Goals of Metabolic Management of Gestational Diabetes

Is it all about the sugar?

MOSHE HOD, MD
YARIV YOGEV, MD

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first recognized in the current pregnancy (1), and it affects ~5–7% of all pregnancies (2). Recently, it was demonstrated in both randomized and cohort studies (3,4) that lack of treatment for GDM is associated with increased risk of serious perinatal morbidities. Although the consequences of poorly controlled GDM are evident, no consensus exists on either diagnostic criteria or metabolic aims in controlling GDM.

Traditionally, GDM is considered as a disorder primarily of carbohydrate metabolism; thus, blood glucose levels have become the main "key player" for monitoring and directing treatment during pregnancy. This focus on glycemic metabolism ignores the role of other potential fetal fuels such as proteins and lipids in the pathophysiology of GDM.

In any disease, understanding normality is necessary before defining goals for treatment. The normal physiology of carbohydrates, proteins, and lipids during pregnancy may serve as the basis for defining metabolic goals in diabetic pregnancy. Nevertheless, only scarce data exist regarding the normal physiology of glucose in nondiabetic pregnancy; furthermore, even less is understood regarding lipid or protein metabolism and other factors.

In this review, we will mainly focus on the glycemic profile in normal pregnancy and in GDM. In addition, the role of other nutrients and metabolic factors will be reviewed.

PATHOPHYSIOLOGY OF GDM

— Normal pregnancy has been characterized as a "diabetogenic state" due to change in the pattern of insulin secretion and sensitivity, resulting in increased postprandial glucose and insulin response in late pregnancy. During the first trimester and early in the second trimester, an increase in insulin sensitivity occurs mainly due to the relatively higher levels of estrogen; however, in the late second and early third trimesters, there is reduced sensitivity to insulin action. Human placental lactogen, leptin, prolactin, and cortisol are involved in these changes. During normal pregnancy, the marked reduction of insulin sensitivity is compensated by an increase in β-cell secretion. When this need is not met, abnormal glucose tolerance will develop. Consequently, pregnancy is characterized as a state of hyperinsulinemia and insulin resistance in response to the diabetogenic effects on carbohydrate metabolism.

UNDERSTANDING "NORMALITY": GLYCEMIC PROFILE IN NORMAL AND DIABETIC PREGNANCIES

— The goal of management in pregnancy complicated by diabetes is to maintain blood glucose as near to normal as possible (5). Various methods of glucose monitoring (urine strips, plasma, capillary, and, more recently, continuous glucose monitoring) as well as different timing have been proposed, including the measurement of fasting, preprandial, postprandial, and mean 24-h blood glucose concentrations (1,6,7). Moreover, several authors have emphasized the association between postprandial glucose determinations and pregnancy outcome (8,9). These recommendations were not based on the extent of deviation from normal glycemic physiology but rather on the association between pregnancy outcome and various levels of glucose.

DIURNAL GLYCEMIC PROFILE IN NONDIABETIC PREGNANCIES

— Until recently, scarce data existed concerning the normal glycemic profile in nondiabetic pregnancies (10–12). Moreover, these pioneering studies included small sample sizes in a hospital setting, under strict diet limitations. In addition, collected data included only a single day of evaluation during the third trimester. Moreover, no stratification was performed for maternal obesity. In a more recent study (13), the maternal glycemic profile was evaluated using self-monitoring of blood glucose in nonobese nondiabetic women during the third trimester and suggested a gradual increase in daily mean glucose during this time.

In a recent study (14), we used continuous glucose monitoring (MiniMed, Sylmar, CA) in nondiabetic obese and nonobese gravid patients. A total of 57 gravid women with singleton pregnancies were studied, after completion of 20 weeks of pregnancy, with normal glucose challenge tests (<130 mg/dl) or normal oral glucose tolerance tests. Women diagnosed with GDM in prior pregnancies were excluded. During the study period, all women were asked to refrain from lifestyle modification or dietary restriction. Patients were monitored for 72 consecutive hours and were unaware of the results of the sensor measurements during the monitoring period. During this period,

From the Perinatal Division and WHO Collaborating Center, Department of Obstetrics and Gynecology, Helen Schneider Hospital for Women, Rabin Medical Center, Beilinson Campus, Petah-Tiqva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Address correspondence and reprint requests to Prof. Moshe Hod, Perinatal Division and WHO Collaborating Center for Perinatal Care, Helen Schneider Hospital for Women, Rabin Medical Center–Beilinson Campus, Petah-Tiqva, 49100, Israel. E-mail: mhod@clalit.org.il.

