A Prospective Cohort Study of the Prevalence of Growth, Facial, and Central Nervous System Abnormalities in Children with Heavy Prenatal Alcohol Exposure

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Background: Most children who are exposed to large quantities of alcohol in utero do not develop fetal alcohol syndrome (FAS). Population-based prospective data on the risk of developing components of fetal alcohol spectrum disorders (FASD), however, are limited.

Methods: This was a prospective cohort study of 9,628 women screened during their first prenatal appointment in Chile, which identified 101 who consumed at least 4 drinks/d (exposed) matched with 101 women with no reported alcohol consumption during pregnancy (unexposed). Detailed alcohol consumption data were collected during the pregnancy. Children were evaluated up to 8.5 years of age by clinicians masked to exposure status.

Results: One or more functional central nervous system abnormalities were present in 44.0% (22/50) of the exposed children compared to 13.6% (6/44) of the unexposed ($p = 0.002$). Growth restriction was present in 27.2% (25/92) of the exposed and 12.5% (12/96) of the unexposed ($p = 0.02$). Abnormal facial features were present in 17.3% (14/81) of the exposed children compared to 1.1% (1/89) of the unexposed children ($p = 0.0002$) by direct examination. Of the 59 exposed children with data available to detect at least 1 abnormality, 12 (20.3%) had no abnormalities. Binge drinking from conception to recognition of pregnancy (OR = 1.48 per day, 95% CI: 1.15 to 1.91, $p = 0.002$) and after recognition of pregnancy (OR = 1.41 per day, 95% CI: 1.01 to 1.95, $p = 0.04$) and total number of drinks consumed per week from conception to recognition of pregnancy (OR = 1.02 per drink, 95% CI: 1.01 to 1.04, $p = 0.0009$) were significantly associated with abnormal child outcome.

Conclusions: After exposure to heavy alcohol consumption during pregnancy, 80% of children had 1 or more abnormalities associated with alcohol exposure. Patterns of alcohol use that posed the greatest risk of adverse outcomes were binge drinking and high total weekly intake. Functional neurologic impairment occurred most frequently and may be the only sign to alert physicians to prenatal alcohol exposure.

Key Words: Alcohol, Pregnancy, Fetal Alcohol Spectrum Disorders, Growth Restriction, Neurodevelopment.

ALTHOUGH PRENATAL EXPOSURE to alcohol is the most common environmental cause of intellectual impairment, the vast majority, 90 to 95%, of children exposed to large quantities of alcohol in utero do not develop fetal alcohol syndrome (FAS; Cronk and Weiss, 2007; Ornoy and Ergaz, 2010). FAS is characterized by abnormalities in 3 areas—growth restriction, central nervous system (CNS) impairment, and a distinctive pattern of dysmorphic facial features. Fetal alcohol spectrum disorders (FASD) is an umbrella term used to define the full spectrum of adverse outcomes that can be associated with prenatal alcohol exposure. Diagnostic classifications such as FAS, partial fetal alcohol syndrome (PFAS), and alcohol-related neurodevelopmental disorders fall under the umbrella of FASD. Establishing population-based prevalence and other epidemiologic characteristics of FASD has been a challenge owing to limitations in prenatal screening, variations in methodology, and incomplete data (May et al., 2009).

Moreover, there is limited information available on how quantity and patterns of alcohol intake influence the likelihood that a child will develop FAS or other outcomes under the umbrella of FASD. Animal models have suggested that

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the peak blood alcohol concentration is correlated with damage to the fetus (Bonthius et al., 1988; Gladstone et al., 1996; Maier et al., 1995). A systematic review of the effects of binge drinking during pregnancy in humans found no convincing evidence that it increased the risk of low birth weight, growth restriction, or birth defects, but could not rule out a possible effect on neurodevelopmental outcome (Henderson et al., 2007).

In the current study, we prospectively identified a cohort of pregnant women consuming large amounts of alcohol during pregnancy and followed their children for up to 8.5 years to evaluate the prevalence of growth restriction, CNS abnormalities, and facial dysmorphology. Detailed alcohol data were collected during the pregnancy to determine how the quantity and pattern of maternal alcohol consumption affected each of these adverse child outcomes.

MATERIALS AND METHODS

Subjects

The subjects were part of the National Institute of Child Health and Human Development (NICHD)—University of Chile Alcohol in Pregnancy Study, which is a prospective cohort study. The study methods for the maternal component of this study have previously been reported in detail (Aros et al., 2006). In brief, 9,628 (of 10,917) women receiving prenatal care at a community health clinic in Santiago, Chile, were assessed for prenatal alcohol use between August 1995 and July 2000. Using a home visit for confirmation of consumption, we enrolled a group of 101 women who reported alcohol consumption of at least 48 g (approximately 2 ounces or 4 drinks) of absolute alcohol daily. Women who were classified to be nondrinkers ($n = 101$) during pregnancy, after home visits, served as the unexposed group and were matched for maternal age and parity.

