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## **Caffeine intake during pregnancy, late miscarriage and stillbirth**

CARE study group

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Caffeine, late miscarriage and stillbirth

## ABSTRACT

Caffeine is a commonly consumed drug during pregnancy with the potential to affect the developing fetus. Findings from previous studies have shown inconsistent results. We recruited a cohort of 2643 pregnant women, aged 18-45 years, attending two UK maternity units between 8-12 weeks gestation from September 2003 to June 2006. We used a validated tool to assess caffeine intake at different stages of pregnancy and related this to late miscarriage and stillbirth, adjusting for confounders, including salivary cotinine as a biomarker of smoking status. There was a strong association between caffeine intake in the first trimester and subsequent late miscarriage and stillbirth, adjusting for confounders. Women whose pregnancies resulted in late miscarriage or stillbirth had higher caffeine intakes (geometric mean = 145 mg/day; 95% CI: 85 to 249) than those with live births (103 mg/day; 95% CI: 98 to 108). Compared to those consuming <100 mg/day, odds ratios increased to 2.2 (95% CI: 0.7 to 7.1) for 100-199 mg/day, 1.7 (0.4 to 7.1) for 200-299 mg/day, and 5.1 (1.6 to 16.4) for 300+ mg/day ( $P_{trend}=0.004$ ). Greater caffeine intake is associated with increases in late miscarriage and stillbirth. Despite remaining uncertainty in the strength of association, our study strengthens the observational evidence base on which current guidance is founded.

**Keywords:** Caffeine; miscarriage; still birth.

### Abbreviations:

CI	Confidence interval
IQR	Interquartile range
OR	Odds ratio
SD	Standard deviation

## **INTRODUCTION**

Caffeine is a commonly consumed drug during pregnancy with the potential to affect the developing fetus.[1-3] Cohort studies have shown that maternal caffeine intake may be associated with decreased birth weight and fetal growth restriction,[4;5] though not consistently.[6] The only trial conducted suggested no substantial effect of caffeine reduction in the second half of pregnancy.[7] The evidence for caffeine consumption earlier in pregnancy to be a risk factor for miscarriage may be stronger,[8-11] but again there is still uncertainty[12-14] and no large pragmatic effectiveness trials have been conducted. Most guidelines recommend limiting caffeine intake immediately before and during pregnancy as a precaution,[15-18] whilst recognising that the strength of any association is still unclear.[19]

The inconsistency in results may be attributable to one or more sources of bias, including imprecise estimation of caffeine intake, assuming that coffee or tea are the only sources of caffeine, retrospective measurement of assessment of caffeine consumption, or inadequate control for important confounding factors, especially smoking and alcohol consumption. To contribute to understanding the role of caffeine during pregnancy, using improved methodology, we examined the association of maternal caffeine intake with late miscarriage and intrauterine fetal death (stillbirth), using a highly detailed caffeine assessment tool, previously validated against both a food and drink diary and repeated biomarkers of caffeine intake (salivary caffeine and paraxanthine), to prospectively quantify total caffeine intake, from all possible sources, in the first trimester and throughout pregnancy.[20] We aimed to adequately correct for potentially important confounding from alcohol intake and most importantly from smoking using cotinine as a biomarker in a large cohort of pregnant women.

## **METHODS**

## **Subjects**

A cohort of 2643 pregnant women aged 18-45 years with singleton pregnancies attending two large UK teaching hospital maternity units was recruited between September 2003 and June 2006 between 8-12 weeks gestation, as described in detail elsewhere.[5] Women with prior chronic disease, psychiatric illness, HIV or hepatitis B infection, were excluded. The demographic details of age, parity, maternal height, weight, socioeconomic status and gestational age were recorded by a questionnaire. Local ethics committee approval was obtained at both centres and written (signed) informed consent was obtained from each volunteer before recruitment.

## **Outcomes and measurements**

Information regarding antenatal pregnancy complications and delivery details were obtained from the electronic maternity databases. The primary outcome of fetal growth restriction has been reported elsewhere.[5] This paper presents our secondary outcome measure of late miscarriage (spontaneous pregnancy loss between 12 and 24 weeks) and stillbirth (delivery  $\geq 24$  weeks with no signs of life at birth).

