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Alcohol-Related Birth Defects: Syndromal Anomalies, Intrauterine Growth Retardation, and Neonatal Behavioral Assessment

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Fetal alcohol effects in 359 infants born to disadvantaged women identified as having a history of alcohol abuse or as controls and who provided reports of alcohol use in pregnancy are being studied in a prospective design. Alcohol abuse was assessed with the Michigan Alcoholism Screening Test (MAST). Alcohol use (AA/day) was based on short-term recall covering 2-week periods prior to each antenatal visit. A tally of anomalies associated with fetal alcohol syndrome was obtained in a blinded examination of each infant. This tally was significantly related to the MAST classification and, for the MAST+ subjects, the tally was related to first trimester AA/day. Birth weight, length, and head circumference were negatively correlated with AA/day (entire pregnancy); however, the effect was attenuated and not statistically significant in models with covariate control. It is possible that these measures were near the threshold of effect. Scale scores of the Brazelton Neonatal Behavioral Assessment Scale and three scale scores of the Graham/Rosenblith Behavioral Examination of the Neonate were unrelated to the MAST classification and to AA/day.

THE TERM alcohol-related birth defects includes, but is not limited to, the conditions characterizing fetal alcohol syndrome (FAS). The major features of the syndrome are (1) specific dysmorphological features, (2) intrauterine growth retardation, and (3) central nervous system dysfunction, including mental retardation.

With documentation of the syndrome, and its reasonably definitive linkage to heavy ingestion of alcohol by the mother, interest has shifted to less dramatic presentations of fetal alcohol effects. These include less complete patterns or reduced effects which may result from light as well as heavy maternal alcohol use.

The present report describes findings with respect to neonatal anomalies, intrauterine growth retardation (IUGR), and neurobehavioral status in the neonatal period. These outcomes were related both to a classification based on the Michigan Alcoholism Screening Test (MAST)[1] and to an index of alcohol use. The alcohol use measure utilized in the analyses of neonatal anomalies was based on first trimester data. The first trimester was chosen because this period is considered to be more crucial to the embryogenesis of dysmorphological features. Alcohol use throughout pregnancy was evaluated for the measures of IUGR and behavior.

Alcohol-related physical anomalies, sometimes in the absence of IUGR or evidence of neuropsychological deficit, have been described by several investigators.[2-5] In contrast, two groups of investigators[6,7] failed to find an association between maternal alcohol use and the anomalies linked with FAS. This raises the possibility that these features may be related to maternal use of marijuana,[6] yet most studies have not included statistical control for marijuana use.

IUGR, typically defined as a reduction in birth weight, length, and/or head circumference for gestational duration, is a frequently studied outcome of maternal use of alcohol in pregnancy. Positive findings have been reported by several investigators.[2,3,5,8-10] The effect may be attenuated among infants of heavy drinkers who reduce consumption.[4] However, this finding contrasts with a report describing reduced birth weight in infants of alcoholics who abstain during pregnancy.[11] As with the reports on neonatal anomalies, results are inconsistent, and some investigators[6,7] have failed to find an association between maternal alcohol use and growth retardation. In one study, such retardation was related to marijuana use.[6]

It has been suggested that "maternal abuse of ethanol during gestation ... appears to be the most frequent known teratogenic cause of mental retardation in the Western world."[12] The evidence for this statement remains very limited. In contrast to the identification of anomalies or size effects, the assessment of mental retardation is best studied by means of prospective research to determine the extent of the effect. However, other characteristics of the newborn may be helpful in describing neuropsychological effects while research cohorts are developing to an age when traditional assessments are feasible. The possibility that the effects of a suspected teratogen are primarily

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behavioral[13] has encouraged investigators to explore the neurobehavioral characteristics of the neonatal period.

This is one of the first reports from the Cleveland prospective study of alcohol-related birth defects and child development. Two important features distinguish this study from other investigations. First, pregnant women were selected on the basis of a history of alcohol abuse, as measured by the MAST. This selection policy served to increase the proportion of alcohol users in the cohort and was itself of interest in relation to the outcome measures. Second, a short-term recall strategy was used in the collection of alcohol exposure data. This reduced the problem of limited recall of amounts consumed and facilitated the determination of trimester effects.

