PATTERN OF MALFORMATION IN OFFSPRING OF CHRONIC ALCOHOLIC MOTHERS

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Summary Eight unrelated children of three different ethnic groups, all born to ıothers who were chronic alcoholics, have a similar attern of craniofacial, limb, and cardiovascular efects associated with prenatal-onset growth deciency and developmental delay. This seems to be ıe first reported association between maternal alcoolism and aberrant morphogenesis in the offspring.

Introduction

THE purpose of this report is to alert physicians ıd other health professionals to a pattern of altered ıorphogenesis and function in eight unrelated children ho have in common mothers who were chronic coholics during pregnancy. Ulleland [1] has called :tention to growth deficiency and developmental elay in such children.

Clinical Findings

lethods of Patient Ascertainment

Eight children born of alcoholic mothers were :ought together and evaluated at the same time by the .me observers (K. J. and D. W. S.). Four of these ıildren were recognised as having a similar pattern ' altered growth and morphogenesis. Thereafter, vo other children were ascertained by the abnormal features identified in the first four patients, while the remaining two affected children were ascertained because their mothers were chronically alcoholic.

The mothers of the affected patients all satisfied the criteria for alcoholism as published in 1972 by the Criteria Committee, National Council on Alcoholism.[2] Complications and duration of maternal alcoholism as well as general background information are outlined in table I. All drank excessively throughout the pregnancy, the mothers of patients 1 and 7 to the extent that they were in hospital with delirium tremens. Patient 3 was born while her mother was in an alcoholic stupor. None of the mothers was known to be addicted to any other drug. Features shared by these eight children are summarised in table II and are illustrated in figs. 1 and 2. Further pertinent data and descriptions are found in the case-reports. Palpebral fissure length was measured from medial to lateral canthus and is shown in fig. 3. The growth and performance are presented in figs. 4 and 5 and in table III, and are summarised following the case-reports.

Case-reports

Patient 1, a 1-year-old girl, had asymmetric maxillary hypoplasia. There was lack of full extension at both elbows and bilateral hip dislocations. At birth the 5th fingers overlapped the 4th bilaterally, but they have subsequently come to be in a normal position. A grade 4 out of 6 systolic murmur was repeatedly noted during the first 6 months, but is no longer audible. It was interpreted as representing a ventricular septal defect which had closed. A single upper palmar crease was present on the right hand. Incomplete development of the superior helix of both ears was present bilaterally. There was a 3×3 cm. capillary hæmangioma over the lateral aspect of the right thigh. The labia majora were hypoplastic. Chromosomal study was normal.

Patient 2, a female, was admitted at 11 weeks of age in congestive heart-failure secondary to an atrial septal

TABLE I—GENERAL DATA

—	Patient no. 1	2	3	4	5	6	7	8	All patients (means or proportions)
aternal history of alcoholism:									
Duration (yr.)	7	3	4	11	2+	10	23	15	9·4
Delirium tremens	+	?	+	+	?	—	+	+	5/6
Cirrhosis	—	?	—	+	?	—	+	—	2/6
Nutritional anæmia	—	?	—	+	?	—	+	—	2/6
aternal age at birth (yr).	26	34	22	31	32	39	40	30	31·7
ight change during pregnancy (lb.)	↓1	?	?	↓5	↓15	↓5	↑19	↑30	..
rth order	5/5	7/7	3/4	6/6	4/7	6/6	4/4	5/5	..
stational age (wk.)	40	40	38	36	38	34	44	37	38
rth-weight (g.)	1850	2500	2500	1600	1673	1550	2345	2250	2034
rth length (cm.)	45	44·5	47	42	43	38	45·7	43·2	43·6
eech presentation	+	—	—	—	+	—	+	—	3/8
gar score at 1 min. and 5 min.	4/4	9/10	8/9	8/9	5/6	5/8	8/9	4/9	..

+ = present; — = absent; ? = unknown.

—	Patient no. and ethnic group								Total
	Native American (American Indian)			Black			White		
	1	2	3	4	5	6	7	8	
Growth features and performance:									
Developmental delay	+	+	+	+	+	+	+	+	8/8
Microcephaly	+	+	+	+	+	+	+	−	7/8
Prenatal growth deficiency	+	+	+	+	+	+	+	+	8/8
Postnatal growth deficiency	+	+	+	+	+	+	+	+	8/8
Craniofacial:									
Short palpebral fissures	+	+	+	+	+	+	+	+	8/8
Maxillary hypoplasia with relative prognathism	+	+	+	−	+	+	+	+	7/8
Epicanthal folds	+	−	−	−	+	−	+	+	4/8
Limbs:									
Joint anomalies *	+	−	−	+	+	−	+	+	5/8
Altered palmar crease pattern	+	−	+	+	+	−	+	+	6/8
Other:									
Cardiac anomaly	+	+	+	+	−	−	−	+	5/8

+ = present; − = absent.

* Limitation of motion at elbow, interphalangeal and metacarpal-phalangeal joints, and hip dislocation (see text).

defect, confirmed by cardiac catheterisation. Incomplete development of the superior helix of the ears was present bilaterally. A 1 × 2 cm. capillary hæmangioma was present over the area of the left scapula.

Patient 3, a girl aged 4 years 3 months, had a grade 3 out of 6 systolic murmur heard before but not after 10 months of age. This was thought to represent a ventricular septal defect which had closed. There was aberrant alignment of the upper palmar crease and a rudimentary mid-palmar crease bilaterally. The superior helix of the right ear was incompletely developed.

Patient 4, a girl aged 3 years 9 months, had esotropia of the left eye and bilateral asymmetric ptosis. She has worn glasses since 2 years of age for bilateral myopia. There was 15 degrees of limitation in extension at both elbows and inability to fully supinate or pronate the forearms. She had a patent ductus arteriosus, diagnosed by clinical evaluation, for which surgery was planned. The upper palmar crease formed an unusually deep furrow between the 2nd and 3rd fingers bilaterally.

Patient 5, a 17-month-old boy, had mild strabismus. He had mild camptodactyly of the 5th fingers bilaterally and clinodactyly of the 2nd, 3rd, and 4th toes on the left an the 2nd and 3rd toes on the right. He had a single uppe palmar crease on the left hand and aberrant alignment o the upper palmar crease with a rudimentary mid-palma crease on the right. A moderate diastasis recti was presen

Patient 6, a boy aged 3 years 3 months, had hypoplasti 2nd and 5th toenails bilaterally.

Patient 7, a girl aged 3 years 9 months, had bilater camptodactyly, with absent distal interphalangeal crease of the 3rd, 4th, and 5th fingers. She also had bilateral hi dislocations. Aberrant alignment of the upper palma crease with a rudimentary mid-palmar crease was prese bilaterally. There was a capillary hæmangioma over th upper back. A pectus excavatum was present. The lab majora were hypoplastic. Chromosome study was norma

Patient 8, a boy aged 2 years 6 months, had limite flexion at all metacarpal-phalangeal joints. There was grade 2 out of 6 systolic murmur noted until 1 year of ag which was thought to represent a ventricular septal defe that had closed. A single upper palmar crease was prese bilaterally. A rudimentary extra nipple was present on eac side. There was a pectus excavatum.

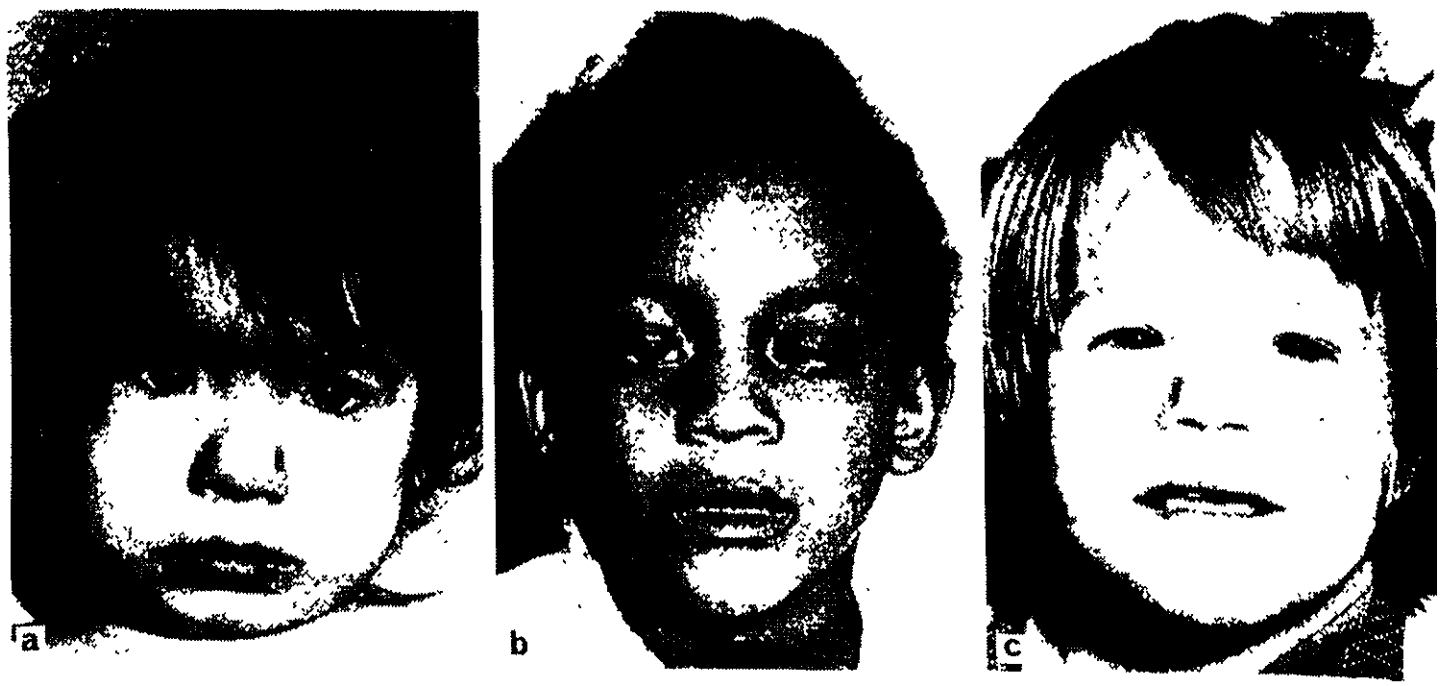

Fig. 1—Patient 1 (a), 4 (b), and 8 (c) at 1 year, 3 years 9 months, and 2 years 6 months, respectively.

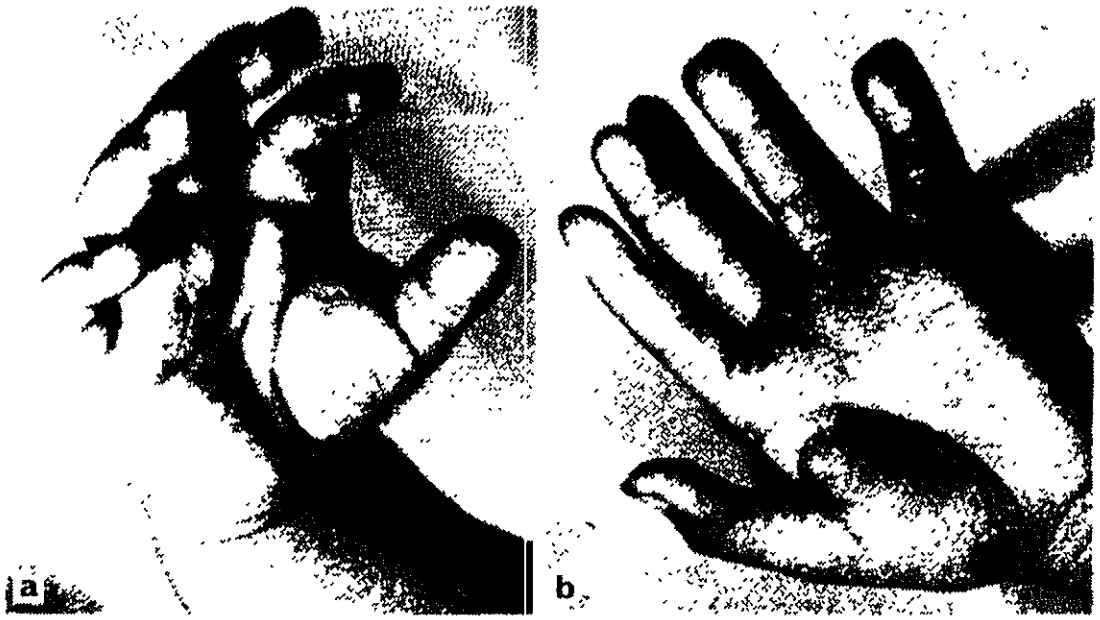

Fig. 2—Aberrant palmar crease patterns in patients 1 (a) and 4 (b).

rowth

All patients had prenatal and postnatal growth eficiency. Though the mean gestational age was 38 eeks, the mean birth length and weight were at the)th percentile for gestation ages of 33 weeks and l weeks, respectively. Thus the degree of linear owth deficiency was more severe than the deficit weight at birth. Since birth, none of the patients is shown catch-up growth either during hospital lmission for "failure to thrive" in six children, during hich time adequate caloric intake was recorded, or ıring foster-care placement in three children. The owth pattern for seven of the eight children is de-cted in fig. 4. After 1 year of age the average linear owth-rate was 65% of normal and the average rate weight gain was only 38% of normal. The mean ily weight increment for the eight patients was 9 g., contrasted to 26·6 g. for upper-middle-class Seattle ildren and 24·4 g. for high-risk children followed in e maternal and infant care programme in this city.[8]

Head circumference, depicted in fig. 5, was below the 3rd percentile for gestational age in seven of the eight children at birth. By 1 year of age it had dropped below the 3rd percentile for height age as well as for chronological age in five of the six patients for whom these data were available.

Performance

Performance testing, except for patient 5, was done by one of us (A. P. S.). As indicated in table III,

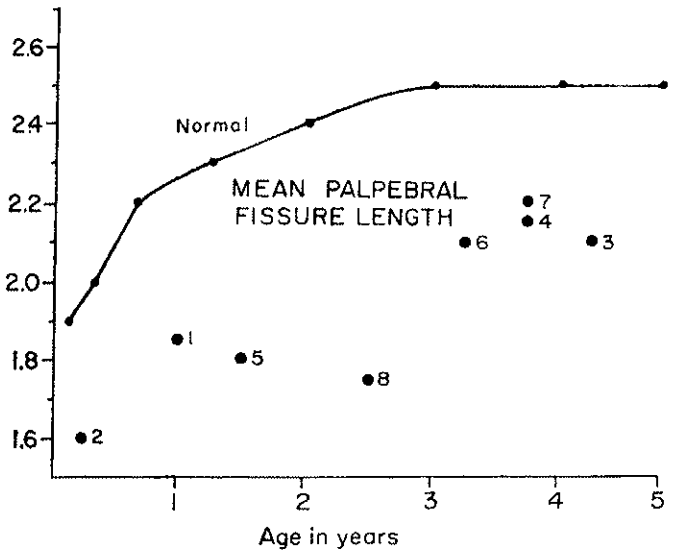

Fig. 3—Palpebral fissure length for patients 1–8.
The normal curve represents the mean for White males and ıales derived from Chouke.[9]

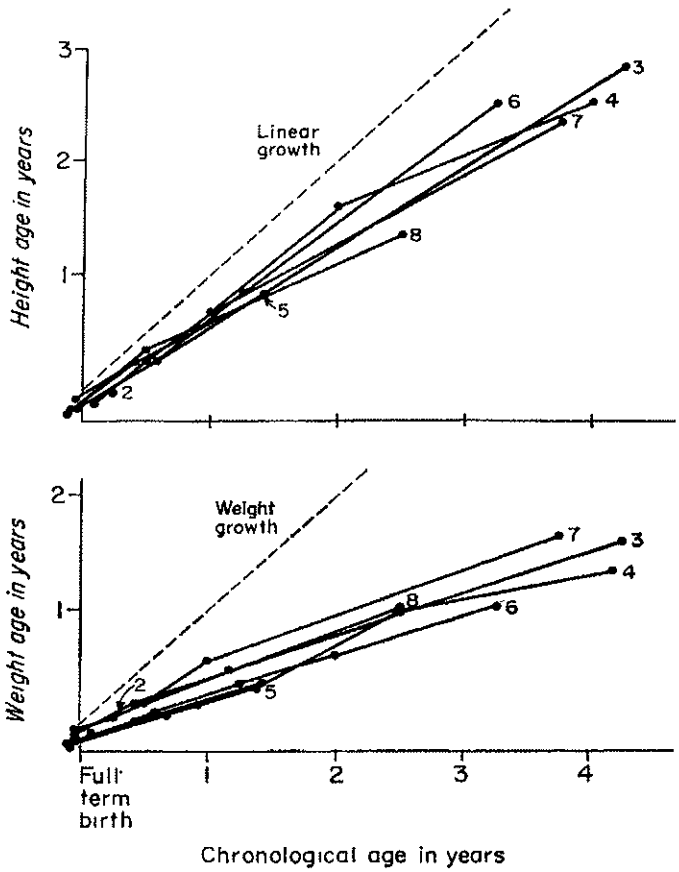

Fig. 4—Growth-rates for patients 2–8.
The dashed lines represent the normal growth-rates, derived from the 50th percentile of the Stuart growth charts.

	Patient no.							
	1	2	3	4	5	6	7	8
Chronological age* (mo.)	14	3	57	46	18	40	48	34
Motor age estimate† (mo.)	..	2	31	30	..	30	27	21
Mental age‡ (mo.)	10	2+	44	26	11	32	34	19
I.Q. or M.D.I.‡	59	83	75	57	..	79	70	<50
Social quotient§ (mo.)	..	..	..	30	..	36	35	23

* Age at time of testing.

† Bayley scales of infant motor development used where appropriate. This is an estimate only, owing to low ceiling on test relative to age of childre Patient 1 is in hip brace, so motor age could not be estimated.

‡ Stanford-Binet intelligence scale, form L-M (yielding a mental age and I.Q.), used for patients 3, 4 (without glasses), 6, and 7. Bayley scales of infa mental development (yielding a mental age and mental development index) used for patients 1, 2, 4, and 8. Denver developmental scale used f patient 5.

§ Vineland social maturity scale administered to one or both parents.

none of the children were performing within the normal range. In all cases, the children's social and motor performance was more in accord with mental age than chronological age. Fine motor dysfunction, including tremulousness, weak grasp, and/or poor eye/hand coordination was present in five out of the six patients tested, and most of them were delayed in gross motor performance. Five of the children were observed or reported to engage in some type of repetitive self-stimulating behaviour such as head rolling, head banging, or rocking.

Discussion

Past evidence from animal experiments and human experience has not given clear indication of an association between maternal alcoholism and aberrant morphogenesis in the offspring.[4] This report points strongly to such an association. Eight unrelated children of three different ethnic groups, all raised in the fetal environment provided by an alcoholic mother, had a similar pattern of craniofacial, limb, and cardiovascular defects with prenatal-onset growth deficiency and developmental delay. The similarity in the pattern of malformation among these eight children suggests a singular mode of ætiology, most likely environmentally determined by some as yet unknown

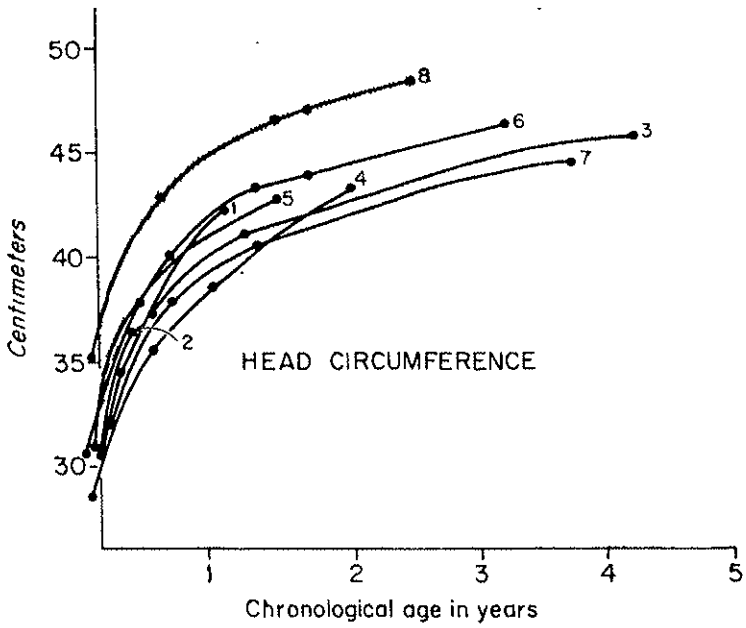

Fig. 5—Head growth of patients 1–8.

effect of the maternal alcoholism. Direct ethanc toxicity is the most obvious possibility. There is goo evidence in man and other animals that ethanol freel crosses the placental barrier.[5] Animal studies hav shown it to be distributed in the amniotic fluid and i multiple fetal tissues, at least during mid or la gestation.[6] Other direct toxic possibilities includ one of the breakdown products of ethanol such a acetaldehyde or an unknown toxic agent in the alc holic beverages which these mothers were consumin The adverse effect on morphogenesis could also be th indirect consequence of general maternal unde nutrition or the deficiency of a specific nutrient vitamin. However, this degree of prenatal growt deficiency and the pattern of malformation have n been previously recognised in offspring of unde nourished women who were not alcoholics.[7]

The following comments and interpretations rela to the specific anomalies of this syndrome. The sho palpebral fissures were interpreted as being seconda to deficient growth of the eyes. A prenatal onset this implied ocular growth deficiency was indicated f at least patients 1 and 7, who were noted in the recor as having "microphthalmia" at the time of birt The hypoplasia of the maxilla, most evident in anterior-posterior dimension, resulted in relati prognathism at an age when this is unusual. T variable alterations in joint mobility and positioni in hands, elbows, hips, and feet could be the cons quence of limited movement and/or aberrant positi during early fetal life. This is further implied by t altered palmar flexional crease patterns, which are nc mally determined by 11 weeks.[8] In terms of severi the hand positioning in patient 1, which has i proved in time, was at first similar to that found babies with the 18 trisomy syndrome. None of t patients have had any serious functional joint d ability except for the problem of hip dislocation patients 1 and 7. Of the five patients with evidence c cardiac anomaly, three were considered to have hac ventricular septal defect which closed before 1 year age.

The prenatal growth deficiency was more profou in terms of linear growth than for weight grow This is in contrast to studies of generalised mater undernutrition in which the newborn is usually und weight for length,[7] and hence suggests that a fac other than nutritional deprivation alone was advers

he cause of growth deficiency in fetal life, the insult o growth-rate has continued during early childhood. The lack of catch-up growth in the face of adequate nutritional intake during hospital admission and/or foster-care placement implies that the postnatal growth deficiency is not secondary to environmental deprivation per se.

The prenatal onset in growth deficiency of the brain, as evidenced by mild neonatal microcephaly in seven of the eight patients, has shown no significant tendency to catch up in early childhood. Thus it is tempting to ascribe the deficient and often aberrant intellectual, motor, and behavioural performance to a problem of early brain morphogenesis, secondary to the maternal alcoholism. It is difficult to determine the extent to which the socioeconomic situation or factors related to continued maternal alcoholism may have adversely affected developmental progress. Although all families are living on welfare, these children come from diverse backgrounds, the extent of education of the biological parents ranging from 8th grade to college and the occupational level from unskilled to professional. The performance in patient 1, who was raised from birth in a foster home, and that of patient 3, who was in a foster home from 2 to 4 years of age, do not provide evidence for better performance in a more stable environment. In addition, the impaired fine and gross motor function manifested by most of these children can scarcely be attributed to some experience.

Experience with other environmental causes of altered morphogenesis would lead one to anticipate variable severity of the syndrome in infants born to alcoholic mothers. Two of the children have partially affected siblings who were also born while their mothers were alcoholic. Others have siblings who are alleged to be normal, some born before and some after the mothers had become alcoholic. Our purpose is to set forth the pattern of malformation in the more severely affected offspring of alcoholic mothers, and we have purposely not included possible mildly affected cases. We feel the data are sufficient to establish that maternal alcoholism can cause serious aberrant fetal development. Further studies are warranted relative to the more specific cause and prevention of this tragic disorder.

We are especially grateful to Nurse Gertrude D. Paxton, whose efforts and understanding of the problems of chronic alcoholic mothers made possible the accumulation of much of these data. We thank Dr Shirley Anderson, who initially arranged for the evaluation of some of these patients, and Dr Nathan J. Smith and Dr Richard P. Wennberg, who were involved in the early studies of some of these patients. Dr Thomas Carlson, Akron Children's Hospital, kindly supplied information on patient 5, who was personally evaluated by one of us (D. W. S.). We acknowledge the contributions of Mrs Lyle Harrah, research librarian, Bradley Hong for photography, and Mrs Mary Pearlman and Mrs Mary Ann Harvey for secretarial assistance. This work was supported by Maternal and Child Health Services, Health Services and Mental Administration, Department of Health, Education and Welfare project 913; by National Institutes of Health grant HD 05961; and by the National Foundation-March of Dimes.

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References at foot of next column

HYPERCALCÆMIA AFTER ORAL CALCIUM-CARBONATE THERAPY IN PATIENTS ON CHRONIC HÆMODIALYSIS

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Summary Oral calcium carbonate is widely used in chronic renal failure as a phosphate-binding antacid. Unexpectedly, severe hypercalcæmia developed in three out of ten hæmodialysis patients treated with 3·2–6·4 g. calcium carbonate per day for 4–8 weeks. In one patient the serum-calcium reached 15·8 mg. per 100 ml., and he had nausea, vomiting, muscular weakness, personality changes, and subconjunctival calcifications. Two other patients were symptom-free with serum-calcium levels of 13·2 and 12·7 mg. per 100 ml. Hyperparathyroidism, raised dialysate calcium concentrations, and vitamin-D intoxication were excluded as causes of this complication. When calcium carbonate was discontinued, serum-calcium promptly returned to normal, and in the first patient all signs and symptoms disappeared. It is concluded that the hypercalcæmia resulted from intestinal absorption of calcium, probably by passive diffusion not dependent upon vitamin D. Calcium carbonate should be used with caution in patients maintained on chronic hæmodialysis.

Introduction

PATIENTS with chronic renal failure who are maintained on chronic hæmodialysis still face several metabolic problems, including acidosis, disorders of mineral metabolism, and peptic-ulcer disease. Phosphate retention, an important factor in the ætiology of renal osteodystrophy,[1] is both common and difficult to manage. Oral phosphate-binding agents must be used, but the most popular of these, aluminium hydroxide and aluminium carbonate, are unpalatable to many patients. Makoff et al.[2] recommended the use of calcium carbonate in chronic uræmic patients. Since these metabolic disorders potentially respond to treatment with calcium carbonate, which is in addition well tolerated, we substituted this agent for aluminium compounds in ten chronic hæmodialysis patients. Unexpectedly, moderate to severe hypercalcæmia developed in three of these patients while they were receiving calcium-carbonate therapy.

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DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS 15: 176–192 (2009)

PREVALENCE AND EPIDEMIOLOGIC CHARACTERISTICS OF FASD FROM VARIOUS RESEARCH METHODS WITH AN EMPHASIS ON RECENT IN-SCHOOL STUDIES

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Researching the epidemiology and estimating the prevalence of fetal alcohol syndrome (FAS) and other fetal alcohol spectrum disorders (FASD) for mainstream populations anywhere in the world has presented a challenge to researchers. Three major approaches have been used in the past: surveillance and record review systems, clinic-based studies, and active case ascertainment methods. The literature on each of these methods is reviewed citing the strengths, weaknesses, prevalence results, and other practical considerations for each method. Previous conclusions about the prevalence of FAS and total FASD in the United States (US) population are summarized. Active approaches which provide clinical outreach, recruitment, and diagnostic services in specific populations have been demonstrated to produce the highest prevalence estimates. We then describe and review studies utilizing in-school screening and diagnosis, a special type of active case ascertainment. Selected results from a number of in-school studies in South Africa, Italy, and the US are highlighted. The particular focus of the review is on the nature of the data produced from in-school methods and the specific prevalence rates of FAS and total FASD which have emanated from them. We conclude that FAS and other FASD are more prevalent in school populations, and therefore the general population, than previously estimated. We believe that the prevalence of FAS in typical, mixed-racial, and mixed-socioeconomic populations of the US is at least 2 to 7 per 1,000. Regarding all levels of FASD, we estimate that the current prevalence of FASD in populations of younger school children may be as high as 2–5% in the US and some Western European countries.
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Key Words: fetal alcohol syndrome (FAS); fetal alcohol spectrum disorders (FASD); partial fetal alcohol syndrome (PFAS); epidemiology; prevalence

The teratogenic effects of alcohol on the developing fetus represent a continuum of disabilities, currently referred to as fetal alcohol spectrum disorders (FASD) [Barr and Streissguth, 2001]. Establishing the population-based prevalence and other epidemiological characteristics of the most severe form of this spectrum, fetal alcohol syndrome (FAS), and of other FASD has been a challenge. Both before [Sullivan, 1899; Abel, 1998a; Armstrong, 2003] and after Jones and colleagues defined and described the specific clinical components of FAS in the medical literature [Jones and Smith, 1973; Jones et al., 1973; Stratton et al., 1996], researchers have struggled with issues of diagnostic criteria, case finding, sampling, and coordination of interdisciplinary activities in epidemiological studies of FASD. Although key diagnostic features of FAS are generally well established, the specific assessment techniques and statistical measurements used to make the definitive diagnosis of FAS and other FASD are still debated [Aase 1994; Aase et al., 1995; Stratton et al., 1996; Astley and Clarren, 2000; Hymbaugh et al., 2002; Chudley et al., 2005; Hoyme et al., 2005; Astley, 2006; Clarren and Lutke, 2008]. Studies that have attempted to determine the prevalence of FAS, let alone other less severe diagnoses within the continuum of FASD, are limited in number, vary in their methodology, and suffer from incomplete data and also from a lack of

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accurate, routine screening in prenatal clinics. Therefore, many children with FASD remain undetected. The result has left scholars puzzled or unclear about the pattern and prevalence of FASD at any age in the US and in most every mainstream population. This is largely due to questions of assessment and major difficulties associated with access to children with FASD and their mothers.

