Review

Etiology and Pathophysiology of Gestational Diabetes Mellitus

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SUMMARY

In pregnancy, several physiologic changes take place, the sum of which tends to reset the glucose homeostasis in the direction of diabetes. About 1–2% of all pregnant women develop an abnormal glucose tolerance in pregnancy, but most often glucose tolerance returns to normal postpartum. This condition is called gestational diabetes mellitus (GDM). The possibility that glucose tolerance deteriorates in pregnancy because of diabetes-like changes in the secretory function of the endocrine pancreas has been investigated in healthy controls and in normal-weight gestational diabetic subjects. The insulin responses to oral glucose and mixed meals are equally large in these two groups, but the insulin response per unit of glycemic stimulus is significantly lower in the gestational diabetic subjects than in the controls. Diabetes-like changes in glucagon secretion are not observed in either group. Insulin degradation is unaffected by human pregnancy and the proinsulin share of the total plasma insulin immunoreactivity does not increase in pregnancy. Insulin receptor binding to monocytes from normal pregnant women is increased in midpregnancy but is significantly decreased in late pregnancy. No difference in insulin binding (at tracer insulin concentration) to monocytes from healthy pregnant controls and gestational diabetic subjects is found. The insulin concentration necessary to reduce tracer insulin binding by 50% (ID_{50}) is lower in the gestational diabetic subjects diagnosed in late pregnancy than in the pregnant controls. Together, these findings indicate that the number of insulin receptors on monocytes is decreased in GDM at this stage of pregnancy. Thus, the cause of GDM could be a decreased insulin receptor binding to target cells combined with a relative lack of circulating insulin, but the possibility of postreceptor defects does also exist.

DIABETES 1985; 34 (Suppl. 2):66–70.

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During normal pregnancy, a gradual deterioration of glucose tolerance takes place so that the plasma glucose values after, for instance, a glucose load or a meal are higher than outside pregnancy.[1,2] In most normal pregnant women, glucose tolerance stays within the normal range, but in 1–2% it deteriorates sufficiently for the diagnostic criteria of diabetes mellitus to be fulfilled.[3] If the fasting glucose concentration in pregnancy remains normal and the oral glucose tolerance test (OGTT) returns to normal postpartum, the condition is termed gestational diabetes mellitus (GDM).[4]

The glucose intolerance of GDM is usually mild, but nevertheless it means a higher incidence of complications during pregnancy[5] and, in some cases, an increased perinatal mortality and morbidity of the infants.[6] As well, GDM also considerably increases the woman's risk of developing manifest diabetes later in life.[7] Thus, it is important to recognize and to treat this disease.

An unavoidable prerequisite for rational treatment of GDM is a significant knowledge of the pathophysiologic background for the condition. Why pregnancy is capable of inducing this temporary diabetic state is still partly unknown. Among the possible explanations are reduced insulin secretion, increased insulin degradation, increased secretion of hormones with an anti-insulin effect (particularly glucagon, human placental lactogen [HPL], estrogens, progesterone, and cortisol), reduced tissue sensitivity to insulin, or a combination of two or more of these mechanisms.

In this review, we will compare aspects of carbohydrate metabolism in normal pregnant women and in normal-weight, gestational diabetic subjects. We consider an OGTT diabetic if at least two of the glucose values exceed the mean ± 3 SD curve pertaining to a group of 46 nonpregnant, nonpotentially diabetic women who have been investigated by exactly the same procedure.[1] These criteria correspond closely to those advocated by the National Diabetes Data Group.[8]

INSULIN AND PROINSULIN SECRETION IN PREGNANCY

In late pregnancy, the fasting serum insulin concentration is almost twice as high as postpartum, both in normal pregnant women and in gestational diabetic subjects.[1,2,9-12] Normal pregnant women and gestational diabetic subjects have comparable fasting insulin levels,[11,12] and fasting serum proinsulin is also similarly elevated in late pregnancy in both groups.[13,14] During gestation, however, serum insulin rises in parallel with proinsulin in both groups, for which reason the proportion of total insulin immunoreactivity constituted by proinsulin remains constant.[13,14]

