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## Alcohol in pregnancy: not recommended at any gestational age

Stephanie V. Sun<sup>1</sup>, Tracy A. Manuck<sup>1,2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

<sup>2</sup>Institute for Environmental Health Solutions, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

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Preterm birth remains a multifactorial, worldwide problem. Though there are multiple established risk factors for preterm birth (e.g., previous preterm birth, short cervix), the association between maternal alcohol consumption and prematurity is less clear, with risk ratios ranging from 0.66 (95% CI 0.52–0.84) to 1.34 (95% CI 1.28–1.41) (Strandberg-Larsen et al. *Eur J Epidemiol* 2017;32:751–64; Aliyu et al. *Eur J Public Health* 2010;20:582–87).

In this issue, Ikehara and colleagues (BJOG xxxx) present findings from the Japan Environment and Children's Study, a large nationwide birth cohort. They reported a J-shaped association between the level of alcohol consumption in the second and third trimesters and preterm birth; specifically, a lower risk of prematurity (aOR 0.78, 95% CI 0.60–1.00) in light drinkers but an increased risk of prematurity (aOR 4.52, 95% CI 1.68–12.2) in heavy drinkers (women consuming >300 grams, ~21 standard drinks of alcohol/week). No relationship between first trimester alcohol exposure and prematurity were found. A major study strength is its size, as over 90,000 pregnancies were included.

However, limitations abound. These data – particularly the suggested lower rate of prematurity among light drinkers – should be interpreted with caution. The stigma of alcohol consumption in pregnancy lends itself to substantial risk of underestimation on self-report. Even among alcohol drinkers, data were collapsed into weekly consumption, reducing the ability to evaluate binge drinking vs. daily lower levels of drinking. These data are limited to a homogenous Japanese population, a group more likely to have a genetic predisposition to alcohol intolerance, which likely 'selected' for individuals who cannot tolerate alcohol, and who had an overall low rate of prematurity (4.2%). Further, women with a history of adverse pregnancy outcomes may be less likely to consume substances but due to their prior pregnancy history are more likely to deliver preterm, biasing the results against the abstainers. Though women with a prior preterm birth were excluded from analysis, no additional information was provided regarding pregnancy history or obstetric risk factors. A sensitivity analysis evaluating whether the observed effects – particularly among light drinkers - persist among nulliparas or those with prior uncomplicated pregnancies could

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tmanuck@med.unc.edu.

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address this specific confounder. Additionally, prematurity is used as a surrogate endpoint for the more important – albeit more difficult to study – long-term outcomes of cognitive function, neurodevelopment, and other life-long health indicators. Lastly, even among heavy drinkers, statistical factors should also be considered, particularly given the size of the cohort, as statistical significance is more easily achieved. Only 0.08% (n=73) of women in this cohort consumed moderate or heavy alcohol in the second and third trimesters. Of these, just eight delivered preterm.

While placing these results in context of current clinical recommendations, it is crucial to remember that alcohol is an established teratogen and any degree of alcohol use during pregnancy can have harmful, with potential irreversible effects on fetal brain structure and function and consequently short- and long-term fetal and childhood neurodevelopment (Williams et al. *Pediatrics* 2015;136:e1395–406).

In conclusion, these data underscore the importance of screening for alcohol consumption across gestation, and reinforce continued recommendations for abstinence from alcohol during pregnancy.

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