Recent writings attest to the dearth of knowledge about FAS and total FASD prevalence. The following are some pertinent quotations from the literature. "So, the question, what the "true" occurrence of FAS/FASD may be in the Western world has been difficult to answer" [Eriksson, 2007]. "The true prevalence of fetal alcohol syndrome and fetal alcohol spectrum disorder is not established ... in Canada nor anywhere else in the world. The difficulty of establishing the true prevalence for FAS/FASD is more complicated than for most conditions" [Clarren and Lutke, 2008]. One difficulty is the interdisciplinary nature of assessing FASD. "The determination and delineation of this complex form of brain dysfunction usually requires a team of investigators ... each doing tests that are unique to their [sic] training" [Clarren and Lutke, 2008]. Many authors have referred to FASD as problems that frequently go undetected, yet prenatal alcohol damage affects children and adults across many areas of life. "This is a hidden epidemic, since the clinical capacity to recognize and diagnose these conditions is simply not present" [Clarren and Lutke, 2008].

For practical public health and educational reasons, and also for more esoteric and basic scientific purposes, it is important to identify children with an FASD and to know the prevalence of FAS and all FASD. For scientific purposes it provides accurately diagnosed cases of an FASD from which we can establish a more complete etiological understanding. Early identification can lead to the development of effective protocols for intervention and assisting children with developmental problems associated with an FASD. As presented in this article, elementary school children are old enough that an accurate diagnosis of various FASD is possible because most physical features, behavioral, and neuropsychological signs are evident, detectable, and testable by this age. Physical examinations and neurobehavioral testing are efficient for making an accurate diagnosis within the FASD continuum at ages 6–7 years. While it is most desirable to diagnose children with FASD and other developmental disabilities at the earliest age possible, diagnosis of an FASD for 1st graders can still lead to interventions that benefit most children and assist them in leading relatively normal lives [Carmichael-Olson et al., 1992; Streissguth et al., 1996; O'Connor and Kasari, 2000; Kalberg and Buckley, 2006; Kalberg et al., 2006; O'Connor and Paley, 2006; O'Connor et al., 2006; Adnams et al., 2007; Kable et al., 2007].

Fetal Alcohol Spectrum Disorders (FASD) and the Institute of Medicine (IOM) Diagnostic Categories

The Institute of Medicine has defined four diagnostic categories within the continuum of FASD (see below) [Stratton et al., 1996]. Components of the IOM categories describe FASD, from severe to mild [Stratton et al., 1996; Hoyme et al., 2005]. The specific diagnoses, from most severe to less severe are: fetal alcohol syndrome (FAS), partial FAS (PFAS), alcohol-related neurodevelopmental disorders (ARND), and alcohol-related birth defects (ARBD). Even though there are competing diagnostic systems which use slightly different criteria for the diagnoses, different thresholds for particular criteria, and different terms for many of the lesser effects of alcohol on humans [Astley and Clarren, 2000; Chudley et al., 2005; CDC, 2008], none dispute that there is a spectrum of damage, from severe to mild, which requires differential diagnosis. Recent diagnostic clarification and operationalization of these categories stress the importance of specific minor anomalies of the face in assigning diagnoses within FASD [Hoyme et al., 2005]. These specific, dysmorphic, craniofacial features include: microcephaly, short palpebral fissures, and a hypoplastic midface (smooth philtrum and thin vermilion border of the upper lip [Jones and Smith, 1973; Clarren and Smith, 1978]. IOM criteria clearly lay out names and theoretical and general clinical criteria for the specific diagnoses within the spectrum.

The two most severe diagnoses of an FASD, FAS, and PFAS, are currently most readily recognized and diagnosed by knowledgeable and experienced clinicians [May et al., 2000, 2006a, 2007a; Viljoen et al., 2005]. According to the revised IOM criteria [Hoyme et al., 2005], for the diagnosis of FAS a child must have: (1) evidence of a characteristic pattern of minor facial anomalies including at least two or more of the key facial features of FAS (palpebral fissures $\leq$10th centile, thin vermilion border, or smooth philtrum), (2) evidence of prenatal and/or postnatal growth retardation (height or weight $\leq$10th centile), (3) evidence of deficient brain growth (structural brain anomalies or occiptofrontal head circumference (OFC) $\leq$10th centile), and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a knowledgeable collateral source. For a diagnosis of partial FAS (PFAS), a child must have: (1) evidence of a characteristic pattern of facial anomalies including two or more of the three mentioned above, (2) one or more other characteristics, such as prenatal or postnatal growth retardation ($\leq$10th centile) in height or weight), (3) small OFC ($\leq$10th centile), and/or evidence of a complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level and unexplainable by genetic composition, family background, or environment alone, and if possible, (4) confirmation of maternal alcohol consumption directly from the mother or a collateral source. A checklist has been developed over the past 25 years to aid in the diagnostic process [Hoyme et al., 2005]. All physical growth and dysmorphology features significant in the IOM criteria are recorded on this weighted checklist. Dysmorphology scores range from 0 to 37. Specific, key features of FASD must be present resulting in a high dysmorphology score for a positive diagnosis of one of the more severe FASD. Furthermore, other similar birth defects and patterns of disabilities (e.g., Williams, Down, de Lange, and fragile X syndromes) must be excluded/ruled out by either a medical geneticist through clinical exam or through genetic testing in highly equivocal cases.

For a diagnosis of alcohol-related neurodevelopmental disorders (ARND), a child must have documented prenatal alcohol exposure, display neurological, or structural brain abnormalities (e.g., microcephaly), or manifest evidence of a characteristic, complex pattern of behavioral, or cognitive abnormalities inconsistent with developmental level not explained by genetic predisposition, family background, or environment alone. For a diagnosis of alcohol-related birth defects (ARBD), a child must

have confirmed prenatal alcohol exposure, evidence of a characteristic pattern of minor facial anomalies, including two or more of the following: short palpebral fissures, thin vermilion, and/or smooth philtrum, as well as either major malformations or a pattern of minor malformations [Hoyme et al., 2005].

Epidemiological Studies and Capture of Highly Dysmorphic Versus Less Dysmorphic Children

Only children diagnosed with the two most severe manifestations of FASD, FAS, and PFAS, are the focus of most studies of the prevalence of FASD. The less severe categories of FASD (ARND and ARBD) are the least likely to be diagnosed in any study, and children with these disorders are rarely presented to the specialized medical practitioners who are capable of making the diagnoses. Even outreach, population-based studies such as in-school studies that are highlighted in this article are not likely to identify large numbers of children with ARND because: (a) dysmorphology is rarely assessed on children with mild mental retardation, (b) a specific battery of neuropsychological tests that are highly definitive for diagnosing the intelligence and behavioral traits of children with ARND have not yet been settled upon, and (c) population-based case finding methodology has been keyed by physical growth, physical development, and dysmorphology. Therefore, major epidemiological studies are most likely to identify children with the more severe forms of FASD, as the dysmorphology of the severe forms is much better established at this stage of understanding. However, in recent in-school studies in Italy, a surveillance study in Australia [Elliott et al., 2008] and pilot, in-school studies in the US, many more cases of PFAS have been identified than FAS, and increasing numbers of cases of ARND are diagnosed as the popular battery of neurobehavioral tests applied to children with a FASD becomes more sensitive and specific [Kodituwakku et al., 2001, 2006b; Aragón et al., 2008a,b]. Also, in very high risk populations such as South Africa, where many extensive population-based studies have been carried out, more severe cases have been encountered because of extremely high levels of maternal risk factors among the low SES, binge-drinking population (binge drinking has been defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and many studies as consuming five or more drinks per occasion, or sitting, for a male, and three or four drinks per occasion for a female). Furthermore, because the maternal risk factors are less extreme in more developed countries, major epidemiological studies have not been pursued to date in US and European populations. Therefore, higher SES populations, and populations with lower proportions of binge drinkers produce more PFAS as a ratio to FAS and other less severe cases when fetal exposure to alcohol occurs [Bingol et al., 1987; Abel and Hannigan, 1995; Abel, 1998a; May et al., 2006a,b, 2007a, 2008].

Researchers have used three main approaches to study the prevalence, characteristics, and patterns of occurrence of various FASD. The approaches are: (1) surveillance and record review systems, (2) clinic-based studies, and (3) active case ascertainment approaches. In-school studies are a special type of active case ascertainment, and the results from such studies in three countries are highlighted.

Review of Previous Studies and Methods Used for the Epidemiological Study of FASD

Researchers have used three main approaches to study the prevalence, characteristics, and patterns of occurrence of various FASD. The approaches are: (1) surveillance and record review systems, (2) clinic-based studies, and (3) active case ascertainment approaches [May and Gossage, 2001a]. Of these approaches, clinic-based studies have been the most common, followed by passive systems, and active case ascertainment. Passive surveillance systems are the least expensive, followed by clinic-based studies. Active case ascertainment is the most costly and time intensive [Stratton et al., 2006]. We review previous studies using the first three approaches to assess the prevalence of FASD and summarize their findings, highlighting biases, strengths, weaknesses, and key findings. Then we provide more detailed description and findings of in-school studies. Such studies may be the most complete and accurate way of determining the epidemiological characteristics of FASD within a population and will come closest to determine the true prevalence and far-reaching effects of FASD in human populations.

Surveillance Systems: Passive and Record Review Systems

Surveillance systems collect data in a particular geographical catchment area (e.g., a town or state) via registration systems or by utilizing existing records and registries. Researchers must first establish the diagnostic criteria of FASD. Then a team of reviewers look for documented or probable cases of children with particular symptoms of an FASD, or children actually diagnosed with an FASD, in a defined time period. Three types of records are generally collected and reviewed: birth certificates, special registries for children with developmental disabilities or birth defects, and/or medical records.

The Centers for Disease Control and Prevention (CDC) maintains the Birth Defect Monitoring Program (BDMP) in hospitals throughout the US, tracking most major birth anomalies, including FAS [Chavez et al., 1988]. The BDMP is a passive surveillance system, as it depends on the diagnosis if an FASD is made at birth by clinicians working in selected hospitals. Many surveillance studies have used more active surveillance where multiple types of records are searched to identify as many cases of alcohol-related anomalies as possible, since a case of a particular FASD can be documented in more than one place (e.g., birth certificates, physician records, registries, and school records over time) [Bower et al., 2000]. These multiple-record approaches are referred to as capture–recapture methods [Egeland et al., 1998].

The major advantage of surveillance methods is an efficient utilization of existing health care systems and

records. This makes them relatively inexpensive and easily implemented. But major disadvantages exist. Some birth defects, such as severe spina bifida and Down syndrome, are easy to recognize and diagnose because the anatomical or genetic markers are obvious at birth and well known. FAS, and especially less severely dysmorphic forms of FASD, however, are complex, involving multiple indicators of physiology, development, and behavior, many of which are neither obvious nor easily identified at birth [Little et al., 1990; Aase, 1994; Clarren et al., 2001]. Therefore, surveillance systems, which generally depend on the efforts and diagnoses of hundreds of nonspecialist physicians and other service providers, lack rigor and consistency. Furthermore, these passive systems suffer from dependence on the quality and completeness of a variety of registries for complete and consistent record compilation.

The CDC has published three estimates of FAS rates in the US, based on passive surveillance, via the BDMP which use hospital discharge data from 10 to 30% (depending on the year) of all births. The estimated rate of FAS at birth was 0.2 per 1,000 births from 1979 to 1992 [CDC, 1993]. Increased rates of 0.37 and 0.67 per 1,000 were reported in 1992 and 1993 [CDC, 1995]. CDC authors have questioned, however, whether this increase reflected a true increase in FAS births or better reporting. A third report from the BDMP estimated FAS rates by ethnic group from 1981 to 1986: 0.6 per 1,000 for African–Americans, 0.08 for Hispanics, 2.9 for American Indians, 0.03 for Asians, and 0.09 for whites [Chavez et al., 1988]. All of the above rates are much lower than those produced by any other method (see Table 1).

Local studies using passive surveillance methods (e.g., the Metropolitan Atlanta Congenital Defects Program) have also produced low estimates of FAS prevalence. Researchers [CDC, 1997] reported FAS among newborns as 0.1 per 1,000. Including partial FAS, the rate was 0.25.

In Alaska, a more active capture–recapture study used multiple sources including: data from hospitals, pediatricians, birth certificates, Alaska Native Health Service records, and genetics, disabilities, and education programs. Researchers reported the FAS rate for 1977–1992 for the non-Native population as 0.2–0.3 per 1,000, and the rate for the Native population (where active case ascertainment methods were also used during this period) as 3.0–5.2 per 1,000 [Egeland et al., 1998]. In North Dakota, Burd et al. [1996] reported rates of 1.1–2.0 per 1,000 from the state's birth registry system. In a passive method study from New Zealand, pediatricians were asked to complete a postal survey on children with alcohol-related birth defects. In 1993, the FAS rate among children <10 years of age was 0.11 per 1,000 [Leversha and Marks, 1995].

The last two surveillance studies in Table 1 further illustrate the low rate of FASD case identification with relatively passive record-based methods. Surveillance research studies in Wisconsin and New York, the later as part of the CDC-funded FASSNet, yielded rates of FAS below 1 per 1,000. The highest rate was in one of two similar counties in New York. The authors attributed the significantly higher rate to one dedicated dysmorphologist who participated in the registry program by regularly diagnosing and reporting cases of FASD [Druschel and Fox, 2007].

Surveillance methods using extensive searches of multiple records have applications other than prevalence studies. Kvigne et al. have successfully used hospital records of the Indian Health Service to report on alcohol use factors among fathers and mothers of children with FASD, maternal risk factors for FASD, physical characteristics of children with FASD, paternal traits of children with FASD, characteristics of grandmothers of children with FASD, and injuries and alcohol use among mothers of children with FASD in three successive pregnancies [Kvigne et al., 1998, 2003, 2004, 2006, 2008a,b].

Good records yield a variety of useful data which can be mined for valuable information on maternal risk and related matters. But, unfortunately few good records exist with accurate and detailed information on alcohol use and FASD. Therefore, surveillance systems clearly report very low rates of FAS and all FASD. A recent CDC-sponsored conference of experts in Atlanta concluded: that "sensitivity is much lower for passive methods of case finding" (p 11); "both the general population and special populations need to be accessed more aggressively"; ages 0–7 is the optimal age range for surveillance (p 12), and in-school screening in the earliest years is a promising setting for research on the prevalence of FASD (p 11) [CDC, 2008]. While earlier screening is desirable for therapeutic reasons, first grade is the first age in most US settings and other countries where all children in a population can be accessed and efficiently and accurately diagnosed in an institution of learning.

Clinic-Based Studies

Clinic-based studies have provided considerable knowledge of the characteristics of FASD in humans but fall short when determining the prevalence in a population [Abel and Sokol, 1987, 1991; Stratton et al., 1996; Abel, 1995, 1998a]. They are studies of treated prevalence rather than a population-based prevalence. Research in prenatal clinics lends itself to consistent design and rigorous methodology that can eliminate some problems inherent with passive methods, as data can be efficiently collected from mothers as they progress in their pregnancies. Researchers use standard screening, interview instruments, and specimen samples to gather information from pregnant women about: diets, jobs, social interactions, psychological health, and the use of alcohol and other drugs. Control groups are relatively easy to obtain from consenting women in the clinics, and one-half to 85% [Floyd et al., 1999] of women report abstinence from alcohol, providing a large comparison group. Because of the prospective nature of these designs, researchers are generally able to examine the infants at birth or in infancy to match maternal behaviors with the pregnancy outcomes. But it is virtually impossible to diagnose most FASD cases in the first 6 weeks of life, and only the most severe cases are obvious and diagnosable even throughout the infant period to approximately age 3.

Clinic-based studies have many advantages: the opportunity to gather maternal history data; the opportunity to study a large number of pregnancies with various levels of alcohol and other drug exposure; health services are provided, which are incentives for participants; and the prospective design provides greater control and rigor in measuring many important variables. However, there are also disadvantages. First, participants are self-selected. The women at highest risk for having a child with FASD are less likely to attend prenatal clinics early in pregnancy, regularly, and/or at all, making consistent and meaningful access to the highest risk cases difficult or impossible. Second, there is extreme variability in the reporting of alcohol use and abuse in various clinics stemming from: the

Table 1. Prevalence of FAS (and Total FASD) in Various Studies by Method

Method and Source Type	Years	Location/ Population	Ages	Rate of FAS per 1,000	Rate of FASD per 1,000	Source
Surveillance/record review methods						
Surveillance and registry based	1979–1992	US General	Newborn(nb)	0.20		CDC, 1993
Registry (BMDP)	1992	US General	nb	0.37		CDC, 1995
Registry (BMDP)	1993	US General	nb	0.67		CDC, 1995
Registry (BMDP)	1981–1986	US: Asian/Hispanic	nb	0.03/0.08		
		White/African American		0.07/0.60		Chavez et al., 1998
		American Indian		2.90		
Registry (BMDP)	1992	US General	nb	0.52		Cordero, 1994
Local surveillances-registry	1981–1989	Atlanta	nb	0.10		CDC, 1997
Surveillances and capture-recapture	1977–1992	Alaska	3–18 years	0.20–0.30 and 3.00–5.00		Egeland et al., 1998
Birth Certificates	1991–1994	North Dakota	nb	1.10–2.00		Burd et al., 1996
Multiple source: Surveillance	1989–1992	Atlanta	nb – 1 year	0.23–0.33		Cordero, 1994
Surveillance form: Pediatricians	2001–2004	Australia	6–14 years	0.06		Elliot et al., 2008
Pediatrician forms	1993	New Zealand	nb–10 years	0.11		Leversha and Marks, 1995
Multiple sources	1998–1999	Wisconsin	nb	0.23		Weiss et al., 2004
Multiple sources	1995–1999	Two Counties in NY	nb	0.90 Country A 0.21 Country B		Druschel and Fox, 2007
Totals				Md = 0.265, $\overline{X}$ = 0.845		Median and mean
Clinic-based studies						
Various studies (avg.)	1976–1987	Western World	nb/infants	1.90 [avg.]		Abel and Sokol, 1987
Various studies (avg.)	1976–1987	US and Canada	nb/infants	2.20 [avg.]		Abel and Sokol, 1987
Prospective studies only	1976–1990	US	nb/infants	0.33 [avg.]		Abel and Sokol, 1991
Prospective and Retrospective: Multiple Sources	1976–1994	Western World	nb/infants	0.97 [avg.]		Abel, 1995
		US Only	nb/infants	1.95 [avg.]		Abel, 1995
		African American	nb/infants	2.29 [avg.]		Abel, 1995
		White	nb/infants	0.26 [avg.]		Abel, 1995
Prospective Screening	Late 1970's	Cleveland	Infants	3.0		Sokol et al., 1986
Prospective Screening	1974–1975	Seattle	Infants	2.8	9.1	Sampson et al., 1997
Prospective Screening	Early 1990's	Detroit	Infants	3.9		Sokol et al., 1993
	1977–1979	Roubaix, France	Infants	1.4	4.7	Dehaene et al., 1981
	1986–1990	Roubaix, France	Infants	1.2	4.8	Dehaene et al., 1991
Prospective Screening	1977	Gothenberg, Sweden	nb	1.6		Olegard et al., 1979
Totals				Md = 1.9, $\overline{X}$ = 1.83	Md = 4.8, $\overline{X}$ = 6.2	Median and mean
Active case ascertainment[a]						
Active recruitment to referral clinics	1969–1982	American Indians:	0–14 years			May et al., 1983
		SW Plains		10.7	19.5	
		Navajo		1.6	2.5	
		Pueblo		2.2	2.7	
		Overall avg.		2.0	3.1	
Active recruitment to referral clinics	1982–1989	American Indians: Plains and Plateau	0–18 years	9.0 (multi-tribe avg.)		May et al., 2002
Active recruitment to referral clinics	1985	Plateau Indians	0–18 years	9.2	18.4	Quaid et al., 1993
Active outreach in centralized health care system	1985	Western BC, Yukon	0–18 years	10 24	25.0 46.0	Asante and Nelms-Matzke, 1985
Active for screening of all children and adolescents	1985	Native–Entire Community in BC, Canada	0–21 years	120	189	Robinson et al., 1987
Active outreach in centralized health care system	1990–1992	Plains Indians in SD	<14 years	3.9–8.5		Duimstra et al., 1993
Active outreach in diagnosis training to pediatricians	1997–2005	Norway (1 County)	<16 years	0.3 before outreach dx training: 1.5 after		Elgen et al., 2007
Totals				Md = 8.5, $\overline{X}$ = 15.61	Md = 19.0, $\overline{X}$ = 38.2	Median and mean

[a]In-school, Active Case Ascertainment Studies covered in Table 2.

way that alcohol questions are asked, the busy nature of many clinics which detracts from the time devoted to the interview, and the stigmas associated with alcohol questions in the prenatal setting [Viljoen et al., 2002; Whaley and O'Conner, 2003; Hannigan et al., in press]. Many of the clinic-based studies conducted in the US have been carried out in publicly-funded hospitals and clinics where disadvantaged populations predominate; therefore, clinic-based studies may accurately or even over-represent the prevalence of FAS in minority populations, while under-representing mainstream middle-class populations [Abel, 1998b]. Third, since FAS is not easily diagnosed at birth, these studies generally underestimate the prevalence of FAS and all FASD [Aase 1994; Stratton et al., 1996; Clarren et al., 2001].

The clinic-based approach has been the most common method used to estimate the prevalence of FASD and define maternal risk factors. Abel and Sokol's [1987] review of 18 clinic-based studies reported an average rate of FAS for the western world of 1.9 per 1,000 and 2.2 per 1,000 births for North America. Abel and Sokol [1991] later reviewed 20 prospective, clinic-based studies (including many of the studies reviewed in 1987), and reported a lower rate of 0.33 per 1,000 for the Western world. By 1994 [Abel, 1995] a total of 35 prospective, clinic-based studies had been conducted in at least 40 sites in the Western world including: the US (12), United Kingdom (15), Australia (4), Spain (3), and Canada, Denmark, France, Italy, Netherlands, Portugal, Sweden, and Switzerland (15 combined). Many of the studies performed outside of the US contained a majority of subjects who were middle class and Caucasian and only a few of these studies reported any FAS cases at all, the total being four cases. This provides a very low average rate, and median and modal rates were 0.0 FAS per study. Abel [1995] concluded that FAS occurred "considerably more often" at some sites than at others, estimating the rate for the Western world at 0.97 per 1,000 and the rate for the US at 1.95 per 1,000. This is a fascinating finding, as the proportion of the population that drinks alcohol in other parts of the Western world, and the per capita consumption of alcohol in much of the Western world is higher than in the US. This has been referred to as the "American Paradox" since it is likely linked to the fact that the US has more abstainers, but also more heavy drinkers when compared with France and other populations of the Western world [Abel, 1998a,b]. Abel concludes that it is not the prevalence of drinkers or the amounts consumed over time in European countries, but rather the proportion which consumes high quantities of alcohol in short periods of time (e.g., binge drinkers) that elevates the frequency of severe symptoms of FASD. Not mentioned by Abel is that European populations and health providers are quite unlikely to: believe that FASD exist or are common, be critical of normative drinking practices (as are health care providers in the US), or to diagnose cases of FASD.

All but four of the US studies (67%) reviewed by Abel [1995] were carried out in general obstetric clinic settings, mostly among African–Americans from inner cities of low socioeconomic status (SES). He concluded that in US sites where the study population was predominantly low SES, the FAS rate was 2.29 per 1,000, 10 times higher than reported for White middle to upper class sites (0.26 per 1,000) (see Table 1). In two of the studies of inner city, low SES populations, the rates of FAS were 3 and 3.9 per 1,000. Therefore, Abel's review concluded that FAS was linked to low SES more than to race [Abel, 1998]. Calculations from another aggregation of these 28 studies indicated that FAS occurred in 4.3% of the births to heavy drinkers [Abel, 1995], and no estimate was given for other diagnoses of FASD.

From Europe, Olegard et al. [1979] and Dehaene et al., [1981, 1991] have reported relatively higher rates of FAS than some other studies of mainstream populations, probably due to the intense nature of the scrutiny exerted by the researchers and the circumscribed nature of these particular health systems and clinics. From infant and young child studies, FAS was reported as 1.6 per 1,000 in Göteberg, Sweden and 1.4 and 1.2 in Roubaix, France, in two different time periods. In France, other levels of FASD that roughly correspond to the IOM classification of PFAS and ARND were combined with the FAS cases for an FASD rate of 4.7 and 4.8 per 1,000 [Dehaene et al., 1981, 1991].

Other clinic-based studies have documented various levels of FASD severity present in cohorts of children born to mothers recruited when receiving prenatal care. At study sites in Seattle, [Streissguth et al., 1991, 1994], Detroit [Jacobson et al., 1993, 1994], and Pittsburgh [Day et al., 1991, 1999], researchers have followed large cohorts of children born to women with various levels of drinking and compared them over time, on physical and psychological growth and development and dysmorphology. By grouping the data in various ways to describe the effects of prenatal alcohol exposure and documenting the link between FASD symptoms and alcohol exposure, these researchers estimate the prevalence of FASD. One longitudinal study from this body of literature [Sampson et al., 1997] estimated the combined rate of FAS and ARND at 9.1 per 1,000 live births (1%) in the general Seattle obstetric population, which is the most quoted estimate for FASD.

Some studies in other parts of the Western world, including former European colonies, have found a similar pattern of FASD symptoms as that found in American studies. For example, French researchers [Rostand et al., 1990] reported that craniofacial morphology was "a sensitive indicator of alcohol exposure in utero" and that "alcoholic" consumption was associated with negative effects on infant weight, length, and head circumference. On the other hand, a study in Australia by Walpole et al. [1989] failed to show any significant relationship between low to moderate maternal alcohol intake and fetal outcome. Therefore, in spite of the similar pattern of anomalies associated with low and moderate levels of alcohol consumed during pregnancy, studies outside the US continue to illustrate the "American Paradox" described by Abel [1998a], where low to moderate use of alcohol (defined liberally as <21 drinks per week by Rostand et al. [1990]) does not cause alarm or result in FAS or features as severe as reported in US studies.

Active Case Ascertainment Methods

Active case ascertainment methods which aggressively search for children with FASD in select populations and provide specialized clinical diagnosis, were first used for the study of FAS in American Indian, Alaskan, and Canadian Native communities [May and Hymbaugh, 1982; May et al., 1983, 2002]. Until 1997, active case ascertainment methods had been used exclusively among American Indians.

Active case ascertainment generally yields the highest rates of FASD. Although the same clinical, diagnostic

criteria are used as in clinic-based studies, differential prevalence rates relate to the selection of children presented to clinicians for diagnosis and the age at which clinical contact is made. Many children who have an FASD are never seen in clinics where the proper diagnosis of an FASD can be made, or at a time when it can be made. For example, Clarren et al. [2001] reported that six of seven first-graders who were diagnosed with FAS in their in-school pilot study had never before received an FAS diagnosis. Similarly, Little et al. [1990] reported that of 40 newborns in a large hospital in Texas who were strong candidates for an FAS diagnosis (i.e., they were born to heavy drinking mothers and had most of the physical features of FAS), 100% left the hospital without an FAS diagnosis and most never received a diagnosis even though follow-up exams estimated that as many as 17 were possible FAS. These studies further emphasize that age at examination is a critical consideration in establishing the prevalence of all FASD; and all FASD are very difficult to diagnose in the newborn period and in the first 3 years of life except in very severe cases [Little et al. 1990; Ernhardt et al., 1995; Stoler and Holmes, 2004].

The active case ascertainment studies conducted among American Indians are generally in very high-risk communities characterized by low SES and a significant proportion of heavy, episodic drinking [May et al., 2002]. Studies of American Indian communities have yielded variable, but generally high, FAS rates. Among Plains and Plateau culture tribes, prevalence rates vary by community: average FAS rates are 9 per 1,000, ages 1–14 [May and Gossage, 2001b]. Among tribes of the southwestern US, rates vary: over time, between tribes, and by cultural group [May et al., 1983]. The average rates (per 1,000) of FAS in 1969–1982 (children, 0–14 years.) ranged from 0.0 to 26.7 from one community to the next. Tribal averages (see Table 1) ranged from 1.6 to 2.2 to 10.7 by major cultural group (Navajo, Pueblo, and southwestern Plains). One active case ascertainment study in Canada examined every child (a total of 102) in a Native village characterized by a concentration of heavy drinkers. The FAS rate reported was 120 per 1,000 children [Robinson et al., 1987]. Findings in such small and unique communities cannot be compared to other populations unless there is evidence that similar social, cultural, economic, behavioral, nutritional, and health conditions exist.

Active case ascertainment methods have at least three advantages. One, the primary focus is aggressive recruitment and case finding of children with an FASD at appropriate ages for accurate diagnosis made by clinical specialists. Two, aggressive outreach into a population or catchment setting is likely to uncover children with an FASD and high-risk alcohol-abusing mothers. Three, by studying entire populations, active methods may eliminate much selectivity and provide more generally applicable findings [Stratton et al., 1996].

