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Fetal Alcohol Spectrum Disorders: A Population Based Study of Premature Mortality Rates in the Mothers

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Abstract

Fetal alcohol spectrum disorders (FASD) are associated with an increase in risk for mortality for people with an FASD and their siblings. In this study we examine mortality rates of birth mothers of children with FASD, using a retrospective case control methodology. We utilized the North Dakota FASD Registry to locate birth certificates for children with FASD which we used to identify birth mothers. We then searched for mothers' death certificates. We then compared the mortality rates of the birth mothers with an age matched control group comprised of all North Dakota women who were born and died in the same year as the birth mother. The birth mothers of children with FASD had a mortality rate of $15/304 = 4.93\%$; (95% CI 2.44–7.43%). The mortality rate for control mothers born in same years as the FASD mothers was $126/114,714 = 0.11\%$ (95% CI 0.09–0.13%). Mothers of children with an FASD had a 44.82 fold increase in mortality risk and 87% of the deaths occurred in women under the age of 50. Three causes of death (cancer, injuries, and alcohol related disease) accounted for 67% of the deaths in the mothers of children with FASD. A diagnosis of FASD is an important risk marker for premature death in the mothers of children diagnosed with an FASD. These women should be encouraged to enter substance abuse treatment.

Keywords

Maternal mortality; Fetal alcohol spectrum disorder; Mother; Etiology; Children

Introduction

Alcohol use disorders result in a substantial fraction of preventable diseases, injury and mortality globally [1]. These disorders comprise the fifth leading risk factor for chronic disease in the world and accounting for 3.5% of the burden of disease [2]. Rates of alcohol use have been increasing among women in the last few years [3]. While drinking is less prevalent in women than men, the health consequences are much greater. At equivalent levels of consumption women's risk exceeds men's in part because they achieve higher blood alcohol concentrations with similar levels of drinking [5]. In Russia 33% of all mortality in women 15–54 is alcohol associated and dose related [4]. In England and Wales, from 1979 to 2000, alcohol-related death rates increased for women from 4 to 7 deaths per 100,000 population [6]. Increased mortality from alcohol related diseases and causes have been reported for Sweden and Finland [7, 8]. The relationship between alcohol use and mortality is not universal in all studies and some studies have demonstrated a protective effect from alcohol use especially at low to moderate levels (1–2 drinks per day) and in the absence of binge drinking [9].

In the United States, alcohol use contributed to 60–90% cirrhosis-related deaths, 40–50% of motor vehicle accident-related fatalities, increased risk for deaths from home injuries, drowning, fire fatalities, and job injuries [10]. The Centers for Disease Control and Prevention attributed 20,918 deaths among women to alcohol use in 2001 [11].

In the United States, alcohol use by pregnant women and women of child bearing age is a substantial public health problem and prevalence rates have changed very little over the past 15 years [12]. Pregnancy is often unplanned in American women and alcohol use is frequent before confirmation of pregnancy. A previous report suggests that 50–60% of women drink in the year of pregnancy and 20% of women report binge drinking or met criteria for alcohol abuse [13]. Rates of self reported alcohol use among women who were later found to be pregnant were 45% [14]. Rates of frequent alcohol use or binge drinking (five or more drinks on one occasion) are at about 3% and have remained fairly constant. Recent prevalence estimates of alcohol use among pregnant women report that 12–15% drink during pregnancy [13].

Prenatal alcohol exposure (PAE) is a common teratogenic cause of developmental disorders, birth defects, and mental illness [15]. Prevalence estimates for fetal alcohol spectrum disorders (FASD) have been reported to be 9.1 per 1,000 live births [16]. However, more recent prevalence studies in school-age populations using improved case ascertainment strategies estimate rates to be about 2 per 100 in school-age children [17]. In some high risk populations the rate may be as high as 8.9 per 100 for 1st-grade students in South Africa [18].

More recently, PAE has been recognized as an important element in the causal chain of risk for fetal, infant, and childhood mortality [19]. The interactions of alcohol with environmental and genetic factors create increased mortality risk for exposed children across multiple vulnerable periods of development (preconceptual, gestational, infancy, and childhood) [19]. In a previous study in North Dakota, we have reported the case mortality rate from all cause mortality in children with a diagnosis of FASD was 2.4% and was 4.5% in their siblings whose FASD status was unknown [20]. It is quite possible that many of these children had an undiagnosed FASD and were either not recognized or died before a diagnosis could be made. The 2.4% mortality rate in the FASD cases accounted for one of every seven deaths of same age children dying in the same year in North Dakota. The sibling mortality rate of 4.5% accounted for one fifth of all deaths in children of the same age dying in the same year in North Dakota.

