Analysis of Metabolism of Urea and Glucose in Normal and Diabetic Pregnancy Woman

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ABSTRACT:
The pregnant woman, who must make many metabolic adjustments, provides an intriguing and useful subject for study, both as a source of fundamental knowledge and also as a means of gaining insight into the management of metabolic disease considering the effect of pregnancy on carbohydrate metabolism helps us to not only uncover hidden aberrations in normal patients but also facilitates the control of diabetic individual during her pregnancy. Pregnancy induces major physiological adaptations in the mother which are less obvious but may in some instances, be so marked as to mimic disease. The changes occurring in carbohydrate metabolism is a good example where "diabetes" is suspected.

KEY WORDS: pregnant woman, disease

INTRODUCTION:
The normal pregnancy has been characterized as a "diabetogenic state" due to change in the pattern of insulin secretion and sensitivity resulting in increased post prandial glucose and insulin response in late pregnancy. In third trimester there is reduced sensitivity to insulin action due to hormones like human placental lactogen, leptin, prolactin and cortisol which are involved in these changes. During normal pregnancy there is marked reduction of insulin sensitivity which is compensated by an increase in β cell secretion when this need is not met, abnormal glucose tolerance will develop resulting in GDM. The pregnancy is a state of insulin resistance. Most pregnant women are able to counteract the insulin resistance in pregnancy by increasing their secretion. But, when the capacity of insulin secretion is not sufficiently large to meet the resistance, then glucose intolerance develops and the woman develops gestational diabetes. In pregnancy, several physiological changes take place, the sum of which tends to reset the glucose homeostasis in the direction of diabetes. About 1-2% of 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 cause of GDM could be decreased insulin receptor binding to target cells combined with a relative lack of circulating insulin.

INCREASED INSULIN SECRETION & INSULIN SENSITIVITY:
During early pregnancy, glucose tolerance is normal or slightly improved and peripheral (muscle) sensitivity to insulin and hepatic basal glucose production is normal. The hyperinsulinemic-euglycemic glucose clamp technique and computer-assisted intravenous-glucose-tolerance test indicate greater-than-normal sensitivity to the blood glucose–lowering effect of exogenously administered insulin in the first trimester than in the second and third trimesters. Insulin responses to oral glucose are also greater in the first trimester than before pregnancy. These observations are consistent with a 120% increase at 12–14 wk gestation in the first phase of insulin response, which refers to the change in insulin concentration relative to the elevation in glucose concentration from 0 to 5 min after intravenous glucose administration. The second phase of insulin

response, which refers to the rate of insulin release relative to the glucose concentration 5 to 60 min after intravenous glucose administration, is not significantly different in early pregnancy from the pregravid state. The cause of the enhanced insulin secretion is uncertain because peripheral insulin sensitivity and hepatic glucose production rates are not different from pregravid values. This metabolic milieu under the influence of cortisol, estrogens, and progestins favors lipogenesis and fat storage.

Longitudinal studies of glucose tolerance during gestation show a progressive increase in nutrient-stimulated insulin responses despite an only minor deterioration in glucose tolerance, consistent with progressive insulin resistance. The hyperinsulinemic-euglycemic glucose clamp technique and computer-assisted intravenous-glucose-tolerance test indicate that insulin action in late normal pregnancy is 50–70% lower than that of normal, nonpregnant women. A progressive increase in basal and postprandial insulin concentrations is seen with advancing pregnancy. By the third trimester, basal and 24-h mean insulin concentrations may double. The first and second phases of insulin release are 3- to 3.5-fold greater in late pregnancy. Obese pregnant women also develop peripheral and hepatic insulin resistance during the third trimester of pregnancy. The hyperinsulinemic-euglycemic glucose clamp technique indicates that insulin-stimulated glucose disappearance, carbohydrate oxidation, and suppression of endogenous glucose production in obese women are reduced in the third compared with the second trimester.

Although the precise mechanism is uncertain, alterations in the hormonal milieu during pregnancy are probably responsible for the reduced insulin sensitivity. Changes in β cell responsiveness occur in parallel with growth of the fetoplacental unit and its elaboration of hormones such as human chorionic somatomammotropin (HCS), progesterone, cortisol, and prolactin. Prevailing insulin resistance produces exaggerated changes in postprandial concentrations of metabolic fuels. Insulin resistance serves to shunt ingested nutrients to the fetus after feeding.

