CLINICAL IMPLICATIONS OF RECENT RESEARCH ON THE FETAL ALCOHOL SYNDROME*

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FETAL ALCOHOL SYNDROME refers to a recognizable pattern of abnormalities observed in children born to alcoholic mothers.[1] It is diagnosed by the presence of abnormalities in each of three categories: prenatal and/or postnatal growth retardation; central nervous system involvement; and a characteristic face, currently qualitatively described as including short palpebral fissures (eye openings), an elongated midface, a long and flattened philtrum (groove between nose and upper lip), thin upper lip, and flattened maxilla (midface).[2]

Case reports of children with the fetal alcohol syndrome have documented central nervous system deficits characteristic of the syndrome and their severe long-term impact on mental and social function.[3,4] Children included in such studies are identified retrospectively, and tend to be severely affected, with physical features or mental handicaps dramatic enough to bring them to attention. Prospective longitudinal studies extend these observations in several important ways. They permit more accurate measurement of prenatal alcohol exposure and other factors that might influence pre and postnatal development. Such measures are needed to determine whether heavy drinking during pregnancy by nonalcoholic women impairs cognitive or neurobehavioral development of their children, and to assess the long-term consequences of prenatal alcohol exposure in children with no obvious physical manifestations. Prospective studies also provide measures of prevalence and factors influencing prevalence.

*Presented in a panel, Scientific Foundations of Clinical Practice, as part of a *Symposium on Pregnancy and Substance Abuse: Perspectives and Directions* held by the Committee on Public Health of the New York Academy of Medicine, the Medical and Health Research Association of New York City, Columbia University School of Public Health, the Maternal and Child Health Program of the New York County Medical Society, the Greater New York March of Dimes, and Agenda for Children Tomorrow March 22, 1990 at the New York Academy of Medicine.

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It is one of the precepts of teratology and developmental toxicology that embryo/fetal toxic effects are a function of the dose of the agent reaching the target tissue.[5] This suggests that, if high doses of alcohol typically taken by alcoholic mothers are associated with severe central nervous system impairments in offspring with the fetal alcohol syndrome, lower doses taken during pregnancy by "social" drinkers may have a less severe, albeit significant, negative impact on cognitive and neurological development. A number of longitudinal studies have been undertaken to investigate this question by assessing subtle aspects of intellectual development and behavior in samples of children who represent general populations and who have had varying degrees of in utero alcohol exposure. Children recruited for these prospective studies are now attaining ages that permit the assessment of cognitive functioning so important in mastering the skills necessary to succeed in school. The present paper summarizes current findings from six studies conducted in the United States and Canada.

It is beyond the scope of the present review to provide detailed methodological descriptions for the six studies; however, in Table I brief summaries are provided of recruitment and follow-up procedures, maternal sociodemographic characteristics, and prenatal alcohol exposures. The Seattle Longitudinal Study on Alcohol and Pregnancy was the first initiated, and it is one of the largest and most comprehensive of the six.[6,7] Assessments were made of neonates,[8-14] at eight months,[15,16] at 18 months, at four years,[17-19] and at 7½ years.[20-25] In Buffalo the Women's Health Study was originally designed to test methods of screening for alcohol-related problems among obstetric and gynecologic outpatients.[26] Subsequently, pregnancy outcome data were abstracted from medical records for newborns of obstetric patients who had participated in the screening study,[27] and a six-year follow-up was conducted.[28] The Ottawa Prenatal Prospective Study addressed "soft" drug use during pregnancy and included women who smoked tobacco and used marijuana, as well as women who drank alcohol in moderation.[29] Children were examined at birth,[30-33] at 13 months,[34] at 12 and 24 months,[35] and at 36 and 48 months.[36] The Cleveland prospective study[37] employed a sophisticated matched sampling design with intensive follow-up, and has extensively investigated threshold[38,39] and risk factors[40] that may moderate alcohol's effect on offspring. Children were assessed at birth,[41] annually from one year to 4 years and 10 months.[42-45] The Georgia Alcohol and Pregnancy Research Project is investigating pregnancy outcome in life-long abstainers and two groups of drinkers. The drinkers had consumed alcohol during their first two trimesters, at which point they entered the study and

were counseled about the negative effects of alcohol, tobacco, and other drug use for their infants and advised to stop using these substances. One group stopped drinking, and the other continued during the third trimester despite counseling. Children were assessed at birth[46,47] and between five and eight years (average six years).[48,49] The Pittsburgh study of Maternal Health Practices and Child Development, the most recently initiated of the six, is part of a larger study that also examines the effects of marijuana and cocaine on development. Children were examined at birth,[50-52] eight months,[53] 18 months, and 36 months.[54]

Data from the six studies on prenatal alcohol exposure and physical development are summarized in Table II. An effect on growth evident in children was reported in the Buffalo, Atlanta, and Pittsburgh studies. By contrast, the rate of fetal-alcohol-syndrome-associated birth anomalies was higher among heavier drinkers in every study in which they were assessed; and in studies that assessed older children for these anomalies, the relationship with prenatal alcohol exposure persisted.

Deficits in cognitive development were associated with prenatal alcohol exposure in the Seattle, Atlanta, and Pittsburgh studies, and with indications of problem drinking in the Buffalo study (Table III). No significant relationships between maternal alcohol use and cognition were observed in either the Ottawa or Cleveland studies. Neurobehavioral deficits were found by the Seattle, Atlanta, and Pittsburgh studies to be associated with prenatal alcohol exposure (Table IV).

