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Dose-response effect of alcohol consumption during pregnancy and prenatal alcohol exposure: A brief review

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Issue:

Fetal Alcohol Spectrum Disorder (FASD) is the most common type of developmental disability worldwide. One of the most important unanswered questions in the field is "how much alcohol in pregnancy is too much?" or what is the "safe" amount of alcohol consumption in pregnancy. The question has been evaluated extensively in humans and in animal models and the answer is not simple unfortunately.

Background:

Whether one is studying drugs for treatment or environmental agents as toxins, the evaluation is done in terms of a "dose-response" which considers 1) the amount of the compound received (dose) and 2) the result (response). When working on the problem of dose-response of alcohol for FASD, both parts of the equation are complex.

Dose:

Generally, people do not know exactly how much alcohol they consume. Liquor and wine are generally poured into glasses of varying sizes, refilled before they are empty and are not often measured, specifically, for quantity. Most people who drink alcohol regularly do not drink the exact same amount on different days and would not remember from week to week how much they consumed. This makes measurement of the precise amount of alcohol consumed in pregnancy, often requested weeks or months after the fact, highly problematic. (1) A further confounding factor is the questionability of self-report data from women related to their alcohol consumption during pregnancy, in some situations. (2)

When alcohol is absorbed it is distributed through the mother's entire body. Alcohol then passes freely through the placenta from the mother's into the fetus' bloodstream. The dose of alcohol that the fetus experiences, however, can be higher than the amount of alcohol in the mother's blood. Because the fetus can only metabolize the alcohol that crosses the placenta to a small extent, the alcohol can accumulate in the amniotic fluid before passing back across the placenta for metabolism and elimination by the mother. This means that the fetus may actually be exposed to a higher dose of alcohol for a longer period of time than the mother. The elimination of alcohol by the mother depends on her metabolism as well as other factors like nutrition, genetics and body weight. (3)

The timing of prenatal alcohol exposure during fetal development is also an important issue. There are a number of critical periods in embryonic development of tissues and structures, some of which are brief and some are prolonged. Data from animal studies and some research in humans shows that organs and tissues that are developing at the time of exposure are particularly susceptible to the teratogenic effects of alcohol. (4,5,6)

It is important to note that damage from alcohol occurs through many different mechanisms at differing times in pregnancy. Thus, a dose exposure at one point during pregnancy can be much more harmful than the same dose at another time. Most of these critical periods in gestation have not been established precisely. But even if they were established, most women do not know the day or hour of their gestation precisely and there are slight variations in the timing of the fetal developmental process.

Beyond these factors of dose amount, maternal factors and gestational timing, different fetuses seem to differ in their genetic susceptibility to prenatal alcohol exposure. Twin studies demonstrate that identical twins seem to be similarly damaged by alcohol while fraternal twins may have very different results, with one twin being much more severally effected than the other. (3)

Response

While the *dose* is difficult to precisely gauge, so too is the *response*. Alcohol does not produce a single abnormality, but instead can produce non-specific clusters of birth defects and/or neurodevelopmental abnormalities (FASD), or the specific birth defect syndrome of FAS.

Each cognitive or behavioural problem can, in turn, vary from severe and obvious early in life, to subtle and apparent only years after birth. Many studies limit their results to finding the more easily recognized Fetal Alcohol Syndrome or major birth defects in newborns or infants (7), but other studies have sought to identify long-term neurodevelopmental abnormalities. (8) However, no study to date has followed alcohol-exposed children for enough years and with enough tests to truly establish the relationship between *any* dose or pattern of alcohol consumption and individual outcomes.

Recommendations:

- Based on the variabilities between mothers and fetuses, metabolism, genetics interactions of environmental factors, it is very unlikely that “absolute risk” for the harmful effects of alcohol consumption during pregnancy will be established and the question of “how much is too much” will remain unanswered. Thus, the best advice is “NO exposure equals NO risk.”
- Public messaging, based on the very best evidence, should suggest abstinence during pregnancy (i.e., “No alcohol is best”, “No safe time, no safe amount, no safe type of alcohol”, etc.)

Bibliography

1. Jacobson, SW, Chiodo LM, Sokol RJ, Jacobson Jl, (2002) Validity of maternal report of prenatal alcohol, cocaine, and smoking in relationship to neurobehavioral outcome. Pediatrics, 109(5) 815-825.

2. Morrow-Tlucak M, Ernhart CB, Sokol RJ, Martier S, Ager J. Underreporting of alcohol use in pregnancy: relationship to alcohol problem history. Alcohol Clin Exp Res. 1989 Jun;13(3):399-401.3. Chudley, AE, (2011) Genetic Factors contributing to FASD in Fetal Alcohol Spectrum Disorder, (eds Riley EP. Clarren, S, Weinberg J and Jonsson E), Wiley-Blackwell, Weinheim, Germany pp 109-126.

4. Clarren, SK (1986) Neuropathology in fetal alcohol syndrome in Alcohol and Brain Development (ed. West, JR) Oxford Press, New York pp 158-166.

5. Michaelis EK (1990) Fetal alcohol exposure: celluar toxicity and molecular events involved in toxicity. Alchol. Clin. Exp. Rep., 14(6), 819-826.

6. Sulik, K Johnston, M, Webb M (1981) Fetal Alcohol Syndrome:embryogenesis in a mouse model,Science 214,936-938.

7. O'Leary HC, Zubiric, SR, Taylor CL, Dixon G, Bower C (2009) Prenatal alcohol exposure and language delay in 2 year old children: the importance of dose and timing on risk Pediatrics 123, 547-554.

8. Streissguth AP, Barr HM, Bookstein FL, Sampson PD, Olson, HC (1999) The long term neurocognitive consequences of prenatal alcohol exposure: a 14 year study Psychology Science 10 186-190.