ARTICLE

# Alcohol Consumption and Other Maternal Risk Factors for Fetal Alcohol Syndrome among Three Distinct Samples of Women before, during, and after Pregnancy: The Risk Is Relative

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Data were obtained from three samples of women of childbearing age. One sample of women is from prenatal clinics serving Plains Indian women. The second sample is of women from the Plains whose children were referred to special diagnostic developmental clinics, as their children were believed to have developmental issues consistent with prenatal alcohol consumption. The third sample is of women from South Africa, each of whom has given birth to a child diagnosed with full fetal alcohol syndrome (FAS). Data across samples conform to expected trends on many variables. For example, the maternal age at time of pregnancy, a major risk factor for FAS, ranged from a mean of 23.5 years for the prenatal clinic sample, to 23.8 years for the developmental clinic sample, to 27.6 for the sample of women who have delivered children with FAS. Other variables of maternal risk for FAS expected from the extant literature, such as high gravidity and parity, binge drinking, heavy intergenerational drinking in the mother's extended family and immediate social network, and length of drinking career, were compared across the three samples with variable results. However, normative measures of drinking problems are unreliable when reported across cultures. An unexpected finding from this three-sample comparison was the differential risk found when comparing U.S. women to South African women. Women in the U.S. Plains Indian samples report a high consumption of alcohol in a binge pattern of drinking, yet there is less detectable damage to the fetus than among the South African women. Body mass index (BMI) and lifelong and current nutrition may have a substantial impact, along with the above factors, in relative risk for an FAS birth. The level of risk for producing a child with FAS is influenced by environmental and behavioral conditions that vary between populations and among individual women. Also, because many syndromes are genetically based, there is a need for full behavioral and genetic histories of the mother, family, and child being studied. Collecting extensive behavioral information as well as genetic histories will provide the requisite information for making an accurate diagnosis of FAS. 

**KEY WORDS:** fetal alcohol syndrome; alcohol; prenatal binge drinking; American Indians; South Africa

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## INTRODUCTION

Fetal alcohol syndrome (FAS) has been found to occur in all human racial and ethnic groups [Abel, 1995]. Estimates of the prevalence of FAS range from 0.5–2.0 per 1,000 births in the United States [May and Gossage, 2001]. A review of studies in American Indian groups, often cited as high risk, has determined that the rate of FAS among American Indians ranges between 1.0 and 8.97 per 1,000 births [Duimstra et al., 1993; May et al., 2002]. A world record rate of FAS (39.2–46.4 per 1,000 births) has been reported for children in South Africa [May et al., 2000].

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The term *fetal alcohol syndrome* was first used when Jones and Smith [1973] and Jones et al. [1973] described all of the major malformations and disabilities in offspring of alcoholic mothers, making FAS a topic of medical and social concern. Prior to this, indications that alcohol was teratogenic were not frequently recognized or were generally ignored [Abel, 1998]. But Sullivan [1899], a physician working in the prisons of London, described some features of FAS (including mental retardation and convulsions) among children of female alcoholics and described the mechanism of damage as prenatal alcohol exposure. Much later, Lemoine et al. [1968] described abnormal features in 127 offspring of alcoholics in France. These abnormal features were later independently catalogued by Jones and Smith [1973], and the diagnosis of FAS was created. It is likely that FAS has been commonly misdiagnosed throughout the world [Little et al., 1989; Abel, 1995; Karp et al., 1995; Institute of Medicine, 1996].

FAS symptoms fall into three major categories: 1) a characteristic pattern of facial anomalies such as short palpebral fissures and abnormalities in the premaxillary zone; 2) evidence of growth retardation—low birth weight for gestational age, decelerating weight over time not due to nutrition, and disproportional low weight to height; and 3) evidence of central nervous system abnormalities (e.g., microcephaly) and neurological hard or soft signs [Institute of Medicine, 1996]. Full FAS can be diagnosed with or without confirmation of alcohol exposure. Furthermore, the Institute of Medicine (IOM) committee described partial FAS'' with confirmed alcohol exposure. Also defined were alcohol-related birth defects (ARBDs, the physical defects) and alcohol-related neurodevelopmental disorders (ARNDs), which evidence central nervous system damage manifested by either structural brain or neurodevelopmental/behavioral abnormalities. Children with ARBDs and ARNDs do not have the full syndrome, but the specific symptoms of these classifications have been linked to prenatal alcohol exposure by research. These later diagnostic categories must be linked to confirmed alcohol exposure in each particular child [Institute of Medicine, 1996]. The entire array of fetal alcohol diagnoses is currently called fetal alcohol spectrum disorder (FASD).

