

Acute Caffeine Ingestion and Glucose Tolerance in Women With or Without Gestational Diabetes Mellitus

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Abstract

Objective: Recent work showing that caffeine impairs glucose tolerance may be of particular concern in pregnancy because of a possible negative effect on fetal outcome. The current study sought to assess the effect of acute caffeine ingestion on glucose tolerance in women with or without gestational diabetes mellitus (GDM).

Methods: Nineteen women whose routine GDM test was negative (control) and eight women with an initial positive GDM screen completed two trials one week apart in a double-blind randomized crossover study. Following an overnight fast, subjects ingested caffeine (3 mg/kg pre-pregnancy body weight) or an identical-appearing placebo (gelatin) capsule and one hour later began a 75 g 2-hour oral glucose tolerance test.

Results: In the control group, caffeine did not significantly affect blood glucose, insulin, or C-peptide. In the GDM group, glucose area under the curve (AUC) was greater ($P < 0.01$), C-peptide AUC was greater ($P < 0.05$), and insulin sensitivity index was lower (18%, $P < 0.05$) after caffeine than after placebo.

Conclusion: Caffeine impaired insulin sensitivity in women with GDM. Additional research regarding more specific dietary caffeine recommendations for women with GDM is warranted.

Résumé

Objectif : De récents travaux indiquent que la caféine altère la tolérance au glucose. Cette situation pourrait s'avérer particulièrement préoccupante au cours de la grossesse, en raison d'un possible effet négatif sur les issues fœtales. Cette étude cherchait à évaluer l'effet de l'ingestion aiguë de caféine sur la tolérance au glucose chez les femmes présentant ou non un diabète sucré gestationnel (DSG).

Méthodes : Dix-neuf femmes dont les résultats du dépistage systématique du DSG s'étaient avérés négatifs (groupe témoin) et huit femmes présentant un dépistage initial positif en ce qui concerne le DSG se sont soumises à deux essais, à une semaine d'intervalle, dans le cadre d'une étude croisée randomisée à

double insu. À la suite d'un jeûne nocturne, les participantes ont ingéré de la caféine (3 mg/kg de poids corporel pré-grossesse) ou une capsule placebo d'apparence identique (gélatine) et, une heure plus tard, se sont soumises à une épreuve d'hyperglycémie provoquée par voie orale (75 g, 2 heures).

Résultats : Dans le groupe témoin, la caféine n'a pas affecté de façon significative les taux sanguins de glucose, d'insuline ou de peptide C. Dans le groupe DSG, après l'ingestion de caféine, la surface sous la courbe (SSC) du glucose était plus élevée ($P < 0,01$), la SSC du peptide C était plus élevée ($P < 0,05$) et l'indice de sensibilité à l'insuline était plus faible (18 %, $P < 0,05$) qu'après l'ingestion du placebo.

Conclusion : La caféine a altéré la sensibilité à l'insuline chez les femmes présentant un DSG. D'autres recherches portant sur des recommandations plus précises quant à l'apport alimentaire en caféine chez les femmes qui présentent un DSG s'avèrent requises.

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INTRODUCTION

Gestational diabetes mellitus, defined as glucose intolerance detected during pregnancy, affects between 3.7% and 18% of the population in Canada, depending on the specific population,¹ and has implications for the fetus and newborn and for the mother.^{2,3} Recognized morbidity for the fetus includes macrosomia, shoulder dystocia, neonatal hypoglycemia, hypocalcemia, and hyperbilirubinemia, and potential long-term obesity and glucose intolerance.^{2,3} For the mother, GDM is a risk factor for subsequent development of type 2 diabetes.⁴ Both the World Health Organization and the Canadian Diabetes Association recommend the 75 g OGTT criteria for diagnosis of GDM.^{5–7} With this one-step approach, a 2-hour 75 g oral glucose load, following an overnight fast, is used with the diagnosis based on two or more values greater than the standards.⁷

Following diagnosis of GDM, therapeutic recommendations include dietary counselling, glucose self-monitoring,

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and possibly insulin therapy. Any factor that increases insulin resistance and impairs maternal blood glucose management may affect fetal or neonatal outcome. A widely ingested and biologically active food component that has been implicated in acute insulin resistance is caffeine (1,3,7-trimethylxanthine). The mean intake per capita of caffeine in Western society is estimated to be 200 to 400 mg/day,⁸ with most of this consumed from coffee, tea, cola drinks, and chocolate. Although 400 to 450 mg of caffeine per day is not associated with any adverse effects for the average adult, pregnant women have been advised to limit their caffeine intake to 300 mg/day.⁹ Recent studies of non-pregnant subjects in our laboratory have demonstrated that caffeine (5 mg/kg body weight or approximately 300 mg for an average woman) acutely increases insulin resistance, resulting in significantly elevated blood glucose following a 75 g OGTT.^{10–14} These findings suggest that caffeine intake in pregnancy may increase the chance of a false positive test for GDM and that it may adversely affect maternal glycemic control in women with GDM.

