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Maternal circulating adipokine profile and insulin resistance in women at high risk of developing gestational diabetes mellitus

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ABSTRACT

Background. Cytokines produced by adipose and placental tissues (adipokines) have been implicated in the development of gestational diabetes mellitus (GDM). There is, however, limited research regarding the relationship between advancing pregnancy, maternal adipokine profile, insulin resistance and the development of GDM. Furthermore, no studies have investigated these parameters in women with a history of GDM who are at the highest risk of recurrence. This study examined the circulating concentrations of a number of adipokines associated with insulin resistance at two points in pregnancy, and determined whether they were altered in women who developed GDM.

Methods. Non-diabetic women with a history of GDM in a previous pregnancy (n = 123) had blood drawn at 14 and 28 weeks of pregnancy for GDM diagnosis, together with assessment of a range of adipokine concentrations by multiplex assay (fatty acid-binding protein 4 [FABP4], leptin, chemerin, adiponectin and resistin).

Results. With advancing pregnancy, maternal adiponectin concentrations decreased, while leptin and resistin levels increased ($p < 0.05$). In women who developed GDM at 28 weeks of pregnancy (42%), fasting and postprandial glucose levels were already significantly elevated by 14 weeks ($p < 0.05$), while adiponectin concentrations were lower ($p < 0.05$). Adiponectin remained lower at the time of GDM diagnosis ($p < 0.05$), while the other adipokines were similar between groups at each timepoint.

Conclusion. Maternal glucose and adipokine profile is altered early in pregnancy in women with a history of GDM who subsequently develop recurrent disease.

1. Introduction

Gestational diabetes mellitus (GDM) affects up to 28% of pregnancies worldwide [1] and the prevalence is increasing [2]. This is of great concern given the serious health consequences of the condition for the woman and her offspring [3]. These include acute complications with pregnancy, labour and delivery, but also extend to the years that

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follow, with increased risk of type 2 diabetes and metabolic syndrome in later life. Furthermore, women with a history of GDM have a high rate of recurrence, with 48% of subsequent pregnancies affected [4]. Accordingly, early identification of the risk of GDM is vital to ensure appropriate management to minimise adverse effects.

The risk of GDM is increased in overweight and obese women [5]. This risk may be related, at least in part, to immunomodulatory factors (adipokines) released from adipose tissue, which have been shown to increase systemic inflammation and contribute to insulin resistance [6]. Many of these adipokines are produced in altered amounts in pregnancy and may be implicated in the development of glucose intolerance and GDM. For instance, the concentrations of leptin, adiponectin and visfatin in early pregnancy have been reported to be predictive of GDM later in pregnancy [7–9]. Other novel adipokines, including fatty acid-binding protein 4 (FABP4), chemerin and resistin, have also been implicated in the development of GDM [10–12]. However, the literature regarding the roles and biological significance of many of these adipokines is inconsistent, prospective studies are lacking, and most research is limited to studies with small sample sizes focused on one or two markers in isolation, rather than the consideration of multiple adipokines simultaneously. More specifically, no research to date has examined the behaviour of these adipokines in women with a history of GDM who are at the highest risk of GDM recurrence.

Given the lack of research regarding the relationship between advancing gestation, maternal adipokine profile, insulin resistance and the development of GDM, the aims of the present investigation were to examine the maternal circulating concentrations of the key adipokines associated with insulin resistance pre- and post-GDM diagnosis, and to determine whether maternal concentrations of these factors reflect early signs of insulin resistance, or are altered in early pregnancy in women who subsequently develop GDM. These issues were addressed in women with a history of GDM in a previous pregnancy given their high risk of recurrence. Studying the patterns of change in these biomarkers may assist in establishing a clinical profile for identifying women at high risk of GDM recurrence.

2. Methods

In our previously reported randomised controlled trial (NCT01283854), women with a history of GDM in a prior pregnancy were randomised (with stratification by maternal age and body mass index [BMI]) between 12 and 14 weeks of pregnancy to a 14 week supervised home-based exercise intervention or to a control group. Full details of the trial, exercise intervention and primary outcomes were described previously [13]. Briefly, the exercise intervention involved three sessions per week of supervised stationary cycling until 28 weeks of pregnancy. Exclusion criteria were pre-existing diabetes, cardiac disease, multiple pregnancy or a medical condition that restricted exercise participation. The study was approved by Women and Newborn Health Service Ethics Committee and all women provided written informed consent.

The primary outcome of the trial was a diagnosis of GDM based on the criteria adopted in Western Australia at the time of the study (fasting venous blood glucose ≥5.5 mmol/L [99 mg/dl] and/or a 2 h OGTT glucose ≥8.0 mmol/L [144 mg/dl]). A range of other outcome measures were assessed at recruitment at 12–14 weeks of pregnancy (pre-intervention) and at 28 weeks of pregnancy (post-intervention). These included a 75 g oral glucose tolerance test (OGTT) performed in the fasted state from which fasting glucose and insulin concentrations, together with glucose tolerance and insulin sensitivity could be assessed. In addition to the main outcomes reported in the trial, blood serum collected in the fasted state at the OGTT was stored for a random subset of participants (n = 123), allowing for the subsequent analysis of a range of factors associated with insulin resistance including FABP4, leptin, chemerin, adiponectin and resistin. These additional analyses conducted for the present investigation were performed using commercially available multiplex assay kits (R&D systems, Bio-Techne, Minneapolis, MN, USA) using the Luminex MAGPIX system (Luminex Corporation, Austin, TX, USA) as per manufacturer's instructions. The assessment of adipokines using multiplex technology has been well validated [14,15]. The intra-assay coefficient of variation was 6.9%, 2.4%, 2.6%, 2.2% and 2.6% for FABP4, leptin, chemerin, adiponectin and resistin, respectively. All samples were analysed in two batches with an inter-assay coefficient of variation of 13%, 8%, 16%, 13% and 3% for FABP4, leptin, chemerin, adiponectin and resistin, respectively. The limits of detection of the FABP4, leptin, chemerin, adiponectin and resistin assays were 0.77, 0.25, 0.25, 0.5 and 0.01 ng/ml. For FABP, 24% of samples were below the limits of detection. These values were replaced with the value of the limit of detection divided by the square root of 2.

2.1. *Statistical Analyses*

Continuous data were summarised using means and standard deviation (maternal age, BMI and blood glucose), or medians and interquartile ranges (maternal insulin and adipokines), depending on data normality. Women randomised to the exercise and control groups in the original trial were well matched for age, BMI and baseline glucose tolerance, with no difference between groups. There was no effect of the exercise intervention on the recurrence of GDM [13], nor did it alter the circulating concentrations of the cohort of adipokines measured here based on repeated measures analysis of variance. Therefore, subsequent data were examined independent of group allocation. The effect of advancing pregnancy (14 versus 28 weeks) on maternal adipokine profile was assessed using Wilcoxon signed ranks tests based on data normality. The metabolic profile of women who developed GDM was compared with women who did not develop GDM at both 14 and 28 weeks of pregnancy using independent samples *t*-tests (blood glucose) or Mann-Whitney *U* tests (insulin, adipokines) depending on data normality. In addition, relationships between maternal adipokine concentrations and other indicators of insulin resistance (glucose and insulin area under the curve [AUC] in response to the 75 g OGTT, together with the homeostatic model of assessment (HOMA) [16] and BMI, were evaluated