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Alcohol consumption during pregnancy and the risk of early stillbirth among singletons

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Abstract

The purpose of this study is to investigate the association between maternal alcohol intake in pregnancy and the occurrence of early stillbirth using a retrospective cohort analysis of singleton births in Missouri that occurred in the period 1989 through 1997 ($N = 655{,}979$). We used Cox proportional hazards regression to generate adjusted risk estimates for total, early, and late stillbirth associated with maternal alcohol intake and used the Robust Sandwich Estimator to adjust for intracluster correlations among sibships. Overall, a total of 3,508 counts of stillbirth were identified, yielding a stillbirth rate of 5.3 per 1,000. Among mothers who consumed alcohol during pregnancy, the stillbirth rate was 8.3 per 1,000. Mothers who consumed alcohol while pregnant were 40% more likely to experience stillbirth as compared with nondrinking mothers (adjusted hazards ratio = 1.4, 95% confidence interval: 1.2–1.7). A dose–response relationship was evident; mothers who consumed five or more drinks per week during pregnancy experienced a 70% elevated risk of stillbirth compared with nondrinking mothers (adjusted hazards ratio = 1.7; 95% confidence interval: 1.0–3.0). The risk of early stillbirth was 80% higher among drinking mothers compared with abstainers (adjusted hazards ratio = 1.8; 95% confidence interval: 1.3–2.3). The elevated risks for both early and late stillbirth did not reach statistical significance when broken down by level of alcohol intake. In conclusion, maternal drinking during pregnancy is associated with an increased risk of early stillbirth. These findings underscore the need to reinforce current counseling strategies toward pregnant women and women who intend to conceive on the detrimental effects of alcohol use in pregnancy.

Keywords: Alcohol use; Pregnancy; Early stillbirth; Singletons; Missouri

Introduction

Alcohol intake during pregnancy is correlated with myriad adverse birth outcomes, including growth restriction (Abel, 1998; Lundsberg et al., 1997; Passaro et al., 1996), congenital malformations (Borges et al., 1997; Day et al., 1990; Ernhart et al., 1987; Mills & Graubard 1987; Rostand et al., 1990), mental and cognitive deficits (American Academy of Pediatrics, 2000), and behavioral and psychosocial problems in childhood and beyond (Nordberg et al., 1994; Spohr et al., 1993). Most studies of alcohol intake in pregnancy have focused on fetal growth and development (Borges et al., 1997) and the causal role of alcohol in the occurrence of stillbirth remains unclear. The findings resulting from the few studies of the association between alcohol and risk of stillbirth have been inconsistent (Alm et al., 1999; Bell & Lumley, 1989; Davis et al., 1982; Faden et al., 1997; Greenwood & McCaw-Binns, 1994; Kaminski et al., 1981; Little & Weinberg 1993; Marbury et al., 1983; Sokol et al., 1980).

The validity of previous studies of the relationship between maternal alcohol intake and stillbirth have been questioned due to study-design considerations (Berkowitz, 1981; Harlap & Shiono 1980; Kline et al., 1980), small sample size (Marbury et al., 1983), errors in classification of exposure (Alm et al., 1999; Faden et al., 1997; Greenwood & McCaw-Binns, 1994; Kaminski et al., 1981; Little & Weinberg, 1993;Marbury et al., 1983), and failure to account for confounding (Bell & Lumley, 1989; Davis

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et al., 1982; Sokol et al., 1980). Finally, most published studies of maternal drinking and stillbirth do not distinguish between timing of stillbirth (i.e., early or late).

The objective of this study is to investigate the independent association between alcohol consumption during pregnancy and early fetal death using a large population-based data set. We hypothesize that:

1. in utero exposure to alcohol impairs fetal survival, regardless of the timing of death,
2. a threshold level exists at which alcohol will result in early stillbirth, and
3. a dose–response relationship can be demonstrated between the quantity of alcohol ingested and the risk of early stillbirth.

Materials and methods

We used the Missouri maternally linked cohort data files covering the period from 1989 through 1997 inclusive. In this data set, siblings are linked to their biologic mothers using unique identifiers. The methods and algorithm used in linking birth data into sibships and the process of validation have been described in detail previously (Herman et al., 1997). The Missouri vital record system is a reliable one that has been adopted as ''gold standard'' to validate U.S. national data sets that involve matching and linking procedures (Martin et al., 2003).

