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Caffeine Metabolism, Genetics, and Perinatal Outcomes: A Review of Exposure Assessment Considerations during Pregnancy

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PURPOSE: To review the methodologic issues complicating caffeine exposure assessment during pregnancy; to discuss maternal and fetal caffeine metabolism, including genetic polymorphisms affecting caffeine metabolism; and to discuss the endogenous and exogenous risk factors known to influence caffeine metabolism.
METHODS: A review of the relevant literature.
RESULTS: There is wide inter-individual variation in caffeine metabolism, primarily due to variations in CYP1A2 enzyme activity. Some variability in CYP1A2 activity is due to genetic polymorphisms in the *CYP1A2* gene which can cause increased or decreased inducibility of the enzyme. Considerable evidence exists that maternal caffeine metabolism is influenced by a variety of endogenous and exogenous factors and studying the genetic polymorphisms may improve understanding of the potential effects of caffeine and its metabolites on perinatal outcomes. There is substantial evidence that measurement of maternal, fetal, and neonatal caffeine metabolites may allow for a more precise measure of fetal caffeine exposure.
CONCLUSIONS: Research on the genetic polymorphisms affecting caffeine metabolism may further explain the potential effects of caffeine and its metabolites on perinatal outcomes.
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KEY WORDS: Caffeine, Cytochrome P450 1A2, CYP1A2, Genetic Polymorphisms, Pregnancy, Reproduction, Fetal Growth Retardation, Gestational Age, Spontaneous Abortion.

INTRODUCTION

Maternal caffeine consumption during pregnancy has been studied for many years but convincing evidence for an association with poor perinatal outcomes remains elusive. Caffeine is an exposure of major public health interest because it is one of the most widely consumed drugs. Coffee makes up the largest percentage of total caffeine intake (75%), followed by tea (15%), and caffeinated sodas (10%) (1). In the United States, per capita consumption of coffee is nearly 3.5 kg of coffee per year, or more than 150 mg/day, and more than 75% of pregnant women consume caffeinated beverages (2, 3).

Epidemiologic studies of caffeine and reproductive outcomes have produced conflicting results. Some epidemiological studies have linked relatively high antenatal caffeine consumption (typically > 300 mg/day) to poor reproductive outcomes, including subfecundity (4–8); fetal growth retardation (2, 9–12); and spontaneous abortion (13–18). One study among smoking women who consumed > 400 mg caffeine per day noted a significant reduction in birthweight (19) and a more recent study reported a small, detrimental effect on birthweight, although it is only likely to be of clinical importance in women consuming large quantities of caffeine (20). Other studies suggest that antenatal caffeine consumption is not a reproductive hazard (21–25).

These equivocal findings are likely due to inconsistent definition and categorization of caffeine exposure among studies, selection and recall biases, and to varying study designs. The major limitations of the extant studies include: lack of control for confounding variables (4, 12), bias due to misclassification of caffeine exposure (4, 9, 21), and imprecise/inadequate measurement of caffeine intake (4, 21). Some studies were retrospective and the exposure information was collected long after the exposure occurred (9, 10, 21). Three prospective cohort studies that found an increase in risk for intrauterine growth retardation (IUGR) with third trimester caffeine consumption suffer from additional methodological problems including lack of a completely unexposed referent group (4, 19) and residual confounding due to inadequate control for the effects of smoking (12). Two retrospective cohort studies, one finding no effect (21) and the other finding an effect in women consuming coffee (26), inadequately assessed caffeine intake. Linn et al. (21)

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Selected Abbreviations and Acronyms

AAMU = 5-acetyl-6-amino-3-methyluracil
AFMU = 5-acetylamino-6-formylamino-3-methyluracil
CYP1A2 = cytochrome P450 1A2
CYP450 = cytochrome P450
NAT2 = N-acetyltransferase 2
SNP = single nucleotide polymorphism
XO = xanthine oxidase
Note: Throughout the manuscript, when the abbreviation is in italics it refers to the gene, otherwise it refers to the gene product.

assessed caffeine consumption in the first trimester only and the caffeine content per cup of coffee was not estimated and McDonald et al. (26) only assessed coffee consumption.

