Risk for Congenital Anomalies Associated with Different Sporadic and Daily Doses of Alcohol Consumption during Pregnancy: A Case–Control Study

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Received 11 August 2003; Accepted 27 January 2004

BACKGROUND: The classic clinical criteria for the diagnosis of fetal alcohol syndrome (FAS) include a "characteristic" facial appearance, pre- and postnatal growth deficiency, microcephaly, mental retardation, and occasional major malformations. However, diagnostic constraints, especially in the newborn period, lead to an underestimate of their prevalence. We report an epidemiological study of the potential risk of congenital defects in the offspring of mothers who ingested different sporadic and daily amounts of alcohol during pregnancy. **METHODS:** The study was based on the data from the ECEMC hospital-based case–control study and surveillance system, with a methodology aimed not only at the surveillance of congenital anomalies, but also at investigating their characteristics, clustering, and causes. For the purposes of this study, we considered as exposed those infants whose mothers reported the ingestion of any amount of alcohol during gestation (4705 mothers of cases and 4329 mothers of controls), and classified them into five groups according to their levels of alcohol consumption. Two groups consisted of mothers who consumed increasing sporadic levels and the other three consisted of mothers who consumed increasing daily levels of alcohol. **RESULTS:** Our study showed that even low sporadic doses of alcohol consumption during pregnancy may increase the risk of congenital anomalies in the offspring and that this risk increases with increasing levels of alcohol exposure. **CONCLUSIONS:** The results of our study suggest that it is necessary to generalize the preventive norm and recommend complete abstinence from alcohol during gestation. *Birth Defects Research (Part A) 70:194–200, 2004.*

Key words: alcohol and pregnancy; risk for congenital anomalies; fetal alcohol syndrome; FAS

INTRODUCTION

Although the first description of children with unusual facial characteristics, growth deficiency, and other abnormalities born to alcoholic women was done in the 1950s (Rouquette, 1957; Bookstein et al., 2001), the effect of prenatal exposure to alcohol went unrecognized by the scientific community until the description of fetal alcohol syndrome (FAS) by Jones and Smith (1973). Since then, numerous studies have confirmed the teratogenic effects of this social drug.

The classic clinical criteria for the diagnosis of FAS include a "characteristic" facial appearance, pre- and postnatal growth deficiency, microcephaly, mental retardation, and occasional major malformations. Short palpebral fissures, shallow philtrum, and thin upper lip are considered essential for the diagnosis, whereas other facial abnormalities, such as epicanthal fold, ptosis of the eyelids, low nasal bridge, short nose, flat midface, and micrognathia, are optional. Major malformations, including central nervous system (CNS) defects, and cardiac, renal, skeletal, ocular, and other structural malformations, have also been reported as part of the syndrome (Clarren and Smith, 1978;

Grant sponsor: Instituto de Salud Carlos III (Ministerio de Sanidad y Consumo); Grant sponsor: Fundación 1000 of Spain; Grant sponsor: Consejerías de Sanidad of Spanish Regions of Aragón, Cantabria, Castilla y León, Castilla La-Mancha, Extremadura, Galicia, Comunidad de Madrid, Región de Murcia, Comunidad Foral de Navarra, La Rioja y Comunidad Valenciana.
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Published online 2 April 2004 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20017

Mills and Graunbard, 1987; Martínez-Frías and Rodríguez-Pinilla, 1991; Swayze et al., 1997; May and Gossage, 2001). Prenatal exposure to alcohol has also been linked to neurodevelopmental disorders, neuropsychiatric abnormalities, and hyperactivity, even in the absence of evident dysmorphism (Sampson et al., 1997; Streissguth and O'Malley, 2000). However, diagnostic constraints, especially in the newborn period, lead to an underestimate of the true prevalence of the problem (Stoler and Holmes, 1999). In addition, controversy still surrounds the definition of the minimal levels of alcohol that may adversely affect embryonic and fetal development (Abel, 1999a, 1999b; Jones and Chambers, 1999; Guerri et al., 1999; Armstrong and Abel, 2000).

We present an epidemiological study of the potential risk of congenital malformations in the offspring of mothers who reported drinking different amounts of alcohol during pregnancy, either sporadically or daily.

