Studies investigating antenatal caffeine consumption and reproductive outcomes show conflicting results, and most studies have used maternal self-reported caffeine consumption to estimate fetal exposure. This study (n = 1,606) was specifically designed to test the association of caffeine and its primary metabolites in umbilical cord blood with intrauterine growth restriction (IUGR). Pregnant women were recruited from 56 obstetric practices and 15 clinics affiliated with six hospitals in Connecticut and Massachusetts between September 1996 and January 2000. In an adjusted model including caffeine only, levels in all quartiles were associated with reduced risk of IUGR. In adjusted analyses including paraxanthine and caffeine, serum paraxanthine levels in the highest quartile were associated with increased risk of IUGR (adjusted odds ratio = 3.29, 95% confidence interval: 1.17, 9.22); caffeine remained protective. These conflicting findings suggest that cytochrome P-450 1A2 (CYP1A2) metabolic activity may be associated with IUGR, so the ratio of paraxanthine to caffeine was then modeled. The likelihood of IUGR increased 21% for every one standard deviation change in the ratio (adjusted odds ratio = 1.21, 95% confidence interval: 1.07, 1.37), suggesting that CYP1A2 activity, and not the absolute levels of paraxanthine, influences fetal growth. No associations were observed between caffeine or any metabolites and preterm delivery.

Maternal caffeine consumption during pregnancy has been studied for decades, but evidence for an association with impaired fetal growth remains equivocal. Nearly all earlier studies relied on maternal self-reported caffeine consumption to estimate exposure, which is problematic because of considerable heterogeneity in caffeine exposure reporting (1). Questionnaire assessment of caffeine exposure does not provide an accurate measure of maternal or fetal dose because it does not necessarily indicate how much caffeine or caffeine metabolites enter the maternal or fetal circulation.

Interindividual caffeine metabolism varies greatly primarily because of variations in cytochrome P-450 1A2 (CYP1A2) enzyme activity (2–4), and numerous endogenous and exogenous factors affect maternal caffeine metabolism and clearance (5). The dose of caffeine and its metabolites to which the fetus is exposed depends not only on maternal consumption but also on the rate at which it is metabolized and cleared.

Caffeine is rapidly and completely absorbed from the gastrointestinal tract with minimal first-pass effect (6). Once caffeine is absorbed, it readily enters all body tissues and...
freely crosses the blood-brain, placental, and blood-testicular barriers (6, 7). Caffeine and its primary metabolites, paraxanthine, theophylline, and theobromine, are detectable in all body fluids and in umbilical cord blood (6, 8). The half-life of caffeine ranges from 2 hours to 4.5 hours (7, 9) but can be as long as 12 hours (10). Caffeine is metabolized in the liver, primarily by CYP1A2, which accounts for 95 percent of caffeine clearance; paraxanthine is the primary metabolite, accounting for 72–80 percent of caffeine metabolism (5).

Cigarette smoking nearly doubles the rate of caffeine metabolism (11) because cigarettes contain polycyclic aromatic hydrocarbons known to increase liver CYP1A2 enzyme activity (12, 13). One study observed that, within each category of reported consumption, smokers had lower serum caffeine concentrations than nonsmokers (14).

Caffeine half-life is unchanged during the first trimester of pregnancy but increases to 10 hours at 17 weeks’ gestation (11). Near term, the half-life in nonsmokers varies from 11.5 hours (15) to 18 hours (11), leading to an accumulation of caffeine and its metabolites. This gestational increase in caffeine half-life is likely related to a reduction in N-acetyltransferase 2 enzyme activity in early pregnancy and a reduction in CYP1A2 activity throughout pregnancy (16, 17). Caffeine clearance is greatly reduced in the third trimester of pregnancy, and fetal exposure to caffeine and its metabolites may be higher than expected based on maternal report (8).

Because neither fetus nor placenta can metabolize caffeine, the fetus may be exposed to caffeine and its metabolites for a prolonged period of time. The human placenta cannot metabolize caffeine because it contains only CYP1A1, not CYP1A2, enzymes (2). The fetus also lacks liver enzymes necessary to metabolize caffeine, which are not present until 8 months after delivery (18).

Caffeine and its metabolites measured in cord blood should be more valid indicators of fetal exposure than maternal levels since they more directly estimate the amount of caffeine and metabolites crossing the placenta (5).