Alcohol Exposure

Detailed data were collected for 2 representative weeks during the pregnancy: one from conception to recognition of pregnancy and one after recognition. The woman was asked to describe the quantity, frequency, and type of alcoholic drinks consumed each day of the week. From this, the interviewer determined and recorded in grams the woman's alcohol consumption. Data were standardized with 1 drink equaling 12 g. Alcohol consumption was then classified by total amount (in grams) consumed during the week, average daily amount (in grams) consumed on days when alcohol was consumed, the peak alcohol intake (in grams) on the day in which the most alcohol was consumed, and the number of days in which >60 g of alcohol was consumed (representative of binge drinking). Alcohol consumption in the weeks from conception to recognition of pregnancy and after recognition of pregnancy was analyzed separately. Data were also collected on maternal history of alcohol consumption prior to this pregnancy and physical response to alcohol represented by episodes of dizziness. Additionally, the interviewer classified the perceived reliability of each mother interviewed.

Child Assessment Protocol

Both the exposed and unexposed children were followed for up to 8.5 years after the start of the study. Birth weight, length, occipital frontal circumference (OFC), and gestational age were documented between 24 and 48 hours after birth by a single physician. Weight, length, and OFC were measured by a trained nurse at 1 month, then every 6 months between 6 months and 3 years of age, and then annually until study completion. A complete neurologic examination was scheduled for ages 6 months, 1 year, and then annually up to 6 years. The pediatric neurologists' evaluation included cranial nerve function and motor performance (including strength, tone, reflexes, and coordination). Age-appropriate standardized testing (Bayley Scales of Infant Development [BSID], Wechsler Preschool and Primary Scale of Intelligence [WPPSI], and Wechsler Intelligence Scale for Children [WISC]) was administered and interpreted by a psychologist at ages 2, 5, and 7 years, respectively. Dysmorphology assessments by a pediatric geneticist with extensive experience in FAS were scheduled for ages 1 month, 6 months, 1 year, and then annually. She focused on facial features —palpebral fissure length, philtrum length and shape, thin upper vermilion border, epicanthal folds, flat nasal bridge, anteverted nares, ear shape and length, and palmar creases—previously associated with fetal alcohol exposures. After each examination, she classified each child as having abnormal facies either highly suggestive for FAS or not concerning for FAS. Frontal and profile photographs were taken at each genetic appointment using a 35-mm film camera. The photographs were scanned and sent to Dr. Susan Astley in Seattle, Washington, for quantitative measurement using the FAS Facial Photographic Analysis Software and Lip-Philtrum Guide (Astley, 2003). All examinations and testing were performed by examiners masked to exposure status and results of other evaluations. When a family missed an appointment, attempts were made to contact them via home visits or telephone calls.

Children were classified based on all data available using the following criteria. Growth restriction was defined as the presence of a birth weight ≤ 10 percentile or birth length ≤ 10 percentile, or the presence of at least 2 childhood weights or heights ≤ 10 percentile on National Center for Health Statistics 2000 charts. The FAS facial phenotype was defined in accordance with each of the following criteria: the geneticist's evaluation and the 4-Digit Code FASD guidelines (Astley, 2004). If data on facial features were available for more than 1 age, the age when the FAS phenotype was expressed the most was used for determination. Criteria for CNS abnormalities were considered in 2 separate categories: structural and functional abnormalities. A CNS structural abnormality was defined as 1 or more OFC measures (birth or later) ≤ 10 percentile on standard Chilean growth charts. A functional abnormality was defined as 1 or more of the following: (i) any standardized score ≤ 80 on the BSID (Mental Development Index or Psychomotor Developmental Index), WPPSI, or WISC; and/or (ii) a suspicion of language delay plus hyperactivity, attention deficit, or both. A standard score of ≤ 80 was chosen to represent functional delay based on the classification of borderline deficiency in intelligence on the Stanford Revision of the Binet–Simon Scale of Intelligence. Children had to be at least 1 year of age for consideration of language delay and 3 years for hyperactivity or attention deficit. We had insufficient data to assess neurologic abnormalities reliably (e.g., motor problems or seizures).