During an OGTT, higher insulin levels are reached in the late-normal and in the GDM pregnancy when compared with postpartum (Figure 1).[1,9-12] However, even though the insulin responses in absolute terms are almost similar in the normal women and in the gestational diabetic subjects, the insulin response per unit of glycemic stimulus (the insulinogenic index) is significantly greater in the normal pregnant women than in the gestational diabetic subjects.[11]

The insulin response to oral glucose is not increased in late pregnancy only as a result of the higher prevailing serum glucose levels. Thus, the insulinogenic index is increased by about 90% and 40% in late-normal and in GDM pregnancy, respectively.[11] Moreover, when glucose is infused intravenously (i.v.) at rates that result in identical elevations of plasma glucose in normal and gestational diabetic women in late pregnancy and postpartum, the insulin response is found to be increased approximately four times in normal late pregnancy[15] and approximately three times in late GDM pregnancy[16] when compared with postpartum.

The ingestion of a protein-rich meal or single amino acids in solution elicits considerably increased insulin responses in late-normal[17-19] and in GDM pregnancy.[20] In response to identical protein-rich meals, normal pregnant women exhibit greater increments in insulin responses compared with postpartum than those found in gestational diabetic subjects (Figure 1).[19,20] However, due to the pregnancy-associated retardation in the absorption of a mixed meal, it is difficult to directly compare the insulin responses obtained in pregnancy and postpartum. This problem has been circumvented by the i.v. infusion of appropriate quantities of a solution of amino acids. In both normal pregnant women and in gestational diabetic subjects, almost identical plasma amino acid concentration curves were obtained in late pregnancy and postpartum.[21] The insulin response to amino acids was significantly increased in late pregnancy in both groups.[21]

After the ingestion of triglycerides, plasma insulin remained unchanged in normal pregnant women and in gestational diabetic subjects (Figure 1).[22]

These results demonstrate that the beta cell sensitivity to glucose and amino acids, but not to lipids, is significantly enhanced in pregnancy. The insulin-secretory capacity of normal-weight gestational diabetic subjects is generally less than that of normal pregnant women. As well, gestational diabetic women exhibit an increased insulin response to oral glucose and amino acids when compared with postpartum, so they are only relatively insulin-deficient in pregnancy compared with normal pregnant controls.

Recent human[23,24] studies have demonstrated that insulin degradation is unaffected by pregnancy. The decrease in glucose tolerance in gestation cannot, therefore, be ascribed to an acceleration of insulin degradation in this state.

GLUCAGON SECRETION IN PREGNANCY

Glucagon secretion is often abnormal in diabetic patients, for which reason it has been proposed that glucagon plays an essential role in the pathogenesis of diabetes.