Evaluating these findings is complicated by a number of methodological factors that may influence relationships observed in prospective studies of prenatal alcohol exposure. Such factors include the sociodemographic characteristics of the mothers recruited, mothers' drinking patterns, fathers' drinking patterns, measurement techniques, timing and number of measurements, retention rates, and analytic techniques, including the selection and treatment of potentially confounding variables. An examination of Table I reveals that the six studies differ with respect to many of these methodological factors. Some issues relevant to the interpretation of data available to date are briefly discussed below.

Socioeconomic Status of Cohorts Studied

Mothers and their children followed in Cleveland, Atlanta, and Pittsburgh were drawn from socially disadvantaged populations, whereas Seattle and Ottawa populations were middle class, and the Buffalo study included both middle and lower class subjects. If interactions with socioeconomic status

TABLE I. PROSPECTIVE STUDIES OF PRENATAL ALCOHOL EXPOSURE AND EARLY CHILDHOOD DEVELOPMENT

Study	*Sample*	*Alcohol exposure*
Seattle 1974	Recruited 1,529 subjects in 5th month of pregnancy; 85% response rate. Followed 250 heavier drinkers and smokers, 250 infrequent drinkers and abstainers. 86% retention rate at age 7½ years. Primarily middle class; 88% white, 87% married.	Characterized as moderate. AA* Prior to pregnancy (AAP): range 0-25; mean 0.8 (SD = 1.8, median 0.4) among 73% drinkers; AA >1.5 for 47 subjects; AA >2.0 for 22. AA during mid-pregnancy (AAD): AAD >1.0 for 30 subjects, mean and median = 1.7 and 1.3 oz. Binge (5 or more drinks at one time, at least once): 29% prior to pregnancy: 32% either prior to or during mid-pregnancy.
Buffalo 1978-1979	Self-administered questionnaire completed by 531 obstetric patients; 91% response rate. Followed 338; 57% tested at age 6 years; after exclusions N = 178. Clinic and private patients; 47% receiving public assistance; 40% black; 54% married.	AAP: range 0-10.8**, mean = 0.7; (SD = 2.0, median 0.5) among 73% drinkers; 18 subjects >1.0, AA for 13 subjects between 1.0 and 3.6, AA for five ranging from 8.2 to 10.8. Indications of problem drinking (IPD): 14 subjects with two or more.
Ottawa, Canada 1980-1983	700 volunteers interviewed; recruited those who used marijuana, drank >.88 AA, or smoked an average >16 mg nicotine, plus 50 nonsmoking abstainers, approximately 250. Middle class population, almost all white, 90% married.	Heavy social drinking defined as AA >.85: 18% prior to pregnancy (mean AAP = 1.86), 6.5% in first trimester, 3.3% in second trimester, 2.6% in third trimester. Binge prior to pregnancy and in 1st, 2nd, & 3rd trimester: among moderate drinkers—34%, 8, 6, 11%; among heavy drinkers—68%, 54, 56, 60%.
Cleveland 1979-1980	Screened 7,764; recruited 176 subjects positive on the Michigan Alcoholism Screening Test (MAST) and 183 controls matched on race, smoking, parity, date of recruitment, drug abuse, prepregnancy weight, and weeks gestation at registration. Mothers were socially disadvantaged, 35% black, 55% married.	Average absolute alcohol intake per drinking day (AADD) reported during pregnancy: range 0-2.1, mean 0.07. AADD reported five years retrospectively: range 0-13.5, mean 0.61. Use during pregnancy thought to be underreported.[57] MAST scores ranged from 0 to 41, mean 5.6.
Atlanta 1981-1983	267 screened; 90% interviewed. Followed 55 lifetime abstainers and 48 drinkers, 22 of whom stopped drinking during the 2nd trimester and 26 of whom continued. Be-	AA at time of interview, usually second trimester: among women who stopped, mean = 1.4; among those who continued, mean = 1.8.

	tween ages 5 and 8 years examined children of 21 abstainers and 47 drinkers. Mothers were predominantly black, of low socioeconomic status.	
Pittsburgh 1983-1986	1,360 screened before 5th month of pregnancy, 85% response rate. Followed women averaging >2 drinks per week during 1st trimester and next woman drinking less, N = 650; 595 singleton live births. 519 examined at 3 years; 88% retention rate. Low socioeconomic status, 50% black, 38% married at delivery.	Heavy use defined as an average of one or more drinks per day: reported by 289 of 650 subjects prior to pregnancy; 124 subjects 1st trimester; 17 2nd trimester; 25 3rd trimester. Drinks per day: 1st trimester range 0-10.6, mean 0.7 (SD 1.3); 2nd trimester range 0-12, mean 0.15 (SD 0.7); 3rd trimester range 0-5.3, mean 0.15 (SD 0.5).[69]

*Absolute alcohol per day in ounces; one ounce is equal to approximately two drinks.
**One woman had an AAP value of 34.8; this was reduced to the next highest level, 10.8. Without this adjustment mean AAP = 0.9 (SD 3.5, median 0.5).