A validated caffeine assessment tool completed during initial hospital registration at 8-12 weeks recorded habitual caffeine intake, divided into the four weeks before pregnancy, weeks 1-4, and weeks 5-12, repeated again for weeks 13-28, and again for weeks 28 to 36 weeks or end of pregnancy.[20] The questionnaire covered all potential dietary sources of caffeine, both food and drink, and over the counter medications. Specific brand names, portion sizes, methods of preparation, quantity and frequency of intake were collected for different gestational periods. Precise caffeine intakes were then estimated based on the published caffeine content for each item,[21] and information provided by manufacturers and coffee houses. Alcohol intake was self-

reported using a tool developed for the UK Women's Cohort study.[22] Self-reported smoking, nausea and vomiting were also collected.

Women provided saliva samples at recruitment for determining nicotine exposure, collected using a Salivette® (Sarstedt, Aktiengesellschaft & Co., Loughborough, UK) kept in the mouth for 5-10 minutes. Saliva was isolated from the salivettes by centrifugation then stored at -80 °C. All samples were analysed at the University of Leeds. A commercial ELISA kit (Cozart Bioscience Ltd, Oxfordshire, UK) was used to measure salivary cotinine concentrations, according to the manufacturer's instructions.

### **Statistical methods**

Derived caffeine intake was expressed in mg/day averaged over the first trimester (defined as the first 12 weeks of pregnancy) and divided into the four weeks before pregnancy, weeks 1-4, and weeks 5-12 of the first trimester. Numbers were too small to investigate associations with intake in the second and third trimesters.

Geometric mean caffeine intakes were compared between those pregnancies resulting in late miscarriage or stillbirth and those resulting in a live birth, based on log-transformed caffeine intake in the first trimester.

Unconditional logistic regression modelling was used to predict late miscarriage or stillbirth, with stratification for the two centres, using Stata version 10 survey facilities,[23] adjusting for mother's age, previous history of miscarriage, salivary cotinine concentrations (as a continuous variable measured in ng/ml) and self-reported alcohol consumption, converted into units/day (one unit of alcohol is 10ml by volume, or 8g by weight, of pure alcohol) and categorised as 0, <0.25, 0.25 to 0.5, 0.5 to 1, and over 1 unit/day.

Tests for linear trend over the continuous measure of caffeine exposure were conducted by inclusion of the uncategorised continuous measure in the models. The robustness of the results to adjustment for nausea was assessed by adding this term to the model. The robustness of the results to adjustment for Index of Multiple Deprivation was also assessed. In addition to adjusting for previous history of miscarriage, the robustness of results to excluding women with previous deliveries was assessed. As a further exploration of possible residual confounding by smoking, the models were repeated using self-reported smoking status and amount smoked added to the model. The models were also repeated using caffeine from each of the two main sources, tea and coffee.

## RESULTS

A total of 13071 eligible women were invited to participate and 2643 (20%) consented. Women who had terminations were no longer at risk of miscarriage or stillbirth, and were therefore excluded (n=8). Of the remaining 2635 pregnancies, 19 resulted in late miscarriage and 9 in stillbirth. The mean (SD) maternal age was 30.0 (6.6) years. The mean pre-pregnant body mass index (SD) was 24.5 (4.5) kg/m<sup>2</sup>. 1228 (47%) of women were primiparous, and 1324 (51%) gave birth to boys. In the cohort, 106 (4%) women went into pre-term labour (<37 weeks gestation) and 67 (3%) had gestational hypertension (systolic blood pressure over 140 mmHg, diastolic blood pressure over 90 mmHg, on at least two occasions 30 minutes apart) or pre-eclampsia (systolic blood pressure over 140 mmHg, diastolic blood pressure over 90 mmHg, with proteinuria). The demographic and clinical characteristics are shown in table 1 according to outcome.

[Insert Table 1 here]

The median (IQR) caffeine intake was 217 (104 to 366) mg/day, 183 (74 to 321) mg/day, and 92 (22 to 217) mg/day in the four weeks before pregnancy, weeks 1 to 4, and weeks 5 to 12 respectively.