Prenatal alcohol damage in children varies tremendously with QFT: *quantity* of alcohol consumed, *frequency* with which it is consumed, and *timing* of the consumption to the gestational age of the fetus [May, 1995]. The QFT and individual characteristics of each mother influence both level and type of damage in the fetus. Heavy and frequent doses of alcohol in the first trimester affect the facial and structural features; spontaneous abortion rates are heightened by drinking during the second trimester; and growth is affected in the third trimester [Little and Wendt, 1991; Russel, 1991; Abel, 1995]. Heavy drinking at any time throughout the pregnancy can cause neurodevelopmental, intellectual, and behavioral problems [West and Goodlett, 1990; Pierce and West, 1986; Abel, 1995]. High blood alcohol concentrations (BACs) cause many symptoms of FAS, making heavy, sporadic drinking a prime risk factor [Pierog et al., 1979; Maier and West, 2001; Viljoen et al., 2002; Kvigne et al., 2003].

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As alcoholism and FAS cluster in certain families, heritability, and therefore some genetically determined susceptibility factors, are issues to be explored. But to date only one identifiable genetic protective factor has been linked to FAS. Among liver isoenzyme polymorphisms, one pattern of alleles, alcohol dehydrogenase (ADH) 2*2, has been suggested as protective. This pattern is relatively rare, yet is found in a higher proportion of control mothers and their children in South Africa than among mothers of children with FAS. Mothers of children with FAS are more likely to have the ADH 2*1 pattern [Viljoen et al., 2001].

The primary cause or risk factor for FAS is consumption of large quantities of alcohol, usually in a heavy, episodic (binge) pattern, during a woman's pregnancy. Past and recent studies have identified additional risk factors among women who give birth to children with FAS: advanced maternal age, high gravidity and parity, unmarried status, use of tobacco and other drugs, low socioeconomic status (SES) indicators (such as low education, unskilled job classifications), low levels of religiosity, and cohabitation with a heavy-drinking male [Sokol et al., 1980, 1986; May et al., 1983; Abel and Sokol, 1986; Darrow et al., 1992; Abel, 1995; Abel and Hannigan, 1995; Bagheri et al., 1998; Astley et al., 2000a,b; Viljoen et al., 2002].

Given our ongoing research efforts on FAS among American Indians and in South Africa, we thought it would be instructive to examine these variables across three samples of women whom we thought would be easily categorized as lowest to highest risk for producing a child with FAS. In other words, from

women attending prenatal clinics to those who had given birth to a child with FAS would theoretically form a continuum from low to high risk.

## METHODOLOGY

A large FAS epidemiology and prevention study is under way in collaboration with Indian tribes of the Northern Plains of the United States. The first two sets of data come from this study. The *prenatal clinic sample* originates from Indian Health Service (IHS) clinics. In the 1990s the Aberdeen Area IHS began assessing the use of tobacco, alcohol, and other drugs via a brief self-administered questionnaire (SAQ) [Bad Hart Bull et al., 1999] and a variation called the prenatal questionnaire. These two questionnaires are about 80% similar. Women typically fill out these questionnaires during their first visit to IHS prenatal clinics. The majority of the women visited the clinic in their first trimester. The questionnaires are reviewed by IHS staff and used as tools for a healthy pregnancy. SAQ data were collected from those women who presented at prenatal clinics in three tribal communities. Data from 840 anonymous SAQs were analyzed. Data were missing from a variety of variables on some questionnaires; hence, there is variance in sample size across analyses. These omissions may mean that these women were hiding their use of these substances, particularly alcohol, or simply indicate a busy clinic schedule. The data were merged into a single set resulting in a usable sample of 755.

The *developmental clinic sample* originates from a broad National Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded epidemiologic study, which uses active case ascertainment for identifying cases of FAS [Institute of Medicine, 1996; May and Gossage, 2001] through outreach in entire Plains Indian communities. Educators, community health representatives, and others are trained to recognize symptoms of FASD and to refer children and mothers to special developmental clinics. Children with a previous diagnosis of FAS or other FASDs, those in the care of social service agencies, and children having difficulties in school or who have behavioral problems are the bulk of the referrals. An interdisciplinary team examines each child for the full range of dysmorphology and known birth defects, IQ, life skills, and neuropsychology. Mothers of these children are interviewed about prenatal experience with the index pregnancy, other pregnancies, diet, medical history, social and demographic conditions, and consumption of alcohol during pregnancy. Data are evaluated for a diagnosis of FAS, partial FAS, ARBDs, ARNDs, and/or another problem, or normal [Institute of Medicine, 1996]. Randomly selected normal children and their mothers are also examined and interviewed as matched case-controls,[1] but controls are not consistently included in this paper, as the emphasis is on comparison across populations. When this paper was prepared, 133 women had been interviewed by one author (P.M.T.) in our developmental clinics. The developmental clinic sample is therefore the group we envisioned as having intermediate maternal risk, as 11% of their children were found to have FAS or partial FAS. Some had diagnosable ARBDs or ARNDs, and others were found to be relatively to completely normal.