influenced the relationship between prenatal alcohol exposure and child development, findings would vary according to the social class of the population studied. Part of the failure to observe direct effects of prenatal alcohol exposure on child development in the Cleveland sample might be attributable to the competing influence of environment, as evidenced by the fact that the Home Observation for the Measurement of the Environment strongly predicted cognitive development in this cohort, and scores on cognitive tests tended to decrease with age.[42] This possibility is not consistent, however, with the demonstration of prenatal alcohol effects in the Pittsburgh and Atlanta cohorts, which were also socially disadvantaged. Careful control of environmental factors may have contributed to the demonstration of prenatal alcohol effects in the Pittsburgh study. Although great attention was given in the Cleveland study to matching heavy drinkers with lighter drinkers on potentially confounding factors and to the measurement of postnatal environment, there is always the possibility that other unmeasured factors obscured the effect of prenatal alcohol exposure. It is also possible that the effects of prenatal alcohol exposure on child development are modest and that, given our power to demonstrate modest effects, some studies will find them and others will not.

THE EFFECTS OF MODERATE VS. "ALCOHOLIC" DRINKING

The level of prenatal alcohol exposure poses both measurement and analytic problems.[55-58] If mothers deny heavy drinking or forget to report some

TABLE II. PRENATAL ALCOHOL EXPOSURE AND PHYSICAL DEVELOPMENT

Study	*Growth*	*Anomalies*
Seattle	No alcohol effect evident on growth at age four years.[18]	11 rated abnormal at birth with features of fetal alcohol syndrome (FAS), nine from heavy drinking group; 2 of 11 diagnosed with FAS, both in heavy drinkers.[8] At age 4 probable, possible FAE observed in 20.4% heavy drinkers vs. 9.3% in comparison group; related to AA prior to pregnancy (AAP; $p=0.002$).[17]
Buffalo* 6 years	Weight (NS) Height and head circumference decreased as AAP increased ($p<0.05$)	Risk of probable, Possible FAE increased with increasing AAP ($p<0.10$). Facial features associated with FAS increased with AAP ($p<0.05$) and indications of problem drinking ($p<0.10$). No FAS cases diagnosed.
Ottawa	No alcohol effect on growth at 12 or 24 months.[31]	
Cleveland	No alcohol effect on growth evident at age five years.[43]	Birth: Tally of anomalies associated with FAS related to positive scores on the Michigan Alcoholism Screening Test, first trimester absolute alcohol per drinking day.[41]
Atlanta[48] 6 years	Weight (NS) Offspring of women who continued to drink were significantly shorter and smaller, and had smaller mean head circumference.	Alcohol dysmorphia scores were significantly higher among children of mothers who continued to drink compared to those who never drank ($p<0.02$); scores were intermediate in children of mothers who stopped drinking (NS).
Pittsburgh[54] 3 years	Weight: 2nd & 3rd trimester drinks per day** Height: 1st & 3rd trimester drinks per day Head circumference: 2nd & 3rd trimester drinks per day Skinfold thickness: 1st trimester drinks per day	Birth:[50] Tally of anomalies associated with FAS related to alcohol use in first month of pregnancy, $p<0.10$.

*Unpublished; all statistical tests were two-tailed.

**Growth parameters are negatively related to alcohol exposures indicated.

drinking episodes, prenatal alcohol exposure will be underestimated. Underestimation could result in heavy drinkers being classified with moderate drinkers. Such misclassification could make it more difficult to detect central nervous system deficits associated with heavy drinking, and it might also produce a situation in which central nervous system deficits that were in fact associated with heavy drinking were mistakenly attributed to moderate drinking.

Because alcoholism is rare among pregnant women, their drinking can be characterized as generally moderate. However, as indicated by the recruitment methods outlined in Table I, it is often necessary to screen large numbers of women to identify enough heavy drinkers to investigate prenatal alcohol effects prospectively. Screening large numbers of women greatly increases the likelihood that pregnant alcoholics will be included in a study, even though they may be atypical of the population from which the sample is drawn. If alcoholics are not excluded from analyses, birth anomalies and developmental deficits associated with prenatal alcohol exposure cannot be attributed to moderate drinking. In the absence of objective measures for alcoholism, such contamination cannot be ruled out. Meanwhile, the six studies differ markedly in the attention given to this critical question.

Because it is suggested that misclassifying alcoholics as moderate drinkers will tend to exaggerate deficits, studies reporting significant cognitive and neurobehavioral delays associated with moderate drinking merit the most careful scrutiny. There are only two such studies among the six, Seattle and Pittsburgh. The Buffalo study found deficits associated only with indications of problem drinking; the Ottawa and Cleveland studies did not report significant alcohol effects. The Atlanta study was designed to investigate the effect of discontinuing drinking during pregnancy rather than the effect of moderate drinking, but maternal alcoholism could also influence the interpretation of its findings.