Fasting plasma glucagon is slightly but significantly in-

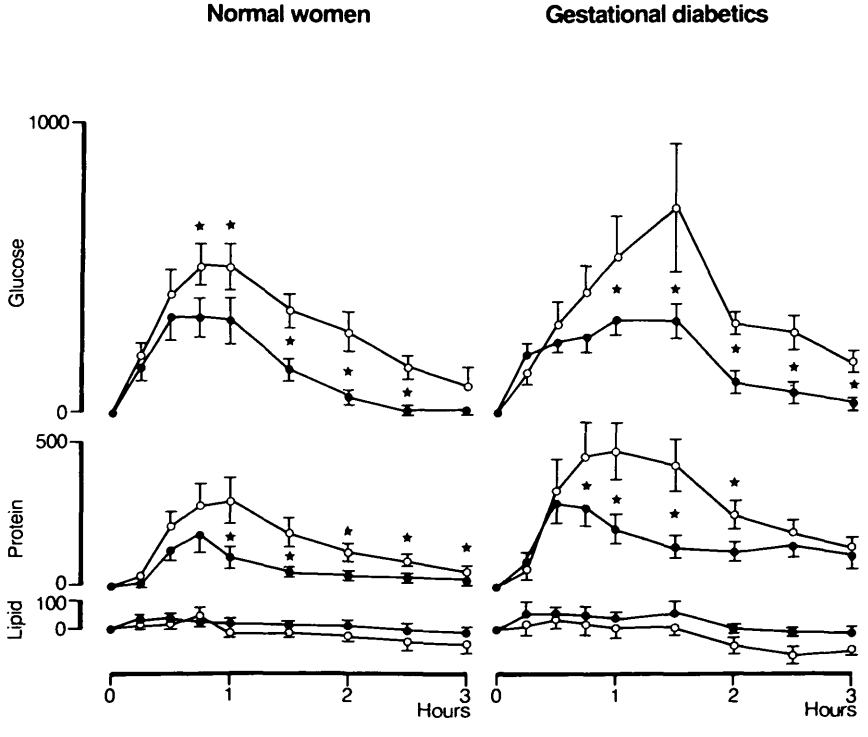

FIGURE 1. Plasma insulin responses (pmol/L) to the ingestion of a 50-g oral glucose load, a protein-rich meal, and a 67-g oral triglyceride load in pregnancy (open circles) and postpartum (closed circles) in normal women and in normal weight gestational diabetic subjects. Asterisks indicate significance of differences between findings in pregnancy and postpartum. Adapted from refs. 12, 19, 20, and 22.

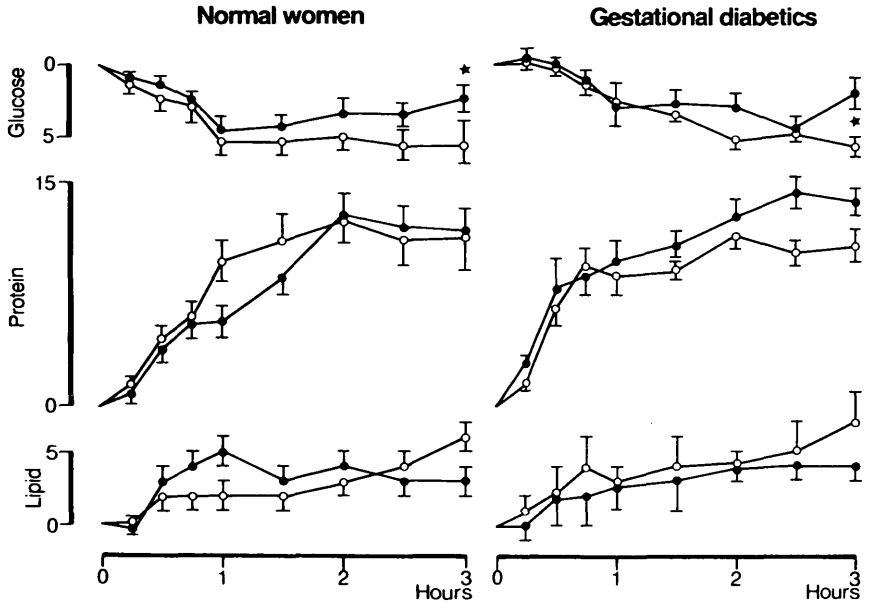

FIGURE 2. Plasma glucagon responses (pmol/L) to the ingestion of a 50-g oral glucose load, a protein-rich meal, and a 67-g oral triglyceride load in pregnancy (open circles) and postpartum (closed circles) in normal women and in normal weight gestational diabetic subjects. Asterisks indicate significance of difference between findings in pregnancy and postpartum. Adapted from refs. 12, 19, 20, and 22.

creased in late-normal pregnancy.[2,11,12,17,25] In late gestational diabetic pregnancy, fasting plasma glucagon has been reported to be either unchanged[11,18] or enhanced.[12,25] However, the fasting molar insulin:glucagon ratio is increased in late-normal and in gestational diabetic pregnancy,[11] whereas the opposite finding is a characteristic of insulin-dependent diabetes.

After oral glucose, glucagon suppression below fasting levels is either unchanged[25] or exaggerated[11,12] in late-normal and gestational diabetic pregnancy (Figure 2). These findings contrast the lack of suppressibility of glucagon during hyperglycemia found in nonpregnant diabetic subjects. The increased suppressibility of glucagon during hyperglycemia seems to be due to the higher plasma glucose levels reached after glucose administration in this state. Thus, if plasma glucose is similarly increased by graded i.v. glucose infusions in the same women in late pregnancy and postpartum, identical suppressions of plasma glucagon below the fasting levels are seen in normal women[15] and in gestational diabetic subjects.[16]

