

WHAT IS ALREADY KNOWN ON THIS TOPIC

Although oncologists prescribe oral chemotherapy for many indications, little is known about associated safety practices

WHAT THIS STUDY ADDS

Few of the safeguards in routine use for infusion chemotherapy have been adopted for oral chemotherapy

Conclusions

Our data indicate that prescribing, monitoring and coordination, pharmacy practices, and education of patients for oral chemotherapy vary substantially. Despite clinicians' concern about oral chemotherapies, there is no apparent consensus among oncology professionals about safe practices for these drugs. Safeguards used for infusion chemotherapy cannot be abandoned for oral treatment. The oncology community must define safe medication practices appropriate for oral chemotherapy, develop practice guidelines, and accelerate their adoption.

We thank the Comprehensive Cancer Center Consortium for Quality Improvement (C4QI) for help in completing this project.

Contributors: SNW, JF, AP, SB, LNS, and MC were responsible for conception and design. SNW, JF, DB, LM, and MC collected the data. SNW, AP, LNS,

and MC analysed and interpreted data. SNW, JF, DB, LM, AP, SB, LNS, and MC drafted and revised the paper. AP and SNW carried out the statistical analysis. SNW, JF, DB, LM, SB, LNS, and MC were responsible for administrative, technical, and material support. SNW and LNS supervised the study. SNW is guarantor.

Funding: Center for Patient Safety, Dana-Farber Cancer Institute, Boston. SNW was also supported by a K08 Mentored Clinical Scientist Career Development Award (1 K08 HS 11644) from the US Agency for Healthcare Research and Quality.

Competing interests: None declared.

Ethical approval: Dana-Farber Cancer Institute's institutional review board.

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Accepted: 5 December 2006

Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial

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BMJ 2007;334:409-12

doi: 10.1136/bmj.39062.520648.BE

This article is an abridged version of a paper that was published on bmj.com on 26 January 2007. Cite this version as: *BMJ* 26 January 2007, doi: 10.1136/bmj.39062.520648.BE (abridged text, in print: *BMJ* 2007;334:409-12).

ABSTRACT

Objective To estimate the effect of reducing caffeine intake during pregnancy on birth weight and length of gestation. **Design** Randomised double blind controlled trial.

Setting Denmark.

Participants 1207 pregnant women drinking at least three cups of coffee a day, recruited before 20 weeks' gestation.

Interventions Caffeinated instant coffee (568 women) or decaffeinated instant coffee (629 women).

Main outcome measures Birth weight and length of gestation.

Results Data on birth weight were obtained for 1150 liveborn singletons and on length of gestation for 1153 liveborn singletons. No significant differences were found for mean birth weight or mean length of gestation between women in the decaffeinated coffee group (whose mean caffeine intake was 182 mg lower than that of the other group) and women in the caffeinated coffee group. After adjustment for length of gestation, parity, prepregnancy body mass index, and smoking at entry to the study the mean birth weight of babies born to women in the decaffeinated group was 16 g (95% confidence interval -40 to 73) higher than those born to women in the caffeinated group. The adjusted difference (decaffeinated

group—caffeinated group) of length of gestation was -1.31 days (-2.87 to 0.25).

Conclusion A moderate reduction in caffeine intake in the second half of pregnancy has no effect on birth weight or length of gestation.

Trial registration Clinical Trials NCT00131690.

INTRODUCTION

Some studies have shown an association between high caffeine intake in pregnancy and an increased risk of giving birth to small for gestational age or low birth weight (<2500 g) babies.¹⁻⁵ Some have also shown an association between caffeine intake during pregnancy and miscarriage.^{6,7}

We carried out a randomised double blind trial to estimate the effect of reducing caffeine intake on birth weight and length of gestation.

METHODS

From April 1996 to April 1998 we sent a questionnaire to all pregnant women booking for delivery at Aarhus University Hospital, to assess coffee intake. At around 16 weeks of pregnancy we contacted those who had stated a daily intake of at least three cups of coffee.