A previous paper[14] described the associations of maternal drinking and smoking during pregnancy with lead levels of maternal and cord blood. The possibility that the fetal alcohol effects are mediated by toxic effects of low level lead exposure is considered in this report.

Methods

Selection Procedure

Approximately 3000 infants are delivered each year at Cleveland Metropolitan General Hospital. During a period of several years, all women presenting for antepartum care were screened for alcoholism through administration of the MAST in a carefully structured interview. A score of 5 or more was considered to be positive. About 11% were identified as alcoholic (having a history of alcohol abuse) by this indicator. Women so identified and a matched control group were recruited for a study of pregnancy and neonatal outcome. In this report, the groups are identified as MAST+ and MAST−, respectively. The matching variables for the selection of the MAST− women were date of recruitment, ethnicity, smoking, drug abuse, parity, weight, and weeks gestation at registration. One-to-one matching was not retained in the prospective study of the offspring of these women. Details of the antenatal data collection procedure[15,16] are summarized below.

Infants born to women from the antenatal study between January 1, 1981, and March 31, 1982, were considered for inclusion in the prospective child development study. The criteria for exclusion were maternal use of narcotics, maternal psychosis, adoption, plans to move from the area, parental refusal, primary language other than English, weekend delivery and discharge, gestational age ≤36 weeks, as determined by the Ballard et al. examination,[17] and placement in the Neonatal Intensive Care Unit. Prematurity and illness as outcomes of fetal alcohol exposure are being assessed in the antenatal study. The exclusion criteria were applied without knowledge of the alcohol and other risk factors. After exclusions, the sample consisted of 359 infants, 176 delivered to MAST+ and 183 to MAST− women.

Antenatal Data

Demographic and Psychometric Data. The population from which these women were recruited consists almost exclusively of members of Social Classes IV and V (Hollingshead Two Factor Index). At the first antenatal visit, routine demographic data were collected and women were questioned about their smoking habits, their height and prepregnancy weight, and the height and weight of the father. At the second visit, a recall of foods eaten during the previous 24-h period was obtained. These data were coded for percent of recommended daily dietary allowances in five categories: (1) dairy, calcium, vitamin D, (2) meat and vegetable protein, (3) fruits, vegetables, fiber, vitamins A and C, (4) breads, cereals, B vitamins, and (5) iron foods. Nutritional deficiencies were common, particularly among MAST+ women.[15] At each antenatal visit, women were interviewed about use of alcohol, as described below, and the use of marijuana and other illicit drugs. The use of marijuana and other illicit drugs (other than narcotics) at any time in pregnancy were each coded as positive or negative.

In the postpartum period each woman was tested with the Peabody Picture Vocabulary Test-Revised (PPVT-R)[18] and the Authoritarian Family Ideology Scale (AFI).[19] The former, a measure of receptive vocabulary, was included in lieu of a longer intelligence test as part of a strategy oriented toward maximizing participation. The AFI Inventory "includes belief in hierarchical family organization, demand for respect from children, and tendency to acquiesce to banal and stereotyped remarks."[19] It has previously been related to preschool cognitive development.[20] Both measures will serve as covariates in the later analyses of preschool test data; here they help to describe the sample. Maternal head circumference was also measured postpartum.

Demographic characteristics of the MAST+ and MAST− groups appear in Table 1. Differences between the groups were tested for significance by *t* test or chi square. The discrepancy between groups in gravidity, though not for parity, indicates a greater frequency of fetal loss and/or elective abortion for the MAST+ group. This is being explored in the antenatal study. Smoking had been one of the matching variables. Nevertheless, the relationship of alcohol use and smoking was so strong that the related measures, number of cigarettes smoked per day and pack years (packs per day by years of smoking), differed significantly between groups. The groups differed significantly on parental education but not on the maternal PPVT-R and AFI inventories. The PPVT-R scores were very low, given the mean level of education.

Alcohol Use Data. Two indicators of maternal alcohol status were used. The first, as indicated above, was the MAST classification. The items of the MAST identify prior alcohol-related problems, but not current drinking. This test was devised for use with men, and some items, such as those involving fighting and arrest, are more characteristic of the male alcoholic. The application of the MAST with women may thus be more specific, though less sensitive, than is the case for men. In other words, a MAST+ classification is probably valid, but the MAST− classification may include some women with alcohol-related problems.

