Caffeine consumption and miscarriage: a prospective cohort study

Caffeine consumption has been equivocally associated with miscarriage, despite an absence of prospective longitudinal measurement of caffeine intake during sensitive windows of human development. In response to this critical data gap, we analyzed daily caffeine consumption while attempting pregnancy through 12 menstrual cycles at risk for pregnancy and found that caffeine consumption did not increase the risk or hazard of miscarriage, even after adjusting for relevant covariates. (Fertil Steril® 2010;93:304–6. ©2010 by American Society for Reproductive Medicine.)

A recent paper reignited concern that caffeine consumption during pregnancy was associated with miscarriage (1–3) and quickly generated letters to the editors regarding the differential capture of caffeine by pregnancy outcome (4, 5). Surprisingly, a negative study published earlier in the year was largely overlooked (6). Both papers were preceded by an equivocal literature relying on retrospective caffeine recall (7–10).

We assessed caffeine consumption during sensitive windows of development in a prospective cohort study comprising women discontinuing contraception for the purpose of becoming pregnant and who were recruited from a larger study that focused on fish consumption and reproductive health (11, 12). The study cohort was restricted to women who reported in 1991 that they may be planning pregnancies in the next 5 years. In 1996, 2,637 women were recontacted, of which 244 (9%) reported planning pregnancies in the next 6 months, from which 113 women (46%) were enrolled. Fourteen women were already pregnant and were subsequently excluded from further participation.

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Women were interviewed by a nurse before first attempting pregnancy and instructed in the accurate use of the home pregnancy tests, reportedly capable of detecting $\leq$50 mIU/mL hCG on the date of expected menses. The fertile window was estimated using the Ogino-Knaus method of counting back 14 days from the end of the cycle (13, 14) and was broadly defined as commencing 5 days before the presumed date of ovulation and ending 2 days after ovulation.

Women completed daily diaries on intercourse, menstruation, caffeine consumption (number of cups of coffee, tea, caffeinated soft drinks), alcohol consumption (number of drinks of beer, wine, wine coolers, hard liquor), and number of cigarettes smoked. Women were followed until hCG-confirmed pregnancy or up to 12 menstrual cycles with at least one act of sexual intercourse during the fertile window; 20 women withdrew from the study. Full human subject approval was granted, and all participants gave their informed consent.

Caffeine, alcohol, and smoking data were standardized to a 28-day cycle to account for varying menstrual cycle lengths, reflecting the heterogeneity of both menstruation and couple fecundity as measured by time to pregnancy (TTP), and to prevent inflation in exposures for women with longer cycles. Standardization was derived by summing the daily number of cigarettes smoked and alcoholic and caffeinated beverages consumed, multiplying by 28 (assumed normal menstrual cycle length), and dividing by the number of observed days in each woman's cycle. Exposures for women who conceived in the first month ($n = 19$) were standardized to 28 days based on observed daily exposure data for the partially observed cycle.

We assessed potential changes in acute caffeine exposure during sensitive windows (in relation to risk of pregnancy loss) by estimating the day of conception as having occurred 14 days and implantation 7 days before the woman's first positive pregnancy test. We formally assessed differences in caffeine consumption between the periovulatory period, defined as the 5 days before ovulation, the day of ovulation, and 2 days after ovulation, and the periimplantation period, which was defined as the subsequent 8 days, using the Wilcoxon signed rank test (15, 16).

Using women as the unit of analysis, we stratified by gravidity and modeled standardized caffeine consumption and risk of pregnancy and miscarriage, adjusting for standardized cigarette smoking (continuous), standardized alcohol consumption (continuous),

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TABLE 1

Risk ratios (RRs) for caffeine consumption and pregnancy loss and hazard ratios (HRs) for caffeine consumption and hazard of pregnancy loss (in days), stratified by gravidity.

	Risk of pregnancy loss			Hazard of pregnancy loss		
Model	**n**	**RR**	**(95% CI)**	**n**	**HR**	**(95% CI)**
Unadjusted						
All women	66	0.98	(0.96–0.99)	66	0.97	(0.95–1.00)
Stratified by gravidity						
Nulligravid women	13	0.98	(0.95–1.00)	13	0.98	(0.94–1.01)
Gravid women	53	0.97	(0.95–0.99)	53	0.97	(0.94–1.00)
Adjusted						
All women[a]	66	0.98	(0.96–0.99)	66	0.97	(0.95–1.00)
Stratified by gravidity						
Nulligravid women[a]	13	0.98	(0.95–1.01)	13	0.98	(0.94–1.02)
Gravid women[b]	53	0.96	(0.94–0.99)	53	0.96	(0.92–1.00)

Note: Log-Poisson regression with empirical error variance was used to estimate the risk of pregnancy loss, and Cox proportional hazards regression with right censoring was used to estimate the hazard ratio, using the average number of daily cups of caffeinated beverages standardized to a 28-day menstrual cycle. CI = confidence interval.