In this paper, we report on a study specifically designed to examine the association between intrauterine growth restriction (IUGR) and fetal caffeine exposure when estimated by serum caffeine and its primary metabolites in umbilical cord blood.

MATERIALS AND 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. Exclusion criteria included gestational age greater than 24 weeks at enrollment, the mother having insulin-dependent diabetes mellitus, the mother speaking neither English nor Spanish, and intent to terminate the pregnancy. All participants consented to participate in the study, which was approved by the Human Investigation Committee at Yale University and participating hospitals.

A total of 11,267 women were screened, and 9,576 (85.0 percent) were eligible to participate. On the basis of preliminary screening questions, all women consuming 150 mg or more of caffeine daily during the prior week \( n = 718 \), and a random sample of those drinking less than 150 mg per day \( n = 2,915 \), were invited to participate. Of the 3,633 women invited to participate, 2,478 (68.2 percent) enrolled, 639 (17.6 percent, same percentage by caffeine exposure) refused, 20 (0.6 percent) were not eligible at the time of home interview, 72 (2.0 percent) miscarried prior to interview, and 424 (11.7 percent) were lost to follow-up or could not be contacted for interview before the eligibility limit of 24 weeks of gestation expired.

Of the 2,478 enrolled women, 187 were excluded from this analysis (70 miscarried, 53 delivered multiple infants, nine terminated their pregnancies, six experienced stillbirths, five withdrew from the study, and 44 could not be traced), leaving 2,291 women who delivered a singleton infant. Of those 2,291 women, umbilical cord blood and IUGR outcome information was available for 1,606.

A final interview was conducted shortly after delivery, usually immediately postpartum in the hospital. Information on reported caffeine consumption and smoking exposure as well as other medical, obstetric, and environmental risk factors during the third trimester was obtained during this interview.

Pregnancy outcomes

Obstetric records were abstracted to identify pregnancy outcomes. We defined fetal growth restriction as less than the 10th percentile of birth weight for gestational age by using an external standard of birth weight for gestational age, adjusted for gender and ethnicity, that we developed from all singleton births in the United States in 1999 (19). Birth weights were obtained within 24 hours of delivery, and low birth weight was defined as less than 2,500 g. Gestational age was calculated as completed days from the first day of the last menstrual period or physician’s estimated date of delivery if the last menstrual period was uncertain: 55.3 percent were confirmed by ultrasound, 37.2 percent were based on dates only, and 7.5 percent were based on a clinical examination of the newborn or were obtained from an unspecified source. Preterm delivery was defined as less than the 37th week of gestation.

Umbilical cord blood collection and assay

Umbilical cord blood samples were collected by obstetricians at participating hospitals. After the cord was cut, umbilical 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. Samples were transported on ice and stored at −80°C. Umbilical cord blood samples were analyzed (at one time) 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 information.

Concentrations of caffeine, paraxanthine, theophylline, and theobromine were determined by using liquid chromatography coupled with tandem mass spectrometry. Stable isotope-labeled analogs of paraxanthine and caffeine were used as internal standards. Following protein precipitation,
samples (0.2 ml) were treated with 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 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. Several assays were below detection limits: $n = 46$ caffeine, $n = 203$ paraxanthine, $n = 63$ theobromine, and $n = 272$ theophylline; they were assigned an analysis value of zero, and all biomarkers were categorized into quartiles.

The ratio of paraxanthine to caffeine is widely used as a marker of CYP1A2 enzymatic activity because caffeine is metabolized to paraxanthine primarily via the CYP1A2 pathway (20). The ratio is independent of the dose of caffeine because it assesses how much of the parent drug is metabolized via one pathway as opposed to competing pathways. This ratio was used to model the influence of CYP1A2 activity on fetal growth.