MATERIALS AND METHODS

The study was based on the data from the Spanish Collaborative Study of Congenital Malformations (ECEMC). This is a hospital-based case–control study and surveillance system with a methodology aimed not only at the surveillance of congenital anomalies, but also at investigating their characteristics, their clustering, and their causes. The ECEMC is made up of two main groups: 1) the data collecting group (peripheral group), which includes physicians in over 86 collaborating hospitals throughout Spain, who, being interested in the problem of congenital defects, collaborate with the ECEMC program and follow a common strict methodology. These physicians identify the cases and control infants and gather the information using a detailed operational manual; and 2) the coordinating group, located in Madrid, which consists of a group of experts in dysmorphology, clinical genetics, cytogenetics, teratology, and epidemiology, and in collaboration with the physicians of the peripheral group, make the diagnosis, codify the congenital anomalies identified in the cases, and perform genetic and epidemiological analyses.

The methodology of the ECEMC can be summarized as follows:

Malformed Infants (Cases)

The collaborating physicians examine all newborn infants in each participating hospital during the first three days of life to identify and describe those with major and/or minor congenital defects (cases). They send the information to the coordinating group on a monthly basis. In many instances, photographs, karyotypes with high-resolution bands (550–850 bands), FISH techniques, imaging studies, pathology reports, and results of other studies are also available for review.

The ECEMC methodology includes the application of a modified version of the ICD-8 codes for congenital defects (by adding two more digits in order to obtain more specificity). This system, which has three coding levels, has been previously published (Martínez-Frías and Urioste, 1994).

Control Children

For each malformed infant (case), the next nonmalformed infant of the same sex born in the same hospital is selected as a control subject, and the same data that was gathered from the malformed infant is obtained. These controls are selected from the same population as the cases and are representative of those who, had they developed malformations, would have been selected as cases.

Exposure Variables

For each infant, whether a case or a control, data for 304 variables are collected. Physicians, who at that time are blinded to any types of prenatal exposure and other variables, identify cases and control infants. After the identification of cases and control infants, the same physicians interview the mothers of cases and control infants within the first three days after delivery. Using defined protocols, they gather information on family history, obstetrical data, and exposures during pregnancy such as acute and chronic maternal diseases, drugs, alcohol, etc. The methodology of the ECEMC has been published previously (Martínez-Frías,1995; Martínez-Frías et al., 1998, 2002).

Information on alcohol consumption is gathered by asking the type of alcoholic beverages ingested during gestation, the amount per day (or other specified periodicity), and the moments of pregnancy during which consumption occurred, e.g., sporadic, throughout the whole pregnancy, or during other specified periods during gestation.

Definition of Absolute Alcohol Ingested

In Spain, the alcohol content of beers ranges between 2–6%, for an average of 4%, while the average for wine is 12%. The alcohol content in distilled spirits ranges from 40–50%. Based on their usual volume and alcohol gradation, it is estimated that in Spain a standard drink of beer or wine contains 10 gm absolute alcohol, and that a standard drink of distilled spirits, has 20 gm absolute alcohol.

Definition of Exposed and Nonexposed Infants

For the purposes of this study, we considered as exposed those infants whose mothers reported drinking any amount of alcohol during pregnancy. According to the volume of the beverages consumed, their alcohol content, and the periodicity of consumption, the infants were grouped into five levels (in addition to the nonexposed group): two levels for those infants whose mothers drank sporadically, and three levels for those infants whose mothers ingested alcohol daily.

Level 1. This group, comprising 1737 cases and 1633 controls, included the offspring of women who reported drinking no more than one or two glasses of wine or beer sporadically during gestation, i.e., 10–20 gm absolute alcohol, sporadically.

Level 2. Mothers of these children indicated that they had sporadically consumed several glasses of wine and/or beer, together with several glasses of distilled spirits such as gin, whisky, or others during gestation. This implies a minimum of 90 gm absolute alcohol and a maximum of sporadic binges. A total of 101 cases and 101 controls were included in this level.

Level 3. This group consisted of infants whose mothers drank 250–500 ml wine or 500–1000 ml beer daily during the whole gestational period. Consequently, their daily ingestion of absolute alcohol ranged from 16–48 gm. A total of 2267 cases met this criterion and 2141 controls were included in this level.