The alcohol use data were based on short-term recall. At each antenatal visit, the women were interviewed regarding their use of alcohol on a day by day basis during the period of 2 weeks prior to that visit. The data base for each woman thus consisted of the number of sampled days, in 2-week segments, and the volume drunk and the specific beverage for each drinking day in those periods. These data were converted to ounces

Table 1. Characteristics of the MAST+ and MAST− Groups

Variable	MAST+ Group		MAST− Group		
	Mean or %	SD	Mean or %	SD	*p*
Demographic data					
Race, % black	37.7%		32.2%		
Married[a]	54.6%		56.3%		
Maternal age	22.31	4.61	21.93	4.18	
Parental education[b]	10.50	1.45	11.00	1.32	0.0007
Registration information					
Gestational age (weeks)	18.18	7.43	17.38	5.81	
Gravidity	2.98	1.89	2.49	1.44	0.0001
Parity	1.21	1.37	1.11	1.21	
Use of other substances					
Smoking	79.5%		77.0%		
No. cigarettes	15.01	13.00	12.42	11.03	0.043
Pack years[c]	6.51	6.99	4.37	4.08	0.0005
Marijuana	44.3%		27.3%		0.0008
Other street drugs	13.1%		5.5%		0.013
Postpartum assessment					
Intelligence (PPVT-R)	73.60	14.75	75.55	15.09	
Attitude (AFI)	27.52	5.38	26.81	6.21	

[a] Also live-in partners.

[b] Mean of two, if known, otherwise maternal.

[c] Packs of cigarettes per day by number of years of smoking.

Table 2. Summary of Alcohol Use Data by Group and Trimester

	First Trimester			Second Trimester			Third Trimester		
		AA/day			AA/day			AA/day	
Group	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD	*n*	$\bar{X}$	SD
MAST+									
Abstainer	34			55			68		
Nonabstainer	40	0.20	0.28	92	0.23	0.44	101	0.17	0.34
MAST−									
Abstainer	47			92			107		
Nonabstainer	18	0.10	0.09	52	0.08	0.10	73	0.05	0.05

In each trimester the MAST+ and MAST− groups differed significantly with respect to the proportion who abstained and, among the nonabstainers, with respect to the means and variances of AA/day.

of absolute alcohol per drinking day (AA/drinking day), proportion of sampled days on which drinking occurred (an index of frequency), and the product of these indices (AA/day).[21] The distributions were positively skewed with a modal zero (abstinence) response. Logarithmic transformation was used in the statistical analyses of each of these variables, although results are reported in the original units.

The number of women in the MAST+ and MAST− groups reporting alcohol use in each trimester is indicated in Table 2. The larger data base in the third trimester reflects the antenatal care patterns followed. In all trimesters there was a significant relationship between the history of alcohol abuse, as identified by the MAST, and drinking in pregnancy. Nevertheless, the numbers of nondrinking MAST+ women and of MAST− women who drank permit a moderate degree of independence in analysis of both variables. The AA/day index of alcohol use is also summarized in Table 2. The means differ significantly, as expected, between the MAST+ and MAST− groups. Similar results were obtained for the AA/drinking day and proportion of days indices.

Examination Procedure

Instruments. The Anomalies Tally was prepared by a developmental pediatrician (Nancy Golden). The frequencies for the tallied items are listed in Table 3. Six additional items were included in the tally but were not observed in any member of the cohort. These were strabismus, ptosis, cleft palate, cleft lip, hernias of diaphragm, and inguinal hernias. The incidence of each item by MAST group is reported in this table; the association with MAST+/− will be described more fully in the "Results" section. The tallies ranged from 0 to 11, with 26 of the 359 neonates presenting no tallied item. The mean was 2.96 with an SD of 1.84.

The neurophysiological variables included a priori cluster scores of the Brazelton Neonatal Behavioral Assessment Scale (NBAS)[22] and a portion of the Graham/Rosenblith Behavioral Examination of the Neonate (G/R).[23] The sensory (auditory and visual) items of the G/R were not administered, and only the summary scores, General Maturation Scale, Soft Sign Score, and Muscle Tonus were coded for analysis.