The Seattle prospective study did not include measures of alcoholism; therefore, this question cannot be examined directly. However, the upper limit for mean ounces of absolute alcohol consumed per day prior to recognizing pregnancy (AAP) was 25, indicating that at least one mother reported drinking an average of 50 drinks a day, hardly moderate. Studies of I.Q. at age four among children of 47 women with AAP >1.5 included two children with fetal alcohol syndrome and eight with anomalies associated with it.[42] To date fetal alcohol syndrome has only been diagnosed in children of alcoholics; therefore, it seems likely that at least two alcoholics have been included in this cohort. The mean I.Q. difference reported at four years, 4.8

TABLE III. PRENATAL ALCOHOL EXPOSURE AND COGNITIVE DEVELOPMENT

Study	*Test*	*Alcohol exposure associated with deficits*
Seattle[22] 7 years	Wechsler Intelligence Scale for Children, revised (IQ) Wide Range Achievement Test, Revised (achievement)	Overall association demonstrated using Partial Least Squares analysis to adjust for multiple exposure and outcome measures
Buffalo* 6 years	Wechsler Preschool and Primary Scale of Intelligence (WPPSI)—Verbal I.Q. Performance I.Q.; Token Test (receptive language); Dichotic listening test	Verbal IQ and Token Test related to indications of problem drinking, even after excluding the five heaviest drinkers from the analyses; however, AA prior to pregnancy was not related to measures of cognitive development
Ottawa[36] 48 months	Reynell Developmental Language Scale Peabody Picture Vocabulary Test (receptive language)	(NS) (NS)
Cleveland	WPPSI at 4 years, 10 months[42] Sequenced Inventory of Communication Development (language) at 3 years[45]	(NS) (NS)
Atlanta[48] 6 years	Kaufman Assessment Battery for Children Preacademic skills (math, reading) Sequential processing (short-term memory and encoding)	Both alcohol exposed groups continued drinking
Pittsburgh[50] 3 years	Stanford-Binet (4th Ed.): Short-term memory subscale Proportion below 10th, 20th IQ percentile Quantitive reasoning Short-term memory Short-term memory, verbal reasoning, and composite score	Second trimester alcohol use Third trimester alcohol use 1st trimester >0.75 drinks per day 2nd trimester >0.75 drinks per day 3rd trimester >0.75 drinks per day

*Unpublished

points, is almost one third of a standard deviation in I.Q.[18] If I.Q. scores were normally distributed in both populations, this would represent a tripling of the risk of having an I.Q. lower than 85. This is an important finding, but cannot be attributed to moderate drinking. To estimate the I.Q. deficit attributable to moderate drinking, it would be necessary to reanalyze these data without including children of mothers suspected of being alcoholic, bearing in mind that such estimates would probably represent upper limits for an effect of

moderate drinking because unsuspected alcoholics might still be included in the sample.

The Pittsburgh study was initiated almost 10 years after the Seattle study, and was conducted in a clinic that screened and referred women for alcoholism prior to their recruitment. No fetal alcohol syndrome cases were observed. The upper range of drinking reported, more than 10 drinks a day, is fairly high, but recent analyses of height and weight at age three indicated deficits associated with moderate drinking ($>0 \leq 0.89$ drinks per day) during the third trimester.[59]

As indicated above, the Atlanta study included two groups of mothers who drank during the first two trimesters of pregnancy, one that stopped drinking, and one that continued. One interpretation of their data is that differences between the two groups are attributable to alcohol exposure during the third trimester. Another interpretation is that women who continue to drink during the third trimester differ from those who stop in some way that has a negative impact on pregnancy outcome. Both possibilities may operate, either independently or interactively. A study of factors predicting continuous drinking during pregnancy in their cohort found that the best predictors were the length of drinking history, reported tolerance to alcohol, a history of alcohol-related illness, and drinking by siblings. In addition, women who continued to drink throughout pregnancy were more likely to report that they drank most often with other family members.[60] These findings were interpreted as suggesting that women who continue to drink during pregnancy may be experiencing more chronic and severe alcohol-related problems than women who discontinue alcohol use.[60] Drinking by siblings and with family members may indicate a familial predisposition to use/abuse alcohol that could be purely cultural or have a genetic component that could also influence the effects of prenatal alcohol exposure.

Binge Drinking vs. Average Alcohol Intakes

Animal models indicate that high blood alcohol levels predict alcohol-related birth defects better than the total volume of alcohol consumed,[61] and data from the Seattle study are consistent with this.[22,24] Binge drinking was assessed in the Ottawa study with negative findings. Although alcohol intake was expressed in terms of drinks per drinking day in the Cleveland study, which should correspond more closely to blood alcohol levels than drinks per day, prenatal alcohol exposure was not found to be related to child development. Other prospective studies have either not measured binge drinking or have not published analyses of pregnancy outcome as a function of binge drinking.