Table 1
Odds Ratio for Different Congenital Defects of Prenatal Exposure to Level 1 of Alcohol*

	Cases		Controls				
Defects	+	−	+	−	OR	CI	*p*
Hypoplastic nose, flat/facial anomalies	85	1327	103	1355	0.84	0.62–1.15	0.258
Central nervous system defects	108	1407	94	1373	1.12	0.83–1.51	0.433
Eye anomalies	44	530	28	547	1.62	0.97–2.72	0.051
Microphthalmia	14	141	6	151	2.50	0.87–7.52	0.060
Microcephaly	12	187	9	184	1.31	0.50–3.47	0.548
Congenital heart defects/vascular anomalies	111	1496	109	1487	1.01	0.76–1.34	0.931
Oral clefts	93	1313	100	1308	0.93	0.68–1.25	0.609
Genital defects	229	3231	237	3168	0.95	0.78–1.15	0.573
Limb reduction defects (excluding hypoplastic phalanges)	60	685	49	701	1.25	0.83–1.89	0.258
Intestinal atresias/TEF/anal atresia	52	606	44	609	1.19	0.77–1.84	0.418
Renal defects	78	1075	94	1052	0.81	0.59–1.12	0.190
Spine/rib defects	25	397	20	402	1.27	0.67–2.41	0.444

*n = 1737 cases and 1633 controls.

Level 4. Mothers of the children in this group drank daily throughout gestation: either 250–500 ml wine or 500–1000 ml beer, plus two glasses of distilled spirits (gin, whisky, or others); or 500–1000 ml wine or 1000–2000 ml beer, and no distilled spirits. That is a daily range of absolute alcohol ingestion of 56–88 gm. A total of 109 cases and 86 controls were included in this level.

Level 5. This group includes children whose mothers reported that they drank more than 500 ml wine or more than 1000 ml beer, plus several glasses of distilled spirits (gin, whisky, or others) daily, and those who reported that they were alcoholic. The absolute alcohol ingestion in this group was over 92 gm per day. Of the malformed infants (cases), 67 were included in this level, and 20 of the controls were included in this level.

Malformed and healthy control infants whose mothers denied having drank during gestation constituted the nonexposed groups.

Selection of Defects To Be Analyzed

We analyzed 11 groups of defects, selected because they have been widely recognized as being related to prenatal exposure to alcohol. These groups were: all types of central nervous system (CNS) defects (including microcephaly); microcephaly; all types of eye anomalies; microphthalmia; facial anomalies (hypoplastic nose, flat/broad nasal bridge, and other facial anomalies described in infants with FAS); cardiovascular defects; oral clefts; genital defects; limb deficiencies (excluding hypoplastic phalanges to avoid diagnostic bias); intestinal atresias (including esophageal and anal atresias); renal defects; and spine/rib defects.

Statistical Analysis

We estimated the odds ratio (OR), 95% confidence intervals, and the Fisher's *p*-value. Between January 1977 and June 2001, the ECEMC surveyed a total of 1,820,862 liveborn infants. Among them, 30,836 were selected as cases because they had major and/or minor/mild anomalies detected during the first three days of life. A similar number of controls were collected. For the present analysis, we excluded all infants with known syndromes and those with chromosomal abnormalities, as well as those who were prenatally exposed to any type of known teratogenic factor other than alcohol. Thus, we analyzed a total of 26,364 malformed infants and 25,836 controls, with specified information of alcohol ingestion during gestation. Among these, 4705 mothers of cases and 4329 mothers of controls reported consuming one or more drinks of alcohol during pregnancy. These numbers are different from those included in the five levels, because we excluded those infants whose mothers answered that they consumed alcohol, but without specifying amount or periodicity.

RESULTS

Sporadic Exposure to Alcohol during Gestation

Table 1 shows the risk of malformations in infants prenatally exposed to low and sporadic amounts of alcohol (Level 1). The risk for eye anomalies showed an OR = 1.62 (95% CI, 0.97–2.62; $p = 0.051$). Among the rest of the defects we studied, the risk for microphthalmia had an OR = 2.50 (95% CI, 0.87–7.52), but with a p value of 0.06.