Statistical methods

Because the biomarkers were not normally distributed, Spearman correlation coefficients were used to test associations between umbilical cord blood biomarkers and continuous variables. Categorical variables and biomarkers categorized into quartiles were compared with the chi-square test. Odds ratios between cord blood biomarkers and outcome variables were calculated from multiple logistic regression. Serum metabolites (ng/ml) were evaluated in quartiles (caffeine: $0–<156, 156–<469, 469–<1,186, 1,186–<3,99$; paraxanthine: $0–<22, 22–<62, 62–<149, 149–<459$; theobromine: $0–<155, 155–<399, 399–<902, 902–<2,99$; theophylline: $0–<18, 18–<45, 45–<102, 102–<272$). For the ratio analysis, values below the detection limit were assigned a value of 0.005, and the ratio was modeled as a continuous variable. Final models were constructed by using backward elimination including potential confounders and exposures of interest. Included were smoking during the third trimester, maternal age at delivery, parity, prior number of abortions, prior number of pregnancies, preterm birth, maternal race, maternal education, alcohol intake during the third trimester, marital status, maternal height, and reported caffeine intake during the third trimester. Nonsignificant confounders were retained if removal resulted in a parameter estimate change of 10 percent or more. PC-SAS version 8.02 software was used for statistical analyses (21).

RESULTS

Higher average reported caffeine consumption during the third trimester ($\geq 150$ mg/day) was associated with being in a higher quartile for each biomarker ($p < 0.0001$ for all associations; data not shown). The highest quartiles of caffeine, paraxanthine, and theophylline were associated with increased parity and gravidity, being unmarried, being Hispanic, and having less than a high school education. The highest paraxanthine and theophylline quartiles were associated with consuming (on average) more than 0.25 ounces (7.5 ml) per day of absolute alcohol during the third trimester. The highest paraxanthine and theobromine quartiles were associated with third-trimester smoking. The highest quartiles of theobromine were associated with increased parity and gravidity, White race, older maternal age, more education, and being married (data not shown). There were no significant differences between women for whom we obtained an infant cord blood sample and those we did not with regard to relevant demographic and medical characteristics.

The biomarkers were highly correlated, with correlation coefficients ranging from 0.37 for theophylline and theobromine to 0.96 for theophylline and caffeine (table 1). All biomarkers were also significantly correlated with average reported intake during the third trimester ($p < 0.0001$ for all associations).

Unadjusted associations for each biomarker with IUGR were examined (table 2). Negative associations for absolute levels of serum caffeine were observed, with 35 percent and 37 percent reductions in IUGR for serum caffeine levels in the highest and next-highest quartiles, respectively, and a 39 percent statistically significant reduction in the first quartile. None of the serum metabolites were associated with IUGR. In adjusted models examining the effect of each biomarker independently (table 2), caffeine levels in the second and third quartiles were associated with a 41 percent decreased risk of IUGR. When the other biomarkers were added to the adjusted model, the negative associations for IUGR with caffeine remained, while paraxanthine levels in the highest quartile were associated with significantly increased risk of IUGR (odds ratio (OR) $= 3.29$, 95 percent confidence interval (CI): 1.17, 9.22). There was a significant positive linear trend for increasing risk among the paraxanthine quartiles ($p = 0.02$) but no trends for the other three biomarkers.

To evaluate whether these seemingly opposing effects of caffeine and paraxanthine might be explained by metabolic activity, we modeled the ratio of paraxanthine to caffeine as a marker of CYP1A2 enzymatic activity. Caffeine or paraxanthine values below the detection limit were given a value of 0.005 ($n = 40$ for caffeine and $n = 186$ for paraxanthine), although the results were nearly identical when...
these samples were excluded from the analysis. Values of the ratio ranged from 0.005 to 1.83. Although the ratio was associated with the absolute levels as well as reported consumption, there was considerable variability in the ratio within each caffeine and paraxanthine quartile (data not shown). Since there was no evidence of departure from linear trend, the ratio was modeled as a continuous variable. In the unadjusted analysis, there was a 30 percent increase in the risk of IUGR associated with each one standard deviation increase in the ratio (OR = 1.32, 95 percent CI: 1.19, 1.46). In an adjusted model controlling for smoking, parity, prepregnant weight, maternal race, and maternal age, the odds ratio for each one standard deviation increase in the ratio was 1.21 (95 percent CI: 1.07, 1.37) (table 3). The addition of average reported consumption during the third trimester did not meaningfully change the ratio estimate for IUGR (adjusted OR = 1.24, 95 percent CI: 1.09, 1.40 for each one standard deviation increase). When the ratio analysis was stratified by preterm status, the adjusted odds ratio for term births was 1.26 (95 percent CI: 1.11, 1.43). The adjusted estimate for preterm births was 0.72 (95 percent CI: 0.22, 2.39), although there were very few preterm births (n = 94) to estimate effects reliably (table 3).

