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Prenatal Caffeine Assessment: Fetal and Maternal Biomarkers or Self Reported Intake?

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Abstract

PURPOSE—To examine associations among measures of caffeine exposure including maternal urine, umbilical cord blood, and maternal self report.

METHODS—Pregnant women were recruited from 56 obstetric practices and 15 clinics associated with six hospitals in Connecticut and Massachusetts between September 1996 and January 2000; 3,633 women were enrolled. Maternal urine throughout pregnancy and umbilical cord blood samples were analyzed for caffeine, paraxanthine, theophylline, and theobromine. Maternal caffeine intake was assessed throughout pregnancy.

RESULTS—Urinary and cord blood biomarkers were correlated with reported intake throughout pregnancy (range $r = 0.35–0.66$; $p<0.0001$). Infants of smokers had higher cord blood concentrations of paraxanthine, reflecting faster caffeine metabolism in smokers, and cord blood paraxanthine levels were more strongly correlated with intake in smokers.

CONCLUSION—Maternal self reported intake may still be the optimal and most valid measure of antenatal caffeine exposure, since biomarkers do not reflect exposure over pregnancy.

Keywords

biomarkers; caffeine; cord blood; pregnancy; self-report

Introduction

Caffeine consumption during pregnancy is quite common. A recent United States Department of Agriculture Survey reported that 89 percent of women aged 18 – 24 consume caffeinated beverages with an average intake of 166 mg caffeine per day, (1). Caffeine readily crosses the placenta into the fetus and into amniotic fluid. The half-life of caffeine increases during pregnancy, reaching 11.5 – 18 hours by the end of pregnancy (2). Such long half-lives lead to an accumulation in the body with regular daily consumption. Neither the fetus nor the placenta can metabolize caffeine because they lack the necessary enzymes, so the fetus is exposed to caffeine and its metabolites in proportion to maternal exposure for a prolonged period of intra-uterine life.

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Assessment of fetal exposure to caffeine is methodologically challenging due to the considerable amount of heterogeneity in maternal caffeine exposure, due in part to wide variation of caffeine content in beverages and large differences in serving sizes of caffeinated beverages (3). Self-report of maternal consumption may not accurately predict fetal exposure because it does not indicate how much caffeine or caffeine metabolites actually enter fetal circulation. Fetal exposure to caffeine depends not only on maternal consumption, but on the rate at which caffeine is metabolized by the mother and cleared from the fetal circulation. Numerous endogenous and exogenous factors influence caffeine metabolism, including cigarette smoking (4–6), pregnancy (4), oral contraceptive use (7,8), liver disorders (9), and certain medications (10). Cigarette smoking nearly doubles the rate of caffeine metabolism due to the enzyme-inducing effects of polycyclic aromatic hydrocarbons, known to increase liver enzyme activity (4–6). Pregnancy slows caffeine metabolism due to a reduction in Cytochrome P-450 1A2 (CYP1A2) activity (11).

To better understand what might be optimal research biomarkers, we investigated the associations between caffeine and its metabolites, paraxanthine, theophylline and theobromine, measured in umbilical cord blood and maternal urine throughout pregnancy, with self-reported maternal caffeine exposure throughout pregnancy.

Materials and Methods

The study included pregnant women delivering at 56 obstetric practices and 15 clinics associated with six hospitals in Connecticut and Massachusetts between September 1996 and January 2000. Exclusion criteria included gestational age greater than 24 weeks at enrollment, mother having insulin-dependent diabetes mellitus, mother speaking neither English or Spanish, and intent to terminate the pregnancy.