INCREASED CARBOHYDRATE USE:

Commensurate with the increased rate of glucose appearance, studies have shown an increased contribution of carbohydrate to oxidative metabolism in late pregnancy. Measured by respiration calorimetry, the 24-h respiratory quotient (RQ) is significantly higher in late pregnancy than postpartum, such that carbohydrate oxidation as a percentage of nonprotein energy expenditure decreases from 66% to 58% from late pregnancy to 6 mo postpartum. Absolute rates of carbohydrate oxidation are significantly higher in pregnancy (282 g/d) than postpartum (210 g/d). RQs during measurements of basal metabolic rate and sleeping metabolic rate are also higher during pregnancy.

In late gestation, rising concentrations of HCS, prolactin, cortisol, and glucagon exert antiinsulinogenic and lipolytic effects that promote greater use of alternative fuels, especially fatty acids, by peripheral tissues. Despite elevated fasting serum prolactin, cortisol, glucagon, and fatty acid concentrations and lowered glucose concentrations, we did not observe a lower RQ or greater use of fatty acids in late pregnancy. On the contrary, as pointed out above, we observed higher mean RQs for 24-h total energy expenditure, sleeping metabolic rate, and basal metabolic rate in late pregnancy than in the postpartum period. RQ gradually decreases during the night fast and the proportion of carbohydrate oxidized becomes progressively smaller in the postprandial period, but the fall in RQ was less precipitous then than postpartum. Higher basal RQs were observed in pregnancy by several investigators. These observations agree with the increased glucose production reported in fasted pregnant women, despite lower fasting plasma glucose concentration. The higher RQ may reflect the obligatory glucose use of the fetus, which uses an estimated 20–25 g glucose/d in late gestation, well within the increment in carbohydrate oxidation seen in our study.

GESTATIONAL DIABETES MELLITUS:

GDM is defined as "carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy". GDM is a heterogeneous disorder in which age, obesity, and genetic background contribute to the severity of the disease. Women with GDM are at risk for later development of type 2

diabetes. Only a 1.6% incidence of islet cell antibodies are found by using a specific monoclonal antibody in women with GDM. GDM is accompanied by alterations in fasting, postprandial, and integrated 24-h plasma concentrations of amino acids, glucose, and lipids. These changes include a 3-fold increase in plasma triacylglycerol concentrations during the third trimester of pregnancy, elevation of plasma fatty acids, delayed postprandial clearance of fatty acids, and elevation of the branched-chain amino acids.

The pathophysiology of GDM remains controversial; GDM may reflect a predisposition to type 2 diabetes expressed under the metabolic conditions of pregnancy or it may represent the extreme manifestation of metabolic alterations that normally occur in pregnancy. GDM is not due to defective secretion of insulin or to disproportionate secretion of proinsulin or glucagon. Only quantitative differences in insulin secretion have been observed between women with GDM and normal pregnant women. Evidence supports the view that GDM is related to a pronounced peripheral resistance to insulin.

Carbohydrate metabolism has been studied by using an intravenous-glucose-tolerance test and hyperinsulinemic-euglycemic clamp with $[6,6-^2H]$glucose before conception and in early and late gestation in nonobese women who were predisposed to and developed GDM. Basal endogenous glucose production increases similarly in patients with GDM and in control subjects throughout gestation. An increase in first-phase insulin response is observed in control subjects and in patients with GDM with advancing pregnancy; however, the increase is greater in control subjects. In late pregnancy, insulin suppression of hepatic glucose production is less in patients with GDM (80%) than in control subjects (96%). Catalano et al (1998) found that decreased insulin-stimulated glucose disposal preceded the development of decreased insulin response in women with GDM and was evident before pregnancy. The relative decrease in first-phase insulin response, as the first manifestation of β cell dysfunction, and impaired suppression of hepatic glucose production becomes evident only after progressive decreased insulin sensitivity in late gestation, resulting in hyperglycemia.