There are also disadvantages of active case ascertainment approaches. First, outreach is labor intensive, time consuming, and costly [Stratton et al., 1996]. The outreach process involves: gaining trust, credibility, and permission to access a community or population; training people to recognize symptoms and refer children who may be involved; locating and securing consent for children and maternal subjects is required; and hiring specialists for the clinical assessments who carry out special "developmental clinics" or screening. Furthermore, the complete diagnostic process involving medical evaluation, child assessment, and maternal interviews requires multiple hours of work by a multidisciplinary team. Second, studies of this type require cooperation from many nonresearchers (e.g., community, political, health and education officials, parents, etc.). If one or more vital community constituencies do not support a study, case finding may be incomplete or selective. High levels of cooperation with research on stigmatized topics such as FASD and maternal drinking are often difficult to achieve. Third, access to particular populations may be selective, and in the early years of FASD research, only high risk, heavy drinking populations were studied. If such selective high or low-risk populations are studied and findings projected to the general population, then the prevalence of FAS will be over or underestimated.

A Summary of Previous Studies, Methods, and Rates of FASD

Estimates of the prevalence of FAS and total FASD vary greatly: from population to population, by method utilized, and by specific study. Some of this variation is a valid reflection of actual differences in FASD rates between populations. But variance in rates is often a function of how aggressive their methods are. As displayed clearly in Table 1, the lowest rates of FASD are found with passive surveillance and the highest rates with clinic-based and active case ascertainment methods. Surveillance studies that have produced rates somewhat comparable to studies using other methods either used hybrid methods or studied very high-risk populations. For example, the study by Egeland et al. [1998] used multiple sources of records and benefited from clinic-based data from the government health care system and an active case ascertainment project carried out among Alaska Natives during the period studied.

Considering the strengths and limitations of the various methods reviewed, and the various prevalence findings produced by each method, a simple average of the results does not produce accurate estimates of the magnitude of FAS and FASD in a population. Abel et al. have demonstrated this clearly in their publications [Abel, 1987, 1991, 1998a,b]. The passive surveillance methods produce, by far, the lowest number of cases and lowest rates of prevalence: a median of 0.265 and a mean of 0.85 per 1,000. Rates produced by the clinic-based studies, which reported any cases of FAS at all, are on average higher than the passive systems: the median is 1.9 and the mean is 1.8 per 1,000 births. But rates produced by clinic studies are lower than those for active case ascertainment methods, and Abel pointed out that the median and modal rates produced by clinic-based studies he reviewed were zero [Abel, 1995]. Based on the active case ascertainment studies in Table 1, the average of FAS rates is a median of 8.5 and a mean of 15.6 per 1,000. Keeping in mind that active case ascertainment studies have generally involved high-risk groups, as did many clinic-based studies, an estimate from these studies may be biased on the high side.

Also in Table 1 are the few rates of FASD (usually reported as FAE or ARND) produced by any of the above methods. For the clinic-based studies the average rates of FASD are: median of 4.8 and a mean of 6.2 per 1,000. For the active case ascertainment methods, the FASD averages are: median 19.0 and mean of 38.2 per 1,000.

Therefore, the conclusion from previous literature reviews and this review are that most studies of prevalence have under-identified cases of FAS and total FASD in mainstream or general populations. Population-based

studies using active outreach and case-identification are needed.

Population-Based Studies Provide a Different View of the Symptoms of FASD—Likely a More Complete Prevalence of Most Categories of FASD

Our experience with in-school research in two other countries and pilot data in US schools indicate that not only is the prevalence of FASD underestimated, but also the characteristics of the children as described in clinic-based studies is substantially different from that which exists in the general population. For example, cleft lip and palate, [Shaw and Lamer, 1999], optic nerve hypoplasia [Stromland, 2004], hemangiomas [Ferraro and Dehaene, 1996], ear malformations [Aase 1994], and other physical traits frequently cited as commonly associated features of FAS and other FASD in clinic-based studies, occur less frequently in FAS and PFAS children in population-based studies. Conversely, some subtle features (e.g., 5th finger clinodactly, insufficient pronation and supination of elbows, and unique palmar creases) are more frequently recorded in the population-based studies. Particularly odd, unique, and rather uncommon but obviously dysmorphic physical features make referral of an FASD child to specialist physicians (who diagnose FASD) more likely and therefore may skew the data on the frequency of these features in FASD children. Similarly, the more subtle signs, symptoms, and co-occurring features of FASD are not detected, referred for diagnosis, and therefore these children may go undetected. Therefore, passive or clinic-based studies will not reflect either the true catalogue of symptoms with their true frequency or the accurate number of children with an FASD.

Similarly, regarding intelligence and behavioral measures for diagnosing FASD, mild to severe mental retardation, and severe behavioral problems have been described as close to universal in the FASD cases referred for clinical assessment. Yet our studies of in-school populations in three different countries indicate that many children with an FASD are not as impaired behaviorally or intellectually as those in clinic-based studies. In fact many are functioning within the normal or low normal range and go unnoticed and undiagnosed unless their morphology or behavior is highly outstanding from the norms. It is therefore likely that only the children with the most obvious physical and behavioral signs and symptoms have been studied and described in clinic-based, passive studies and even in the active ascertainment studies if they rely on referrals from schools, health care providers, or other sources. Severe anomalies and behaviors associated with FASD are likely to be less common among all children with an FASD in the general population. In other words, children who meet criteria for FAS, PFAS, and ARND overall may have higher intelligence and may function well enough to avoid detection and referral. In fact, the severe physical, behavioral, and intellectual abnormalities and deficits are most often examined in clinics that lead to diagnosis, and children with less obvious or severe physical deformities or behavior go undiagnosed even though they are affected.

Many cases of FASD may only be detected in the broader population when expert diagnosticians examine them in the field. Nevertheless, undiagnosed FASD children may have substantially limiting learning disabilities, inappropriate of challenging behavior, or suffer from diminished functioning in a number of academic areas. Unless diagnosed (preferably early in their life) and placed in the proper curricula and activities in school, they may not pass or succeed in their studies, may be labeled as "bad" or incapable, drop out, or otherwise not reach their full potential. Diagnosis of all children with an FASD has implications for both their long-term development and for the attributions that others make of them.

In-School Studies: The Methodology and the Prevalence of FASD

In-school studies are a special type of active case ascertainment. Rare until recently, researching the epidemiology of FASD in schools increases efficiency of case identification and logistics, reduces costs, provides needed services, and theoretically solves many of the problems of selectivity. First, school children are representative of entire local populations. Second, identification of many more cases is achieved and complications of logistics are reduced, as the clinicians go to the children in the schools. Third, intellectual testing services are provided early in life which is a bonus to the students, their families, and the schools. Fourth, the credibility of the educational system and services that they provide locally, lend confidence to reluctant parents and provide needed evaluative and remedial services that might otherwise be unavailable. Not only children with suspected FASD, but normal controls are involved in these studies. The children receive benefits from the special testing, which makes the impact even broader. Also the control methodology decreases stigma that would otherwise affect the quality of the research, particularly the maternal reports of maternal risk.

In one of the counties in Washington studied by Clarren et al., [2001], the Board of Education required active consent from guardians, and less than 25% of the students were allowed to participate. Therefore, no useable results were produced in that county. In the other county, passive consent was allowed (a child participated unless the guardian specifically requested exclusion) and participation was much higher, although the specific percentage is not provided in the article. In this second county the estimated rate of FAS was 3.1 per 1,000 [Clarren et al. 2001]. The researchers did not describe in detail the specific social conditions in this county or what behavioral testing (if any) and maternal risk factor information was used for diagnosis. But this FAS rate is high for a mainstream population, especially when compared with rates produced by other methods. Virtually all active case ascertainment studies carried out in schools have reported higher rates of FAS and other FASD than those produced by other methods, and likely access to a broad cross section of the population at an optimal age for diagnosis by expert clinicians. Clarren et al. [2001] identified seven cases of FAS, only one of which had been previously diagnosed.

One community study in Sweden using active case ascertainment methods in younger children was conducted and described in the literature [Hagberg et al., 1981a,b]. Examining the causes of mild mental retardation (MMR) in Gothenberg schools, 8% of all MMR cases (intelligence quotient (IQ) 50–70), and also cases of children with IQ's of 71–75, were attributed to prenatal alcohol consumption. Translating this to a rate, 0.45 per 1,000 children were found to have FAS. These data are also quoted by Olegard et al., [1979].

South Africa

The most extensive and complete series of in-school studies has been carried out in South Africa in the Western Cape Province. Four studies have been initiated among first graders [May et al.,

2000, 2007a; Viljoen et al., 2005]. These studies of FAS and later PFAS as well were among a population of mixed race (colored) people generally low SES living in rural and small town settings. Most people labor on the farms and in small industries there and a regular weekend pattern of heavy drinking is practiced by many people. The rates of FAS are the highest reported to date in the world, 41–46 per 1,000, 65–74 per 1,000, and 51–67 per 1,000 for the in-school, first grade population (ages 5–7) for the three waves [May et al., 2000, 2007a; Viljoen et al., 2005]. Furthermore, when the cases of PFAS were added to the FAS cases in the third cohort, the rate of FAS and PFAS combined was 68–89 per 1,000 (6.8–8.9%) in this population. This region of South Africa has a long history of wine production, workers were formerly paid a portion of their wages in wine, people currently have relatively easy access to inexpensive commercial alcoholic beverages, and drinking heavily is practiced by a substantial proportion of colored laborers as a major form of recreation on weekends [May et al., 2008]. Viljoen et al., and Urban et al. have carried out similar in-school studies in two cities in the Northern Cape Province of South Africa [Urban et al., 2008]. Very high rates of FAS and FASD were also reported: 67.2 per 1,000 for FAS and 88.0 for FASD (FAS and PFAS only).

Italy

Two in-school studies have been completed in the Lazio region in the Province of Rome, Italy [May et al., 2006a,b; Kodituwakku, 2006b; Aragón et al., 2008a]. Carried out in conditions more similar to those in the US pilot studies reported below, the populations are generally well educated, middle class people, the majority of whom practice moderate drinking of one-half to two glasses of wine with meals, and less binge drinking than reported in most other populations studied with active case ascertainment. Nevertheless, the rates of FASD identified in Italy have been higher than were predicted by the scant literature on FAS in Italy [May et al., 2006a,b] and other mainstream Western European populations. The proportion of PFAS cases far exceeds those of FAS in Italy. The rates of FAS reported from the Italian studies ranged from 3.7 to 9.2 per 1,000, PFAS from 15.7 to 43.8 per 1,000, and the prevalence of total FASD is estimated as 2–5.5% in the first grade children.

US pilots

In addition to the Washington State study, two additional in-school studies have recently been completed in the US. Carried out in first grade classrooms, these studies have identified children with an FASD who would not otherwise have been recognized in other settings at other ages. Many would likely not be recognized at birth or referred into clinical settings where the diagnosis is likely. These two in-school studies were short term, low budget pilot studies completed by the same research team that completed studies in South Africa and Italy. Both were carried out in a smaller city in the Western United States where they were requested by public health and public school officials. Participation has been good (55 and 56%) utilizing only one mail out of consent forms with minimal explanation of the study. Therefore the outreach was active, but not nearly as intense as desirable. The FAS rate for the first pilot wave was 1.4–2.5 per 1,000 and a total FASD rate was 9.5–17.4 per 1,000 (1–1.7%). In the second pilot wave (2008) the rate of FAS was 6.4–11.3 per 1,000 and of all FASD (FAS and PFAS combined) were 14.1–24.8 per 1,000 or 1.4–2.5%. The variance in rates in the two different years may be accounted for by variations in maternal drinking by cohort, selectivity in consent to participate, and small samples generally experience greater variation in annual rates. Nevertheless, these pilot studies demonstrate the need for more extensive studies of this type in US schools with larger samples over time.

In the Western US city and in Italy, it has been more difficult to obtain participation rates much higher than half of the enrolled children (see Table 2), for both studies at both sites were underfunded and completed within a very short time frame; less than 1 year per wave and in each wave of study 15–25 schools were involved at each site. However in a third pilot currently underway in this same US city, minimal efforts at simpler and clearer information in the first letter sent out, community comfort is growing, enhanced attention to, and recruitment by, administrators has resulted in an increased consent rate, over 60%. In the future, other techniques of active recruitment could potentially raise the consent percentage even further. Unlike the predominance of the one problematic drinking style that is common among the studied colored population of South Africa, in US mainstream communities there is a greater variation in drinking styles. This variation and the mix of risk and protective maternal factors (e.g., adequate nutrition), variable SES, and various prenatal behaviors produce a variety of diagnoses within the continuum of FASD. In the pilot US studies and in Italy there are more moderate drinkers and fewer drinking in a binge manner. Therefore as in Italy, the number of PFAS cases is far greater than the cases of FAS. Local officials believed that in-school screening was a natural route to take for identifying more cases of children with an FASD who were in need of early identification. Officials were aware that in-school screening had been efficacious in South Africa and Italy.

Child Physical Growth and Development and Dysmorphology Data from In-School Studies

In Table 3 a summary is presented of selected data on children examined and diagnosed in some of our in-school projects in South Africa, Italy, and the Western City of the United States. Generally, the case control samples drawn by in-school methods of FASD case selection, using low physical growth and development to efficiently intensify case identification and random methods for picking controls, do not produce any significant differences in the age and sex of children in the FASD groups versus controls. But other features and variables which are integral to the diagnosis of FASD consistently distinguish children with FASD from controls selected from the same schools and grade. We have highlighted only some of the variables that are used to compare and distinguish between FASD and normal children. And in the case of the South Africa data, we have presented comparisons of FAS and PFAS as well. Considerably more detail of the children's physical features, including key indicators of facial and limb dysmorphology, is found in publications [May et al., 2000, 2006a, 2007a; Viljoen et al., 2005]. Briefly, children with FAS and PFAS are shorter, weigh less, and have smaller heads (low OFC or microcephaly) than do their peers. They have short palprebral fissures, large inner canthal distances, long and smooth philtrums, thin vermilion borders to the upper lip, epicanthic folds, ptosis, and more frequent heart murmurs (see Table 3).

The purpose of Table 3 is to highlight how the physical component of the diagnosis is made and showcase

Table 2. Sampling and Prevalence Findings from In-School Studies of Various Populations

Study	Setting	Nature of Sampling	Participation Rate and Type of Consent	Population	Socioeconomic Status (SES)	FAS (PFAS) and total FASD per 1,000
Hagberg et al., 1981a,b	Gothenberg, Sweden	91 school children (8–12 y.o.) w/mild MR (IQ 50–70) studied for cause. Eight children w/MMR and 3 w/ IQ 71–75 were classified as fetal alcohol exposure	100% Consent: unknown	White	Middle SES	0.45
May et al., 2000	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 12 schools (rural and urban) in one town	99% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	40.5 – 46.4
Clarren et al., 2001	Washington State, USA 2 counties	Passive consent of all 1st grade children w/ nurse screening and <10% hgt. and/or wgt. Or teacher referral or file info on prenatal exposure	County A = 95% Passive Consent County B <25% Active Consent	Mixed ethnic	Middle SES	3.1
Viljoen et al., 2005	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. from all 1st graders in 12 schools (rural and urban) in one town	94% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	65.2 – 74.2
May et al., 2006a	Lazio Region, Italy	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 25 randomly-selected schools of subregion – (rural, suburban and urban)	50% Active Consent	Mixed race Italian Mostly white	Middle SES	3.7 – 7.4 (15.7 – 31.3) 20.3 – 40.5
May et al., 2007a,b,c	Western Cape, South Africa	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 12 schools (rural and urban) in one town	81% Active Consent	Mixed race (coloured) 85% and white	• Coloured population Low and Middle SES • White Population Middle and Upper SES	51.3 – 67.2 (16.8 – 22.0) 68.0 – 89.2
May et al., 2007a poster	Lazio Region, Italy	Children ≤10% on OFC or hgt. and wgt. From all 1st graders in 25 randomly-selected schools of subregion – (rural, suburban and urban)	49% Active Consent	Mixed race Italian Mostly white	Middle SES	4.4 – 9.2 (21.0 – 43.8) 26.6 – 55.4
Urban et al., 2008	Northern Cape, South Africa	Children ≤% on OFC, or hgt.and wgt. 1st grade schools in 2 cities	Not reported Active Consent	Mixed ethnic/race 64% Coloured 36% Black	Low and Middles SES	6.4 – 11.3 (7.7 – 13.5) 14.1 – 24.8
May et al., unpublished	Western City, USA	Children ≤25% on OFC or hgt. or wgt. From 1st grades in all 15 public schools in school district, urban, and suburban	55% Active Consent	Mixed race about 75% white 25% American Indian Black and Asian	Middle SES with full range from low to upper	1.4 – 2.5 (8.1 – 14.9) 9.5 – 17.4
May et al., unpublished	Western City, USA	Children ≤25% on OFC or hgt. or wgt. From 1st grades in all 17 public and private schools in school district, urban, and suburban	56% Active Consent	Mixed race about 75% white 25% American Indian Black and Asian	Middle SES with full range from low to upper	6.4 – 11.3 (7.7 – 13.5) 14.1 – 24.8

some of the range of data collected and analyzed. Also, by providing data on several populations, we are highlighting the fact that these features will vary slightly from one child to the next and from one ethnic or racial population to the next; but in general, similar variables cut across populations. As many of these features are slight variations on normal, a clinical team must understand ethnic and racial relativity in clinical assessments and may establish slightly different statistical parameters for each race and culture based on comparisons with an adequate number of controls in each population.

Child Intelligence, Developmental, and Behavioral Characteristics from In-school Studies

In Table 4 we have provided a sampling of the types of data that are used for the behavioral domain of the diagnosis for the in-school studies. A focus on children in the first grade per-

Table 3. Child Characteristics for Selected In-School Studies

Trait	South Africa[a] (2002) (n = 218)			Italy[b] (2005) (n = 89)		Western City, USA[c] (2007) (n = 57)		Western City, USA[d] (2008) (n = 71)	
	FAS	PFAS	Control	FASD	Control	FASD	Control	FASD	Control
Sex (% male)	58.2	61.1	47.6	50.0	44.8	42.9	62.0	45.5	60.0
Age (years)	7.8***	7.6	7.3	6.7	6.7	7.5	7.1	6.9*	6.5
Height (cm)	114***	115	119	116***	121	118*	124	119.5***	125.1
Weight (kg)	18.3***	19.3	21.8	22.0**	25.5	22.3	25.9	23.5*	27.5
BMI (mean)	13.9***	14.6	15.3	16.2	17.3	15.7	16.9	16.3**	17.6
Head circumference (OFC) (cm)	48.3***	48.5	50.9	50.7***	51.9	50.3***	52.4	50.9***	52.9
Palpebral fissure length (PFL) (cm)	2.3***	2.3	2.5	2.4**	2.5	2.3***	2.5	2.4*	2.5
Philtrum length (PL) (cm)	1.4	1.4	1.4	1.4**	1.5	1.3	1.4	1.5	1.4
Ptosis (%)	18.2**	5.6	2.1	13.6**	0.0	0.0	0.0	0.0	1.7
Epicanthal folds (%)	61.8	55.6	48.7	40.9*	14.9	42.9	12.0	18.2	23.3
Heart murmur (%)	10.9**	22.2	3.4	0.0	1.5	0.0	0.0	9.1	1.7
Hypoplastic nails (%)	10.7**	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.7
Limited elbow supination (%)	3.6*	11.1	0.7	13.6	3.0	0.0	0.0	0.0	1.7
Clinodactyly (%)	50.9	61.1	43.8	31.8	26.9	57.1	36.0	36.4	36.7
Camptodactyly (%)	36.4**	27.8	8.3	22.7**	7.5	0.0	8.0	27.3*	6.7
Altered palmar crease (%)	43.6*	38.9	26.2	45.5*	19.4	57.1	20.0	27.3	28.3
Total dysmorphology score (mean)	18.4***	17.8	8.1	12.5***	3.3	12.4***	4.1	12.5***	4.4
Adoptive/foster placement (%)	20.4***	33.3	5.3	—	—	—	—	—	—

[a]May et al., 2007a.
[b]May et al., 2006a.
[c]May et al. (as of October 1, 2008) unpublished pilot study data.
[d]May et al. (as of April 20, 2009) unpublished pilot study data.
*$P < 0.05$.
**$P \leq .01$.
***$P \leq 0.001$.

mits testing to properly measure differential ability. At this age, tests exist that can readily distinguish between children who are doing well and those who are not, and children with an FASD perform less well than controls in a variety of areas. It is important that children with FASD are compared with their normal peers from the same culture and the same schools to define local population norms, and compare them fairly to determine differences resulting from prenatal alcohol exposure.

In Table 4, children with an FASD score lower in verbal and nonverbal intelligence in each comparison, have more behavioral problems, and perform more poorly on a variety of specific tasks such as coding, reading, numerical manipulation, making choices, and discriminating between options (e.g., executive functioning). They may be deficient in many skills, especially more complex cognitive skills, required for successful daily living [Kodituwakku et al., 2006a,b; Aragon et al., 2008a,b]. At the bottom of Table 4, diagnoses are associated with total dysmorphology scores and generally with particular drinking levels reported by the mother, especially drinks per drinking day (among those who drink), a key measure of heavy drinking. While variation on these selected tests is found across populations, relatively poor performance is consistently linked to particular patterns of maternal alcohol use and to relative levels of FASD-linked dysmorphology.

Maternal Risk and Protective Factors

Studies of school children allow initiation of successful and effective data collection of maternal risk factors. Most mothers of children suspected of an FASD are interviewed regarding maternal risk: demographic, childbearing, social, religious, nutrition, physical, alcohol and drug use, and genetics. Mothers of control children receive the same interview. We believe that retrospective collection of data is a strength because of time-line follow back techniques, careful sequencing of questions, a presumed lack of anxiety over viability of the children, calibrated drink (vessel) size measurement [Kaskutas and Graves, 2000, 2001; Kaskutas and Kerr, 2008], and the reduction of exposure anxiety on the part of the mothers 6- to 7-year postpartum [May, 1995; Viljoen et al., 2002; May et al., 2005, 2008]. In fact, some studies have found that retrospective assessments of prenatal drinking are more accurate than those gathered in prenatal clinics [Czarnecki et al., 1990; Robles and Day, 1990; Jacobson et al., 1993, 1994; Alvik et al., 2006]. In prenatal clinics stigma and threat of discovery are often supressors of accurate preporting of alcohol use data [Hannigan et al., in press].

As can be seen in Table 5, mothers of children with an FASD are generally older than comparison mothers, are more likely to live in impoverished or low SES areas (rural farms in our South African studies), have lower educational attainment and other low SES indicators, are less likely to married (except in Italy), have high gravidity and parity, are more frequently suffering from poor nutrition, and are smaller in height and weight, with a lower body mass (measured by Body Mass Index (BMI)). Other variables, not listed in Table 5, also discriminate between and within populations. In many populations it has been found that mothers of children with an FASD are significantly more likely to be: less regular in the practice of a religion, lower occupation status, lower income, more depressed, and in relationships with men with substantial drinking problems themselves [Viljoen et al., 2002; May et al., 2005, 2006, 2008].

Also in Table 5 some highlights are presented for drinking variables that distinguish the mothers of children with FASD from controls. Binge drinking variables are generally most discriminating, although the particular patterns and amounts of alcohol reported vary from

Table 4. Intelligence, Developmental, and Behavioral Characteristics of Children and Related Maternal Drinking Data from Previous In-School Studies of FASD: Selected Findings

	South Africa[a] (2002) (n = 151)			Italy[b] (2005) (n = 89)		Western City, USA[c] (2007) (n = 55)		Western City, USA[c] (2008) (n = 69)	
	FAS[(test)]	PFAS	Control	FASD[(test)]	Control	FASD[(test)]	Control	FASD[(test)]	Control
Test measure									
Full scale IQ						84.85[f]	108.60***	84.18	106.40***
Verbal IQ	10.9[d]	14.0	24.1***	3.4[e]	4.9**	88.14[f]	110.62***	85.00	107.66***
NonVerbal IQ	9.4[e]	10.7	21.1***	102[g]	109**	84.85[f]	104.62***	87.36	104.60***
Behavior	12.6[f]	12.2	6.5***	8.5[h]	3.9***	14.1[h]	5.9**	16.5	6.4***
Coding				9.43[i]	11.71*	8.57[i]	11.22	11.40	10.88
Digit span	6.8[i]		10.05***	8.13[i]	10.23*	7.14[i]	10.31*	7.50	10.35**
Mazes				9.78[i]	12.66*	8.14[i]	11.66	7.10	10.31**
Reading						89.28[j]	110.3*	99.82	112.03**
Adaptive measures									
Composite						81.86[k]	106.79***	93.55	110.02**
Communication						79.71[k]	100.2***	90.09	109.57***
Daily living						83.00[k]	108.06***	95.91	109.50**
Social						89.14[k]	105.02*	97.91	105.19
Maternal drinking data									
Total dysmorphology score	18.4	17.8	8.1***	12.4	3.3***	12.4	4.1***	12.5	4.4***
Drinkers only: Current drinks per week	7.5	6.3	8.9****[l]	11.9	1.5**	2.0	2.3	0.0****	2.0
Current drinks per drinking day	3.5	1.8	0.8	2.1	0.8*	1.3	1.9	2.0	2.2

[a]May et al., 2007a and unpublished data.
[b]May et al., 2006a and unpublished data.
[c]May et al. (as of October 1, 2008) unpublished pilot data.
[d]Tests of Reception of Grammar (TROG)(std. score).
[e]Rustioni Qualitative Tests (# endorsed – higher = poorer).
[f]Personal Behaviors Checklist (PBCL)-36(# endorsed – higher = poorer).
[g]Raven Coloured Progressive Matrices(std. score).
[h]Wechsler Adaptive Scales of Intelligence (WASI)(std. score).
[i]Wechsler Intelligence Scales for Children (WISC)(std. score).
[j]Wide Range Achievement Test (WRAT-3)(std. score).
[k]Vineland Adaptive Behavior Scales (VABS)(std. score).
[l]The control group current average drinks per week exceeds that of FAS and PFAS mothers because: many FASD mothers seem to have cut down several years after the birth of the affected child; drinking is only one of a number of influential risk factors in S.A. (e.g., BMI, nutritional deficiencies, are others); only 27% of the control mothers drink at all, and as information increases over time in a population, mothers of children with an FASD child are more likely to under-report their consumption (see May et al., 2007a,b,c, 2008).
*$P < .05$.
**$P \leq .01$.
***$P \leq .001$.

population to population. Obtaining accurate drinking data from women in developed countries, especially from those of middle to high education, is difficult, not because of recall, but because of a tendency to under-report [Czarnecki et al., 1990; Robles and Day, 1990; Jacobson et al., 1993, 1994; Alvik et al., 2006]. The interview format, sequence, and questions must be adapted to individual populations to ensure specificity and sensitivity to the local culture, norms, behaviors, and conditions.

Higher-Level Statistical Modeling from Larger In-School Studies

Because of the substantial sample sizes, and the greater number of FASD cases in South Africa, higher-level statistical techniques can be used to produce controlled models of the factors that are most highly associated with the physical and dysmorphological characteristics of children with FAS and PFAS [May et al., 2007c]. Generally the findings indicate that alcohol use variables such as a binge drinking pattern and large quantities drunk per occasion, especially during pregnancy, combine to produce the most significant factor that explains the severity of the dysmorphology including: head circumference, lip configuration, palprebral fissure size, height and weight, total dysmorphology score, and final diagnosis. Also significant are the mother's physical characteristics. For example, in both Italy and South Africa it has been documented that smaller mothers are more likely to bear a child with an FASD, presumably due to higher blood alcohol concentrations produced in the mother and therefore reaching the fetus [Khaole et al., 2004], Also significant in such models are the mother's social status and living conditions (e.g., low SES) which are highly influential on both drinking pattern [May et al., 2008] and in fetal outcome [Bingol et al., 1987].

The combination of the three major data sets (child growth and dysmorphology, child development and behavior, and maternal risk factors) collected via (South African) in-school studies, and the access to large numbers of children and mothers, permit modeling to address studies of associated, and possibly etiological, human factors relating to FASD. Some of the structural equation models of associations with physical features of FASD have explained over 60% of the variance in FASD physical features in the South African population [May et al., 2007c].

Similar multiple correlation analyses predicting behavioral characteristics (verbal and nonverbal IQ, specific executive functioning, and problem behavior) of children with FASD in South Africa, can also be used with large in-school studies elsewhere to define associations with the behavioral characteristics of children with FASD. Structural equation models of the differential behavior among South African children explain over 50% of the variance, even with a set of rather limited and imper-

Table 5. Maternal (Risk and Protective Factor) Characteristics from In-School Studies of FASD: Selected Findings

	South Africa[a] (2002) (n= 206)			Italy[b] (2005) (n= 81)		Western City, USA[c] (2007) (n= 57)		Western City, USA[d] (2008) (n= 38)	
	FAS	PFAS	Control	FASD	Control	FASD	Control	FASD	Control
Variable									
Age (mean) at interview	37.6	32.3	33.9***	37.9	36.6	35.9	33.1	34.4	33.5
Rural residence during pregnancy (%)	71.2	47.1	33.8***	29.4	20.6	–	–	–	–
Educational attainment (years)	4.6	6.5	8.0***	9.1	11.3*	H.S. or GED+ (%)		H.S. or GED+ (%)	
						75	100***	71	100**
Childbearing									
Gravidity	3.6	3.1	2.9**	2.9	2.2	4.1	2.8*	4.6	3.4
Parity	3.2	2.9	2.7*	2.5	1.9*	3.5	2.5*	3.9	2.8
Birth order of child	3.2	2.3	2.2***	2.0	1.5	2.5	1.9	2.7	1.7*
Age at birth of child	28.8	24.8	25.7**	31.8	29.7	26.5	29.3	26.7	26.6
Marital status (% married)	18.0	50.0	45.7***	82.4	82.5	50.0	76.3	57.1	71.0
Body mass index	22.5	23.5	27.4***	25.0	23.4	23.2	26.5	28.1	27.4
Alcohol/drug use									
Drinker at time of interview	65.9	46.7	26.7***	91.7	100.0*	d	d	d	d
Drank in 3 months before pregnancy (%)	96.0	80.0	25.4***	91.7	87.5	d	d	d	d
Drank during index pregnancy (%)	96.0	93.8	24.8***	69.2	64.6	d	d	d	d
Drank during 3rd trimester (%)	94.1	92.9	25.4***	50.0	33.3	d	d	d	d
Estimated peak BAC of drinkers in 3rd trimester (among those who drank)	0.191	0.102	0.076*	–	–	d	d	d	d
Smokers: cigarettes per week (#)	31.7	19.5	10.7**	56	66.5	d	d	d	d
Smoked during index pregnancy (%)	84.3	82.4	35.8***	40	37.5	37.5	14.5	28.6	16.7

[a]May et al., 2007a, 2008.
[b]May et al., 2006a,b and unpublished data.
[c]May et al. (as of) unpublished pilot data.
[d]Comparable data across populations do not exist in these individual studies, or maternal risk factor data have not yet been analyzed for these entire samples (for more detail see May et al., 2006a,b for Italy and May et al., 2008 for South Africa Wave III).
*$P < 0.05$
**$P < 0.01$
***$P < 0.001$.

fect measures of assessment as dependent variables [May et al., 2007b].

