors is also mitigated by the significance of the finding for the relationship between prenatal drinking and CD. One would expect that the effect of the 17-year time lapse in reporting would have decreased the possibility of finding any effect, with mothers misreporting their drinking that long ago. Instead, the significance of the effect appears to be strong enough to have overpowered any tendency of mothers to downplay or forget their history of pregnancy drinking.

An additional consideration relates to our use of a twin sample. Twins are known to receive less utero-placental blood flow per twin compared to singletons, and to have increased likelihood of preterm birth and lower average birth weights.⁵⁷ It is possible that some of the unique characteristics of being a twin could have interacted with the alcohol exposure to affect our findings. Thus, replication of our results in a non-twin sample is important.

In summary, results of this investigation indicate that prenatal alcohol exposure may play a significant role in the prediction of risk for CD, separate from postnatal environmental and genetic risk factors likely to be associated with antisocial and alcoholic parents. While the role of additional confounding variables cannot be conclusively ruled out by this inherently correlational design, these results suggest the importance of prevention programs directed at reducing even small amounts of alcohol consumption in pregnancy.

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Abbreviations

AAB	Adult antisocial behavior
APD	Antisocial Personality Disorder
CBCL	Child Behavior Checklist
CD	Conduct Disorder
DICA-R	Diagnostic Interview for Children and Adolescents-Revised

FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
MTFS	Minnesota Twin Family Study
SAM	substance abuse module (of the World Health Organization's Composite International Diagnostic Interview)
SCID-II	Structured Clinical Interview for DSM-III-R Personality Disorders

Table 1
Comparison of families with mothers who used alcohol during pregnancy to families with mothers who did not

Family Characteristic	Percentages of Family Characteristics by Maternal Prenatal Alcohol Use Groups		Statistical Tests for Differences by Maternal Prenatal Alcohol Use Groups	
	Yes (N=1088)	No (N=164)	χ^2	p
Offspring % female	55.3%	43.9%	3.65	.06
Maternal Alcohol Dependence	9.6%	20.7%	5.48	.02
Paternal Alcohol Dependence	41.4%	52.7%	3.28	.07
Maternal Illicit Drug Abuse/Dep.	7.9%	14.6%	2.65	.10
Paternal Illicit Drug Abuse/Dep.	15.0%	20.3%	1.31	.29
Maternal Nicotine Dependence	35.5%	60.9%	16.57	<.001
Paternal Nicotine Dependence	51.1%	58.2%	1.25	.26
Maternal Antisocial Diagnosis	10.1%	4.9%	3.61	.06
Paternal Antisocial Diagnosis	39.5%	45.9%	1.08	.30
Maternal Smoking in Pregnancy	18.8%	47.6%	20.30	<.001

Note. Sample Ns reflect the numbers of offspring; N/2 = number of mothers.

Table 2
Effect of maternal alcohol use in pregnancy and related variables on conduct disorder in offspring

	Base Model <i>d.f.</i> = 622		Parental Psychopathology Model <i>d.f.</i> = 542		Prenatal Nicotine Exposure Model <i>d.f.</i> = 541	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Parental Psychopathology						
Alcohol Dependence			26.26	<.001	26.27	<.001
Nicotine Dependence			11.16	<.001	11.17	<.001
Illicit Substance Abuse/Dependence			9.44	.002	9.45	.002
Antisocial/Behavioral Disorder			1.87	.17	1.87	.17
Prenatal Nicotine Exposure					0.22	.64
Gender	134.04	<.001	139.72	<.001	139.78	<.001
Prenatal Alcohol Exposure	10.62	.001	10.57	.001	11.59	<.001
Gender X Prenatal Alcohol Exposure	0.11	.74	0.00	.95	0.00	.98

Note: The bolded row represents the primary finding of interest indicating the effect of maternal alcohol consumption on offspring CD symptoms (Base Model), the same effect after adjusting for parental psychopathology, and this effect after adjusting for parental psychopathology and prenatal nicotine exposure.