A total of 11,267 women were screened and 9,576 (85%) were eligible to participate. All women drinking 150 mg or more of caffeine daily in the prior week (n=718) and a random sample of those drinking no caffeine or less than 150 mg per day (n=2,915), were invited to participate (total n=3,633). Of these women, 2,478 (68.2%) enrolled; 639 declined to participate (17.6%, same percentage by caffeine exposure), 20 (0.6%) were ineligible at time of home interview, 72 (2.0%) miscarried prior to interview, and 424 (11.7%) were lost to follow-up or could not be contacted for interview before the 24^{th} gestational week. Of the 2,478 women enrolled in the study, 187 were excluded from this analysis (70 miscarried, 53 delivered multiple infants, 9 terminated their pregnancies, six experienced stillbirths, five withdrew from the study, and 44 could not be traced) leaving 2,291 women who had a singleton birth.

Based on gestational age at interview, caffeine consumption and random selection, these 2,291 women were placed into one of three subgroups: 1) a telephone group, 2) an intensively monitored group (if <= 13 weeks gestation), or 3) a biochemically monitored group. The telephone group (n=1,882) was interviewed once during pregnancy at a randomly assigned week (20, 28, or 36) of gestation. The intensively monitored (n=164) and biochemically monitored (n=245) groups were interviewed at all three time points; the intensively monitored group also provided urine samples at each time point while the biochemically monitored group provided a urine sample at one randomly selected time point. Of those 2,291 women, 1,672 women provided an umbilical cord blood sample, 268 women gave a urine sample at the home interview and at least one additional urine during pregnancy, 141 women gave a urine sample at 20 weeks gestation, 144 women gave a urine sample at week 28, 134 women gave a urine sample at week 36, and 99 women provided a urine sample at delivery.

We compared women who gave a cord blood sample with those who did not with regard to age, race, education, parity, marital status, and alcohol, smoking and caffeine consumption

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during the first and third trimesters. The only differences were for education and alcohol consumption. Women with less than a high school education were more likely to give a sample than those who were more educated. Conversely, heavier alcohol consumers (> 1 absolute ounce/day) were less likely to provide a cord blood sample, compared to women who drank less alcohol.

Because of the sampling strategy, more women provided information on reported intake during the first and third trimesters (n=2292 and 2157 respectively). All data from each reporting period were used for each analysis to maximize the information collected.

Assessment of Caffeine Exposure

All women were interviewed at home by a trained research assistant before 25 weeks gestation; the majority were enrolled by 14 weeks (IQR = 12–17 weeks). Women were asked whether they consumed caffeinated and decaffeinated coffee, tea, and soda since becoming pregnant as well as in the past week, and the day prior. Each of these questions was followed by detailed questions about the type of coffee (regular or instant), tea (hot or iced and including herbal tea), and soda, method of preparation (percolated, auto drip, steeping time), and brand name. Information was also collected on frequency of coffee, tea and soda consumption and volume of each beverage consumed. To improve recall, respondents were shown a series of model cup sizes from which to choose their usual size. After the initial interview, women in the telephone, biochemically monitored and intensively monitored groups were contacted at selected points in pregnancy to evaluate changes in caffeine exposure using these same detailed questions. Women were also asked about consumption of hot chocolate, cocoa, and chocolate milk, and chocolate candy, cakes, cookies and ice cream.

Third trimester exposure was ascertained postnatally, usually during the hospital stay, to assess exposure to caffeine and to obtain smoking and other risk factor information for the last three months of pregnancy. Caffeine exposures assessment was identical among women in all study groups.

Calculation of Caffeine Content in Coffee and Tea

During two, randomly selected time points, we collected samples of caffeinated and decaffeinated coffee and tea from every woman in the intensively monitored group. The samples were either prepared by the woman using her usual method, or were obtained from her usual place of purchase. Based on these sample analyses, a 10-oz cup of coffee contained 100 mg caffeine and tea brewed for more than 3 minutes contained 42 mg caffeine (3). These results differed from the usual standards which are 300 mg for a 10-oz cup of coffee and 94 mg caffeine for tea brewed for more than 3 minutes (12). We computed daily caffeine intake (mg/day) from coffee and tea for all women in the study based on our analysis of the actual beverages consumed. Caffeine content for sodas was based on values printed on the container.