The exposure of interest in this study was maternal alcohol consumption during pregnancy. Following delivery (live birth or fetal death) information was obtained from the mothers regarding sociodemographic factors (including alcohol intake during pregnancy) and other pregnancy-related experiences. The information on alcohol was quantified as the number of drinks per week as an average measure. The information was then documented and transmitted in highly confidential files to the vital records registry for storage and further processing for administrative purposes. All the data benefited from confidentiality rules and regulations prevalent and in effect in the State of Missouri during the period of the study. The data was subsequently deidentified completely and made available as public records to the investigators for analysis. No information is sought concerning the trimester(s) in which consumption occurred during pregnancy, or whether the mothers stopped drinking at any point in time when pregnant. Based on previous research (Kesmodel et al., 2002), we further categorized level of alcohol consumption in drinks per week as follows: 0, 1–2, 3–4, ≥5, and Unspecified. The ''Unspecified'' category represents women who reported consuming alcohol during pregnancy but did not provide information on the number of drinks consumed per week.

The main outcome of interest was stillbirth among singleton gestations. Stillbirth was defined as in utero fetal death at ≥20 weeks gestation. Only births within the gestational age range of 20–44 weeks were selected. Analysis was also separated into categories of early and late stillbirth. The former is defined as stillbirth occurring less than 28 weeks gestation and the latter reflects stillbirth that occurs at 28 weeks gestation or greater. Our choice of 28 weeks to demarcate the transition between late and early fetal death is in agreement with previous studies (Cnattingius et al., 1998; Panduro Barón et al., 2006; Walles et al., 1994). The evidence suggests different etiologic factors and causality pathways for early versus late stillbirth (Sharma et al., 2007) and examining stillbirth as a homogeneous entity may mask important and critical information regarding periods of heightened vulnerability and risk thresholds in relation to insult to the fetus.

Gestational age was computed in weeks as the interval between the last menstrual period and the date of delivery of the fetus. We subsequently used this time scale in the estimation of hazard ratios.

The distribution of the following selected maternal sociodemographic characteristics was compared among drinking and nondrinking mothers to assess differences in baseline characteristics: age, smoking habits, marital status, educational status, parity, and adequacy of prenatal care. Adequacy of prenatal care was assessed using the revised graduated index algorithm, which has been found to be more accurate than several others, especially in describing the level of prenatal care utilization among groups that are high risk (Alexander & Cornely, 1987; Alexander & Kotelchuck, 1996). This index assesses the adequacy of care based on the trimester prenatal care began, number of visits, and the gestational age of the infant at birth. In this study, inadequate prenatal care utilization refers to women who either had missing prenatal care information, had prenatal care but the level was considered suboptimal, or mothers who had no prenatal care at all. We performed crude frequency comparisons among the maternal subgroups for the presence of common obstetric complications, namely, anemia, insulin-dependent diabetes mellitus, other types of diabetes mellitus, chronic hypertension, preeclampsia, eclampsia, placental abruption, and placenta previa.

Statistical analysis

Stillbirth rates were computed by dividing the number of stillbirths by the sum of live birth and stillbirth and multiplying by 1,000. Chi-square test was used to determine differences in sociodemographic characteristics and maternal pregnancy complications between nondrinking and drinking mothers. We used the Cox Proportional Hazards Regression models to generate risk estimates with censoring of those fetuses not at risk. The traditional logistic regression modeling will be inappropriate in this case because the generated adjusted odds ratios consider all stillbirth and live births as part of the denominator, a concept that is increasingly recognized as flawed in perinatal epidemiology (Kramer et al., 2002). We confirmed the nonviolation of

the proportionality assumption by plotting the log-negative-log of the Kaplan–Meier estimates of the survival function versus the log of time. The results were parallel. Adjusted hazards ratios were derived by loading all variables considered to be potential confounders into the model. Potential confounders were selected based on literature report and biologic plausibility. The Robust Sandwich Estimator was used to adjust for intracluster correlation, as repeat pregnancies violate the independence assumption (Lin & Wei, 1989). Adjusted estimates were derived in all cases by using nondrinking mothers as the referent category.

