

## MATERNAL SERUM PARAXANTHINE, A CAFFEINE METABOLITE, AND THE RISK OF SPONTANEOUS ABORTION

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**ABSTRACT**

**Background** Whether the consumption of caffeine during pregnancy increases the risk of spontaneous abortion is controversial. Prior studies have determined caffeine consumption by questionnaire. We used a biologic marker, serum paraxanthine, a metabolite of caffeine, to measure the dose of caffeine.

**Methods** In a nested case-control study, we measured serum paraxanthine in 591 women who had spontaneous abortions at less than 140 days' gestation and in 2558 matched women from the same clinic who gave birth to live infants at 28 weeks' gestation or later and who had serum drawn on the same day of gestation as the women who had abortions. The women were enrolled in the Collaborative Perinatal Project during the period from 1959 to 1966, and serum paraxanthine was measured over 30 years later.

**Results** A total of 487 women who had spontaneous abortions (82 percent) and 2087 controls (82 percent) had quantifiable serum paraxanthine concentrations. However, the mean serum paraxanthine concentration was higher in the women who had spontaneous abortions than in the controls (752 vs. 583 ng per milliliter,  $P < 0.001$ ). The odds ratio for spontaneous abortion was not significantly elevated in the women who had serum paraxanthine concentrations of 1845 ng per milliliter or lower, corresponding to the 95th percentile of the matched women. However, the adjusted odds ratio for spontaneous abortion among women with serum paraxanthine concentrations higher than 1845 ng per milliliter, as compared with women who had concentrations below 50 ng per milliliter, was 1.9 (95 percent confidence interval, 1.2 to 2.8).

**Conclusions** Only extremely high serum paraxanthine concentrations are associated with spontaneous abortion. This suggests that moderate consumption of caffeine is unlikely to increase the risk of spontaneous abortion. (N Engl J Med 1999;341:1639-44.)

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**W**HETHER consumption of caffeine during pregnancy increases the risk of spontaneous abortion is controversial. Several studies have indicated that even moderate caffeine consumption is associated with a risk of fetal loss that is more than double the risk in women who do not consume caffeine.<sup>1,2</sup> Others have reported that the risk is elevated only for women who consume three or more cups of coffee per day<sup>3</sup> or those who consume large amounts of caffeine and

who are nauseated during pregnancy.<sup>4</sup> Still other studies have found no increase in risk even among women who consume large amounts of caffeine.<sup>5-8</sup>

Possible reasons for these discrepant results include small samples, particularly with respect to the groups of women who consumed large amounts of caffeine; retrospective or prospective ascertainment of caffeine consumption, spontaneous abortion, or both; changes in caffeine consumption during pregnancy; differences in the adequacy of statistical control for nausea during pregnancy; and problems of assessing caffeine intake on the basis of responses to a questionnaire.<sup>9</sup> Wide variations in individual rates of caffeine metabolism make it difficult to translate even an accurately reported intake into serum concentrations of caffeine and its metabolites.<sup>10</sup> We measured serum paraxanthine, the primary metabolite of caffeine, to determine whether the consumption of caffeine is associated with spontaneous abortion.

**METHODS****Study Subjects**

Our sample consisted of women enrolled in the Collaborative Perinatal Project, a prospective study of pregnancy, labor, and child development conducted at 12 sites in the United States from 1959 to 1966. The women in that study were enrolled when they presented for prenatal care and were followed for the remainder of their pregnancy. There were approximately 55,000 births to 42,000 women.<sup>11</sup> Although no information was collected on the consumption of coffee, tea, or soft drinks, serum was obtained approximately every two months during pregnancy, at delivery, and six weeks after delivery. Information about vomiting was obtained at enrollment and at each prenatal visit, and gestational age was estimated on the basis of the reported first day of the last menstrual period.