The primary objective of the present study was to investigate the effect of caffeine on glucose tolerance and metabolism during a 75 g OGTT in pregnant women with or without GDM. We hypothesized that caffeine ingestion prior to an OGTT would exaggerate blood glucose and insulin responses, leading to an acute insulin resistant state.

MATERIALS AND METHODS

Subjects in the study were recruited from obstetrical clinics following either a negative screen or a diagnosis of GDM (defined below) as part of routine screening for GDM at 24 to 28 weeks of gestation. Thus, subjects were initially identified by their obstetricians, informed of the opportunity to participate in the study, and then agreed to speak to the study nurse who provided additional information. Informed, written consent was obtained from each subject prior to study participation. Subjects consented to two 75 g fasting OGTTs (with or without caffeine) with serial blood sampling for two hours after the glucose load.

Women with an initial negative 50 g glucose screen (1-hour glucose value < 7.8 mmol/L) were assigned to the control group. Women with an initial positive 50 g glucose screen

were assigned to the GDM group if they also had two or more glucose values greater than 5.3 mmol/L (fasting), 10.6 mmol/L (1 h), or 8.9 mmol/L (2 h) on a subsequent 75 g fasting OGTT. A 1-hour glucose value of ≥ 10.3 mmol/L after a 50 g glucose screen was also considered diagnostic for GDM.

Self-reported pre-pregnancy weight and height were recorded for each subject and BMI was calculated (kg/m²). Subjects were excluded if they had a pre-pregnancy BMI > 30 kg/m², were smokers, were taking medications that could interfere with glucose uptake or metabolism (i.e., insulin or oral hypoglycemic drugs), or had known medical or obstetrical complications. Subjects were instructed to keep a three-day food record before each experiment and to refrain from caffeine-containing products, alcohol, and strenuous physical activity for 48 hours before each experiment. Food records were analyzed for total energy and macronutrient intake using ESHA Research, version 7.11.

Within the control and the GDM group, women underwent two further 75 g fasting OGTTs at approximately 28 to 29 and 29 to 30 weeks' gestation (i.e., one week apart). Treatments were randomized, and investigators and study participants were blinded to the order of the treatments. Subjects reported to the Kingston General Hospital Clinical Investigation Unit after an overnight (10–12-hour) fast. For blood sampling, a catheter was inserted into an antecubital vein by an obstetrical research nurse and kept patent with an infusion of normal saline for the duration of the trial. A baseline blood sample was taken (–60 minutes) followed by ingestion of 250 mL of water with either caffeine (3 mg/kg maternal body weight; equivalent to 1–2 cups of coffee) or a placebo (gelatin) capsule. One hour following capsule ingestion (0 minutes), a blood sample was taken and a standard 2-hour OGTT was initiated by ingestion of 75 g of dextrose (TRUTOL 75, Custom Laboratories Inc). Blood samples were obtained at 15, 30, 60, 90, and 120 minutes following the glucose load. Subjects remained resting over the 2-hour test, with continuous fetal monitoring and with an obstetrical research nurse present at all times.

Blood samples were used for assays of glucose, insulin, C-peptide, proinsulin, free fatty acids, epinephrine, and methylxanthines. Whole blood for glucose analysis was collected in a heparinized tube, placed on ice, and an aliquot was analyzed immediately using a Radiometer EBL105. Heparinized blood was then centrifuged (1200 × g for 10 minutes at room temperature), and plasma was stored at –800°C for later determination of plasma methylxanthines by high performance liquid chromatography.¹⁵ For determination of epinephrine levels, 120 µL of 0.24 mol/L EGTA and reduced glutathione were added to heparinized blood and centrifuged (1200 × g for 10 minutes at room

ABBREVIATIONS

AUC	area under the curve
GDM	gestational diabetes mellitus
ISI	insulin sensitivity index
OGTT	oral glucose tolerance test

Table 1. Physical and clinical characteristics of pregnant women with or without gestational diabetes mellitus*

