OBSTETRICS

Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study

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Background and Objective

Caffeine (3,7-trimethylxanthine) is among the most frequently ingested pharmacologically active substances in the world. Caffeine can readily cross the placental barrier.

Although numerous studies on maternal caffeine consumption and the risk of miscarriage have been published since the 1980s, the issue remains controversial because of methodologic limitations in these studies. The objective of our population-based prospective study was to examine the effect of maternal caffeine intake during pregnancy on the risk of miscarriage and account for a number of potential confounders, particularly nausea and vomiting.

Materials and Methods

The study was conducted among pregnant members of the Kaiser Permanente Medical Care Program (KPMCP), a group model–integrated health care delivery system. From October 1996 through October 1998, all women in the program from the San Francisco and South San Francisco areas with a positive pregnancy test were identified as potentially eligible subjects. The program requires all women who suspect that they are pregnant to undergo a pregnancy test at the KPMCP laboratory regardless of whether they have performed home pregnancy tests.

Information on caffeine consumption during pregnancy was obtained during in-person interviews conducted soon after pregnancy was confirmed. The median gestational age at interview was 71 days. Women were asked to report all beverage intake since their last menstrual period. Subjects were asked about types of drink ingested, timing of initial drink, frequency and amount of intake, whether they had changed their consumption patterns since becoming pregnant, and if so, how. Also collected during the interview was information on potential confounders: maternal age; race; education; household income; marital status; previous miscarriage; smoking; alcohol consumption; Jacuzzi use; exposure to magnetic fields during pregnancy; and symptoms related to pregnancy, such as nausea and vomiting.

Pregnancy outcomes up to 20 weeks of gestation were determined for all participants. Average daily caffeine intake during pregnancy was categorized as 0, less than 200 mg/day, or 200 mg/day or more in the analysis of the overall effect.

Results

Of 2729 eligible women, 164 (6%) were contacted too late in pregnancy (more than 15 weeks) to permit an interview to be scheduled; 317 (12%) initially agreed to participate, but were unable to schedule an interview; and 1185 (43%) refused to participate. Ultimately, 1063 (39%) women completed the interview.

Of the 1063 participants, 172 (16.18%) miscarried. A total of 264 women (25%) reported no consumption of caffeine-containing beverages during pregnancy, 635 (60%) subjects had consumption up to 200 mg/day, and 164 (15%) had 200 mg or more daily consumption.

An increased intake of caffeine was associated with increased risk for miscarriage (Table). Women who consumed up to 200 mg daily had a greater risk of miscarriage than nonusers (15% vs 12%, respectively); the corresponding risk was much greater (25%) among women who consumed 200 mg/day or more. After adjustment for potential confounders, the hazard ratio of miscarriage was 1.42 (95% confidence interval [CI] 0.93 to 2.15) and 2.23 (95% CI 1.34 to 3.69) for daily consumption of less than 200 mg and 200 mg or more caffeine, respectively (P for trend $< .01$). We performed a stratified analysis according to the source of caffeine; the association remained regardless of the source.

A total of 631 women (79%) had reduced their caffeine consumption since becoming pregnant and 152 (19%) had maintained the same consumption pattern, whereas 16 (2%) had increased their consumption during the pregnancy. Caffeine intake of 200 mg/day or more remained associated with an increased risk for miscarriage regardless of whether a woman reduced her caffeine intake after becoming pregnant. The number of women who increased their caffeine intake after becoming pregnant was too small to permit a meaningful interpretation.

To examine whether the observed association was influenced by other risk factors, we conducted additional analy-

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OVERVIEW

We provide new evidence that the association between caffeine intake and miscarriage is not likely the result of pregnancy-related symptoms such as nausea, vomiting, and aversion to caffeine.

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For Editors' Commentary, see Table of Contents

TABLE
Caffeine intake during pregnancy and the risk of miscarriage

	Miscarriage			
Caffeine intake (mg/d)	Yes n (%)	No n (%)	cHR	aHR[a]
Nonuser	33 (12.50)	231 (87.50)	1	1
Overall				
Less than 200	97 (15.30)	538 (84.72)	1.23 (0.83 to 1.82)	1.42 (0.93 to 2.15)
200 or more	42 (25.45)	122 (74.39)	2.44 (1.54 to 3.85)	2.23 (1.34 to 3.69)
From coffee only				
Less than 200	19 (16.81)	94 (83.19)	1.32 (0.76 to 2.33)	1.18 (0.64 to 2.18)
200 or more	12 (30.77)	27 (69.23)	2.82 (1.43 to 5.57)	2.49 (1.22 to 5.08)
From noncoffee only				
Less than 200	54 (18.95)	231 (81.05)	1.61 (1.05 to 2.49)	2.04 (1.29 to 3.21)
200 or more	2 (25.00)	6 (75.00)	2.69 (0.65 to 11.22)	5.72 (1.29 to 25.37)
From both coffee and noncoffee				
Less than 200	24 (10.17)	212 (89.83)	0.80 (0.47 to 1.36)	0.87 (0.50 to 1.53)
200 or more	28 (23.73)	90 (76.27)	2.23 (1.35 to 3.70)	1.89 (1.09 to 3.30)

cHR, crude hazard ratio.

[a] Hazard ratio adjusted for maternal age, race, education, family income, marital status, previous miscarriage, nausea and vomiting since LMP, smoking status, alcohol drinking, Jacuzzi use, and exposure to MFs.