All tests of hypothesis were two tailed with a type 1 error rate fixed at 5%. SAS version 9.1 (SAS Institute, Cary, NC) was used to perform all analyses. This study was approved by the Office of the Institutional Review Board at the University of South Florida.

Results

During the specified time frame (1989–1997), 691,046 singleton deliveries were recorded in the Missouri data set. We excluded pregnancies before 20 weeks and those beyond 44 weeks of gestation (32,126 or 4.6%). The remaining observations included nearly 100% complete information on the exposure variable, with less than 0.4% missing data on alcohol consumption during pregnancy, resulting in a total of 655,979 singleton deliveries available for analysis.

A comparison of drinking and nondrinking mothers with respect to selected sociodemographic characteristics is presented in Table 1. Mothers who consumed alcohol during pregnancy were more likely to be older, multiparous, of black maternal race, and smokers when compared to nondrinking mothers. In contrast, abstaining gravidas were more likely to be married, have a higher level of educational attainment, and to have received adequate prenatal care.

Table 1
Selected sociodemographic characteristics by drinking status, Missouri, 1989–1997

	Drinkers (N = 14,454) %	Nondrinkers (N = 641,488) %	P-value
Maternal age			
≥ 35 years	15.7	8.8	<.01
Parity			
Multiparous	69.3	58.4	<.01
Race			
Black	23.6	15.7	<.01
White	75.5	82.5	
Education			
≥ 12 years	75.7	80.1	<.01
Married	57.8	70.0	<.01
Smoking	55.3	21.0	<.01
Adequate prenatal care[a]	35.9	46.7	<.01

[a]Adequacy of prenatal care was assessed on the basis of the revised graduated index algorithm, which takes into consideration the trimester prenatal care began, number of visits, and the gestational age of the infant at birth.

Table 2 presents the prevalence of common medical and obstetric complications among drinking and nondrinking gravidas. Anemia, placental abruption, and placental previa occurred more frequently among mothers who consumed alcohol during pregnancy. Conditions such as diabetes and pre-eclampsia were more common among abstaining gravidas. However, significant differences were not observed in the occurrence of eclampsia or chronic hypertension between the two maternal groups.

A total of 3,508 counts of stillbirth were identified in the entire study sample yielding a stillbirth rate of 5.3 per 1,000. More than 3% (N = 120) occurred among mothers who consumed alcohol during pregnancy resulting in a stillbirth rate of 8.3 per 1,000. The stillbirth rate among the reference group, nondrinking or abstaining mothers, was 5.3 per 1,000. Figure 1 depicts the rates of early stillbirth (less than 28 weeks gestation) and late stillbirth (occurring at 28 weeks gestation or greater) among drinking mothers and abstainers.

Results of the association between drinking during pregnancy and stillbirth are shown in Table 3. The likelihood of stillbirth was 40% greater if a mother was a drinker compared to nondrinking mothers. Notably, the risk of early stillbirth was 80% higher among drinking mothers compared abstainers whereas the risk of late stillbirth exhibited a 20% increase that did not reach statistical significance.

We present in Table 4 results of the association between the number of drinks consumed per week and stillbirth. Women who consumed five or more drinks per week during pregnancy experienced a 70% elevated risk of stillbirth. The risk of early stillbirth suggested a J-shaped trend, with a hazard ratio of 1.5 (95% confidence interval: 1.0–2.1) for women consuming 1–2 drinks per week, no increased risk for women consuming 3–4 drinks and a spike in risk (hazard ratio = 2.0 [95% confidence interval: 0.9–4.6] among women consuming five or more drinks per week. The greatest risk for experiencing stillbirth, early, or late, was exhibited among those women who reported drinking during pregnancy but failed to provide information on the number of drinks they consumed per week.

