Key messages

- Serum CA 125 measurement has an established role in monitoring, but not yet in screening for, ovarian cancer
- This study shows that raised serum CA 125 concentration is a powerful index of risk of ovarian cancer in asymptomatic postmenopausal women
- The risk in the year after a serum CA 125 concentration ≥100 U/ml is similar to the lifetime risk to women in high risk families
- The importance of a raised serum CA 125 concentration in relation to risk of other cancers is not yet known
- The role of CA 125 as a component of a screening strategy for ovarian cancer is under investigation, but the impact on mortality is not known

effective intervention to be possible. This issue will be resolved only when the results of the large scale randomised controlled trials that are under way in our own unit and elsewhere are available.

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Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study

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Abstract

***Objectives*—To examine the association of plasma caffeine concentrations during pregnancy with fetal growth and to compare this with relations with reported caffeine intake.**

***Design*—Prospective population based study.**

***Setting*—District general hospital, inner London.**

***Subjects*—Women booking for delivery between 1982 and 1984. Stored plasma was available for 1500 women who had provided a blood sample on at least one occasion and for 640 women who had provided a sample on all three occasions (at booking, 28 weeks, and 36 weeks).**

***Main outcome measure*—Birth weight adjusted for gestational age, maternal height, parity, and sex of infant. The exposures of interest were reported caffeine consumption and blood caffeine concentration. Cigarette smoking was assessed by blood cotinine concentration.**

***Results*—Caffeine intake showed no changes during pregnancy, but blood caffeine concentrations rose by 75%. Although caffeine intake increased steadily with increasing cotinine concentration above 15 ng/ml, blood caffeine concentrations fell. Caffeine consumption was inversely related to adjusted birth weight, the estimated effect being a 1.3% fall in birth weight for a 1000 mg per week increase in intake (95% confidence interval 0.5% to 2.1%). The apparent caffeine effect was confined to cigarette smokers, among whom the estimated effect was –1.6%/1000 mg a week (–2.9% to –0.2%) after adjustment for cotinine and –1.3% (–2.7% to 0.1%) after further adjustment for social class and alcohol intake. Adjusted birth weight was unrelated to blood caffeine concentrations overall (P = 0.09, but a positive coefficient), after adjustment for cotinine (P = 0.73), or among current smokers (P = 0.45).**

***Conclusions*—Smokers consume more caffeine than non-smokers. Blood caffeine concentrations during pregnancy are not related to fetal growth, but caffeine intake is negatively associated with**

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birth weight, with this effect being apparent only in smokers. The effect remains of borderline significance after adjustment for other factors. Prudent advice for pregnant women would be to reduce caffeine intake in conjunction with stopping smoking.

Introduction

Caffeine is commonly consumed during pregnancy, but elimination from the blood is slowed.[1] Fetal concentrations are believed to be in equilibrium with maternal concentrations.[1] Although it is biologically plausible that caffeine consumption could adversely affect the outcome of pregnancy, the epidemiological evidence is inconsistent, though the strongest evidence is for an effect on intrauterine growth.[2]

The lack of consistency may reflect methodological differences.[3] A major weakness of all previous studies is that they have relied on reported consumption of caffeine. Such questionnaire measures are unreliable, and intake may be a poor reflection of blood concentrations. A second weakness is a reliance on self reported smoking status. Smoking is known to increase caffeine metabolism appreciably,[4] and recent reports have emphasised that cotinine is a better predictor of reduced birth weight than questionnaire measures of smoking,[4-6] raising the possibility of residual confounding.[7] We previously reported that caffeine intake, estimated by questionnaire, was inversely related to fetal growth, with some evidence that the effect was present only in smokers.[8] We have now measured cotinine and caffeine concentrations in stored plasma to address two issues: (*a*) whether blood caffeine concentrations are related to fetal growth and (*b*) whether the inverse association between caffeine intake and fetal growth are due to inadequate adjustment for cigarette smoking.