The median (IQR) caffeine intake over the whole first trimester was 132 (58 to 241) mg/day. The median (IQR) caffeine intake over the whole pregnancy was 134 (63 to 232) mg/day. In our study, tea contributed more than half of all caffeine consumption during pregnancy.[5] The median (IQR) alcohol intake during the first trimester was 0.2 (0 to 0.6) units/day, with the highest consumption occurring, as might be expected, pre-pregnancy, and dropping rapidly in the first few weeks.

The geometric mean caffeine intake during the first trimester for women whose pregnancies resulted in a live birth was 103 (95% CI: 98 to 108) mg/day. The geometric mean caffeine intake during the first trimester for women whose pregnancies resulted in late miscarriage or stillbirth was 145 (85 to 249) mg/day.

There was a strong association between caffeine intake in the first trimester and subsequent late miscarriage between 12 and 24 weeks or stillbirth after 24 weeks adjusting for maternal age, parity, alcohol intake and amount smoked measured by salivary cotinine (table 2). Compared to those consuming <100 mg/day, the odds ratio for late miscarriage or stillbirth increased to 2.2 (95% CI: 0.7 to 7.1) for intakes between 100 and 199 mg/day, to 1.7 (0.4 to 7.1) for those taking between 200 and 299 mg/day and to 5.1 (1.6 to 16.4) for those consuming over 300 mg/day ( $P_{trend}=0.004$ ). There were insufficient events to present these separately for late miscarriage and stillbirth. This relationship appeared strongest in relation to caffeine consumption in the first few weeks of pregnancy, though confidence intervals are wide.

[Insert Table 2 here]

The results were unchanged by further adjustment for nausea: Compared to those consuming <100 mg/day of caffeine during the first trimester, the odds ratio for late miscarriage or stillbirth increased to 2.2 (95% CI: 0.7 to 7.1) for intakes between 100 and 199 mg/day, to 1.7 (0.4 to 7.1) for those taking between 200 and 299 mg/day and to 5.2 (1.6 to 16.6) for those consuming over 300 mg/day ( $P_{trend}=0.004$ ). When adjusting for Index of Multiple Deprivation, again the results were



unchanged: Compared to those consuming <100 mg/day of caffeine during the first trimester, the odds ratio for late miscarriage or stillbirth increased to 2.2 (95% CI: 0.7 to 7.0) for intakes between 100 and 199 mg/day, to 1.2 (0.2 to 6.0) for those taking between 200 and 299 mg/day and to 5.3 (1.6 to 17.1) for those consuming over 300 mg/day ( $P_{trend}=0.005$ ). Conclusions were also unchanged when women with previous deliveries were excluded, though confidence intervals were wider than before because of the reduced numbers of cases ( $P_{trend}=0.001$ ). When the model was repeated using self-reported smoking status and amount smoked added to the model, estimates were again very similar: Compared to those consuming <100 mg/day of caffeine during the first trimester, the odds ratio for late miscarriage or stillbirth increased to 2.3 (95% CI: 0.7 to 7.4) for intakes between 100 and 199 mg/day, to 1.7 (0.4 to 7.2) for those taking between 200 and 299 mg/day and to 5.3 (1.6 to 17.4) for those consuming over 300 mg/day ( $P_{trend}=0.003$ ).

[Insert Table 3 here]

Tea and coffee were the dominant sources of caffeine during pregnancy. Results for these sources are presented in table 3 with caffeine intake categories combined to compare <200mg/day with 200+mg/day. Wide confidence intervals reflect the small numbers of cases in the higher intake categories for these sources. The number of women with >200mg/day from other sources of caffeine was too low to investigate those sources.

## **DISCUSSION**

Though the outcomes are rare, we have shown that there is a potentially strong association between caffeine and late miscarriage or stillbirth. Our results of increased late miscarriage and stillbirth with greater caffeine intake add further support to claims of an association between caffeine and negative birth outcomes.[8-12;14] Many previous studies suffered from the potential

for measurement error in the exposure. Our methods minimised the potential for exposure misclassification by including all sources of caffeine, including all caffeine-containing foods, beverages and medications, in a detailed validated questionnaire. Similarly, misclassification of important confounders can lead to bias through residual confounding. In our study, alcohol intake was recorded through the same detailed tool used for caffeine, and the important covariate of smoking status was recorded objectively using salivary cotinine as a biomarker of exposure. Many previous studies, particularly case-control studies, have collected exposure information retrospectively, with the potential for recall bias. However, in our study the exposure was assessed prospectively.