Umbilical Cord Blood Collection and Assay

Umbilical cord blood samples were collected at delivery by the obstetrician. After cutting the cord, blood (venous and arterial) was drained into a tube and refrigerated immediately. Serum was separated, spun off within 24 hours of collection, and immediately frozen. Umbilical cord blood samples were analyzed for caffeine, paraxanthine, theophylline, and theobromine at the Clinical Pharmacology Laboratory at the University of California, San Francisco. Chemists were blinded to any exposure and pregnancy outcome information.

Concentrations of caffeine, paraxanthine, theophylline, and theobromine in plasma and urine were determined by using liquid chromatography coupled with tandem mass spectrometry.

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Stable isotope-labeled analogs of paraxanthine and caffeine were used as internal standards. Following protein precipitation, samples (0.2 ml) were treated with a phosphate buffer and were extracted with a mixture of methylene chloride, ethyl acetate, and isopropyl alcohol. Extracts were evaporated, reconstituted in the liquid chromatography mobile phase, and injected into the system of liquid chromatography coupled with tandem mass spectrometry. A mass spectrometer was operated by using atmospheric pressure chemical ionization, and selected reaction monitoring was used for quantitation. Calibration curves were constructed by using the peak area ratio of analyte/internal standard and linear regression.

Quantitation limits for the plasma analytes were 10 ng/ml. Precision ranged from 1.7 percent to 10.3 percent, and accuracy (percentage of expected value) ranged from 88 percent to 118 percent for concentrations of 10–5,000 ng/ml for analysis of plasma samples. Quantitation limits for urine analytes were 100 ng/ml and precision ranged from 0.5 – 2.2%. Accuracy (percent of expected value) ranged from 96 – 105% for concentrations from 100 ng/ml to 10,000 ng/ml. Assays below the detection limit were assigned an analysis value of zero.

Results

Reported Caffeine Consumption

More than half of the women (57%) consumed some caffeine during the first trimester of pregnancy, with 12% consuming >=150 mg/day. Consumption decreased during the third trimester, with 49 % consuming some caffeine daily; 42% consuming 1 – 149 mg/day, 7% consuming >= 150 mg/day; and 34 women (1.6%) consuming >= 300 mg/day. Most women reporting no caffeine consumption in the first trimester did not consume in the third trimester either (77%); only 5 women who reported zero caffeine consumption in the first trimester consumed >= 150 mg/day during the third trimester. Among consumers (n=1309), mean reported maternal caffeine intake during the first trimester was 98 mg/day (SD = 140) and median intake was 49 mg/day (IQR = 103). Average caffeine intake for smokers during the first trimester was higher than that for non-smokers (156 and 38mg/day respectively; $p< 0.0001$). Consumption decreased during the third trimester to an average of 75 mg/day (SD = 104; n=1057) and a median of 38 mg/day (IQR = 85). Smokers still consumed more caffeine in the third trimester, but average intake decreased to 129 mg/day (SD = 169; n=154) compared to 28 mg/day (SD = 59; n=1979) for non-smokers ($p < 0.0001$).

Metabolites in Maternal Urine

Mean maternal urinary caffeine and methylxanthine levels (ng/ml) throughout pregnancy are presented in Table 1. Levels were lowest at the home interview, increased throughout pregnancy, and then dropped markedly during delivery reflecting reduced consumption at this time. There is wide variability for all biomarkers at each time point. When maternal urinary methylxanthine levels were stratified by reported intake categories, women reporting no caffeine consumption during the first trimester (n=92) had urinary caffeine levels at the home interview ranging from 0 – 1,524 ng/ml and paraxanthine levels of 0 – 5,038 ng/ml, suggesting substantial underreporting of caffeine intake by some women. Of these women, just 55.4% had zero or undetectable levels of caffeine in their urine, and 28% had undetectable levels of paraxanthine.