Methods

The study has been described in detail elsewhere.[9] At St George's Hospital, a teaching hospital in south London, 1860 white women booking for antenatal care were invited to participate. These women represented consecutive bookings between August 1982 and March 1984, excluding those who spoke insufficient English, booked after 24 weeks, had insulin dependent diabetes, or had a multiple pregnancy. Women were interviewed at booking (mean 14 weeks) and at 28 and 36 weeks by trained researchers using a structured questionnaire. Whenever possible a blood sample was taken and plasma stored at −80°C until assayed for cotinine and caffeine in 1994. Blood samples were not collected at standard times. The assays were sensitive and specific, using gas chromatography with nitrogen and phosphorous detection respectively (C Feyerabend *et al*, unpublished data).[10] The detection limits of the assays were 0.1 ng/ml for cotinine and 0.01 μg/ml for caffeine. Non-detectable concentrations were coded as 0.05 ng/ml and 0.005 μg/ml respectively.

Caffeine intake at the three points in pregnancy was defined as the number of cups of tea, coffee, cocoa, and cola drunk in the previous week. These were converted to milligrams of caffeine by using estimates for tea and coffee of 70 mg/cup and 92 mg/cup respectively[11] and for cocoa and cola of 5 mg/cup and 40 mg/serving respectively.[12] On each occasion women were also asked about their alcohol consumption in the preceding week.[8] Social class of head of household was coded according to the Registrar General's classification.[13]

Obstetric data and fetal outcome were obtained from the structured obstetric record.[9] Gestational age at delivery was calculated from date of delivery, dates of menstruation, and early ultrasound examination. The outcome measure for this analysis was a birth weight ratio adjusted for gestational age, maternal height, sex of infant, and parity of mother. The adjustment was carried out in two stages.[14] Firstly, the birth weight was adjusted for gestational age by taking the ratio of the observed birth weight to the expected birth weight for that week of gestational age at birth using an external standard. The resultant birth weight ratio was then adjusted for the other biological factors with multiple regression. This gave an adjusted birth weight ratio suitable for use as the outcome variable in a linear regression model. As all the mean adjusted birth weight ratios presented are close to 1.0, differences between the ratios are equivalent to percentage differences—for example, the difference between the birth weight ratios 1.04 and 1.01 is 0.03, which is about a 3% difference in the two mean birth weights.

Because of the relatively short half life of caffeine, a single measurement of the blood concentration will not provide an accurate measure of average exposure. Most analyses in this report are thus based on the women for whom measurements were available on all three occasions. Average caffeine intake was defined as the mean intake estimated from the three questionnaires administered at booking, 28 weeks, and 36 weeks. Average blood concentrations of caffeine during pregnancy were defined as the geometric mean blood caffeine concentration; the geometric mean was used because the dispersion of blood caffeine increased with increasing concentration.

Statistical analyses were carried out using the SAS statistical package (SAS Institute, North Carolina). The GLM procedure was used to fit multiple regression models with the adjusted birth weight ratio as the outcome variable. A cut off of about 15 ng/ml cotinine seems optimal for distinguishing smokers from non-smokers[15,16] and was used to divide women into two exposure groups, smokers and non-smokers. To test formally for trends in the birth weight ratio with caffeine intake and blood caffeine concentration we regressed the ratio on caffeine intake or blood caffeine concentration, with intake and concentrations treated as continuous variables. Adjustments for the effect of smoking were made by including both log(cotinine) and its square in a regression model as there was evidence that the relation with log(cotinine) was not linear. Additional adjustment included alcohol as a continuous variable and social class as a factor with seven levels.

Results

RESPONSE RATES

Of 1860 women who were invited, 1724 (93%) took part in the study. At least one blood sample was available for 1500 women. Complete data, including birth weight and questionnaire, were available on all three occasions (at booking, 28 weeks, and 36 weeks) for 640 women.

BLOOD CAFFEINE CONCENTRATIONS DURING PREGNANCY

Blood caffeine concentrations at booking and at 28 weeks were moderately correlated ($r = 0.50$) as were the measurements at 28 and 36 weeks ($r = 0.58$). The corresponding correlations for the intake data were both 0.67. At each time point the distribution of blood caffeine measurements was highly positively skewed and showed increasing variability with increasing intake.

