OBSTETRICS

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

Xiaoping Weng, PhD; Roxana Odouli, MSPH; De-Kun Li, MD, PhD

OBJECTIVE: The objective of the study was to examine whether the risk of miscarriage is associated with caffeine consumption during pregnancy after controlling for pregnancy-related symptoms.

STUDY DESIGN: This was a population-based prospective cohort study.

RESULTS: An increasing dose of daily caffeine intake during pregnancy was associated with an increased risk of miscarriage, compared with no caffeine intake, with an adjusted hazard ratio (aHR) of 1.42 (95% confidence interval 0.93 to 2.15) for caffeine intake of less than 200 mg/day, and aHR of 2.23 (1.34 to 3.69) for intake of 200 or more mg/day, respectively. Nausea or vomiting during pregnancy did not materially affect this observed association, nor did the change in intake pattern of caffeine during pregnancy. In addition, the magnitude of the association appeared to be stronger among women without a history of miscarriage (aHR 2.33, 1.48 to 3.67) than that among women with such a history (aHR 0.81, 0.34 to 1.94).

CONCLUSION: Our results demonstrated that high doses of caffeine intake during pregnancy increase the risk of miscarriage, independent of pregnancy-related symptoms.

Key words: abortion, caffeine, miscarriage, spontaneous

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Caffeine, 1,3,7-trimethylxanthine, is among the most frequently ingested pharmacologically active substances in the world.[1] Caffeine can readily cross the placental barrier to the fetus[2]; its clearance is prolonged in pregnant women, and its metabolism rate is low in the fetus because of low levels of enzymes.[3,4] It may also influence cell development through increasing cellular cyclic adenosine monophosphate concentrations[5] and decrease intervillous placental blood flow via increasing circulating catecholamines.[6] Therefore, caffeine could have an adverse effect on fetal development. Indeed, caffeine intake has been reported to increase the risk of miscarriage.[7-10]

Although numerous studies on maternal caffeine consumption and the risk of miscarriage have been published since the 1980s, the effect of caffeine intake on the risk of miscarriage remains controversial because of methodological limitations in past studies.[10] Many studies have relied on retrospective information, which is subject to recall bias.[8,11,12] Some had only a small number of participants, which limited their power to detect an effect.[13] Some did not take into account potential confounding factors such as smoking, alcohol consumption, and most importantly, pregnancy-related symptoms including nausea and vomiting.[7,14,15] Finally, some recruited women who sought prenatal care at their 13th to 28th weeks of gestation, therefore too late in pregnancy to study miscarriage.[15-17] Such controversy has led to the uncertainty about the health effects of caffeine consumption during pregnancy among both clinicians and pregnant women alike.

In the United States, coffee, tea, and carbonated soft drinks are the main sources of caffeine intake. Mean daily caffeine consumption from these sources was estimated around 106-170 mg per day for adults and 58 mg per day for pregnant women, respectively.[18] The objective of this population-based prospective study was to examine the effect of maternal caffeine intake during pregnancy on the risk of miscarriage, taking into account a number of potential confounders, especially the impact of nausea or vomiting during pregnancy.

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. During a 2 year period from October 1996 through October 1998, all KPMCP women who resided in the San Francisco and South San Francisco areas and had a positive pregnancy test in these facilities were identified as potentially eligible subjects. The KPMCP facilities require all women who suspect

From the Division of Research, Kaiser Permanente, Oakland, CA.

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Reprints: Dr. De-Kun Li, Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612. dkl@dor.kaiser.org.

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that they might be pregnant to undergo a pregnancy test at the KPMCP laboratory regardless of whether they have already performed home pregnancy tests. Any woman who submitted a urine or blood sample for a pregnancy test was given a flyer explaining the purpose of the study and was informed of the possibility of being contacted for this study. A postage-paid and self-addressed return refusal postcard was included with the flyer so that women who did not wish to be contacted for the study could inform us. Specially trained female interviewers contacted all women who did not return their refusal cards. Any woman who spoke English and intended to carry her pregnancy to term at the time of contact was considered eligible for the study. Women already included in the study for 1 pregnancy were not eligible to be included for subsequent pregnancies during the study period.

