A CRITICAL REVIEW of “Risk for congenital anomalies associated with different sporadic and daily doses of alcohol consumption during pregnancy: A case-control study.” Martínez-Frias, ML, Bermejo, E, Rodríguez-Pinilla, E, Frias, JL, Birth Defects Research (Part A), 2004; MMWR, 2004;70(4):194-200.1

Alcohol consumption by the pregnant woman can result in negative effects in the unborn child. This is known as Fetal Alcohol Spectrum Disorder (FASD), which includes the full-blown Fetal Alcohol Syndrome (FAS). These effects can manifest both physically and mentally in the child and have major impact on quality of life.1,2 Given the paucity of information regarding the exact quantity of alcohol consumption that can result in these detrimental effects, the Surgeon General of the United States as well as Health Canada advise women to refrain from consuming any alcohol-containing beverages during pregnancy.3,4

While problem drinking is associated with adverse fetal outcome, the threshold of this phenomenon has not been established. In efforts to address this lack of knowledge, Martínez-Frias et al. conducted a case-control study aimed at examining the association of sporadic and daily consumption of alcohol. In this case control study, data from the Spanish Collaborative Study of Congenital Malformations (ECEMC) were used.

The ECEMC surveillance system facilitates the performance of case-control studies. This unique system comprises of 86 hospitals in Spain that collect case and control infants. Infants in these facilities with major or minor congenital defects are diagnosed in the first three days of life. The next gender-matched non-malformed infant in the same facility serves as the control for each case. Test results of the infants as well as information regarding maternal exposures are sent to a coordinating center in Madrid.

Infants were grouped into five categories based on their mother’s drinking reports. Level 1 consisted of mothers who reported drinking no more than one or two glasses of wine or beer (10-20gm absolute alcohol) sporadically during gestation. Level 2 consisted of mothers who reported drinking several glasses of wine and/or beer coupled with distilled spirits (at least 90gm absolute alcohol). Level 3 consisted of mothers who reported 250–500mL of wine or 500–1000mL of beer (16-48gm) daily throughout the pregnancy. Level 4 consisted of mothers who reported drinking either 250–500 ml wine or 500–1000 mL beer, plus two glasses of distilled spirits; or 500–1000 mL wine or 1000–2000 mL beer, and no distilled spirits (56-88gm). Level 5 consisted of mothers who reported drinking more than 500 ml wine or more than 1000 ml beer, plus several glasses of distilled spirits daily (greater than 92 gm absolute alcohol) and those who reported that they were alcoholic. The non-exposed group consisted of mothers who denied any drinking during their pregnancy.

The authors selected 11 groups of common effect associated with prenatal alcohol exposure to analyze: all types of central nervous system (CNS) defects; all types of eye anomalies; microphthalmia; facial anomalies; cardiovascular defects; oral clefts; genital defects; limb deficiencies; intestinal atresias; renal defects; and spine/rib defects. After excluding infants with chromosomal abnormalities and known teratogenic exposures, the odds ratios, 95% confidence interval and Fisher’s p-value were calculated.

From January 1977 to June 2001, ECEMC assessed 1,820,862 liveborn infants, of which 30,836 infants were diagnosed as having major
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and/or minor abnormalities. The matching control infants were collected. After excluding infants with chromosomal abnormalities and known exposure to other teratogens, 26,354 malformed and 25,836 control infants remained for analysis. 4,705 mothers of the malformed infants and 4,329 mothers of the control infants reported alcohol consumption. Women who were not able to specify the quantity and frequency of alcohol consumption were excluded.