The *South African sample* of mothers consists only of those women who have given birth to a child with FAS. In the South Africa study, a two-tiered process in elementary schools identified children with FAS. All children in first-grade classrooms of community elementary schools were screened for height, weight, and head circumference (OFC), and those at or below the 10th centile on both of the first two variables and/or on the third received a full dysmorphology/birth defects screening, including physical, IQ, behavioral, and neuropsychological measures [May et al., 2000; Adnams et al., 2001]. Biological mothers or guardians of those children and matched case-controls[2] were interviewed on a large range of maternal risk variables, including the mother's use of alcohol during gestation of the index child [Viljoen et al., 2002]. There have been three waves of research in South Africa, beginning in 1997, 1999, and 2002. Data from waves 1 and 2 were merged into a single data set for the third sample of women ($n = 88$) in this paper. Since all South African women in this third group had given birth to a child with FAS, we envisioned it to be the highest-risk group. All but one of the South African mothers were Colored (mixed ancestry from Black, European, and Asian origins).

In both our Plains and South Africa studies, we gathered drinking data with an extensive questionnaire utilizing a modified timeline follow-back technique [Sobell et al., 1988, 2001] and photographs of the most popular sizes and brands of each type of alcoholic beverage. In this way we were able to establish standard ethanol units more precisely for calculating the number of drinks consumed [Kaskutas and Graves, 2001].

In addition to Institutional Review Board (IRB) committee approvals in the United States (from our university and the IHS) and ethics committee approvals in South Africa, a formal tribal council resolution of approval preceded all activity in the Northern Plains, as did a single site assurance committee approval from the South African community.

The *Epi-Info* software package was used to analyze the data. Chi-square tests were calculated on frequencies for those research questions (variables) that involved data with nominal or ordinal level measurement. In these comparisons percentages are reported in the tables for the reader's convenience. Analyses of variance (ANOVAs) and *t*-tests were utilized for testing differences of means with interval-level data. All analyses

[1]Control children for the developmental clinic part of the study were matched by sex and age (±6 months) to children with a diagnosis of FAS. Mothers of those two samples of children became the matched cases and controls.

[2]For the first wave of data from South Africa, once the children with a diagnosis of FAS were identified, they were matched by sex, age, and classroom to control children. For the second wave of data from South Africa, control children were randomly selected. Mothers of those four samples of children became the matched cases and controls.

were two-tailed. In those analyses where cases were compared to controls, matched statistics were used.

## RESULTS

Selected sociodemographic and maternity variables are presented in Table I. The mean maternal age at time of pregnancy ranged from 23.5 years for the prenatal clinic sample, to 23.8 for the developmental clinic sample, to 27.6 for the South African sample of women. Older women are at higher risk for producing FAS births. Concerning educational attainment, 47.1% of the women in the developmental clinic sample had not graduated from high school or