A total of 830 women had early fetal losses (less than 140 days after the first day of the last menstrual period); serum was obtained during the pregnancy from 704 of these women. The relatively small number of women with early fetal losses was due to the late gestational age at which many women were enrolled in the study.<sup>11</sup> The women were stratified according to the clinical center and the day of gestation on which the earliest serum sample was obtained. For the women with early fetal losses in each stratum, we selected four times the number of women at the same center who gave birth to live infants after at least 28 weeks of gestation and who had serum drawn on the same day of gestation (con-

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trols). Serum was obtained at an unknown time of day during clinic visits and during hospitalization for delivery.

Serum caffeine and paraxanthine were assayed. In a pilot study,<sup>12</sup> serum caffeine and paraxanthine concentrations were positively correlated with the caffeine consumption reported by pregnant women, but the serum paraxanthine concentration was more closely correlated with caffeine consumption than was the serum caffeine concentration, particularly among smokers. The serum concentration of paraxanthine is less sensitive than that of caffeine to very recent caffeine intake.<sup>10</sup> Accordingly, our primary objective was to test the hypothesis that the mean serum paraxanthine concentration was higher in women who had spontaneous abortions than in women who delivered live infants. An additional objective was to determine whether there was a threshold above which the serum paraxanthine concentration was associated with spontaneous abortion.

### Biochemical Assays

Serum caffeine and paraxanthine were measured with the use of high-performance liquid chromatography.<sup>12</sup> The limit of quantitation was established at 50 ng per milliliter for caffeine and paraxanthine; the limit of detection was 25 ng per milliliter. The intraassay and interassay coefficients of variation were less than 6.9 percent at 200, 800, and 2000 ng per milliliter. The laboratory personnel who performed the assays were unaware of the outcome of each pregnancy. Serum samples from the women who had spontaneous abortions and from the matched controls were analyzed in the same batch; the order of the samples varied from batch to batch. Since this analysis involved previously collected specimens from which identifying information had been removed, the Office of Human Subjects Research found it to be exempt from the requirement for approval by an institutional review board.

### Statistical Analysis

Continuous variables were compared with use of Student's *t*-test or analysis of variance, and categorical variables were compared with use of the chi-square test. The standard deviation for the serum paraxanthine concentration was proportional to the mean, violating the assumptions of the *t*-test and analysis of variance. Log transformation of the serum paraxanthine values solved this problem. Since the results with the use of log-transformed data did not differ substantially from the results with the use of untransformed data, only the latter are reported here. The association between the serum paraxanthine concentration and spontaneous abortion was analyzed by conditional logistic regression.<sup>13</sup>

## RESULTS

There were 704 women who had early fetal losses and 2816 controls. Since the Collaborative Perinatal Project had only one code for all early fetal losses, the original study records were reviewed to identify the women who had spontaneous abortions. Forty-six of the women with early fetal losses had induced abortions, ectopic pregnancies, or iatrogenic termination of pregnancy or died during pregnancy. For the group of 658 women in whom fetal loss was due to spontaneous abortion, it was not possible to determine from a review of the records whether serum drawn on the day of spontaneous abortion was obtained before or after the event, so the 57 women in whom the serum sample had been obtained on the day of abortion were excluded from the analysis. In an additional 10 women who had spontaneous abortions, insufficient serum was available for analysis. The exclusion of these 113 women required the exclusion of 208 matched controls, and in 50 additional controls, in-

sufficient serum was available for analysis. The final study group thus comprised 591 women who had spontaneous abortions and 2558 matched controls.

We compared the group of 591 women with spontaneous abortions whose serum samples were available for analysis with the group of 193 women with spontaneous abortions for whom serum samples were not available. The median date of enrollment was January 1963 for the former group and December 1960 for the latter ( $P < 0.001$ ), suggesting that study procedures improved over time, and the two groups of women were enrolled on day 76 and day 80 of gestation, respectively ( $P = 0.02$ ). On average, 24 days elapsed from enrollment to the spontaneous abortion for women for whom serum was available, as compared with 12 days for women for whom serum was not available ( $P < 0.001$ ). The proportion of women from whom serum was obtained varied significantly among the study sites, ranging from 70 to 100 percent.