Statistical Analysis

Demographic variables and child outcomes were compared using Student's *t*-test, Fisher's exact test, or the Wilcoxon's rank sum test. A 2-tailed $\alpha < 0.05$ was considered statistically significant. Unconditional logistic regression was used to compute odds ratios and 95% confidence intervals for the associations between maternal alcohol consumption and child outcome. Separate logistic regression models were completed for each child outcome (any abnormality, growth restriction, facial abnormalities, OFC $\leq$ 10 percentile, any test score ≤ 80, language delay plus hyperactivity or attention deficit). For each individual outcome, the starting models included all covariates (maternal age [years], education [years], parity [nulliparious or multiparious], reliability of mother's report of alcohol use

Table 1. Demographic Characteristics of Unexposed and Exposed Women and Children

Characteristic		Exposed ($N = 92$)	Unexposed ($N = 97$)	p-Value
Maternal age (years)	Mean ± SD	24.25 ± 6.90	24.73 ± 6.90	0.6318
Maternal education (years)	<12	56 (60.9)	42 (43.3)	0.0213
	12	22 (23.9)	33 (34.0)	
	>12	14 (15.2)	22 (22.7)	
Marital status	Single	69 (75.0)	58 (60.0)	0.0476
	Married	21 (22.8)	37 (38.0)	
	Divorced	2 (2.2)	2 (2.0)	
Parity	Primiparous	49 (53.3)	53 (54.6)	0.8846
	Multiparous	43 (46.7)	44 (45.4)	
Age mother started drinking alcohol (years)[a]	<13	15 (16.3)	2 (2.0)	0.0008
	13–17	56 (60.9)	52 (53.6)	
	≥18	20 (21.7)	35 (36.1)	
Duration of mother's alcohol consumption (years)[a]	<1–5	39 (42.4)	44 (45.3)	0.4431
	6–10	25 (27.2)	20 (20.6)	
	11–15	15 (16.3)	16 (16.5)	
	≥16	12 (13.0)	9 (9.3)	
Mother has been dizzy when drinking alcohol prior to this pregnancy	Yes	89 (96.7)	38 (39.2)	<0.0001
	No	2 (2.2)	59 (60.8)	
Reliable information provided by mother during interview	Yes	41 (44.6)	97 (100.0)	<0.0001
	No	51 (55.4)	0 (0.0)	
Gestational age at study enrollment (weeks)	Mean ± SD	18.92 ± 7.82	12.29 ± 4.73	0.0001
Gestational age (weeks)	Mean ± SD	39.28 ± 1.17	39.15 ± 1.09	0.3252
Sex of infant	Male	45 (48.9)	45 (46.4)	0.8840
	Female	47 (51.1)	51 (52.6)	

[a]Unexposed mothers reported no alcohol consumption during pregnancy; this value represents the pre-pregnancy state in unexposed mothers.

during pregnancy, and age at which mother started drinking alcohol [years]). Each covariate resulted in a >10% change in the beta coefficient for at least 1 classification of the main exposures; therefore, the final models for all outcomes included all of the covariates and a single exposure measure. Additional regression analysis including all classifications of the main exposure, with backward elimination, was performed to identify the strongest alcohol consumption predictor for each child outcome. SAS versions 9.1 and 9.2 (SAS Institute, Cary, NC) were used for the analyses.

RESULTS

Of the 101 exposed and 101 unexposed children, 9 (8.9%) and 4 (4.0%), respectively, were lost to follow-up, leaving 92 exposed and 97 unexposed children with partial to complete data available for analysis. Mothers of the exposed infants were significantly more likely to have less education, to be single, to begin prenatal care at a later gestation, to be considered unreliable during the interviews, and to begin drinking alcohol at a younger age (Table 1). The 2 groups did not differ significantly in gestational age at birth or male–female ratio. Of the exposed women, 91.3% (84 of 92) recognized they were pregnant during the first trimester, with more than half recognizing pregnancy prior to 8 weeks of gestation.

Child Outcomes

Not all children had data available in all areas; partial data were included in the analysis, resulting in variable denominators in the specific outcomes analyzed. Of the 92 exposed children, 59 (64.1%) had data available to identify at least 1 abnormality—growth, facial features, head circumference, standardized testing, or language delay plus hyperactivity or attention deficit. Of those children, 12 (20.3%) had no abnormalities detected in any area, and 47 (79.7%) had at least 1 abnormality detected. Of the 97 unexposed children, 44 (45.4%) had sufficient data to determine whether they had at least 1 abnormality. Of those children, 21 (47.7%) had no abnormalities detected in any area and 23 (52.3%) had at least 1 abnormality detected. The prevalence of growth restriction, abnormal facies, and CNS abnormalities was significantly higher in the alcohol-exposed group relative to the unexposed group (Table 2).

Growth restriction occurred in only 27.2% of the 92 exposed children who had growth data available in comparison with 12.5% of the unexposed ($p = 0.02$).