TABLE IV. PRENATAL ALCOHOL EXPOSURE AND NEUROBEHAVIORAL DEVELOPMENT

Study	*Test*	*Alcohol exposure associated with deficits*
Seattle	Continuous Performance Test	Drinking prior to pregnancy:
7½ years	(vigilance):[20]	
	Mean Reaction Time	Linear (log drinks per occasion)
	Errors of Commission	Linear (log AA)
	Vigilance Summary Score	Quadratic (log AA)
	17 neuropsychological tests (164 scores)[24]	Overall association demonstrated using Partial Least Squares analysis to adjust for multiple exposure and outcome variables
	Myklehurst Pupil Rating Score (classroom)[25]	
	Connors Parent Rating Scale[25]	
Buffalo*	Child Behavior Check List	(NS)
6 years	(CBCL)	
	Draw-a-Line slowly (impulse inhibition)	(NS)
	Connors Parent Rating Scale	(NS)
	Visual Motor Integration	(NS)
Ottawa[36]	McCarthy Scales of Childrens'	(NS)
48 months	Abilities	(NS)
	Pegboard Test: hand-eye coordination	(NS)
	Tactile Form Recognition Test	
Cleveland[44]	Vigilance test	(NS)
4 years, 10 months		
Atlanta[49]	Teachers' CBCL	Continued drinking
6 years	Maternal CBCL	(NS)
	Sustained attention	Continued drinking
	Impulse control	(NS)
	Observed maternal-child interactions	(NS)
Pittsburgh[50]	Temperament: less emotionality	2nd & 3rd trimester drinks per day
3 years	Behavioral assessment	2nd & 3rd trimester drinks per day
	Motor abilities:	
	Refusal to walk line	1st & 3rd trimester drinks per day
	Refusal to walk board	1st & 3rd trimester drinks per day

*Unpublished

PATERNAL DRINKING

Despite wide recognition that it is unusual for a woman to drink more than her mate and documentation of assortative mating between alcoholics,[62,63] the role of paternal drinking in alcohol-related birth defects began to receive attention only recently.[64,65] Accordingly, few prospective studies of prenatal alcohol exposure have investigated paternal drinking. The Buffalo study assessed paternal drinking retrospectively. An association between maternal indications of problem drinking and cognitive development was observed after controlling for paternal drinking; however, these findings need replication because the sample was small, and response rates were low.

VULNERABILITY FACTORS

Genetic sensitivity is thought to moderate prenatal alcohol effects,[66] but this issue has been investigated only in the Cleveland cohort.[67] If vulnerability to prenatal alcohol exposure could be reliably and validly measured in prospective studies, this would greatly improve their predictive power. In the absence of such measures, it may be difficult to demonstrate prenatal alcohol effects in populations that are genetically heterogenous with respect to vulnerabililty factors.

EXPLORATORY VS. CONFIRMATORY ANALYSES

There are many ways in which prenatal alcohol exposure could be measured and many ways in which such exposure could affect child development. To test adequately to test all possible combinations requires extensive analysis, which increases the likelihood of Type I errors. A Type I error occurs when a relationship that occurs by chance is mistaken for a meaningful one. For example, a relationship significant at the 0.05 level is likely to occur by chance only one time in 20 tests; if 20 statistical tests are conducted, one should be statistically significant at the 0.05 level, on the basis of chance alone.

The Seattle study used a recently developed analytic approach, Partial Least Squares, for data reduction and analysis of 158 neurobehavioral measures as they relate to 13 aspects of prenatal alcohol exposure.[21] The Partial Least Squares approach addresses the issue of Type I errors by employing an omnibus test adjusted for the number of variables in the analysis. However, when individual variables are examined, the independence of the statistical

tests becomes an issue; and alpha levels should be corrected for multiple tests.[68] Because overall omnibus tests of the Seattle data do not reflect strong relationships between the latent variables,[22,24] individual tests may no longer be statistically significant if the alpha levels are adjusted. Although this analytic approach is potentially powerful, it should be regarded as exploratory; additional studies are needed to confirm the results obtained.

A second Seattle analysis of prenatal alcohol effects on child I.Q. and learning problems at age 7½ years employed multiple regression.[25] It was reported that consuming more than two drinks a day during pregnancy was related to a seven point decrement in I.Q. It should be noted, however, that only 30 women drank at this level, and that the analyses of prenatal alcohol effects included interactions with paternal educational levels and the number of children in the house. It seems likely that, given the small number of exposed children available for analysis, the complexity of the relationship observed, and the absence of an analytic plan predicting such a relationship, the reported I.Q. decrement owes much to chance. This finding, too, needs to be replicated by other investigators to establish its reliability and validity.

CONCLUSIONS

The preceding discussion focussed on factors that complicate the interpretation of data from prospective studies of prenatal alcohol exposure. Despite their limitations, these studies provide valuable measures of the degree to which prenatal alcohol exposure represents a pregnancy risk. Even though large numbers of women who drink will quit during pregnancy, there is generally a lag between the time they conceive and the time that they recognize their pregnancy and stop drinking. This leaves a window of vulnerability which may put at risk substantial numbers of children who would otherwise be born into circumstances highly favorable for their growth and development. In addition to this source of exposure, there are also women who are not aware of the dangers of drinking during pregnancy, or who are unable or unwilling to reduce their alcohol consumption. Additional prospective studies are needed to investigate factors that influence continued drinking during pregnancy and the long-term consequences of this pattern of exposure.

Difficulties in defining groups of moderate drinkers that do not include mothers suspected of being problem drinkers or alcoholics suggest the possibility that alcohol abuse is more prevalent among pregnant women than previously suspected. For example, 7% of the obstetric patients in the Buffalo cohort reported two or more indications of problem drinking, and at age six their children had verbal I.Q. scores an average of 7.6 points lower than

children of women with fewer indications, even when the heaviest drinkers were not included in the analysis.

It should also be noted that there appear to be developmental deficits associated with prenatal alcohol exposure in the absence of the fetal alcohol syndrome or physical anomalies. Clinicians are often told, "I drank during my first two pregnancies, and my babies were okay." Yet, many alcohol-related anomalies are subtle, likely to go unrecognized. Moreover, it may take six years for underlying learning disabilities to emerge, and by then the drinking during pregnancy is long forgotten. These studies suggest that it may be misleading to conclude that prenatal alcohol exposure has done no damage simply because a child looks "okay" at birth.