Table 2
Frequency of common medical and obstetric complications by drinking status, Missouri 1989–1997

	Drinkers (N = 14,441) %	Nondrinkers (N = 641,006) %	P-value
Anemia	1.7	1.4	<.01
Insulin-dependent diabetes	0.2	0.6	<.01
Other forms of diabetes	1.5	1.9	<.01
Chronic hypertension	0.8	0.8	.7
Pre-eclampsia	2.7	4.1	<.01
Eclampsia	0.1	0.1	.2
Placental abruption	1.4	0.8	<.01
Placental previa	0.5	0.4	<.01

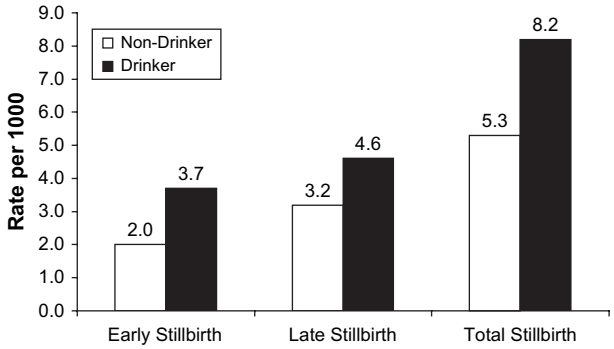

Fig. 1. Crude rates for early, late, and total stillbirth rates by drinking status, Missouri 1989–1997.

Discussion

In this large retrospective cohort study of more than 650,000 pregnancies, we report elevated risks of stillbirth among mothers who admit to alcohol ingestion during pregnancy. Our findings are in agreement (Faden et al., 1997; Kaminski et al., 1978; Kesmodel et al., 2002) and at variance (Davis et al., 1982; Greenwood & McCaw-Binns, 1994; Kaminski et al., 1981; Marbury et al., 1983; Sokol et al., 1980) with previous studies addressing the topic. Using linked outcome data from the Danish National Birth Registry and a validated questionnaire, Kesmodel et al. (2002) found that women who consumed ≥5 drinks per week during pregnancy were three times as likely to have a stillbirth as compared with women who consumed <1 drink per week. Similar findings were reported by Kaminski et al. (1978) who found a 2.5 times increased risk of stillbirth among women who consumed >3 drinks per day. An analysis of birth outcomes from the U.S. National Maternal and Infant Health Survey also suggested a dose–response relationship between alcohol and stillbirth, with each drink increasing the risk of stillbirth by 1% (Faden et al., 1997).

On the other hand, Marbury et al. (1983) found that alcohol intake of fewer than 14 drinks per week was not associated with an increased risk of any adverse outcome, after adjusting for confounding by demographic characteristics, smoking, parity, and obstetric history. Their findings were supported by others (Davis et al., 1982; Sokol et al., 1980). The increased risk of stillbirth in abstainers reported by some studies (Bell & Lumley, 1989; Little & Weinberg, 1993) has been attributed to a possible "healthy drinker effect," that is, women with a poor obstetric history are more likely to abstain from drinking alcohol in pregnancy (Stoler et al., 2002).

Even though we demonstrated a dose–response relationship between alcohol intake and the risk of total stillbirth with a possible threshold effect at ≥5 drinks per week, we were unable to replicate this finding for early and late stillbirth outcomes. This may not be unrelated to the small number of events in the subgroups. The presence of a dose–response relationship and a threshold effect supports our first two hypotheses and is similar to findings by other investigators (Faden et al., 1997; Kaminski et al., 1978; Kesmodel et al., 2002).

The exact pathway by which alcohol predisposes to stillbirth remains to be determined, but several intermediate mechanisms are possible. First, alcohol has been demonstrated by animal models to decrease blood flow in the placenta by increasing the risk of intravascular coagulation (Jones et al., 1981). Placental abruption is a major cause of fetal mortality (Salihu et al., 2005) and alcohol has been shown to disrupt placental function via an elevated risk of this condition (Conner, 1984; Kaminski et al., 1981; Sokol et al., 1980). For instance, Kaminski et al. (1981) found that the risk of fetal death from placental abruption was elevated among a cohort of 9,000 women consuming excess of three drinks per day. Kesmodel et al. (2002) also reported an increased risk of stillbirth that was predominantly due to complications arising from fetoplacental insufficiency. Other postulated pathways include changes in homeostatic function (Tønnesen et al., 1992), hypoglycemia (Kesmodel et al., 2002), and increased production of prostaglandins E_2 and $F_{2\alpha}$ which in turn increase cyclic 3',5'-adenosine monophosphate activity thereby decreasing cell division and ultimately resulting in fetal demise (Anton et al., 1990; Kesmodel et al., 2002; Pennington, 1988; Randall et al., 1987).

