Safe Caffeine Exposure Levels in Vulnerable Populations: Pregnant Women and Infants

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Maternal Caffeine Exposure and Outcomes of Interest in Pregnancy

- Spontaneous abortion
- Major congenital anomalies
- Intrauterine growth restriction
- Preterm birth
Maternal Caffeine Exposure and Outcomes of Interest in During Lactation

- CNS – e.g., irritability
- Infant growth
Measurement issues

- Few RCT
- Measures most frequently rely on
  - Maternal report of major sources
    - Misclassification of exposure in terms of timing and dose
    - Not all sources ascertained, and imprecise measures of dose
  - Recall with varying length of time since event
- Studies that incorporate biomarker assessment typically do so at only selected time points so not necessarily reflective of exposure over time
Bias Issues

• Possible (likely) confounding by:
  • Comorbidities such as maternal psychiatric disorders, autoimmune diseases, diet, maternal BMI
  • Co-exposures such as alcohol, tobacco use
  • Change in usual caffeine consumption due to symptoms of pregnancy (i.e., nausea and vomiting)
Spontaneous Abortion

• Most difficult pregnancy outcome to study appropriately
  • Highly prevalent adverse outcome – most due to chromosomal aberrations
  • Most occur in clinically unrecognized pregnancies
  • May be misclassified by maternal report (e.g., really a medically induced abortion)
  • Nausea and vomiting of pregnancy is highly protective for spontaneous abortion
  • Many of the known environmental risk factors poorly measured in studies, e.g., tobacco use

• Nevertheless, several studies have suggested an increased risk particularly at higher doses
Spontaneous Abortion

  - 1,063 women enrolled in Kaiser health care plan
  - Positive pregnancy test
  - Interviewed at median 10 weeks gestation and asked about previous caffeine consumption
  - HR <200 mg/day 1.42 (95% CI 0.93, 2.15)
  - HR >= 200 mg/day 2.23 (95% CI 1.34, 3.69)
  - Adjusted for nausea and vomiting of pregnancy
  - Exposure assessment occurred either before or after spontaneous abortion event
Spontaneous Abortion

  - 2,407 women enrolled in a cohort either prior to or in early pregnancy and caffeine consumption measured by maternal interview
  - Caffeine consumption unrelated to increased risk of spontaneous abortion if the event occurred after data collection on caffeine
  - Caffeine consumption related to increased risk of spontaneous abortion if data collected on caffeine use after the abortion event occurred
Congenital Anomalies

- Studies have examined increased risks relative to a variety of specific defects
  - CL with or without CP, CP alone
  - Heart defects
  - Renal anomalies
  - Cryptorchidism
  - Anencephaly
  - Anorectal atresia
- Variable results; ORs, if positive, typically <2
- Typically case control designs with exposure recall months/years after the end of pregnancy
- Little evidence of dose relation; multiple testing
Fetal Growth

- Studies have examined increased risks for fetal growth, small for gestational age on birth weight, length, head circumference, and low birth weight
  - No consistent association
  - CARE Study Group (2008)
  - SGA (<10th centile on birth weight) in one 2008 study of 2,635 women showed little evidence of a dose relation compared to women who consumed <100 mg/day
    - 100-199: OR 1.2 (95% CI 0.9, 1.6)
    - 200-299: OR 1.5 (95% CI 1.1, 2.1)
    - >=300: OR 1.4 (95% CI 1.0, 2.0)
  - Positive studies suggest relatively small effects that might be clinically insignificant
Preterm Birth

- Bech et al (2007) RCT for caffeine reduction in 1,207 women found no effect on length of gestation at average intake of 182 mg/day

- Clausson et al (2002) found no association in 873 pregnancies between caffeine consumption at any level and preterm birth
Biomarkers of Exposure and Genetic Susceptibility

- Few studies have incorporated urine, blood, cord blood markers of exposure
  - When done, these seem to be correlated with maternal report, but are spot measures that may not reflect intra-individual variability
- Data on the relation between polymorphisms for metabolizing enzymes and caffeine-associated outcomes have been somewhat conflicting
Animal Models

- In general, at relevant human exposure levels, animal models have not been too concerning.
Caffeine in Breastmilk

- Appears rapidly after maternal ingestion
- Anecdotal reports of fussiness, jitteriness, poor sleep patterns in infants born to mothers who consume the equivalent of 10 or more cups of coffee daily
- Effects amplified in preterm or very young infants who metabolize caffeine more slowly and may attain serum levels similar to their mothers
- Coffee intake of more than 450 mL daily may decrease breastmilk iron concentrations
What is Missing?

• Better and more continuous measures (biomarkers) of exposure at specific time points in pregnancy
• Is there a peak exposure effect at critical windows?
• Any neurobehavioral effects of high dose exposure independent of the effects of known co-exposures such as alcohol and tobacco?
• What is the dose, and potential effect, in women, more than half of whom do not plan pregnancies, in the 5-6 weeks before they know they are pregnant?
  • Is the amount of alcohol and pattern of consumption (binging) increased in women who consume energy drinks and are not yet aware they are pregnant?
  • Is high caffeine consumption in an unrecognized pregnancy associated with poor dietary habits, e.g., low folate intake?
• What are effects, if any, of other ingredients in caffeinated products, such as energy drinks?