Summary of the In-School Prevalence of FASD

In Table 6, nine in-school studies from three countries are summarized. South African prevalence of FASD is the highest with an average of 72.3 per 1,000 or 7.2%. FAS rates are proportionally higher than PFAS in South Africa with 3.1 cases of FAS to each PFAS case [May et al., 2007a] and 3.2 to one PFAS case [Urban et al., 2008] in the two most recent studies published. However, these studies concentrated on screening for children ≤10th centile (on height, weight, and OFC) which may have reduced the number of taller and heavier affected children with PFAS entering the diagnostic tier of the study (see Table 2).

In Italy the rates of FASD are lower than South Africa, but higher than in the US Western City. Italy has an average FASD rate of 35.7 per 1,000 (3.6%) with a rate of FAS of 6.2 per 1,000 and PFAS rate of 27.9 per 1,000. This makes 0.22 cases of FAS to each case of PFAS; and the same size criteria were used for initial entry into the study as in South Africa (≤10th centile on height, weight, and OFC). Therefore, more severe damage is found in South Africa than in Italy.

Finally, the Western City Pilot Studies in the USA have produced an FASD rate of 16.5 per 1,000. The rate of FAS is 4.9 per 1,000 and 11.0 for PFAS. The ratio of FAS to PFAS is 0.44, which is more like Italy than the South African ratio. The inclusion criteria used in the Western City were more liberal (see Table 2) as children were included who were ≤25th centile on height, weight and OFC.

CONCLUSION: THE PREVALENCE OF FAS AND TOTAL FASD IN MAINSTREAM POPULATIONS IS LIKELY HIGHER THAN PREVIOUSLY ESTIMATED

The study of the prevalence and characteristics of FASD have generally progressed slowly since the 1970s, but progress has accelerated in the past decade. We believe that in-school studies advance the assessment and understanding of prevalence beyond that of other methods. The overall prevalence of FAS in the US was estimated in 1996 by the IOM Committee [Stratton et al., 1996] to be between 0.5 and 3.0 per 1,000 births. And in a previous review by two of the authors of this article, FAS was estimated to be between 0.5 and 2.0 per 1,000 births [May and Gossage, 2001a], an estimate made from the clinic-based studies and referral-based, population outreach studies in relatively small communities. Also, as cited above, the prevalence of all FASD combined is commonly believed to be at least 9.1 per 1,000, or 1% [Sampson et al., 1997].

In the past, our multidisciplinary team of researchers has examined the prevalence, specific characteristics, and targeted etiology of FAS and other FASD in humans in multiple settings: medical clinics, referral clinics, and school populations. This experience, and the data that we have presented here, have demonstrated that in-school studies are innovative, straight-forward, and a most promising method for establishing an accurate and complete epidemiology of FASD within a population, especially for the diagnoses of FAS and PFAS. Yet they are expensive, time-consuming, labor intensive, and involve

Table 6. Summary of the Prevalence of FASD from In-School Studies: Rates per 1,000 Children

Diagnosis	South Africa Western Cape (1997)[a,b]	South Africa Western Cape (1999)[b,c]	South Africa Western Cape (2002)[d]	South Africa Northern Cape (2008)[e]	South Africa Mean	Italy[f] (2005)	Italy[g] (2006)	Italy Mean	USA Washington State Pilot[h] (2001)	USA Western City Pilot[i] (2007)	USA Western City Pilot[j] (2008)	USA Mean
FAS	(n = 42)	(n = 37)	(n = 55)	(n = 123)	50.1	(n = 4)	(n = 4)	6.2	(n = 7)	(n = 1)	(n = 5)	4.9
	40.0 – 42.3	40.1 – 42.9	51.2 – 67.2	67.2		3.7 – 7.4	4.4 – 9.2		3.1	1.4 – 2.5	6.4 – 11.3	
PFAS	(n = 4)	(n = 29)	(n = 18)	(n = 38)	18.9	(n = 17)	(n = 19)	27.9	–	(n = 6)	(n = 6)	11.0
	3.8 – 4.0	31.4 – 33.6	16.8 – 22.0	20.8		15.7 – 31.3	21.0 – 43.8			8.1 – 14.8	7.7 – 13.5	
ARND	–	(n = 10)	–	–	11.3	(n = 1)	–	1.4	–	–	–	–
		10.9 – 11.6				0.9 – 1.8						
ARBD	–	–	–	–	–	–	(n = 1)	1.7	–	–	–	–
							1.1 – 2.3					
Total FASD	(n = 46)	(n = 76)	(n = 73)	(n = 161)	72.3	(n = 22)	(n = 24)	35.7	–	(n = 7)	(n = 11)	16.5
	43.8 – 46.4	82.4 – 88.16	68.0 – 89.2	88.0		20.3 – 40.5	26.6 – 55.4			9.5 – 17.4	14.1 – 24.8	

[a]May et al., 2000.
[b]Figures in this column differ slightly from published figures as the revised IOM criteria have been applied to the cases resulting in new cases of PFAS and ARND whereas all cases were FAS in publications.
[c]Viljoen et al., 2005.
[d]May et al., 2007a.
[e]Urban et al., 2008.
[f]May et al., 2006a.
[g]May et al., 2006b (poster).
[h]Clarren et al., 2001.
[i]May et al., unpublished.
[j]May et al., unpublished.

complicated interdisciplinary and interagency interactions. But the more formal, more adequately-funded, and longer term in-school studies that have been supported by NIAAA and conducted in two foreign countries, South Africa and Italy, have yielded rich and very valuable information. Yet in schools in the United States, only pilot studies with: very limited budgets and resources; limited, part-time field personnel; and short time frames have been conducted to date. Therefore, the population-based prevalence and characteristics of FASD in any US population are still relatively unknown. However, the methods, logistics, and analyses of in-school studies have developed nicely, have been refined in the foreign studies and US pilot studies, and could potentially yield accurate and meaningful results that will help move epidemiological studies of FASD forward to benefit both basic and clinical science. Such studies for the US and Western Europe are lacking and long overdue.

While the epidemiological context, extent, and impact of FASD in mainstream US populations remain relatively undefined, studies in Italy and pilots in the US indicate that the rate and impact of FASD in mainstream populations may be significantly greater than previously thought or estimated. Professionals need to continue population-based studies in search of: more accurate estimates of FASD in the mainstream US population, better assessments of the physical and behavioral characteristics of children with the various diagnoses within the continuum of FASD, and further define specific behavioral and medical risk factors for various levels of prenatal alcohol damage [Dehaene et al., 1991; Stratton et al., 1996; Hoyme et al., 2005]. The challenge is to employ better and more sophisticated diagnostic criteria in population-based studies assessing FASD in a representative cross section of the population.

With experience gained recently, we believe that the upper limit of the IOM report (3.0 FAS per 1,000) is a more realistic estimate of the prevalence of FAS, or even a bit low. Therefore, we believe that the prevalence of FAS in typical, mixed-racial, and mixed-SES populations the US is at least 2 to 7 per 1,000. Also, with employment of improved diagnostic procedures within school populations, our belief is that there is a higher prevalence of the lesser levels of FASD than previously believed. It is clear that there are many more

cases of PFAS and ARND than have been diagnosed in the past.

Regarding all levels of FASD, we currently estimate that the prevalence of FASD, using IOM recommended methodology in populations of younger school children, may be 2–5% in the US and many Western European countries. If this is true, then FASD present a larger public health problem than most researchers have estimated in the past. The problems of FASD require immediate attention and emphasis from the public health, obstetric, pediatric, and education communities. Clearly the US Surgeon General's warning of 1981, which was reissued in 2005, was accurate and sage advice. "The Surgeon General advises women who are pregnant (or considering pregnancy) not to drink alcoholic beverages and to be aware of the alcoholic content of food and drugs" [Koop, 1981; Carmona, 2005]. Epidemiological and clinical researchers must work diligently to improve the ability to access cases of FASD and produce evidence of, and insight into the far-reaching effects of alcohol on child growth and development. ■

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Neurocognitive and neurobehavioral impairments in individuals with fetal alcohol spectrum disorders: Recognition and assessment

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Abstract: Fetal Alcohol Spectrum Disorders (FASDs) represent a continuum of development disabilities associated with maternal consumption of alcohol during pregnancy. This spectrum of disorders, which includes the Fetal Alcohol Syndrome (FAS), is characterized by a wide range of physical, cognitive, and behavioral impairments. Estimates of the number of live births in the United States meeting criteria for a diagnosis of FAS range from .5 to 2 infants per 1,000, with the prevalence of the entire continuum of FASDs estimated to be 1 in 100. This paper discusses some of the complexities involved in diagnosing individuals affected by prenatal alcohol exposure, provides a review of the neurocognitive and neurobehavioral deficits commonly seen in this population, and examines how such deficits may manifest during different developmental periods across the life span. Additionally, strategies for assessing these deficits are described, and specific measures that are appropriate for alcohol-exposed individuals are presented. The challenges of working with this under-identified and underserved population are highlighted, as well as the importance of early diagnosis and intervention.

Keywords: Fetal Alcohol Syndrome, Fetal Alcohol Spectrum Disorders, neurocognitive impairments

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INTRODUCTION

Prenatal alcohol exposure is considered the leading cause of developmental disabilities of known etiology (1). Fetal Alcohol Syndrome (FAS), the most severe consequence of such exposure, is defined by a characteristic pattern of facial anomalies, growth retardation, and central nervous system dysfunction (1). Significant cognitive, behavioral, and emotional difficulties have been documented among individuals with FAS (2-7), as well as in individuals with prenatal alcohol exposure but without all the features of FAS (4,8,9). The term *Fetal Alcohol Spectrum Disorders* (FASDs) (10) has been proposed to represent individuals experiencing significant impairments associated with prenatal alcohol exposure, including not only those with FAS but also those who might be diagnosed with other related conditions, such as Partial FAS, *Alcohol Related Neurodevelopmental Disorder* (ARND), or *Alcohol Related Birth Defects* (ARBD).

The number of live births in the United States meeting the criteria for a diagnosis of FAS is estimated to range from .5 to 2 infants per 1,000, with the prevalence of the entire continuum of FASDs estimated to be 1 in 100 (11). The cost of FAS alone in the United States is estimated to be over 2 billion dollars per year (12). This paper will briefly review the diagnostic criteria for FAS and some of the challenges in diagnosing FAS and other alcohol-related conditions, provide an overview of the neurocognitive and neurobehavioral deficits found among individuals with FASDs, and describe some of the methods for assessing such deficits.

DIAGNOSIS OF FAS AND OTHER ALCOHOL-RELATED CONDITIONS

In 2004, the United States Centers for Disease Control and Prevention (CDC) National Center on Birth Defects and Develop-mental Disabilities in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effects published guidelines on diagnosing FAS (13). According to these guidelines, a diagnosis of FAS is based on the following: (a) evidence of three essential facial abnormalities: short palpebral fissures, a smooth philtrum, and a thin vermillion border or upper lip; (b) evidence of either prenatal or postnatal growth deficiency; and (c) evidence of central nervous system (CNS) dysfunction, which may include: structural abnormalities (e.g., microcephaly), neurological problems (e.g., seizures that

are not due to some type of postnatal insult), or functional impairments (e.g., global cognitive delay). Although confirmation of prenatal alcohol exposure can provide increased evidence for the diagnosis of FAS, it is not required. In many cases, prenatal alcohol exposure may be reasonably suspected, but cannot be confirmed (e.g., child was adopted and the biological mother was an alcoholic). In cases in which prenatal alcohol exposure cannot be confirmed, ruling out other disorders that might present similarly to FAS is especially important. Exposure to other teratogens, such as Dilantin®, can cause presentations similar to FAS. Certain genetic disorders, such as Williams syndrome or Noonan syndrome, also can present similarly to FAS.

Fetal Alcohol Spectrum Disorders is a relatively new term that has come into usage to convey that although some individuals with prenatal alcohol exposure will meet the full criteria for a diagnosis of FAS, in reality, the majority of individuals with prenatal alcohol exposure exhibit some but not all of the criteria of FAS. The term FASDs is meant to convey the presence of a continuum of effects, and that some individuals can be mildly affected in one area but moderately or severely affected in another area. For example, an individual might not exhibit the characteristic facial dysmorphology, but still experience profound cognitive and behavioral impairments. The term FASDs is not a clinical diagnosis in and of itself but rather is an umbrella term intended to include several alcohol-related diagnoses, including FAS, Partial FAS (also referred to as Atypical Fetal Alcohol Syndrome in some diagnostic systems), ARND, and ARBD. The latter three diagnostic terms (Partial FAS, ARND, and ARBD) were proposed in the Institute of Medicine's report, Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment (14), for individuals who do not meet all the criteria for FAS. Currently, however, some debate remains regarding the precise criteria that distinguish among these other diagnostic categories. The term Fetal Alcohol Effects (FAE), which has been used in prior research to describe individuals who do not exhibit all the sequelae of FAS but still have experienced significant impairments associated with prenatal alcohol exposure, is used less commonly now in the current literature.

Several diagnostic approaches have been proposed to evaluate individuals for FAS and related conditions (13,15-19). Although there is general agreement among these various approaches regarding the basic criteria for FAS, several important differences exist regarding the specific thresholds that must be met for the various criteria. For example, these approaches can differ regarding what specific criteria to use as thresholds for growth deficiency or facial dysmorphology. Furthermore, a clear agreement has not yet been reached regarding how to distinguish FAS diagnostically from other related conditions, such as Partial FAS or ARND. Despite such challenges, these approaches offer both clinicians and researchers better methods for evaluating individuals with prenatal alcohol exposure that will lead to increased validity and reliability in their diagnostic decisions.

NEUROCOGNITIVE AND NEUROBEHAVIORAL IMPAIRMENTS

Facial anomalies and growth retardation may be the most easily recognized sequelae of prenatal alcohol exposure, but the CNS abnormalities affecting neurocognitive and neurobehavioral functioning are clearly the most debilitating. Numerous studies have provided evidence of differences in brain size, shape, and symmetry among individuals with prenatal alcohol exposure (20), as well as abnormalities in specific brain structures, including the corpus callosum, cerebellum, and basal ganglia (20-25).

Specifically, alcohol-exposed individuals have a smaller overall brain volume. In addition to reductions in brain volume, white matter density appears to be reduced, but gray matter density is increased in certain regions (25). The cerebellum, which plays a role in movement, especially balance and coordination, as well as attentional abilities, has been found to be smaller and characterized by abnormalities, particularly in the anterior regions of the vermis (21,22,24). The basal ganglia, which governs voluntary movement, and certain cognitive functions, such as the ability to shift from task to another, the inhibition of inappropriate behavior, and spatial memory, is smaller, primarily due to the reduced size of the caudate (26). The corpus callosum, which plays a role in attention, reading, learning, verbal memory, and executive functioning, has been found to be smaller, thinning or completely absent (agenesis) (27). Agenesis is present in about 6.8% of the FAS population, compared with about 2.3% in developmentally disabled populations, and 0.3% in the general population (20). Among alcohol-exposed individuals, the reduction in the size of the corpus callosum appears specific to the splenium (28). In addition to the decreased size of the corpus callosum, abnormalities in shape and location have been documented (25). In light of the significant impact that in utero alcohol exposure can have on fetal brain development, not surprisingly alcohol-affected individuals

show a vast range of cognitive and behavioral impairments.

Among alcohol-exposed individuals, cognitive functioning, as reflected by standardized scores on IQ tests, can vary widely, with studies documenting scores that can range from profoundly retarded to above average (4). Indeed, most alcohol-exposed individuals are not mentally retarded but they typically fall below the average range of intellectual functioning (29-31). For example, researchers found in a sample of 415 adolescents and adults a mean IQ of 80 for patients diagnosed with FAS and a mean IQ of 88 for those diagnosed with FAE (7). In a sample of children with prenatal alcohol exposure, the mean IQ was 74.4 among those who met full criteria for FAS, and 83.6 for those who did not exhibit the physical features of FAS (29).

In addition to deficits in general intellectual functioning, a wide range of neurocognitive deficits among individuals with prenatal alcohol exposure is well-documented. Attentional problems are among the most common deficits observed in this population (32-34). Individuals with FASDs frequently present with clinical symptoms consistent with a diagnosis of ADHD and are most often diagnosed as the inattentive subtype of ADHD as defined by the DSM-IV (35). The prevalence rates of ADHD appear to increase significantly with increasing levels of prenatal alcohol exposure (36). Notably, there may be differences in the types of attentional problems exhibited by individuals with FASDs as compared with non-alcohol exposed individuals with ADHD. In a study examining different aspects of attention, children with FAS or FAE performed most poorly on measures of encoding (the ability to learn and manipulate new information and shifting attention); in contrast, non-exposed children with ADHD performed most poorly on measures of focused and sustained attention (37). Noteworthy, however, are the findings that children with FASDs also show deficits in focused and sustained attention when compared with non-exposed, non-psychiatric controls (33,38,39).

Learning and memory problems have also been frequently observed in this population. Difficulties learning from experience are considered one of the hallmark impairments associated with prenatal alcohol exposure. In a classic animal study (40,41), alcohol-exposed chicks (alcohol was injected into the airspace of the chicks' eggs) had much greater difficulty learning how to circumvent a barrier to reach a reward (food) compared with non-exposed chicks. Indeed, some of the exposed chicks were never able to learn how to avoid the barrier even after being shown the correct route for 4 days in a row. In comparison, none of the non-exposed chicks had this much difficulty learning the correct route. Among humans, clinical reports frequently describe alcohol-exposed individuals as having great difficulty learning from previous experiences. Many parents report that their alcohol-exposed children are unable to predict that the same behavior will produce the same result no matter how many learning trials they have. Other parents lament that their children seem unable to learn from negative consequences. For many of these individuals, unfortunately, their difficulty in avoidance learning might be interpreted as demonstrating a lack of remorse or as a moral failing rather than as a function of their cognitive deficits. Some studies suggest that individuals with prenatal alcohol exposure also have difficulties acquiring new verbal information, although their ability to retain verbal information appears to be less affected (42,43).

Problems in executive functioning, including difficulties in planning, organizing, and sequencing behavior, and problems in abstract and practical reasoning, also appear to be quite prominent in individuals with prenatal alcohol exposure (6,44,45). Such individuals show deficits in working memory (46-48), verbal and nonverbal fluency (49,50), verbal reasoning and concept formation (51), and nonverbal reasoning and concept formation (30,43). Impairments in planning (47,51), cognitive flexibility (47,50-52), and response inhibition (50,51) have also been reported. Such deficits have been found to be greater in exposed individuals than what would be predicted from their IQ scores (53) and are still apparent even when controlling for IQ (50,54). Notably, such deficits are evident in alcohol-exposed individuals, regardless of whether they meet or do not meet the full criteria for FAS (43,51,53,54), and continue into adulthood (3,31,53,55).

Individuals with FASDs can often be quite talkative, and some may appear to have good language skills at a superficial level. Because of their talkativeness, deficits in speech and language can often be overlooked. Indeed, when their communication skills are examined at a more meaningful level, impairments in several areas emerge. Speech disorders, including articulation problems, are not uncommon (56). Additionally, a myriad of language impairments have also been reported, including receptive (4,30) and expressive (56) language deficits, difficulties with naming and word comprehension (43), and poor semantics, syntax, and pragmatics (57).

Strong evidence has been presented for a host of other neurocognitive impairments among individuals

with prenatal alcohol exposure. Impairments in both spatial and auditory memory are well documented in this population (52,58). A number of studies have found such individuals to have poor arithmetic skills (7,48,59), including deficits in calculation (60) and number comparison (61). Clinical reports suggest that alcohol-exposed individuals often have difficulties with the concepts of time and money. Visual-spatial problems have also been noted, including problems processing hierarchical stimuli (62), visual motor integration problems (43), and delays in the development of visual perception (59). Motor problems are also commonly observed in this population. Infants and young children exposed to alcohol in utero have been found to exhibit delays in motor development (63). Numerous other studies of individuals with prenatal alcohol exposure have found fine motor deficits (43,64,65), poor balance (64,66), and poor coordination (67).

Several studies have also examined the relation between prenatal alcohol exposure and adaptive functioning. Researchers have documented significant impairments across all three domains of the Vineland Adaptive Behavior Scales among children, adolescents, and adults with FAS or FAE (7). In a study of clinic-referred alcohol exposed and nonexposed children, deficits were documented in both groups across the Communication, Daily Living, and Socialization domains of the Vineland Adaptive Behavior Scales; among the alcohol-exposed group, however, deficits in socialization beca me increasingly significant with age even after controlling for IQ differences between groups (68). Other studies also found evidence for deficits in socialization in particular. Both parents (69) and teachers (70) rate children with prenatal alcohol exposure as having greater deficits in social skills than unexposed children. Such impairments include difficulty in interpreting social cues, in anticipating the consequences of one's actions, and in understanding social cues, and having problems with communicating in social contexts (55,71-73). Moreover, such deficits do not appear to be merely a function of general cognitive delays because prenatally exposed children have shown greater impairments socially when compared with non-exposed children having similar levels of developmental delay (74). Rather, such interpersonal deficits may be related to the impairments in executive functioning commonly seen in this population (75). Furthermore, findings suggest that social-skills deficits are evident well past childhood into adolescence and adulthood (55,76).

Finally, individuals with FASDs present with high rates of secondary disabilities. Children and adults with FAS or other alcohol related conditions are at increased risk for a myriad of comorbid psychiatric disorders (2,31,36,77-80) and are overrepresented in psychiatric samples (81). School problems are extremely common among children and adolescents with FASDs, including lagging academic skills and a greater likelihood of dropping out of school (7,43,59). Adults with FASDs are highly likely to experience employment problems, and are much less likely to be able live independently (31). Among the most troubling of these secondary disabilities, however, is the increased risk for delinquent and criminal behavior (7,9). Furthermore, recent studies suggest that in juvenile detention and correctional settings, individuals with FASDs are over-represented (82) but frequently unidentified (83).

FASDS ACROSS THE LIFE SPAN

FASDs are not disorders that are 'outgrown' (73), but rather are associated with deficits throughout the life span. The impairments associated with prenatal alcohol exposure, however, are likely to manifest differently during different developmental periods. Both animal (84) and human (85,86) studies demonstrate that the effects of prenatal alcohol exposure are evident as early as infancy. Among infants with prenatal alcohol exposure, studies have revealed higher rates of negative affect and disturbances in attachment relationships (5,87), and poorer habituation (86) and orientation (85). Problems with state (86) and autonomic (85) regulation, increased post-stress cortisol levels (88), and less mature motor behavior and increased level of activity (89,90) have also been shown. Prenatally exposed infants may also frequently present with feeding difficulties and failure to thrive (73). Delays in cognitive development, including language and visual-motor deficits, also have been documented among 2-year olds who were exposed to alcohol throughout pregnancy (91,92).

Although cognitive deficits may be evident very early on, learning and academic problems may become especially salient during early and middle childhood. Children with FASDs are at increased risk for learning disorders (2) and more likely to be in need of special education services (59). Such children also commonly present with externalizing behavior, including attentional problems and impulsivity (36,80,93,94). Continuing problems in attachment relationships and the emergence of internalizing problems and mood disorders has also been observed in children with prenatal alcohol exposure during this period (95,96). Such behavioral and emotional difficulties are likely to interfere further with

their school functioning and academic performance. Social-skills deficits may also become quite salient during this period, and such deficits should represent an important focus of assessment and intervention. Poor peer relationships in latency aged children are associated with a significantly increased risk for delinquency and early withdrawal from school (97-99), outcomes to which individuals with FASDs are already vulnerable.

Adolescents with FASDs are more likely to engage in high-risk behaviors, placing the children at increased risk for both victimization and delinquency (7,9,100). Among adolescents with FASDs, difficulties with peer interactions continue, and problems in romantic relationships are likely to come to the fore. In a longitudinal study of alcohol-exposed individuals, almost 60% of adolescents with FAS or FAE had problems with peer interactions, and almost half had engaged in some type of inappropriate sexual behavior (7). Adolescents with prenatal alcohol exposure are also at high risk for drug and alcohol abuse (101). Academic problems are likely to persist, with a recent study finding that found that approximately 53% of adolescents with FAS or FAE had received suspensions, 29% had been expelled, and 25% had dropped out of school (7). Academic failures can be extremely demoralizing to individuals with FASDs. When not detected early, such failures persist and often become worse, and may set alcohol-exposed individuals on a course of quitting school, socializing with peers who exert negative influences on them, and becoming increasingly marginalized from the rest of society. Parents of children with FASDs have noted significant challenges in obtaining adequate and consistent school-based services (102). Unfortunately, research results suggest that individuals who do not meet full criteria for FAS are those who fare more poorly in school and in the legal system, most probably because they are never identified and not provided with early intervention (31).

During adulthood, such basic responsibilities as maintaining a steady job and handling one's finances can overwhelm individuals who had prenatal alcohol exposure (73,101). Furthermore, adults diagnosed with FAS or FAE have been found to be at increased risk for serious psychopathology, including alcohol or drug abuse or dependence, depression, psychotic disorders, and various personality disorders (77,103). High rates of legal problems persist into adulthood, and prenatally exposed adults are at increased risk for being incarcerated or confined to a psychiatric hospital (7). Clearly, the long-term course for individuals affected by prenatal alcohol exposure raises significant concerns. A number of variables have been identified that can serve as protective factors for such individuals, including an early diagnosis (7). Such findings further highlight the importance of evaluating alcohol-exposed individuals, particularly with regard to the multitude of cognitive and behavioral impairments that may place them at increased risk for developing secondary disabilities.

ASSESSMENT OF NEUROCOGNITIVE AND NEUROBEHAVIORAL IMPAIRMENTS

A multidisciplinary approach is essential when medical and mental health professionals are presented with the challenge of conducting an evaluation of an individual with prenatal alcohol exposure (17,100,104). Alcohol-exposed individuals frequently present with impairments across multiple domains of functioning and thus are most likely to benefit from an evaluation by a team of professionals who possess expertise across those domains. The broad range of expertise and skills of the team's members will likely lead to the most integrative and comprehensive evaluation of an alcohol-exposed individual's deficits and strengths, and to the recommendation of interventions that best serve the needs of the individual and their family.

The components of a multidisciplinary evaluation typically include a clinical interview with parents or with other caregivers, as well as the patient or client when appropriate; a thorough record review; information obtained from teachers, therapists, or other relevant informants either through interviews or questionnaires (e.g., rating scales); behavioral observations; and standardized testing. In addition, a physical examination should be conducted to both assess for dysmorphology and for any medical problems, especially those that are frequently associated with prenatal alcohol exposure. For the purposes of this paper, we will focus our discussion of assessment on the methods most commonly used for evaluating the neurocognitive and neurobehavioral deficits usually seen in individuals with prenatal alcohol exposure—namely, behavioral observations and standardized testing.