Women reporting no caffeine intake during the third trimester (n=69) had urinary caffeine ranging from 0 – 2,154 ng/ml and paraxanthine levels of 0 – 10,581 ng/ml. Of these women, 25% and 15% had zero or undetectable levels of caffeine and paraxanthine respectively in their urine, suggesting underreporting of intake during the third trimester as well.

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Reported Caffeine Consumption and Metabolites in Umbilical Cord Blood

Table 2 reports mean umbilical cord blood methylxanthine levels by maternal reported intake during the first and third trimesters. There is substantial variation for each biomarker at both consumption periods. Mean caffeine levels in umbilical cord blood among non-consuming women during the third trimester were 476 ng/ml, which increased as consumption increased.

Caffeine levels in umbilical cord blood ranged from 0 – 10,491 ng/ml among women reporting no caffeine consumption during the third trimester, and paraxanthine levels ranged from 0 – 1,002 ng/ml. Among mothers reporting no caffeine consumption during the first or third trimester, only five percent of infants had zero ng/ml of caffeine in umbilical cord blood and 21% had zero levels of paraxanthine in umbilical cord blood. Women consuming >= 300 mg/day in both trimesters (n=14) had infants with umbilical cord blood caffeine levels ranging from 199 – 4,253 ng/ml. Umbilical cord blood paraxanthine levels in these infants ranged from 109 – 1,953 ng/ml.

Table 3 conveys the mean umbilical cord blood methylxanthine levels by smoking and reported caffeine intake during the third trimester. Smokers had babies with higher cord blood levels of paraxanthine within every reported consumption category and had lower caffeine levels, reflecting faster caffeine metabolism in smokers.

Umbilical cord blood levels of caffeine, paraxanthine and theophylline were correlated with average maternal reported caffeine consumption throughout pregnancy, with the highest correlations during the third trimester (range r = 0.49 to 0.55) (Table 4). Levels of theobromine (found in chocolate, tea and cocoa products) were not strongly correlated with reported caffeine consumption (range r = 0.02 to 0.12). When correlations were examined by third trimester smoking status, correlations between average reported intake during the third trimester and umbilical cord blood paraxanthine concentrations were higher among smokers compared to non-smokers; correlation coefficients were 0.59 and 0.53 respectively. Correlations between reported intake and caffeine were less strong (0.42 for smokers and 0.52 for non-smokers). Coefficients for theophylline were similar for smokers and non-smokers but theobromine was more strongly correlated with reported intake in smokers (0.30) than in non-smokers (0.10) (data not shown).

Maternal Self-Reported Caffeine Intake and Maternal Urinary Metabolite Levels

The three primary caffeine metabolites measured in urine were correlated with self report of caffeine consumption at all five points in pregnancy (Table 5). The strongest correlations with reported intake were during gestation week 36. Correlation coefficients for caffeine, paraxanthine, and theophylline at 36 weeks were 0.65, 0.66, and 0.65 respectively. Theobromine concentrations in maternal urine were not correlated with average reported maternal caffeine consumption during the third trimester except at delivery (r = 0.25). For the three major metabolites, the correlations of caffeine consumption with urine were uniformly higher than with cord blood (Table 4).

At the time of urine collections (home interview, 20, 28, 36 weeks and postpartum), women in the intensively monitored group were asked about caffeine intake in the past twenty-four hours. Correlation coefficients for maternal urinary methylxanthines and reported caffeine intake in the past twenty fours hours are presented in Table 6. Reported intake within twenty four hours of the home interview was more strongly correlated than reported intake averaged over the first trimester with the methylxanthine concentrations in urine obtained at the home interview. Correlation coefficients were slightly lower between reported consumption in the past twenty four hours and the respective urines obtained throughout pregnancy (Table 5).