***Older women are at higher risk for producing FAS births.***

**TABLE I. Demographic, Socioeconomic, and Maternity Variables for Women in Three Studies**

| Variable | Plains prenatal clinic | Plains developmental clinic | South African mothers of children with FAS | Statistical tests |
|---|---|---|---|---|
| Age when pregnant with index child, yrs | | | | |
| n = | 755 | 133 | 88 | |
| Mean (SD) | 23.5 (5.80) | 23.8 (5.96) | 27.6 (6.81) | $F = 18.79$, $P < .01$ |
| Educational attainment, % | | | | |
| n = | — | 119 | 89 | |
| <HS diploma or GED | — | 47.1 | 98.9 | |
| HS diploma or GED | — | 31.9 | 1.1 | |
| Vocational school + | — | 21.0 | 0.0 | $X^2 = 68.64$, 2 df, $P < .01$ |
| Religiosity, % | | | | |
| n = | — | 117 | 76 | |
| Not at all religious | — | 11.1 | 10.5 | |
| Somewhat religious | — | 78.6 | 71.1 | |
| Very religious | — | 10.3 | 18.4 | $X^2 = 2.64$, 2 df, $P =$ NS[a] |
| Marital Status, %[b] | | | | |
| n = | — | 118 | 89 | |
| Married | — | 25.4 | 23.6 | |
| Widowed/separated/ divorced | — | 5.1 | 1.1 | |
| Single | — | 29.7 | 28.1 | |
| Not married but living with partner | — | 39.8 | 47.2 | $X^2 = 3.11$, 3 df, $P =$ NS |
| Maternity | | | | |
| n = | — | 119 | 93 | |
| Gravidity (mean) (SD) | — | 4.7 (2.20) | 3.7 (1.51) | $t = 3.75$, $P < .01$ |
| Parity (pre-term) (mean) (SD) | — | 0.2 (0.74) | 0.4 (0.65) | $t = 1.72$, $P =$ NS |
| Parity (full-term) (mean) (SD) | — | 3.5 (1.88) | 3.0 (1.47) | $t = 2.77$, $P < .01$ |
| Miscarriages (mean) (SD) | — | 0.5 (0.89) | 0.3 (0.64) | $t = 0.52$, $P =$ NS |
| Induced abortions (mean) (SD) | — | 0.2 (0.43) | — | |
| Stillbirths (mean) (SD) | — | 0.0 (0.19) | — | |
| Number of living children (mean) (SD) | — | 3.9 (1.87) | 3.1 (1.24) | $t = 3.07$, $P < .01$ |
| Birth order of index child | | | | |
| n = | — | 294 | 89 | |
| Mean (SD) | — | 3.0 (1.73) | 2.9 (1.57) | $t = 0.56$, $P =$ NS |

[a]NS, not statistically significant.

[b]During pregnancy, or at birth of the index child.

earned a GED; among the South African women that percentage was 98.9%. Data on religiosity were mixed and not significant across populations, probably due to normative and definitional differences and because of time lag (6.5 years) between the FAS birth and interview in both samples. Marital status comparisons conformed to expectations; both the developmental clinic mothers and South African mothers were frequently not married, and a high percentage were living in common-law relationships.

There were some significant and contradictory differences between the higher-risk developmental clinic mothers and South African mothers on the various maternity variables (gravidity, full-term parity, and number of living children) and also some nonsignificant differences (miscarriages and birth order of the child). Although case-control studies in many populations have demonstrated that women who have children with FAS are more likely to be higher gravidity and parity and to suffer more miscarriages than the general maternity population [Abel, 1998; Bagheri et al., 1999; Astley et al., 2000a,b; May and Gossage, 2001], the developmental clinic mothers of children referred for screening had significantly higher values on most of these measures than did the South African mothers of children with FAS in spite of being a younger sample.

Alcohol consumption among family and friends can have a profound impact on female drinking. Data on problem drinking by the woman's father, mother, brother, sister, or biological father of the index child, and the woman's closest female and male friends are presented in Table II. All of these trends are significantly opposite what we would expect.

***Alcohol consumption among family and friends can have a profound impact on female drinking.***

Prenatal clinic and developmental clinic women report that 47.7–83.3% of the individuals in their social network have had problems with alcohol. South African women, on the other hand, reported substantially lower rates of problem drinking in their extended family, 0.0–39.1% (odds ratios (ORs) were 2.27 for the woman's mother, 6.35 for the father, and 52.50 for the first brother). Even the father of the index child was reported to have more problems in the developmental clinic sample (OR = 7.41). London [1999, 2000], Parry [2000], and Parry et al. [2002] report, and our own research has revealed, very high risk drinking among farm workers in the Western Cape, particularly on weekends. The low rates of perceived/reported drinking problems among South African women seem to be simply a matter of norms, expectations, and defining and interpreting "problem drinking" in this subculture. These assumptions are essentially confirmed when we transition to the data in Table III.

**TABLE II. Prevalence of Drinking Problems Within Woman's Social Network**

| Variable | Plains prenatal clinic | Plains developmental clinic | South African mothers of children with FAS | Statistical tests |
|---|---|---|---|---|
| Has individual had problems with alcohol | | | | |
| Woman's father, % | | | | |
| Yes | — | 66.3 | 23.6 | $X^2 = 24.05$, $P < .01$, OR 6.35 |
| Woman's mother, % | | | | |
| Yes | — | 59.4 | 39.1 | $X^2 = 2.79$, $P =$ NS[a], OR 2.27 |
| Woman's brother, %[b] | | | | |
| Yes | — | 83.3 | 8.7 | $X^2 = 39.00$, $P < .01$, OR 52.50 |
| Woman's sister, %[b] | | | | |
| Yes | — | 50.0 | 14.0 | $X^2 = 11.50$, $P < .01$, OR 6.17 |
| Father of index child during the index pregnancy, % | | | | |
| Yes | — | 82.1 | 38.3 | $X^2 = 20.88$, $P < .01$, OR 7.41 |
| Woman's best/closest female friend, % | | | | |
| Yes | — | 47.7 | 10.5 | $X^2 = 8.51$, $P < .01$, OR 7.75 |
| Woman's best/closest male friend, % | | | | |
| Yes | — | 38.5 | 0.0 | $X^2 = 1.23$, $P =$ NS |

[a]NS, not statistically significant.

