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Adipokines and Insulin Resistance According to Characteristics of Pregnant Women with Gestational Diabetes Mellitus (*Diabetes Metab J* 2017;41:457-65)

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Gestational diabetes mellitus (GDM) is defined when diabetes is first diagnosed during the second or third trimester of pregnancy without overt diabetes mellitus (DM) prior to gestation [1]. Prevalence has been increasing over the past decades, possibly due to increases in mean maternal age and obesity epidemic in Korea, the prevalence has reached 11.8% in 2010 [2]. The clinical implications of GDM are primarily associated with adverse outcomes in pregnancy, such as preeclampsia, Cesarean delivery, macrosomia, and birth injury [3]. In addition, GDM has long-term consequences both for the mother and her offspring, including the development of metabolic syndrome, type 2 DM, and cardiovascular diseases [4]. Therefore, detection of GDM is important to minimize the risk of poor pregnancy outcomes and to predict and manage the risk of metabolic complications in later life.

Pregnancy is accompanied by insulin resistance, which begins in the second trimester and peaks in the third trimester, mediated primarily by placental secretion of diabetogenic hormones including growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone [5]. These metabolic changes ensure that the fetus has a sufficient supply of nutrients for growth. GDM develops during pregnancy in women whose pancreatic β-cell function is insufficient to overcome the insulin resistance during pregnancy [6]. It is well-known that the risk of GDM increases in women who are overweight/obese in pre-pregnancy or excessively gain weight during early pregnancy [7]. Therefore, many studies have focused on the role of adiposity in GDM.

Adipose tissue is an endocrine organ that secretes various proteins (leptin, adiponectin, resistin, etc.) that are collectively called adipokines. Adipokines have an important role in the regulation of insulin resistance by mediating crosstalk between insulin-sensitive tissues. Leptin plays a key role in the regulation of energy intake, expenditure, and circulating leptin levels are positively related to insulin resistance. Adiponectin has potent insulin-sensitizing properties and enhances insulin secretion. They are also produced in placenta during pregnancy [8]. Recent studies have assessed the role of adipokines in GDM pathogenesis. During pregnancy, there is a significant increase in leptin and decrease in adiponectin than compared with non-pregnant state. Also, adiponectin levels are lower in the first or second trimester of pregnancy among women who later develop GDM than non-GDM women, whereas leptin levels are higher [9].

In Korea, Oh et al. [10] reported the role of adipokines in the development of gestational glucose intolerance. They studied 129 pregnant women who received 100 g oral glucose tolerance test during the 24th to 28th weeks of gestation. They compared the concentrations of adipokines in women with GDM and normal glucose tolerance (NGT). Pregnant subjects with

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NGT were matched with non-pregnant controls for pre-pregnancy body mass index (BMI) and age. Pregnant women with NGT exhibited significantly decreased adiponectin levels and elevated leptin levels compared with non-pregnant controls. Meanwhile, mean plasma resistin level was significantly higher in women with GDM than in women with NGT. Recently, in the retrospective study by Jeon et al. [11], they reported the features of adipokines and insulin resistance according to the well-known risk factors of GDM such as pre-pregnancy BMI (<25 kg/m^2 vs. ≥25 kg/m^2), maternal age at pregnancy (<35 years old vs. ≥35 years old), and weight change from pre-pregnancy to GDM screening period (24th to 28th weeks of gestation) according to 2009 Institute of Medicine gestational weight gain (GWG) category (weight gain below, within, and in excess of the recommended range) in 59 pregnant women with GDM. Leptin, homeostasis model assessment of insulin resistance (HOMA-IR), and HOMA2-%B (β-cell function) at diagnosed GDM were increased in the GDM with obesity (BMI ≥25 kg/m^2) before pregnancy. Leptin and HOMA-IR were positively correlated with BMI both before pregnancy and at screening for GDM. The correlations between adipokines and insulin resistance were not statistically significant. The significance of maternal age at pregnancy and weight change during pregnancy at GDM screening on adipokines and insulin resistance might be less pronounced in this study.

However, this study has some limitations to be considered in evaluating the roles of adipokines and insulin resistance in GDM. To assess the role of adipokines in GDM, it might be better to compare adipokines concentration in pregnant women with GDM and NGT matched for pre-pregnancy BMI and age. Weight change category (below, within, and in excess of the recommended range) during pregnancy at GDM screening was also not related to adipokines and insulin resistance in this study. Cho et al. [12] showed that early pregnancy (from pre-pregnancy to the screening test for fetal anomaly) rate of gestational weight gain (RGWG) is highly associated with the development of adverse pregnancy outcomes including GDM in normal pre-pregnancy BMI (18.5≤ BMI <25.0 kg/m^2) group. Therefore, it might be better to analyze the relationship between RGWG in early pregnancy and adipokines or insulin resistance according to pre-pregnancy BMI (BMI <25 or ≥25 kg/m^2). In this study, more than half (31/57) of GDM subjects had pre-pregnancy BMI <25 kg/m^2. If we consider that GDM develops when pancreatic β-cells of pregnant women are incapable of secreting insulin sufficiently to counteract the corresponding fall in tissue sensitivity to insulin during pregnancy, the biochemical (adipokines, insulin secretion, and insulin resistance) characteristics of non-obese GDM group should be compared with non-obese NGT group or non-obese non-pregnant group matched for pre-pregnancy BMI and age.

GDM is an early indicator of underlying defects in insulin sensitivity or secretion that are unmasked during pregnancy. Identifying women with GDM is important not only to minimize maternal and neonatal morbidity but also to prevent long-term metabolic and vascular diseases. This study retrospectively investigated adipokines and insulin resistance in GDM. In the future, well-designed prospective studies with longitudinal assessment of adipokines and insulin resistance during pregnancy are needed to understand the dynamic roles of adipokines and insulin resistance in GDM pathogenesis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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