The Chilean geneticists evaluated 81 exposed and 89 unexposed children for the FAS facial features. The geneticists classified 17.3% (14 of 81) exposed and 1.1% (1 of 89) unexposed children as having abnormal facies. The geneticists considered numerous features previously associated with fetal alcohol exposure, but focused on the 3 cardinal features when making a diagnosis. Prior to the study, the experienced geneticists recognized that palpebral fissures are smaller in most Chilean children and took this minor ethnic variation into consideration during classification of the children. The Lip-Philtrum Guide was not used during the study; therefore, Hoyme and the Centers for Disease Control and Prevention criteria were not applied to the 3-dimensional assessments.

Photographs were obtained on 162 of the 170 children evaluated by the geneticists. Due primarily to low resolution,

Table 2. Child Outcomes for Which Exposed and Unexposed Were Compared

Outcome		Prenatal alcohol exposed ($N = 92$)[a] *n* (valid%)	Unexposed ($N = 97$)[a] *n* (valid%)	*p*-Value
Growth				
Growth restriction[b]	Yes	25 (27.2)	12 (12.5)	0.0164
	No	67 (72.8)	84 (87.5)	
Face				
Abnormal facies[c]	Yes	14 (17.3)	1 (1.1)	0.00018
(Direct Assessment)	No	67 (82.7)	88 (98.9)	
FAS phenotype[d]	Yes	0 (0.0)	0 (0.0)	NA
(Photograph analysis)	No	73 (100.0)	75 (100.0)	
	Unknown	7	1	
CNS				
CNS: Structure				
OFC $\leq$ 10%[e]	Yes	12 (15.0)	5 (5.7)	0.0455
	No	68 (85.0)	83 (94.3)	
CNS: Function				
One or more functional abnormalities	Yes	22 (44.0)	6 (13.6)	0.0015
	No	28 (56.0)	38 (86.4)	
BSID, WPPSI, and/or WISC Standard Score ≤ 80[f]	Yes	18 (35.3)	3 (6.3)	0.0004
	No	33 (64.7)	45 (93.7)	
Language delay[g]	Yes	29 (42.0)	19 (23.8)	0.0223
	No	40 (58.0)	61 (76.3)	
Hyperactivity[h]	Yes	15 (26.8)	1 (1.5)	<0.0001
	No	41 (73.2)	64 (98.5)	
Attention deficit[h]	Yes	8 (14.3)	3 (4.6)	0.1100
	No	48 (85.7)	62 (95.4)	

CNS, central nervous system; BSID, Bayley Scales of Infant Development; FAS, fetal alcohol syndrome; OCF, occipital frontal circumference; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

[a]Not all children had data for each outcome. Percentages are reported to reflect the proportion of children with an adverse outcome among the subset of children with data on that outcome.

[b]Birth weight $\leq$10% or birth length $\leq$10% or the presence of at least 2 childhood weights or heights $\leq$10% on a standard Chilean growth chart.

[c]Classification of abnormal facial features by a pediatric geneticist in Chile through direct examination of the child.

[d]4-Digit Code FAS facial phenotype Rank 4: All 3 of the following: palpebral fissure length $\leq$ 3%, Smooth philtrum (Rank 4 or 5 on Lip-Philtrum Guide, and Thin upper lip (Rank 4 or 5 on Lip-Philtrum Guide).

[e]One OCF (birth or later) $\leq$10th percentile.

[f]BSID Mental Development Index (MDI), Physical Development Index (PDI); WPPSI: Full Scale IQ; WISC: Full Scale IQ.

[g]Classified by the neurologist among the subset of children who had a neurodevelopmental evaluation at 1 year of age or older.

[h]Classified by the neurologist among the subset of children who had a neurodevelopmental and behavioral evaluation at age 3 years or older.

not all photographs were of sufficient quality to rule out or confirm the FAS facial phenotype. Photographs were of sufficient quality to accurately rule out the FAS facial phenotype (4-Digit Code Rank 4) in 95% (140/148) of the children's photographs. No child in the exposed (0/73) or unexposed (0/75) group met the 4-Digit Code criteria for the full Rank 4 FAS facial phenotype. One child in the exposed group (1/73) met the 4-Digit Code criteria for moderate FAS facial features (Face Rank 3).

CNS functional abnormalities were the most common problem seen in the exposed group, 44.0% (22 of 50). The exposed children were significantly more likely to have a single test score of 80 or less and be diagnosed with language delay and hyperactivity.

No child in the study met the 4-Digit Code criteria for a diagnosis of FAS. One of the exposed children met the 4-Digit Code criteria for a diagnosis of PFAS (4-Digit Code 1334). This would translate into a PFAS prevalence estimate among the alcohol-exposed group of 1.4% (1/73) (95% CI 0.3 to 7.4) using the 4-Digit Code guidelines.