The Level 1 group consisted of 1,737 cases and 1,633 controls. Prominent risks noted with 10-20g of alcohol exposure included eye anomalies OR=1.62 (95% CI=0.97-2.62; p=0.051). The odds ratio for microphthalmia was 2.50 (95% CI=0.87-7.52; p=0.06). The Level 2 group consisted of 101 cases and 101 controls. Prominent risks noted with a maximum of 90gm absolute alcohol and sporadic binges included limb deficiencies (excluding hypoplastic phalanges) OR=7.16 (95% CI=0.89-155.3; p=0.03). The risk of oral clefts was OR=3.49 (95% CI=0.67-24.29; p=0.097). The Level 3 group consisted 2,267 cases and 2,141 controls. Prominent risks noted with 16-48 g absolute alcohol exposure included facial anomalies OR=1.15 (95% CI=1.17-2.06; p=0.001). The Level 4 groups consisted of 109 cases and 86 controls. Prominent risks noted with 56-88 g of alcohol exposure included eye anomalies OR=1.01 (95% CI=0.62-1.63; p=0.007). The Level 5 group consisted of 67 cases and 20 controls. Prominent risks noted with over 92 g alcohol exposure included hypoplastic nose, flat/facial anomalies, central nervous system defects, eye anomalies, microcephaly, congenital heart defects/vascular anomalies, and oral clefts. The risk for microphthalmia and limb deficiencies was statistically significant. However the sample size was too small to reach statistical significance for the other anomalies investigated.

In both Level 4 and Level 5, differences were observed in birth weight, length, and occipital-frontal circumference (OFC). In addition increased anomalies were observed with increased alcohol consumption. In unexposed infants, the mean birth weight was 3,174 g (SD=4.07, n=13) and 32.93cm (SD=2.52, n=14), respectively). Additional differences were noted in the Level 5 group. The mean birth weight was 2275.97 gm (SD=669.50; n=67); mean birth length was 42.00 cm (SD=4.22; n=21); mean OFC was 30.57 cm (SD=2.46; n=21).

The authors concluded that even very low sporadic doses of alcohol during gestation may increase eye anomalies and at higher doses would increase the risk of congenital defects associated with the timing of the exposure. This is one of the first epidemiological case-control studies investigating the association of congenital anomalies arising from prenatal alcohol exposure. Other authors conducting case-control studies have also reported relationship between prenatal alcohol exposure and congenital defect. The association of facial anomalies with increased alcohol consumption supports the characteristics commonly associated with FAS. The results are also consistent with that of Shaw and Lammer 1999 who found an increased risk of cleft lip with or without cleft palate in women who ingested low quantities of alcohol during pregnancy. On the other hand, the findings of this study refute those of Lundsberg, et al. who reported no effect of small amounts of alcohol consumption during pregnancy.

The main limitation of this study is that with low level drinking (Level 1), none of the associations was statistically significant, including the two “more likely”, yet the authors interpret their results as if an association was proven. Moreover, it is quite possible that women who drink in pregnancy are very different from those choosing not to drink in important determinants of fetal health, and hence mild alcohol use may be marker rather than a cause.

A second limitation in the study is the fact that the data were based on self-reported alcohol consumption. Bias associated with retrospective self-reporting may be a major limitation as women may not want to be associated with a negative stigma. Because of the decision of the mother to under report or deny the use of alcohol...
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some infants classified as non-exposed, may in fact be prenatally exposed to alcohol. In cases where mothers had malformed infants, they are likely not to answer all questions in detail.\textsuperscript{11}

A potential limitation is that there are 86 hospitals participating in this registry. In total, Spain has 747 hospitals.\textsuperscript{12} Participants in this registry may be biased toward tertiary health care centers or a skewed population and not accurately reflect that of Spain as a whole.

Another potential limitation is that pregnancies that are therapeutically aborted are not evaluated for congenital anomalies. Another matter to consider is that therapeutic abortions were illegal in Spain until 1985. As such, there may have been an increased rate of termination after that period, thus, skewing the overall results. Other factors that may not be controlled include the use of other medications, the mother's socioeconomic condition, and education level.

It is currently not known how much alcohol is required to cause adverse fetal effects. Although the American and Canadians guidelines advise women abstain from alcohol consumption during pregnancy, the British Royal College of Obstetricians and Gynaecologists states that “it is recommended that women should be careful about alcohol consumption in pregnancy and limit this to no more than one standard drink (120gm) per day.”\textsuperscript{13} The present study claims to show evidence that mild drinking is teratogenic, a claim not supported by the author’s data.

REFERENCES


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