Behavioral observations

In an individual with suspected or known prenatal alcohol exposure, observations should focus on multiple aspects of their behavior and ideally in multiple settings. Thus, the information obtained by observing such an individual in a clinical setting (e.g., during testing at a psychologist's office or during a pediatric visit) can be quite valuable, but it is also likely to be extremely helpful to observe an alcohol-exposed child in the school setting as

Table 1: Behavioral observations of individuals with prenatal alcohol exposure

- Physical appearance
  - Does the individual exhibit any apparent facial dysmorphology or other physical anomalies that might be associated with prenatal alcohol exposure?
  - Is the individual's appearance consistent with his/her chronological age, or does he appear smaller or younger than would be expected, possibly suggesting growth delay?
  - Does he/she have any obvious injuries due to falls or accidents, which might be suggestive of poor balance or coordination?
- Activity level
  - Does the individual exhibit an excessive level of motor activity? For younger individuals, this may manifest as running around the room or climbing on furniture; for older individuals, this may be evident in frequent fidgeting or constantly moving about in one's chair.
- Attention
  - Can the individual focus on a particular task for a sustained period of time in a manner that is consistent with his/her developmental level?
  - Is the individual easily distractible by meaningless stimuli?
  - Does he/she move rapidly from one activity or stimulus (e.g., toys, games) to another, without ever really demonstrating any meaningful interest in any one activity or stimulus?
- Impulsive behavior
  - Is the individual's level of impulsivity appropriate to his/her developmental level?
  - Does he/she seem to think before acting?
  - Does he/she engage in high-risk behavior (e.g., trying to climb up to or jump from high places) with little recognition of possible danger?
- Social interaction/relatedness
  - What is the individual's behavior like upon first meeting or encountering new people? Does he/she seem to differentiate between friends and strangers, or is he/she socially indiscriminant, immediately interacting with strangers or new acquaintances in an overly friendly manner?
  - What is the nature and quality of the individual's interactions with adults?
    - Does the individual make social bids or initiate interactions with parents/caregivers, and with examiners? Does he/she show a preference for parents/caregivers over a less familiar adult?
    - How does the individual respond when others try to engage him/her?
    - Is the individual able to maintain meaningful interactions with others or does he/she lose interest quickly?
  - What is the nature and quality of the individual's interactions with peers?
    - Is he/she overly friendly to the point of intrusiveness?
    - Does he/she have difficulty respecting physical boundaries (e.g., personal space)?
    - Does the individual have difficulty reading social cues (e.g., doesn't recognize when other children don't wish to play)
- Affect and mood
  - What kind(s) of affect does the individual display? Does he/she display a range of affect across different situations?
  - Does the individual's affect appear to change predictably or does his/her affect change without warning?
  - How does the individual describe his/her mood state? Is the individual able to articulate his/her internal mood states in an accurate and coherent way?
- Emotional regulation skills
  - What is the individual's capacity to regulate his/her own emotional arousal?
  - What types of strategies does the individual use to soothe him/herself when distressed?
  - Does the individual seek comfort out from others when distressed?
  - How does the individual respond to the emotional expressions of his/her parents or caregivers? Does he/she appear to notice when others are distressed and can he/she respond appropriately?
- Motivation and response to frustration
  - Does he/she appear to appraise or be aware of his/her own successes or failures?
  - How does the individual handle frustration?
    - Does he/she persist when faced with difficult tasks or give up easily?
    - Does he/she become angry or throw a tantrum if he/she cannot successfully complete a task?
    - Is he/she able to ask others for help?
    - Is the individual receptive if others offer unsolicited help?
- Response to reinforcement and limits
  - Does the individual respond to limits set by the parents/caregivers and/or examiners fairly easily or is he/she largely noncompliant?

Table 1 (cont): Behavioral observations of individuals with prenatal alcohol exposure

- ❑ Does the individual respond well to positive reinforcement, such as praise or some type of tangible reinforcer (e.g., a sticker)?
- ❑ Does the individual seem to have difficulty understanding contingencies?
- ❑ Does the individual appear to have difficulty learning from negative consequences?
- ❑ Does the individual repeat the same behavior over and over again with little ability to predict the same outcome?

❑ Structure, routines, transitions
- ❑ How does the individual function with varying degrees of structure? Does he/she tend to have more difficulty in unstructured situations?
- ❑ Does the individual appear to function better if consistent routines are followed?
- ❑ How does the individual respond to transitions? Is the individual likely to become upset or throw tantrums when having to transition from one environment or activity to another?

❑ Play
- ❑ Is the individual's play appropriate to his/her development level (e.g., functional vs. imaginative)?
- ❑ Does the individual perseverate on one object or theme when playing, or is play more elaborative and varied?
- ❑ Does the individual attempt to solicit others to participate in his/her play, or is he/she content to play alone, and perhaps in fact, resists others' attempts to enter into his/her play?
- ❑ Is the individual responsive to others' attempts to redirect the play in another direction?

❑ Speech and language
- ❑ Is the individual's articulation appropriate to his developmental level? Can he/she be understood by others or does he appear to have some phonological difficulties?
- ❑ Does the individual exhibit difficulties in receptive language?
  - ❑ Does he/she recognize simple words?
  - ❑ Does he/she understand basic questions?
  - ❑ Can he/she understand and respond to basic and multi-step instructions?
- ❑ Does the individual have difficulties in expressive language?
  - ❑ Does he/she use language spontaneously?
  - ❑ Is he/she able to use language in a functional/ communicative manner?
  - ❑ Can the individual relate a story in a logical, coherent manner or does he/she relate events in a confusing manner?
- ❑ What is the quality of the individual's pragmatics?

❑ Motor functioning
- ❑ How are the individual's fine motor skills?
  - ❑ Can he/she manipulate small objects?
  - ❑ Does he/she have difficulty with drawing or writing?
- ❑ How are the individual's gross motor skills?
  - ❑ Does he/she have difficulty walking, running, jumping, hopping, etc.?
- ❑ Does the individual have difficulty with balance or coordination?
  - ❑ Does the individual fall or trip easily, frequently stumble?

Behavioral observations of older individuals should also focus on:

❑ Judgment
- ❑ Is the individual able to plan out his/her actions and foresee the potential consequences of those actions?
- ❑ Does the individual appear able to make decisions in a thoughtful manner and is he/she able to communicate the rationale for his/her decisions?

❑ Insight
- ❑ Does he/she seem to have an appreciation for the motivations and feelings that underlie his/her behavior?
- ❑ Does he/she seem to recognize the impact of his/her behavior on others and can he/she adjust his/her behavior accordingly?

❑ Ability to problem-solve and think abstractly
- ❑ Does the individual primarily use trial and error to solve problems or can he/she solve problems hypothetically?
- ❑ Does he/she appear to understand metaphors, figures of speech?
- ❑ Does he/she appear to understand humor or does he/she respond concretely to sarcasm, jokes, or teasing?

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well, for example. Observations in settings like school can provide information regarding how the individual functions with varying degrees of structure (e.g., classroom vs. the playground). Observing the individual in different settings can also reveal deficits or strengths that are evident in one environment but not in another.

For example, it is not uncommon for parents of children with FASDs to not recognize their children's

significant social impairments, perhaps not only because these children can appear quite friendly (overly friendly actually) but also because parents may compensate, perhaps without even realizing it, for some of the child's difficulties in ways that mask the degree of their child's impairment in this domain. Thus, the opportunity to observe the alcohol-exposed child interacting with his/her peers on the playground may (a) better inform a clinician's understanding of how the child fares when having to function more independently, and (b) ultimately identify an important focus of intervention.

Another benefit of observing the alcohol-exposed individual in multiple settings is that it can provide important information about aspects of the individual's environment that may serve to enhance or, alternatively, further compromise the individual's functioning. For example, as noted earlier, individuals with FASDs commonly experience significant problems in school. Undoubtedly, some of these problems can be attributed to the child's primary cognitive and behavioral deficits. Nevertheless, a classroom that does not provide enough structure or consistency for that particular child, or perhaps teachers who are unaware of or do not fully understand the extent and nature of the child's impairments—particularly if the child has never been properly diagnosed—may have a further impact on the child's functioning.

Conversely, school observations can reveal that the child's classroom environment is functioning in such a way that enhances the child's potential. For example, a teacher might have developed very effective strategies for teaching an alcohol-exposed child and for managing behavior problems, strategies that the parents would benefit from incorporating at home. Obviously such observations can greatly inform the evaluation process, but collecting such data is not always feasible (e.g., observing an alcohol-exposed adult at work would be difficult). In such cases, efforts should be made at least to interview and/or to collect rating scales from other informants (with the appropriate consents), such as school counselors, employers, or spouses, regarding the individual's behavior in other settings.

The behavioral domains noted in table 1 would be relevant for any individual presenting in a psychiatric setting, but many are especially important to note in an alcohol-exposed child or adult. Observations should focus on both positive and negative aspects of the individual's presentation and behavior so that areas of both strength and deficit can be identified. Understandably, parents, teachers, and other informants may be more likely to provide information regarding problematic behavior because they are typically seeking help for such behavior. Equally important, however, is that clinicians also note the positive aspects of the individual's presentation or behavior, so that the clinician can not only provide feedback that includes a balanced view of the patient but also make recommenddations that both address areas of impairment and capitalize on existing strengths. In addition to the behavioral domains described in table 1, The Fetal Alcohol Behavior Scale (105), a rating scale that parents typically complete, can also be used by the clinician as a guide regarding specific behaviors to look for that commonly present in individuals with prenatal alcohol exposure.

Standardized measures

A comprehensive testing battery that includes measures of cognitive, neuropsychological, achievement, adaptive, behavioral, social, and emotional functioning is optimal when assessing individuals who have been exposed to alcohol prenatally. Such measures can include tests such as IQ tests that are administered to the patient directly, and rating scales or interviews that are administered to other informants, such as parents or teachers. When conducting such evaluations, one must keep in mind that many alcohol-exposed individuals will have a normal IQ, which may obscure deficits in other areas of cognitive functioning. As noted earlier, prior research has found that executive functioning in individuals with FASDs is often lower than what would be expected based on IQ (53). In light of such discrepancies, tests of intelligence may not adequately capture the full range of cognitive deficits that may be associated with prenatal alcohol exposure. Consequently, an evaluation of the individual's functioning across multiple domains is necessary to provide useful information to guide treatment planning. Additionally, speech and language testing and occupational and/or physical therapy evaluations might be conducted, or patients may be referred for such assessments if the relevant professionals are not part of the evaluation team.

The assessment battery should include measures that have been standardized and normed on a diverse sample. Testing results should be interpreted in light of relevant cultural factors, language issues, and environmental experiences. Histories of past abuse, neglect, or deprivation, exposure to trauma, and disrupted attachment experiences are not uncommon among individuals with prenatal alcohol exposure, and such experiences may have significant and long-lasting effects on an individual's development even if the

Table 2: Standardized measures for individuals with prenatal alcohol exposure

Achievement
- The Wechsler Individual Achievement Test – Second Edition (115)

Adaptive
- Vineland Adaptive Behavior Scales, 2nd edition (116)

Attention
- Conners' Rating Scales – Revised (117)
- Conners' Continuous Performance Test-II (118)
- Wechsler Intelligence Scale for Children – Third Edition as a Process Instrument: Digit Span and Spatial Span Subtests (119)

Behavioral/Emotional/Social
- Antisocial Process Screening Device (120)
- Beck Depression Inventory-II (121)
- Brief Symptom Inventory (122)
- Child Behavior Checklist, Caregiver-Teacher Report Form, Teacher Report Form, and Youth Self-Report (123)
- Children's Depression Inventory (124)
- Fetal Alcohol Behavior Scale (105)
- NIMH Diagnostic Interview Schedule for Children Version IV (125)
- Pictorial Depression Scale (126)
- Structured Clinical Interview for DSM-IV™ Axis I Disorders, Clinician Version (127); Structured Clinical Interview for DSM-IV™ Axis II Disorders (128)

Cognitive
- Bayley Scales of Infant Development – Third Edition (129)
- Wechsler Preschool and Primary Scale of Intelligence – Third Edition (130)
- Wechsler Intelligence Scale for Children – Fourth Edition (131)
- Wechsler Adult Intelligence Scale – Third Edition (132)

Executive
- Behavior Rating Inventory of Executive Function: Parent and Teacher forms (133)
- Children's Color Trails Test (134)
- Delis-Kaplan Executive Function System (135)
- NEPSY (136)
- Wisconsin Card Sorting Test (137)

Language
- Clinical Evaluation of Language Fundamentals, 3rd edition (138)
- Preschool Language Scale, 4th edition (139)
- Test of Language Competence – Expanded Edition (140)

Memory
- California Verbal Learning Test – Children's Version (141)
- Children's Memory Scale (142)
- Wechsler Memory Scale – Third Edition (143)

Visual Spatial/Fine Motor
- Beery-Buktenica Developmental Test of Visual Motor Integration- Fifth Edition (144)
- Finger Tapping Test (145)
- Grooved Pegboard Test (146)

individual has since been placed in a more supportive and stable environment. Several studies have shown that many alcohol-affected children experience one or more changes in custody during their lives, either being placed in foster care or being adopted, or being institutionalized (14). Estimates are that two-thirds of affected children are not raised in their biological homes (106), and many experience multiple placements in their lifetime, often of varying quality. Some of the children we see in our clinical practice have been adopted from

other countries and may have learned English or begun formal schooling only recently. Thus, an initial evaluation can provide important baseline data regarding the individual's functioning, but once interventions have been consistently implemented and/or the individual has had the benefit of living in a more supportive, stable environment, following the individual for further evaluation is essential.

Provided in table 2 is a list of standardized measures that can be used to evaluate individuals with prenatal alcohol exposure across multiple domains of functioning. These measures have been found to be useful when evaluating individuals for FASDs, based on research or clinical experience or both. Within each domain, different measures are noted for use during different developmental periods. For certain domains (e.g., executive functioning), multiple measures are listed that can be used to assess different aspects of functioning within that particular domain. The particular battery selected for each patient should, however, be based on the referral questions, the goals of the evaluation, and on what data are available from previous evaluations. Depending on the needs of the particular patient and their family, administering a particular measure in its entirety may be indicated, or conversely administering only a selected battery of subtests. Other researchers have also provided helpful recommendations regarding measures that may be useful for this population (17,100,107).

CONCLUSIONS

Although awareness and knowledge of the impact of alcohol on fetal development has increased among medical and mental health professionals over the last 30 years since FAS was first identified in the United States, the identification and treatment of FASDs continues to present a number of challenges. Health care professionals may believe that obtaining reliable and accurate information regarding an individual's history of prenatal alcohol exposure is too difficult, and there remains a significant need to improve the training and education of professionals regarding FAS and related conditions (108,109). Current research suggests, however, that overcoming these obstacles is indeed possible (110, 111). Given the multitude of primary deficits, as well as the increased risk for secondary disabilities seen in individuals with FASDs, it is essential that professionals working with children, adolescents, and adults who present in medical and/or psychiatric settings remain vigilant for individuals who are affected by prenatal alcohol exposure but remain undiagnosed or even misdiagnosed. Moreover, it is critical that evaluation and interventions focus not only on the alcohol-exposed individual, but on their families as well. Parents of children with FASDs report high levels of stress, and their increased stress seems to be at least partly related to the degree of behavioral and cognitive impairment experienced by their children (93,112). Early identification and diagnosis can play a profoundly important role in preventing many of the adverse outcomes frequently seen in alcohol-exposed individuals, and support for the efficacy of evidence-based interventions for this population is emerging (113,114). Such early identification and intervention likely offers the best hope for such individuals and their families.

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RESEARCH ARTICLE

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Fetal Alcohol Spectrum Disorders: Extending the Range of Structural Defects

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Although the structural phenotype of fetal alcohol syndrome (FAS) is established, prenatal exposure to alcohol may produce a broader spectrum of defects, fetal alcohol spectrum disorder (FASD). Documenting the full spectrum of defects associated with FASD is critical to determining the true incidence of this disorder. We examined 831 children from the Collaborative Initiative on Fetal Alcohol Spectrum Disorders using a structured protocol for diagnosis of FAS using the cardinal facial and growth features, and assessment of additional structural defects thought to occur more often in children with prenatal alcohol exposure. Subjects were classified as FAS, Deferred (some characteristic features of FAS), or No FAS, Groups were compared on prevalence of additional features and number of additional features observed, stratified by diagnostic category, sex, race, and age. Prevalence of most additional features was greatest among subjects with FAS and least among No FAS. A higher frequency of additional features was observed among FAS and Deferred subjects ≥12 years of age than among those under 12. FAS and Deferred Whites had greater frequency of additional features than Cape Colored. Prenatal alcohol exposure may produce a broad spectrum of structural defects that goes beyond FAS with implications regarding the impact of alcohol on the developing fetus, a prerequisite for ultimate prevention of FASD.

Key words: fetal alcohol spectrum disorders; fetal alcohol syndrome; dysmorphic features; diagnostic criteria

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INTRODUCTION

The fetal alcohol syndrome (FAS) is a specific pattern of altered growth, performance, and structure resulting from prenatal exposure of the developing fetus to alcohol [Lemoine et al., 1968; Jones et al., 1973]. Although a number of investigators have set forth specific criteria necessary for diagnosis of FAS, four publications are of most importance relative to this issue [Stratton et al., 1996; Astley and Clarren, 2000; Chudley et al., 2005; Hoyme et al., 2005]. Despite some differences that exist among them, all four of the previously published guidelines require growth deficiency and microcephaly, as well as alterations in facial development including short palpebral fissures, a smooth philtrum, and a thin vermillion border of the upper lip for diagnosis of this disorder. Strict adherence to these guidelines may be necessary for diagnosis of FAS. However, it is likely that prenatal exposure to alcohol leads to a much broader spectrum of defects referred to as fetal alcohol spectrum disorders (FASD). Although the phenotype of FAS, the most severe end of the spectrum, has been well-characterized, the

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structural defects that are associated with the broader spectrum of defects (FASD) have not been well described.

The purposes of this study are to: (1) describe the frequency of a number of specific minor structural defects that are thought to occur more often in children with prenatal alcohol exposure but are not part of the constellation of features required for diagnosis of FAS, (2) to compare the frequency of these additional specific features among children who do and do not have some or all of the key features of FAS, and (3) to determine if the number of these additional features varies by age, sex, or race of the child. Ultimately, this will be important in establishing the full range of structural anomalies resulting from prenatal exposure to alcohol.

Only by documenting the full spectrum of structural defects that constitute FASD will it be possible to fully appreciate the true incidence of problems that alcohol imposes on the developing human fetus, a requirement for developing and carrying out programs to prevent it.

MATERIALS AND METHODS

Study Population

This study was part of the Collaborative Initiative on fetal alcohol spectrum disorders (CIFASD). The CIFASD is an international consortium of basic science and clinical investigations sponsored by the U.S. National Institute of Alcohol Abuse and Alcoholism (NIAAA) and focused on addressing critical questions regarding the prenatal effects of alcohol. As part of the CIFASD, a Dysmorphology Core was established to assure accurate and consistent diagnosis of FAS in children at all consortium sites through implementation of a standard protocol based on documentation of the clinical phenotype of FAS. Children at these sites were ascertained using a variety of methods including cross-sectional, retrospective, and prospective study designs.

As of 2009, 841 children from 10 consortium sites (Atlanta, GA; Buffalo, NY; Los Angeles, CA; Plains States of the US; San Diego, CA; Rome, Italy; Moscow, Russia; Helsinki, Finland; Cape Town, South Africa; and Rivne, Ukraine) were examined by at least one of us (HEH, LKR, MdelC, MAM, and/or KLJ). Of these, 831 examinations had complete information on the additional features. The study was prospectively reviewed and approved by Human Subject Protection Programs at all participating clinical sites and at the University of California (San Diego).

Dysmorphology Assessment

A structured protocol was used for assessment of specific dysmorphologic features that constitute FAS. Palpebral fissure length (PFL) was measured with a rigid ruler marked in millimeters. Occipital frontal circumference (OFC) was measured by a cloth measuring tape. Height and weight were also measured. Age-specific centiles for height, weight, OFC, and PFL were determined using previously published charts (Kuczmarski et al., 2000; Thomas et al., 1987; Tanner, 1978; Nelhaus, 1968). The morphologic characteristics of the upper lip and philtrum were assessed and scored with the lip/philtrum guide described by Astley and Clarren [2000]. Likert scale scores between 1 and 5 were assigned for the thinness of the vermilion border of the upper lip and the flatness/smoothness of the philtral ridges, with higher scores indicating greater thinness or flatness/smoothness. Scores of 4 or 5 for each scale were considered to be consistent with FAS.

Children were given a preliminary diagnosis solely on the basis of key facial features (PFL $\leq$ 10th centile, a smooth philtrum, a thin vermilion border, microcephaly (OFC $\leq$ 10th centile), and growth deficiency (height and/or weight $\leq$10th centile). In addition to the diagnosis of FAS, children could be classified in a "Deferred" group if they had features suggestive of FAS but that were insufficient to meet the specific diagnostic criteria. Specifically, children were classified as Deferred if they had only one of the key facial features necessary for diagnosis of FAS, or if they had growth deficiency and microcephaly, or if they had either growth deficiency or microcephaly and one of these specific additional features that are not part of the constellation of features required for diagnosis but occur more frequently in children prenatally exposed to alcohol.

Those additional features, set forth by Hoyme et al., include a "railroad track" configuration of the ears (see Fig. 1), ptosis of the eyelids, a "hockey stick" palmar crease (see Fig. 2), other palmar crease abnormalities, lack of complete extension of one or more digits, decreased supination/pronation at the elbows, other joint contractures including inability to completely extend and/or con-

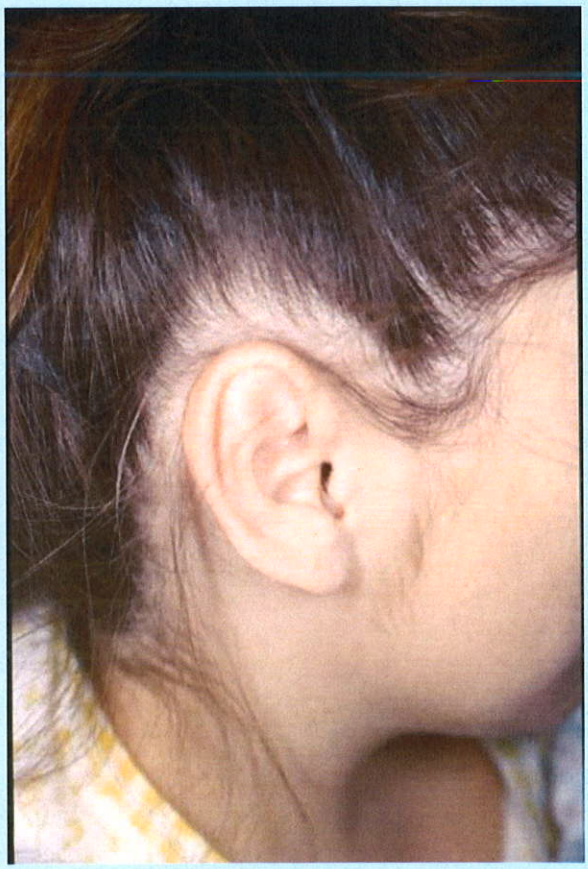

FIG. 1. Railroad track configuration of the ear: Note that the prominent horizontal crus of the helix in combination with a prominent and parallel inferior crus of the antihelix.[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

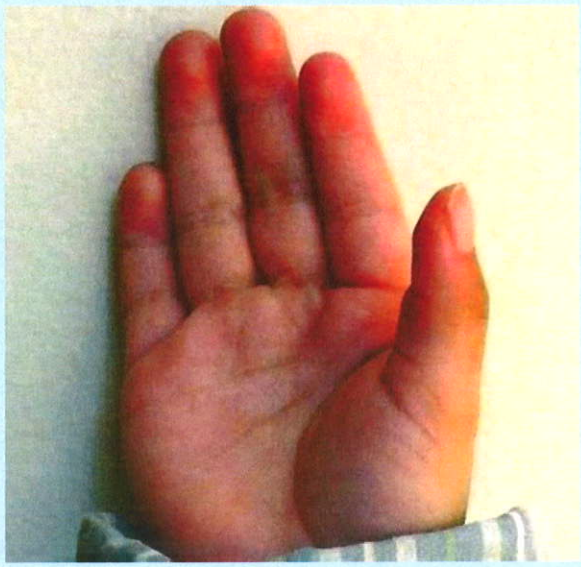

FIG. 2. Hockey stick crease: Note that the distal palmar crease curves distally and terminates between the index and middle fingers.[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tract at the hips, knees, and ankles, as well as a heart murmur [Stratton et al., 1996]. Assessment of these additional features was subjective in some cases. For example, a goniometer was not used to specifically determine the degree of joint contractures, incomplete extension of one or more digits, or decreased supination/pronation at the elbows. With respect to palmar creases, any deviation from the usual three deep creases on the palm was categorized as "other palmar crease abnormality." Children who did not meet the criteria for either the FAS or Deferred group were classified into a "No FAS" group.

Statistical Analysis

All statistical analyses were performed in SPSS (Release 15.0.1.1, Version 17.0; SPSS, Inc. (Chicago, IL), 1989–2006 and SAS Release 9.1, SAS Institute, Inc., Cary, NC, 2002–2003). The frequency of specific features (present or absent) and number of features (0, 1, $\geq$2) were compared between children in the three categories: FAS, Deferred, and No FAS using chi-squared or Fisher's exact test as appropriate. For comparison of the number of features by race, cells that contained fewer than 15 subjects resulted in exclusion of that stratum from the analysis. For the comparison of number of features by age, a cutoff of 12 years of age was used in order to account for changes in structure that occur as a result of the adolescent growth spurt.

RESULTS

The number of children by site and by category (FAS, Deferred, No FAS) for the 831 children in the sample is shown in Table I. Of the 244 subjects classified as Deferred, 25 (10%) were so classified because they had either growth deficiency or microcephaly and one of the specific eight additional features. Those 25 subjects were excluded from further analysis in order that the definition of each of the categories not include the presence or absence of one of the features that are being investigated. The racial distribution of subjects is as follows: Native American or Alaskan Native (n = 38), Asian (n = 9), Hawaiian/Pacific Islander (n = 2), Black/African American (n = 26), White (n = 486), Cape Colored (n = 100), multiracial (n = 3), unknown race (n = 142).

TABLE I. Subjects by Project Site and FAS Diagnostic Category

Site	FAS	Deferred	No FAS	Total
Atlanta, GA	4	6	6	16
Buffalo, NY	22	14	39	75
Los Angeles, CA	3	6	7	16
Plains States, US	15	15	21	51
San Diego, CA	15	39	65	119
Finland	55	30	57	142
Rome, Italy	14	78	121	213
Moscow, Russia	64	19	6	89
South Africa	51	36	16	103
Rivne, Ukraine	2	1	4	7
Total	245	244	342	831

The prevalence of each of the eight specific additional features for the three FAS categories is shown in Table II. For seven of the eight additional features, there was a "dose–response" relation with FAS category ($P < 0.05$), with the children in the FAS group having the highest prevalence of each feature and those in the No FAS group having the lowest prevalence. Only "other joint contractures" showed no such association.

As shown in Table III, sex of the child was not a significant predictor of number of additional structural defects (0, 1, $\geq$2) in either the FAS, Deferred, or No FAS groups ($P > 0.05$).

As is shown in Table IV, a statistically significant difference in the number of additional features was noted in children $\geq$12 years of age versus children <12 years of age in the FAS and Deferred groups but not in the No FAS group.

Due to the requirements for minimum cell size, the comparison by race included only White and Cape Colored groups. As shown in Table V, in the FAS group, significantly more children of White race had more additional features than Cape Colored Children ($P < 0.05$), whereas there was not a statistically significant relation between race and number of features in the Deferred and No FAS groups.

It is possible that for some of the additional features, particularly those that required a subjective judgment, two examiners might not agree to categorize the feature as present or absent. For 310 children in the study, two examiners evaluated the child. Interrater reliability in those cases was excellent (kappa statistic <0.001). However, there was not 100% concordance (data not shown). To address this issue, the data set was restricted to the 327 children seen by the same examiner (K.L.J.) and the analysis repeated. Results were essentially the same (data not shown).

DISCUSSION

These data document the frequency of a number of specific structural defects that have not traditionally been considered

TABLE II. Prevalence of Additional Features by FAS Diagnostic Category

Feature	N (%)	*P*-value[a]
Railroad track ears		
FAS	29 (11.8)	<0.001
Deferred	9 (4.1)	
No FAS	6 (1.8)	
Ptosis		
FAS	30 (12.2)	<0.001
Deferred	8 (3.7)	
No FAS	4 (1.2)	
Heart murmur		
FAS	25 (10.2)	<0.001
Deferred	5 (2.3)	
No FAS	5 (1.5)	
Decreased elbow pronation/supination		
FAS	36 (14.7)	<0.001
Deferred	10 (4.6)	
No FAS	4 (1.2)	
Incomplete extension of one or more digits		
FAS	90 (36.7)	<0.001
Deferred	36 (16.4)	
No FAS	21 (6.1)	
Other joint contractures		
FAS	6 (2.5)	0.028
Deferred	1 (0.5)	
No FAS	1 (0.3)	
Hockey stick crease		
FAS	53 (21.6)	<0.001
Deferred	19 (8.7)	
No FAS	18 (5.3)	
Other palmar crease abnormalities		
FAS	38 (15.5)	<0.001
Deferred	16 (7.3)	
No FAS	13 (3.8)	

[a]Chi-square or Fisher's exact test.

TABLE III. Number of Additional Features by Sex and FAS Diagnostic Category

	Number of additional features			
	0	1	≥2	*P*-value[a]
FAS				
Male	39 (30.7)	40 (31.5)	48 (37.8)	0.538
Female	34 (28.8)	45 (38.1)	39 (33.0)	
Deferred				
Male	74 (63.2)	28 (23.9)	15 (12.8)	0.300
Female	72 (70.6)	23 (22.6)	7 (6.9)	
No FAS				
Male	143 (79.9)	31 (17.3)	5 (2.8)	0.605
Female	137 (84.0)	22 (13.5)	4 (2.4)	

[a]Pearson chi-squared or Fisher's exact test.

TABLE IV. Number of Additional Features by Age and FAS Diagnostic Category

	Number of additional features			
	0	1	≥2	*P*-value[a]
FAS				
<12 years	49 (31.2)	63 (40.1)	45 (28.7)	0.008
≥12 years	24 (27.3)	22 (25.0)	42 (47.7)	
Deferred				
<12 years	117 (70.9)	38 (23.0)	10 (6.1)	0.002
≥12 years	29 (53.7)	13 (24.1)	12 (22.2)	
No FAS				
<12 years	194 (81.5)	37 (15.6)	7 (2.9)	0.861
≥12 years	86 (82.7)	16 (15.4)	2 (1.9)	

[a]Pearson chi-squared test.

necessary for the diagnosis of FAS in a group of children diagnosed with FAS relative to those classified as Deferred or No FAS. Of the eight additional features evaluated, there was a statistically significant increase in seven of them with a "dose–response" relation documented in which the children in the FAS group had the highest prevalence of additional features and those in the No FAS had the lowest suggesting that children with the more "severe" phenotype are at increased risk for one or more specific structural defects. Only "other joint contractures" lacked statistical significance.