Oral intake of alanine elicited a greater rise in plasma glucagon in the normal women investigated in their late pregnancy as compared with postpartum.[18] Despite the rise in plasma glucagon, blood glucose remained unchanged at both occasions.[18] This is probably due to the concomitant increase in plasma insulin, which was much higher in pregnancy than postpartum.[18]

The glucagon response to a protein-rich meal has been reported to be either reduced[2] or unaffected[17,19] by normal pregnancy and to be unaffected by gestational diabetic pregnancy[20] (Figure 2). The discrepancies are probably due to the fact that meals often differ with regard to the content of protein, sugar, and fat. Moreover, glucose and fat may both modulate glucagon secretion after stimulation by the amino acid components of the ingested meal. More easily interpretable data have been obtained by graded i.v. amino acid infusions, which led to almost identical plasma amino acid levels in pregnancy and postpartum in normal and gestational diabetic women.[21] The glucagon responses were similar in pregnancy and postpartum in the normals, whereas in the gestational diabetic subjects, an enhanced glucagon response to amino acids was found in pregnancy as compared both to postpartum and to the pregnant normal women.[21] The physiologic implications of the higher glucagon levels reached in the gestational diabetic subjects after i.v. amino acids are unknown as is the reason why these differences in glucagon levels were not seen after the ingestion of a protein-rich meal.[19,20]

Oral intake of triglycerides does not influence plasma glucagon levels in normal pregnant women or gestational diabetic subjects (Figure 2).[22]

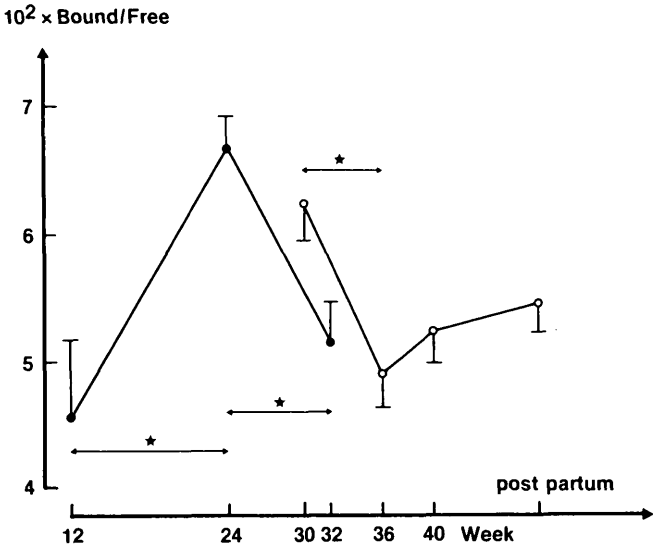

FIGURE 3. Insulin receptor binding (mean ± SEM) during normal human pregnancy. Maximal specific binding to monocytes is shown as the ratio between bound and free insulin at tracer insulin concentration (34 pmol/L). Five women were investigated at weeks 12, 24, and 32 of gestation (closed circles). Eight women were investigated at weeks 30–32 and 36 of gestation, at delivery, and postpartum (open circles). * Indicates $P < 0.05$.

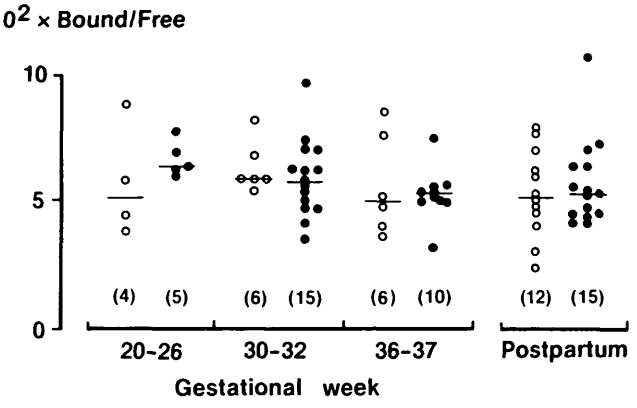

FIGURE 4. Insulin receptor binding in gestational diabetic women (open circles) and normal pregnant women (closed circles). Maximal specific binding to monocytes is shown as the ratio between bound and free insulin at tracer insulin concentration (34 pmol/L). The gestational diabetic women were investigated at the time of diagnosis when they were still on a normal full diet. Numbers are shown in parentheses and bars indicate medians.

