A Study Evaluating for a Threshold Effect of Alcohol Consumption in Pregnancy on Infant Physical Characteristics Ideally has a Control Group Not Ingesting Alcohol

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To the Editor:

A RECENT ARTICLE BY Feldman and colleagues (2012) examined alcohol consumption during pregnancy in regard to infant physical characteristics with particular attention to those associated with fetal alcohol syndrome. The study provides valuable information on defining the specific time intervals during pregnancy when a woman is most susceptible to alcohol-induced abnormalities.

However, the authors state in their conclusions in the final paragraph of the article that "Based on our findings there is no safe threshold for alcohol consumption during pregnancy with respect to alcohol-related physical features." The data from which this major conclusion derives are not presented in the article. The only support for this conclusion is the following statement by the authors: "Assessment for nonlinear relationships for each outcome did not reveal any clustering. Additionally, quadratic models were constructed and did not demonstrate any nonlinear relationships." The data that this summary statement derives from are not shown.

Specifically, the outcome data as presented in Table 3 and Table 4 in the study do not provide any information on whether there is a threshold effect in regard to alcohol ingestion and infant physical features at low levels of alcohol ingestion. Table 3 compares outcomes in infant physical features of those women ingesting less than an average of 1 drink a day (30 drinks per month) and those averaging 1 or more drinks a day (including individuals who averaged over 10 drinks per day). There is not a group in the study that ingested no alcohol to serve as a control group for comparison purposes. Women who drank no alcohol during pregnancy were excluded from this study. Although some infants of women drinking <1 drink daily were found to have physical features such as decreased head circumference and decreased birth weight, there is no group with a lower alcohol intake to compare them with. Particularly, given the select group of women being studied (women who contacted a teratogen counseling phone number for pregnant women), it would not be valid to compare the frequency of the physical abnormalities in the group drinking <1 drink a day with the frequency found in a nondrinking pregnant population from another study.

Table 4 shows evidence that the number of drinks per day is associated with effects on physical characteristics, particularly during the second half of the first trimester of pregnancy. The authors note that for every 1 drink increase in the average number of drinks consumed daily, there is 25% increase (risk ratio of 1.25) in the presence of a smooth philtrum and a 12% increase (risk ratio of 1.12) in microcephaly.

However, the statistical technique of risk ratio calculation, very roughly, in a sense, "averages" the effect of an incremental increase of 0 compared to 1 drink, 1 compared to 2 drinks, 2 compared to 3 drinks, etc. *If there is a consistent step up in the frequency of abnormalities at higher levels of drink intake, there can be a risk ratio of 1.25 for every 1 drink increase in the average drinks consumed per day, even if the data show no step up in risk between no alcohol intake and an average of 1 drink per day (i.e., 30 drinks per month)*. In reality, risk ratio analysis occurs over a continuum of the data, rather than at a discrete step up in values, but the analogy remains the same. The risk ratio of 1.25 can potentially result solely from the extrapolation of the effects of higher levels of alcohol ingestion in this type of statistical analysis.

Hence, the study does not supply the reader with data to directly review to support the conclusion that this study shows "there is no safe threshold of alcohol ingestion with regard to alcohol-related physical abnormalities." *Furthermore, a study examining for the presence of a threshold effect of alcohol ingestion would optimally include a group of nondrinkers as a comparison group to the low-level alcohol ingestion group*.

Would the study's authors publish the scatter plots or detailed tables subdividing alcohol intake showing the physical finding outcomes of smooth philtrum, microcephaly, and reduced birth weight plotted against the amount of alcohol ingestion with particular detail to lower levels of alcohol

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intake for the second half of the first trimester, the time period when the effects of alcohol were most pronounced?

Simply publishing the results of the quadratic equation evaluation would not be sufficient and again would result in the reader having no basis of directly seeing the data that led to this important conclusion.

REFERENCE

Feldman HS, Jones KL, Lindsay S, Slymen D, Klonoff-Cohen H, Kao K, Rao S, Chambers C (2012) Prenatal alcohol exposure patterns and alcohol-related birth defects and growth deficiencies: a prospective study. Alcohol Clin Exp Res 36:670–676.