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Maternal Urine Metabolites and Umbilical Cord Blood

Cord blood levels were highly correlated with all maternal urinary levels of the three major metabolites at each time point in pregnancy. Theobromine was very weakly correlated with urinary caffeine and metabolites. Metabolites in cord blood were most highly correlated with maternal urinary levels at the post partum interview (caffeine, r=0.75; paraxanthine, r=0.80; theophylline, r=0.84; and theobromine, r=0.72) (data not shown).

Discussion

This is the first study to examine methylxanthine associations in maternal urine, umbilical cord blood, and maternal self report. Maternal self reported caffeine intake was correlated with urinary concentrations of caffeine and its primary metabolites throughout pregnancy, but less strongly correlated with cord blood levels. The lower correlation between reported intake and urine is not surprising since less than 2% of caffeine is excreted as such (2). We observed evidence of caffeine exposure misclassification throughout pregnancy when assessing caffeine consumption via maternal self reported intake, since women reporting no consumption in either the first or third trimester had caffeine and methylxanthines in their urine and in their infants' cord blood. Similarly, Klebanoff et al., in a study of pregnant women, reported that 53% of smokers and 79% of non-smokers in the lowest category of reported intake during the second trimester had detectable caffeine concentrations in serum (13). It is unlikely that the caffeine and metabolite amounts in this study were due to medication use, because we assessed medication use throughout pregnancy and only 1.6% of women used caffeine-containing medications at some point during pregnancy.

For each level of reported consumption, caffeine metabolite levels in cord blood were higher in the third than in the first trimester, despite overall decreased average consumption in the third trimester. This may be due to decreased caffeine metabolism at the end of pregnancy. The effect seemed to be particularly strong in the highest caffeine consuming group, perhaps because it is particularly difficult to clear larger intakes when metabolism is slowed by advanced pregnancy.

Infants of smokers had higher cord blood concentrations of paraxanthine, compared to infants of non-smokers, reflecting faster caffeine metabolism in smokers. Correlation coefficients between reported third trimester intake and cord blood paraxanthine concentrations were higher among smokers (r = 0.59) compared to non-smokers (r = 0.53) but caffeine and reported intake were less strongly correlated among smokers. These findings are similar to those from an earlier study comparing reported intake and maternal serum obtained during the second trimester (13).

In the absence of regular and frequent biomarker collection, with concurrent interview data throughout pregnancy it remains uncertain which measures most accurately reflect caffeine consumption. Because urinary and umbilical cord blood biomarkers represent one point in time, and do not reflect exposure over pregnancy, maternal self reported caffeine intake may be the best measure of exposure since it is reflects consumption over time. Urinary biomarkers however, do capture recent methylxanthine exposure, although the absence of detectable concentrations cannot necessarily be interpreted to reflect non-consumption particularly when the time of urine collection is not concurrent with the consumption period of interest. Furthermore, renal clearance of caffeine and its metabolites depends in part on urine flow (14) and therefore these values may not always be accurate reflections of exposure.

A limitation to this study is the lack of maternal serum samples throughout pregnancy. Correlations among maternal serum concentrations of caffeine and its metabolites with

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reported intake and cord blood levels would further our understanding of the relationship among these biomarkers.

In conclusion, umbilical cord blood and maternal urinary biomarkers for caffeine exposure are indicative of recent consumption however, values below the detection limit do not indicate non-exposure. These issues deserve more investigation since it is technically (because of respondent burden) and economically not feasible to use continuous monitoring on large numbers of women. Until such studies are completed and in light of the expense associated with collecting and analyzing frequent biomarker data, it seems that maternal self reported caffeine intake may be the optimal and most valid measure of antenatal caffeine exposure.