In overweight patients with GDM, similar rates of fasting glucose appearance are achieved, but with elevated insulin concentrations relative to nondiabetic pregnant control subjects. Oxygen consumption, carbon dioxide production, and RQ are similar in patients with GDM and control subjects.

We studied substrate utilization in women with insulin-treated GDM and in healthy control subjects at 32–36 wk of gestation and 6 wk postpartum by using respiration calorimetry and ^{13}C-labeled substrates. Total energy expenditure, basal metabolic rate, and whole-body net carbohydrate and fat utilization did not differ significantly between insulin-treated patients with GDM and control subjects. Exogenous (dietary) glucose oxidation was determined by ^{13}C recovered in breath carbon dioxide from $[^{13}C$]glucose. The time to peak $^{13}CO_2$ enrichment did not differ significantly between groups, indicating similar rates of delivery of substrate to the site of oxidation. ^{13}C recovery from $[^{13}C]$ glucose was not significantly different between patients with GDM and control subjects, or between antepartum and postpartum time intervals. These findings are consistent with previous studies of well-controlled GDM during pregnancy.

Controversy exists regarding the effectiveness of tight glucose control for reducing macrosomia in GDM. Recent findings from the Diabetes in Early Pregnancy Trial indicate that postprandial glucose concentrations, not fasting concentrations, are predictive of birth weight. A lack of association between birth weight and plasma glucose concentrations in other studies may be due to differences in study design, treatment, the extent to which glucose control was documented accurately, and method of analysis. Positive correlations between maternal basal plasma free fatty acids and triacylglycerols and birth weight have been reported in diabetic pregnancies, suggesting that lipid flux across the fetoplacental unit may contribute to macrosomia.

LIPID METABOLISM DURING NORMAL PREGNANCY AND IN GDM:

Changes in hepatic and adipose metabolism alter circulating concentrations of triacylglycerols, fatty acids, cholesterol, and phospholipids. After an initial decrease in the first 8 wk of pregnancy, there is a steady increase in triacylglycerols, fatty acids, cholesterol, lipoproteins, and phospholipids. The higher

concentration of estrogen and insulin resistance are thought to be responsible for the hypertriglyceridemia of pregnancy. Cholesterol is used by the placenta for steroid synthesis and fatty acids are used for placental oxidation and membrane formation. Changes in total cholesterol concentration reflect changes in the various lipoprotein fractions. HDL cholesterol increases by 12 wk of gestation in response to estrogen and remains elevated throughout pregnancy. Total and LDL-cholesterol concentrations decrease initially, but then increase in the second and third trimesters. VLDL and triacylglycerols decrease in the first 8 wk of gestation and then continuously increase until term. In the second half of pregnancy, VLDL clearance is altered because of the decreased activity of lipoprotein lipase (LPL) in the adipose and liver and because of the increased activity in the placenta.

Changes in lipid metabolism promote the accumulation of maternal fat stores in early and mid pregnancy and enhance fat mobilization in late pregnancy. In early pregnancy, increased estrogen, progesterone, and insulin favor lipid deposition and inhibit lipolysis. LPL activity in the adipose tissue from the femoral region, but not from the abdominal region, is elevated at 8–11 wk of gestation. Lipolysis in response to catecholamines is markedly higher in the abdominal than in the femoral region. The femoral cells are virtually unresponsive to catecholamines in pregnancy.

In late pregnancy, HCS promotes lipolysis and fat mobilization. The increase in plasma fatty acid and glycerol concentrations is consistent with mobilization of lipid stores. This shift from an anabolic to a catabolic state promotes the use of lipids as a maternal energy source while preserving glucose and amino acids for the fetus. With prolonged fasting (48 h), as well as shorter periods of fasting (18 h), there is a rapid diversion of maternal metabolism to fat oxidation, with an elaboration of ketones. Decreases in plasma glucose, insulin, and alanine, and increases in plasma fatty acid and β-hydroxybutyrate are seen in pregnant women hours before these changes are seen in nonpregnant women. The enhanced lipolysis and ketogenesis allow pregnant women to utilize stored lipid to subsidize energy needs and minimize protein catabolism. GDM induces a state of dyslipidemia consistent with insulin resistance. During pregnancy, women with GDM do have higher serum triacylglycerol concentrations but lower LDL-cholesterol concentrations than do normal pregnant women. Total cholesterol, HDL cholesterol, and apolipoprotein concentrations are not significantly different between GDM patients and control subjects.