An abnormal glucagon secretion in pregnancy is thus not involved in the pathogenesis of GDM. The pregnancy-associated changes in plasma glucagon concentrations together with those of plasma insulin are, on the other hand, well compatible with the maternal metabolic adaptations to pregnancy designated by Freinkel[26] as "accelerated starvation" in the fasting state and "facilitated anabolism" in the fed state.

INSULIN RESISTANCE IN PREGNANCY

In pregnancy, glucose tolerance deteriorates in spite of steadily increasing levels of insulin in plasma. This points to pregnancy as a state of insulin resistance.

The explanation for the insulin resistance in pregnancy is unknown. The available data on insulin receptor binding in normal pregnant women are conflicting. Increased insulin binding to monocytes,[27,28] unchanged binding to monocytes,[29] and decreased binding to monocytes[30] and to adipocytes[31] have been reported. In diet-treated gestational diabetic women, increased insulin binding to monocytes was recently found when compared with healthy pregnant controls,[27] whereas in insulin-treated gestational diabetic women, the insulin binding to adipocytes was decreased.[31] Data on insulin binding in untreated gestational diabetic subjects have thus far not been published.

In Copenhagen, a serial study of insulin receptor binding to monocytes in normal women investigated during pregnancy and postpartum and a study on insulin receptor binding to monocytes in untreated gestational diabetic subjects compared with nondiabetic pregnant controls have just been completed.

In the normal pregnant women, a significant increase in insulin receptor binding to monocytes was found in mid pregnancy; this was followed by a significant decrease in late pregnancy and probably again an increase postpartum (Figure 3). The insulin concentration necessary to reduce tracer insulin binding by 50% (ID_{50}) remained unchanged in the normal pregnant women. No differences in insulin binding at tracer insulin concentration to monocytes from gestational diabetic and normal pregnant women were found (Figure 4), but the ID_{50} was significantly lower in gestational diabetic women diagnosed in late pregnancy than in healthy pregnant women. Since the insulin binding at tracer insulin concentration was similar in the two groups, it seems that the number of insulin receptors on monocytes is decreased in women with GDM diagnosed late in pregnancy compared with normal pregnant controls. Thus, GDM could, at least partly, be the result of a decreased insulin receptor binding to target cells combined with a relative deficiency of circulating insulin. The existence of postreceptor defects is, however, also possible.

As glucose tolerance in pregnancy decreases in parallel with increasing levels of the pregnancy hormones and of cortisol, it has been suggested that one or more of these hormones might be implicated in bringing about alterations in carbohydrate metabolism.[32] The hyperinsulinemia of pregnancy would thus be an adaptive response of the pancreatic islets to a hormone-induced, insulin receptor- and/or postreceptor-mediated diminished tissue sensitivity to insulin. In this connection, we have mainly focused attention on the possible role of cortisol.

During a normal pregnancy, total and free plasma cortisol levels are increased.[33,34] Furthermore, the increases during normal pregnancy in total and free plasma cortisol concentrations and urinary cortisol excretion rates on one hand, and the deterioration of glucose tolerance on the other hand, are significantly positively correlated.[34] On the contrary, there is no correlation between the increase in cortisol levels or excretion rates and the changes in insulin and glucagon responses to glucose in pregnancy.[34] It is thus conceivable that cortisol influences carbohydrate metabolism in pregnancy through an action outside the endocrine pancreas.

CONCLUSIONS

The data presented in this review clearly point to pregnancy as a state of insulin resistance. The cellular basis for the insulin resistance of pregnancy and how it is brought about is not yet fully understood. Most pregnant women are able to counteract the insulin resistance in pregnancy by increasing their insulin secretion. However, when the capacity of insulin secretion is not sufficiently large to meet the resistance, glucose intolerance develops and the woman develops gestational diabetes.

ACKNOWLEDGMENTS

Marie-Louise Borgen, Connie Kühl, Jette Madsen, Susanne Nielsen, Lene Poulsen, and Lisbet Schmølker are thanked for expert technical assistance.

These studies have been supported by grants from the Danish Medical Research Council; the Danish Hospital Foundation for Medical Research, Region of Copenhagen, the Faroe Islands and Greenland; the Danish Diabetes Foundation; and the Novo Foundation.

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