Of 2729 eligible women, 164 (6%) were contacted too far along in their pregnancy (more than 15 weeks) for interview; 317 (12%) initially agreed to participate but were unable to schedule an interview; 1185 (43%) refused to participate; and ultimately 1063 (39%) completed the interview. The main reasons for refusal were too busy, not interested, and too stressful to participate. A more detailed description of the study design and methods can be found elsewhere.[19]

Exposure assessment

Information on exposure to caffeine consumption during pregnancy was obtained during an in-person interview conducted soon after a woman's pregnancy was confirmed (the median gestational age at interview was 71 days). Women were asked to report their intake of beverage including caffeine-containing beverages since their last menstrual period (LMP). They were asked about the types of their drinks; timing of initial drink; the frequency and amount of the intake; whether they changed consumption patterns since becoming pregnant; and, if so, the time, the frequency, and the amount of consumption after the change. Women might report their caffeine intake on either a daily or weekly basis and then average daily intake was calculated. Sources of caffeine included coffee (caffeinated or decaffeinated), tea (caffeinated or decaffeinated), caffeinated soda (including 17 brands, such as Coca-Cola, Big Red, and Pepsi-Cola, etc), and hot chocolate. We used the following conversion factors to estimate the amount of caffeine intake: for every 150 mL of a beverage, we estimated 100 mg for caffeinated coffee, 2 mg for decaffeinated coffee, 39 mg for caffeinated tea, 15 mg for caffeinated soda, and 2 mg for hot chocolate.[8]

Information on potential confounders, such as maternal age, race, education, household income, marital status, smoking, alcohol consumption, Jacuzzi use, exposure to magnetic fields (MF) during pregnancy, and symptoms related to pregnancy such as nausea and vomiting were also collected during the in-person interview.

Pregnancy outcome

Pregnancy outcomes up to 20 weeks of gestation were determined for all participants through the following 3 methods: (1) searching the KPMCP inpatient or outpatient databases, (2) reviewing medical records, and (3) contacting participants whose outcomes could not be determined by using the previous 2 methods. Because, by definition, no miscarriage occurs after 20 weeks of gestation, pregnancy status was censored at 20 weeks of gestation for those pregnancies that continued beyond 20 weeks. We had information on pregnancy outcomes for all participants at 20 weeks of gestation. More than 95% of miscarriages in our study population occurred before 15 weeks of gestation. Because we recruited women at an early gestational age, a total of 102 subjects (59%) had already had a miscarriage at the time of initial contact for their participation. These subjects were interviewed soon after their miscarriage (median delay 19 days), and information on caffeine intake was ascertained only up to the end of pregnancy.

Statistical analysis

The Cox proportional hazards regression was used to take into account possible differing gestational ages at study entry between the exposed (caffeine intake) and unexposed.[20,21] By using the Cox model with left truncation, we examined the association between caffeine consumption and the risk of miscarriage at any specific gestational age only for those women who had entered into the study and remained pregnant at the beginning of that specific gestational age. The interval between conception and study entry was truncated in this case (ie, treated as missing follow-up time). Using the Cox model also enabled us to easily assess whether the effect of caffeine consumption on the risk of miscarriage changed with gestational age.

Entry time was defined as gestational age at the positive pregnancy test because we started to follow up a woman's pregnancy at her positive pregnancy test. The median gestational age at entry for the entire cohort was 40 days. The follow-up time was gestational age in days. Gestational age was determined by ultrasound (16.4%), an obstetrician (50.9%), or the self-reported last menstrual period (32.7%) if the determination by ultrasound or obstetricians was not available. All participants were followed up until miscarriage, termination of pregnancy because of other causes (eg, ectopic pregnancy), or 20 weeks of gestation.

