

Hormonal Effect in Normal and Diabetic Pregnancy

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Abstract

Gestational Diabetes Mellitus is carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy. The predominant pathogenic factor in GDM could be inadequate insulin secretion. It has been convincingly demonstrated that GDM occurs as a result of combination of insulin resistance and decreased insulin secretion. Pregnancy is associated with profound hormonal changes that have a direct effect on carbohydrate tolerance. In early pregnancy, both progesterone and estrogen levels rise, but their action on insulin is counterbalanced, as progesterone causes insulin resistance

and estrogen is protective. In the second trimester, HPL, cortisol and prolactin levels all rise, causing decreased phosphorylation of IRS-1 and profound insulin resistance. In most subjects, pancreatic insulin secretion rise to meet this need, but in those with underlying beta-cell defects, hyperglycemia ensues. In women with GDM, the insulin resistance of pregnancy is exaggerated, especially if fasting hyperglycemia is present, and is related to additional defective tyrosine phosphorylation of the insulin receptor beta-subunit.

Keywords: *insulin resistance, gestational diabetes, human hormones*

Introduction

Pregnancy is a period marked by profound changes in a woman's hormonal status and metabolism. The ability to regulate nutrient balance during this period is critical to the health of the mother and the growing fetus. Insulin is one of the key regulators of metabolism. The cellular mediators of insulin resistance in late pregnancy have long been ascribed to alterations in cortisol and placental-derived hor-

mones including human placental lactogen (HPL), progesterone and estrogen^(1,2). Although pregnancy is a carbohydrate-intolerant state, only a small proportion of pregnant women (3-5%) develop gestational diabetes mellitus (GDM). As pregnancy advances, the increasing tissue resistance to insulin creates a demand for more insulin. In the great majority of women, insulin requirements are readily met, so the balance between insulin resistance and

insulin supply is maintained. However, if resistance becomes dominant due to impaired insulin secretion, hyperglycemia develops. In the majority of such cases, it develops in the last half of pregnancy, with insulin resistance increasing progressively until delivery, when, in most cases, it rapidly disappears.

Historically, placental hormones are considered the primary mediators of insulin resistance during gestation^(1,2,3). The concept of insulin

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resistance during pregnancy is easy to understand but quantitative assessment of insulin sensitivity, which is the reverse of resistance and the ability to determine exactly who is insulin resistant is more difficult in a clinical setting.

Estrogen and progesterone

In early pregnancy, both progesterone and estrogen rise but their effects on insulin activity are counterbalanced. Progesterone causes insulin resistance whereas estrogen is protective⁽³⁾. An IVGTT test (Intravenous Glucose Tolerance Test) given to estrogen-treated rats showed a significant decrease in glucose concentrations and a twofold increase in insulin concentration⁽⁴⁾; the addition of progesterone was associated with a 70% increase in the insulin response to a glucose challenge test, but there were alterations in glucose tolerance⁽⁵⁾. In cultured rat adipocyte tissue treated with estrogen, there was no effect on glucose transport, but maximum insulin binding was increased. However, progesterone decreased both maximum transport and insulin binding. During late pregnancy, when both plasma concentrations of 17 β -estradiol and progesterone are high, the role of 17- β -estradiol may serve to antagonize the effect of progesterone, diminishing insulin sensitivity⁽⁶⁾.

Cortisol

Cortisol levels increase as pregnancy advances and by the end of pregnancy concentrations are threefold higher than in the non-pregnant state⁽⁷⁾. Rizza et al⁽⁸⁾, in a clamp study, demonstrated that under infusion of high amounts of cortisol, hepatic glucose production increased and insulin sensitivity decreased. Findings in a skeletal muscle model showed that an excess of glucocorticoid is characterized by decreased total tyrosine phosphorylation of the insulin receptor; therefore, it seems logical that glucocorticoid-induced insulin resistance is related to a post-receptor mechanism.

In a study by Ahmed and Shalayel, 30 pregnant women with GDM and 30 pregnant women with impaired glucose tolerance (IGT) were compared with 30 pregnant women with normal glucose tolerance: the GDM and IGT groups were found to have significantly higher levels of serum cortisol than the control group⁽⁹⁾.