It has become increasingly difficult to investigate the effect of prenatal alcohol use on child development because the use of drugs other than alcohol has greatly increased among women in their childbearing years, especially among heavy drinkers. Heightened concern about other drugs and other risk factors should not be allowed to detract from attention to prenatal alcohol exposure as a pregnancy risk factor. Women who drink during pregnancy still far outnumber those who abuse drugs. Moreover, alcohol use among women who abuse other drugs has the potential to increase their likelihood of a suboptimal pregnancy outcome.

Four of the six studies found significant deficits in cognitive or neurobehavioural development associated with maternal drinking during pregnancy or indications of problem drinking. The evidence that moderate drinking causes alcohol-related birth defects is not yet compelling, and rigorous testing of this hypothesis awaits the development of objective measures of alcohol intake, alcoholism, and vulnerability factors. Although the precise level of alcohol intake associated with the cognitive and neurobehavioral deficits observed is unclear, the importance of these long-term consequences justifies increased attention to prenatal alcohol exposure. The effects reported gain signficance when considered in terms of the many women of childbearing age who drink.

REFERENCES

1. Jones, K.L. and Smith, D.W.: Recognition of the fetal alcohol syndrome in early infancy. *Lancet 2*:999–1001, 1973.
2. Sokol, R.J. and Clarren, S.K.: Guidelines for use of terminology describing the impact of prenatal alcohol on the offspring. *Alcoholism 13*:597–98, 1989.
3. Streissguth, A.P. and Randels, S.: Long Term Effects of Fetal Alcohol Syndrome. In: *Alcohol and Child/Family Health*, Robinson, G.C. and Armstrong, R.W., editors. Vancouver, B.C., University of British Columbia, 1988. pp. 135–51.
4. Spohr, H.L. and Steinhausen, H.C.:

Follow-up studies of children with fetal alcohol syndrome. *Neuropediatrics 18*:13–17, 1987.
5. Vorhees, C.V.: Concepts in teratology and developmental toxicology derived from animal research. *Ann. N.Y. Acad. Sci. 562*:31–41, 1989.
6. Streissguth, A.P., Martin, D.C., Martin, J.C., and Barr, H.M.: The Seattle longitudinal prospective study on alcohol and pregnancy. *Neurobehav. Toxicol. Teratol. 3*:223–33, 1981.
7. Streissguth, A.P., Sampson, P.D., and Barr, H.M.: Neurobehavioral dose-response effects of prenatal alcohol exposure in humans from infancy to adulthood. *Ann. N.Y. Acad. Sci. 562*:145–58, 1989.
8. Hanson, J.W., Streissguth, A.P., and Smith, D.W.: The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. *J. Pediatr. 92*(3):457–60, 1978.
9. Landesman-Dwyer, S., Keller, L.S., and Streissguth, A.P.: Naturalistic observations of newborns: Effects of maternal alcohol intake. *Alcoholism 2*(2):171–77, 1978.
10. Martin, J., Martin, D.C., Lund, C.A., and Streissguth, A.P.: Maternal alcohol ingestion and cigarette smoking and their effects on newborn conditioning. *Alcoholism 1*(3):243–47, 1977.
11. Streissguth, A.P., Barr, H.M., and Martin, D.C.: Maternal alcohol use and neonatal habituation assessed with the Brazelton scale. *Child. Dev. 54*:1109–18, 1983.
12. Martin, D.C., Martin, J.C., Streissguth, A.P., and Lund, C.A.: Sucking Frequency and Amplitude in Newborns as a Function of Maternal Drinking and Smoking. In: *Currents in Alcoholism*, Vol V, Galanter, M., editor. New York, Grune and Stratton, 1979. pp. 359–66.
13. Stock, D.L., Streissguth, A.P., and Martin, D.C.: Neonatal sucking as an outcome variable: Comparison of quantitative and clinical assessments. *Early Hum. Dev. 10*:273–78, 1985.
14. Streissguth, A.P., Barr, H.M., and Martin, D.C.: Offspring effects and pregnancy complications related to self-reported maternal alcohol use. *Dev. Pharmacol. Ther. 5*:21–32, 1982.
15. Barr, H.M., Streissguth, A.P., Martin, D.C., and Herman, C.S.: Infant size at 8 months of age: Relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. *Pediatrics 74*(3):336–41, 1984.
16. Streissguth, A.P., Barr, H.M., Martin, D.C., and Herman, C.S.: Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months. *Alcohol. Clin. Exp. Res. 4*(2):152–64, 1980.
17. Graham, J.M., Hanson, J.W., Darby, B.L., et al.: Independent dysmorphology evaluations at birth and 4 years of age for children exposed to varying amounts of alcohol in utero. *Pediatrics 81*(6):772–78, 1988.
18. Streissguth, A.P., Sampson, P.D., Barr, H.M., et al.: IQ at age 4 in relation to maternal alcohol use and smoking during pregnancy. *Dev. Psychol. 25*:3–11, 1989.
19. Streissguth, A.P., Martin, D.C., Barr, H.M., et al.: Intrauterine alcohol and nicotine exposure: Attention and reaction time in 4-year-old children. *Dev. Psychol. 20*(4):533–41, 1984.
20. Streissguth, A.P., Barr, H.M., Sampson, P.D., et al.: Attention, distraction, and reaction time at age 7 years and prenatal alcohol exposure. *Neurobehav. Toxicol. Teratol. 8*:717–25, 1986.
21. Streissguth, A.P., Barr, H.M., Sampson, P.D., et al.: Neurobehavioral effects of prenatal alcohol: Part I. Research strategy. *Neurotoxicol. Teratol. 11*:461–76, 1989.
22. Sampson, P.D., Streissguth, A.P., Barr, H.M., and Bookstein, F.L.: Neurobehavioral effects of prenatal alcohol: Part II. Partial least squares analysis. *Neurotoxicol. Teratol. 11*:477–91, 1989.
23. Streissguth, A.P. and Giunta, C.T.: Mental health and health needs of infants and preschool children with fetal alcohol syndrome. *Int. J. Fam. Psych. 9*:29–47, 1988.
24. Streissguth, A.P., Bookstein, F.L., Sampson, P.D., and Barr, H.M.: Neurobehavioral effects of prenatal alcohol: Part III. PLS analysis of neuropsychiatric tests. *Neurotoxicol. Teratol.*