	Pregnant control n = 19	Gestational diabetes n = 8	P†
Age (years)	30.1 ± 1.2	33.4 ± 1.2	0.13
Body mass (kg)	60.9 ± 1.9	69.5 ± 3.5	0.03
Body Mass Index (kg/m ²)	22.6 ± 0.5	27.1 ± 1.2	< 0.001
Fasting blood glucose (mmol/L)	4.4 ± 0.1	4.9 ± 0.2	0.001
2 h blood glucose (mmol/L)‡	7.5 ± 0.3	10.3 ± 0.5	< 0.001
Serum insulin (pmol/L)	33.2 ± 4.6	72.1 ± 10.9	< 0.001
Serum C-peptide (nmol/L)	0.50 ± 0.05	0.76 ± 0.18	0.08
Serum proinsulin (pmol/L)	6.1 ± 0.8	8.0 ± 2.4	0.34
Serum free fatty acids (μmol/L)	446 ± 33	462 ± 54	0.81

*Values are mean ± SEM. All data are fasting measurements unless otherwise indicated.

†P values refer to differences between control and GDM group

‡Blood glucose concentration at 2-hour during placebo trial.

temperature), and plasma was stored at -800°C until analyzed (Adrenaline Radioimmunoassay kit, Labor Diagnostika, Nord GmbH). For serum metabolite analysis, blood samples were collected in non-heparinized tubes and were allowed to clot at room temperature. Samples were then centrifuged ($1200 \times g$ for 10 minutes at room temperature), and serum was stored at -200°C until assayed for insulin, C-peptide, proinsulin (0, 30, and 120 minutes only), and free fatty acids. Radioimmunoassay kits were used to measure serum insulin (Coat-a-Count Insulin, Intermedico Diagnostic Products Co., Los Angeles, CA), C-peptide in samples treated with aprotinin (Human C-peptide RIA kit, Linco Research Inc., St. Charles, MO), and proinsulin (Human Proinsulin RIA kit, Linco Research Inc.). Serum free fatty acids were measured using a non-esterified free fatty acid kit from Wako Bioproducts (Richmond, VA). Consistently, our in-house interassay variabilities are similar to those reported by the manufacturer for each assay (insulin 7%, C-peptide < 5%, proinsulin < 4%, epinephrine 6%, and free fatty acids 4%). To minimize the effects of assay variability, samples from each subject were assayed together. All blood metabolites were determined in duplicate.

A one-way ANOVA was used to determine baseline differences in fasting blood metabolite data between control and GDM subjects. Within control and GDM groups, blood data were analyzed for time and treatment effects using a two-way ANOVA with repeated measures, and a Tukey post-hoc analysis (Sigma Stat 2.03, 1997) was used to identify differences. The AUC for glucose, insulin, and C-peptide was calculated for caffeine and placebo trials during the 2-hour OGTT (time 0 to 120 minutes), using the trapezoid method.¹⁶ The proinsulin/insulin ratio was calculated at 0