Whilst our study identified only small numbers of late miscarriages and stillbirths, the proportion of pregnancies resulting in these outcomes (1.1%) is similar to that found in a large survey of late miscarriage in Canada (0.6%).<sup>[24]</sup> However the small number of events limited our power to investigate subgroups, and resulted in very wide confidence intervals for the estimates. Our findings therefore need further replication in larger prospective population-based studies. Our response rate (20%) was disappointing and reflects the demanding requirements of the study. For ethical reasons responders could not be compared to non-responders. However, mean birth weights for gestational age, rates of late miscarriage and stillbirth, and caffeine intakes were comparable to those found in other studies.<sup>[24-26]</sup> In addition, there is no reason to assume that caffeine metabolism phenotype should differ between responders and non-responders, other than in those confounders that we have adjusted for, e.g. smoking status.

Whilst it has been suggested that the relationship between caffeine and miscarriage or stillbirth is confounded by nausea,<sup>[8;27]</sup> which may lead to both a reduction in caffeine intake and risk to the fetus, we consider that nausea is more likely to be either a marker for a healthy pregnancy, rather than causative, or that caffeine intake may lead to nausea in some.<sup>[8;27;28]</sup> Wherever nausea lies on the causal pathway, analyses both with and without adjustment for nausea gave very similar

results that did not alter the conclusions. In addition, we found an association with caffeine intake before pregnancy, which could not be influenced by physiological changes and processes during pregnancy (such as slowing caffeine metabolism and increasing the half life of serum caffeine).

It may be that higher caffeine intake increases risk of late miscarriage in susceptible women. A case-control study of women with recurrent pregnancy loss found a statistically significantly increased risk of pregnancy loss only in women with the homozygous (A/A) genotype representing the high inducibility genotype for CYP1A2, which increases the rate of caffeine metabolism.[29] Studies in monkeys have shown a high rate of stillbirths and miscarriage with maternal caffeine intakes of 10-15 mg/kg body weight per day given via the drinking water, though experimental research such as this tends to provide evidence at doses of exposure that are not relevant to most human populations. For example, this is equivalent to a 60 kg woman consuming 8 to 12 average cups of coffee per day (assuming 75 mg caffeine/cup). Interestingly, the main serum metabolite of caffeine in monkeys is theophylline, whereas in humans it is paraxanthine. The comparative toxicities of these two metabolites is unknown.[16] Klebanoff et al., using paraxanthine as a marker for caffeine intake, found an increased risk of late miscarriage only for very high intakes,[13] though it is unclear whether it is caffeine, paraxanthine, or another caffeine metabolite that is the potentially causative agent.

## **CONCLUSION**

Our study identified only small numbers of late miscarriages and stillbirths, limiting power to detect small associations, and resulting in very wide confidence intervals. Therefore, although reaching statistical significance, there is considerable uncertainty in the size of the association. However, given the careful methodology employed, and the advances over some earlier studies, our findings make a valuable contribution to the literature in this field. Given also the paucity of randomised

controlled trials in this area, and the practical and ethical difficulties in conducting them, our study strengthens the observational evidence base on which current guidance is founded.

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## **DISCLOSURE OF INTERESTS**

None declared.

## **CONTRIBUTION TO AUTHORSHIP**

Darren C Greenwood conceived the paper, performed and interpreted statistical analyses, and wrote the manuscript. Principal Investigators were Janet E Cade (Leeds) and Marcus S Cooke (Leicester). Co-Investigators were Nigel Simpson, James Walker, Christopher P Wild (Leeds) and Justin C. Konje (Leicester). All authors were given the opportunity to comment on and approve the paper.

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**Table 1.** Demographic and clinical characteristics of 2635 subjects, according to outcome.

