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SHORT REPORT

Higher maternal serum prolactin levels are associated with reduced glucose tolerance during pregnancy

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ABSTRACT

It is unknown if high prolactin levels during pregnancy contribute to the development of gestational diabetes. We hypothesized that higher prolactin levels are associated with reduced glucose tolerance, as determined by higher 2-h glucose level from an oral glucose tolerance test in pregnancy. The 75-g oral glucose tolerance test was carried out at 28 weeks of gestation in 69 participants. A multiple regression analysis was used to determine the relationship between serum prolactin and 2-h glucose levels. Multivariable regression analysis showed an independent and significant relationship between third trimester prolactin and 2-h glucose levels post oral glucose tolerance test. Higher prolactin levels were associated with higher glucose levels independent of age, body mass index, gravidity and parity. Higher prolactin levels associated with reduced glucose tolerance in the third trimester of pregnancy suggests the possible independent role of prolactin in the pathogenesis of gestational diabetes.

INTRODUCTION

Gestational diabetes is associated with adverse maternal, fetal and neonatal outcomes[1]. During pregnancy, the concentration of prolactin rises, under the influence of elevated oestrogen and progesterone levels[2,3]. The effect of prolactin on glucose metabolism during pregnancy is unknown. During pregnancy, a steady five- to tenfold rise in the plasma prolactin levels occurs[3].

The stimulating action of prolactin on the mammary gland leads to post-partum lactation, which is thought to be the main role for prolactin during pregnancy. Beside this lactogenic role, prolactin influences fertility, metabolism and immune regulation. Prolactin has been shown to have different effects on glucose metabolism depending on the physiological state. High prolactin levels exacerbate insulin resistance when elevated in a pathological context, such as in patients with diabetes mellitus or with pituitary prolactinoma[2]. Dopamine agonists, such as bromocriptine, that inhibit prolactin secretion are approved antihyperglycemic agents[4]. While the exact mechanism of action of this agent remains unclear, it is known that bromocriptine does not change insulin secretion or enhance insulin sensitivity in peripheral tissues. This implies that high prolactin levels have a potential independent role in inducing insulin resistance. However, in contrast to this, in *in vivo* studies, prolactin has been reported to induce insulin secretion and improve hepatic insulin sensitivity[4].

The association between serum prolactin and glucose might not be revealed until the third trimester of pregnancy, as insulin resistance is most prominent in the third trimester. Because of marked accelerated starvation and postprandial hyperglycemia in pregnancy, glucose intolerance is more pronounced on administration of a glucose load rather than through measurement of fasting blood sugar or 1-h post oral glucose tolerance test (OGTT) serum glucose. We, therefore, aimed to evaluate the relationship between gestational glucose tolerance and prolactin levels in a prospective study of healthy pregnant women. We hypothesised that higher maternal serum prolactin levels in the third trimester are associated with reduced glucose tolerance, as determined by the 2-h glucose level of the OGTT.

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Table 1 | Baseline characteristics of the study participants

	n = 69
Age (years)	31.2 ± 4.86
BMI (kg/m^2)	26.52 ± 6.41
Gravidity	2.63 ± 1.40
Parity	0.96 ± 1.01

Data presented as mean ± standard deviation. BMI, body mass index.

METHODS

Study participants

The present study population represents a cohort of healthy pregnant women, recruited for a prospective, longitudinal study to determine trimester and method-specific reference intervals for thyroid function tests[5].

Pregnant women, at or before 13 weeks' gestation, who presented to the Mercy Hospital for Women, Melbourne, Australia, were recruited between May 2006 and February 2011 for the present prospective, observational study. Exclusion criteria included a past medical history of pituitary or thyroid disease, diabetes mellitus and the presence of major systemic illnesses. Baseline characteristics, such as age, body mass index (BMI), gravidity and parity, were collected at the time of enrollment into the study. This project was approved by the Mercy Hospital for Women Ethics Committee (MHAC HREC Project Reference Number: R06/R07), and written informed consent was obtained from each participant.

Study design

Blood samples (20 mL each) were taken at 35–39 weeks of gestation to represent trimester 3. All serum specimens were frozen after collection and prolactin levels were measured at the conclusion of the study.

A standard, 75-g OGTT was carried out at approximately 28 weeks of gestation (date confirmed by ultrasound) in accordance with Mercy Hospital for Women universal gestational diabetes mellitus screening policy and the Australian Diabetes in Pregnancy Society guidelines. Women fasted for 12 h before the initiation of the OGTT. Venous blood was then sampled at 0-, 1- and 2-h time-points after administration of the 75-g oral glucose load. Based on the International Association of Diabetes and Pregnancy[6] guidelines, gestational diabetes mellitus was diagnosed when one or more of the glucose values equalled or exceeded 5.1, 10.0 and 8.5 mmol/L for 0-, 1- and 2-h time-points after a 75-g oral glucose load, respectively.

Assay methods

Serum prolactin concentrations were measured by the electrochemiluminescence immunoassay using a Roche e602 autoanalyzer (Roche, Indianapolis, Indiana, USA). Traditional immunoassay techniques for the measurement of prolactin levels are susceptible to generating false positive results due to the interference caused by macroprolactin. Macroprolactin, which is a high molecular mass prolactin, is immunologically reactive but predominantly inactive *in vivo*, and hence has no clinical significance[7]. To eliminate this, prolactin levels were measured using the Elecsys® Prolactin II assay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland), which is minimally reactive with most forms of macroprolactin[8].