The characteristics of the women who had spontaneous abortions and the controls are shown in Table 1. Serum was drawn on the same day of gestation in the two groups. The mean duration of pregnancy was slightly more than 14 weeks among the women who had spontaneous abortions and was 39 weeks among the controls. The median interval from the collection of serum to abortion was 17 days. The women who had spontaneous abortions were significantly older than the controls ( $P < 0.001$ ), more likely to smoke ( $P < 0.001$ ), and less likely to have vomited ( $P < 0.001$ ) or to have taken medications containing caffeine ( $P = 0.02$ ) during pregnancy.

The serum paraxanthine concentrations are shown in Table 2 according to the outcome of pregnancy and maternal characteristics. In both the group of women who had spontaneous abortions and the control group, higher serum paraxanthine concentrations were associated with increasing age, white race, smoking, and the absence of vomiting during pregnancy. The serum paraxanthine concentration was positively associated with the level of education only in the control group. In almost every category of each of these characteristics, the serum paraxanthine concentration was higher in the women who had spontaneous abortions than in the controls (Table 2).

A total of 487 women who had spontaneous abortions (82 percent) and 2087 controls (82 percent) had quantifiable serum paraxanthine concentrations ( $P = 0.64$ ). However, the mean serum paraxanthine concentration was significantly higher in the abortion group than in the control group (752 vs. 583 ng per milliliter,  $P < 0.001$ ). The odds ratios for spontaneous abortion according to the serum paraxanthine concentration, with the women who had unquantifiable serum paraxanthine concentrations ( $< 50$  ng per milliliter) used as the reference group and with adjustment for smoking status, age, and race or ethnic group, are

**TABLE 1. CHARACTERISTICS OF THE WOMEN WHO HAD SPONTANEOUS ABORTIONS AND THOSE WHO GAVE BIRTH TO LIVE INFANTS (CONTROLS).**

CHARACTERISTIC	WOMEN WITH SPONTANEOUS ABORTIONS (N=591)		CONTROLS (N=2558)	
Length of gestation when blood sample obtained (days)				
Mean	78		78	
Median	76		76	
Length of gestation at time of abortion or delivery (days)				
Mean	100		274	
Median	99		278	
Interval between blood sample and abortion (days)				
Mean	22		—	
Median	17			
Mean age at enrollment (yr)	27		25	
Smoker (%)*	46		39	
Vomiting since last menstrual period (%) <sup>†</sup>	38		56	
Education (%) <sup>‡</sup>				
<12 yr	50		40	
12 yr	31		37	
≥13 yr	19		23	
Race or ethnic group (%)				
White	61		65	
Black	33		29	
Other or unknown <sup>§</sup>	6		6	
Diagnosis of diabetes mellitus before pregnancy (%)	3		2	
Use of medications containing caffeine (%)				
During month serum sample was obtained	6		9	
During month before serum sample was obtained	4		6	

\*Data were available for 591 women who had spontaneous abortions and 2542 controls.

<sup>†</sup>Data were available for 515 women who had spontaneous abortions and 2544 controls.

<sup>‡</sup>Data were available for 447 women who had spontaneous abortions and 2518 controls.

<sup>§</sup>Eleven percent of the women in this category were Asian, 85 percent were Puerto Rican, and 4 percent were unclassified with respect to race or ethnic group.

shown in Figure 1. Data on vomiting during pregnancy and educational level were missing for a substantial number of women. However, adjustment for these factors did not substantially change the odds ratios (data not shown). The increased risk of spontaneous abortion was almost entirely restricted to women with serum paraxanthine concentrations higher than 1845 ng per milliliter, corresponding to the 5 percent of controls with the highest concentrations (adjusted odds ratio, 1.9; 95 percent confidence interval, 1.2 to 2.8). For the remainder of the analyses, the women were grouped according to their serum paraxanthine concentrations (<50 ng per milliliter, 50 to 1845 ng per milliliter, and >1845 ng per milliliter, corresponding roughly to <20th percentile of serum paraxanthine values in the controls, 20th to 95th percentile, and >95th percentile).