Our study was limited by the method of ascertainment of alcohol intake. Underreporting of alcohol intake is a well-recognized phenomenon in pregnant women, especially if such history was obtained in the postpartum period (Marbury et al., 1983; Little et al., 1977). There is also the possibility that mothers with poor outcomes will systematically underreport alcohol intake to a greater extent than mothers with better outcomes because of the social stigma

Table 3
Risk of total, early, and late stillbirth by drinking status, Missouri 1989–1997

	Stillbirth		Early (<28 weeks)		Late (≥28 weeks)	
	N	AHR[a] (CI)[b]	*N*	AHR (CI)	*N*	AHR (CI)
Non–drinker	3,388	1.0	1,312	1.0	2,076	1.0
Drinker	120	1.4 (1.2–1.7)	54	1.8 (1.3–2.3)	66	1.2 (1.0–1.6)

[a]AHR: Adjusted hazard ratio (adjusted for smoking habits, maternal age, maternal race, parity, marital status, maternal education, adequacy of prenatal care, fetal gender, and year of birth).

[b]CI: 95% confidence interval.

Table 4
Risk of total, early, and late stillbirth by level of alcohol consumption, Missouri 1989–1997

	Stillbirth		Early		Late	
	N	AHR[a] (CI)[b]	*N*	AHR (CI)	*N*	AHR (CI)
Nondrinker	3,388	1.0	1,312	1.0	2,076	1.0
1–2 Drinks/week	62	1.1 (0.9–1.4)	29	1.5 (1.0–2.1)	33	0.9 (0.7–1.3)
3–4 Drinks/week	9	1.1 (0.6–2.1)	3	1.0 (0.3–3.1)	6	1.1 (0.5–2.6)
≥5 Drinks/week	15	1.7 (1.0–3.0)	7	2.0 (0.9–4.6)	8	1.6 (0.8–3.2)
Unspecified	34	3.0 (2.2–4.4)	15	3.7 (2.2–6.2)	19	2.8 (1.8–4.4)

[a]AHR: Adjusted hazard ratio (adjusted for smoking habits, maternal age, maternal race, parity, marital status, maternal education, adequacy of prenatal care, fetal gender, and year of birth).
[b]CI: 95% confidence interval.

associated with this behavior (Marbury et al., 1983). However, Verkerk (1992) has shown that in the absence of overreporting, even substantial underreporting has little impact on the association between exposure and outcome, especially when the population of nonexposed is large. In addition, the net effect of underreporting in this study would be to bias our findings toward the null. That we still report elevated risks of stillbirth in our study cohort strengthens the validity of our findings. We were also unable to document levels of alcohol intake for a sizeable proportion of our population (our ''unspecified'' group). Finally, we did not explore the effect of binge drinking on risk of stillbirth in our cohort as our database did not include such information.

The strengths of this study include the population-based design, which has the advantage of minimizing biases arising from sample selection, a source of concern in data derived from individual health facilities. The effect of this is the enhanced external validity of our findings. In addition, as one of the largest studies to date of this topic, the large sample size used reduces the likelihood of a type 2 error resulting from insufficient power. Another strength of this study is the nearly 100% complete information on the exposure variable, with less than 0.4% missing data on alcohol consumption during pregnancy over an 8-year period.

In summary, we report elevated risk of stillbirth among mothers who admit to alcohol ingestion during pregnancy. These risks were maximal in mothers who admitted to drinking during pregnancy but failed to quantify the amount of alcoholic drinks they consume on a weekly basis. Our findings will prove beneficial in counseling pregnant mothers or women intending to conceive on the risks associated with alcohol abuse in pregnancy.

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References

Abel, E. L. (1998). *Fetal alcohol abuse syndrome*. New York, NY: Plenum Press.

Alexander, G. R., and Cornely, D. A. (1987). Prenatal care utilization: Its measurement and relationship to pregnancy outcome. Am. J. Prevent. Med *3*, 243–253.

Alexander, G. R., and Kotelchuck, M. (1996). Quantifying the adequacy of prenatal care: A comparison of indices. Public Health Rep *3*, 408–418.

Alm, B., Wennergren, G., Norvenius, G., Skjaerven, R., Oyen, N., Helweg-Larsen, K., Lagercrantz, H., and Irgens, L. M. (1999). Caffeine and alcohol as risk factors for sudden infant death syndrome. Nordic Epidemiological SIDS Study. Arch. Dis. Child *81*, 107–111.