Table 1 presents the mean blood caffeine and the mean caffeine intake by occasion during pregnancy for those women for whom measurements were available at all three occasions. Although intake showed no particular pattern, the blood levels increased by 75% from 2.35 μg/l at booking to 4.12 μg/l at 36 weeks.

CAFFEINE INTAKE, SMOKING, AND BLOOD CAFFEINE

A clear positive relation existed between average blood caffeine concentrations and average caffeine intake both in smokers and non-smokers (fig 1), but

Table 1—*Blood caffeine concentrations (μg/ml) and estimated caffeine intake (mg/week) for 640 women at three time points during pregnancy*

Time point	Mean blood caffeine (SD)	Mean caffeine intake (SD)
Booking	2.35 (1.68)	2323 (1458)
28 Weeks	3.20 (2.04)	2605 (1375)
36 Weeks	4.12 (2.76)	2427 (1480)

with a wide range of blood concentrations at each intake level. Moreover, at each intake level, blood concentrations were lower in smokers than in non-smokers. Figure 2 shows the effect of cigarette smoking on caffeine metabolism. While caffeine intake increased steadily with increasing cotinine above 15 ng/ml, blood caffeine concentrations fell.

CAFFEINE INTAKE AND BIRTH WEIGHT RATIO

Overall, the birth weight ratio decreased with increasing caffeine intake (table 2). Regressing the birth weight ratio on caffeine intake yielded a regression coefficient of −1.29%/g per week (95% confidence interval −2.05% to −0.53%), which was halved to −0.60%/g per week when cotinine was adjusted for (table 3). The inverse relation seemed, however, to be present only among smokers. Table 3 shows the effect of adjusting for confounding variables. The pattern remained unchanged after cotinine was adjusted for; the regression slope in non-smokers was −0.06%/g per week (−1.04% to 0.92%, P = 0.90), whereas in smokers it was −1.55%/g per week (−2.86% to −0.24%, P = 0.02). A formal test of the equivalence of the two slopes provided some evidence that they differed even after adjustment (P = 0.08). Further adjustment for alcohol and social class on slightly reduced numbers (n = 617) left a regression slope in smokers of −1.33%/g per week (−2.72% to 0.06%, P = 0.06).

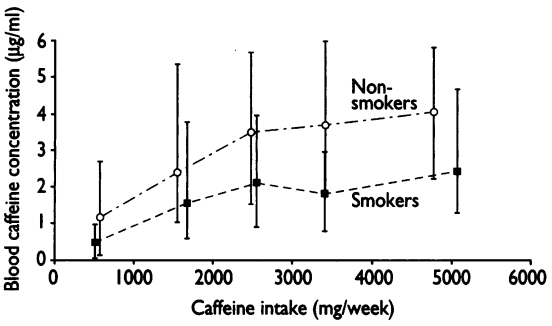

Fig 1—*Median, 10th, and 90th centiles of blood caffeine concentration by caffeine intake*

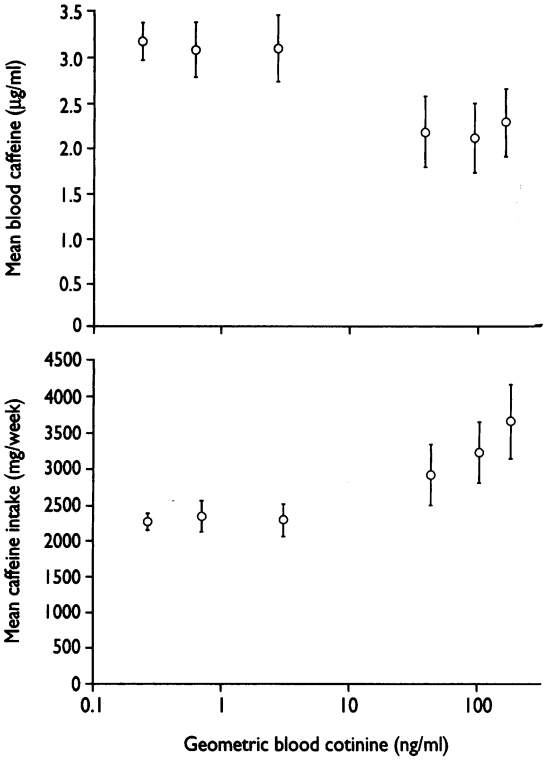

Fig 2—*Mean blood caffeine concentrations and caffeine intake (with 95% confidence intervals) by blood cotinine concentration*