The association between serum paraxanthine con-

**TABLE 2. MEAN SERUM CONCENTRATIONS OF PARAXANTHINE ACCORDING TO THE OUTCOME OF PREGNANCY AND MATERNAL CHARACTERISTICS.**

CHARACTERISTIC	WOMEN WITH SPONTANEOUS ABORTIONS		CONTROLS	
	SERUM PARAXANTHINE (ng/ml)	P VALUE	SERUM PARAXANTHINE (ng/ml)	P VALUE
Age				
<20 yr	447	<0.001*	359	<0.001*
20–24 yr	512		498	
25–29 yr	835		681	
30–34 yr	1068		713	
≥35 yr	1024		870	
Education		0.74*		0.01*
<12 yr	714		515	
12 yr	748		593	
≥13 yr	680		612	
Smoker		<0.001		<0.001
Yes	899		762	
No	626		474	
Vomiting		<0.001		<0.001
Yes	585		536	
No	849		646	
Race or ethnic group		<0.001		<0.001
White	931		679	
Black	435		357	
Other or unknown	652		659	

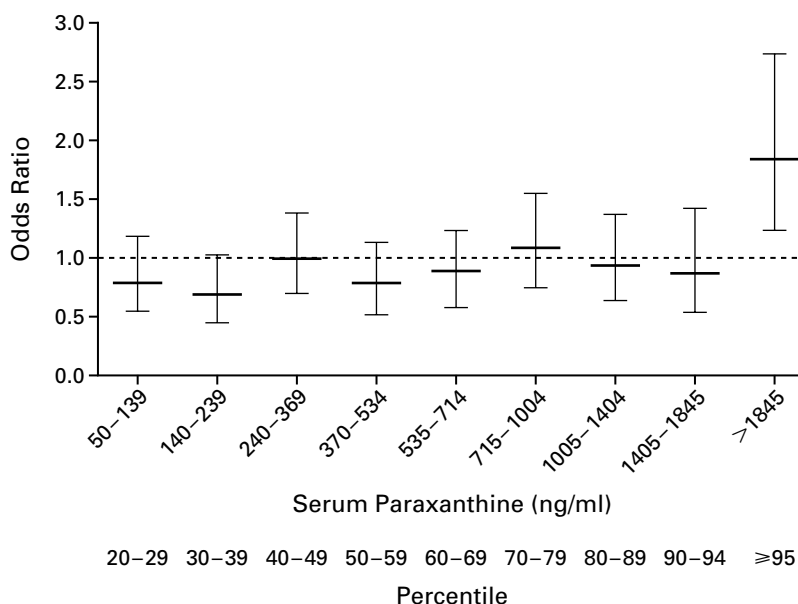
\*The P value is for trend.

centrations and spontaneous abortion according to other factors is shown in Table 3. All odds ratios were adjusted for maternal age, smoking status, and race or ethnic group. For women with very high serum paraxanthine concentrations, the odds ratio for spontaneous abortion did not differ significantly according to whether the abortion occurred at 100 or more days of gestation or earlier (100 days was the median interval), whether the serum sample had been obtained 17 or fewer days before spontaneous abortion or more than 17 days earlier (17 days was the median interval), or whether the woman had or had not vomited since her last menstrual period.

To determine whether differences in desiccation over time affected the results, we measured serum sodium in 3057 samples, using direct potentiometry with ion-selective electrodes. The mean (±SD) serum sodium concentration was 137±27 mmol per liter. After standardization of the serum paraxanthine concentration to a serum sodium concentration of 135 mmol per liter, the results shown in Figure 1 were largely unchanged.

## DISCUSSION

Our results indicate that the serum concentration of paraxanthine, the primary metabolite of caffeine, is higher in women who have spontaneous abortions than in women who give birth to live infants. However, the risk of spontaneous abortion is not in-



**Figure 1.** Adjusted Odds Ratios and 95 Percent Confidence Intervals for Spontaneous Abortion According to the Serum Concentration of Paraxanthine.