Patterns of Alcohol Exposure

The alcohol consumption patterns of the exposed mothers during pregnancy are presented in Table 3. They consumed significantly more alcohol from conception to recognition of pregnancy than after recognition of pregnancy, and 14.1% of the mothers (13 of 92) reported ceasing alcohol intake once they became aware they were pregnant.

Associations between classifications of alcohol consumption and child outcomes are presented in Table 4. Binge drinking and total number of drinks per week were found to be the most predictive of child adverse outcome when using regression analysis with backward elimination. Binge drinking and total alcohol intake were independent risk factors from conception to recognition of pregnancy, suggesting that both meaningfully contribute to the child's outcome. In the period after the pregnancy was recognized, binge drinking was the strongest predictor of adverse child outcomes.

DISCUSSION

We monitored a large group of heavy-drinking women during pregnancy and followed their children to identify adverse outcomes associated with prenatal alcohol exposure. Functional CNS abnormalities were found in 44% of our exposed children. Notably, 40.9% (9/22) of those with functional abnormalities showed none of the more readily identifiable features associated with alcohol exposure, facial abnormalities, and/or growth restriction. This is consistent with what is reported in the literature: neurologic impairment occurs in approximately 30 to 40% of children born to heavy drinkers, and not all children with CNS dysfunction present with facial or growth abnormalities (Koren et al., 2003; Mattson et al., 1997). The lack of the facial features or growth deficiency may lead to a delayed or missed diagnosis, increasing the risk of poor long-term outcome in comparison with children with more easily recognized features of FAS (Streissguth et al., 2004).

Making investigators aware that cognitive and behavioral phenotypes are relatively common in FASD may increase the diagnostic acumen. Language problems and attention deficits are well-recognized functional CNS impairments of fetal alcohol exposure (Adnams et al., 2001; Kodituwakku et al., 2006; O'Malley and Nanson, 2002). In our population, we found suspicion for language delay in 42% and

Table 3. Alcohol Consumption Patterns During Pregnancy of Exposed Subjects Prior to Recognition of Pregnancy and After Recognition of Pregnancy ($N = 92$)

Alcohol consumption		Period of alcohol consumption during pregnancy: Conception until pregnancy awareness	Period of alcohol consumption during pregnancy: After pregnancy awareness	*p*-Value
Total amount of alcohol consumed in a representative week (g)	Range	94–4,219	0–1,941	<0.0001
	Mean ± SD	902.95 ± 683.09	445.63 ± 530.73	
	Median	711.50	230.00	
Average amount of alcohol consumed per drinking day in a representative week (g)	Range	32.0–996.33	0–772.50	<0.0001
	Mean ± SD	242.06 ± 177.91	133.08 ± 159.61	
	Median	195.50	84.07	
Number of drinking days in a representative week that mother drank >60 g/d (indicator of binge drinking)	0	0 (0.0)	36 (39.1)	<0.0001
	1	12 (13.1)	10 (10.9)	
	2	36 (39.1)	26 (28.2)	
	3	18 (19.6)	9 (9.8)	
	4	7 (7.6)	2 (2.2)	
	5	5 (5.4)	1 (1.1)	
	6	0 (0.0)	0 (0.0)	
	7	14 (15.2)	8 (8.7)	
Maximum alcohol intake on any 1 day in a representative week (g)	Range	68–1,250	0–1,250	<0.0001
	Mean ± SD	388.58 ± 258.42	195.85 ± 241.51	
	Median	345.00	122.00	

hyperactivity in 26.8% of children exposed to alcohol prenatally, both significantly increased in comparison with the unexposed. Some have suggested that the attention profile in FASD is unique (O'Malley and Nanson, 2002; Peadon and Elliott, 2010). An improved understanding of the differences in the attention profiles of FASD children may help in differentiation and recognition of prenatal alcohol exposure (Nash et al., 2008). The high prevalence of behavioral abnormalities in our exposed children suggests a continued need for understanding of the behavioral presentations of FASD.

In contrast to the high prevalence of functional CNS abnormalities, growth restriction was less common and was only moderately associated with binge drinking. The association between prenatal alcohol exposure and growth restriction is well reported, but often retrospective studies utilize growth restriction to identify affected children and there are a limited number of prospective studies. One study with a large clinic population found 34.1% of those exposed presented with growth <10 percentile (Astley, 2010). Additionally, we found very few children that met the 4-Digit Code criteria for an FAS or PFAS phenotype by photograph analysis. Our finding of a low prevalence of growth restriction and FAS facies in children with known heavy prenatal alcohol exposure emphasizes the importance of not relying on the physical features for a consideration of a diagnosis of FASD.