BLOOD CAFFEINE CONCENTRATION AND BIRTH WEIGHT RATIO

In contrast, adjusted birth weight showed no relation with blood caffeine either overall or in current cigarette smokers (table 2). When the birth weight ratio was regressed on average blood caffeine concentration while cotinine was controlled for, there was no evidence that the slopes differed in smokers and non-smokers (P = 0.35) (table 3), though the regression slope among smokers was weakly negative after adjustment for cotinine at −0.57%/μg/ml (P = 0.47). Using the log of blood caffeine in the regression analyses did not alter these findings.

EFFECT OF RESTRICTING ANALYSES TO WOMEN WITH ALL THREE MEASUREMENTS

We examined the effect of restricting our analyses to women for whom we had blood measurements on all three occasions by: (*a*) carrying out regressions on women with blood samples available at booking

Table 2—*Birth weight ratio by caffeine consumption and blood caffeine concentration in all women and in non-smokers and smokers separately*

	All women		Non-smokers		Smokers	
Caffeine consumption	No of women	Adjusted birth weight ratio (SD)	No of women	Adjusted birth weight ratio (SD)	No of women	Adjusted birth weight ratio (SD)
Mean caffeine intake (mg/week)*:						
0-1000	53	1.052 (0.127)	45	1.051 (0.133)	8	1.060 (0.086)
1001-2000	207	1.052 (0.111)	182	1.055 (0.109)	25	1.024 (0.120)
2001-3000	216	1.029 (0.134)	170	1.042 (0.131)	46	0.981 (0.136)
3001-4000	92	1.025 (0.129)	72	1.044 (0.125)	20	0.955 (0.124)
>4000	72	0.989 (0.110)	31	1.042 (0.109)	41	0.948 (0.093)
Geometric mean blood caffeine (μg/ml):						
0.005-1	76	1.029 (0.115)	48	1.039 (0.119)	28	1.013 (0.106)
1.01-2	150	1.021 (0.128)	103	1.049 (0.119)	47	0.959 (0.127)
2.01-3	138	1.026 (0.132)	100	1.047 (0.133)	38	0.970 (0.115)
3.01-4	124	1.041 (0.113)	109	1.041 (0.115)	15	1.038 (0.102)
≥4.01	152	1.046 (0.125)	140	1.056 (0.120)	12	0.938 (0.138)

Non-smokers: mean geometric cotinine <15 ng/ml; smokers: mean geometric cotinine ≥15 ng/ml.
*Determined from results of questionnaire (see methods).

Table 3—*Summary of regression coefficients of birth weight ratio on caffeine intake and blood caffeine concentration in all women and in non-smokers and smokers separately and with adjustment for confounding variables. Values are percentage changes in birth weight ratio/g caffeine intake/week and in birth weight/μg caffeine/ml blood*

Explanatory variable	All women		Non-smokers (n = 500)		Smokers (n = 140)		Test for different slopes (P value)
	Slope (SE)	P value	Slope (SE)	P value	Slope (SE)	P value	
Mean caffeine intake:							
No adjustment	−1.29 (0.39)	0.001	−0.05 (0.50)	0.92	−1.75 (0.66)	0.008	0.04
Adjusted for cotinine	−0.60 (0.40)	0.14	−0.06 (0.50)	0.90	−1.55 (0.67)	0.02	0.08
Adjusted for cotinine, alcohol, and social class (n=617)	−0.50 (0.41)	0.23	−0.08 (0.51)	0.88	−1.33 (0.71)	0.06	0.15
Geometric mean blood caffeine:							
No adjustment	0.49 (0.29)	0.09	0.20 (0.31)	0.52	−0.59 (0.79)	0.45	0.35
Adjusted for cotinine	0.10 (0.35)	0.73	0.20 (0.31)	0.51	−0.57 (0.78)	0.47	0.36