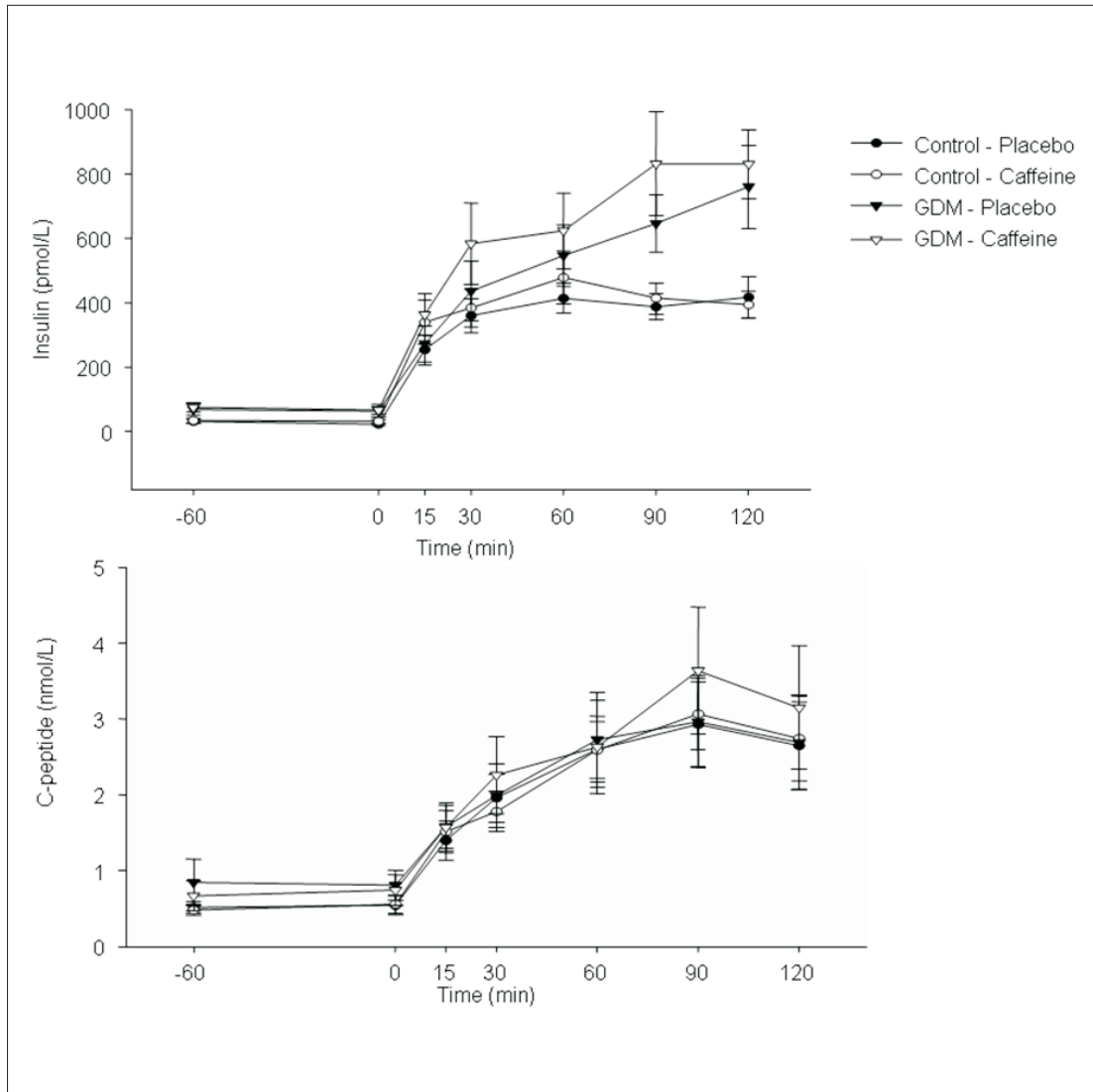
and 30 minutes, as it has been suggested that this accurately reflects beta cell secretion.¹⁷ Whole body insulin sensitivity during the OGTT was estimated using the equation described by Matsuda and DeFronzo.¹⁸ This equation gives an ISI that is significantly correlated with the rate of whole-body glucose disposal during a hyperinsulinemic-euglycemic clamp.¹⁸ Our calculation of ISI was based on serum insulin and whole blood glucose, as opposed to plasma concentrations as originally described,¹⁸ but these data were used for comparative purposes only. A one-way ANOVA was used to determine treatment differences in AUC and ISI within control and GDM groups. The change in epinephrine concentration between -60 minutes and 0 minutes was calculated and analyzed by two-way (treatment by group) ANOVA. For technical reasons, C-peptide and epinephrine levels were measured for a subset of control subjects ($n = 16$ and $n = 10$, respectively). All values are presented as mean ± SEM. Differences were considered significant at $P \leq 0.05$.

Ethics approval for the study was given by Queen's University Research Ethics Board.

RESULTS

Subject characteristics are presented in Table 1. Both fasting blood glucose and serum insulin levels were significantly higher in GDM than in control subjects, whereas there was no difference between groups in fasting serum C-peptide, proinsulin, or free fatty acid concentrations (Table 1). Self-reported food records showed that total energy and macronutrient intake of each subject did not differ between experiments, while self-reported caffeine

Figure 1. Effect of caffeine on serum (A) insulin and (B) C-peptide before and during an OGTT in women with or without gestational diabetes. Caffeine (3 mg/kg) or placebo (dextrose) was ingested at time = -60 min followed by ingestion of 75 g dextrose (time = 0 min) to initiate a 2 h oral glucose tolerance test (OGTT). Data are mean \pm SEM, n = 19 (insulin) or 16 (C-peptide) control women, n = 8 women with GDM. Closed symbols represent placebo OGTT, open symbols represent caffeine OGTT. Overall, compared with placebo, caffeine ingestion did not significantly affect the serum insulin or C-peptide response during the OGTT in either control or GDM subjects.



consumption ranged from low to moderate (100–400 mg/day) with no significant differences between GDM and control groups (data not shown).