[b]Data pertain to the first brother or sister for South African women.

**TABLE III. Initiation and Current Use of Alcohol Among Women**

| Variable | Plains prenatal clinic | Plains developmental clinic | South African mothers of children with FAS | Statistical tests |
|---|---|---|---|---|
| Age first tried alcohol, yrs | | | | |
| n = | — | 119 | 83 | |
| Mean (SD) | — | 14.0 (3.39) | 19.5 (3.95) | $t = 20.12$, $P < .01$ |
| Age began drinking regularly, yrs | | | | |
| n = | — | 115 | 82 | |
| Mean (SD) | — | 17.4 (3.84) | 20.8 (4.29) | $t = 11.66$, $P < .01$ |
| Age at interview, yrs | | | | |
| n = | 755 | 119 | 87 | |
| Mean (SD) | 23.5 (5.82) | 31.2 (7.06) | 35.4 (6.79) | $F = 211.67$, $P < .01$ |
| Drinking career, yrs | | | | |
| n = | — | 108 | 73 | |
| Mean (SD) | — | 13.6 (6.75) | 15.8 (6.72) | $t = 74.78$, $P < .01$ |
| Has women ever had a problem with alcohol, % | | | | |
| n = | — | 117 | 50 | |
| Yes | — | 91.5 | 6.0 | $X^2 = 113.78$, $P < .01$, OR 167.63 |

As shown in Table III, developmental clinic women first tried alcohol 5.5 years earlier than South African women (mean = 14.0 vs. 19.5) and also began drinking regularly 3.5 years earlier (17.4 vs. 20.8). But South African women, because the sample was older at interview, had a significantly longer "drinking career" with a mean of 15.8 vs. 13.6 years. Almost all of the developmental clinic women who were suspected of drinking during pregnancy (91.5%) reported that they had had problems with alcohol at some time in their life. Conversely, while *every one* of the South African women in the 1999 study had given birth to a child with FAS, only 6% admitted to having had problems with alcohol at some time in their life (OR = 167.63). Normative definitions are again important, as the developmental clinic women define problem drinking to be significantly greater. While not shown in the table, these South African mothers of a child with FAS worked on farms and consumed twice as many drinks as did the prenatal clinic sample (mean = 14.0 vs. 6.6 drinks) in the seven days preceding their interview. Virtually all (94.9%) South African drinking occurred on weekends (Friday–Sunday), thereby indicating binge drinking as the major pattern. This conforms with the FAS literature from both animal [Maier and West, 2001] and human [Viljoen et al., 2002] studies.

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A woman's consumption of alcohol in the months just before pregnancy is key to reconstructing the risk for FASDs. In Table IV, 74.5–88.9% of the women of the three samples consumed alcohol before pregnancy, conforming to expectations of high risk for FASDs. For the rest of the variables in that table, the developmental clinic women of higher risk who reported drinking before learning they were pregnant consumed the most drinks per occasion (11.3, $P < 0.01$). The developmental clinic women also drank alcohol on more days of the month (7.6) than the prenatal clinic women, but not more often than the South African FAS women (10.2). Developmental clinic women also had the highest percentage, binging at the three- and five-drink thresholds (89.7 and 81.8%, respectively). Developmental clinic women who drank consumed an average of over 100 drinks over a 30-day period, while the South African women consumed an average of 55 drinks over that same time frame. These data place both the developmental clinic women and the South African women at high risk for FASDs.