Studies investigating the association between maternal caffeine consumption and spontaneous abortion are also fraught with methodological complexity. A comprehensive review of this literature was conducted by Signorello et al. (27). Cross-sectional and case-control studies suffer from a variety of methodologic issues including recall bias; inaccurate recall of caffeine exposure due to exposure assessment several years later; confounding due to cigarette and alcohol consumption (18, 28); and selection bias (27). Confounding due to pregnancy symptoms is another important issue complicating the relation between caffeine consumption and spontaneous abortion. Nausea may influence the amount of caffeine consumed in early pregnancy and it is also related to fetal viability. Women with nonviable pregnancies may have little or no nausea and therefore do not decrease their caffeine intake, falsely suggesting that their higher caffeine intake is related to the spontaneous abortion (29).

Change in caffeine consumption over pregnancy is another important factor complicating exposure assessment. Women frequently have an aversion to caffeinated beverages in the first trimester of pregnancy and therefore decrease caffeine intake. They may also decrease caffeine intake upon confirmation of the pregnancy (30, 31). It is therefore crucial that caffeine exposure be assessed at multiple time periods throughout pregnancy.

Measurement Heterogeneity of Caffeine Exposure

There is a considerable amount of heterogeneity in caffeine exposure because caffeine content of caffeinated beverages varies widely and there are large differences in caffeine content per serving of coffee, tea, and soft drinks (7, 19, 32). Methodological issues related to retrospective ascertainment of exposure include inaccurate recall by the subject due to unawareness and/or forgetfulness of consumption and biased recall. Caffeine content of caffeinated beverages varies considerably, depending on brewing method, serving size, and portion of serving consumed. Estimates of caffeine content per serving for coffee, tea, and soft drinks range from 92 to 120 mg/serving, 34 to 65 mg/serving, and 34 to 47 mg/serving, respectively, and current ranges for soft drinks may be considerably higher (7, 19, 32).

The caffeine content of coffee is quite variable and depends on brand, whether it is a blend or a pure variety (33), quantity brewed, brewing method, and type of coffee bean. Caffeine extraction efficiency varies from 75% to 100%, depending on whether coffee is boiled, filtered, percolated, or prepared as espresso (34). Serving sizes range from 5 to 32 ounces and the caffeine content per cup is reported to range as much as 19 to 160 mg depending on brewing method and cup size (34). Considerable variation in caffeine content was found, even when the same study participant brewed coffee or tea under the same conditions on the same day (35).

Variation in caffeine consumption categorization also contributes to exposure misclassification and decreased comparability among studies. Categorization for the lowest levels of consumption (often used as the referent category) varies from no intake (21) to $\leqslant$ 400 mg/day (32) and for the highest categories of consumption from $>$ 300 mg/day (19) to $>$ 800 mg/day (32). If caffeine consumption of approximately 300 mg/day or more is associated with poor perinatal outcomes, grouping such exposed individuals with the lesser exposed or unexposed would dilute any effect of caffeine exposure.

In most studies of caffeine consumption and perinatal outcomes, self-reported caffeine exposure is calculated using a standard measure of caffeine per unit exposure that has been obtained by laboratory analyses. In a recent study, samples of caffeinated and decaffeinated coffee and tea were collected from the study participants and analyzed for actual caffeine content (35). It was observed that for all cup sizes, the actual amounts of caffeine in both coffee and tea were much lower than the amounts predicted using widely used laboratory estimates. For example, a 10 oz. cup of drip brewed coffee is estimated to contain 300 mg caffeine, according to Bunker and McWilliams (36), but Bracken et al. (35), found that a 10 oz. drip brewed cup of coffee typically contained 100 mg caffeine. Similarly, a 10 oz. cup of tea brewed for more than 3 minutes was found to contain 42 mg caffeine compared with the predicted 94 mg (35).

Use of Caffeine Biomarkers

Even among well designed studies with valid exposure assessment, nearly all of them relied on self-reported caffeine consumption to estimate exposure. This does not provide an accurate measure of maternal or fetal dose because it does not necessarily indicate how much caffeine or caffeine metabolites enter maternal or fetal circulation. A variety of endogenous and exogenous risk factors are known to influence caffeine metabolism and it is possible that