Table 1 | Differences in anthropometric data for liveborn singletons of mothers randomised to decaffeinated or caffeinated coffee

Variable	No of babies	Decaffeinated coffee group	Caffeinated coffee group	Crude difference	Adjusted difference* (95% CI)	No of babies	Adjusted difference† (95% CI)
Mean birth weight (g)	1150	3519	3539	-19.4	4.6 (-53.5 to 62.7)	1112	16.3 (-40.0 to 72.6)
Mean length of gestation (days)	1153	279.3	280.2	-0.92	-0.92 (-2.45 to 0.61)	1115	-1.31 (-2.87 to 0.25)
Mean birth length (cm)	1146	51.9	52.0	-0.14	-0.05 (-0.30 to 0.21)	1108	-0.03 (-0.29 to 0.22)
Mean ponderal index	1145	2.5	2.5	0.01	0.01 (-0.02 to 0.04)	1107	0.02 (-0.01 to 0.05)
Mean head circumference (cm)	1006	35.1	35.1	0.03	0.07 (-0.14 to 0.27)	974	0.11 (-0.10 to 0.32)
Mean abdominal circumference (cm)	979	33.4	33.4	-0.03	-0.001 (-0.27 to 0.27)	949	0.07 (-0.19 to 0.33)
Mean placenta weight (g)	984	659	673	-14.7	-11.3 (-31.0 to 8.4)	954	-10.6 (-30.5 to 9.3)

Differences are for decaffeinated minus caffeinated groups. Number of babies differs owing to missing data.

*Adjusted for gestational age.

†Adjusted for length of gestation, parity, prepregnancy body mass index, and smoking at entry to study.

From April 1998 to January 2002 we recruited eligible participants through the Danish national birth cohort.⁸ These women completed a telephone interview around 12 weeks of pregnancy.

The women were randomised to receive caffeinated instant coffee or decaffeinated instant coffee. They were allocated to either group by a computer generated randomisation schedule and assigned serial numbers in balanced blocks of six. The women could request as much coffee as they needed.

We asked the women to replace their usual coffee with that provided, but we did not advise them on how much to drink or ask them to avoid regular coffee offered by others or intake of other caffeinated beverages such as tea, cocoa, or cola. The women were interviewed at gestational weeks 20, 25, and 34 and at four weeks after the expected date of delivery to obtain data on daily consumption of the study coffee, other caffeinated beverages, and smoking status. In the final interview we asked the women to guess the type of coffee they had received.

The main outcomes were birth weight and length of gestation, obtained from the Danish national birth register, along with date of birth. If data were missing (n=29) we used information from the final interview. From the national birth register we obtained information on length, head circumference, abdominal circumference, placental weight, and Apgar score to use for secondary analyses.

Statistical analysis

We analysed data on an intention to treat basis, blinded to coffee exposure. We adjusted for several potential confounders linked to fetal growth; gestational age, prepregnancy body mass index, parity, and smoking status. We used analysis of variance for the adjusted analyses and to compare anthropometric measures between the groups. The risk of preterm birth, being small for gestational age, and an Apgar score of less than 7 at five minutes was assessed by logistic regression analyses. Small for gestational age was defined as a birth weight more than two standard deviations below the mean for gestational age on the reference curve.⁹ Preterm birth was defined as delivery before 37 completed weeks of gestation. In secondary analyses we stratified the main results on smoking status at baseline.

To determine if women who received decaffeinated coffee increased their consumption of other caffeinated beverages, we calculated the mean intake of caffeine from study coffee, other caffeinated coffee, tea, cola, and drinking chocolate for women in both groups on the basis of information from the interviews.

RESULTS

Overall 1207 pregnant women were randomised. After exclusions 568 women were randomised to caffeinated coffee and 629 to decaffeinated coffee (see [bmj.com](#)). The groups showed only minor differences in baseline characteristics (see [bmj.com](#)).

A total of 1153 women with a liveborn singleton were included in the analysis of birth weight and length of gestation. Of these, 8.6% (54/629) randomised to the decaffeinated group and 4.9% (28/568) randomised to the caffeinated group dropped out. The outcomes for these women were included in the main analysis.

Primary analyses

Women randomised to caffeinated coffee had a higher mean caffeine intake during the study period. The mean difference in caffeine intake between the groups was 182 mg a day (see table 2 on [bmj.com](#) for caffeine intake from other beverages).

The mean birth weight for babies born to women in the caffeinated group was 3539 g (SD 604 g) compared with 3519 g (SD 607 g) for babies born to women in the decaffeinated group (table 1). Using the Wilcoxon rank sum test no significant difference was found in gestational age between the groups (table 1); P=0.48).

After adjustment for baseline determinants of birth weight the mean difference in birth weight between babies of women randomised to decaffeinated minus caffeinated coffee was 16 g (95% confidence interval -40 to 73; P=0.57).