The reference category is values of less than 50 ng per milliliter. The odds ratios have been adjusted for smoking status, age, and race or ethnic group. The percentiles are for the serum paraxanthine values in the controls.

creased until extremely high serum paraxanthine concentrations are reached. Our results support previous studies showing that the consumption of large amounts of caffeine is associated with an increased risk of spontaneous abortion<sup>1-4</sup> but that moderate consumption does not increase the risk.<sup>3-8</sup>

Since there is no precise way to equate a serum paraxanthine concentration with an amount of caffeine intake, our results cannot directly answer the question of how much caffeine is safe during pregnancy. However, there may be indirect ways to answer this question. Our pilot study<sup>12</sup> involved women who had participated in the Birmingham, Alabama, study of infant growth in the mid-1980s.<sup>14</sup> The highest caffeine intake in that cohort was 1530 mg per day (equivalent to approximately 15 cups of coffee). The highest measured serum paraxanthine concentration was 1165 ng per milliliter, which was substantially lower than the value at the 95th percentile in this study (1845 ng per milliliter). Even with allowance for volume loss during storage, the 95th percentile of serum paraxanthine in this study is higher than the highest value in the Birmingham study. Extrapolating from our pilot data, a 60-kg woman who did not smoke and who consumed 600 mg of caffeine (about 6 cups of coffee) per day or a 60-kg woman who smoked and who consumed 1100 mg of caffeine (about 11 cups of coffee) per day would have an estimated serum paraxanthine concentration of 1845 ng per milliliter.

Additional information to equate serum paraxanthine concentrations with caffeine intake comes from the California Child Health and Development Studies,<sup>15</sup> involving a prospective cohort of pregnant women in the 1960s. In that study, women were asked about their intake of coffee and tea. Assuming that a cup of tea contains half the caffeine of a cup of coffee, the 95th percentile of caffeine intake was equivalent to 8.5 cups of coffee per day, which is consistent with the extrapolated data from our pilot study and conservatively suggests that the 95th percentile of caffeine intake in the current study was the equivalent of more than 5 cups of coffee per day.

Several caveats should be noted. First, the women in the Collaborative Perinatal Project were enrolled relatively late in gestation, and the majority of abortions occurred in the second trimester. Furthermore, karyotype analyses were not performed for any of the aborted fetuses. Fetuses aborted early in gestation are more likely to have chromosomal abnormalities than are fetuses aborted later.<sup>16</sup> However, abortion of chromosomally normal fetuses is a more sensitive indicator of exogenous risk factors.<sup>16</sup> The association between caffeine intake and spontaneous abortion has been reported to be similar for chromosomally normal and abnormal fetuses,<sup>8</sup> suggesting either that caffeine increases the risk of loss for both types of fetuses or that the association is not causal.

Second, the Collaborative Perinatal Project recorded data on vomiting during pregnancy but not on

**TABLE 3.** ADJUSTED ODDS RATIOS FOR SPONTANEOUS ABORTION ACCORDING TO THE SERUM PARAXANTHINE CONCENTRATION AND ADDITIONAL FACTORS.

FACTOR	WOMEN WITH SPONTANEOUS ABORTIONS		TOTAL	ADJUSTED ODDS RATIO (95% CI)†	
	CONTROLS*	number			
<b>&gt;17 Days between collection of serum and spontaneous abortion‡</b>					
Serum paraxanthine, <50 ng/ml		50	240	290	1.0
Serum paraxanthine, 50–1845 ng/ml		206	879	1085	1.0 (0.6–1.5)
Serum paraxanthine, >1845 ng/ml		33	62	95	2.0 (1.2–3.6)
<b>≤17 Days between collection of serum and spontaneous abortion‡</b>					
Serum paraxanthine, <50 ng/ml		54	231	285	1.0
Serum paraxanthine, 50–1845 ng/ml		212	1078	1290	0.8 (0.5–1.1)
Serum paraxanthine, >1845 ng/ml		36	68	104	1.8 (1.0–3.1)
<b>Spontaneous abortion at ≥100 days' gestation‡</b>					
Serum paraxanthine, <50 ng/ml		51	255	306	1.0
Serum paraxanthine, 50–1845 ng/ml		205	1042	1247	1.0 (0.7–1.4)
Serum paraxanthine, >1845 ng/ml		33	79	112	1.7 (1.0–3.0)
<b>Spontaneous abortion at &lt;100 days' gestation‡</b>					
Serum paraxanthine, <50 ng/ml		53	216	269	1.0
Serum paraxanthine, 50–1845 ng/ml		213	915	1128	0.8 (0.6–1.1)
Serum paraxanthine, >1845 ng/ml		36	51	87	2.1 (1.2–3.6)
<b>Vomiting since last menstrual period§</b>					
Serum paraxanthine, <50 ng/ml		49	190	239	1.0
Serum paraxanthine, 50–1845 ng/ml		221	860	1081	1.1 (0.7–1.6)
Serum paraxanthine, >1845 ng/ml		47	73	120	2.2 (1.2–4.0)
<b>No vomiting since last menstrual period§</b>					
Serum paraxanthine, <50 ng/ml		49	277	326	1.0
Serum paraxanthine, 50–1845 ng/ml		133	1087	1220	0.7 (0.5–1.0)
Serum paraxanthine, >1845 ng/ml		16	57	73	1.8 (0.8–3.8)