It is important to note that Autti-Rämö et al. [2007] analyzed a similar group of structural defects in 77 older children and adolescents with FASD in Finland. They found an increased frequency of the same structural defects as noted in this larger sample, with the exception of railroad track configuration of the ear. The data from the 77 Finnish children in that study were included in the present analysis.

It is of particular interest that four of the seven additional features that were associated with the FAS category, including decreased elbow pronation/supination, decreased finger extension, "hockey stick" palmar crease, and other palmar crease abnormalities, could

TABLE V. Number of Additional Features by Race

	Number of additional features			
	0	1	≥2	*P*-value[a]
FAS				
White	43 (27.6)	48 (30.8)	65 (41.7)	0.004
Cape Col	19 (38.0)	23 (46.0)	8 (16.0)	
Deferred				
White	69 (60.0)	29 (25.2)	17 (14.8)	0.055
Cape Col	25 (73.5)	9 (26.5)	0 (0.0)	
No FAS				
White	178 (82.8)	30 (14.0)	7 (3.2)	1.000
Cape Col	14 (87.5)	2 (12.5)	0 (0.0)	

[a]Pearson chi-squared or Fisher's exact test.

be related to decreased fetal movement as a result of prenatal alcohol exposure's effect on early brain development. Furthermore, the increased frequency of ptosis noted in the FAS and Deferred groups could be the result of the adverse effect of alcohol on early development of the brain.

The increased incidence of heart murmur in children in the FAS and Deferred groups in this study is expected in that cardiac defects have been documented to occur in 5% to as many as 72% of children with FASD [Burd et al., 2007]. In this study, no echocardiogram or other confirmatory tests were performed to document the prevalence of true cardiac defects.

Based on the fact that five of the eight children initially described with FAS had joint anomalies [Jones et al., 1973], the lack of an increased frequency of "other joint contractures" in children with FAS or in the group designated Deferred in this study is of some surprise [Jones et al., 1973]. However, it is important to recognize that in the initial description of FAS, "other joint anomalies" was a broad category and encompassed anomalies of the palmar and interphalangeal creases, as well as decreased elbow pronation/supination and inability to completely extend the fingers. In our study, we evaluated these features individually and found all to occur more frequently in both the FAS and the Deferred groups.

Although sex of the child was not related to number of additional features in this study, the frequency of additional features varied by age at the time of examination and by race of the child in the limited subset available for this analysis. With respect to age at the time of diagnosis, greater number of additional features noted in children $\geq$12 years of age in both the FAS and Deferred groups is unexplained. It seems unlikely however that it is the result of factors related to normal structural changes associated with the adolescent growth spurt. It is possible, however, that this is due to some bias at some or all sites in children referred into the study at an older age who might be more likely to be more severely affected and/or to have more extensive physical features.

The significantly increased number of additional structural defects seen in children of White race compared to Cape Colored children is also unexplained. However, these data suggest that prenatal alcohol exposure might lead to a different phenotype based on age and racial background.

Limitations of this study included small sample size for selected race/ethnic groups across age groups and differences in methods for sample selection at each site. There was also variability across sites in the available information on quantity and frequency of prenatal alcohol exposure. In addition, there could be some diagnostic suspicion bias on the part of examiners who may have been more likely to recognize one or more additional features if the child was being examined already exhibited some or all of the key features of FAS. However, the study included a highly structured and systematic method for conducting these examinations across all sites, and examiners were all highly experienced in differentiating these subtle features. Other strengths of this study include the cross-cultural nature of the sample, and the unprecedented number of children with FAS or some features of FAS who were examined in a standard fashion.

A better understanding of the prevalence of these additional structural defects will be important in documenting the full spectrum of physical features that constitute FAS. This can contribute to a better understanding of the developmental pathogenesis of the disorder, while at the same time aid the practicing clinician in appreciating the breadth of features that might indicate that a patient has been affected by alcohol.

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Comparison of the Adaptive Functioning of Children Prenatally Exposed to Alcohol to a Nonexposed Clinical Sample

Shannon E. Whaley, Mary J. O'Connor, and Brent Gunderson

Background: Several studies show impairments in the social and adaptive behaviors of children prenatally exposed to alcohol. However, there remains limited consensus on whether the alcohol exposure directly affects social functioning or whether its effect is mediated by deficits in IQ. In addition, no studies have investigated whether deficits in social functioning are significantly more pronounced in children prenatally exposed to alcohol than in children referred to psychiatric treatment who were not prenatally exposed. We explored the effect of alcohol exposure on social and adaptive functioning and explored whether or not social and adaptive functioning are significantly more impaired in children prenatally exposed to alcohol than in a clinical sample of children.

Methods: A sample of 33 alcohol-exposed children was compared with a sample of 33 clinic-referred nonexposed children. The groups were compared on measures of communication, daily living skills, and socialization. The groups were matched on sex, age, IQ, and outpatient or inpatient status.

Results: Analyses revealed that the prenatally alcohol-exposed children did not differ significantly from the nonexposed children in any of the domains of adaptive functioning. However, with age, exposed children showed a more rapid decline in socialization standard scores compared with the nonexposed clinical sample.

Conclusions: Young children who were exposed to alcohol prenatally show deficits in all domains of adaptive functioning. Although these deficits do not seem to differ from those exhibited by young children with psychiatric problems but no prenatal exposure, deficits in socialization behavior of prenatally exposed children may become more significant with age.

Key Words: Prenatal Alcohol Exposure, Fetal Alcohol Syndrome, Vineland, Adaptive Behavior.

CONSUMPTION OF ALCOHOL during pregnancy has been shown to have deleterious effects on fetal and child development in multiple domains. Both animal and human studies have revealed hyperactivity, problems with response inhibition, attention deficits, poor habituation, poor coordination, and poor state regulation to be associated with alcohol use during pregnancy (Mattson and Riley, 1998; Riley, 1990). Many of these deficits have been demonstrated in the offspring of women who drank light to moderate amounts during pregnancy, and these children do not necessarily meet criteria for a diagnosis of fetal alcohol syndrome (FAS; Brown et al., 1991; Coles et al., 1991; Goldschmidt et al., 1996; Jacobson et al., 1993; Larroque et al., 1995; Russell, 1991; Streissguth et al., 1993).

FAS, characterized by pre- and postnatal growth retardation, facial anomalies, and central nervous system dysfunction, is estimated to occur in 0.5 to 3 infants per 1000 live births. Deficits in children exposed to alcohol prenatally, but who do not meet criteria for the full syndrome, are estimated to occur in as many as 9.1 in 1000 live births. Thus, clarifying domains of relative strength and weakness in children exposed to alcohol prenatally has widespread implications for the identification and treatment of these children through their life span.

Results from a number of studies have demonstrated impairments in the social and adaptive behaviors of children prenatally exposed to alcohol. In studies of adolescents and adults with FAS, clear deficits in social skills and adaptive functioning have been documented (LaDue et al., 1992; Streissguth et al., 1991). On average, 13- to 33-year-olds with FAS displayed social skills at a 6-year-old level, and these deficits were present even in individuals whose IQ scores were in the average range. Thus, children exposed to alcohol prenatally show an array of deficits in social and adaptive functioning that persist throughout the life span.

In studies of children who were alcohol exposed, but did not meet criteria for a diagnosis of FAS, the significance of alcohol exposure on adaptive functioning is less clear. One study (Coles et al., 1991) concluded that prenatal alcohol

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exposure, in the absence of FAS and mental retardation, does not impair social and adaptive abilities. Thus, the presence of mental retardation was suggested as a primary factor contributing to impairments in adaptive functioning in children who were exposed to alcohol prenatally. To address this question, Thomas et al. (1998) conducted a study to compare children with FAS with children with similar deficits in verbal IQ. Results of this study showed that children with FAS were significantly more impaired in their interpersonal relationship skills than developmentally delayed children, suggesting that social deficits in children with FAS go beyond what can be explained by low IQ scores alone.

The studies by Coles et al. (1991) and Thomas et al. (1998) examined adaptive functioning by using the Vineland Adaptive Behavior Scales (VABS), a scale administered to caregivers who rate the child in the domains of Communication, Socialization, and Daily Living Skills. Other studies that used the Child Behavior Checklist (CBCL; Achenbach, 1978), Teacher Rating Form (Edelbrock and Achenbach, 1984), or both have identified similar social and adaptive functioning problems in alcohol-exposed children. Steinhausen and Spohr (1998) administered the CBCL to caregivers and the Teacher Rating Form to teachers of children with FAS and found that social relationship problems characterized the childrens' profiles on both checklists. Similarly, Carmichael Olson et al. (1998) showed clear deficits in CBCL social competence scores in a sample of children with FAS, compared with an IQ comparison subgroup and a cohort comparison group. The FAS group also showed deficits in adaptive behavior on the VABS compared with the comparison samples, with performance relatively worse in the Socialization Domain. Thus, social deficits in children prenatally exposed to alcohol have been demonstrated across multiple studies, and with multiple methods.

A question that remains is whether the social deficits in children prenatally exposed to alcohol are more profound than those displayed by other clinical samples of children. A large body of literature highlights the deficits in adaptive functioning in children with a wide array of clinical disorders, including attention-deficit/hyperactivity disorder, conduct disorder, language disorders, and depression (Manikam et al., 1995; Paul et al., 1991; Powell and Germani, 1993; Speltz et al., 1999; Stein et al., 1995; Vig and Jedrysek, 1995). In addition, many of the studies showing social deficits in children exposed to alcohol prenatally are uncontrolled clinical studies of a small population of children with FAS. Those studies not showing strong associations between prenatal alcohol exposure and social behavior (e.g., Coles et al., 1991) most often are longitudinal prospective studies that did not select a clinical sample. Thus, the goal of this study was to expand on earlier work by comparing the adaptive functioning of a sample of alcohol-exposed children to a clinical sample of children with no prenatal alcohol exposure.

It was hypothesized that children exposed to alcohol prenatally, whether or not they met criteria for a diagnosis of FAS, would show significant deficits in adaptive functioning. The second question addressed by this research was whether the adaptive functioning of children exposed to alcohol prenatally is significantly different from the adaptive functioning of a clinical sample of nonexposed children, controlling for intelligence. The question is particularly important for the development of a behavioral phenotype for FAS and alcohol-related neurodevelopmental deficits (ARND). If, in fact, children exposed to alcohol prenatally show significant deficits in their adaptive functioning, compared with a clinical sample of children, then these deficits may be considered a behavioral hallmark of prenatal alcohol exposure. However, if children exposed to alcohol prenatally show similar deficits in adaptive functioning to a clinical sample of children, then the diagnostic relevance of adaptive functioning behaviors for FAS or prenatal exposure becomes less clear.

METHODS

Participants

Sixty-six children participated in the study. Thirty-three alcohol-exposed children were referred to the University of California–Los Angeles (UCLA) Fetal Alcohol Syndrome and Related Disorders Clinic or the HUB Clinic at the King/Drew Medical Center. Eight of these children (four with FAS, four with prenatal exposure) were referred to the FAS clinic from the UCLA child psychiatry inpatient ward of the Neuropsychiatric Institute. To be eligible to be in the study, children had to have documented prenatal alcohol exposure, either by maternal report, birth record review, or official documentation in a Department of Child and Family Services file. When relevant, the child's caseworker was contacted directly by the FAS clinic staff to further clarify the records regarding prenatal alcohol exposure. All of the children had histories of heavy prenatal alcohol exposure, but specifics about the amount of alcohol consumed during pregnancy were not available. Children ranged in age from 20 months to 10.5 years. Nine children met criteria for a diagnosis of FAS. Twenty-two (67%) of the prenatally exposed children also met criteria for at least one psychiatric diagnosis. Diagnoses were comparable to those described below for the clinic sample. Thirteen children were living with their biological parents, 9 with adoptive parents, 10 with foster parents (6 of these children were in the process of adoption), and 1 in residential treatment. Twenty-two children had been in one home since birth, and the remaining 11 children had been in multiple home placements.

A matched clinical sample of 33 nonexposed children was selected by using a chart review of children evaluated in the child psychiatry outpatient clinic, the infant and preschool psychological evaluation clinic, and the child inpatient ward at the UCLA Neuropsychiatric Institute. As part of the admission process to these programs, all caretakers are queried regarding prenatal alcohol and other drug exposure of the child. In addition, birth records and, when relevant, Department of Child and Family Services files were reviewed for prenatal exposure. Only those children with confirmed nonexposure were used in matching. Nonexposed children were matched to the alcohol-exposed children on the basis of age, sex, IQ, and inpatient/outpatient status. Children ranged in age from 22 months to 11 years.

Inclusion in the clinical sample was not restricted to any particular disorder; however, children with autism, Asperger's syndrome, or other pervasive developmental disorders were not included in the sample. The most common disorders in the outpatient sample included receptive and

expressive language disorders, adjustment disorders, mental retardation, and attention-deficit/hyperactivity disorder. Disorders of the inpatients included bipolar disorder, major depressive disorder, intermittent explosive disorder, and posttraumatic stress disorder. Fourteen children (42%) met criteria for more than one psychiatric diagnosis; thus, comorbidity of disorders was common. Twenty-nine children were living with their biological parents, two with their adoptive parents, one with their foster parents, and one in residential treatment. Thirty children had been in one home since birth, and the remaining three children had been in multiple home placements.

Procedures

Prenatal alcohol exposure was documented for the exposed group of children before scheduling their appointment. Similarly, documentation of no prenatal exposure was made before enrolling children in the clinical sample into the study. The 25 outpatient children in each sample were seen during two visits with a primary caregiver. The eight inpatient children in each sample were seen over one to two visits during their inpatient stay. Caregivers for all children were interviewed in person, at which time an extensive family history was taken and the VABS were administered. All children in the alcohol-exposed group seen at UCLA were assessed for FAS by John Graham, MD, a pediatric geneticist and dysmorphologist with expertise in FAS. All children in the alcohol-exposed group seen at King/Drew Medical Center were assessed for FAS by Richard Findlay, MD, a pediatrician trained in FAS assessment by Kenneth Jones, MD. Intelligence testing was carried out with each child by an experienced examiner while the caregiver was interviewed in a separate room.

Measures

FAS/ARND Diagnosis. Strict criteria set forth in the *Diagnostic Guide for Fetal Alcohol Syndrome (FAS) and Related Conditions Manual* (Astley and Clarren, 1999) were used for diagnosing the children. This system uses a four-digit diagnostic code reflecting the magnitude of expression of four key diagnostic features of FAS: (1) growth deficiency; (2) the FAS facial phenotype, including short palpebral fissures, flat philtrum, and thin upper lip; (3) brain dysfunction; and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a four-point Likert scale, with 1 reflecting complete absence of FAS features and 4 reflecting the full manifestation of the features.

Adaptive Behavior. The VABS (Sparrow et al., 1984) were administered to a caregiver of all participants. For the two children in residential treatment (one prenatally exposed, one nonexposed), a counselor or primary nurse who knew the child well was administered the VABS. The items on the VABS fall into one of three subdomains: (1) Communication, (2) Daily Living Skills, and (3) Socialization. Caregivers of children under the age of 6 years were also queried about motor skills, but this subdomain was not included in analyses because many of the children in the sample were older than 6 years. A standard score was obtained for each subdomain (mean = 100, SD = 15), and an Adaptive Behavior Composite score across all three subdomains was also calculated.

Intelligence. Assessment of intelligence was conducted in a quiet room in the Child Psychiatry Departments at the UCLA or the King/Drew Medical Center. Depending on the age of the child, the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991) or the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R; Wechsler, 1989) was administered to 58 children in the sample. Eight children in the sample were under the age of 4 years and were administered the Bayley Scales of Infant Development (Bayley, 1993). The Bayley provides a developmental quotient that cannot be equated with IQ scores obtained by the WISC-III and WPPSI-R. Thus, the eight individual children were matched on Bayley developmental quotient scores, and these children's IQ data were analyzed separately.

Table 1. Demographic and IQ Data for the Prenatal Alcohol-Exposed and-Nonexposed Groups

Variable	Alcohol exposed (n = 33)	Nonexposed (n = 33)
Age (yr)	6.15 (2.38)	6.15 (2.30)
Sex, n (%)		
Male	20 (60.6)	27 (81.8)
Female	13 (39.4)	6 (18.2)
Full Scale IQ		
WWPSI/WISC (n = 29)	83.5 (13.1)	83.3 (15.2)
Bayley (n = 4; age in months)	19.5 (5.7)	20.5 (4.3)
Home placement, n (%)		
Number of children with >1 home placement since birth	11 (33.3)	3 (9.1)*

Data are presented as mean (SD) unless otherwise noted.
* $p < 0.05$.

Table 2. Summary of Standard Scores on Vineland Adaptive Behavior Scales for Prenatal Alcohol-Exposed and -Nonexposed Groups

Vineland Adaptive Behavior Scales	Alcohol exposed (n = 33)	Nonexposed (n = 33)
Communication	77.61 (17.04)	75.09 (20.70)
Daily Living Skills	73.12 (20.18)	78.21 (24.03)
Socialization	74.94 (15.11)	77.94 (14.04)
Composite	70.85 (17.17)	73.06 (18.98)

Data are presented as mean (SD).
Hotellings's $T^2(3,64) = 4.43$; $p = 0.24$.

RESULTS

Matching Data

The groups were compared regarding age, sex, inpatient status, and Full Scale IQ (Table 1). Results revealed no statistically significant differences on age, inpatient status, Full Scale IQ, or Bayley Developmental Age equivalents. Although there was a higher percentage of males in the nonexposed sample than the alcohol-exposed sample, the difference was not statistically significant (Fisher's exact test, $p > 0.10$). Thus, any differences in adaptive functioning are not attributable to differences in age, sex, inpatient status, or IQ. The groups did differ significantly, however, in home placement. Children in the alcohol-exposed sample were more likely to have been in multiple home placements compared with children in the nonexposed sample (Fisher's exact test, $p < 0.05$).

Adaptive Behavior of Prenatally Exposed Children

As expected, children exposed to alcohol prenatally exhibited significant deficits in adaptive functioning across all domains (Table 2). The VABS is normed such that standard scores express in SD units the extent to which the individual's score exceeds or falls below the mean scores of persons of the same age on whom the instrument was standardized (Sparrow et al., 1984). VABS scores have a mean of 100 and an SD of 15; thus, the mean Adaptive Behavior Composite score of children prenatally exposed to alcohol (70.85) was 2 SD below the mean. Overall, 45.5% of the alcohol-exposed sample scored below 70 on the VABS composite score, 33.3% scored between 70 and

Table 3. Stepwise Multiple Regression Analyses of Predictors of VABS Socialization Scores

Variable entered	Multiple R	R^2	Change in R^2	F	Probability of F
Placement	0.071	0.005	0.005	0.31	0.58
Group	0.110	0.012	0.007	0.48	0.49
Age	0.434	0.188	0.176	13.41	0.0005
Group × age	0.495	0.245	0.057	4.62	0.036
Group × placement	0.532	0.283	0.038	3.22	0.078
Age × placement	0.550	0.302	0.019	1.61	0.209
Group × age × placement	0.561	0.315	0.013	1.06	0.307

84, and 21.2% scored between 85 and 115. No child scored higher than 115 (the highest score was 104). According to VABS norms on the Adaptive Behavior Composite score, only 2.5% of children should score below 70, 14.2% between 70 and 84, 66.7% between 85 and 115, 14.2% between 115 and 130, and 2.5% above 130. The distribution for the alcohol-exposed sample compared with the standardization sample was found to be statistically different by using a χ^2 goodness of fit test $\chi^2 = 1042.37$, $p < 0.001$. Mean VABS subscale scores showed comparable deficits and distributions.

IQ and Adaptive Behavior

Given the past debate over whether IQ deficits, as opposed to prenatal alcohol exposure, are responsible for deficits in adaptive behavior, it was of interest to evaluate the relationship between the two. Groups were matched for IQ, and the mean IQ in both groups was just greater than 1 SD below the mean (Table 1). Correlations were run between IQ and adaptive behavior scores for the 58 children who were tested with the WISC-III or WPPSI-R and were low for both the prenatally exposed and nonexposed children. In the prenatally exposed group, IQ and Vineland Daily Living Skills showed a trend toward a significant correlation ($r = 0.30, p = 0.08$). IQ and Vineland Communication skills were significantly correlated for the nonexposed group ($r = 0.43, p < 0.05$). IQ and Vineland Socialization skills were uncorrelated for both groups.

Adaptive Behavior: Alcohol Exposed Versus Nonexposed

A Hotelling's T^2 comparing the alcohol-exposed group with the nonexposed group on three subdomains of the VABS (Communication, Daily Living Skills, and Socialization) was not significant [$T^2(3, 64) = 4.43, p = 0.24$]. Thus, a clinical sample of nonexposed children also showed significant deficits in their adaptive behavior that seemed comparable to those exhibited by children prenatally exposed to alcohol (Table 2). Both groups were functioning in the borderline range of adaptive functioning (1–2 SD below the mean). Hotelling's T^2 tests comparing the adaptive behavior of the children with an FAS diagnosis ($n = 9$) with their nonexposed matches, and comparing the inpatient-exposed to the inpatient-nonexposed children ($n = 8$), also yielded no significant differences in adaptive behavior between groups.

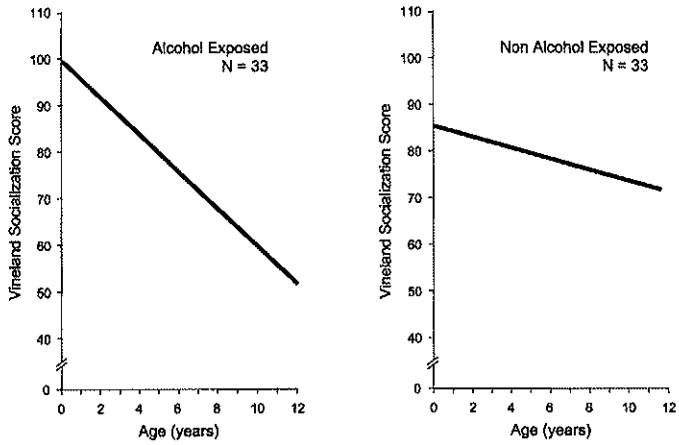

Fig. 1. Comparison of changes in Vineland Socialization Standard Scores as a function of age for children in the prenatal alcohol-exposed sample versus the nonexposed clinical sample, controlling for placement.

Home Placement, Age, and Adaptive Behavior: Alcohol Exposed Versus Nonexposed

Three hierarchical multiple regressions were used to determine the effect of home placement (dichotomous: one placement versus more than one placement), group status (alcohol exposed versus nonexposed), and age on each of the VABS subscale scores (Communication, Daily Living, and Socialization). For each analysis, home placement was always entered first into the equation, followed by group and age status. All two- and three-way interactions were then entered last.

There were no significant home placement or group main effects for any of the VABS outcome measures (Table 3). Age was a significant predictor of all domains of adaptive behavior, with children from both groups showing declines in Socialization, Communication, and Daily Living Skills with age. These declines were most apparent in the socialization domain for the alcohol-exposed group, as evidenced by the significant group × age interaction on this variable after the effects of home placement had been partialled out (Table 3 and Fig. 1).

To further explore this interaction effect, regression analyses were computed that examined the association between age and socialization for the alcohol-exposed and the nonalcohol-exposed clinical groups separately while controlling for placement effects. The age effect was significant in the alcohol-exposed group ($\beta = -0.38, p < 0.0001$) but was not significant in the nonexposed clinical sample ($\beta = -0.10$, $p = 0.29$). This finding suggests that, with age,

children prenatally exposed to alcohol show a more significant decline in standard scores in the socialization domain compared with a nonexposed clinical cohort, and these differences cannot be accounted for by an increased number of placements. Thus, it seems that as the prenatally exposed children get older, they begin to show more marked difficulties in socialization compared with their nonexposed clinical peers.

The group × placement interaction showed a borderline significant association with VABS socialization scores ($p < 0.10$). Further examination of this interaction showed that the mean socialization scores of prenatally exposed children remained stable regardless of placement status, whereas nonexposed children with multiple home placements ($n = 3$) had a lower mean socialization score than nonexposed children with a single placement since birth ($n = 30$). The one child who was living in a residential treatment home accounted for the low mean socialization score of the nonexposed children with multiple home placements. Thus, although the group × placement interaction trend suggests that the socialization behavior of children in the nonexposed group may be more negatively affected by multiple home placements, this effect was essentially carried by the socialization behavior of one child. It is more interesting to note that socialization behavior was consistent for the prenatally exposed group regardless of placement status.

DISCUSSION

It is clear from both this study and previous studies that the adaptive behavior of children exposed to alcohol prenatally is significantly compromised. Children prenatally exposed show deficits in communication, daily living skills, and socialization behavior, evidenced by low standardized scores on the VABS, and these deficits are not attributable to deficits in IQ. It is also clear from this study, however, that the adaptive functioning deficits exhibited by children prenatally exposed to alcohol are not unique to this group, but are also evidenced in a clinical sample of children who were not exposed to alcohol. Thus, although adaptive behavior deficits may be significant for prenatally exposed children, compared with normal control children, they do not seem to be a hallmark of prenatal alcohol exposure.

Further, although the sample size was small and conclusions should be drawn carefully, children with a diagnosis of FAS do not seem to differ significantly from children with ARND in their levels of adaptive functioning. These findings suggest that deficits in adaptive behavior are not specific to children with the most severe form of exposure. Given the lack of clear differences in adaptive functioning among children with FAS, ARND, and other clinical disorders, the diagnostic relevance of adaptive functioning behavior for young children with FAS or prenatal alcohol exposure is limited.

That said, deficits in adaptive behavior might become a more salient feature of prenatal alcohol exposure as children get older. The children in the current sample were young (mean age = 6.3 years), and the finding that standard scores were lower at older ages suggests that deficits in socialization skills may become more debilitating for older prenatally exposed children. The finding that social deficits in the children with FAS increase with age has been shown by others (Thomas et al., 1998), and it has been suggested that the deficits for children with FAS represent an arrest of social development at the age of 6 years (Streissguth et al., 1991). Future cross-sectional studies are needed to investigate the adaptive behaviors of older children exposed to alcohol in utero so that the current findings may be examined further. In addition, longitudinal studies are needed to track adaptive behavior over time to measure rates of developmental decline.

Although the groups in this sample were well matched on IQ, age, sex, and inpatient status, the groups were not well matched on home placement. Significantly more children in the prenatally exposed group had experienced multiple home placements, compared with their nonexposed counterparts. Thus, one could argue that children who are moved through multiple home placements are likely to have experienced more negative caregiving environments, placing them at higher risk of experiencing deficits in adaptive behavior. Additionally, caregivers who have raised the child since birth may rate children higher than caregivers who have more recently gained custody of the child.

In this study, these arguments seem less credible given the lack of a significant main effect of home placement on adaptive behavior across groups. The borderline significant group × placement interaction ($p < 0.10$) on socialization scores might suggest that multiple placements have a more significant effect on the socialization behaviors of a nonexposed clinical sample of children than on prenatally exposed children. As noted in "Results," the prenatally exposed group showed consistent socialization scores regardless of home placement. The nonexposed children in multiple placements showed lower scores than the nonexposed children with a single home placement, but this effect was attributable to the very low socialization score of the one nonexposed child in residential treatment. The prenatally exposed child in residential treatment did not show a comparable deficit in socialization behaviors.

These findings suggest that although home placement status did not seem to have an effect on the socialization of prenatally exposed children in this sample, it is an important variable to consider. Residential treatment falls at the extreme in terms of negative home placements, and children in these settings are likely to show adaptive behavior deficits regardless of prenatal exposure. Unfortunately, measures of the home environment were not taken in the current study; thus, it is unclear how rearing variables may directly affect adaptive behavior skills in these samples of children. However, one study of the relationship between alcohol and drug use by female caregivers on factors that

affect the child-rearing environment of prenatally exposed children demonstrated that current alcohol use was related to poorer family functioning, low quality of parental intellectual stimulation, and higher levels of domestic violence (Jester et al., 2000). Additional studies such as these would allow the relationship between home environment and adaptive behaviors to be addressed more adequately.

There are some limitations to this study that need to be addressed. First, the sample size is relatively small, so replications are critical. Second, the VABS is not a particularly sophisticated test of adaptive behavior, and it may be that other more sensitive measures may better discriminate between exposed and nonexposed clinical groups. The VABS also tends to be less sensitive at younger ages, and this may have contributed to the significant association between age and socialization behavior. However, because the samples of children in this study were matched on age, it is unlikely that VABS insensitivity at young ages would account for the significant group × age interaction. Observational studies of adaptive behaviors have yet to be done with prenatally exposed children and would provide a wealth of data that are not accessible through standardized measures such as the VABS. It may be that more sophisticated measures of adaptive behavior would illustrate clear deficits in prenatally exposed children that are not evidenced in other clinical samples of children. Such findings would lend more support to using adaptive functioning as a diagnostic component of prenatal exposure.

Finally, as with many of studies of prenatally exposed children, prenatal alcohol exposure was identified retrospectively. Thus, limited information is available with regard to when and how much alcohol was used by the mother and what types of other substances may have been used during pregnancy. In this study, general alcohol use during pregnancy was clearly determined, but quantity and frequency measures were not obtained for children raised by nonbiological parents and were obtained retrospectively from biological mothers. Conclusions drawn from this study, therefore, can be made only for general prenatal exposure of unknown amount. It may be that several ongoing prospective studies that follow mothers during pregnancy and then track the child's development will better elucidate the relationship between adaptive behavior and the amount of alcohol ingested during pregnancy.