The average daily caffeine intake during pregnancy was categorized as 0, less than 200 mg/day, or 200 or more mg/day in the overall analysis. Potential confounders, such as maternal age, race, education, household income, marital status, smoking, alcohol consumption, Jacuzzi use, MF exposure, and nausea and vomiting were included into the COX model for adjustment. A test for trend was performed with the categories of caffeine intake as an ordinal scale. All statistical analyses were performed using SAS 9.0 (SAS Institute, Cary, NC).

RESULTS

Overall 172 of women (16.18%) miscarried. Whereas 264 women (25%) reported no consumption of any caffeine-

TABLE 1
Characteristics of the study population by caffeine intake

	Total (n = 1063)	Caffeine intake					
		0 mg/day		0-200 mg/day		200 mg/day or greater	
		(n = 264)	%	(n = 635)	%	(n = 164)	%
Maternal age (y)							
24 or younger	153	45	(17.05)	97	(15.28)	11	(6.71)
25-29	294	77	(29.17)	181	(28.50)	36	(21.95)
30-34	358	83	(31.44)	219	(34.49)	56	(34.15)
35 or older	258	59	(22.35)	138	(21.73)	61	(37.20)
Race							
White	405	91	(34.60)	235	(37.24)	79	(48.77)
Black	77	25	(9.51)	48	(7.61)	4	(2.47)
Hispanic	221	53	(20.15)	141	(22.35)	27	(16.67)
Asian or Pacific Islander	296	80	(30.42)	176	(27.89)	40	(24.69)
Other	57	14	(5.32)	31	(4.91)	12	(7.41)
Education							
Less than college	589	147	(55.89)	350	(55.29)	92	(56.10)
College degree	307	74	(28.14)	183	(28.91)	50	(30.49)
Graduate school	164	42	(15.97)	100	(15.89)	22	(13.41)
Household income							
Less than $50,000	618	160	(63.49)	374	(62.44)	84	(53.55)
$50,000 or more	389	92	(36.51)	225	(37.56)	72	(46.15)
Marital status							
Married	850	220	(83.65)	497	(78.89)	133	(79.17)
Single	63	15	(5.70)	41	(6.51)	7	(4.17)
Living together or having a regular partner	114	23	(8.75)	76	(12.06)	15	(8.93)
Other	34	5	(1.90)	16	(2.54)	13	(7.74)
Previous miscarriage							
0	844	219	(82.95)	511	(80.47)	114	(69.51)
1	164	35	(13.26)	92	(14.49)	37	(22.56)
2 or more	55	10	(3.79)	32	(5.04)	13	(7.93)
Vomiting since LMP							
Yes	421	109	(41.29)	264	(41.64)	48	(29.27)
No	641	155	(58.71)	370	(58.36)	116	(71.73)
Aversion to caffeine							
Yes	—	—	—	221	(34.85)	69	(41.82)
No	—	—	—	413	(65.15)	96	(58.18)
Smoked since LMP							
Yes	107	8	(3.03)	63	(9.92)	36	(21.95)
No	956	256	(96.97)	572	(90.08)	128	(78.05)

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TABLE 1
Characteristics of the study population by caffeine intake

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	Total (n = 1063)	Caffeine intake: 0 mg/day (n = 264)	%	0-200 mg/day (n = 635)	%	200 mg/day or greater (n = 164)	%
Alcohol use since LMP							
Yes	439	77	(29.17)	272	(42.83)	90	(54.88)
No	624	187	(70.83)	363	(57.17)	74	(45.12)
Jacuzzi use							
Yes	105	25	(9.51)	57	(9.03)	23	(14.02)
No	953	238	(90.49)	574	(91.97)	141	(85.98)
Drug use during pregnancy							
Yes	60	14	(5.3)	36	(5.67)	10	(6.10)
No	1003	250	(94.7)	599	(94.33)	154	(93.90)
Exposure to MF, mG							
16 or greater	780	195	(73.86)	458	(72.13)	127	(77.44)
Less than 16	283	69	(26.14)	177	(27.87)	37	(22.56)
Gestational age at entry, d							
0-48	768	198	(75.00)	456	(71.81)	114	(69.51)
49-69	240	57	(21.59)	146	(22.99)	37	(22.56)
70-140	55	9	(3.41)	33	(5.20)	13	(7.93)