Deaths in mothers of FASD cases have been reported in prior studies [21–25]. One paper suggested that as many as 75% of mothers may die within 5 years of the birth of a child with fetal alcohol syndrome [26]. In one sample of 570 women who drank during pregnancy, 9.5% had died within 20 years compared to 3.6% of women who stopped drinking during pregnancy [24]. In a clinic-based sample, the rates of maternal mortality in mothers of children diagnosed with an FASD was 12.3% for children with FAS, 8.8% in a sample of children with static encephalopathy and 9.6% in alcohol-exposed children with a diagnosis of neurodevelopmental disorder [27]. Another study of Indian women from the Northern Plains found that 5.1% of mothers whose children were diagnosed with an FASD had died compared to none in the matched controls [25].

These previous studies were all clinic-based samples and may have some bias due to sampling error. We were unable to identify any population based studies to estimate mortality risk for mothers of subjects with FASD. In this study, we investigated the mortality rates for birth mothers of children with FASD when compared with all women from North Dakota born in the same year who died in the same year.

Methods

Development of the FASD Registry

The North Dakota FASD Registry has been described previously and will be briefly described here [28]. The diagnostic component of the FASD Registry is funded by the State of North Dakota to make diagnostic services for FASD and other genetic or congenital conditions available for the entire state. The clinics are held across the state at six locations, at least annually, and at two locations monthly or by appointment. Each referral is seen for evaluation by a medical geneticist and other disciplines as needed. This schedule provides adequate access to diagnostic services for the 632,000 people living in North Dakota and for the annual birth cohort of 7,800. Referrals are made by pediatricians, family practice physicians, obstetricians, Indian Health Service physicians, parents, foster care providers, social services agencies, and multiple other referral sources. We utilize a multiple source method of case ascertainment, which captures nearly 100 percent of FASD cases in North Dakota. These cases are then recorded in the Registry which allows for population-based estimates of FASD in North Dakota. The North Dakota FASD Registry contained

information on consecutive subjects who were seen for diagnostic evaluation in the statewide genetic and dysmorphology clinics across the State of North Dakota over a 20 year period (1984–2004). Cases in the FASD Registry also meet the criteria presented by Hoyme et al. [29] and Stratton et al. [15] The Registry includes subjects with FAS, partial fetal alcohol syndrome (PFAS), and alcohol related neurodevelopmental disorder (ARND).

Mortality Data

After completion of the memorandum of agreement with the North Dakota Department of Health (Division of Vital Records) and approval from the University of North Dakota Institutional Review Board for this project, the names, birth dates, and genders of the 486 cases of FASD from the North Dakota FASD Registry were sent to Division of Vital Records. An electronic search was completed, along with a hand search, where necessary, to link each case in the FASD Registry to the corresponding North Dakota birth certificate to the mother of the child with FASD. The mothers were identified by the mother's name on the North Dakota resident birth certificate for the FASD case. Of the 486 FASD cases, we identified 304 (62.5%) birth mothers. The difference of 182 might be due to multiple births from same mothers, name changes, and births occurring outside North Dakota. We then searched for a maternal death certificate over the period from 1972 to 2007. Searching an expanded timeframe of 35 years for maternal death certificates was necessary in order to capture mortality data for mothers that may have died before or after the FASD diagnosis was made for their child. Causes of mothers' deaths on the death certificate were classified according to the International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10). Data for 1999 to present were classified according to the ICD-10, and the data from earlier years were classified by ICD-9 criteria [30].

In order to examine the effects of age-dependent mortality risks, a comparison group was constructed from the North Dakota birth and death certificate files to identify all females who were born and died in the same year as each of the mothers of an FASD child. By matching the case and control mortality events by year of birth and year of death, we were able to control for changes in health care services over many years and also control for age related mortality risk. This age matching produced a comparison group of 126 women. Because this group was matched with the actual population of mothers of FASD children in North Dakota, these 126 women are a representation of North Dakota's general population. Due to privacy restrictions and our agreement with the North Dakota Department of Health, we restricted our comparison group search to North Dakota residents.

Statistical Analysis

The mortality proportion was calculated utilizing 95% confidence intervals (CIs) for the FASD cohort and their controls. We calculated all-cause mortality rates and the mortality risk ratio for the mothers of FASD children compared with the matched control group. We then ranked the leading causes of mothers' death for this case cohort. Life expectancy was calculated using the 2004 national life tables from the Centers for Disease Control and Prevention in 2004 [31]. We used this data to estimate years of potential life lost for the FASD mothers and the controls.