To our knowledge, this is the first study to compare a sample of prenatally exposed children to a nonexposed clinical sample of children matched on age, sex, and IQ. The findings demonstrate the importance of querying about prenatal alcohol exposure in every clinical inpatient and outpatient setting. This study suggests that prenatally exposed children often "blend in" in clinical settings, exhibiting similar behavior patterns to nonexposed children, and thus their special needs may be ignored in treatment. A growing literature highlights positive outcomes for prenatally exposed children who are diagnosed and treated early (Streissguth, 1997). It may be that early treatment could prevent the social skills deficits evidenced in these children as they grow older. For this reason, there is a need for clinicians to screen patients for prenatal alcohol exposure when making decisions about treatment options. Specifically, social skills training is needed for these children, as well as for those in the general psychiatric population, to increase their ability to function adaptively in interaction with others.

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CONSENSUS STATEMENT

Recognizing Alcohol-Related Neurodevelopmental Disorder (ARND) in Primary Health Care of Children

October 31–November 2, 2011 ▪ Rockville, MD 20852

Consensus Statement on

Recognizing Alcohol-Related Neurodevelopmental Disorder (ARND) in Primary Health Care of Children

A Conference Organized by the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD)

Oct. 31–Nov. 2, 2011, Rockville, MD

Introduction

The nondiagnostic umbrella term "fetal alcohol spectrum disorders (FASD)" is now used to characterize the full range of damage from prenatal alcohol exposure, varying from mild to severe and encompassing a broad array of physical defects and cognitive, behavioral, emotional, and adaptive functioning deficits. FASD includes diagnoses such as fetal alcohol syndrome (FAS), partial FAS (pFAS), ARND, and alcohol-related birth defects (ARBD), which are congenital anomalies including malformations and dysplasias of the cardiac, skeletal, renal, ocular, auditory, and other systems.

The negative effects of prenatal alcohol exposure on the developing brain and the resulting neurological and/or cognitive, behavioral, emotional, and adaptive functioning deficits are seen in individuals with FAS, pFAS, and ARND. Significant alcohol exposure early in prenatal development often results in growth retardation and facial anomalies. These physical characteristics have been useful tools for diagnosing FAS and pFAS. Identifying persons who do not have the physical characteristics of FAS but do have neurodevelopmental disorders induced by prenatal alcohol exposure has proven to be much more challenging, with broad implications. Current prevalence estimates for FAS range from 0.5 to 7 cases per 1,000 live births in the United States, and the prevalence of FAS and ARND combined is thought to be three times that of FAS alone.

In 2004, the National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention and the National Task Force on FAS and Fetal Alcohol Effect issued *Guidelines for Referral and Diagnosis of FAS*. Evidence for recommending screening and referral for diagnosis of ARND was considered insufficient at that time. In the past 7 years, a large body of research evidence has been published on further characterization and differentiation of the cognitive, behavioral, emotional, and adaptive functioning deficits

associated with prenatal alcohol exposure. Based on this evidence and identification of the principal issues with researchers and clinicians, ICCFASD determined that the time had come to reassess whether sufficient evidence now existed to recommend screening and/or referral for diagnosis of ARND in primary health care of children. ICCFASD then proceeded to convene a conference during which a multidisciplinary panel would respond to the principal issues, with the objective of arriving at a statement that would advance an understanding of the issue and that would be useful to health care professionals. This document summarizes the outcome of the conference.

Process

In late 2011, ICCFASD assembled a broad-based, independent panel of knowledgeable and unbiased critical thinkers to hear and evaluate evidence presented by experts in the field of FASD. The goal of the conference was to arrive at recommendations and future directions on whether to encourage screening and diagnosis (or referral for diagnosis) of ARND in primary health care of children.

The consensus statement that follows was prepared by the panel, which included health care professionals, biomedical researchers, academics, educators, and child advocate/policy/legal representatives. It is based on (1) relevant published studies assembled by the scientific committee of the conference, (2) presentations of data from the peer-reviewed scientific literature by experts working in areas relevant to the conference questions, (3) questions and comments from conference attendees during open discussion periods, and (4) closed deliberations by the panel. This statement is an independent report of the panel and is not a policy statement of ICCFASD or the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health; the Centers for Disease Control and Prevention; or the American Academy of Pediatrics, which cosponsored the conference.

Conference Questions

The panel used the evidence presented to them by the experts in the field to develop answers, in the form of a consensus statement, to the following questions:

1. What is ARND; how can it be diagnosed (classical, current diagnostic schemes, in practice today)?
   Part A: Evidence of Central Nervous System Developmental Abnormalities
   Part B: Evidence of a Complex Pattern of Behavior and Cognitive Abnormalities
2. Can ARND be differentiated from other disorders?
3. What prenatal alcohol exposure evidence is necessary for an ARND diagnosis?
4. What signs/symptoms will be useful as screening criteria?
5. What are the treatment needs for those diagnosed with ARND?

Preamble

Children, adults, and families who live with disabilities related to prenatal alcohol exposure (PAE) face extraordinary challenges daily. The work of clinicians and researchers who have worked to understand and improve outcomes on their behalf must be commended. Together, this community has pioneered medical, educational, social, and scientific initiatives, all in pursuit of improving the quality of life for those affected and their families and of reducing the public health burden resulting from PAE.

PAE can cause significant neurodevelopmental and behavioral disorders as well as adaptive and self-regulatory impairments that can have lifelong consequences. Early diagnosis and intervention may help to reduce the long-term challenges potentially facing individuals with PAE. Therefore, primary health care clinicians serving children[1] should be alert to evidence of any maternal use of alcohol during pregnancy in order to provide timely evaluations and appropriate interventions for affected children and help prevent PAE during future pregnancies.

Question 1: What is ARND; how can it be diagnosed (classical, current diagnostic schemes, in practice today)?

Alcohol-related neurodevelopmental disorder (ARND) refers to a complex range of disabilities in neurodevelopment and behavior, adaptive skills, and self-regulation in the presence of confirmed PAE. ARND is one of the fetal alcohol spectrum disorders that also include fetal alcohol syndrome (FAS), which is additionally characterized by distinct facial features and growth retardation.

The term ARND was used in a 1996 report developed under the auspices of the Institute of Medicine (IOM)[2] to recognize the existence of neurodevelopmental disorders associated with confirmed PAE. Specifically, individuals with ARND do not present with the FAS facial phenotype (reduced palpebral fissure length, smooth philtrum, and thin upper vermillion border), but may present with structural and/or functional central nervous system (CNS) abnormalities, and may or may not present with growth deficiencies or decreased cranial size at birth. Acknowledging some degree of uncertainty that PAE caused the presenting adverse effects in any particular individual, the 1996 IOM report on FAS defined ARND as CNS neurodevelopmental abnormality evidenced by decreased cranial size at birth, or structural brain

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[1] Primary health care clinicians for children include pediatricians, pediatric nurse practitioners, family medicine physicians, family nurse practitioners, pediatric and family physician assistants, and certain nurses in public health clinics or school-based health clinics.

[2] Stratton K, Howe C, Battaglia F. (Eds.) *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment.* Washington, DC: National Academies Press, 1996. Available online at: http://www.nap.edu/openbook.php?isbn=0309052920.

abnormalities, or neurological hard or soft signs in the presence of a pattern of confirmed excessive maternal prenatal alcohol use. Alternatively, ARND could be defined by evidence of a complex pattern of behavioral and cognitive abnormalities that are inconsistent with developmental level and cannot otherwise be explained by the genetic contribution of the biological parents, nor by impairments in brain maturation conferred by adverse environmental factors. Alternative descriptors have emerged, including "neurodevelopmental disorder/alcohol exposed" and "static encephalopathy/alcohol exposed."[3] In the ensuing years, animal research and human studies have helped families, clinicians, and researchers develop a deeper understanding of the relationship between PAE and neurodevelopmental manifestations subsequently evident in children, adolescents, and adults.

Part A: Evidence of CNS Developmental Abnormalities

The brain is susceptible to the neurotoxic effects of alcohol at all stages of gestation. Based on extensive, mutually reinforcing animal and clinical research, there appear to be patterns of significant structural and functional changes in the CNS attributable to PAE. Basic research suggests that numerous processes of neuronal development and functioning can be affected by PAE. Animal studies demonstrate that the timing, dose, and frequency of PAE differentially harm specific neuronal structures and brain circuits. Brain imaging and cognitive and behavioral studies have substantiated similar structural and functional alterations in humans.

Part B: Evidence of a Complex Pattern of Behavior and Cognitive Abnormalities

There is clear and compelling evidence from animal studies that PAE negatively affects behavior, cognition, motor function, self-regulation and adaptive function, executive function, activity, and mood in a complex way. Children with PAE frequently exhibit behavioral and emotional problems such as inattention, hyperactivity, anxiety, and mood dysregulation. These problems may emerge early in life and continue to significantly impair an individual's functioning in numerous domains throughout the lifespan. Identified problems may be primary to PAE, be primary to a comorbid condition, or result from the contribution of and interaction among a number of factors, including interactions with the environment. Research with children suggests that PAE can be associated with general cognitive impairments and specific impairments in the following areas: information processing, attention, executive function, language, memory/learning, social cognition, number processing, and sensorimotor function. One or more behavioral and cognitive phenotypes specific to PAE have been elusive. Identification of specific phenotypes is confounded by variability of exposure (dose, duration, and timing) and potential interactions among other factors, which may include qualities of the prenatal and postnatal environments, genetics, and exposure to other toxic substances.

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[3] Currently, there are several commonly accepted diagnostic schemes and interpretations of the diagnostic guidelines presented in the 1996 IOM report on FAS (see Resources for Further Information and Application at the end of this statement for commonly accepted diagnostic schemes providing guidelines on diagnosing ARND). This panel is not advocating any particular system for the diagnosis of ARND or the use of these alternate descriptors.

Question 2: Can ARND be differentiated from other disorders?

Alcohol is a known teratogen and is strongly associated with a range of neurodevelopmental and behavioral disorders that may affect numerous domains of functioning across the lifespan. Emerging evidence from animal and human studies suggests that there is a constellation of symptoms attributable to PAE that may include (1) neurocognitive impairments, (2) self-regulatory challenges, and (3) impairments in adaptive functioning. However, differentiating ARND from other complex neurodevelopmental disorders can be challenging due to limited available studies attempting to distinguish ARND phenotype(s) from other disorders.

Even when a history of PAE is available, diagnosing ARND and distinguishing it from other complex developmental disorders requires prudent clinical judgment and consideration of other potential causes. In the future, we anticipate that clinicians will be assisted in making this diagnosis through advances in the identification of biomarkers sensitive to the detection of significant PAE and the development of tests that are both sensitive to and specific for alcohol-induced neurobehavioral disorders. We recommend additional rigorous scientific investigation to further refine understanding of the cognitive, behavioral, neurologic, and psychiatric clinical profiles attributable to PAE, as well as of the patterns of development evidenced by individuals with PAE. We further recommend that investigations of other complex developmental disorders include inquiry about PAE to identify the contribution of PAE to the phenotypes of other developmental disorders.

Question 3: What prenatal alcohol exposure evidence is necessary for an ARND diagnosis?

An ARND diagnosis requires confirmed, significant PAE. Determination of alcohol exposure can be based on maternal self-report; the report of a spouse, partner, relative, or friend who observed the birth mother drinking alcohol during the index pregnancy; and/or documentation in medical or other records about maternal alcohol use during the index pregnancy.

Data from animal studies across multiple species confirm that, at the highest levels of alcohol exposure in the first trimester, facial abnormalities and brain maldevelopment occur in concert. However, alterations in brain development that subsequently affect behavior can occur with a range of alcohol dosages throughout gestation, even when the face and brain appear to be structurally normal. Variable patterns of maternal drinking, including binge drinking resulting in significant peak levels or sustained drinking resulting in significant cumulative exposures, may lead to differential fetal outcomes. In addition, evidence suggests that variability in both maternal and fetal characteristics affects the potential for alcohol-induced alterations in brain

development. Thus, because there is no known safe threshold for PAE, it is not currently possible to define a safe limit of alcohol consumption during pregnancy.[4]

Question 4: What signs/symptoms will be useful as screening criteria?

The U.S. Surgeon General recommends regular screening of every woman of childbearing age for alcohol use. Screening should be conducted by adult primary health care clinicians and obstetric caregivers to protect the health of women and any subsequent offspring. For children, pediatric primary health care clinicians should obtain medical records about PAE and other potential risks from the birth mother's obstetric caregiver. For children who are not living with their birth parents, clinicians should obtain any available records that may provide information about PAE or other relevant family history. Clinicians should query families in a nonjudgmental way about all risks to a child's development, including maternal alcohol use prior to and during pregnancy. We recommend that clinicians be trained regarding the most effective ways to ask about alcohol use to ensure that this practice is adopted as routine.[5] Regular screening of parental alcohol use should continue as part of the process of child health supervision and developmental surveillance.

If PAE is confirmed, primary care clinicians should be alert for signs and symptoms that can occur during the child's development. Primary care clinicians should complete a comprehensive history for any child at risk for ARND that includes questions about developmental milestones, school functioning, peer and family relationships, adaptive and self-help skills, and specific areas of impairment, and they also should conduct a physical and neurological examination. A concern identified in any of these areas warrants a referral for a complete evaluation and followup. Absence of a concern should result in continued developmental surveillance of the child, as problems related to PAE may emerge during maturation, particularly during adolescence and young adulthood when latent ARND as well as other comorbidities commonly arise.

Question 5: What are the treatment needs for those diagnosed with ARND?

Given that the manifestations of PAE are heterogeneous, vary across development, and can be lifelong, treatment plans need to be multimodal and specific to the strengths and weaknesses of the affected individual and family across the lifespan. Treatment begins with support of the affected individual and family and education on the manifestations of ARND, risks for other

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[4] The 1996 IOM report on FAS describes necessary or required confirmed alcohol exposure as "a pattern of excessive intake characterized by substantial, regular intake or heavy episodic drinking. Evidence of this pattern may include frequent episodes of intoxication, development of tolerance or withdrawal, social problems related to drinking, legal problems related to drinking, engaging in physically hazardous behavior while drinking, or alcohol-related medical problems such as hepatic disease." New data are accumulating to suggest that ARND can occur at lower levels of alcohol exposure than indicated in the 1996 IOM report.

[5] See Resources for Further Information and Application at the end of this statement for a list of commonly used screening tools for parental alcohol use.

problems, and available treatments. Treatments should draw on evidence-based practices as they pertain to an individual's specific needs. Treatment should be implemented flexibly, but with fidelity, in addressing the specific developmental strengths and weaknesses of the individual and family. Modifications of evidence-based treatments should only be considered when those treatments have been implemented with integrity over an adequate period of time and have failed to yield improvement.

Some interventions for ARND have targeted common manifestations of PAE, including problems with mathematics, attention, self-regulation, adaptive functioning and problem-solving, social impairment, and working memory. Other interventions have focused on individual and group-based skills development or training of caregivers in behavior management. Large, well-controlled behavioral intervention studies specific to ARND are needed. First, studies are needed to determine whether currently available evidence-based interventions for problems common to children without PAE yield similar benefits in children with ARND. Second, when evidence indicates a reduced or inadequate benefit, modifications of existing interventions or development of entirely new interventions need to be completed and evaluated. In addition, these research objectives also may be accomplished by assessing for PAE those participants with other mental health disorders and developmental disabilities in treatment outcome studies. Finally, these studies should target children across the developmental spectrum, with special attention directed at the periods of challenging transitions from childhood to adolescence and from adolescence to adulthood.

Some medications have been shown to effectively treat emotional and behavioral problems in children. Although there is an impression that many of these medications may be less effective in children with PAE or may lead to an atypical response, the literature is sparse and inconclusive. High-quality randomized controlled trials of medication treatments are needed for individuals across the lifespan in order to identify which medications work best for the specific problems affecting individuals with ARND.

Many of the problems experienced by children with PAE manifest as academic impairments or other problems at school. Given the limited number of educational interventions specific to children with ARND, clinicians may need to draw on evidence-based educational interventions for other disorders. For any school-based educational, medical, or mental health intervention, it is particularly important to engage educators, school health and mental health professionals, and other staff in assessing, planning, and implementing the intervention with high fidelity to enhance the effectiveness of the specific intervention plan.

Problems in self-regulation and social and adaptive functioning can manifest as early as infancy and continue throughout the lifespan. For young children, it is important to educate caregivers and early intervention providers about the manifestations of ARND as well as the usefulness of specific intervention strategies for this age group. In addition, individuals with ARND can have poor decision-making skills, placing them at risk for a range of behavioral problems that may

lead to contact with school-based professionals and other community service providers who may be unaware of how ARND can affect a child's functioning. It is therefore important to help affected individuals and families become self-advocates and to broadly educate the public and relevant professionals about behavior problems associated with ARND.

In conclusion, children and youth with PAE have a Special Health Care Need[6] and should have ongoing developmental and behavioral surveillance by their primary health care clinician in a "medical home."[7] This surveillance should continue throughout their lifespan to assess ongoing treatment and referral needs.

[6] As adopted in 1998 by the American Academy of Pediatrics (AAP), children with Special Health Care Needs are those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally. This definition originally was proposed in McPherson M, Arango P, Fox HB. A new definition of children with special health care needs. *Pediatrics.* 1998;102:137–40.

[7] The AAP defines a "medical home" as one in which the care of infants, children, and adolescents is delivered or directed by well-trained physicians who provide primary care and help to manage and facilitate essentially all aspects of pediatric care. The physician should be known to the child and family and should be able to develop a partnership of mutual responsibility and trust with them. Ideally, care is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. The Affordable Care Act of 2010 endorses the medical home model throughout the lifespan. For more information, see *http://aappolicy.aappublications.org/cgi/content/full/pediatrics;110/1/184*.

Resources for Further Information and Application

Commonly Accepted Diagnostic Schemes Providing Guidelines on Diagnosing ARND:

Astley SJ. *Diagnostic guide for fetal alcohol spectrum disorders: The 4-digit diagnostic code. 3rd ed.* Seattle, WA: University of Washington Publication Services, 2004. Available online at: *http://depts.washington.edu/fasdpn/pdfs/guide2004.pdf.*

Chudley AE, Conry J, Cook JL, Loock C, Rosales T, LeBlanc N. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *Can. Med. Assoc. J.* 172(5 Suppl.):S1–S21, 2005. Available online at: *http://www.cmaj.ca/content/172/5_suppl/S1.full.*

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 Institute of Medicine criteria. *Pediatrics.* 115(1), 39–47, 2005. Available online at: *http://pediatrics.aappublications.org/content/115/1/39.full.pdf+html.*

Stratton K, Howe C, Battaglia F. (Eds.) *Fetal alcohol syndrome: Diagnosis, epidemiology, prevention, and treatment.* Washington, DC: National Academies Press, 1996. Available online at: *http://www.nap.edu/openbook.php?isbn=0309052920.*

Commonly Used Screening Tools for Screening Men and Women for Alcohol Use:

National Institute on Alcohol Abuse and Alcoholism. *Helping patients who drink too much: A clinician's guide: Updated 2005 edition.* Bethesda, MD: National Institutes of Health. Publication No. 07-3769, 2007. Available online at: *http://www.niaaa.nih.gov/Publications/EducationTrainingMaterials/Pages/guide.aspx*. (Related resources, most of which are available online only, include professional support resources, manuals, forms, and a slide show. An online training is approved for continuing medical education/continuing education credit.)

Other Alcohol Screening Instruments Recommended for Use With Women:

Barry KL, Caetano R, Chang G, DeJoseph MC, Miller LA, O'Connor MJ, et al., National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect. *Reducing alcohol-exposed pregnancies: A report of the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect*. Atlanta, GA: Centers for Disease Control and Prevention, March 2009. Available online at: *http://www.cdc.gov/ncbddd/fasd/documents/redalcohpreg.pdf.*

Acknowledgments

Conference Moderator **Tom Donaldson**, Chief Executive Officer and President, National Organization on Fetal Alcohol Syndrome, Washington, DC, maintained the smooth conduct of the meeting, ensuing ample opportunity for speaker presentations and scheduled discussions.

Expert Chair **Claire D. Coles, Ph.D.**, Professor, Departments of Psychiatry and Behavioral Sciences and Pediatrics, Emory University School of Medicine; Director, Fetal Alcohol and Drug Exposure Center, Marcus Autism Center, Atlanta, GA, led the assembled experts in presenting the available scientific and clinical evidence on ARND to the panel during public sessions.

Panel Members

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Speakers and Topics

Overview of Topic

Alcohol-Related Neurodevelopmental Disorder (ARND): Clinical and Empirical Evidence for an Independent Effect on Behavior
Claire D. Coles, Ph.D., Professor, Department of Psychiatry and Behavioral Science and Pediatrics, Emory University School of Medicine; Director, Fetal Alcohol Program, Marcus Autism Center

Question 1: What is ARND and how is it diagnosed (classical, current schemes, in practice today)?

Part A: Evidence of Central Nervous System Neurodevelopmental Abnormalities

The Role of a Neurological Exam in the Evaluation of FASD
Sterling K. Clarren, M.D., FAAP, Chief Executive Officer and Scientific Director, Canada Northwest Research Network; Clinical Professor, Pediatrics, University of Washington, Seattle, and University of British Columbia, Vancouver, British Columbia, Canada

Biobehavioral Markers of ARND
Sandra W. Jacobson, Ph.D. [presenter], and Joseph L. Jacobson, Ph.D., Professors, Department of Psychiatry and Behavioral Neuroscience, Wayne State University School of Medicine; Honorary Professors, Departments of Human Biology and Psychiatry, University of Cape Town Faculty of Health Sciences, South Africa

The Brain in Children With FASD
Elizabeth R. Sowell, Ph.D., Professor, Department of Pediatrics, University of Southern California/Children's Hospital Los Angeles, California; Director, Developmental Cognitive Neuroimaging Laboratory, University of California, Los Angeles

Animal Models of FASD: Pathologies Inform Behavior
Susan Smith, Ph.D., Professor, Department of Nutritional Sciences, University of Wisconsin, Madison

Part B: Evidence of a Complex Pattern of Behavior and Cognitive Abnormalities

Neurocognitive Profile of Children With ARND
P.W. Kodituwakku, Ph.D., Clinical Neuropsychologist and Associate Professor, Center for Development and Disability, University of New Mexico School of Medicine, Albuquerque

Socioemotional and Mental Health Issues in Individuals Prenatally Exposed to Alcohol
Mary J. O'Connor, Ph.D., ABPP, Adjunct Professor, David Geffen School of Medicine, University of California, Los Angeles (UCLA) and Training Director, UCLA Tarjan Center for Excellence in Disabilities Education, Research, and Service

ARND Symptoms of Dysregulation and Poor Adaptive Functioning
Julie A. Kable, Ph.D., Assistant Professor, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA; Assistant Director, Fetal Alcohol and Drug Exposure Center, Marcus Autism Center, Atlanta, GA

Animal Models of FASD: Focus on Behavior
Joanne Weinberg, Ph.D., Professor and Distinguished University Scholar, Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, British Columbia, Canada

Question 2: How can ARND be differentiated from other disorders?

The Role of Genetic Investigations in the Assessment of Children at Risk for FASD
Albert Chudley, M.D., FRCPC, FCCMG, Professor, University of Manitoba, Winnipeg, Canada; Medical Director, Winnipeg Regional Health Authority Program in Genetics and Metabolism, Canada

Differential Diagnosis of ARND: Other Toxic Exposures
Joseph L. Jacobson, Ph.D. [presenter], and Sandra W. Jacobson, Ph.D., Professors, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI; and Honorary Professors, Departments of Human Biology and Psychiatry, University of Cape Town Faculty of Health Sciences, South Africa

Ecological Factors: Influence of Diagnostic Criteria for ARND
Ira J. Chasnoff, M.D., President, Children's Research Triangle and Professor, Clinical Pediatrics at the University of Illinois College of Medicine, Chicago

Specificity of the Neurobehavioral Profile of ARND: Comparisons With Attention Deficit Hyperactivity Disorder (ADHD)

Jeffrey R. Wozniak, Ph.D., Associate Professor, Division of Child and Adolescent Psychiatry, University of Minnesota, Minneapolis [Presenter], and Sarah Mattson, Ph.D., Professor, Department of Psychology, San Diego State University and Associate Adjunct Professor, Department of Psychiatry, University of California, San Diego

ARND: Mechanisms of Phenotype Expression and Comorbidity
Larry Burd, Ph.D., Professor, Department of Pediatrics, University of North Dakota School of Medicine; Director, North Dakota Fetal Alcohol Syndrome Center and FAS Clinic, Grand Forks

Question 3: What prenatal alcohol exposure evidence is necessary for an ARND diagnosis?

Models of FASD/ARND: What Moderate Ethanol Exposure Paradigms Suggest About Fetal Alcohol Effects and Fetal Alcohol Exposure
Daniel Savage, Ph.D., Regents' Professor and Chair, Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque; Director, New Mexico Developmental Alcohol Research Center, Albuquerque

What Evidence Is Necessary for an ARND Diagnosis? What Do We Know About the Effects of Low and Moderate Levels of Prenatal Alcohol Exposure?
Nancy L. Day, Ph.D., Professor, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pennsylvania

What Prenatal Alcohol Exposure Is Necessary for an "ARND" Diagnosis?
Susan Astley, Ph.D., Professor, Center on Human Development and Disability, University of Washington, Seattle; Director, Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network

Population Issues and Moderators of Risk for FASD
Philip A. May, Ph.D., Research Professor, Gillings School of Global Public Health, University of North Carolina, Chapel Hill; Adjunct Professor Of Pediatrics, Sanford School of Medicine, University of South Dakota, Sioux Falls; Professor Emeritus, Center on Alcoholism, Substance Abuse, and Addictions, University of New Mexico, Albuquerque; and Extraordinary Professor, Faculty of Health Sciences, University of Stellenbosch, South Africa

Question 4: What signs and symptoms will be useful as screening criteria?

Screening for ARND in the Context of Developmental Delay and Other Red Flags: Perspectives From Primary Care and Subspecialty Practice
Christine Loock, M.D., FRCPC, DABP, Associate Professor and Developmental and Social Pediatrician, University of British Columbia, Vancouver, British Columbia, Canada

Collaboration With Schools To Screen for ARND
Molly N. Millians, D.Ed., Special Educator Evaluator, Fetal Alcohol and Drug Exposure Clinic, Marcus Autism Center, Atlanta, GA

The Minnesota Experience: Establishing Systems of Care for Fetal Alcohol Spectrum Disorders (FASD)—Screening, Referrals, Diagnosis, and Interventions
Mary Jo Spencer, R.N., CPNP, M.P.H., FASD Clinical Consultant, Minnesota Organization on Fetal Alcohol Syndrome; Pediatric Nurse Practitioner, University of Minnesota Physicians, Department of Pediatrics and University of Minnesota/St. Joseph's Home for Children Clinic Collaboration, Minneapolis, MN

Question 5: What are the treatment needs for those diagnosed with ARND?

What Are the Treatment Needs of Individuals With ARND and Their Families? General Overview
Heather Carmichael Olson, Ph.D., Faculty, Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine; Fetal Alcohol Syndrome Diagnostic and Prevention Network, Seattle Children's Hospital Child Psychiatry Outpatient Clinic, Seattle Children's Research Institute, Families Moving Forward Program

Early Intervention for Fetal Alcohol Spectrum Disorders
Blair Paley, Ph.D., Clinical Professor, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, David Geffen School, University of California, Los Angeles

Empirically Validated Treatment Approaches for School-Age Children With FASD
Joanne F. Rovet, Ph.D., Professor, University of Toronto, Ontario, Canada; Senior Scientist, Neuroscience and Mental Health Program, Hospital for Sick Children, Toronto

Treatment Needs and Interventions for Adolescents With an FASD
Jacqueline Pei, Ph.D., R.Psych., Assistant Professor, Department of Educational Psychology, and Assistant Clinical Professor, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

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Disclosure Statement

All of the panel members who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all of them signed forms attesting to this fact. Unlike the expert speakers who presented scientific data at the conference, the individuals invited to participate on the consensus panel were reviewed prior to selection to ensure that they were independent and unbiased, and not proponents of any advocacy position with regard to this topic.

Comments

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Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD)

ICCFASD (formerly called the Interagency Coordinating Committee on Fetal Alcohol Syndrome) was created in October 1996, following a recommendation in the Institute of Medicine's *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment* report that the National Institute on Alcohol Abuse and Alcoholism chair a broad Federal effort to coordinate activities associated with FAS and related health conditions. The mission of ICCFASD is to enhance and increase communication, cooperation, collaboration, and partnerships among disciplines and Federal agencies to address health, education, developmental disabilities, alcohol research, and social services and justice issues that are relevant to disorders related to prenatal alcohol exposure. (More information about ICCFASD, its mission, vision, membership, work groups, and past activities is available at *http://www.niaaa.nih.gov/AboutNIAAA/Interagency/Pages/default.aspx*.)

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FASD Resources

Several organizations are involved in ongoing research, program evaluation, and advocacy for improved diagnosis, treatment, and public awareness of FASD, including ARND. A few of these organizations are:

Centers for Disease Control and Prevention, Fetal Alcohol Spectrum Disorders, at *http://www.cdc.gov/ncbddd/fasd/index.html*.

National Institute on Alcohol Abuse and Alcoholism, at *http://www.niaaa.nih.gov*.

Substance Abuse and Mental Health Services Administration, FASD Center for Excellence, at *http://www.fasdcenter.samhsa.gov*.

American Academy of Pediatrics, at: *http://aappolicy.aappublications.org/index.dtl*.

Collaborative Initiative on Fetal Alcohol Spectrum Disorders, at *http://www.cifasd.org*.

Fetal Alcohol Spectrum Disorders Study Group, at *http://fasdsg.org*.

National Organization on Fetal Alcohol Syndrome, at *http://www.nofas.org*.