Secondary analyses

The difference in mean birth weight and length of gestation between the groups was not modified by coffee consumption at study entry or by compliance with the protocol (table 2). Women who smoked more than 10 cigarettes a day at study entry, however, had babies with a lower mean birth weight of 263 g (97 to 430; P=0.002) if they were randomised to caffeinated coffee

compared with babies born to women who were randomised to decaffeinated coffee (table 2, test for interaction $P < 0.001$). For women smoking more than 10 cigarettes a day the mean difference in caffeine intake between the groups was 242 mg/day. For non-smokers the mean difference in caffeine intake between the groups was 154 mg/day. When length of gestation was the dependent variable no statistically significant interaction was found between smoking at study entry and group (test for interaction $P = 0.25$).

In the caffeinated and decaffeinated groups, respectively, 4.2% (23/552) and 5.2% (31/601) of infants were born preterm, 4.5% (25/552) and 4.7% (28/598) were small for gestational age, and 0.8% (4/527) and 1.0% (6/578) had an Apgar score of less than 7 after five minutes. None of these differences was statistically significant.

Compliance

At about 35 weeks' gestation 53% (295/552) of women in the caffeinated group and 45% (271/601) in the decaffeinated group drank less than one cup of other caffeinated coffee a day; 24% (132/552) and 24% (147/601) drank one to three cups of other caffeinated coffee a day, whereas 9% (50/552) and 8% (51/601) drank more than three cups of other caffeinated coffee a day. Information on consumption of other caffeinated coffee at 35 weeks' gestation was missing for 18% (207/1153) of the women. Data from diaries were available on daily caffeine intake from study coffee, other coffee, tea, cocoa, and cola, but only 51% (293 in each arm) of women returned the diaries (data available on request).

Blinding

In the caffeinated group 35% (191/552) of women guessed the type of coffee they received compared with 49% (296/601) in the decaffeinated group; 20% (123/601) in the decaffeinated group and 22% (121/552) in the caffeinated group could not guess. This difference in guessing was statistically significant.

DISCUSSION

Providing decaffeinated coffee to women who drank three cups of coffee or more a day in early pregnancy had no effect on birth weight or length of gestation.

We found only small differences in potential confounders at baseline between pregnant women allocated to caffeinated instant coffee and those allocated to decaffeinated instant coffee, and we adjusted for these in analyses.

To ensure good compliance we did not impose a strict protocol on the use of caffeinated beverages during the trial. Still, we obtained a difference in caffeine intake of a magnitude that has previously been reported to have an effect on birth weight.¹⁰ The difference in caffeine intake we found (182 mg a day) corresponds to almost three cups of instant coffee a day. We cannot, however, rule out that larger reductions in caffeine may increase birth weight.

Caffeine intake is associated with smoking and alcohol intake, which may influence birth weight. It is possible that a modification of caffeine intake could also influence other lifestyle factors. However, we found no difference between the groups in smoking or alcohol consumption (data not shown).

Table 2 | Differences in birth weight and length of gestation between mothers, of liveborn singletons, randomised to receive decaffeinated or caffeinated coffee, stratified on coffee consumption at baseline, compliance to study protocol, and smoking at baseline

Variable	No of women*	Birth weight		P value‡	No of women*	Length of gestation		
		Mean difference†	(95% CI)			Mean difference§	(95% CI)	P value‡
Coffee consumption (cups/day) at baseline:								
<3	131	-31	(-202 to 240)	0.40	131	-2.50	(-7.4 to 2.3)	0.58
4-7	480	7	(-78 to 92)		482	-0.27	(-2.6 to 2.0)	
>7	497	57	(-28 to 142)		498	-2.06	(-4.5 to 0.3)	
Missing data	4				4			
Consumption (cups/day) of other caffeinated coffee¶:								
0	283	-9	(-125 to 107)	0.24	283	0.38	(-2.0 to 2.8)	0.35
<1	266	-39	(-150 to 72)		267	-1.45	(-0.8 to 3.7)	
1-3	271	115	(3 to 226)		271	-1.65	(-4.3 to 1.0)	
4-7	76	-120	(-354 to 113)		76	-0.41	(-5.1 to 4.3)	
≥8	21	92	(-475 to 659)		21	-4.39	(-18.1 to 9.4)	
Missing data	195	152	(9 to 295)		197	-2.40	(-8.5 to 3.7)	
Smoking (cigarettes/day) at baseline:								
Non-smoker	692	-48	(-118 to 23)	<0.001	694	-0.44	(-2.5 to 1.6)	0.25
1-10	272	36	(-78 to 149)		272	-1.80	(-4.9 to 1.3)	
>10	148	263	(97 to 430)		149	-4.19	(-8.4 to 0.01)	

Differences are for decaffeinated minus caffeinated groups.