Table V addresses alcohol use during the index pregnancy. Conforming to expectations, the South African women who have borne children with FAS significantly exceed the other two groups on the percentage who report consuming alcohol during that pregnancy (94.3 vs. 47.0 vs. 16.2%). Five South African women claimed no alcohol consumption during pregnancy even though they gave birth to a child with FAS. The developmental clinic women who continued to drink consumed more average drinks per occasion (7.7), with the South African women consuming only slightly less (7.0). The data conform to expecta-

**TABLE IV. Use of Alcohol Among Women Before Pregnancy**

| Variable | Plains prenatal clinic | Plains developmental clinic | South African mothers of children with FAS | Statistical tests |
|---|---|---|---|---|
| Percent who consumed alcohol | | | | |
| n = | 741 | 112 | 81 | |
| Yes | 74.5 | 80.4 | 88.9 | $X^2 = 9.48$, 2 df, $P < .01$ |
| Among those who were drinking, on days she drank, how many drinks did woman usually drink | | | | |
| n = | 542 | 83 | 72 | |
| Mean (SD) | 6.6 (5.05) | 11.3 (10.86) | 6.7 (5.08)** | $F = 21.92$, $P < .01$ |
| Among those who were drinking, how often over 30 days did woman drink her usual amount | | | | |
| n = | 455 | 81 | 72 | |
| Mean (SD) | 2.4 (2.33) | 7.6 (8.73) | 10.4 (1.51)** | $F = 178.57$, $P < .01$ |
| Among those who were drinking, did woman binge (consume three or more drinks), % | | | | |
| n = | 544 | 88 | 72 | |
| Yes | 87.3 | 89.7 | 76.4** | $X^2 = 25.96$, 2 df, $P < .01$ |
| Among those who were drinking, did woman binge (consume five or more drinks), % | | | | |
| n = | 544 | 88 | 72 | |
| Yes | 63.6 | 81.8 | 63.9** | $X^2 = 11.33$, 2 df, $P < .01$ |
| Among those who were drinking, total number of drinks woman consumed over 30 days | | | | |
| n = | 551 | 80 | 72 | |
| Mean (SD) | 16.5 (27.65) | 102.2 (201.50) | 55.0 (55.93)** | $F = 51.06$, $P < .01$ |

**Estimated from drinking logs at time of inverview, daily, seven and 30 days.

tions on the number of days each woman consumed her usual amount of alcohol. Here the South African women drank 2.3 more days per month than the developmental clinic women and 8.1 more days than the prenatal clinic women. A substantial percentage of women binged at the three-drink threshold at least once during pregnancy (68.8–89.1%), with the developmental clinic women the highest ($P < 0.05$). The percentages are relatively high at the five-drink threshold as well, with 40.6–73.6% of the women drinking five or more drinks per occasion during pregnancy. The developmental clinic women (suspected risk) and the South African women (highest risk) on average consumed significantly more drinks over a typical 30 days during pregnancy than did the prenatal clinic women (prenatal clinic women = 8.6, developmental clinic women = 69.8, South African women = 55.4). The developmental clinic women who continued to drink consumed 15 to 16 more drinks during pregnancy than did the South African women.

From Tables IV and V, therefore, it seems quite apparent that the developmental clinic women are more likely to quit drinking (over 50%) once pregnancy is suspected or confirmed, but those who continue to drink consume more alcohol per occasion, but slightly less often than the South African mothers of children with FAS.

Just as we have compared the three groups of women, we digress to compare women within the developmental clinic sample. We separated those women into two subgroups: those who have given birth to children with FAS or partial FAS (FAS = 22, partial FAS = 16) and the other 95 women whose children did not have FAS or partial FAS. Examining four current drinking measures, the data reveal that the mothers of FAS or partial FAS children consumed 8.3 drinks in the seven days preceding their interview, compared to 6.2 for the women whose children did not have FAS or partial FAS. During that same time frame, 33.3% of the mothers of FAS or partial FAS children binged (3+), while 40.3% of the mothers whose children did not have FAS or partial FAS binged. Both groups of women consumed similar amounts of alcohol in the 30 days preceding their interview; mothers of FAS or partial FAS children consumed 32.7 drinks vs. 33.7 for the mothers whose children did not have FAS or partial FAS. The women whose children did not have FAS or partial FAS report being "high" or drunk a few more times in the 12 months preceding their interview than the women whose children were diagnosed as FAS or partial FAS (17.1 vs. 15.8). None of these comparisons reached a level of statistical significance. These data suggest that even those women whose children do not have FAS could be considered at risk for producing a future child with FAS, but threshold and outcomes are different individual by individual. One protective factor in this comparison is age. The Plains women whose children did not have FAS were significantly younger than the women giving birth to children with FAS or partial FAS at the time of the interview (30.7 vs. 38.1, $t = 3.65$, $P < 0.01$) and at the birth of the index child (23.4 vs. 27.8, $t = 2.49$, $P = 0.014$). We will explore some of these differential risk factors below.