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Abbreviations: GDM, gestational diabetes mellitus; LGA, large-for-gestational-age; PNM, perinatal mortality.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Ambulatory glycemic profile and postprandial glucose levels in nondiabetic pregnancies*

Mean blood glucose (mg/dl)	83.7 ± 18
Fasting glucose (mg/dl)	75 ± 12
Preprandial glucose (mg/dl)	78 ± 11
Peak postprandial glucose value (mg/dl)	110 ± 16
Peak postprandial time (min)	70 ± 13
Mean blood glucose of 3-h postprandial measurements (mg/dl)	98 ± 12
1-h postprandial glucose value (mg/dl)	105 ± 13
2-h postprandial glucose value (mg/dl)	97 ± 11
3-h postprandial glucose value (mg/dl)	84 ± 14
Mean blood glucose at nighttime (mg/dl)	68 ± 10

Data are means ± 1 SD. From Yogev et al. (14).

they also performed fingerstick capillary glucose measurements in the morning after overnight fasting and 2 h after meals (six to eight times per day) using a reflectance monitor and self-coded the data into the monitor. Quality control measures of glucose levels from the meter, sensor, and plasma glucose were performed at the initial time of connection to the continuous glucose monitoring system and again at study completion. The system measures glucose levels in subcutaneous interstitial tissue. It is composed of a disposable subcutaneous glucose-sensing device and an electrode impregnated with glucose oxidase connected by a cable to a lightweight monitor. The system takes a glucose measurement every 10 s, based on the electrochemical detection of glucose by its reaction with glucose oxidase, and stores an average value every 5 min, for a total of 288 measurements each day. The time delay between glucose values of venous plasma and subcutaneous concentrations is generally no more than 5 min. The software for the download of the sensor data takes this delay into consideration, avoiding the need for further corrections. It has been demonstrated that the correlation coefficient (*r*) between the glucose measurements by the sensor and meter was 0.93 ± 0.04 and between the plasma glucose, reflectance meter monitoring, and sensor recording, 0.91 ± 0.02 (15). The patients were instructed to code the time of beginning each meal into the monitor. The patients' level of physical activity was not standardized and all were instructed to go about their normal daily routines.

Approximately 750 glucose determinations were obtained for each subject during this time period. Thus, ambulatory glycemic profile during the second half of pregnancy was characterized, enabling us to define normal glycemia (Table 1). When we further analyzed the ambulatory glycemic profile, we found no difference in preprandial values throughout the day and significantly lower mean blood glucose levels during nighttime (2300 to 0600 h) in comparison to daytime (Table 1). These findings are lower than some have previously reported (10,11) but in agreement with others (13). Thus, our data may provide the characterization of glycemic profile in the second half of pregnancy, which would inform the level of glycemia to be targeted to mirror normoglycemia in the pregnant diabetic subject. Whether normoglycemia should be targeted and whether there are any dangers implicit in targeting normoglycemia for women who have GDM is a subject for future investigation.

POSTPRANDIAL GLYCEMIC PROFILE

— Controversy also exists regarding the postprandial interval when glucose measurement correlates the best with perinatal outcome: 1- or 2-h postprandial glucose determinations. Controversy further exists with regard to the appropriate threshold (<140 mg/dl in 1-h and <120 mg/dl 2-h postprandial) to define normality (8,9,16,17). We demonstrated (14) in nondiabetic gravid subjects that peak glucose value is achieved at ~70 ± 13 min postprandial at a mean glucose level of 110 ± 16 mg/dl. Therefore, whether the postprandial threshold should be modified in GDM patients or the targeted postprandial values in the pregnant diabetic woman should remain higher than the postprandial values found in nondiabetic women requires further study.

Our data are limited by the fact that they are not supported by clinical intervention trials. Prospective studies are needed to evaluate whether pregnancy outcome is enhanced in GDM subjects when ideal target range of glycemic profile by our results is achieved during diabetic pregnancy. It may be, that by achieving glycemic thresholds in GDM higher than "normal" (as recommended by different societies [Table 2]), pregnancy outcome is nevertheless normalized in comparison to the nondiabetic population. Thus, the degree of deviation from normality and pregnancy outcome in GDM should be further studied.