Table 2, which portrays the risks of malformations in the offspring of women in Level 2 of alcohol ingestion (high doses, but sporadically during gestation), shows that the OR for limb deficiencies (excluding hypoplastic phalanges) was 7.16 (95% CI, 0.89–155.3; $p = 0.03$). However, due to the small sample size, the lower confidence interval is below unity, while the upper confidence interval is very large. Similarly, the risk for oral clefts was 3.49 with a confidence interval between 0.67 and 24.29.

Daily Exposure to Alcohol during Gestation

Table 3 summarizes the risks observed in the children born to women classified in Level 3 of prenatal alcohol ingestion, which included women who drank 16–48 gm absolute alcohol daily during gestation. In this group, the OR for facial anomalies (corresponding to those described in FAS) was 1.55 (95% CI, 1.17–2.06; $p < 0.001$). None of the other malformations reached a level of statistical significance.

Among the offspring of mothers who ingested 56–88 gm of alcohol daily during gestation (Table 4), the frequency of eye anomalies was significantly higher ($p < 0.007$) than in the offspring of mothers who did not drink during gestation. Among the rest of the defects, all but genital defects, limb deficiencies, and spine/ribs defects had ORs over

Table 2
Odds Ratio for Different Congenital Defects of Prenatal Exposure to Level 2 of Alcohol*

Defects	Cases +	Cases −	Controls +	Controls −	OR	CI	*p*
Hypoplastic nose, flat/facial anomalies	5	1327	9	1355	0.57	0.17–1.85	0.304
Central nervous system defects	7	1407	7	1373	0.98	0.31–3.09	0.964
Eye anomalies	3	530	4	547	0.77	0.14–4.10	0.738
Microphthalmia	0	141	0	151	—	—	—
Microcephaly	0	187	3	184	0.00	0.00–2.23	0.082
Congenital heart defects/vascular anomalies	5	1496	3	1487	1.66	0.35–8.73	0.485
Oral clefts	7	1313	2	1308	3.49	0.67–24.29	0.097
Genital defects	14	3231	20	3168	0.69	0.33–1.42	0.279
Limb reduction defects (excluding hypoplastic phalanges)	7	685	1	701	7.16	0.89–155.3	0.032
Intestinal atresias/TEF/anal atresia	4	606	3	609	1.34	0.25–7.55	0.701
Renal defects	2	1075	6	1052	0.33	0.05–1.78	0.149
Spine/rib defects	2	397	1	402	2.03	0.14–56.59	0.557

*n = 101 cases and 101 controls.

unity, but possibly due to the very small sample sizes, the results were not statistically significant.

Table 5 depicts the results observed in the group of mothers included in Level 5, which corresponds to those who drank over 92 gm absolute alcohol per day throughout gestation. The results indicate an increased risk for all the studied defects except for three of them (genital defects, intestinal/esophageal/anal atresias, and vertebral/rib defects) in which the results were not statistically significant, and two (microphthalmia and limb deficiencies),

Table 3
Odds Ratio for Different Congenital Defects of Prenatal Exposure to Level 3 of Alcohol*

Defects	Cases +	Cases −	Controls +	Controls −	OR	CI	*p*
Hypoplastic nose, flat/facial anomalies	143	1327	94	1355	1.55	1.17–2.06	0.001
Central nervous system defects	133	1407	151	1373	0.86	0.67–1.11	0.225
Eye anomalies	39	530	40	547	1.01	0.62–1.63	0.979
Microphthalmia	15	141	12	151	1.34	0.57–3.17	0.470
Microcephaly	16	187	25	184	0.63	0.31–1.27	0.167
Congenital heart defects/vascular anomalies	72	1496	87	1487	0.82	0.59–1.15	0.232
Oral clefts	133	1313	107	1308	1.24	0.94–1.63	0.115
Genital defects	316	3231	297	3168	1.04	0.88–1.24	0.617
Limb reduction defects (excluding hypoplastic phalanges)	65	685	56	701	1.19	0.81–1.75	0.365
Intestinal atresias/TEF/anal atresia	45	606	51	609	0.89	0.57–1.37	0.571
Renal defects	63	1075	49	1052	1.26	0.84–1.88	0.239
Spine/rib defects	33	397	28	402	1.19	0.69–2.08	0.507

*n = 2267 cases and 2141 controls.