**TABLE V. Use of Alcohol Among Women During Pregnancy**

| Variable | Plains prenatal clinic | Plains developmental clinic[a] | South African mothers of children with FAS[b] | Statistical tests |
|---|---|---|---|---|
| Percent who consumed alcohol | | | | |
| n = | 661 | 116 | 88 | |
| Yes | 16.2 | 47.0 | 94.3 | $X^2 = 257.57$, 2 df, $P < .01$ |
| Among those who were drinking, on days she drank, how many drinks did woman usually drink | | | | |
| n = | 106 | 50 | 83 | |
| Mean (SD) | 4.3 (2.83) | 7.7 (5.04) | 7.0 (5.64)[c] | $F = 13.23$, $P < .01$ |
| Among those who were drinking, how often over 30 days did woman drink her usual amount | | | | |
| n = | 97 | 49 | 82 | |
| Mean (SD) | 1.7 (1.32) | 7.7 (8.36) | 10.0 (1.96) | $F = 95.48$, $P < .01$ |
| Among those who were drinking, did woman binge (consume three or more drinks), % | | | | |
| n = | 106 | 55 | 83 | |
| Yes | 68.9 | 89.1 | 75.9[c] | $X^2 = 8.08$, 2 df, $P < .05$ |
| Among those who were drinking, did woman binge (consume five or more drinks), % | | | | |
| n = | 106 | 53 | 83 | |
| Yes | 40.6 | 73.6 | 68.7[c] | $X^2 = 22.28$, 2 df, $P < .01$ |
| Among those who were drinking, total number of drinks woman consumed over 30 days | | | | |
| n = | 105 | 47 | 83 | |
| Mean (SD) | 8.6 (12.51) | 71.2 (107.66) | 55.4 (54.76)[c] | $F = 24.44$, $P < .01$ |

[a]Control children for the developmental clinic part of the study were matched by sex and age (±6 months) to children with a diagnosis of FAS. Mothers of those two samples of children became the matched cases and controls.

[b]For the first wave of data from South Africa, once the children with a diagnosis of FAS were identified, they were matched by sex, age, and classroom to control children. For the second wave of data from South Africa, control children were randomly selected. Mothers of those four samples of children became the matched cases and controls.

[c]Estimated from drinking logs at time of interview: daily, seven and 30 days.

## DISCUSSION

Substantial alcohol consumption just before and during pregnancy is confirmed in all three of these samples, and many of the risk factor levels conform to expectations from the literature. Included in the prenatal clinic sample are some questions about each woman's knowledge, attitudes, and beliefs about the use of alcohol during pregnancy. Ninety-eight percent of the prenatal clinic women knew that they should not drink any alcohol during their pregnancy; however, 6–10% were continuing to binge drink occasionally. One or more of the children born to women from the developmental clinic sample were suspected of prenatal alcohol exposure or were having problems that were believed to be related to alcohol exposure. More than half of the children in the developmental clinic sample were exposed to alcohol. At the time of interview, all but a few of these women were still in the childbearing years (15–44). Among those developmental clinic women who confirmed drinking just before and during pregnancy, an average of 70 drinks was reported over a 30-day period, a higher mean number of drinks than the South African women who have borne at least one child with FAS (52 drinks). In addition to confirming the value of cutting down or quitting drinking during pregnancy, this raises the question of different thresholds of consumption in different populations.

While binge drinking is described in the literature as the consumption of five or more drinks per occasion, we also include a threshold in our studies of three drinks per occasion for women because of physiologic differences between women and men and because there is a major risk for FASDs even at this level of sporadic drinking. Indeed, research by Day et al. [2002], Baer et al. [2003], and others [Jacobson and Jacobson, 1994; Streissguth et al., 1990, 1994, 1996] suggests that alcohol, even in relatively light doses, may change the fetus in ways that persist long after birth, particularly behavior and intellectual functioning.

Certainly, higher age at pregnancy has been confirmed in this paper as a major risk factor for FAS. Length of drinking career is also a factor. But additionally, from our studies over the years, we have begun to suspect that smaller women are more likely to have lower thresholds of drinking for producing FAS symptoms than larger women. Furthermore, heavy alcohol consumption can interfere with regular eating habits and result in less body mass, as can poor nutrition. Body mass index (BMI) data conform to these observations; the women in the developmental clinic sample who bore children with FAS or

partial FAS (n = 8) had an average BMI of 29.7 vs. 31.5 for the women whose children did not have FAS or partial FAS (n = 35) ($t = 0.55$, $P = 0.583$).