<b>Characteristic</b>	<b>Late miscarriage or stillbirth (n=28)</b>	<b>Live birth (n=2607)</b>	<b>All (n=2635)</b>
Mother's mean age (years) (SD)	30.2 (5.0)	30.0 (6.6)	30.0 (6.6)
Mother's mean pre-pregnant weight (kg) (SD)	66.6 (13.4)	66.8 (13.1)	66.8 (13.1)
Mother's pre-pregnant BMI (kg/m <sup>2</sup> ) (SD)	24.9 (4.3)	24.5 (4.5)	24.5 (4.5)
History of previous miscarriage (%)	4 (14%)	611 (23%)	615 (23%)
Gestational hypertension / pre-eclampsia (%)	0 (0%)	67 (3%)	67 (3%)
Mean alcohol intake in 1 <sup>st</sup> trimester (units/day) (SD)	0.5 (0.7)	0.5 (0.8)	0.5 (0.8)
Salivary cotinine concentration (ng/ml) (%)			
< 1 ng/ml	19 (70%)	1816 (73%)	1835 (73%)
1 – 5 ng/ml	5 (19%)	302 (12%)	307 (12%)
>5 ng/ml	3 (11%)	364 (15%)	367 (15%)
Child's gender (male) (%)	6 (32%)*	1318 (52%)	1324 (51%)
Mean birth weight (g) (SD)	1880 (1300)	3460 (540)	3450 (550)

\* Child's gender not recorded for 9 late miscarriages.

**Table 2.** Odds ratios (95%CI) of late miscarriage and stillbirth by caffeine intake categories.

	Caffeine (mg/day)	No. of cases / total	Unadjusted OR	(95% CI)	$P_{trend}$	Adjusted OR*	(95% CI)	$P_{trend}$
Average over 1 <sup>st</sup> trimester	<100	6/998	1	-	0.04	1	-	0.004
	100-199	7/656	1.8	(0.6, 5.3)		2.2	(0.7, 7.1)	
	200-299	3/402	1.2	(0.3, 5.0)		1.7	(0.4, 7.1)	
	300+	9/426	3.6	(1.3, 10.1)		5.1	(1.6, 16.4)	
4 weeks before pregnancy	<100	3/604	1	-	0.002	1	-	<0.001
	100-199	5/570	1.8	(0.4, 7.5)		1.4	(0.3, 6.3)	
	200-299	5/460	2.2	(0.5, 9.3)		2.2	(0.5, 9.4)	
	300+	12/870	2.8	(0.8, 10.0)		3.0	(0.8, 10.9)	
Weeks 1 to 4	<100	3/781	1	-	0.001	1	-	<0.001
	100-199	5/572	2.3	(0.5, 9.6)		1.8	(0.4, 8.2)	
	200-299	6/441	3.6	(0.9, 14.4)		3.8	(0.9, 16.7)	
	300+	11/706	4.1	(1.1, 14.8)		4.7	(1.2, 18.7)	
Weeks 5 to 12	<100	12/1302	1	-	0.6	1	-	0.2
	100-199	3/497	0.7	(0.2, 2.3)		0.8	(0.2, 3.0)	
	200-299	6/325	2.0	(0.8, 5.4)		2.5	(0.9, 7.0)	
	300+	4/373	1.2	(0.4, 3.6)		1.6	(0.5, 5.5)	

\*Adjusted odds ratios take account of maternal age, parity, amount smoked (cotinine concentration as a continuous variable, ng/ml) and alcohol intake (categorised as 0, <0.25, 0.25-0.5, 0.5-1 and 1+ units/day). Where numbers do not total to 2635, this is due to a small proportion of missing data. A total of 271 women were excluded from adjusted analyses with missing covariate information.

**Table 3.** Odds ratios (95%CI) of late miscarriage and stillbirth by tea and coffee intake categories.

	Caffeine (mg/day)	No. of cases / total	Unadjusted OR	(95% CI)	$P_{trend}$	Adjusted OR*	(95% CI)	$P_{trend}$
Tea	<200	17/2021	1	-	0.07	1	-	0.02
	200+	8/500	1.9	(0.8, 4.5)		2.2	(0.9, 5.4)	
Coffee	<200	24/2414	1	-	0.4	1	-	0.3
	200+	1/107	0.9	(0.1, 7.0)		1.2	(0.1, 9.4)	

\*Adjusted odds ratios take account of maternal age, parity, amount smoked (cotinine concentration as a continuous variable, ng/ml) and alcohol intake (categorised as 0, <0.25, 0.25-0.5, 0.5-1 and 1+ units/day). Where numbers do not total to 2635, this is due to a small proportion of missing data. A total of 271 women were excluded from adjusted analyses with missing covariate information.