Table 5
Odds Ratio for Different Congenital Defects of Prenatal Exposure to Level 5 of Alcohol*

Defects	Cases +	Cases −	Controls +	Controls −	OR	CI	*p*
Hypoplastic nose, flat/facial anomalies	35	1327	0	1355	—	—	0.000000
Central nervous system defects	18	1407	1	1373	17.57	2.49–353.8	0.0001
Eye anomalies	16	530	0	547	—	—	0.00009
Microphthalmia	3	141	0	151	—	—	0.075
Microcephaly	13	187	0	184	—	—	0.0004
Congenital heart defects/vascular anomalies	12	1496	1	1487	11.93	1.62–246.0	0.002
Oral clefts	9	1313	2	1308	4.48	0.91–30.06	0.036
Genital defects	8	3231	3	3168	2.61	0.63–12.41	0.141
Limb reduction defects (excluding hypoplastic phalanges)	6	685	1	701	6.14	0.74–135.7	0.055
Intestinal atresias/TEF/anal atresia	6	606	2	609	3.01	0.55–21.65	0.157
Renal defects	4	1075	0	1052	—	—	0.048
Spine/rib defects	2	397	0	402	—	—	0.155

*n = 67 cases and 20 controls.

Table 4
Odds Ratio for Different Congenital Defects of Prenatal Exposure to Level 4 of Alcohol*

	Cases		Controls				
Defects	+	−	+	−	OR	CI	*p*
Hypoplastic nose, flat/facial anomalies	10	1327	5	1355	2.04	0.64–6.86	0.184
Central nervous system defects	12	1407	8	1373	1.46	0.56–3.92	0.403
Eye anomalies	7	530	0	547	—	—	0.007
Microphthalmia	1	141	0	151	—	—	0.302
Microcephaly	3	187	1	184	2.95	0.27–74.31	0.328
Congenital heart defects/vascular anomalies	4	1496	2	1487	1.99	0.32–15.60	0.419
Oral clefts	8	1313	5	1308	1.59	0.47–5.60	0.410
Genital defects	8	3231	12	3168	0.65	0.24–1.72	0.349
Limb reduction defects (excluding hypoplastic phalanges)	3	685	4	701	0.77	0.14–4.05	0.729
Intestinal atresias/TEF/anal atresia	5	606	3	609	1.67	0.35–8.86	0.477
Renal defects	3	1075	1	1052	2.94	0.27–73.31	0.328
Spine/rib defects	2	397	3	402	0.68	0.08–4.97	0.666

*n = 109 cases and 86 controls.

in which the p values were within the limit of statistical significance. However, we need to consider that the sample sizes in these five defects were too small to reach statistical significance.

In addition, differences in birth weight, length, and occipital-frontal circumference (OFC) were observed between the groups of nonexposed malformed infants and infants with prenatal exposure to alcohol in Levels 4 and 5, with increasing differences from Level 4 to Level 5. In nonexposed infants, these parameters were: mean birth weight (n = 21,488), 3174.40 gm (SD = 591.76); mean gestational age (n = 20,339), 39.09 weeks (SD = 2.24); birth length (n = 7803), 49.08 cm (SD = 3.10); and OFC (n = 7803), 34.01 cm (SD = 1.97).

In Level 4, only the birth length and the OFC were different. The birth length was 47.15 cm (n = 13), SD = 4.07, $p < 0.05$, and the OFC (n = 14), was 32.93 cm (SD = 2.52), $p < 0.05$.