When the adjusted ratio analysis was stratified by smoking status (table 3), there was a 19 percent increase in the risk of IUGR for every one standard deviation increase in the ratio among nonsmokers (OR = 1.19, 95 percent CI: 1.01, 1.40). Among smokers, the risk was also increased (adjusted OR = 1.24, 95 percent CI: 1.00, 1.54), although the estimate was based on a small number of smokers (n = 112). The ratio analysis was also stratified by average reported caffeine consumption categories during the third trimester (0 mg/day, 1–149 mg/day, and ≥150 mg/day). The adjusted estimates, for each one standard deviation increase in the ratio, increased by consumption category (for nonconsumers, OR = 1.19, 95 percent CI: 0.99, 1.42; for women consuming 1–149 mg/day, OR = 1.36, 95 percent CI: 1.05, 1.74; and for women consuming ≥150 mg/day, OR = 1.77, 95 percent CI: 1.13, 2.75).

**DISCUSSION**

In this cohort of women selected on the basis of reported caffeine consumption, higher caffeine levels were associated with a decreased risk of IUGR, while higher serum

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**TABLE 2.** Crude and adjusted associations between umbilical cord blood biomarkers and IUGR* among pregnant women recruited in Connecticut and Massachusetts in 1996–2000

<table>
<thead>
<tr>
<th>Biomarker and quartile (ng/ml)</th>
<th>IUGR (no.)</th>
<th>Crude OR*</th>
<th>95% CI*</th>
<th>Adjusted† OR</th>
<th>95% CI</th>
<th>Adjusted‡ OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caffeine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–&lt;156</td>
<td>47</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>156–&lt;469</td>
<td>30</td>
<td>0.61</td>
<td>0.38, 0.99</td>
<td>0.59</td>
<td>0.35, 0.97</td>
<td>0.38</td>
<td>0.16, 0.90</td>
</tr>
<tr>
<td>469–&lt;1,186</td>
<td>31</td>
<td>0.63</td>
<td>0.39, 1.02</td>
<td>0.59</td>
<td>0.36, 0.99</td>
<td>0.31</td>
<td>0.10, 0.92</td>
</tr>
<tr>
<td>≥1,186</td>
<td>32</td>
<td>0.65</td>
<td>0.41, 1.05</td>
<td>0.69</td>
<td>0.41, 1.15</td>
<td>0.52</td>
<td>0.14, 1.99</td>
</tr>
<tr>
<td><strong>Paraxanthine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–&lt;22</td>
<td>37</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22–&lt;62</td>
<td>31</td>
<td>0.83</td>
<td>0.50, 1.36</td>
<td>0.83</td>
<td>0.49, 1.39</td>
<td>1.45</td>
<td>0.72, 2.92</td>
</tr>
<tr>
<td>62–&lt;149</td>
<td>32</td>
<td>0.86</td>
<td>0.52, 1.40</td>
<td>0.89</td>
<td>0.53, 1.49</td>
<td>2.25</td>
<td>0.94, 5.37</td>
</tr>
<tr>
<td>≥149</td>
<td>40</td>
<td>1.09</td>
<td>0.68, 1.74</td>
<td>1.00</td>
<td>0.59, 1.70</td>
<td>3.29</td>
<td>1.17, 9.22</td>
</tr>
<tr>
<td><strong>Theophylline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–&lt;18</td>
<td>42</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–&lt;45</td>
<td>33</td>
<td>0.77</td>
<td>0.48, 1.24</td>
<td>0.73</td>
<td>0.45, 1.21</td>
<td>1.07</td>
<td>0.43, 2.66</td>
</tr>
<tr>
<td>45–&lt;102</td>
<td>38</td>
<td>0.90</td>
<td>0.57, 1.43</td>
<td>0.79</td>
<td>0.48, 1.29</td>
<td>2.25</td>
<td>0.94, 3.30</td>
</tr>
<tr>
<td>≥102</td>
<td>27</td>
<td>0.62</td>
<td>0.37, 1.02</td>
<td>0.64</td>
<td>0.37, 1.10</td>
<td>0.45</td>
<td>0.11, 1.89</td>
</tr>
<tr>
<td><strong>Theobromine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–&lt;155</td>
<td>34</td>
<td>Referent</td>
<td>Referent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>155–&lt;399</td>
<td>41</td>
<td>1.24</td>
<td>0.77, 1.99</td>
<td>1.08</td>
<td>0.65, 1.80</td>
<td>1.14</td>
<td>0.66, 1.98</td>
</tr>
<tr>
<td>399–&lt;902</td>
<td>33</td>
<td>0.97</td>
<td>0.59, 1.59</td>
<td>0.99</td>
<td>0.58, 1.69</td>
<td>1.14</td>
<td>0.63, 2.04</td>
</tr>
<tr>
<td>≥902</td>
<td>32</td>
<td>0.94</td>
<td>0.57, 1.55</td>
<td>0.88</td>
<td>0.51, 1.52</td>
<td>0.96</td>
<td>0.51, 1.82</td>
</tr>
</tbody>
</table>