Procedure

Staffing and Reliability. An experienced nurse practitioner measured weight, length, and head circumference and conducted the assessment for gestational age. The neonatal data were collected by two other experienced research nurses. The first nurse (M.J.K.) was certified in the administration of the NBAS by Brazelton's staff. She was then trained in the administration of the Anomalies Tally and practiced the items of the G/R in accord with the manual. The backup nurse was then trained by the first nurse to the criterion of 90% agreement. Bimonthly reliability examinations were conducted thoughout the study. The postpartum examiners were not the same individuals who had conducted the antenatal interviews, and precautions were taken to shield examiners from knowledge of the risk factors of the study.

Neonatal Examinations. As each participating woman delivered, the research nurses determined whether the infant met the inclusion criteria and obtained informed consent. When the infant was over 24 h of age, and at a mid-feeding period, he or she was examined in a quiet, minimally lighted section of the nursery. No child was examined within 6 h after circumcision. The order of the neonatal examinations was designed to progress (1) from relatively subjective to more objective items to minimize inter-test effects, and (2) from items assessed during infant sleep to items more likely to disturb the infant.

If the infant was in the appropriate state, the examination began with the NBAS Habituation Scale. If not, this scale was omitted. The balance of the NBAS and the G/R were then administered. While administering the NBAS, the examiner observed the infant for jitteriness, tremor, etc. These observations augmented the abbreviated G/R procedures for making the G/R ratings. The nurse then described the infant's performance to the mother, answered her questions, measured her head circumference, and administered the PPVT-R and the AFI.

Table 3. Items of the Anomalies Tally

	MAST+	MAST−		MAST+	MAST−
Facial Characteristics			Other Anomalies		
Eyes			Cardiac		
Epicanthal folds	7	2	Murmurs, nonfunctional	22	15
Short palpebral fissures	31	26	Cutaneous		
Nose			Hirsutism	69	66
Short	48	40	Hemangiomas	0	1
Upturned	42	38	Accessory nipples	4	1
Broad deep bridge	97	92	Nail hypoplasia, especially 5th	11	9
Hypoplastic	4	0*	Abnormal palmar crease	9	6
Ears			Renogenital		
Posterior rotation	60	36**	Labial hypoplasia	2	2
Simply formed	46	34	Hypospadias	1	0
Maxilla			Skeletal		
Hypoplastic philtrum	24	17	Pectus excavatum	3	2
Mandible			Limited joint movement (especially fingers, elbows)	0	1
Micrognathia	19	17	Hip dislocation	1	0
Lips			Muscular		
Thin upper vermilion	48	33*	Hernias of umbilicus	4	6
			Diastasis recti	33	22

* $p < 0.05$; ** $p < 0.002$, chi square tests.

Covariate Control Procedures

Covariate measures were selected on the basis of an expected association with the respective outcome measures[24,25] considered in conjunction with a reasonable concern with parsimony. Some of the intercorrelated variables were entered into the analyses as sets. The variables selected for all models were race, a set consisting of maternal age and parity, a set consisting of the five nutritional measures, maternal smoking, use of marijuana, use of other illicit drugs, and sex of infant. One additional set, parental size measures, was entered for analyses of the IUGR measures.

Nutritional data were available for 337 of the 359 mothers. The contribution of the remaining 22 subjects to the dataset required the use of a missing data strategy. This consisted of the formation of a dichotomy reflecting the presence or absence of the datum and a plugged constant for the missing value.[24] Smoking was coded ordinally, representing nonsmoking, 0–9 cigarettes, 10–39 cigarettes, or 40 or more cigarettes per day. Parent size data were missing for six subjects. These were also handled by use of the missing data strategy.

RESULTS

The major mode of analysis for each outcome measure was multiple regression with entry of the specified covariates, the MAST classification (MAST+/−), AA/day, and the interaction of MAST+/− and AA/day. Although the attribute measured by MAST+/− may be assumed to have a temporal priority and, possibly, some degree of causality in relation to the drinking behavior, separate tests of AA/day without prior entry of MAST+/− were conducted for comparison with other studies. Given a statistically significant AA/day effect, a further test was made to evaluate whether the identified effect was associated with the proportion of days on which drinking occurred or with AA/drinking day. First order correlations (or multiple correlations for sets) with the outcome measures are provided for comparison with other reports.