In infants prenatally exposed to Level 5 of alcohol, most of the measures were lower and the differences, statistically significant: mean birth weight (n = 67) was 2275.97 gm (SD = 669.50; $p << 0.001$), while gestational age was not significantly different from the nonexposed group (means of 38.17 and 39.09, respectively); mean birth length was (n = 21), 42.00 cm (SD = 4.22; $p << 0.001$, and the mean OFC (n = 21) was 30.57 cm (SD = 2.46; $p < 0.001$). In summary, the mean birth weight of malformed infants with prenatal exposure to the highest doses of alcohol (Level 5) was 898.43 gm lower than the mean birth weight of malformed infants who were not exposed to alcohol, while their mean gestational ages were not significantly different. Similarly, the mean birth length and OFC were, respectively, 7.07 cm and 3.44 cm lower than those of the nonexposed infants. We also analyzed the birth weight controlling for maternal smoking and observed that birth weight in children born to smoking and nonsmoking mothers in Level 5 of alcohol consumption was significantly lower than those of nondrinking smoking and nonsmoking mothers, respectively.

DISCUSSION

As with all human teratogens, the effects of alcohol on prenatal development should vary in relation to the level of exposure, the moment in pregnancy when this exposure occurs, and the genetic susceptibility of the mothers, among other factors. Our results suggest that even very low sporadic doses of alcohol during gestation may increase the risk of eye anomalies and that the sporadic ingestion of higher doses of alcohol may increase the risk of different types of congenital defects, depending on the moment of gestation when the exposure occurs.

In the three groups that ingested alcohol on a daily basis, we observed an increasing magnitude of the ORs and the number of defects reaching statistical significance from the level with less alcohol ingestion (Level 3) to the highest alcohol consumption (Level 5). Although a significant association in some cases (Tables 3 and 5) is with facial anomalies, as stressed by others (Streissguth and O'Malley, 2000; Coles et al., 2000; Sood et al., 2001), it is important to recognize that these may be an indication of CNS abnormalities leading to varying degrees of mental retardation and other neurodevelopmental disorders.

While numerous studies of children with different manifestations of FAS characteristics have been published (Clarren and Smith, 1978; Mills and Graunbard, 1987; Martínez-Frías and Rodríguez-Pinilla, 1991; Swayze et al., 1997; Sampson et al., 1997; Astley and Clarren, 2000; Streissguth and O'Malley, 2000; May and Gossage, 2001), we have failed to identify any epidemiological case–control study on newborn infants investigating the association of different types of congenital defects with prenatal alcohol exposure. Case–control studies have been published that report on the relationship between prenatal exposure to alcohol and a particular congenital defect (Werler et al, 1991; Munger et al., 1996). In the case–control study conducted by Shaw and Lammer (1999), the authors found an increased risk of cleft lip with or without cleft palate in the offspring of women who ingested relatively low quantities of alcohol during pregnancy and a greater risk among the offspring of those who ingested larger quantities. In our data, the ORs for oral clefts were over unity in Levels 2–5 (Tables 2–5), and similarly to the results observed by Shaw and Lammer (1999), the magnitude of the ORs increased from 1.24 (Level 3), to 1.59 (Level 4), to 4.48 (Level 5). The high magnitude of the OR (3.49) for oral clefts observed in mothers who drank high sporadic amounts of alcohol (Table 2) may be the result of consumption of large doses during the critical period of embryogenesis.

In a recent statement of the Public Affairs Committee of the Teratology Society, Adams et al. (2002) highlighted the difficulties of recognizing the effects of prenatal alcohol exposure in children under four years of age, with the possible exception of those at the most severe end of the spectrum, who represent classic FAS. In the present study, we found that prenatal exposure to alcohol increases the risk of different congenital malformations detected at birth and that the likelihood of malformations as well as the number of defects increases with increasing prenatal alcohol consumption. It is well recognized that the effect of alcohol during pregnancy is a continuum from prenatal lethality (Windham et al., 1997), intrauterine growth retardation, perinatal mortality, nonspecific congenital malformations, classical FAS, and neurodevelopmental or neuropsychiatric disorders. Thus, we feel it would be more appropriate to refer to any infant prenatally exposed to alcohol presenting with any of these problems as having "alcohol embryofetopathy" to denote the variability in expression of prenatal exposure to alcohol.