During the placebo trial, plasma caffeine concentrations at 120 min were 0.52 ± 0.24 and 1.2 ± 0.4 $\mu\text{mol/L}$ ($P > 0.05$) in control and GDM subjects, respectively. Following caffeine ingestion, plasma caffeine concentrations increased from baseline (control: 0.25 ± 0.08 $\mu\text{mol/L}$, GDM: 1.0 ± 0.4 $\mu\text{mol/L}$) to reach peak concentrations at 60 minutes of 23.0 ± 1.4 $\mu\text{mol/L}$ and 24.5 ± 2.3 $\mu\text{mol/L}$ in control and

GDM subjects respectively ($P < 0.01$). Plasma caffeine concentrations then declined in both control and GDM groups, but remained significantly greater than baseline, as well as greater than concentrations observed during the placebo trials (data not shown). As expected, concentrations of caffeine metabolites (paraxanthine, theophylline, and theobromine) closely paralleled those of caffeine (data not shown). A comparison between control and GDM groups revealed no differences ($P > 0.05$) in plasma caffeine concentration either prior to or during the OGTT (data not shown).

Table 2. AUC for blood metabolites and insulin sensitivity index during a 2-hour OGTT in women with or without gestational diabetes mellitus*

	Pregnant control, n = 19		Gestational diabetes, n = 8		P†
	Placebo	Caffeine	Placebo	Caffeine	
Glucose (mmol/L/2h)	381 ± 28	392 ± 23	518 ± 35	616 ± 42	0.001
Insulin (pmol/L/2h)	39236 ± 4653	42632 ± 4675	53661 ± 9141	67207 ± 12538	0.07
C-peptide (nmol/L/2h)‡	241 ± 43	241 ± 37	188 ± 45	226 ± 54	0.03
Insulin Sensitivity Index	8.65 ± 0.74	8.24 ± 0.90	4.81 ± 1.05	3.96 ± 1.02	0.01

*Values are mean ± SEM. There was no effect of caffeine on glucose, insulin or C-peptide AUC or the insulin sensitivity index in control subjects.

†P values indicate effect of treatment (placebo vs. caffeine) on AUC calculated for each blood metabolite and insulin sensitivity index in GDM subjects.

‡For technical reasons, C-peptide was analyzed in a subset of control subjects (n = 16).

There was no effect of caffeine on serum insulin or C-peptide concentrations prior to OGTT initiation (from -60 minutes to 0 minutes, Figure 1) in either control or GDM subjects. As expected, serum insulin and C-peptide increased significantly following dextrose ingestion in both placebo and caffeine trials, and remained significantly elevated at the end of the OGTT in both control and GDM subjects (Figure 1). In control subjects, caffeine did not significantly affect insulin or C-peptide concentrations or AUC (Figure 1, Table 2). In the GDM group, although serum insulin during the OGTT tended to be higher in the caffeine group, statistical analysis demonstrated no significant difference ($P = 0.1$, Figure 1) between placebo and caffeine. Furthermore, it is noteworthy that in women with GDM the insulin AUC after caffeine ingestion was increased by 25% ($P = 0.07$, Table 2) compared with placebo, while C-peptide AUC was 20% greater after caffeine ($P < 0.05$, Table 2).

The proinsulin/insulin ratio decreased significantly from 0 minutes to 30 minutes after dextrose ingestion in both the placebo trial (control: 0.32 ± 0.06 to 0.06 ± 0.01 , GDM: 0.18 ± 0.07 to 0.05 ± 0.01) and the caffeine trial (control: 0.32 ± 0.08 to 0.06 ± 0.01 , GDM: 0.09 ± 0.02 to 0.04 ± 0.01). Caffeine had no effect ($P > 0.05$) on either absolute proinsulin concentrations or the proinsulin/insulin ratios (data not shown).