* IUGR, intrauterine growth restriction; OR, odds ratio; CI, confidence interval.
† Adjusted for smoking during the third trimester (yes/no), parity (0, 1, 2), prepregnant weight in pounds (1 pound = 0.454 kg; <120, 120–139, 140–159, ≥160), maternal race (White, Black, Hispanic, Asian/other), and maternal age at delivery in years (<24, 25–29, 30–34, ≥35).
‡ Effect of each biomarker adjusted for the covariates in the previous footnote and the other three biomarkers listed in column 1.
paraxanthine concentrations were associated with an increased risk of IUGR. However, the paraxanthine association was seen only when caffeine was included in the same model, suggesting that it may be CYP1A2 enzymatic activity that influences fetal growth. Our results suggest that this possibility may be true. For each one standard deviation increase in the ratio, risk of IUGR increased 20 percent, suggesting that women who metabolize caffeine more quickly are at higher risk than slower metabolizers. The adjusted ratio model was repeated by controlling for the absolute values of caffeine and paraxanthine, and the ratio estimate was unchanged (results not shown), supporting the hypothesis that indeed CYP1A2 enzymatic activity may influence fetal growth. Because women with very high and women with very low levels of paraxanthine could have the same paraxanthine:caffeine ratio, these findings suggest that it is not the amount of caffeine or paraxanthine in the serum but how quickly caffeine is metabolized into paraxanthine. The more quickly caffeine is metabolized, the more paraxanthine is found in serum (and correspondingly less caffeine) and the higher the risk of IUGR.

Adjusted analysis categorizing paraxanthine into quartiles showed that growth restriction was three times more likely in infants with absolute paraxanthine levels in the fourth quartile. This effect was seen in both smokers and nonsmokers, suggesting that the effects are not due to confounding from smoking. The ratio effect was observed at all consumption levels but was greater with higher consumption, suggesting a possible interaction with consumption and metabolic activity.

These findings may help to explain the conflicting results in the literature. The heterogeneity in caffeine exposure reporting, and the fact that it may be CYP1A2 activity and not caffeine intake per se, complicates the association between antenatal caffeine intake and fetal growth.

Our findings for paraxanthine are generally consistent with those of Klebanoff et al. (22), who found that maternal serum paraxanthine concentration during the third trimester of pregnancy increased the risk of IUGR although for only those women who smoked. Klebanoff et al. (22) reported no effect of maternal serum caffeine concentration at week 26 on fetal growth but, from the same study population, found an increased risk of spontaneous abortion for women whose serum paraxanthine concentration was more than 1,845 ng/ml (the highest decile of exposure) compared with women in the lowest decile, below 50 ng/ml (OR = 1.9, 95 percent CI: 1.2, 2.8) (23). Although Klebanoff et al. (22) reported measuring theobromine and theophylline metabolites, these results have not been published.

Another study using maternal serum caffeine as a biomarker did not find an association between caffeine and ratio of birth weight to gestational age, which estimates fetal growth restriction, but did find that the birth weight ratio decreased with increasing reported caffeine intake among smokers (14). Soyka et al. (24) (n = 36 cord blood serum samples) observed that cord blood caffeine concentrations of greater than 3,000 ng/ml (compared with less than 50 ng/ml) were associated with an increased incidence of birth weight of more than 4 kg (p < 0.05), suggesting agreement with our observation, although potentially important covariates were not considered.

Caffeine is metabolized to paraxanthine primarily by CYP1A2, and the ratio of paraxanthine to caffeine measured in blood is an indicator of CYP1A2 activity (20). Within any given level of caffeine intake, higher CYP1A2 activity will be associated with higher paraxanthine and lower caffeine levels, which is the pattern we observed in relation to IUGR. Although there is considerable variability in the ratio depending on when the sample is obtained after consumption (25), this ratio is more stable when consumption occurs throughout the day (26).