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Table 1

Maternal Urinary Methylxanthine Levels Throughout Pregnancy

	N*	Mean (ng/ml)	Standard Deviation	Minimum	Maximum
Home Interview**	262	524	850	0	5,989
Caffeine		2,531	4,139	0	25,182
Paraxanthine		185	380	0	2,361
Theophylline		8,772	9,830	0	48,895
Theobromine					
Week 20	138	708	1,181	0	8,060
Caffeine		3,038	5,703	0	42,325
Paraxanthine		312	647	0	4,194
Theophylline		10,297	10,712	0	59,753
Theobromine					
Week 28	140	834	1,016	0	4,982
Caffeine		3,217	6,065	0	54,320
Paraxanthine		397	564	0	3,742
Theophylline		12,078	12,753	0	58,919
Theobromine					
Week 36	132	1,092	1,336	0	7,937
Caffeine		2,394	3,933	0	23,401
Paraxanthine		442	637	0	4,075
Theophylline		11,055	11,138	0	60,192
Theobromine					
Delivery	98	779	998	0	5,307
Caffeine		838	1,439	0	8,484
Paraxanthine		191	260	0	1,206
Theophylline		3,123	4,068	0	27,947
Theobromine					

* Repeated measurements in the same sub-sample of women

** Average 13 weeks gestation

Assays below detection limit: Week 20: *n* = 42 caffeine, *n* = 14 paraxanthine, *n* = 4 theobromine and *n* = 79 for theophylline; Week 28: *n* = 34 caffeine, *n* = 16 paraxanthine, *n* = 7 theobromine and *n* = 59 for theophylline; Week 36: *n* = 19 caffeine, *n* = 10 paraxanthine, *n* = 5 theobromine and *n* = 41 for theophylline; Delivery: *n* = 20 caffeine, *n* = 27 paraxanthine, *n* = 7 theobromine and *n* = 48 for theophylline.

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Table 2

Mean (Standard Deviation) Umbilical Cord Blood Methylxanthine Levels by Maternal Reported Intake During the First and Third Trimesters

	Umbilical Cord Blood Methylxanthine Levels (ng/ml)			
Average Reported Intake During the First Trimester (mg/day)	**Caffeine**	**Paraxanthine**	**Theophylline**	**Theobromine**
0 (n=675)	591 (912)	665 (104)	46 (59)	655 (817)
1 – 149 (n=742)	1091 (1340)	135 (156)	88 (96)	669 (760)
150 – 299 (n=120)	1677 (1638)	272 (256)	132 (120)	790 (903)
>= 300 (n=72)	1600 (1465)	376 (424)	136 (112)	608 (637)
Average Reported Intake During the Third Trimester (mg/day)				
0 (n=794)	476 (730)	58 (88)	38 (49)	639 (808)
1 – 149 (n=654)	1357 (1452)	165 (180)	106 (99)	699 (763)
150 – 299 (n=86)	1861 (1667)	310 (246)	161 (135)	812 (926)
>= 300 (n=23)	2098 (1660)	652 (508)	193 (133)	652 (671)

Assays below detection limit: *n* = 46 caffeine, *n* = 203 paraxanthine, *n* = 63 theobromine and *n* = 272 for theophylline

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Table 3

Mean (Standard Deviation) Umbilical Cord Blood Methylxanthine Levels by Smoking Status and Maternal Reported Intake During the Third Trimester

	Umbilical Cord Blood Methylxanthine Levels (ng/ml)			
Average Reported Intake During the Third Trimester (mg/day)	**Caffeine**	**Paraxanthine**	**Theophylline**	**Theobromine**
		Non-Smokers		
0 (n=659)	591 (916)	64 (96)	46 (60)	656 (821)
1 – 149 (n=687)	1136 (1368)	135 (155)	92 (98)	666 (748)
150 – 299 (n=86)	1850 (1710)	238 (228)	146 (130)	735 (779)
>= **300** (n=37)	1945 (1620)	258 (259)	156 (124)	584 (625)
		Smokers		
0 (n=13)	705 (828)	209 (273)	56 (63)	568 (718)
1 – 149 (n=47)	588 (766)	149 (173)	49 (59)	794 (945)
150 – 299 (n=29)	1114 (1045)	350 (292)	96 (67)	1010 (1229)
>= **300** (n=26)	1160 (1227)	538 (579)	111 (99)	636 (625)

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Table 4

Spearman Correlation Coefficients between Average Reported Maternal Consumption throughout P regnancy (mg/day) and Umbilical Cord Blood Methylxanthine Concentrations (ng/ml).