Anomalies Tally

Table 3 included the tabulation of the incidence of each item of the Anomalies Tally by MAST group. While these figures are interesting descriptively, the tests of the research hypotheses were made using the full Tally scores in statistical models incorporating the appropriate covariates, the MAST classification, and the amount of maternal drinking (AA/day) in the first trimester. First trimester AA/day data were available for 139 women. Missing data for this variable, as for the two covariate sets, were handled by the missing data strategy. In this way, it was possible both to test for bias associated with the absence of first trimester data and to use all available data for the covariates and the MAST classification. The test of the interaction of the MAST and AA/day used only the data of the 139 subjects for whom first trimester data were available.

As shown in Table 4, the presence or absence of first trimester data was unrelated to the Anomalies Tally. Among the covariates, race, maternal age and parity, and the use of other drugs were related significantly ($p < 0.05$) to the Anomalies Tally. The Tally was higher for black

Table 4. Hierarchical Analyses of Factors Affecting the Anomalies Tally

Variables in Models	*r* or *R*	Increment in Variance (%)	*p*
Covariates			
Race	0.21[a]	4.37	0.000
Maternal age, parity	0.17[a]	2.13	0.018
Missing nutritional data,	0.07	0.62	NS[b]
Nutrition set	—[c]	1.65	NS
Maternal smoking	0.03	0.35	NS
Use of marijuana	0.09	0.62	NS
Use of other drugs	0.11	1.27	0.027
Sex of infant	0.04	0.04	NS
Model I			
MAST+/−	0.22[a]	3.07	0.001
Missing data	0.04	0.20	NS
AA/Day, 1st trimester	—[c]	1.07	0.038
Model II			
Missing data,	0.04	0.32	NS
AA/Day, 1st trimester	—[c]	1.53	0.015
MAST+/−	0.22[a]	2.49	0.002

[a] $p < 0.001$.
[b] Not significant.
[c] Because of "plugged" values, correlations are not meaningful.

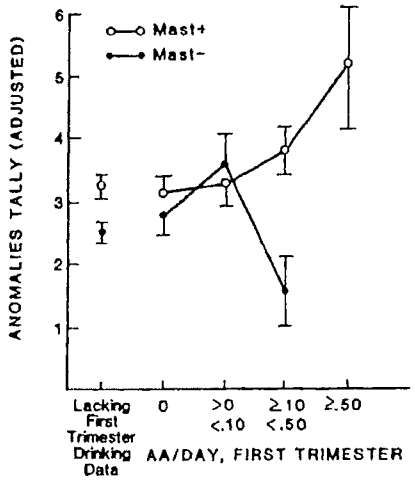

Fig. 1. Neonatal anomalies as a function of MAST classification and first trimester alcohol consumption.

infants, for infants of older mothers, and for infants of women who used other drugs during pregnancy. With statistical control of the full set of covariates, both MAST+/− and AA/day (first trimester) were significantly related to the Anomalies Tally. This finding is applicable for either order of entry of the MAST+/− and AA/day variables (models I and II). The test of the interaction just failed statistical significance. The increment in variance, after entry of the covariates, MAST+/− and AA/day was 2.00%, $p = 0.057$.

As shown in Fig. 1, the effect for MAST+/− is obtained both for the subjects lacking first trimester data and those for whom these data were available. With respect to the Anomalies Tally, the MAST+ subjects presented a greater effect for larger quantities of alcohol used. The results for the MAST− subjects are less definitive, in part, because fewer of these mothers were in the higher AA/day categories. None were in the highest category.

AA/day is the product of two component variables, the

proportion of the sampled days on which drinking occurred (frequency) and AA/drinking day (quantity at a given time). These were tested with the same set of covariates. The proportion of days on which drinking occurred was significantly related to the Anomalies Tally ($p = 0.025$); the corresponding analysis of AA/drinking day was not.

As previously reported, AA/day was related to maternal and cord blood lead levels. The correlation of cord blood lead level and the Anomalies Tally was 0.09 for 196 infants. Maternal blood lead level correlated 0.04 ($n = 225$) with the Tally. The p values for each were greater than 0.20. The possibility that the AA/day effect on the Anomalies Tally was mediated by toxic effects of lead exposure was not supported.

IUGR

The three measures of infant size were birth weight, length, and head circumference. Birth weight was converted to percentile equivalents for the respective gestational ages on the basis of accrued data from our hospital population.[26] The data for each variable were analysed in two ways: (1) as a dichotomous variable with IUGR determined by division at the tenth percentile, and (2) as a continuous variable. The continuous measures were more sensitive to all conditions affecting size; hence, only these are included in this report.