Statistically significant findings on facial features were only found in the 3-dimensional geneticist assessments, not the 2-dimensional photographic assessments. This may reflect the ability of direct observation rather than photographic imaging. As we did not utilize the Lip-Philtrum Guide, we were unable to apply the diagnostic criteria of the Hoyme FASD guidelines (Hoyme et al., 2005) or the Centers for Disease Control and Prevention FAS guidelines (Bertrand et al., 2005). Without the utilization of diagnostic criteria for the clinical facial examination, we are limited in direct comparison between the geneticists' classification and the 4-Digit Code diagnostic criteria.

In addition to generating prevalence estimates for each area of FAS, our prospective study identified children with no evidence of impairment. Based on our classification scheme, 20.3% of the exposed children with data available in the areas of growth, face and structural CNS abnormalities, and functional CNS abnormality had no abnormality detected. Previous reports of children born to alcoholic mothers found 4 to 50% of children may have no detected abnormalities (Aronson and Hagberg, 1998; Halliday et al., 1982; Hollstedt et al., 1983). A majority of these studies were limited by short follow-up of the infants and small numbers. In a clinical population of 1,400 patients, Astley (2010) found that in subjects with heavy alcohol exposure, 9.3% presented with no evidence of abnormalities. Our finding of 20.3% of children without abnormalities is not surprising because in clinical studies, individuals with difficulties are more likely to be referred for evaluation, which would inflate the percentage with abnormalities. Our prospective study provides an estimate in an unselected population of the prevalence of children presenting without abnormalities after heavy prenatal alcohol exposure.

Our prevalence estimates may be limited by the incomplete data for outcomes among the exposed and unexposed children in the study. Only 64.1% (59 of 92) exposed subjects and 45.4% (44 of 97) unexposed had data in every area of interest (growth, facial features, OFC, standardized testing, language delay, and hyperactivity or attention deficit). The

Table 4. Adjusted Odds Ratios and 95% CI for Adverse Child Outcomes by Maternal Alcohol Consumption Patterns During Pregnancy

Alcohol consumption during pregnancy	Child outcome													
	Any abnormality[a]		Growth restriction[b]		Facial abnormalities[c]		OFC ≤ 10%[d]		BSID, WPPSI, and/or WISC Standard Score ≤80[e]		Language delay[f]		Hyperactivity[g]	
	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value
Prior to recognition of pregnancy														
Number of days per week mother binge drank (>60 g/d) (effect per each additional day mother binged)	1.48 (1.15, 1.91)	0.0023	1.25[i] (1.05, 1.49)	0.01	1.80[i] (1.30, 2.50)	0.0004	1.40[i] (1.08, 1.81)	0.01	1.44 (1.10, 1.87)	0.0070	1.09 (0.89, 1.34)	0.39	1.55[i] (1.16, 2.07)	0.0032
Total number of drinks (12 g) per week (effect per each additional drink)	1.02[i] (1.01, 1.04)	0.0009	1.01 (1.00, 1.01)	0.06	1.02 (1.01, 1.03)	0.0061	1.02 (1.00, 1.03)	0.02	1.02[i] (1.01, 1.04)	0.0013	1.01 (1.00, 1.01)	0.25	1.02 (1.01, 1.03)	0.0030
Average number of drinks per day alcohol was consumed (effect per each additional drink)	1.05 (1.01, 1.09)	0.01	1.02 (0.99, 1.04)	0.20	1.05 (1.00, 1.09)	0.04	1.03 (0.98, 1.07)	0.17	1.06 (1.02, 1.10)	0.0059	1.00 (0.97, 1.03)	0.94	1.06 (1.02, 1.11)	0.0039
Maximum number of drinks in 1 day (effect per each additional drink)	1.03 (1.01, 1.05)	0.02	1.02 (1.00, 1.03)	0.07	1.02 (0.99, 1.04)	0.21	1.02 (1.00, 1.05)	0.12	1.03 (1.00, 1.05)	0.03	1.00 (0.98, 1.02)	0.95	1.03 (1.01, 1.06)	0.01
After recognition of pregnancy														
Number of days per week mother binge drank (>60 g/d) (effect per each additional day mother binged)	1.41[i] (1.01, 1.95)	0.04	1.09 (0.88, 1.35)	0.43	2.01[i] (1.37, 2.93)	0.0003	1.05 (0.73, 1.51)	0.79	1.27 (0.95, 1.70)	0.11	1.20 (0.95, 1.51)	0.13	2.44[i] (1.53, 3.91)	0.0002

Continued.