Average Reported Maternal Consumption During	Umbilical Cord Blood			
	Caffeine	Paraxanthine	Theophylline	Theobromine
First Trimester (n=1609)†	0.35 p< 0.0001	0.44 p< 0.0001	0.39 p< 0.0001	0.05 p=0.06
Week 20 (n=455)†	0.46 p< 0.0001	0.52 p< 0.0001	0.51 p< 0.0001	0.09 p=0.05
Week 28 (n=563)†	0.25 p< 0.0001	0.50 p< 0.0001	0.35 p< 0.0001	0.02 p=0.67
Week 36 (n=559)†	0.44 p< 0.0001	0.50 p< 0.0001	0.48 p< 0.0001	0.12 p=0.004
Third Trimester (n=1557)†	0.49 p< 0.0001	0.55 p< 0.0001	0.53 p< 0.0001	0.10 p<0.0001

† Sample size includes women with information on both measures of exposure

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Table 5

Spearman Correlation Coefficients between Average Reported Maternal Caffeine Consumption (mg/day) throughout Pregnancy and Maternal Urinary Methylxanthine Concentrations throughout Pregnancy.

Average Reported Maternal Consumption	Maternal Urinary Methylxanthine Concentrations at Home Interview			
	Caffeine	**Paraxanthine**	**Theophylline**	**Theobromine**
First Trimester (n=262)†	0.50 p< 0.0001	0.57 p< 0.0001	0.57 p< 0.0001	0.02 p=0.70
	20 Weeks			
	Caffeine	**Paraxanthine**	**Theophylline**	**Theobromine**
20 Weeks (n=128)†	0.58 p< 0.0001	0.60 p< 0.0001	0.50 p< 0.0001	0.002 p=0.99
	28 Weeks			
	Caffeine	**Paraxanthine**	**Theophylline**	**Theobromine**
28 Weeks (n=137)†	0.60 p< 0.0001	0.60 p< 0.0001	0.61 p< 0.0001	− 0.07 p=0.43
	36 Weeks			
	Caffeine	Paraxanthine	Theophylline	Theobromine
36 Weeks (n=132)†	0.65 p< 0.0001	0.66 p< 0.0001	0.65 p< 0.0001	− 0.02 p=0.86
	Delivery			
	Caffeine	**Paraxanthine**	**Theophylline**	**Theobromine**
Third Trimester (n=98)†	0.55 p< 0.0001	0.60 p< 0.0001	0.62 p< 0.0001	0.25 p=0.01

† Sample size includes women with information on both measures of exposure

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Table 6

Spearman Correlation Coefficients between Maternal Urinary Methylxanthines and Reported Caffeine Consumption in the Past 24 Hours throughout Pregnancy.

	Maternal Urinary Caffeine	Maternal Urinary Paraxanthine	Maternal Urinary Theophylline	Maternal Urinary Theobromine
Reported intake in the past 24 hours				
Home Interview (n=263)	0.66 p < 0.0001	0.71 p < 0.0001	0.68 p < 0.0001	0.05 p = 0.47
Week 20 Interview (n=130)	0.48 p < 0.0001	0.55 p < 0.0001	0.54 p < 0.0001	0.170.05
Week 28 Interview (n=140)	0.60 p < 0.0001	0.61 p < 0.0001	0.56 p < 0.0001	0.03 0.70
Week 36 Interview	0.61 p < 0.0001	0.62 p < 0.0001	0.60 p < 0.0001	− 0.01 0.94
Post Partum Interview	0.49 p < 0.0001	0.46 p < 0.0001	0.52 p < 0.0001	0.14 0.16