The first order correlations and the results of the regression models are presented in Table 5. Smaller size was associated with being black, with having smaller parents, and with being female. Birth weight was also depressed by maternal smoking and length by less optimal maternal nutrition. In contrast to the findings with neonatal anomalies, the size measures were not sensitive to the history of alcohol abuse (MAST+/−). First order correlations of AA/day (entire pregnancy) with each of the size measures were small, but statistically significant. However, when AA/day was entered into regression models with prior entry of the covariates, the rather small increments in variance failed to reach statistical significance. The data, thus, did not allow an inference of a size effect when other factors related to size were controlled.

Neurobehavioral Measures

Administration of the Habituation Scale requires that the infant be in a light sleep state. Because of this, 51 infants were not assessed for this variable. The possibility of bias exists if the awake state reflects an alcohol-related inability to habituate to the routine activities of the nursery. As a test of bias, the 51 excluded infants were contrasted with the 308 infants for whom habituation data were available. Excluded infants did not differ with respect to MAST+/−, AA/day, or smoking.

First order correlations, the increments in variance associated with MAST+/− and AA/day (entire pregnancy), and the covariates found to be significant for each behavioral outcome measure are provided in Table 6. In each analysis, the order of entry was: covariate set, MAST+/−, and AA/day. The models reversing the order of MAST+/− and AA/day yielded results only slightly different from those provided.

Females were superior on the Habituation Scale. Black infants did more poorly than white infants on the Orientation Scale and had a significantly higher score on the Abnormal Reflexes Scale. Maternal use of illicit drugs was associated with poorer scores on the Habituation, Autonomic Regulation, Neurological Soft Signs, and Poor Muscle Tonus scales. Maternal use of marijuana was related to poorer performance on the Regulation of State Scale.

MAST+/− was related significantly to the Range of State Scale in the first order correlation, but this association was not significant with control of relevant covariates. No other MAST+/− effect approached significance. Two outcome measures, Abnormal Reflexes and General Maturation, were related minimally, but significantly, to AA/day. The direction of effect, however, was contrary to expectations and most of the first order correlations for AA/day, including that with the Habituation Scale, were not consistent in sign with the hypothesized direction of effect. The power for these statistical tests was reasonable. Given the sample size for the Habituation Scale analysis (308), alpha set at 0.05, and the postulated effect size at 3% of variance, the power is 0.85. In other words, if there was an effect size of 3% or greater, the probability of detecting it was 0.85. The inference of a chance effect is reasonable.

Table 5. Increment in Variance of Size Measures Associated with Maternal Alcohol Abuse (MAST) and Alcohol Use (AA/day) in Pregnancy

	r		Variance Increment (%)			
Variable	MAST+/−	AA/day	Initial	MAST+/−	AA/day	Significant Covariates
Weight (adjusted for gestational age)	−0.03	−0.15*	22.9	0.01	0.55	Race, parent size, smoking, and sex
Length	−0.04	−0.13**	21.0	0.00	0.45	Race, parent size, nutrition, smoking, and sex
Head circumference	0.01	−0.12**	21.2	0.07	0.46	Race, parent size, and sex

*$p < 0.05$; **$p < 0.01$.

Table 6. Increment in Variance of Behavioral Measures Associated with Maternal Alcoholism (MAST+/−) and Alcohol Use (AA/day) in Pregnancy

Variables	r		Variance Increment (Percent)			Significant Covariates
	MAST+/−	AA/day	Initial	MAST+/−	AA/day	
Brazelton						
Habituation	−0.10	0.07	7.84	0.59	1.02	Drug use, sex
Orientation	0.01	−0.04	4.73	0.04	0.00	Race
Motor performance	−0.05	0.09	5.28	0.15	0.95	
Range of state	−0.12[b]	0.02	6.38	0.51	0.41	Marijuana use
Regulation of state	−0.05	0.06	3.13	0.11	0.47	
Autonomic regulation	−0.04	0.02	5.15	0.02	0.14	Drug use
Abnormal reflexes[a]	−0.02	−0.06	7.15	0.08	1.18[c]	Race
Graham/Rosenblith						
General maturation	−0.05	0.10	5.27	0.13	1.73[c]	
Soft Sign Score[a]	0.03	0.03	4.27	0.02	0.00	Drug use
Muscle Tonus[a]	0.00	0.00	7.13	0.15	0.08	Drug use

For Habituation, $n = 308$; for all others, $n = 359$.