Prolactin

During pregnancy, maternal prolactin levels increase seven to ten fold. Gustafson et al reported that the basal insulin concentration, and post-challenge glucose and insulin responses were greater in women with hyperprolactinemia than in healthy controls⁽¹⁰⁾. Skouby et al investigated the relationship between the deterioration in glucose

tolerance and plasma prolactin levels in patients with normal and diabetic pregnancies and he concluded that there was no correlation between these in either group⁽¹¹⁾. The prolactin levels were also not altered during the OGTT tolerance tests, and there was no correlation between the deterioration in glucose tolerance and the prolactin concentrations in either group. Thus, abnormal prolactin levels are not of any physiopathological importance in the development of GDM.

Human placental lactogen

Human placental lactogen levels rise at beginning of the second trimester, causing a decrease in phosphorylation of insulin receptor substrate (IRS)-1 and profound insulin resistance⁽¹²⁾. Beck and Daughday⁽¹³⁾ demonstrated the overnight infusion of HPL results in abnormal glucose tolerance, and increased insulin and glucose concentration in response to an oral glucose challenge. Brelje et al found that in islet cell culture, HPL directly stimulates insulin secretion⁽¹⁴⁾. This may indicate that HPL directly regulates islet cell function and is probably the principal hormone responsible for the increase in islet function observed during normal pregnancy.

Leptin

Leptin is a 16 kDa protein encoded by the ob/ob (obesity) gene secreted by adipocyte tissue. It can modulate energy expenditure by direct action on the hypothalamus. Fasting insulin and leptin concentrations correlate closely with body fat, making leptin a good marker of obesity and insulin resistance. As receptors to leptin are found in skeletal muscle, the liver, the pancreas, adipocyte tissue, the uterus and placenta, it may be responsible for both peripheral and central insulin resistance. Leptin levels are significantly higher in pregnancy than in the non-pregnant state, especially during the second and third trimesters^(15,16). Vitoratos et al⁽¹⁷⁾ investigated the changes in leptin levels and the relationship between leptin substance and insulin and glucose in pregnant women with GDM. Plasma leptin levels were measured in peripheral vein blood samples from healthy and diabetic women at 29 and

33 weeks gestation results showed a correlation of plasma leptin levels with fasting plasma insulin levels and plasma glucose levels measured one hour after oral administration of 50 grams of glucose. Serum leptin levels were significantly higher in the women with GDM than in the women with uncomplicated pregnancies. The GDM group also showed a significant, positive correlation of serum of leptin levels with glycosylated hemoglobin levels, fasting serum insulin levels and plasma glucose levels measured one hour after administration of 50 grams of glucose. Thus, levels of leptin are elevated in women with GDM, and leptin metabolism depends on insulin levels and the severity of the diabetes.

Yamashita et al⁽¹⁸⁾ suggested that an alteration in leptin action might play a role in GDM and fetal overgrowth weight gain. They found that pregnant mice treated with leptin had markedly lower glucose levels than controls during glucose and insulin challenge tests. However, despite the reduced energy

intake and improved glucose tolerance, fetal overgrowth was not reduced. Results provide evidence that leptin administration during late gestation can reduce adiposity and improve glucose tolerance in the model of spontaneous GDM. These data suggest that alterations in placental leptin levels may contribute to the regulation of fetal growth independently of maternal glucose levels.

Adrenomedullin

Adrenomedullin is a newly discovered hypotensive peptide involved in the insulin regulatory system and it may play a role in modifying diabetes in pregnancy. Adrenomedullin concentrations were measured in maternal and fetal plasma, and in amniotic fluid in diabetic and non-diabetic pregnancies. Overall amniotic fluid concentration was higher in the pregnant diabetic women (Type 1 or GDM) but there was no between group difference in maternal and fetal plasma levels. These findings suggest that placental adrenomedullin production is upregulated in diabetic

pregnancy and that it may be important to prevent excessive vasoconstriction of placental vessels⁽¹⁹⁾.

Conclusions

These data suggest that whereas the placental hormones and cortisol have specific functions in the mother and feto-placental unit, their association with maternal insulin resistance is limited (placental growth hormone not assessed). However, this does not preclude the possibility that these hormones can play a permissive role in insulin resistance in pregnancy by potentiating the effects of more direct mediators. Alternatively, these hormones could have an effect on other non-placental-derived mediators of insulin resistance such as some mediators of inflammation: indeed, because TNF α has been implicated in the regulation of glucose and lipid metabolism, and in insulin resistance, there are data that are consistent with the hypothesis that TNF α is involved in the pathogenesis and/or progression of GDM⁽¹⁹⁾. ■

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