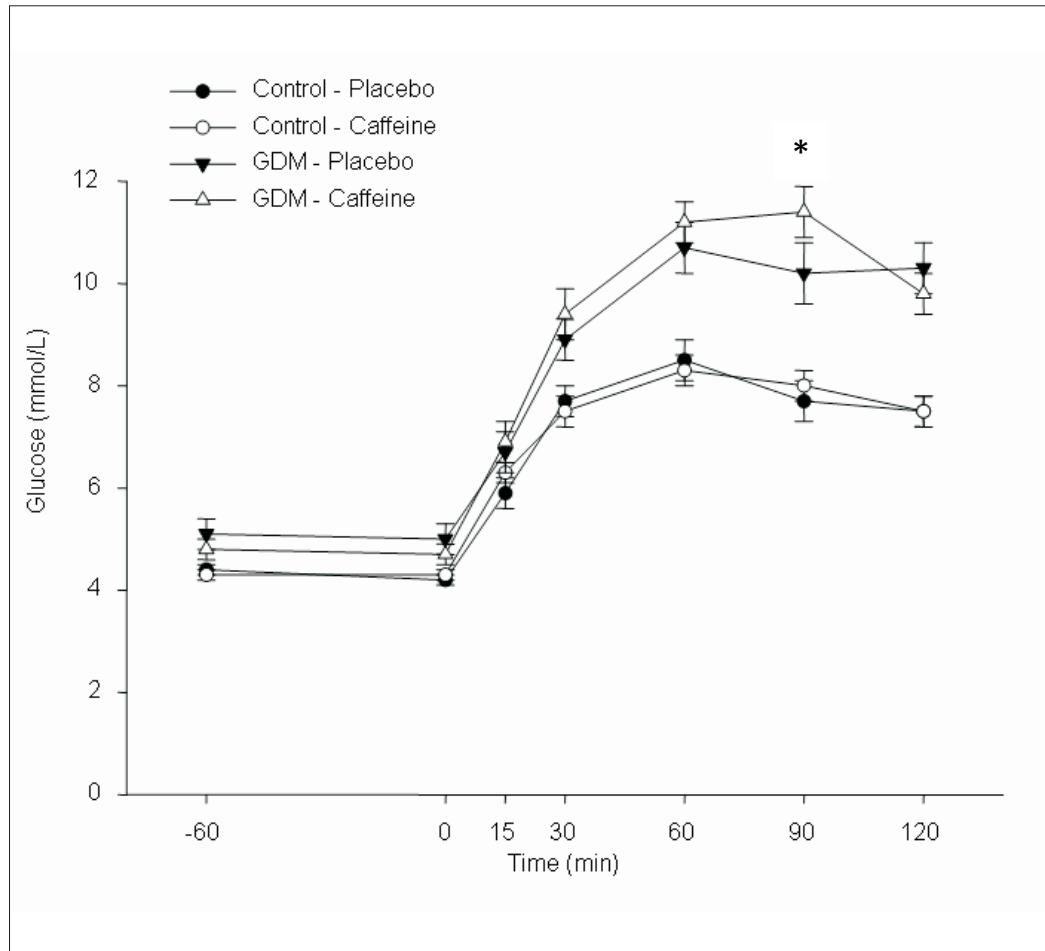
Caffeine ingestion did not affect blood glucose concentration prior to OGTT initiation (from -60 minutes to 0 minutes) in either the control or GDM groups (Figure 2). As expected, blood glucose concentration increased ($P < 0.01$) following ingestion of dextrose in both placebo and caffeine trials in all subjects. Blood glucose remained significantly higher than fasting values at the end of the OGTT (Figure 2) in all subjects in both the placebo and caffeine

trials, suggesting that the insulin response (described above) was not sufficient to clear the ingested glucose during the 2-hour postprandial period. Similar to the serum insulin response in control subjects, caffeine ingestion did not significantly affect blood glucose concentrations (Figure 2) or glucose AUC (Table 2) in this group. In contrast, in the GDM group, blood glucose at 90 minutes of the OGTT was significantly higher ($P < 0.05$) after caffeine compared with placebo (Figure 2). Furthermore, AUC analysis showed a higher glucose response (19%, $P < 0.01$) after caffeine than after placebo in women with GDM (Table 2). This difference between caffeine and placebo was further corroborated by a significantly lower ISI (18%, $P = 0.01$) after caffeine compared with placebo. In contrast, caffeine ingestion did not affect ISI in control subjects (Table 2).

After caffeine ingestion, serum free fatty acid concentration increased ($P < 0.01$) from -60 minutes to 0 minutes in control subjects only (Table 3) and remained higher than after placebo during the OGTT ($P < 0.01$, Table 3). Interestingly, caffeine ingestion did not significantly affect serum free fatty acids in GDM subjects (Table 3). With initiation of the OGTT (0 minutes) and the subsequent increase in serum insulin (Figure 1), serum free fatty acid concentrations started to decrease, and at 30 minutes were no longer different from fasting (-60 minutes) values in the caffeine trial in control subjects. In both control and GDM subjects, serum free fatty acids in all trials were lower at the end of the OGTT (120 minutes) than at baseline (Table 3).