[a] Higher score indicates poorer performance; for the other scales, a higher score represents more optimal performance. [b] $p < 0.05$. [c] $p < 0.05$ in the direction contrary to the hypothesis.

DISCUSSION

The most striking feature of the results of this study was the association of the history of alcohol abuse with the tally of neonatal anomalies associated with FAS. Furthermore, among the subjects who were positive for the history of alcohol abuse, the effect was markedly stronger for infants of women consuming large amounts of alcohol in the first trimester. The importance of the history of alcohol abuse, or alcoholism, has previously been suggested by Abel[27] and by Streissguth et al., [28] and has been stated most strongly by Majewski and Goecke.[29] Our major findings for the MAST+/− effect and for the effect of AA/day for the MAST+ group support this position. The small difference among abstaining members of the two groups is also consistent with an interpretation that the effect is due to moderately heavy alcohol consumption by women who have a history of alcohol abuse. Few of the MAST− women consumed large amounts of alcohol and the number of such cases was not sufficient for a clear test of the possibility of a minimal dose-related effect for the control subjects.

Another of the research questions concerned the relative role of the quantity consumed on a drinking day and the frequency of drinking. Frequency (persistent exposure), at least in the first trimester, was the crucial factor in the determination of the increased occurrence of neonatal anomalies.

It had been anticipated that IUGR would be more closely related to the consumption of alcohol in pregnancy than to the history of alcohol abuse, and the data were consistent with that expectation. None of the size measures was related to the history of alcohol abuse, but each was correlated negatively with reported alcohol consumption. However, with entry of the full set of covariates into the statistical models, this association was attenuated and not statistically significant. The discrepancy between positive findings with the first order correlation and the marked decrease in effect sizes with covariate control illustrates the importance of control of confounding variables in this area of research. While size effects are clearly a feature of the FAS, these effects have not been obtained consistently by others studying lesser effects of alcohol exposure. The seeming inconsistency among reports may be indicative of reasonable fluctuations of a small, but true, effect being assessed at or near threshold.

The third area of reported alcohol-related birth defects includes neurobehavioral functioning. The major concern in this regard is, of course, mental retardation, or, at a less drastic level, various degrees of deficit in intelligence, cognition, language skills, and vigilance. The prospective study, of which this is an early report, includes measures of these areas of performance made at appropriate ages in the preschool years. These will be reported in due course.

In general, the results using the NBAS were disappointing since the findings were not even consistent in direction with the hypothesis of alcohol-related birth defects. The Habituation Scale of the NBAS had been of particular interest in that inability to inhibit response has been reported in animal studies and in one study, by Streissguth and her associates,[30] in the human neonate. We were unable to replicate the Streissguth findings even with respect to the direction of effect. Since the effect size in the Streissguth study was very small, it is possible that habituation is only minimally sensitive to fetal alcohol exposure in the range of consumption under consideration. Streissguth et al. also reported that alcohol exposure decreased arousal or excitability during the examination. Items reflecting arousal were scored differently in the two studies so that direct comparability in this regard is less feasible. The significant correlation linking MAST+/− to Range of State is interesting in that it was consistent with the findings of a previous report[13] relating this measure to prepregnancy alcohol consumption. This effect, however, was attenuated and no longer significant with appropriate entry of control variables.

The NBAS was supplemented by the administration of another standardized instrument for the assessment of neonates. Of particular interest were the Soft Sign Score

and the Muscle Tonus Score since FAS children are described as presenting various signs of central nervous system disturbance, including hypo- or hypertonia and being tremulous, irritable, or jittery. We were unable to identify alcohol-related deficiencies in performance for these scales, but note that the Soft Sign and Muscle Tonus Scores were sensitive to the use of illicit drugs. Even these effect sizes were small.

It appears that the neonatal tests were not sufficiently sensitive to the levels of impairment found with the amounts of alcohol consumed by this cohort of women. The critical tests of neuropsychological deficit will be those related to intelligence and attention deficit in the preschool years.

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