\*Controls were women who gave birth to live infants after at least 28 weeks of gestation, who were at the same clinic as the women who had spontaneous abortions, and who had serum drawn on the same day of gestation as the women who had spontaneous abortions.

†Odds ratios have been adjusted for maternal age, smoking status, and race or ethnic group. The reference group is women in both study groups who had serum paraxanthine concentrations of less than 50 ng per millimeter. CI denotes confidence interval.

‡Controls were randomly matched with women who had spontaneous abortions in this stratum.

§Data on vomiting were available for 515 women who had spontaneous abortions and 2544 controls.

nausea. Nausea is thought to be a marker for a healthy pregnancy, and nausea and food aversions may cause women to reduce their consumption of coffee and other foods with strong aromas.<sup>17</sup> If so, then even the elevated risk of spontaneous abortion among women with extremely high serum paraxanthine concentrations may simply reflect the fact that a viable pregnancy causes a woman to reduce her intake of caffeine. Since nauseated women consume less caffeine than women without nausea and also have a reduced risk of spontaneous abortion, the likely effect of incomplete data on nausea and vomiting would be to overestimate the level of risk associated with high levels of caffeine consumption.

Third, although unlike the serum caffeine concentration, the serum paraxanthine concentration does not fluctuate greatly during the day, the serum half-

lives of the two substances are similar: approximately 5 hours during the first trimester and 10 hours during the second trimester.<sup>18,19</sup> Therefore, serum paraxanthine is a marker only of short-term caffeine intake. Although we are unaware of any data that confirm this observation, the likelihood that caffeine intake is relatively constant from day to day provides support for the use of serum paraxanthine as a biologic marker of caffeine intake.

Fourth, the serum samples we used had been stored for over 30 years. The stability of paraxanthine during long-term storage at  $-20^{\circ}\text{C}$  is unknown. In our pilot study,<sup>12</sup> we found that the paraxanthine concentration in serum samples stored for eight years at  $-70^{\circ}\text{C}$  was closely correlated with the reported caffeine intake, suggesting that paraxanthine remains stable under these conditions. We quantified paraxan-

thine in 82 percent of the serum samples from the Collaborative Perinatal Project and detected it below the limit of quantitation in an additional 4 percent. In the California Child Health and Development Studies, 13 percent of the women reported that they consumed neither coffee nor tea. This finding is consistent with our 85 percent detection rate and suggests that marked deterioration of paraxanthine was unlikely to have occurred.

Our study has several strengths. The serum samples were collected in the 1960s, when few pregnant women were advised to reduce their intake of caffeine. Per capita coffee consumption in the United States peaked in 1962 and then declined, particularly among people less than 40 years old.<sup>20</sup> The Collaborative Perinatal Project is therefore likely to have enrolled many women who consumed large amounts of caffeine. Most investigators have found it difficult to enroll sufficient numbers of women who consumed large quantities of caffeine.<sup>1-4,6,7</sup>

In conclusion, if caffeine causes spontaneous abortion, it does so only at serum paraxanthine concentrations, and presumably levels of caffeine intake, that were uncommonly high in the 1960s, and these high levels are probably even less common now.

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