American Academy of Pediatrics. Committee on Substance Abuse and Committee on Children With Disabilities (2000). Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. Pediatrics *106*, 358–361.

Anton, R. F., Becker, H. C., and Randall, C. L. (1990). Ethanol increases PGE and thromboxane production in mouse pregnant uterine tissue. Life Sci *46*, 1145–1153.

Bell, R., and Lumley, J. (1989). Alcohol consumption, cigarette smoking and fetal outcome in Victoria, 1985. Community Health Stud *13*, 484–491.

Berkowitz, G. S. (1981). An epidemiologic study of preterm delivery. Am. J. Epidemiol *113*, 81–92.

Borges, G., Tapia-Conyer, R., López-Cervantes, M., Medina-Mora, M. E., Pelcastre, B., and Marina, F. F. (1997). Alcohol consumption and pregnancy in the Mexican national addiction survey. Cad. Saude. Publica *13*, 205–211.

Cnattingius, S., Haglund, B., and Kramer, M. S. (1998). Differences in late fetal death rates in association with determinants of small for gestational age fetuses: population based cohort study. BMJ *316*, 1483–1487.

Conner, C. S. (1984). Marijuana and alcohol use in pregnancy. Drug. Intell. Clin. Pharm *18*, 233–234.

Davis, P. J., Partridge, J. W., and Storrs, C. N. (1982). Alcohol consumption in pregnancy. How much is safe? Arch. Dis. Child *57*, 940–943.

Day, N. L., Richardson, G., Robles, N., Sambamoorthi, U., Taylor, P., Scher, M., Stoffer, D., Jasperse, D., and Cornelius, M. (1990). Effect of prenatal alcohol exposure on growth and morphology of offspring at 8 months of age. Pediatrics *85*, 748–752.

Ernhart, C. B., Sokol, R. J., Martier, S., Moron, P., Nadler, D., Ager, J. W., and Wolf, A. (1987). Alcohol teratogenicity in the human: a detailed assessment of specificity, critical period, and threshold. Am. J. Obstet. Gynecol *156*, 33–39.

Faden, V. B., Graubard, B. I., and Dufour, M. (1997). The relationship of drinking and birth outcome in a US national sample of expectant mothers. Paediatr. Perinat. Epidemiol *11*, 167–180.

Greenwood, R., and McCaw-Binns, A. (1994). Does maternal behaviour influence the risk of perinatal death in Jamaica? Paediatr. Perinat. Epidemiol *8*, 54–65.

Harlap, S., and Shiono, P. H. (1980). Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet *2*, 173–176.

Herman, A. A., McCarthy, B. J., Bakewell, J. M., Ward, R. H., Mueller, B. A., Maconochie, N. E., Read, A. W., Zadka, P., and Skjaerven, R. (1997). Data linkage methods used in maternally-linked birth and infant death surveillance datasets from the United States (Georgia, Missouri, Utah and Washington State), Israel, Norway. Scotland and Western Australia. Paediatr. Perinat. Epidemiol *11*, 5–22.

Jones, P. J., Leichter, J., and Lee, M. (1981). Placental blood flow in rats fed alcohol before and during gestation. Life Sci *29*, 1153–1159.

Kaminski, M., Franc, M., Lebouvier, M., du Mazaubrun, C., and Rumeau-Rouquette, C. (1981). Moderate alcohol use and pregnancy outcome. Neurobehav. Toxicol. Teratol *3*, 173–181.

Kaminski, M., Rumeau, C., and Schwartz, D. (1978). Alcohol consumption in pregnant women and the outcome of pregnancy. Alcohol Clin. Exp. Res *2*, 155–163.

Kesmodel, U., Wisborg, K., Olsen, S. F., Henriksen, T. B., and Secher, N. J. (2002). Moderate alcohol intake during pregnancy and risk of stillbirth and death in the first year of life. Am. J. Epidemiol *155*, 305–312.

Kline, J., Shrout, P., Stein, Z., Susser, M., and Warburton, D. (1980). Drinking during pregnancy and spontaneous abortion. Lancet *2*, 176–180.