Non-smokers: mean geometric cotinine <15 ng/ml; smokers: mean geometric cotinine ≥15 ng/ml.
Cotinine was adjusted for by including log (geometric mean cotinine) and (log (geometric mean cotinine))^2 in the regression.
†Determined from results of questionnaire (see methods).

(n = 1138); (*b*) carrying out three separate regressions that included women for whom we had all three, only two, or only one blood measurement (n = 1500). Data (not shown) did not suggest that looking more widely at women for whom we had fewer than three measurements (including preterm births) in any way altered our conclusions on blood caffeine concentration or that blood caffeine had different effects at different times in pregnancy. For caffeine intake the relations with birth weight also remained closely similar. Based on subjects with data on intake at booking, and after adjustment for cotinine, social class, and alcohol intake at booking, the evidence for a greater effect of caffeine intake in smokers than in non-smokers was of borderline significance (P = 0.07).

Discussion

We found no relation between blood caffeine concentrations during pregnancy and birth weight. This contrasts with the negative association that we and others have found between reported intake of caffeine and birth weight. A 1992 review noted that 10 out of 13 studies had reported a negative association, though not all were significant.[2]

EFFECT OF SMOKING ON CAFFEINE METABOLISM

A key element in understanding these apparently contradictory findings comes from recognising the importance of factors other than caffeine intake in determining blood concentrations. The metabolism of caffeine is known to slow during the course of pregnancy,[1] and the effect of this is clearly seen in our data with a rise in blood concentrations from 2.35 μg/ml at booking to 4.12 μg/ml at 36 weeks, during which time intake changed little. More important is that cigarette smoking increases caffeine metabolism.[17] We found that caffeine intake rose steadily with cotinine concentrations above 15 ng/ml whereas blood caffeine concentrations fell.

CONTROLLING FOR EFFECT OF SMOKING

That blood caffeine concentrations are not associated with reduced fetal growth seems therefore to reinforce the view that the negative relation between caffeine intake and birth weight in previous studies might be due to inadequate control for the confounding effects of cigarette smoking.[7] We used cotinine concentration rather than self reported smoking status to control for the effect of cigarette smoking because recent reports have suggested that cotinine is a better predictor of birth weight.[4-6] In our study, however, the relation between reported caffeine intake and birth weight, although much reduced, remained of borderline significance despite adjustment for cotinine concentrations based on three measurements. Moreover, our previous suggestion that the effect of caffeine intake is stronger in or restricted to smokers[8] remains and is supported by three other reports.[18-20] Any factors not considered are unlikely to explain the relation of caffeine intake and reduced birth weight in smokers; in our study a wide range of social, psychological, and obstetric factors had little or no direct effect on fetal growth.[9]

Another explanation of why intake but not blood concentrations are related to birth weight arises if fetal blood concentrations are not in equilibrium with those in the mother, as is commonly supposed.[1] The disposal of caffeine in newborn infants or by a fetus is very slow. High caffeine intake might result in raised fetal exposure, despite the high rate of metabolism in smokers. Alternatively it may be raised concentrations of some metabolite that are important. Only a trivial amount of caffeine is excreted unchanged, and the major metabolites of caffeine are pharmacologically active. It is known that smoking influences the demethylation processes involved in producing and eliminating these metabolites,[1] and we know too little about these processes to rule out some biological interaction. Others have suggested that by blocking adenosine receptors, caffeine interferes with the normal physiological response to the raised carboxyhaemoglobin concentrations in smokers and thus exaggerates the effect of smoking on oxygen uptake.[20] Such an explanation depends on the effect of smoking being due to its effect on carboxyhaemoglobin concentrations rather than being due to nicotine. In fact, studies of the effect of chewing tobacco during pregnancy suggest that nicotine has a direct effect.[21-22]

Given the limited power of individual studies to examine interactions between smoking and cotinine in their effect on fetal growth, data from all previous studies should be reviewed to establish whether such an interaction exists. Future studies should be designed with sufficient power to examine any biological interaction with the effect of cigarette smoking and should also include measurement of blood caffeine and its active metabolites.