Results

Mortality Events

We found death certificates for 15 of the 304 FASD case mothers with a mean age of death of 41.5 years (range 24 to 66 years of age) and a median age of death of 40 years. Table 1 shows the age, years of birth and death, cause of death, and the years of life lost for the 15 deceased mothers of FASD children. All but one of these mothers died prior to their life expectancies, which was statistically significant ($Z = 3.4$; $df = 14$; $p < 0.001$). In this sample, 87% (13/15) of the deaths occurred before age 50. Maternal mortality alone accounted for 470 years of productive life lost in North Dakota. Table 2 shows the main causes of death for the 15 deceased mothers of FASD children and for the control group. The three leading causes of death for the mothers of children with FASD were: cancer 4 of 15 (27%); injuries 3 of 15 (20%); and alcohol related causes 3 of 15 (20%), which accounted for 67% of the deaths in the mothers of children with FASD. These same three conditions accounted for only 28.6% of the deaths in the control group, a difference that was statistically significant ($Z = 3.3$; $p < 0.001$).

The duration between birth of a youngest child diagnosed with an FASD and maternal death ranged from 44 days to 24 years, with a mean duration of 12 years and a median of 9.9 years. The birth mothers of children with FASD in North Dakota from 1972 to 2007 had a mortality proportion of $15/304 = 4.9\%$ (95% CI 2.4–7.4%), which translates to a mortality rate of 493 per 10,000.

Comparative Mortality

We then compared the mortality rates of the FASD case mothers to our comparison population consisting of all females born in North Dakota who were born and died in the same year as each of the FASD mothers. The control group was comprised of 126 women with a mean age at death of 49.8 (SD = 11.42) (range 24–71 years). Total years of productive life lost (YPLL) was 2,455 years (mean YPLL 19.5 ± 16.0).

The mortality rate for the control group was $126/114,714 = 0.11\%$ (95% CI 0.09–0.13%). Mothers of children with an FASD had a 44.8-fold increase in mortality risk. The difference between the mortality rates for the mothers of an FASD child and the control group was statistically significant ($Z = 23.17$; $df = 303$; $p < 0.001$).

Discussion

Our population-based study confirmed an increased risk of premature death among birth mothers of FASD children in North Dakota. Birth mothers of children later diagnosed with an FASD had a mortality proportion of 4.9%, which was almost 44 times greater than the mortality proportion of a control group of women from North Dakota. These women were not selected by natality status, so we were unable to control for maternal factors between the groups.

In 2007, the age-adjusted alcohol-induced mortality rate for North Dakota was 8.6 per 100,000 [11]. When compared to the FASD birth mother mortality proportion of 4.9% (4,930 per 100,000), this is a 573-fold increase in mortality risk for these women.

A study of FASD birth mothers from Northern Plains Indians found that 5.1% had died [25]. This study also reported high rates of intentional injuries, accidental injuries, and a 40% rate of attempted suicide in the survivors [25]. This study also found that more than half of the mothers with a child with FAS or possible FAS also had alcohol-related disorders including cirrhosis, trauma or delirium tremens [25]. Several previous studies from multiple countries have identified increased rates of mortality in people with alcoholism [2, 4, 7, 9, 10, 32-34]. Those studies which have gender data indicate an increased risk for women with alcoholism when compared to women without alcoholism [32]. The standardized mortality ratio for females from Italy was 2.4 [35]. Results of the current study are in approximate accord with the findings of these prior studies. However, in our data, North Dakota birth mothers of children with an FASD are also included in the population of women dying from alcohol-related causes. This likely obscures the increased mortality risk for the mothers of children with an FASD. Alcohol-related causes of death (in total) are an important women's health issue. The very morbidity and mortality risks associated with being the birth mother of a child with an FASD suggests that this subgroup represents a unique population for increased surveillance and prevention efforts.

In previous studies, we also found large and significant increases in mortality for children diagnosed with an FASD and their siblings whose diagnostic status is unknown [20]. Thus, a diagnosis of FASD can be conceptualized as a marker for familial mortality risk for the mother and her additional children, regardless of whether the additional children have a diagnosis of an FASD or their FASD status is unknown. A primary outcome from this research should be to call attention to the magnitude and pervasiveness of mortality risks associated with FASD, not just for the affected child but also for siblings and the mother. FASD is a preventable condition, and the alarming risk for excess mortality would presumably be greatly reduced by abstinence during pregnancy. Elimination of the increased mortality risk for the mother and siblings would probably require more sustained changes in multiple substance-abuse and life style behaviors.

The results of this study suggest that potentially large and significant reductions in mortality are possible in these populations through modification of risky behavior. If we reclassify the cause of death categories as: "alcohol-related" (3 = alcohol dependence, alcohol liver disease); "smoking-related" (3 = emphysema, lung cancer, tongue cancer), and "injuries" (3 = drowning, fire, motor vehicle accident); "mental illness" (1 = suicide) and "other" (5 = breast cancer, infection, pending) several potential cause-specific prevention strategies emerge.

The current results indicate that more aggressive efforts may be needed aimed at promoting early entry into substance abuse treatment for women who are likely to become pregnant. In addition, frequent assessments of overall health status and risk may be a useful strategy for health professionals caring for families with a child diagnosed with an FASD.