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containing beverages during pregnancy, 635 women (60%) reported 0-200 mg of caffeine intake per day, and 164 women (15%) had 200 mg or more of daily caffeine consumption. Table 1 compares the various characteristics of women who were at different levels of caffeine consumption. Caffeine intake was associated with a variety of risk factors for miscarriage, such as age of 35 years or older; having had a prior miscarriage; an absence of vomiting; and smoking, alcohol consumption, and use of Jacuzzi during pregnancy. Also, women with higher caffeine consumption were more likely to be white and to have a higher household income.

An increasing amount of caffeine intake was associated with an increased risk of miscarriage (Table 2). Compared with nonusers, women who consumed 0-200 mg caffeine daily had an increased risk of miscarriage (15% vs 12%), and the corresponding risk was much greater (25%) among women who consumed more than 200 mg caffeine daily. After adjustment for potential confounders including maternal age, race, education, household income, marital status, previous miscarriage, smoking, alcohol consumption, Jacuzzi use, MF exposure, and nausea and vomiting, 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 caffeine consumption of 0-200 mg and 200 mg or more, respectively (P for trend $< .01$). Regarding the sources of caffeine, 63% of total caffeine consumed was from coffee. There were 152 women (19%) whose source of caffeine was solely from coffee, 293 (36.7%) from sources other than coffee, and the remaining 351 women (43.9%) from coffee and noncoffee sources (coffee, tea, soft drinks, etc). We performed a stratified analysis according to the source of caffeine, and the association remained, regardless of the sources.

Table 3 shows the relationship between caffeine consumption and the risk of miscarriage separately for women whose pattern of caffeine consumption changed during pregnancy. A total of 631 women (79%) reduced their caffeine consumption since they became pregnant and 152 (19%) maintained the same consumption pattern, whereas 16 (2%) increased their consumption during the pregnancy. Caffeine intake of 200 mg or greater remained associated with an increased risk of miscarriage, regardless of whether a woman changed her pattern of caffeine intake after pregnancy, although the estimate in each stratum was no longer statistically significant because of reduced sample size from stratification. The number of women who increased their caffeine intake after pregnancy was too small to have a meaningful interpretation.

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

TABLE 2
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 presence or absence of nausea, smoking during pregnancy, and a history of miscarriage. To increase the stability of the estimates in these analyses, we categorized the caffeine consumption into less than 200 mg/day or 200 mg/day or more because the risk of miscarriage among women without any consumption of caffeine and those with consumption of caffeine less than 200 mg/day was quite similar.

The association existed among women both with and without the symptom of nausea during pregnancy, although the association was slightly stronger among women with the symptom (Table 4). A similar pattern of the association was observed for the symptom of vomiting during pregnancy.

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 the smoker group (aHR 1.49, 95% CI, 0.36 to 6.08) and was only statistically significant in the nonsmoker group. In addition, caffeine's effect on the risk of miscarriage remained strong among women without a history of miscarriage

TABLE 3
Caffeine intake during pregnancy and the risk of miscarriage in relation to the pattern of caffeine consumption change during pregnancy

	Miscarriage					
Caffeine intake (mg/d)	Yes n (%)	No n (%)	cHR	aHR[a]	cHR	aHR[a]
Nonuser	33 (12.50)	231 (87.50)	1	1		
Reduction						
Less than 200	62 (12.06)	452 (87.94)	0.94 (0.62 to 1.43)	0.89 (0.58 to 1.38)	1	1
200 or more	20 (17.09)	97 (82.91)	1.50 (0.86 to 2.61)	1.31 (0.73 to 2.37)	1.59 (0.96 to 2.63)	1.47 (0.87 to 2.51)
No change						
Less than 200	31 (28.44)	78 (71.56)	2.62 (1.60 to 4.27)	2.87 (1.70 to 4.83)	1	1
200 or more	20 (46.51)	23 (53.49)	5.61 (3.21 to 9.83)	5.08 (2.71 to 9.52)	2.15 (1.22 to 3.79)	1.77 (0.92 to 3.40)

cRH, crude hazard ratio.