Table 4 (Continued)

Alcohol consumption during pregnancy	Child outcome													
	Any abnormality[a]		Growth restriction[b]		Facial abnormalities[c]		OFC $\leq$ 10%[d]		BSID, WPPSI, and/or WISC Standard Score $\leq$ 80[e]		Language delay[f]		Hyperactivity[g]	
	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value	Adjusted OR[h]	*p*-Value
Total number of drinks (12 g) per week (effect per each additional drink)	1.02 (1.00, 1.03)	0.06	1.01 (1.00, 1.02)	0.16	1.02 (1.01, 1.04)	0.0052	1.00 (0.99, 1.02)	0.67	1.02 (1.00, 1.03)	0.06	1.00 (0.99, 1.01)	0.47	1.03 (1.01, 1.31)	0.0004
Average number of drinks per day alcohol was consumed (effect per each additional drink)	1.03 (0.98, 1.07)	0.23	1.01 (0.98, 1.05)	0.43	1.06 (1.01, 1.10)	0.02	1.01 (0.97, 1.06)	0.57	1.08[i] (1.02, 1.15)	0.01	1.00 (0.97, 1.03)	0.98	1.08 (1.03, 1.13)	0.001
Maximum number of drinks in 1 day (effect per each additional drink)	1.01 (0.99, 1.04)	0.38	1.01 (0.99, 1.04)	0.21	1.02 (1.00, 1.05)	0.11	1.01 (0.98, 1.04)	0.34	1.05 (1.01, 1.09)	0.02	1.00 (0.98, 1.02)	0.96	1.04 (1.01, 1.07)	0.003

BSID, Bayley Scales of Infant Development; OCF, occipital frontal circumference; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

[a]Children with any abnormality ($n = 70$) were compared with children with no abnormality detected when data were available in all areas (growth, geneticist face, classification of face by Hoyme criteria, test score ≤ 80, a head circumference $\leq 10\%$, and language delay plus attention deficit hyperactivity disorder) ($n = 33$).

[b]Defined by the presence of a birth weight $\leq 10\%$ or birth length $\leq 10\%$ or the presence of at least 2 childhood weights or heights $\leq 10\%$ on a standard Chilean growth chart.

[c]Abnormal facial features classified by a pediatric geneticist in Chile through direct examination of the child.

[d]Any 1 OCF (birth or later) $\leq 10\%$ on standard Chilean growth chart.

[e]Any 1 test score (Bayley Motor, Bayley Mental, WPPSI, or WISC) ≤ 80.

[f]Classified by the neurologist and conditional on having an appointment to assess neurodevelopment at 1 year of age or older.

[g]Classified by neurologist and conditional on having an appointment to assess neurodevelopment and behavior at age 3 years or older.

[h]Logistic regression used to estimate adjusted odds ratios and 95% confidence intervals. Covariates included in all models were maternal age, education, parity, reliability of mother's report of alcohol use during pregnancy, and age at which mother started drinking alcohol.

[i]Alcohol factor most predictive of outcome, determined through backward elimination.

design of the study resulted in some subjects not reaching the appropriate age for standardized testing or diagnosis of hyperactivity or attention deficit prior to study completion. Most of the missing data on outcomes were for functional CNS abnormalities.

Our study had several strengths. We prospectively followed women and children from a large unselected population up to 8.5 years. Despite the difficulty of following a population of heavy alcohol users, we had very few lost to follow-up, 8.9% of the exposed and 4.0% of the unexposed. We collected detailed alcohol consumption data during pregnancy and validated the data with home visits. We attempted to address the unreliability of self-reported alcohol consumption through interaction with family members during these home visits.

These detailed alcohol data enabled us to examine dose, and pattern or timing of alcohol exposure as possible determinates of child outcome. In our population, binge drinking and total amount consumed per week were the most predictive of abnormal outcome. The high correlation between these factors made distinguishing between them impossible. Binge drinking has been associated with poor neurodevelopmental outcomes in previous studies, but there were no consistent effects on growth or complete facial phenotype (Henderson et al., 2007). Some of these studies were unable to adjust for confounders. We were able to adjust for some maternal factors that may affect child outcome—education, overall length of alcohol consumption, and reliability. We were unable to adjust for additional comorbid risk factors—smoking, illicit drug use, poor nutrition, and other aspects of home environment which could affect CNS development. It is noteworthy that, although women in our cohort were drinking very large quantities of alcohol, binge drinking still had an independent effect.

Our study provides important data on the rate of growth abnormalities, and facial and CNS abnormalities in children who were heavily exposed to alcohol in utero in an unselected sample of prospectively monitored pregnancies. Functional CNS abnormalities were the most common problem and often presented without the obvious indicators of growth restriction and facial phenotype, emphasizing the need to consider prenatal alcohol exposure as a possible cause of CNS damage in the absence of classic facial features or growth deficits. Our data indicated that women should be counseled that both binge drinking and total intake are important risk factors.