Statistical analysis

Because of the skewed nature of the distribution of serum prolactin values and 2-h glucose levels post-OGTT, median regression analysis was used to investigate the association between 2-h glucose and prolactin levels, with age, BMI, gravidity and parity entered in the model as covariates. Gravidity and parity were included in the statistical model because of the previously

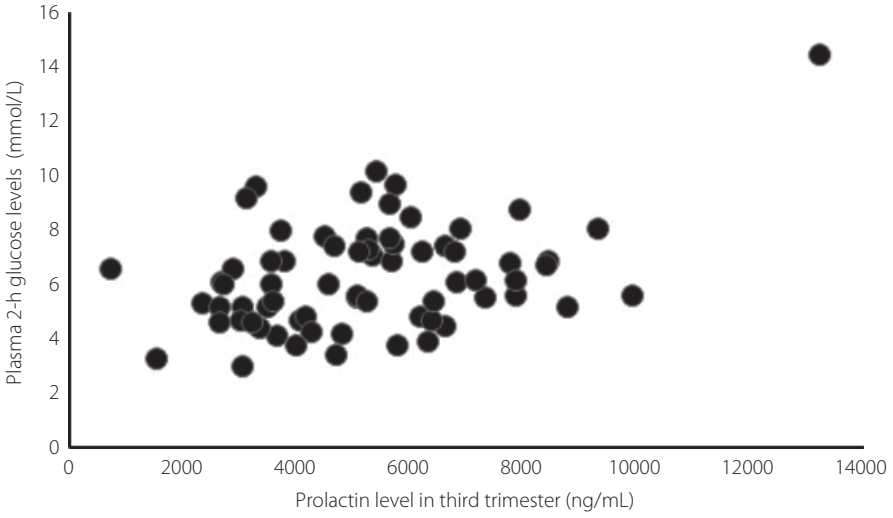

Figure 1 | The association between prolactin levels and serum 2-h glucose levels after a 75-g oral glucose tolerance test in the third trimester in pregnant women (*n* = 69).

established relationship between serum prolactin levels and gravidity[9], and parity[10]. Age and BMI were included in the statistical model, as they have been shown to be predictive of the risk of developing gestational diabetes[11]. The statistical analysis was carried out using Stata IC v13 statistical software (StataCorp Inc, College Station, Texas, USA). *P*-values of <0.05 were regarded as indicative of statistical significance.

RESULTS

Out of the 154 participants originally recruited, 69 had sufficient sample to determine the correlation between 28-week 2-h serum glucose levels post-OGTT results and third trimester prolactin levels.

At baseline, the mean age of participants was 31.3 years, BMI was 26.5 kg/m^2, gravidity was 2.6 and parity was 0.9 (Table 1). There was no significant difference between the baseline characteristics of participants who developed gestational diabetes mellitus and those who did not.

Using the median regression model, there was a statistically significant independent relationship between third trimester maternal prolactin and 2-h glucose levels post-OGTT, adjusted for age, gravidity, parity and BMI. Specifically, assuming a similar age, gravidity, parity and BMI, an increase of 1,000 units (ng/mL) in prolactin was associated with a median increase in 2-h post-OGTT glucose levels of 0.34 mmol/L (95% confidence interval 0.01–0.69, $P = 0.04$; Figure 1).

DISCUSSION

We found higher third trimester prolactin levels to be independently associated with reduced glucose tolerance as determined from the results of the 2-h glucose levels post-OGTT.

Insulin resistance, most prominent in the third trimester of pregnancy, is a well-recognized and normal physiological adaption in pregnancy, and up to a particular level, is believed advantageous to ensure adequate delivery of nutrients, in particular, glucose, to a rapidly growing fetus.

Although the findings of the present study confirm previous suggestions that prolactin has metabolic impacts beyond lactation, we propose that high levels of prolactin might contribute to pregnancy-induced hyperglycemia. It has been shown that the effect of prolactin on glucose metabolism and insulin resistance depends on prolactin concentration in the non-pregnant population[12]. Although high levels of prolactin in patients with prolactinomas and diabetes mellitus have been shown to be associated with insulin resistance and hyperglycemia, physiologically elevated prolactin levels are proposed to expand β-cell mass and improve insulin sensitivity[12].

Dopamine agonists, such as bromocriptine and possibly cabergoline, have shown improvements in metabolic parameters, such as glycemic control and lipid profile, in patients with type 2 diabetes mellitus and prolactinoma[13]. Suppressed glucose production, enhanced splanchnic glucose uptake after oral intake and possibly a direct effect on the hypothalamus are potential mechanisms for this[13].

The current study is the first study with a larger number of participants to show that higher prolactin levels to be associated with reduced glucose tolerance during pregnancy. Although no relationship was previously seen between prolactin levels and the risk of gestational diabetes[3], the small sample size of <40 might have led to negative findings in that study.

The current study was limited by its observational nature and as such being hypothesis generating. Further study is, therefore, necessary to elucidate the nature of this relationship between prolactin levels and the risk of development of gestational diabetes.

In conclusion, we showed that higher prolactin levels were associated with reduced glucose tolerance in the third trimester of pregnancy, suggesting a possible independent role of prolactin in the pathogenesis of gestational diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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