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

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TABLE 4
Caffeine intake during pregnancy and the risk of miscarriage in relation to other risk factors for miscarriage

	Miscarriage		
Caffeine intake (mg/d)	Yes n (%)	No n (%)	aHR[a]
Nausea since LMP			
No			
Less than 200	60 (32.26)	126 (67.74)	1
200 or more	21 (44.65)	25 (54.35)	1.57 (0.84 to 2.93)
Yes			
Less than 200	70 (9.83)	642 (90.17)	1
200 or more	21 (17.95)	96 (82.05)	2.02 (1.18 to 3.45)
Smoking status			
No			
Less than 200	117 (14.18)	708 (85.82)	1
200 or more	35 (26.72)	96 (73.28)	2.04 (1.35 to 3.09)
Yes			
Less than 200	11 (15.71)	59 (84.29)	1
200 or more	9 (24.32)	28 (75.68)	1.49 (0.36 to 6.08)
History of miscarriage			
No			
Less than 200	102 (13.97)	628 (86.03)	1
200 or more	32 (28.07)	82 (71.93)	2.33 (1.48 to 3.67)
Yes			
Less than 200	28 (16.57)	141 (83.43)	1
200 or more	10 (20.00)	40 (80.00)	0.81 (0.34 to 1.94)

[a] Adjusted for maternal age, race, education, family income, marital status, previous miscarriage, smoking status, alcohol drinking, Jacuzzi use, and exposure to MFs except when those variables themselves were evaluated for interaction.

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(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) (Table 4). The test for the interaction was borderline significant ($P = .05$).

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. A total of 57 miscarriages (33%) occurred before 8 gestational weeks, and 115 (67%) occurred on or after that. Higher caffeine consumption was associated with higher risk for both early and late miscarriage. However, the association appeared to be more pronounced for later rather than earlier miscarriage (Table 5).

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 caffeine consumption at 200 mg or greater per day. This observed effect was independent of many potential confounders including pregnancy related symptoms such as nausea, vomiting, and aversion to caffeine consumption. Even among women who never changed caffeine consumption pattern during pregnancy, there was an almost 80% increased risk of miscarriage associated with caffeine consumption of 200 mg/day or greater, although it was not statistically significant because of reduced sample size by stratification. Finally, the increased risk of miscarriage appeared to be due to caffeine itself rather than other possible chemicals in coffee because caffeine intake from noncoffee sources showed the similarly increased risk of miscarriage (Table 2).

Although an increased risk of miscarriage associated with caffeine intake during pregnancy has been previously reported,[7,8,15,17,22,23] a lack of adequate control of potential confounders, especially pregnancy-related symptoms such as nausea, vomiting, and aversion to caffeine, limited the validity of those findings.[10] Some argued that the association was an artifact because of confounding by nausea and vomiting, which are generally associated with a low risk of miscarriage and possible reduction of the consumption of caffeine because of the symptoms.[7,8,10,13] We ascertained detailed information on nausea and vomiting since the LMP and for the immediate 7 days before the interview. The association between caffeine intake and the risk of miscarriage remained after adjustment for nausea and vomiting, and the association also continued to exist among women both with and without nausea and vomiting during pregnancy.

To address this issue more thoroughly, we examined the association among women with and without actual change in caffeine consumption during pregnancy (a direct control of possible changes in caffeine consumption because of underlying risk of miscarriage that had been the critical point of the criticism of the association). We examined the association separately among those who reduced and who did not change their caffeine consumption during pregnancy. (The sample size was too small to evaluate this issue for those who increased their caffeine consumption during pregnancy.) The increased risk of miscarriage associated with caffeine consumption still existed after the stratification. These results did not support the argument that the observed association

was due to confounding by the pregnancy-related symptoms that reduced both caffeine intake and the risk of miscarriage.