Baseline epinephrine concentrations were similar in control and GDM subjects prior to ingestion of caffeine or placebo ($P > 0.05$, Table 3). Analysis of plasma epinephrine levels during the first 60 minutes following ingestion of caffeine or placebo capsules demonstrated that caffeine resulted in a significant ($P < 0.001$) but modest elevation in plasma

Figure 2. Effect of caffeine on blood glucose response before and during an OGTT in women with or without gestational diabetes. Caffeine (3 mg/kg) or placebo (dextrose) was ingested at time = -60 min followed by ingestion of 75 g dextrose (time = 0 min) to initiate a 2 h oral glucose tolerance test (OGTT). Data are means \pm SEM, n = 19 control women, n = 8 women with GDM. Closed symbols represent placebo OGTT, open symbols represent caffeine OGTT. In the control group, caffeine ingestion did not significantly affect the blood glucose response during the OGTT. Asterisk (*) indicates a significant difference between placebo and caffeine treatment for a given time point in GDM subjects ($P < 0.05$).



epinephrine concentrations in both control and GDM subjects (Table 3), with no differences between subject groups ($P > 0.05$).

DISCUSSION

On the basis of previous studies showing that acute caffeine ingestion results in a transient decrease in insulin sensitivity in non-pregnant subjects,^{11–14,19–22} including those with type 1²³ and type 2¹² diabetes, we hypothesized that caffeine would exaggerate blood glucose and insulin responses following an OGTT, leading to an acute insulin resistant state in pregnant women with or without GDM. Our key finding was a significant decrease in insulin sensitivity in women with GDM who consumed 3 mg/kg caffeine (equivalent to

1–2 cups of coffee, or a plasma caffeine dose of 23–25 μ M) prior to an OGTT. This is the first report of a caffeine-induced impairment in glucose metabolism in women with GDM, and, given the direct correlation between glycemic control and adverse fetal and neonatal effects,² may have implications regarding use of this common biologically active food component in this population.

Overall, GDM subjects, but not control subjects, demonstrated a response similar to previous studies.^{12,23} These showed that in response to caffeine, women with GDM had a small (but significant) increase in plasma epinephrine, an elevated glucose and C-peptide response, and a trend towards a greater insulin response, contributing to an impairment in insulin sensitivity of a similar magnitude to

Table 3. Free fatty acid and epinephrine concentrations during the OGTT in women with or without gestational diabetes*

	Pregnant control		Gestational diabetes	
	Placebo	Caffeine	Placebo	Caffeine
Free Fatty Acids ($\mu\text{mol/L}$)				
-60 min	438 \pm 47	455 \pm 47	452 \pm 91	471 \pm 66
0 min	519 \pm 44†	621 \pm 47	538 \pm 79	641 \pm 70
30 min	386 \pm 33	419 \pm 29	528 \pm 63	530 \pm 83
60 min	234 \pm 22	268 \pm 24	360 \pm 58	305 \pm 46
120 min	136 \pm 16	192 \pm 29	159 \pm 36	244 \pm 71
Epinephrine (nmol/L)				
-60 min	0.30 \pm 0.07	0.24 \pm 0.06	0.33 \pm 0.05	0.25 \pm 0.06
0 min	0.17 \pm 0.04	0.41 \pm 0.06	0.26 \pm 0.04	0.33 \pm 0.04
Delta‡	-0.13 \pm 0.05	0.18 \pm 0.05	-0.07 \pm 0.04	0.08 \pm 0.04

*Values are mean \pm SEM. For free fatty acid data, n = 19 control subjects and n = 8 GDM subjects. For epinephrine data, n = 10 control subjects and n = 8 GDM subjects.

†Significant difference between placebo and caffeine treatment for a given time point in control subjects ($P < 0.01$). Caffeine ingestion did not significantly affect serum free fatty acid concentration in GDM subjects. In both control and GDM subjects, serum free fatty acid concentrations in all trials were lower at the end of the OGTT (120 min) compared with those seen at -60 min (statistics not shown).

‡Treatment effect ($P = 0.001$) on delta -60 to 0 min, but no significant difference between control and GDM groups or treatment by group interaction.

previous studies in subjects with diabetes.^{12,23} Although we used a lower dose of caffeine than in previous studies (3 mg/kg vs. 5 mg/kg), to account for alterations in caffeine pharmacokinetics in pregnancy,²⁴ the magnitude of the carbohydrate response was similar.¹² Interestingly, Goldman and Ovadia²⁵ found that glucose tolerance was reduced with ingestion of two cups of coffee (mean caffeine dose of 250–300 mg) prior to an intravenous glucose tolerance test in pregnant, non-diabetic women, with a more marked impairment seen when prediabetes was suspected.