Recovery of exogenously administered [^{13}C]Hiolein (Martek, Columbia, MD), a biosynthetic triacylglycerol, as breath $^{13}CO_2$ is significantly higher antepartum than postpartum. The cumulative dose recovery as breath $^{13}CO_2$ is significantly lower in the patients with GDM antepartum and postpartum, indicating lower oxidation of exogenous triacylglycerols. The mechanism underlying the lower recovery of [^{13}C]Hiolein as $^{13}CO_2$ is unclear, but possibilities include the following: 1) decreased hydrolysis, 2) reduced fatty acid uptake and subsequent oxidation, and 3) increased hepatic oxidation and esterification of fatty acid in support of increased synthesis of VLDL. Higher plasma insulin may suppress fatty acid oxidation. With a hyperinsulinemic-euglycemic clamp and [^{2}H]glycerol and [^{13}C]palmitate, insulin was shown to decrease fatty acid oxidation by 55% and lipolysis by 71% and to completely suppress extracellular fatty acid reesterification in healthy subjects. The reduced oxidation of exogenously administered [^{13}C]Hiolein must have been counterbalanced by a greater contribution of intracellular lipid stores to whole-body lipid oxidation, because this did not differ between patients with GDM and control subjects as measured by 24-h calorimetry. We speculate that lower oxidation of exogenous (dietary) triacylglycerols in GDM may allow greater availability of triacylglycerols to the fetoplacental unit. Fatty acids derived from maternal triacylglycerols cross the placenta and could contribute to fetal macrosomia.

RESULT:

Table – 1

The levels of the serum protein (S.Protein), albumin, globulin, blood urea (B.Urea), creatinine and A/G (Albumin/Globulin in thirteen normal pregnant women

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S. No.	Serum Protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Blood Ureal (mg/dl)	Serum Creatinene (mg/dl)	A/G
1	6.8	3.4	3.4	5	0.4	1.0:1
2	6.7	3.1	3.6	11	0.5	0.1:1
3	6.8	3.5	3.7	9	0.5	1.1:1
4	6.1	3	3.1	16	0.7	1.0:1
5	7.6	3.6	4	8	0.4	1.9:1
6	6.3	2.8	3.5	25	1	0.8:1
7	5.8	3	208	8	0.4	1.0:1
8	7.2	3.2	4	9	0.4	0.8:1
9	5.9	2.9	3	4	0.4	0.9:1
10	6.3	3.2	3.1	8	0.4	1.0:1
11	6	3	3	20	0.4	1.0:1
12	6.7	3.7	3.2	8	0.6	1.1:1

Table-2
The levels of the fasting blood sugar [FBS], Post – prandial blood sugar [PPBS], Glycated haemoglobin [HBA1C] in thirteen normal pregnant women

SL.No	FBS(mg/dl)	PPBS(mg/dl)	HBA1C(%)
1	120	248	5.1
2	142	150	4.3
3	150	142	5.1
4	88	176	5.6
5	110	110	5.2
6	120	153	4.9
7	125	128	5.8
8	88	179	5.2
9	135	198	5.3
10	103	190	4.8
11	112	199	5.6
12	106	145	5.3

CONCLUSION:
GDM represents a continuing challenge for both clinicians and investigators even after 40 yrs since the concept of GDM was introduced, the clinical significance of this disorder, sparks great debate. Controversy also remains concerning screening techniques, diagnostic criteria, thresholds for insulin initiation and whether oral hypoglycemic agents are suitable treatments. The mother becomes almost a new person physiologically during the nine months of pregnancy. Virtually every system undergoes some change. In this respect, the pregnant woman is a natural laboratory in which to observe the effects of pregnancy hormones and nutritional demands of the foetus. The metabolic changes taking place in normal pregnancy will provide milestones for what to expect and when, in the management of diabetes in pregnancy.

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