CONCLUSION

In the absence of definitive evidence and given the widespread consumption of caffeinated drinks during pregnancy, two points need wider appreciation: (*a*) the metabolism of caffeine is appreciably slowed during pregnancy, leading to a pronounced rise in blood concentrations with no change in intake; and (*b*) smokers have a higher caffeine intake but a faster metabolism, resulting in lower blood concentrations. Thus anyone stopping smoking will show a pronounced rise in blood caffeine concentrations if their caffeine consumption remains unchanged.[4] Prudent advice would seem to be to reduce caffeine intake in conjunction with stopping smoking.

Key messages

- Cigarette smokers consume 50% more caffeine than non-smokers, but their caffeine metabolism is faster, resulting in lower blood concentrations
- Blood caffeine concentrations during pregnancy are not related to birth weight
- Caffeine intake assessed by questionnaire is negatively associated with birth weight, with evidence that this effect is apparent only in smokers
- As most studies have limited power to detect an interaction between smoking and effects of caffeine intake on birth weight, a meta-analysis of existing studies is recommended
- It seems reasonable to advise women who smoke to reduce their caffeine intake as well as to stop smoking during pregnancy

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Comparison of effect of cafetière and filtered coffee on serum concentrations of liver aminotransferases and lipids: six month randomised controlled trial

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Abstract

***Objective*—To study the effects of prolonged intake of cafetière coffee, which is rich in the diterpenes cafestol and kahweol, on serum aminotransferase and lipid concentrations.**

***Design*—Randomised parallel controlled trial.**

Subjects—46 healthy men and women aged 19 to 69.

***Intervention*—Consumption of five to six strong cups (0.9 litres) a day of either cafetière (22 subjects) or filtered coffee (24 subjects) for 24 weeks.**

***Main outcome measures*—Mean changes in serum aminotransferase and lipid concentrations.**

***Results*—Cafetière coffee raised alanine aminotransferase concentration by up to 80% above baseline values relative to filtered coffee. After 24 weeks the rise was still 45% (9 U/l (95% confidence interval 3 to 15 U/l), P = 0.007). Alanine aminotransferase concentration exceeded the upper limit of normal in eight of the 22 subjects drinking cafetière coffee, being twice the upper limit of normal in three of them. Cafetière coffee raised low density lipoprotein cholesterol concentrations by 9-14%. After 24 weeks the rise was 0.26 mmol/l (0.04 to 0.47 mmol/l) (P = 0.03) relative to filtered coffee. Triglyceride concentrations initially rose by 26% with cafetière coffee but returned close to baseline values within six months. All increases were reversible after the intervention was stopped.**

***Conclusions*—Daily consumption of five to six cups of strong cafetière coffee affects the integrity of liver cells as suggested by small increases in serum alanine aminotransferase concentration. The effect does not subside with prolonged intake. High intakes of coffee brews rich in cafestol and kahweol may thus be responsible for unexplained increases in this enzyme activity in apparently healthy subjects. Cafetière coffee also raises low density lipoprotein cholesterol concentration and thus the risk of coronary heart disease.**

Introduction

Scandinavian boiled coffee raises serum cholesterol concentrations in humans.[1-4] The diterpenes cafestol and kahweol are responsible for this effect.[5 6] They do not pass through paper filters, which explains why filtered coffee does not raise cholesterol concentrations,[7 8] but they do occur in other unfiltered coffee brews, such as cafetière coffee and Turkish coffee.[9]

Cafestol and kahweol seem to affect liver cells: short term intake of boiled coffee[5] or preparations rich in cafestol and kahweol [5 10-12] raise the serum concentration of