To our knowledge, the mechanism by which CYP1A2 activity may be related to IUGR has not been elucidated. One possibility is that greater CYP1A2 activity itself has negative consequences. This process could occur either by accelerating the metabolism of some critical endogenous chemical or by increased generation of some toxic metabolite from either endogenous or exogenous sources. Alternatively, CYP1A2 activity may be a marker for exposure to an environmental chemical (such as cigarette smoking) that has adverse effects on fetal growth. In our analysis, potential confounding from cigarette smoking was managed by stratification. Environmental exposure to chemicals, such as polybrominated biphenyls, also accelerates CYP1A2 activity (27, 28), and this may be a marker for such exposures.

### Table 3. Crude and adjusted ORs between the paraxanthine:caffeine ratio and IUGR* stratified by gestational age, smoking, and average reported consumption during the third trimester for pregnant women recruited in Connecticut and Massachusetts in 1996–2000

<table>
<thead>
<tr>
<th>Paraxanthine:caffeine ratio†‡</th>
<th>Crude OR 95% CI</th>
<th>Adjusted OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term birth</td>
<td>1.32 (1.19, 1.46)</td>
<td>1.21 (1.07, 1.37)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>1.26 (1.11, 1.43)</td>
<td>1.11 (0.98, 1.25)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>1.19 (1.01, 1.40)</td>
<td>1.10 (0.95, 1.27)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.24 (1.00, 1.54)</td>
<td>1.17 (0.96, 1.41)</td>
</tr>
<tr>
<td>Average reported consumption during the third trimester (mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.19 (0.99, 1.42)</td>
<td>1.10 (0.89, 1.36)</td>
</tr>
<tr>
<td>1–149</td>
<td>1.36 (1.05, 1.74)</td>
<td>1.19 (0.89, 1.59)</td>
</tr>
<tr>
<td>≥150</td>
<td>1.77 (1.13, 2.75)</td>
<td>1.56 (1.01, 2.40)</td>
</tr>
</tbody>
</table>

* OR, odds ratio; IUGR, intrauterine growth restriction; CI, confidence interval.
† Adjusted for smoking during the third trimester (yes/no), parity (0, 1, >2), prepregnant weight in pounds (1 pound = 0.454 kg; <120, 120–139, 140–159, ≥160), maternal age at delivery in years (18, 24, 25–29, 30–34, ≥35).
‡ Change is for a one standard deviation increase in the paraxanthine:caffeine ratio; range, 0.055–1.83.
Higher CYP1A2 activity may reflect a relative deficiency of maternal hormones. Pregnancy, as well as oral contraceptive use, is associated with a marked reduction in CYP1A2 activity because of the inhibitory effects of sex hormones (29). These effects result in a slowing of caffeine metabolism. A relative deficiency of sex hormones might be a marker of an abnormal pregnancy and would be expected to be associated with less inhibition of CYP1A2 activity. Thus, one would see higher CYP1A2 activity in hormone-deficient versus non-hormone-deficient pregnant mothers; as a result, higher levels of paraxanthine and lower levels of caffeine and theophylline would be observed as being associated with fetal growth restriction. Associations found with the paraxanthine:caffeine ratio, based on this explanation, would reflect reverse causality; however, the effect was seen in term births, making reverse causality an unlikely explanation for the findings. More research on the association of CYP1A2 activity with fetal development is needed.

One potential limitation of this study is that maternal serum was unavailable for analysis. Correlations between maternal and fetal serum with maternal-reported consumption during the third trimester would provide information on the validity of reported consumption as a marker for fetal exposure. In this study, higher average reported caffeine consumption during the third trimester (≥150 mg/day) was associated with being in a higher quartile for each biomarker. In our data from an intensively monitored group of subjects (n = 70), metabolites in maternal urine at delivery were highly correlated with the same metabolites in cord blood (Spearman r > 0.7 for all metabolites), suggesting that cord blood levels reflect recent maternal consumption. Finally, we observed no associations with preterm delivery, which is consistent with the overwhelming body of prior research that found no association with antenatal caffeine consumption and preterm delivery (30).

ACKNOWLEDGMENTS

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