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REFERENCES

Adnams CM, Kodituwakku PW, Hay A, Molteno CD, Viljoen D, May PA (2001) Patterns of cognitive-motor development in children with fetal alcohol syndrome from a community in South Africa. Alcohol Clin Exp Res 25:557–562.

Aronson M, Hagberg B (1998) Neuropsychological disorders in children exposed to alcohol during pregnancy: a follow-up study of 24 children to alcoholic mothers in Goteborg, Sweden. Alcohol Clin Exp Res 22:321–324.

Aros S, Mills JL, Torres C, Henriquez C, Fuentes A, Capurro T, Mena M, Conley M, Cox C, Signore C, Klebanoff M, Cassorla F (2006) Prospective identification of pregnant women drinking four or more standard drinks (> or = 48 g) of alcohol per day. Subst Use Misuse 41:183–197.

Astley SJ (2003) Fetal Alcohol Syndrome Facial Photograph Analysis Software. 1st ed. University of Washington, Seattle, WA. Ref Type: Audiovisual Material.

Astley SJ (2004) Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. 3rd ed. University of Washington Publication Services, Seattle, WA. Ref Type: Pamphlet.

Astley SJ (2010) Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network. Can J Clin Pharmacol 17:e132–e164.

Bertrand J, Floyd LL, Weber MK (2005) Guidelines for identifying and referring persons with fetal alcohol syndrome. MMWR Recomm Rep 54:1–14.

Bonthius DJ, Goodlett CR, West JR (1988) Blood alcohol concentration and severity of microencephaly in neonatal rats depend on the pattern of alcohol administration. Alcohol 5:209–214.

Cronk C, Weiss M (2007) Diagnosis, surveillance and screening for fetal alcohol syndrome spectrum disorders: methods and dilemmas. Int J Disabil Hum Dev 6:343–359.

Gladstone J, Nulman I, Koren G (1996) Reproductive risks of binge drinking during pregnancy. Reprod Toxicol 10:3–13.

Halliday HL, Reid MM, McClure G (1982) Results of heavy drinking in pregnancy. Br J Obstet Gynaecol 89:892–895.

Henderson J, Kesmodel U, Gray R (2007) Systematic review of the fetal effects of prenatal binge-drinking. J Epidemiol Community Health 61:1069–1073.

Hollstedt C, Dahlgren L, Rydberg U (1983) Outcome of pregnancy in women treated at an alcohol clinic. Acta Psychiatr Scand 67:236–248.

Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, Buckley DG, Miller JH, Aragon AS, Khaole N, Viljoen DL, Jones KL, Robinson LK (2005) A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: clarification of the 1996 institute of medicine criteria. Pediatrics 115:39–47.

Kodituwakku P, Coriale G, Fiorentino D, Aragon AS, Kalberg WO, Buckley D, Gossage JP, Ceccanti M, May PA (2006) Neurobehavioral characteristics of children with fetal alcohol spectrum disorders in communities from Italy: preliminary results. Alcohol Clin Exp Res 30:1551–1561.

Koren G, Nulman I, Chudley AE, Loocke C (2003) Fetal alcohol spectrum disorder. CMAJ 169:1181–1185.

Maier SE, Strittmatter MA, Chen WJ, West JR (1995) Changes in blood alcohol levels as a function of alcohol concentration and repeated alcohol exposure in adult female rats: potential risk factors for alcohol-induced fetal brain injury. Alcohol Clin Exp Res 19:923–927.

Mattson SN, Riley EP, Gramling L, Delis DC, Jones KL (1997) Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. J Pediatr 131:718–721.

May PA, Gossage JP, Kalberg WO, Robinson LK, Buckley D, Manning M, Hoyme HE (2009) Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev 15:176–192.

Nash K, Sheard E, Rovet J, Koren G (2008) Understanding fetal alcohol spectrum disorders (FASDs): toward identification of a behavioral phenotype. ScientificWorldJournal 8:873–882.

O'Malley KD, Nanson J (2002) Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. Can J Psychiatry 47:349–354.

Ornoy A, Ergaz Z (2010) Alcohol abuse in pregnant women: effects on the fetus and newborn, mode of action and maternal treatment. Int J Environ Res Public Health 7:364–379.

Peadon E, Elliott EJ (2010) Distinguishing between attention-deficit hyperactivity and fetal alcohol spectrum disorders in children: clinical guidelines. Neuropsychiatr Dis Treat 6:509–515.

Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK (2004) Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr 25:228–238.