We also observed that the association appeared to be stronger among women without other risk factors for miscarriage, for example, women with no history of miscarriage, no smoking during pregnancy, and the presence of nausea and/or vomiting (Table 4). Although the underlying reason for this interaction is not known at this time, it could be that caffeine intake is a lesser risk factor in the presence of other risk factors of miscarriage as is the likely case among women with a history of repeated miscarriages. If our interpretation is correct, this observation is consistent with our other finding that the association was stronger among later miscarriage (Table 5), which, unlike early miscarriage, are not largely due to known strong risk factors such as chromosomal abnormalities.

One limitation of the study is the potential misclassification of caffeine intake. Caffeine content in a cup of tea/coffee varies by different brands and brewing methods; it is not practical to perform laboratory analysis on caffeine content from consumed coffee and tea in epidemiological studies. Even assays of biological specimens have limitations because they can measure only caffeine intakes in the very recent past. Therefore, most studies including ours used certain conversion factors to calculate caffeine amount given the sources of caffeine and amount of intake provided by the participants.[8,13,15-17,22]

Another concern is the potential recall bias because of some participants who were interviewed soon after their miscarriage. To assess the potential existence of recall bias, we conducted a stratified analysis based on whether the interview was conducted before or after their miscarriage. The results were essentially the same, providing no evidence of recall bias. Therefore, we combined the data in the final analyses. Because of low participation rates, selection bias could be a potential concern. Although we do not have information on caffeine intake for nonparticipants, we compared a few characteristics, including age and the rate of miscarriage between participants and nonparticipants. Both average age (30 vs 29 years) and the rate of miscarriage (16.4% vs 17.2%) for participants and nonparticipants were very similar, providing some assurance against participation bias.

The strengths of the present study included: (1) a cohort design, (2) a large study sample size, (3) recruitment of pregnant women at early gestational ages for identification of early miscarriages, (4) detailed information on caffeine intake including all sources, changing patterns of intakes, and timing and amount of intakes since LMP, and (5) ascertainment of detailed information on pregnancy-related symptoms including nausea, vomiting, and aversion to caffeine consumption during pregnancy. The available information on nausea, vomiting, and existence of aversion to caffeine consumption allowed us to examine whether these factors explained the observed association of caffeine intake during pregnancy with the risk of miscarriage.

In conclusion, the results from our prospective cohort study supported previous findings that high caffeine consumption during pregnancy may increase the risk of miscarriage. We provided new evidence that the observed association was not likely the result of confounding by the pregnancy-related symptoms of nausea, vomiting, and aversion to caffeine consumption. Therefore, it may be prudent to stop or reduce caffeine intake during pregnancy. ■

TABLE 5
Risk of miscarriage and caffeine intake during pregnancy by gestational age at miscarriage*

	Miscarriage		
Gestational age at miscarriage	n (%)	Person-days	aHR[a]
Less than 8 wks			
0	13 (0.34)	3791	1
Less than 200	29 (0.32)	9022	1.04 (0.50 to 2.18)
200 or more	15 (0.73)	2064	1.41 (0.60 to 3.31)
8 wks or more			
0	20 (0.11)	18,607	1
Less than 200	68 (0.15)	44,645	1.72 (1.01 to 2.92)
200 or more	27 (0.29)	9169	2.79 (1.46 to 5.34)

[a] 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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De-Kun Li conceived the concept, designed the study, obtained funding, oversaw the data collection and analyses, and was involved in the interpretation of results and preparation of the manuscript. Xiaoping Weng was responsible for data analysis, interpretation of the data, and preparation of the manuscript. Roxana Odouli was involved in the data collection and preparation of the manuscript. De-Kun Li is the guarantor of this paper, who took full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

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