11:493–507, 1989.
25. Streissguth, A.P., Barr, H.M., and Sampson, P.D.: Moderate prenatal alcohol exposure: Effects on child IQ and learning problems at age 7½ years. *Alcoholism* 1990. *Alcoholism 14*(5):662–69, 1990.
26. Russell, M.: Screening for Alcohol-Related Problems in Obstetric and Gynecologic Patients. In: *Fetal Alcohol Syndrome,* Vol. II, Abel, E.L., editor. Boca Raton, FL, CRC Press, 1982. pp. 1–19.
27. Russell, M. and Skinner, J.B.: Early measures of maternal alcohol misuse as predictors of adverse pregnancy outcomes. *Alcoholism 12*:824–30, 1988.
28. Russell, M., Cowan, R., and Czarnecki, D.: Prenatal alcohol exposure and early childhood development. *Alcoholism 11*(2):225, 1987.
29. Fried, P.A., Watkinson, B., Grant, A., and Knights, R.M.: Changing patterns of soft drug use prior to and during pregnancy: A prospective study. *Drug Alcohol Depend. 6*:323–43, 1980.
30. Staisey, N.L. and Fried, P.A.: Relationships between moderate maternal alcohol consumption during pregnancy and infant neurological development. *J. Stud. Alcohol 44*(2):262–70, 1983.
31. Fried, P.A. and O'Connell, C.M.: A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicol. Teratol. 9*:79–85, 1987.
32. Fried, P.A., Watkinson, B., Dillon, R.F., and Dulberg, C.S.: Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana, and alcohol. *J. Dev. Behav. Pediatr. 8*:318–26, 1987.
33. Fried, P.A. and Makin, J.E.: Neonatal behavioral correlates of prenatal exposure to marihuana, cigarettes and alcohol in a low risk population. *Neurotoxicol. Teratol. 9*:1–7, 1987.
34. Gusella, J.L. and Fried, P.A.: Effects of maternal social drinking and smoking on offspring at 13 months. *Neurobehav. Toxicol. Teratol. 6*:13–17, 1984.
35. Fried, P.A. and Watkinson, B.: 12- and 24-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes and alcohol. *Neurotoxicol. Teratol. 10*:305–13, 1988.
36. Fried, P.A. and Watkinson, B.: 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J. Dev. Behav. Pediatr. 11*(2):49–58, 1990.
37. Sokol, R.J., Miller, S.I., Debanne, S., et al.: The Cleveland NIAAA prospective alcohol-in-pregnancy study: The first year. *Neurobehav. Toxicol. Teratol. 3*(2):203–09, 1981.
38. Ernhart, C.B., Sokol, R.J., Martier, S., et al.: Alcohol teratogenicity in the human: A detailed assessment of specificity, critical period, and threshold. *Am. J. Obstet. Gynecol. 156*:33–39, 1987.
39. Ernhart, C.B., Sokol, R.J., Ager, J.W., et al.: Alcohol-related birth defects: Assessing the risk. *Ann. N.Y. Acad. Sci. 562*:159–72, 1989.
40. Sokol, R.J., Ager, J., Martier, S., et al.: Significant determinants of susceptibility to alcohol teratogenicity. *Ann. N.Y. Acad. Sci. 477*:87–102, 1986.
41. Ernhart, C.B., Wolf, A.W., Linn, P.L., et al.: and Filipovich, H.F.: Alcohol-related birth defects: Syndromal anomalies, intrauterine growth retardation, and neonatal behavioral assessment. *Alcoholism 9*:447–53, 1985.
42. Greene, T., Ernhart, C.B., Ager, J., et al.: Prenatal alcohol exposure and cognitive development in the preschool years. 1990. *Neurobehav. Toxicol. Teratol. 13*:57–68, 1991.
43. Ernhart, C.B. and Kawano, T.: Prenatal alcohol exposure and catch up growth to age five years. *Alcoholism 13*:343, 1989.
44. Boyd, T.A., Ernhart, C.B., Greene, T.H., et al.: Prenatal alcohol exposure and sustained attention in the preschool years. 1990. *Neurobehav. Toxicol. Teratol. 13*:49–56, 1991.
45. Greene, T., Ernhart, C.B., Martier, S., and Sokol, R.J.: Prenatal alcohol exposure and language development. 1989. *Alcoholism 14*:937–45, 1990.
46. Coles, C.D., Smith, I., Fernhoff, P.M., and Falek, A.: Neonatal neurobehavioral characteristics as correlates of maternal alcohol use during gestation. *Alcoholism 9*:454–60, 1985.
47. Smith, I.E., Coles, C.D., Lancaster, J., et al.: The effect of volume and duration