Although the mechanism by which acute caffeine ingestion decreases insulin sensitivity is not fully known, it has been shown that caffeine decreases glucose uptake by 50% in skeletal muscle,¹¹ the tissue predominantly responsible for whole-body glucose disposal. Since caffeine is a known adenosine receptor antagonist,^{26,27} it has been suggested that this may account for the major action of caffeine in inducing acute insulin sensitivity, although this remains controversial.^{20,28,29} Nonetheless, since adenosine A1 receptor antagonism is known to mobilize free fatty acids, enhance epinephrine secretion, and antagonize insulin action, it is possible that caffeine may exert its action through one or all of these mechanisms, with the resulting rise in blood glucose leading to an exaggerated insulin response and impairment in insulin sensitivity. Free fatty acids are important regulators of insulin resistance, with elevated circulating free fatty acids known to inhibit

insulin-mediated glucose uptake in skeletal muscle.³⁰ Circulating levels of free fatty acids tend to be higher in women with GDM,^{31,32} although we observed no difference between control and GDM subjects in baseline free fatty acid levels. Furthermore, although caffeine ingestion was associated with impaired insulin sensitivity in GDM subjects, this occurred in the absence of an effect of caffeine on circulating free fatty acids, suggesting that other mechanisms must be involved. A previous hyperinsulinemic clamp study in non-pregnant subjects supports this finding.¹⁹

Caffeine's effect of reducing insulin sensitivity also requires, to some extent, the presence of epinephrine, because acute caffeine ingestion does not impair glucose tolerance in individuals with tetraplegia (who lack the characteristic elevation in circulating epinephrine in response to caffeine³³), and beta blockade has been shown to negate caffeine's effect on insulin resistance.³⁴ Epinephrine is known to impair insulin-mediated glucose disposal,^{35,36} but a caffeine-induced increase in epinephrine is likely not sufficient to account for the entire caffeine response.²¹ Additional mechanisms must be involved. In our study, the caffeine-induced increase in plasma epinephrine in the control group did not affect insulin sensitivity. Yet, in GDM subjects who already exhibit impaired glucose metabolism, a similar caffeine-induced increase in epinephrine led to a further impairment in insulin sensitivity. This substantiates the study by

Batram et al.,²¹ which suggested that epinephrine is not the only mechanism involved.

A surprising finding was that pregnant women without GDM did not show the typical impairment in insulin sensitivity after caffeine ingestion. However, control subjects did have some metabolic response to caffeine, as demonstrated by an increase in levels of circulating free fatty acids and epinephrine prior to ingestion of the glucose load; these increases support the expected caffeine-induced increase in adipose tissue lipolysis and sympathetic nervous system response, respectively. It is unlikely that differences in baseline insulin resistance, demonstrated by a markedly lower ISI in women with GDM compared with controls, were responsible for the lack of caffeine effect on insulin sensitivity in control subjects. Previous studies in lean and obese subjects with varying degrees of insulin resistance describe a caffeine-induced decrease in insulin sensitivity during an OGTT^{10,12,37} and an insulin clamp.²² While it is possible that skeletal muscle in control subjects was non-responsive, this is unlikely because control subjects were reasonably sensitive to insulin in the placebo trial, as indicated by a mean ISI of 8.65 ± 0.74 . Overall, we cannot elucidate whether the lack of a glucose and insulin response after caffeine ingestion in control subjects is due to a change in skeletal muscle glucose uptake or hepatic glucose output in comparison with GDM subjects.

It is noteworthy that since pregnancy increases caffeine's half-life,²⁴ adverse health outcomes in pregnant women could develop in response to less caffeine than in non-pregnant women. Furthermore, recent epidemiological studies showing that coffee decreases the incidence of type 2 diabetes³⁸ may possibly motivate women to drink coffee to achieve this reported benefit. However, the consequences of this in women with GDM requires further study.

CONCLUSION

Ingestion of caffeine impaired insulin sensitivity in women with GDM. However, our sample size was small, and further investigation is required before dietary recommendations regarding caffeine use and glycemic control can be established in this population. It is imperative that women with GDM receive sound dietary advice regarding intake of caffeine.

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