Consumption data for the South African women seem puzzling at first. The South African women had little prior knowledge of the risk of drinking during pregnancy. Most of the South African women who had children with FAS came from families with several generations of individuals who drank heavily, and the mothers themselves continued to drink heavily during the index pregnancy. Equally important is the issue of nutrition. In South Africa, we have been impressed by the relative smallness of many Colored women and their children. The mothers of children with FAS were not only much smaller than women in the United States, specifically Plains Indian women, but they were smaller than many other South African Colored women in the same population. It follows then that even though the South African women report consuming less alcohol per occasion, they have less body mass to assist in dispensing and metabolizing the alcohol they consume. There may be, therefore, substantial differential risk based on body size and also nutrition. The South African mothers of children with FAS had a mean BMI of 24.9 vs. 27.2 for South African controls ($t = 2.184$, $P = 0.03$). Therefore, even at lower levels of gravidity, age, and other risk variables, these small, less adequately nourished South African women may be at higher risk than the Plains Indian women because of body size.

### Differential Diagnosis

Because high-risk environmental and behavioral conditions vary between populations and risk factors also vary among individual women (e.g., size and differential genetic traits yet to be determined), we conclude with some comments on the importance of collecting a full behavioral and genetic history of the child and his/her family. The "face" of FAS is not unique [Jones, 1997]. By means of a variety of mechanisms, ethanol leads to a highly characteristic pattern of abnormalities related to cell migration and cell death in the premigratory and migratory neural crest cells that normally populate midfacial structures. This hypoplasia of the midface can be considered to be in the spectrum of holoprosencephaly, a severe problem with early morphogenesis of the forebrain [Cohen and Shiota, 2002]. In fact, recent data suggest that ethanol causes a marked downregulation of *sonic hedgehog* (*Shh*) and other components of the hedgehog gene-signaling network, a network necessary for early forebrain and midfacial development [Ahlgren et al., 2002]. *Shh* may represent a pivotal checkpoint in craniofacial development on which many environmental and growth factors act. Thus, the facial characteristics of FAS are the nonspecific visible end results of the effects of alcohol on the developing forebrain.

Therefore, in the evaluation of children with disabilities who have been prenatally exposed to alcohol, it is important to rule out both genetic and other teratogenic disorders with similar abnormalities in midfacial development that may have morphological similarities to children with FASDs. Children with prenatal toluene exposure (following maternal inhalant abuse) have been shown to manifest facial characteristics similar to those observed in FAS [Pearson et al., 1994]. Similarly, children with a variety of genetic disorders, including chromosomal anomalies, Cornelia deLange syndrome, Williams syndrome, blepharophimosis syndrome, and velocardiofacial syndrome, among others, can be associated with short palpebral fissures and midfacial hypoplasia [Jones, 1997]. Thus, a careful family history, maternal and pregnancy history (including exposure to other potential teratogens), and dysmorphology examination are essential in evaluating children with prenatal alcohol exposure.

## CONCLUSIONS

Comparisons of these three samples from two very distinct racial/ethnic populations underscore the fact that maternal risk may vary substantially by population. Also, as shown in case-control studies within these populations, risk is not equal from one individual to the next [Viljoen et al., 2002]. The threshold of alcohol consumption for FAS, normative patterns of consumption before, during, and after pregnancy, and social, cultural, and demographic patterns/variables differ widely by human group and individual. Abel [1998] has written of the American paradox. It holds that even though Americans have a lower per capita consumption of alcohol than most every European country, higher rates of FAS have been reported in the United States [see also Institute of Medicine, 1996]. Binge drinking has been suggested as one major factor for the higher FAS rate in the United States, and this pattern is also very influential in South Africa. Nutrition, body size, normative perceptions (expectations), education, low SES, and cultural practices, including patterns of food consumption, also play a role in alcohol metabolism, BACs, and the teratogenic effects on the fetus. The prenatal clinic and developmental clinic samples, although practicing binge drinking in the prepregnancy period similar to or even more severe than the South African women who have children with FAS, are more likely to quit drinking or cut down during pregnancy. Furthermore, the developmental clinic women are much larger women (BMI = 31.0 vs. 24.9 for South African women) who are better nourished in both the short and long term. These factors may produce a relative protection for the developmental clinic women and an increased relative risk for the South African women.

Finally, it should be noted that some women in the prenatal clinic sample and many women in the developmental clinic sample are candidates for selective prevention (e.g., information and referral for alcohol abuse screening). Those women who have given birth to children with FAS must receive indicated prevention, such as case management and alcohol abuse therapy as outlined in the IOM report [Institute of Medicine, 1996, Chapter 7].

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