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ses of the association stratified by the presence or absence of nausea, smoking during pregnancy, and history of miscarriage. The association between caffeine intake and miscarriage persisted among women both with and without nausea during pregnancy, although the association was slightly stronger among women with nausea. The effect of caffeine consumption on miscarriage was higher in the nonsmoker group (adjusted hazard ratio [aHR] 2.04; 95% CI 1.35 to 3.09) than in the smoker group (aHR 1.49; 95% CI 0.36 to 6.08). Caffeine's effect on the risk for miscarriage remained strong among women without a history of miscarriage (aHR 2.33; 95% CI 1.48 to 3.67), whereas the association no longer existed among women with such a history (aHR 0.81; 95% CI 0.34 to 1.94).

To determine whether the effect of caffeine on the risk of miscarriage varied by gestational age at miscarriage, we examined the effect separately for miscarriages that occurred before and after 8 weeks of gestation. Higher caffeine consumption was associated with higher risk for both early and late miscarriage. The association appeared to be more pronounced for later than for earlier miscarriage, however.

Comment

In this prospective cohort study, we demonstrated an elevated risk of miscarriage associated with caffeine consumption during pregnancy and a dose-response relationship, with most of the risk associated with consumption of 200 mg/day or more. This observed effect was independent of many potential confounders, including pregnancy-related symptoms such as nausea, vomiting, and aversion to caffeine. Even among women who did not change their caffeine consumption pattern during pregnancy, we observed an almost 80% increased risk of miscarriage associated with caffeine consumption of 200 mg/day or more; this finding was not statistically significant, however, because of the small sample size after stratification. Finally, the increased risk of miscarriage appeared to be caused by caffeine itself rather than other chemicals in coffee because caffeine intake from sources other than coffee showed a similar increase in the risk for miscarriage.

Some researchers argue that the association between caffeine intake and miscarriage is confounded by nausea and vomiting, which are generally associated with a low risk for miscarriage and possible reduction of caffeine intake caused by these symptoms. We ascertained detailed patient information on nausea and vomiting since the last menstrual period and for the 7 days before the interview. The association between caffeine intake and risk for miscarriage remained after adjusting for nausea and vomiting and continued to exist among women both with and without nausea and vomiting during pregnancy.

To address this issue more thoroughly, we examined the association for those who reduced and those who did not alter their caffeine consumption during pregnancy. The sample size was too small to evaluate an association among women who increased their caffeine consumption during pregnancy. The increased risk for miscarriage associated with caffeine consumption continued after stratification. These results did not support the argument that the observed association was caused by nausea and/or vom-

iting, which reduced both caffeine intake and risk for miscarriage.

We also observed that the association appeared to be stronger among women without other risk factors for miscarriage, for example, women who had no history of miscarriage, did not smoke during pregnancy, and had nausea and/or vomiting while pregnant. Although the underlying reason for this interaction is not known, caffeine intake could be a lesser risk factor in the presence of other risk factors for miscarriage. Thus, a lack of increased risk from caffeine is probably the case in women with a history of recurrent miscarriages.

To assess the potential existence of recall bias, we conducted a stratified analysis based on whether the interview was conducted before or after the subject's miscarriage. The results were essentially the same, providing no evidence of recall bias. Therefore, we combined the data in the final analyses.

Selection bias may have resulted from low participation rates. Although information on caffeine intake for nonparticipants was lacking, we compared some characteristics, including age and the rate of miscarriage, between participants and nonparticipants. Both average age (30 vs 29 years for participants and nonparticipants, respectively) and the rate of miscarriage (16.4% vs 17.2%, respectively) were similar, providing some assurance against participation bias.

In conclusion, the results from our prospective cohort study support previous findings that high caffeine consumption during pregnancy may increase the risk for miscarriage. We provided new evidence that the observed association is not likely the results of confounding by the pregnancy-related symptoms of nausea, vomiting, and aversion to caffeine.

CLINICAL IMPLICATIONS

- High caffeine consumption during pregnancy may increase the risk for miscarriage.
- Caffeine's effect on the risk for miscarriage was not likely due to confounding by the pregnancy-related symptoms such as nausea, vomiting, and aversion to caffeine.
- It may be prudent to counsel patients to stop or reduce caffeine intake during pregnancy. ■

Maternal C-reactive protein and developmental programming of atherosclerosis

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BACKGROUND AND OBJECTIVE

Extensive epidemiologic evidence suggests that in utero conditions influence susceptibility to hypertension, diabetes mellitus, and cardiovascular disease later in life. Specific maternal conditions program increased susceptibility to atherosclerosis in adult offspring. Both temporary hypercholesterolemia during pregnancy and chronic maternal hypercholesterolemia enhance the formation of early atherosclerotic lesions (fatty streaks) in human fetal aortas. Studies in experimental models with diet-induced hypercholesterolemia showed that the size of these lesions at birth is proportional to maternal cholesterol levels.

★ EDITORS' CHOICE ★

OVERVIEW
Maternal C-reactive protein, a marker of inflammation, was associated with increased atherosclerosis in offspring.

The first indication that maternal hypercholesterolemia influences postnatal susceptibility to atherosclerosis was provided by the Fate of Early Lesions in Childhood (FELIC) study, an autopsy study of normocholesterolemic children. Children of hypercholesterolemic mothers showed accelerated progression of atherosclerosis in the aortic arch and abdominal aorta that could not be explained by conventional risk factors. Although the mechanisms of in utero programming remain largely unknown, they may involve inflammatory processes that are analogous to those that promote atherosclerosis in adults.

C-reactive protein (CRP), a nonspecific acute-phase reactant and downstream biomarker of proinflammatory

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For Editors' Commentary, see Table of Contents