Our study has several limitations that should be noted. We do not have evidence of the accuracy of mortality events or the cause of death recorded on the death certificates for the FASD birth mothers or controls. We could not compare important factors between two groups, for example, race, ethnicity, smoking, drug use, or intimate partner violence. The data is from one state, and generalizations made to other states with differing demographics should be done with due caution. North Dakota is a very rural state and has one primary minority population comprised of Native Americans. Future studies could improve mortality estimates by using the National Death Index to locate additional deaths occurring outside of a State. While we used multiple rounds of data ascertainment for the death certificates of cases and attempted to link them with birth mothers, the ascertainment rates were not complete. For some mothers we were unable to obtain a match with the name on the birth certificate or on the mothers' death certificates. Other states with large FASD registries could replicate our mortality estimates but this is a significant challenge since it took us nearly 30 years to produce the current FASD registry.

It may be worth noting that this study may actually underestimate the magnitude of risk for mothers of FASD cases. Firstly, we were unable to identify deaths occurring outside of North Dakota for mothers of children on the FASD Registry and since people with alcohol use disorders represent a more transient population than the overall citizenry of North Dakota. Secondly, since FASD is frequently under diagnosed, it is likely that some of the women in the control group may have had children with an undiagnosed FASD. In North Dakota the prevalence rate of FASD is about 1% of live births in study populations (Early Periodic Screening and Diagnostic Testing and two community based population studies ongoing for over 20 years) [17]. This effect would bias (underestimate) the magnitude of the differences between the groups and produce lower mortality estimates for the mothers of FASD children.

The diagnosis of FASD is a very useful risk marker for infant and child mortality and is also an important marker of mortality risk of death for their mothers. In the United States 4,138,000 live births were reported for 2007 [36]. If the FASD rate is 1% in the United States as a whole (41,380 cases), and the mortality rate in their mothers is 4.9% the mortality estimates for FASD birth mothers in the United States would be 2,027 (95% CI 1,941–2,115) deaths annually. The Centers for Disease Control attributed 20,918 deaths among women to alcohol use in 2001 [11]. If 2,027 of these deaths occur in mothers of children with an FASD about 10% of the deaths in this mortality category could be associated with FASD. This data would support the important role of a diagnosis of FASD as an important focus for women's health initiatives and especially for programs to reduce mortality in women under age 50 where 87% of the deaths in this study occurred.

FASD is an important risk marker for increased familial risk of premature mortality in the affected child, siblings, and the mother. Mortality rates for fathers of children with an FASD remain unknown at this time and future research should focus on this issue. Increased attention to this information may be useful in efforts to identify populations at increased risk for premature mortality. This may have important implications in the management of family members of children with FASD and in reducing premature mortality in general.

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Table 1

Age at death, causes of death and years of life lost for mothers of children with FASD

Year death (Age)	Year birth	Cause of death	Life expectancy	Years of potential life lost (YPLL)
2002 (66)	1936	Emphysema	61.9	-4.1
2005 (60)	1945	Lung cancer	69.5	9.5
1988 (37)	1950	Breast cancer	72.2	35.2
1993 (41)	1952	Drowning	72.6	31.6
1989 (34)	1954	Alcohol dependence	73.7	39.7
1998 (43)	1955	Breast cancer	73.7	30.7
2006 (49)	1956	Tongue cancer	73.9	24.9
2005 (47)	1957	Infection	73.7	26.7
1995 (36)	1958	Fire	73.9	37.9
2000 (39)	1960	Pending	74.1	35.1
2003 (41)	1961	Alcohol liver disease	74.6	33.6
2003 (41)	1962	Infection	74.5	33.5
1989 (24)	1964	Suicide-hanging	74.7	50.7
2002 (37)	1964	Motor vehicle accident	74.7	37.7
1998 (28)	1970	Alcohol liver disease	75.6	47.6
41.53 ± 10.86 *			72.89 ± 3.36 *	31.35 ± 13.70 *

* Average age at death, life expectancy, and YPLL

Table 2

Cause of death listed on the death certificate for mothers of children with FASD and the matched controls from North Dakota

Cause	FASD n (%)	Controls n (%)	P
	15	126	
Cancer	4 (26.67)	8 (14.29)	0.19
Accident	3 (20) *	3 (10.32)	0.25
Alcohol related	3 (20) **	5 (3.97)	0.02
Infection	2 (13)	1 (0.79)	0.25
Suicide	1 (6.67)	2 (1.59)	0.37
Emphysema	1 (6.6)	1 (0.79)	0.25
Other	1 (6.6)	86 (68.25)	—

Bold value denotes amongst alcohol-related deaths, there is a significant increase ($P < .05$) in mortality for mothers of FASD cases when compared to the control group

* Drowning, Fire, MVA

** Alcohol dependence and liver disease