*Number with information on all covariates and outcome measure.

†Adjusted for parity, smoking, prepregnancy body mass index, and length of gestation.

‡Test for interaction.

§Adjusted for parity, smoking, and prepregnancy body mass index.

¶Consumption at time of third interview (median 35 gestational weeks).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Caffeine intake in pregnancy has been linked to adverse outcome, but evidence from non-experimental studies on impaired fetal growth remains equivocal
Evidence from randomised controlled trials is lacking

WHAT THIS STUDY ADDS

A moderate decrease in caffeine intake in the second half of pregnancy had no overall effect on birth weight or length of pregnancy

Women in the decaffeinated group guessed their type of coffee more often than women in the caffeinated group. Participants consumed at least three cups of coffee a day at baseline, and it is likely that some in the decaffeinated arm had withdrawal symptoms.¹¹

Slightly more women were randomised to decaffeinated coffee because women receiving caffeinated coffee requested additional coffee more often than women receiving decaffeinated coffee. This modification affects only the power and not the internal validity of the study.

Comparison with other studies

Our finding of a possible caffeine effect in smokers may be due to chance, but it has some biological plausibility. Smokers metabolise caffeine faster than non-smokers because smoking induces the CYP1A2 pathway for caffeine metabolism. A previous study found that the caffeine metabolite paraxanthine was associated with fetal growth in smokers, whereas serum caffeine was not.¹² A recent study suggested that CYP1A2 activity, and not the absolute levels of metabolites of caffeine, influences fetal growth.¹³

Unanswered questions and future research

Our trial was carried out in the second half of pregnancy when the net increase in fetal weight is highest. If caffeine has an effect on birth weight by mechanisms that only operate early in pregnancy we would not detect it. Furthermore, we cannot rule out that substances other than caffeine in coffee may influence birth weight. Our results emphasise that care should be taken when extrapolating results to smokers.

We thank the women who participated in the study, J Sønderskov for her support, and M Vaeth for statistical advice.

Contributors: See bmj.com.

Funding: The project is supported by a grant from the Health Insurance Foundation (No 1105-93 and 11099-96). The Danish National Research Foundation established the Danish Epidemiology Science Centre that initiated and created the Danish national birth cohort. The birth cohort is furthermore a result of a major grant from this foundation. Additional support for the birth cohort was obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. Nestlé was not involved in the design, analyses, or writing of this paper.

Competing interests: None declared.

Ethical approval: This study was approved by regional science ethics committees in Denmark and the Danish Data Protection Agency.

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Accepted: 28 November 2006.

Today's facts are tomorrow's fallacies

Electricity was used in antiquity as treatment for various illnesses. During the reign of Nero, the Greek physician Dioscorides used the electrical properties of ray fish to treat headache. The first specific use of electrotherapy in angina was by the eminent French neurologist Guillaume Benjamin Duchenne of Boulogne.

He tried it for the first time on a patient "Pérone, aged fifty, a currier, residing at Belleville, 25 Tourtil Street, of a short build and sanguine temperament, rather fat and with a short neck." On the patient's first visit, on 28 April 1853, Duchenne observed: "He rode from Belleville to my house, and when coming up to my apartment, which is on the second floor, he was obliged to stop on every stair, on account of the constriction in his chest."

Of the treatment, he wrote: "I brought on a second paroxysm [attack of angina] by making Pérone walk, and I applied to his nipple the extremity of my induction-apparatus graduated to maximal intensity

and working with very rapid intermissions. As the nipple was galvanised, he uttered such a loud shriek that I had to interrupt the current. The pain had been excruciating, but merely instantaneous, and to my great surprise, after the artificial pain which I had brought on, the pain of the angina also disappeared completely, as well as the sensation of the numbness and formication which accompanied it; respiration had become quiet again; patient felt at once normal again."

Another famous French physician, Armand Trousseau, commented on this response in his *Lecture Notes on Clinical Medicine* (1868): "It [electricity] affords another proof that the most violent angina pectoris may not be due to an organic lesion of the heart or the great vessels, because had such been present, electricity might have relieved the pain, but never have cured the patient, particularly in such a short time."

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