[a] Adjusted for age and average alcohol and cigarette consumption per standardized 28-day cycle.

[b] Adjusted for age, average alcohol and cigarette consumption per standardized 28-day cycle, and prior spontaneous pregnancy loss (yes/no).

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age (continuous), and history of prior spontaneous pregnancy loss (among gravid women; binary) using log-Poisson modeling (17, 18). Using cycles as the unit of analysis, we estimated hazard of pregnancy loss using Cox proportional hazards regression with right censoring (19). Risk ratios (RRs) and hazard ratios (HRs) were estimated along with 95% confidence intervals (CIs). Pregnancy loss denoted both early (n = 10) and clinical (n = 4) losses in all analyses. To address the known clustering of pregnancy outcome (20), we stratified by gravidity and assessed prior miscarriage among gravid women. Recognizing that women's behaviors may change in relation to timeliness in which she becomes pregnant, we assessed caffeine intake per cycle by women's intentions to change caffeine consumption as reported at the baseline interview.

Sixty-eight women (86%) became pregnant, of which 54 (79%) had live births and 14 (21%) experienced pregnancy losses. Eleven women (14%) did not achieve pregnancy. The 79 women who fully completed the study contributed 419 menstrual cycles for the analysis, including 275 cycles contributed by women with pregnancies.

No significant differences were observed for caffeine consumption or other study covariates and pregnancy outcome (data not shown). Parity, however, varied, with a significantly higher percentage of parous women having live births or having withdrawn compared with women with losses or no pregnancy (i.e., 83%, 77%, 57%, and 18%, respectively; P=.001). Twenty-two women reported a history of prior spontaneous pregnancy loss, including four infertile women (18%), two women with index losses (9%), 14 women with index births (64%), and two women who withdrew (9%). The daily mean number (±SD) of caffeinated beverages varied from a high among women who withdrew (1.9 ± 0.7) or had live births (1.8 ± 1.5) to a low for women experiencing miscarriage (0.8 ± 0.8).

Caffeine consumption was not associated with becoming pregnant in adjusted models (RR 1.00, 95% CI 0.99–1.01), with increased miscarriage risk (RR 0.98, 95% CI 0.96–0.99), or with increased hazard of miscarriage (HR 0.97, 95% CI 0.95–1.00), even when stratifying by gravidity (Table 1). The absence of a caffeine effect suggests that infecundity or inability to conceive was not a competing risk for pregnancy loss. Caffeine consumption during sensitive windows was not associated with miscarriage risk nor was an effect seen when restricting analysis to nonsmoking women or when estimating the effect of previous pregnancy loss (HR 1.00, 95% CI 0.99–1.00). Few women changed caffeine consumption despite 44% reporting plans to reduce at baseline. Our findings agree with a recent cohort study that included preconception enrollment of some women and prospective measurement of caffeine consumption (6).

Studies to date have largely assessed caffeine and TTP or miscarriage by asking pregnant women to recall consumption, raising concern about possible selection and recall biases (1, 7, 10, 21). In the present study, 10 out of 14 pregnancy losses would have been missed without preconception enrollment of women. Caffeine consumption has been measured differently, with some authors estimating risk by daily milligrams (mg) of caffeine (22) or by source (21, 23). Only 24% of women in our cohort who failed to become pregnant or who had live births reported consuming more than three caffeinated beverages daily, which is approximately equivalent to >300 mg of daily caffeine, assuming higher caffeine content for coffee than tea or soft drinks (24). Earlier studies have associated caffeine intake of >300 mg per day with miscarriage risk (22, 25). The extent to which the present findings may be generalizable to women with unplanned pregnancies is uncertain, particularly because the latter group is at risk for adverse pregnancy outcomes (26). However, we are unaware of any data to support systematic differences in day-specific caffeine consumption by women's pregnancy intentions. Moreover, women's daily reporting of caffeine consumption in the present cohort was most likely unaffected by intentions to change behaviors, given that women were unaware of their eventual pregnancy outcome.

These findings have important methodologic limitations, including potential measurement error in caffeine intake, less exposure data on women who conceived during the first cycle compared with women requiring more time, and the highest consumption among women who withdrew from the study, albeit amounts similar to women with live births. In sum, we found no evidence that caffeine consumption increases miscarriage risk among women with light or moderate caffeine consumption.

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