Lin, D. Y., and Wei, L. J. (1989). The robust inference for the Cox proportional hazards model. J. Am. Stat. Assoc *84*, 1074–1078.

Little, R. E., Mandell, W., and Schultz, F. A. (1977). Consequences of retrospective measurement of alcohol consumption. J. Stud. Alcohol *38*, 1777–1780.

Little, R. E., and Weinberg, C. R. (1993). Risk factors for antepartum and intrapartum stillbirth. Am J Epidemiol *137*, 1177–1189.

Lundsberg, L. S., Bracken, M. B., and Saftlas, A. F. (1997). Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. Ann. Epidemiol *7*, 498–508.

Marbury, M. C., Linn, S., Monson, R., Schoenbaum, S., Stubblefield, P. G., and Ryan, K. J. (1983). The association of alcohol consumption with outcome of pregnancy. Am.. J. Public Health *73*, 1165–1168.

Martin, J., Curtin, S., Saulnier, M., and Mousavi, J. (2003). *Development of the matched multiple birth file. In: 1995–1998 matched multiple birth dataset. NCHS CD-ROM series 21, no. 13a*. Hyattsville (MD): National Center for Health Statistics.

Mills, J. L., and Graubard, B. I. (1987). Is moderate drinking during pregnancy associated with an increased risk for malformations? Pediatrics *80*, 309–314.

Nordberg, L., Rydelius, P. A., and Zetterström, R. (1994). Parental alcoholism and early child development. Acta. Paediatr *404*, 14–18.

Panduro Barón, J. G., Vázquez Granados, M. D., Pérez Molina, J. J., and Castro Hernández, J. F. (2006). Prenatal risk factors in late fetal death. Ginecol. Obstet. Mex *74*, 573–579.

Passaro, K. T., Little, R. E., Savitz, D. A., and Noss, J. (1996). The effect of maternal drinking before conception and in early pregnancy on infant birthweight. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Epidemiology *7*, 377–383.

Pennington, S. (1988). Ethanol-induced growth inhibition: the role of cyclic AMP-dependent protein kinase. Alcohol Clin. Exp. Res *12*, 125–129.

Randall, C. L., Anton, R. F., and Becker, H. C. (1987). Alcohol, pregnancy, and prostaglandins. Alcohol Clin. Exp. Res *11*, 32–36.

Rostand, A., Kaminski, M., Lelong, N., Dehaene, P., Delestret, I., Klein-Bertrand, C., Querleu, D., and Crepin, G. (1990). J. Epidemiol. Community. Health *44*, 302–306.

Salihu, H. M., Bekan, B., Aliyu, M. H., Rouse, D. J., Kirby, R. S., and Alexander, G. R. (2005). Perinatal mortality associated with abruptio placenta in singletons and multiples. Am. J. Obstet. Gynecol *193*, 198–203.

Sharma, P. P., Salihu, H. M., and Kirby, R. S. (2007). Stillbirth recurrence in a population of relatively low-risk mothers. Pediatr. Perinat. Epidemiol *21*, 24–30.

Sokol, R. J., Miller, S. I., and Reed, G. (1980). Alcohol abuse during pregnancy: an epidemiologic study. Alcohol Clin. Exp. Res *4*, 135–145.

Spohr, H. L., Willms, J., and Steinhausen, H. C. (1993). Prenatal alcohol exposure and long-term developmental consequences. Lancet *341*, 907–910.

Stoler, J. M., Ryan, L. M., and Holmes, L. B. (2002). Alcohol dehydrogenase 2 genotypes, maternal alcohol use, and infant outcome. J. Pediatr *141*, 780–785.

Tønnesen, H., Petersen, K. R., Højgaard, L., Stokholm, K. H., Nielsen, H. J., Knigge, U., and Kehlet, H. (1992). Postoperative morbidity among symptom-free alcohol misusers. Lancet *340*, 334–337.

Verkerk, P. H. (1992). The impact of alcohol misclassification on the relationship between alcohol and pregnancy outcome. Int. J. Epidemiol *21*, S33–S37.

Walles, B., Tydén, T., Herbst, A., Ljungblad, U., and Rydhstrøm, H. (1994). Maternal health care program and markers for late fetal death. Acta. Obstet. Gynecol. Scand *73*, 773–778.