Controversy still exists regarding the minimal level of alcohol consumption that may cause adverse effects on embryonic or fetal development. Abel (1999a, b), considers that human alcohol teratogenesis is linked to alcohol abuse, and that the difficulties of determining a "safe dose" of alcohol consumption during pregnancy arise from the tendency to report drinking as estimated daily averages, rather than actual daily consumption. The Guidelines of the British Royal College of Obstetricians and Gynaecologists (RCOG, 1996) on alcohol consumption during pregnancy, state that "no adverse effects on pregnancy outcome have been proven with a consumption of less that 120 gm (15 units) per week." They further recommend that "women should be careful about alcohol consumption in pregnancy and limit this to no more than one standard drink per day." While these guidelines have been criticized by some authors (Guerri et al., 1999), they are congruent with the views of others (Abel 1999a, b; Armstrong and Abel, 2000), who opine that it has not been proven that low doses of alcohol have an adverse effect on embryonic or fetal development. Our study shows that very low and sporadic doses of prenatal exposure to alcohol were associated with an increased risk of eye anomalies and possibly others. For this reason, we strongly disagree with the RCOG (1996) statement.

In the present study, we also found that the effects of high sporadic doses, as those observed in the offspring of women in Level 2 (Table 2), were different from the effects of daily consumption (Tables 3–5). As stated above, the effects of high sporadic doses of alcohol (usually weekend ingestion) may vary in type and severity in relation to the period of gestation when ingestion occurred. In fact, as depicted in Table 2, the risks have different magnitudes and some of them reach the level of significance; e.g. the risk for limb deficiencies (excluding phalanges) was OR = 7.16 (95% CI, 0.89–155.3; $p = 0.03$), while other defects, commonly seen in prenatal alcohol exposure, did not show increased risks.

A limitation of our study, which is common to all studies of alcohol consumption during gestation, is the difficulty to determine the true maternal ingestion of alcoholic beverages. It is widely accepted—and it is also our experience—that in retrospective interviews regarding alcohol consumption during gestation, mothers tend to not admit that they consumed alcoholic beverages during pregnancy or to minimize the real amounts they drank. Moreover, as we previously observed in our population (Martínez-Frías, 1993), when the interview of the mothers takes place immediately after birth (as it is in our program), the mothers of malformed infants tend not to answer all questions in detail. Consequently, some infants classified as nonexposed may in reality have been prenatally exposed to alcohol. However, these biases would modify the magnitude of the risk towards the null hypothesis, and would not affect the statistically significant ORs observed in our study, but it would affect those in which the results did not reach statistical significance. It is also possible that some women reported the ingestion of alcohol considering their consumption from the time they recognized their pregnancy on. This underreporting would decrease the proportion of exposed infants and, consequently, the magnitude of the risk. As stated above, this would not affect the risks that are statistically significant, although they could affect those that did not reach the level of significance.

Another limitation of our study is that we have not controlled for other potential confounders. Nonetheless, we excluded from the analysis all malformed infants who had recognizable syndromes and chromosomal abnormalities as well as those who were prenatally exposed to any type of known teratogenic factor other than alcohol. Illicit drugs could be considered as confounder factors, but in our data very few mothers consume these drugs, and the majority of those who do are in the groups with the highest levels of alcohol consumption and in similar proportions among mothers of cases and controls. Maternal socioeconomic level is another potential confounder factors. In a previous study (Martínez-Frías et al., 2003), we demonstrated a relationship between the level of maternal education and the amount of alcohol ingested and showed that this was similar among mothers of cases and controls.

The teratogenicity of prenatal alcohol exposure has been well established. While it is true that the minimal level that may have an adverse effect on pregnancy outcome has not been proven (RCOG, 1996; Abel 1999a, b; Armstrong and Abel, 2000), it is also true that neither has the dose of alcohol that could be considered safe during pregnancy. Consequently, total abstinence during pregnancy should be recommended. Although it is possible that the dose–effect relationship varies according to genetic predisposition or susceptibility of the exposed women (McCarver et al., 1997; Jacobson et al., 2000; Viljoen et al., 2001; Stoler et al., 2002), it is not currently possible to identify individuals at higher or lower risk. This makes it necessary to generalize the preventive norm and recommend complete abstinence during gestation. Our observation of an increased risk for some congenital anomalies that are suggestive of a neurological affectation in the offspring of mothers who drank very low and sporadic doses of alcohol reaffirms this recommendation.

ACKNOWLEDGMENTS

We thank all the physicians who collaborated with the ECEMC program in collecting the data.

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