Initiative of the

Diagnostic Issues Work Group

Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders

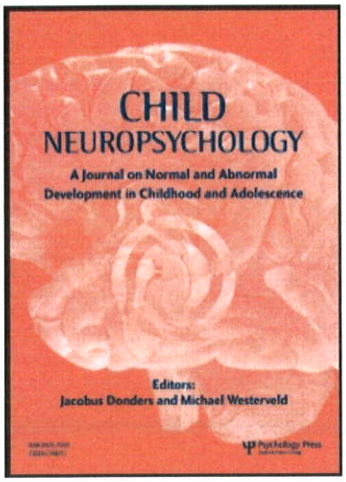
Sponsored by the

Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health

Centers for Disease Control and Prevention

American Academy of Pediatrics



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Executive Functioning Predicts Social Skills Following Prenatal Alcohol Exposure

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EXECUTIVE FUNCTIONING PREDICTS SOCIAL SKILLS FOLLOWING PRENATAL ALCOHOL EXPOSURE

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Adverse sequelae of prenatal alcohol exposure include executive function and social skills impairments, although these two domains have not been empirically linked in alcohol-exposed individuals. This study investigated this relationship using the BRIEF and the SSRS in 98 children aged 6 to 11 years. Executive functions explained a significant percentage of variance in parent and teacher rated social skills. No differences were found among children with diagnoses of FAS, partial FAS, or alcohol-related neurodevelopmental disorder. It may be helpful to consider executive functioning in designing social skills interventions for alcohol-exposed children whether or not they have full FAS.

INTRODUCTION

Background

In 1996, the Institute of Medicine (IOM; Stratton, Howe, & Battaglia, 1996) released a report containing broadly defined diagnostic criteria for fetal alcohol syndrome (FAS), partial FAS, alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorders (ARND). These diagnostic categories represent a continuum of effects due to in utero alcohol exposure and are subsumed under the rubric of fetal alcohol spectrum disorders (FASD). Full FAS is estimated to occur in .5 to 2 infants per 1000 live births in the United States (May & Gossage, 2001) and is reported to be the leading known nongenetic cause of mental retardation (NIAAA, 2000; Pulsifer, 1996). The incidence of FASD that includes FAS, partial FAS, ARBD, and ARND is estimated to affect 1 in 100 children (May & Gossage, 2001). The high incidence of prenatal alcohol exposure in combination with reports of rising rates of binge drinking in pregnant women (CDC, 2002) indicate that prenatal alcohol exposure continues to represent a significant public health concern.

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Neuropsychological Sequelae

Among the most striking outcomes for individuals with FASD are CNS abnormalities (Mattson & Riley, 1998) that include structural anomalies in the brain in loci such as the corpus callosum, cerebellum, and caudate nucleus of the basal ganglia (Mattson et al., 1996; Riley, McGee, & Sowell 2004). This latter structure, part of the frontal-subcortical circuitry necessary for higher cognitive functions (Cummings, 1993), is particularly interesting as this population is known to have impaired neurocognitive abilities, many of which are subsumed under the area of executive functioning (EF). EF refers to an individual's ability to engage in cognitive processing in novel situations in order to reach a desired goal (Lezak, 2004). Such problems appear to be pronounced in children and adults with prenatal alcohol exposure (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Kodituwakku, Kalberg, & May, 2001; Mattson et al., 1999; Noland et al., 2003). These deficits are particularly debilitating, as they affect the extent to which an individual functions independently. These deficits involve difficulty with novel problem solving, planning behavior before action, working with more than one bit of information in memory at a time (i.e., working memory), inhibiting behavior in order to maximize effectiveness in a situation, or exhibiting flexibility in one's thinking and behavior. All of these deficits have been described in individuals with prenatal alcohol exposure with and without FAS (Adnams et al., 2001; Carmichael Olson et al., 1998a; Connor et al., 2000; Kodituwakku et al., 1995; Kodituwakku et al., 2001; Korkman et al., 1998; Mattson et al., 1999; Rasmussen, 2005; Schonfeld et al., 2001). Alcohol-exposed children have been noted by Kodituwakku and colleagues to have EF difficulties in working memory, flexibility, and planning, when compared to nonexposed children with similar verbal abilities. Tests employed measured nonverbal matrix reasoning, auditory attention, phonemic fluency, set shifting, and planning ability (Kodituwakku et al., 1995). Mattson and associates (Mattson et al., 1999) also demonstrated several EF deficits in prenatally exposed children with and without FAS. Children with FAS had more difficulty on tests of cognitive flexibility than children with exposure but without FAS, although both groups had difficulties on tests of inhibition and verbal reasoning. Schonfeld, Mattson, and Riley (Schonfeld et al., 2001) reported nonverbal fluency deficits above and beyond deficits in general intellectual functioning, demonstrating that fluency deficits were not restricted to just the verbal domain.

Social Skills Deficits

Social information-processing theory suggests that skills related to EF are necessary for social interaction (Crick & Dodge, 1994) and some neuropsychological literature points to EF as a necessary component for social competence (Lezak, 2004). Some evidence of association between EF and social deficits exists for children with developmental disabilities including those with autism or congenital brain dysfunction (McEvoy et al., 1993; Warschausky et al., 2003). However, no study has examined the association between EF and social skills in children with prenatal alcohol exposure. This lack of investigation is surprising given the evidence for poor EF in children with prenatal alcohol exposure and clinical reports describing impaired social behavior in these children such as poor social judgment and failure to learn from experience. Additionally, children with prenatal alcohol exposure have been described as exhibiting

indiscriminant social behavior and as having difficulties considering the consequences of actions, understanding social cues, and communicating in social contexts (Carmichael Olson et al., 1998a; Carmichael Olson et al., 1998b; Streissguth & Kanter, 1997; Streissguth et al., 1991). When rated by both caregivers (Roebuck, Mattson, & Riley, 1999) and teachers (Brown et al., 1991), children with prenatal alcohol exposure have been found to have poorer social skills than nonexposed controls even when compared to peers with similar verbal IQs (Thomas, Kelly, Mattson, & Riley, 1998). Similarly, in a comparison of clinic-referred alcohol-exposed and nonexposed children, socialization scores were significantly more impaired at most ages for the former group, and most significant in older alcohol-exposed children (Whaley, O'Connor, & Gunderson, 2001). Further, social skills deficits exhibited by children with a diagnosis of FAS did not differ significantly from deficits seen in children without the full syndrome, suggesting that impairments in social behavior are not specific to children with the most severe form of exposure.

Implications of Social Skills Deficits

The above findings are important for several reasons. It has been shown that poor social skills put children at risk for delinquency later on (Kupersmidt, Coie, & Dodge, 1990). One possible explanation for this linkage is that the child with impaired social behavior may be rejected by well-adjusted peers and then left to socialize with maladaptive or socially deviant children where he/she may be accepted more easily. This is concerning in light of reports that individuals with prenatal alcohol exposure have high rates of trouble with the law and that those with exposure, but without FAS, appear to be more vulnerable (Fast, Conry, & Loock, 1999; Schonfeld et al., 2005; Streissguth, Barr, Kogan, & Bookstein, 1996; Streissguth et al., 2004). This was most recently demonstrated in a study on moral judgment and delinquent behavior in which children without full FAS were more likely to engage in delinquent behavior suggestive of conduct problems (Schonfeld et al., 2005). Thus, children with prenatal alcohol exposure who lack the full syndrome appear to be at equal or greater risk for delinquent behaviors compared to those with full FAS. Based on reports of other socially impaired populations, this vulnerability to delinquency may be mitigated by improved social behavior.

Study Aims

Deficits have been identified on standardized EF tasks administered to alcohol-exposed children in a laboratory setting; however, it is unknown how these deficits affect daily interactions with others (i.e., functional deficits at home and school). It has been suggested that separate frontal brain regions mediate EF test performance and behavior, including social skills, potentially making laboratory tests of EF poor predictors of affective and social interactions (Sarazin et al., 1998). Therefore, the purpose of this study was to investigate how standardized functional measures of EF related to social skills in the child's day-to-day encounters, as reported by both parents and teachers. A second aim was to examine the neurocognitive and social functioning of children with different diagnoses in the fetal alcohol spectrum of disorders to determine whether or not significant differences in EF and social skills existed.

METHODS

Participants

Participants consisted of 98 children with prenatal alcohol exposure between the ages of 6 and 11 years. All children had documented prenatal alcohol exposure, measurable social skills deficits, and a verbal IQ of ≥ 70.[1] IQ estimates were obtained from the *Kaufman Brief Intelligence Test* (Kaufman & Kaufman, 1990). Children were excluded from the study if they had medical conditions that might preclude study participation, major sensory or motor deficits, or a diagnosis of pervasive developmental disorder. All children scored one standard deviation or more below the mean in socialization with a mean standard score of 62.8 (*SD* = 8.1) on the *Vineland Adaptive Behavior Scales* (Sparrow, Balla, & Cicchetti, 1984).

The majority of the children resided in adoptive or foster homes as opposed to biological homes, although some adoptive families were biologically related (e.g., kinship care such as grandparents = 21%). See Table 1 for participant demographics.

Physical Examination and Diagnosis

Every child received a physical examination to assess for the presence of the diagnostic features of FASD using the *Diagnostic Guide for Fetal Alcohol Syndrome (FAS) and Related Conditions* (Astley, 2004; Astley & Clarren, 1999). This system uses a four-digit diagnostic code reflecting the magnitude of expression of four key diagnostic features of prenatal alcohol exposure: (1) growth deficiency; (2) the FAS facial phenotype,

Table 1 Participant Characteristics.

Variable	
Gender (%)	
Males	52
Females	48
Age (yr)	
Mean (*SD*)	8.61 (1.5)
Ethnicity (%)	
Caucasian	53
Hispanic	17
African-American	17
Other	12
Composite IQ	
Mean (*SD*)	97.1 (15.1)
Verbal IQ	
Mean (*SD*)	93.5 (15.1)
Home Placement (%)	
Biological	21
Nonbiological	79
Maternal Education (yrs)	
Mean (*SD*)	16.33 (2.6)

[1]For a minority of children recently adopted from Russia (n = 3/13), Verbal IQ's lower than 70 were accepted if a 95% confidence interval around this score included 70 and if estimates of their Nonverbal IQs were greater than 70. The mean Verbal IQ presented for this sample includes these three children.

including short palpebral fissures, flat philtrum, and thin upper lip; (3) Central Nervous System (CNS) dysfunction; and (4) gestational alcohol exposure. Using the four-digit diagnostic code, the magnitude of expression of each feature was ranked independently on a four-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting the full manifestation of the feature. The study physician administered this examination after achieving reliability with the lead investigator.

History regarding prenatal alcohol exposure was obtained from the biological mothers by self-report using the *Health Interview for Women* (O'Connor, Kogan, & Findlay, 2002), and/or through collateral reports by caregivers who had observed the biological mother drinking during pregnancy. For adopted or foster children, medical or legal records were obtained documenting known exposure.

Using Astley's adaptation (Astley, personal communication) of the four-digit diagnostic system to fit IOM criteria, 10 children were diagnosed with FAS, 45 with partial FAS, and 43 with ARND. No child met criteria for ARBD.

Procedures

The University of California at Los Angeles and the Centers for Disease Control and Prevention Institutional Review Boards approved all procedures and a Certificate of Confidentiality was obtained from the NIAAA prior to participant recruitment. Participants were recruited through various clinical and community contacts, including the UCLA child psychiatry programs. Letters and fliers were mailed to local health care providers, nonclinical community contacts (e.g., YMCA) and were posted within the UCLA Medical Center and the community. Web based information on the program was also posted. Interested participants contacted the project and a project coordinator conducted a screening interview by telephone to determine initial eligibility. If participants were initially eligible, testing was scheduled prior to initiating a social skills intervention for a larger study examining the efficacy of parent-assisted social skills training following prenatal alcohol exposure. Ineligible families were provided with a list of social skills program referrals in the local community. Following consenting procedures, the child and parent(s) participated in testing that involved obtaining demographic information, child IQ, the physical examination, and parent report of EF and social skills. Subsequently, and with parent consent, teachers were mailed a teacher version of the social skills measure to complete and return.

Measures

Demographic questionnaire. All participants completed a demographic questionnaire developed especially for the study. Demographic variables included child gender, age, ethnicity, percent time in the United States, family living arrangement (biological/nonbiological home), number of placements, and maternal education.

The Behavior Rating Inventory of Executive Functioning (BRIEF). The BRIEF (*Gioia et al., 2000*) is a parent report measure of the child's executive functioning standardized for children ages 5–18. This scale reports high internal consistency (Cronbach's alpha = .80–.98) and test-retest reliability for normative (.81) and clinical (.79) samples. Convergent validity has been established with other measures of inattention, impulsivity, and learning skills and divergent validity demonstrated against measures of emotional and behavioral functioning. There are eight clinical subscales that comprise

two indices: The Behavioral Regulation Index (BRI) and the Metacognition Index (MI). The BRI includes subscales of Inhibit (controls impulses), Shift (transitions and solves problems flexibly and as appropriate for a situation), and Emotional Control (monitors emotional responses appropriately). The MI includes Initiate (begins tasks independently), Working Memory (maintains information in mind during tasks in order to complete task), Plan/Organize (plans behavior to reach future goals and carries out steps in a systematic manner), Organization of Materials (keeps possessions and work/play spaces orderly), and Monitor (self-monitors work or behavior during and after tasks). The instrument is scaled using *T*-Scores of which a 65 (1.5 *SD* above the mean) or higher is considered clinically significant (higher scores indicate poorer executive functioning).

Social Skills Rating System (SSRS). Social skills were evaluated with the Social Skills Rating System, Parent (SSRS-P) and Teacher (SSRS-T) Forms (Gresham & Elliott, 1990). The SSRS measures a child's competence with respect to social skills and also measures the extent to which problem behaviors of clinical significance are present. Two main subscales comprise the SSRS: Social Skills and Problem Behaviors, presented as standard scores ($M = 100$; $SD = 15$). This scale reports high internal consistency (Cronbach's alpha = .84–.90) and test-retest reliability for teacher (.84–.85) and parent ratings (.65–.87) on the two main subscales. Correlations between teacher and parent ratings range from .60–.80. The SSRS also demonstrates high criterion related validity, correlating significantly with other established measures of child social and problem behaviors by parent and teacher report (Gresham & Elliott, 1990). The Social Skills subscale is comprised of the following domains: Cooperation (helping, sharing, and complying with rules and directions), Assertion (initiating social behaviors such as introducing self or responses to others actions), Responsibility (the ability to communicate with adults and regard for property or work), and Self-Control (how conflict and nonconflict peer situations are handled). Responsibility is measured only on the parent rating form. Lower standard scores on this subscale represent poorer functioning (≤1 *SD* below the mean indicates fewer social skills than average). The Problem Behaviors subscale is comprised of Internalizing (anxiety, poor self-esteem), Externalizing (aggression, bad temper), and Hyperactivity (impulsivity, fidgety) domains. Higher standard scores on this subscale represent greater problem behaviors (≥1 *SD* above the mean indicates more problem behaviors than average).

Data Analysis Plan

Bivariate correlations were used to identify potential confounding variables that might be associated with social skill development. Any potential covariate that was significantly correlated with the SSRS was included in subsequent analyses examining the relation between EF and social behavior. To reduce the number of potential predictors from the BRIEF, bivariate correlations were used to examine the relationship between BRIEF subscales (described above) and the SSRS subscales (Social Skills and Problem Behaviors). Specific subscales found to be significantly correlated served as predictors. Multiple regressions were used to test the main hypotheses that parent-reported BRIEF scores were predictive of parent and teacher-reported social skills using the SSRS Social Skills and Problem Behaviors subscales. All significant covariates and BRIEF predictors were entered simultaneously in each regression equation. This method allows for examination of the association of each predictor variable to the outcome variable after controlling for all other variables.

RESULTS

Tests for Potential Covariates

First, bivariate correlations among demographic variables and SSRS standard scores were calculated to test for possible covariates that might relate to social skill development. These variables included: child age, IQ, number of previous home placements, percent of lifetime living in the United States, years of maternal education, gender, biological/nonbiological home placement, and ethnicity. Results revealed that child age was significantly correlated with the Social Skills ($r = .24$; $p = .02$) and Problem Behaviors ($r = -.20$; $p < .05$) standard scores identified by the parents on the SSRS-P. Parents identified older children as having higher social skill development and fewer problem behaviors. Data for 92 children were available on the SSRS-T and IQ was found to be related to the Problem Behaviors standard scores ($r = -.23$; $p < .05$), suggesting that teachers perceived children with lower IQs as having more problem behaviors. Number of home placements, percent of lifetime living in the United States, and years of maternal education were not significantly correlated with the SSRS-P or SSRS-T standard scores ($ps > .05$). Using analysis of variance (ANOVA), no differences were found between ethnic groups on any of the outcome variables, therefore for the purposes of correlational analysis, ethnicity was changed to a categorical variable (white and nonwhite) that revealed no significant relationship to the outcome variables ($ps > .05$). Female gender was significantly related to parent report on the Social Skills subscale ($r = -.21$; $p < .05$), but not Problem Behaviors. Gender was unrelated to teacher report of Social Skills or Problem Behaviors. Results from the analysis on biological versus nonbiological home placement revealed that children raised in nonbiological homes received higher ratings by both parents and teachers on Problem Behaviors ($r = -.26$; $p < .01$; $r = -.23$; $p < .05$) but not for the Social Skills subscale ($ps > .05$).

Selection of EF Predictor Variables for Regression Analyses

Simple correlations between the parent BRIEF subscales and parent and teacher SSRS subscales (Social Skills and Problem Behaviors) were computed in order to determine which independent variables were related to the outcome variables. Because the individual BRIEF subscales did not suggest that specific EF abilities were more strongly related to Social Skills or Problem Behaviors on the SSRS when compared to the BRIEF Index scores, the BRIEF Behavioral Regulation Index (BRI) and Metacognition Index (MI) served as the predictor variables of interest in the regression analyses. Four separate regression analyses were computed for each of the SSRS standard scores that served as outcome variables (Social Skills-P, Problem Behaviors-P, Social Skills-T, and Problem Behaviors-T). The statistical significance of the overall model, individual standardized beta coefficients, and significance levels were calculated. See Table 2.

SSRS-P Social Skills

Since age and gender were significantly related to parent ratings of Social Skills, they were entered into the regression equation with the BRIEF BRI and MI. The overall model was significant (F (4, 93) = 16.44; $p < .001$, $R^2 = .41$). Analyses revealed that

Table 2 Predictors of Parent and Teacher Rated Social Skills and Problem Behaviors on the SSRS.

Predictors	b	Std Error	β
Predictors of parent-rated Social Skills			
BRIEF BRI	−.62	.12	−.58**
BRIEF MI	2.69	.15	.02
Age	.11	.06	.16
Gender	−6.11	2.12	−.23**
Predictors of parent-rated Problem Behaviors			
BRIEF BRI	.67	.12	.59**
BRIEF MI	.16	.14	.12
Age	−5.8	.06	−.08
Home Placement	.91	2.66	.03
Predictors of teacher-rated Social Skills			
BRIEF BRI	.11	.14	−.10
BRIEF MI	−.42	.18	−.30*
Predictors of teacher-rated Problem Behaviors			
BRIEF BRI	.50	.16	.40**
BRIEF MI	3.95	.20	.03
IQ	−.21	.10	−.22*
Home Placement	3.61	3.58	.10

Note: SSRS = Social Skills Rating System; BRIEF = Behavior Rating Inventory of Executive Functioning; BRI = Behavior Regulation Index; MI = Metacognition Index.

*$p < .05$; **$p < .01$.

gender and BRI remained significant predictors indicating that girls with prenatal alcohol exposure who were rated as having poorer behavioral regulation were viewed by parents as having more social skill deficits.

SSRS-P Problem Behaviors

Since age and home placement were significantly related to parent ratings of Problem Behaviors, they were entered into the regression equation with the BRIEF BRI and MI. The overall model was significant (F (4, 93) = 22.48; $p < .001$, $R^2 = .49$). The analysis revealed that only the BRIEF BRI was a significant predictor after controlling for age and home placement. This indicates that parent ratings of poorer behavioral regulation were highly associated with higher rates of problem behaviors in children with prenatal exposure to alcohol.

SSRS-T Social Skills

For teacher ratings of Social Skills, only the BRIEF BRI and MI were found to be statistically related and were entered into the regression equation. Although the overall model was significant (F (2, 89) = 7.29; $p < .01$, $R^2 = .14$), in contrast to parent ratings, teachers viewed metacognition as the most relevant predictor of social skills in children with *in utero* alcohol exposure.

SSRS-T Problem Behaviors

Since IQ and home placement were significantly related to teacher's ratings of Problem Behaviors, they were entered into the regression equation with the BRIEF BRI and MI. The overall model was significant (F (4, 87) = 7.45; $p < .001$, $R^2 = .26$). Analyses revealed that the BRIEF BRI and IQ remained significant suggesting that teachers view poorer behavioral regulation and lower intellectual functioning as the best predictors of increased problem behaviors in children with prenatal alcohol exposure.

EF and Social Skills Development as a Function of Diagnostic Classification

In order to determine whether or not children belonging to different diagnostic categories would differ on either EF or social skills development, one-way ANOVAs were conducted using the diagnostic categories of FAS, partial FAS, and ARND as the independent variables. Scores on the BRIEF BRI and MI and on the SSRS Social Skills and Problem Behaviors subscales served as the dependent variables. Results revealed that the groups did not differ significantly on the dependent variables of interest ($ps > .05$). In spite of a failure to find differences across different diagnostic classifications, mean scores revealed that children in all groups scored in the clinical range on all dependent variables as reported by their parents, and either scored in the clinical range or approached clinical significance on reports by their teachers. See Figures 1–2 for pattern of performance across diagnostic groups on the BRIEF and SSRS.

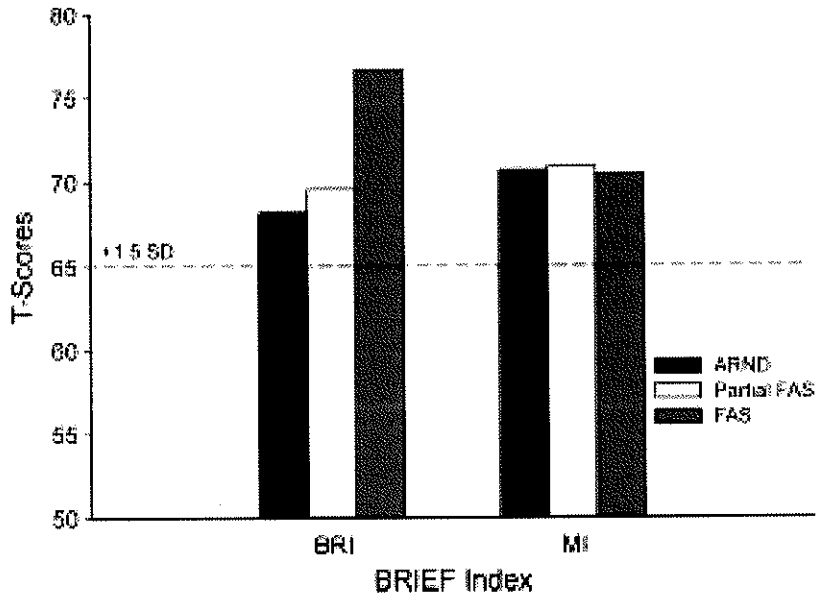

Figure 1 Performance of FAS, Partial FAS, and ARND subgroups on the BRIEF Behavioral Regulation Index (BRI) and Metacognition Index (MI).

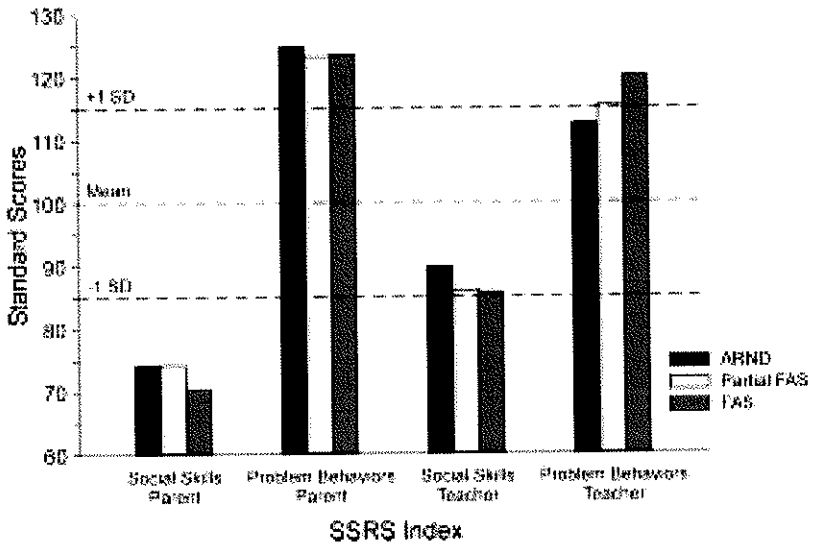

Figure 2 Performance of FAS, Partial FAS, and ARND subgroups on the SSRS Parent and Teacher rated Social Skills and Problem Behaviors subscales.

DISCUSSION

Both executive functioning (EF) deficits (which include poor planning, organization, understanding consequences of actions, and learning from past behavior) and social skills deficits have been reported for individuals with prenatal alcohol exposure, regardless of FAS diagnosis (Connor, 2000; Kodituwakku et al., 1995; Kodituwakku et al., 2001; Mattson et al., 1999; Rasmussen, 2005; Roebuck et al., 1999; Whaley et al., 2001). Although EF impairment has been shown to be related to poor social functioning in children with developmental disabilities (McEvoy et al., 1993; Warschausky et al., 2003), the current study is the first to demonstrate this relationship for children prenatally exposed to alcohol. Consistent with previous reports on children with *in utero* alcohol exposure, the current study revealed clinically significant impairment in EF and social functioning as reported by both parents and teachers. In addition, the primary hypothesis in this study was supported in that functional neurocognitive deficits in EF were predictive of the social behaviors in these children. Importantly, it was both parent and teacher ratings of social behavior that were predicted by parent ratings of EF exclusively. This underscores the fact that the pervasive EF deficits in this population impact their poor social behaviors across multiple settings. Specifically, according to parent report, difficulty with regulation of behavior as defined by the BRIEF BRI (e.g., ability to be flexible appropriately in a situation and regulate one's own emotions by being able to inhibit more automatic or competing responses) was predictive of poorer social skills as defined by the SSRS (e.g., cooperation, initiating conversations, making friends, and responding appropriately in conflict situations). Poor behavioral regulation, according to parents, was also predictive of greater problem behaviors (e.g., aggression, temper, low self-esteem, or impulsivity) as defined by the SSRS. Teachers' reports indicated that metacognition, as measured by the BRIEF MI (i.e., the child's ability to plan, problem solve, and self-manage and monitor task performance), was the most important indicator of social competence. Teachers also viewed children with lower IQs and poor behavioral

regulation as having more behavioral problems. The finding that predictors (i.e., parent-rated EF) of parent and teacher rated social skills were different may be attributable to the fact that teachers observe children in structured academic settings, thereby having a greater opportunity to evaluate cognitive skills (e.g., metacognition used by children when interacting with their peers) whereas parents may view the child's ability to behave appropriately (e.g., behavioral regulation) with other children in less structured play situations in the home environment as more important. In particular, girls with poor behavioral regulation skills were perceived by their parents as having poorer social skills although, clinically, the magnitude of difference from boys was small. Results may suggest that for girls to be identified as needing treatment, they must have more significant behavioral problems as opposed to boys who may be identified and targeted for intervention more easily. Support for this hypothesis comes from studies of children with ADHD in which more severe social deficits in girls with ADHD have been reported (Rucklidge & Tannock, 2001).

Consistent with the literature (Whaley et al., 2001), when the three diagnostic groups in the spectrum of fetal alcohol disorders (FAS, partial FAS, ARND) were compared, EF and social skills were clinically impaired across all groups and no statistically significant group differences were found. The similar profile of deficits in children with FAS and in those with prenatal alcohol exposure who did not meet the full criteria for FAS has important clinical implications associated with the identification and treatment of children falling along the continuum of prenatal alcohol effects. Children with prenatal alcohol exposure but without FAS are likely to be in equal need of services, but they may be less likely to receive them. Further, there are more children with exposure, but without FAS than children with FAS. Notably, many of these children will have IQs that do not fall in the range of mental retardation (and consequently they are less likely to be identified as needing services), but nonetheless exhibit significant impairments in other important domains (e.g., executive functioning and social skills). Thus, the majority of children affected by prenatal alcohol exposure may potentially be overlooked for interventions that, if provided, could greatly enhance their ability to function more adaptively in society. Consequently, appropriately tailored assessments should be conducted for all children with fetal alcohol spectrum disorders so that resources may be allocated to those in need, not simply based on diagnostic classification.

Some limitations and directions for future study emerge from this investigation. First, while not ideal, it is common in the literature on prenatal alcohol exposure to have only retrospective accounts of alcohol exposure from the biological mother and/or to rely on records or collateral reports for this information as was necessary for this study. Second and also common among children exposed to alcohol prenatally, the majority of children did not reside with their biological parents. Our study showed that biological parents rated their children more favorably on EF and social skills, so it would be helpful in future studies to investigate EF and social skills in children remaining in their biological homes using a larger sample. Third, children with mental retardation (MR) were not included in this study because the larger study of which this was part focused upon a social skills program for children without significant cognitive delays. As this limits the representation of prenatally exposed children in the sample, it is possible that as child IQ decreases into the range of mental retardation, ratings of EF and social skills would be more dependent on intellectual functioning than was found in the current study. Fourth, although this study utilized parent report measures of EF, it would be important in future study to corroborate this information with direct cognitive measures of EF administered to the child.

These findings suggest that tailoring interventions in accordance with an individual's neurocognitive challenges in mind (i.e., EF) may be important when developing treatment

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