of prenatal ethanol exposure on neonatal physical and behavioral development. *Neurobehav. Toxicol. Teratol. 8*:375–81, 1986.
48. Coles, C.D., Brown, R.T., Smith, I.E., et al.: Effects of prenatal alcohol exposure at school age: I. Physical and cognitive development. *Neurobehav. Toxicol. Teratol.* 1990. In press.
49. Brown, R.T., Coles, C.D., Smith, I.E., et al.: Effects of prenatal alcohol exposure at school age. II. Attention and behavior. 1990. In press.
50. Day, N.L., Jasperse, D., Richardson, G., et al.: Prenatal exposure to alcohol: Effect on infant growth and morphologic characteristics. *Pediatrics 84*(3):536–41, 1989.
51. Scher, M.S., Richardson, G.A., Coble, P.A., et al.: The effects of prenatal alcohol and marijuana exposure: Disturbances in neonatal sleep cycling and arousal. *Pediatr. Res. 24*(1):101–05, 1988.
52. Richardson, G.A., Day, N.L., and Taylor, P.M.: The effect of prenatal alcohol, marijuana, and tobacco exposure on neonatal behavior. *Infant Behav. Dev. 12*:199–209, 1989.
53. Day, N.L., Richardson, G., Robles, N., et al.: The effect of prenatal alcohol exposure on growth and morphology of the offspring at eight months of age. *Pediatrics 85*:748–52, 1990.
54. Nancy Day. Personal communication, March 1990.
55. Day, N.L. and Robles, N.: Methodological issues in the measurement of substance use. *Ann. N.Y. Acad. Sci. 562*:8–13, 1989.
56. Day, N.L., Wagener, D.K., and Taylor, P.M.: Measurement of Substance Abuse During Pregnancy: Methodologic Issues. In: *Current Research on the Consequences of Maternal Drug Abuse,* Pinkert, T.M., editor. DHHS Pub. No. (ADM) 85–1400. Washington, D.C., Govt. Print. Off., 1985, pp. 36–47.
57. Ernhart, C.B., Morrow-Tlucak, M., Sokol, R.J., and Martier, S.: Underreporting of alcohol use in pregnancy. *Alcoholism 12*:506–11, 1988.
58. Russell, M.: Growing Up With Fetal Alcohol Syndrome. In: *Research Monograph No. 81. Problems of Drug Dependence. 1987. Proceedings of the 49th Annual Scientific Meeting. The Committee on Problems of Drug Dependence, Inc.,* Harris, L.S., editor. DHHS Publication No. ADM 88-1564. Washington, D.C., Govt. Print. Off., 1988. pp. 368–78.
59. Day, N., Richardson, G., Robles, N., et al.: *Effect of prenatal alcohol exposure on growth and morphology of the offspring at age three.* Poster presented at ISBRA/RSA Congress, June 17–22, 1990, Toronto, Canada.
60. Smith, I.E., Lancaster, J.S., Moss-Wells, S., et al.: Identifying high-risk pregnant drinkers: Biological and behavioral correlates of continuous heavy drinking during pregnancy. *J. Stud. Alcohol 48*(4):304–09, 1987.
61. Bonthius, D.J. and West, J.R.: Alcohol-induced neuronal loss in developing rats: Increased brain damage with binge exposure. *Alcoholism 14*:107–18, 1990.
62. Hall, R.L., Hesselbrock, V.M., and Stabenau, J.R.: Familial distribution of alcohol use: I. Assortative mating in the parents of alcoholics. *Behav. Genet. 13*:361–72, 1983.
63. Hall, R.L., Hesselbrock, V.M., and Stabenau, J.R.: Familial distribution of alcohol use: II. Assortative mating of alcoholic probands. *Behav. Genet. 13*:373–82, 1983.
64. Abel, E.L. and Lee, J.A.: Paternal alcohol exposure affects offspring behavior but not body or organ weights in mice. *Alcoholism 12*:349–55, 1988.
65. Abel, E.L. and Tan, S.E.: Effects of paternal alcohol consumption on pregnancy outcome in rats. *Neurotoxicol. Teratol. 10*:187–92, 1988.
66. Goodlett, C.R., Gilliam, D.M., Nichols, J.M., and West, J.R.: Genetic influences on brain growth restriction induced by developmental exposure to alcohol. *Neurotoxicology 10*:321–34, 1989.
67. Sokol, R.J., Smith, M., Ernhart, C.B., et al.: A genetic basis for alcohol-related birth defects (ARBD)? *Alcoholism 13*(2):343, 1989.
68. Michael Windle. Personal communication. April 2, 1990.
69. Nadine Robles. Personal communication. July 7, 1990.