GLYCEMIC PROFILE IN RELATION TO MATERNAL WEIGHT

— To date, the differences in glycemic profiles between obese and nonobese nondiabetic pregnant women remain poorly understood despite the differences in insulin resistance and secretion (21–23). Obese subjects were characterized by higher postprandial glucose peak values, increased 1- and 2-h postprandial glucose levels, and increased time interval for glucose peak in comparison to nonobese subjects. No difference was found in the postprandial glucose profile between breakfast, lunch, and dinner in both obese and nonobese subjects. In addition, in nonobese subjects, the difference in glucose levels between fasting and preprandial values during the day was minimal, suggesting that in nonobese subjects, fasting plasma levels may reflect preprandial values.

Moreover, obese subjects had significantly lower mean blood glucose during the night in comparison to nonobese subjects (Table 3). Because prior studies typically did not include obese patients in their analysis (which leaves out the majority of women with GDM), we demonstrated a different glycemic profile between obese and nonobese subjects. It may be that different glycemic thresholds should be specifically tailored to the obese GDM patients. Furthermore, it may be that different metabolic goals should be adopted in obese and nonobese GDM patients. Answering this interesting question necessitates prospective study.

POSTPRANDIAL GLYCEMIC PROFILE IN GDM: IMPLICATIONS FOR MANAGEMENT

— By using continuous glucose monitoring, we evaluated postprandial glycemic profile in diabetic pregnancies (24). We showed that the time interval from meal to peak postprandial glucose levels was ~90 min, a finding that was similar in all GDM patients unrelated to mode of treatment and was not affected by the level of glycemic control. This was

Table 2—*Ambulatory glycemic profile in relation to recommended glycemic thresholds*

	Recommended glycemic thresholds				Glycemic profile in nondiabetic subjects
	ACOG (18)	American Diabetes Association (19)	Fourth International Workshop-Conference (1)	Canadian Diabetes Association (20)	Yogev et al. (14)
Fasting (mg/dl)	60–90	<105	<95	—	75 ± 12
Premeal (mg/dl)	60–105	—	—	95	78 ± 11
Postmeal (mg/dl)					
1 h	<130–140	<155	<140	<140	105 ± 13
2 h	<120	<130	<120	<120	97 ± 11
Mean (mg/dl)	100	—	—	—	84 ± 18
Nighttime (mg/dl)	60–90	—	—	—	68 ± 10

Data are means ± 1 SD.

somewhat later than the 70-min peaks we observed in nondiabetic control subjects. No difference was obtained in postprandial glycemic profile between breakfast, lunch, or dinner. The question remains whether the peak postprandial glucose or the time to return to preprandial value will be a better reflection of quality of control. However, because all the thresholds that are recommended currently (140 mg/dl at 1 h and 120 mg/dl at 2 h) are not related to preprandial values, it is reasonable to speculate that the glucose value at the 90-min interval should be the reflection of achievement of level of control. This idea is supported by the finding in our study that, in patients with well-controlled diabetes, the peak glucose value was 103 ± 26 mg/dl, and in patients whose diabetes was poorly controlled, the peak value was 164 ± 53 mg/dl.

Thus, it would be logical to combine both studies (14,24) and to suggest that blood glucose determinations should be taken at 90 min postmeal, with a desired glucose value of ~110 mg/dl. Nevertheless, we recognize that future studies qualified by the frequency and timing of testing are needed for evaluating the association between pregnancy outcome and these glycemic goals before advocating using these criteria for routine management guidelines.

DIURNAL GLYCEMIC PROFILE IN GDM: UNDIAGNOSED HYPER- AND HYPOGLYCEMIA

— Consensus exists that normoglycemia is desirable in the management of diabetic pregnancies; however, the degree of deviation from normality characterized in daily glycemic profiles is poorly defined. We used continuous glucose monitoring to assess the glycemic profile in comparison to routine self-monitoring of blood glucose in diabetic pregnancies. We showed (25) that mean total time of undetected hyperglycemia averaged 90 and 130 min/day for diet- and insulin-treated GDM. respectively. Conversely, hypoglycemic events (defined as blood glucose <50 mg/day) were evaluated using continuous glucose monitoring (25,26). We identified hypoglycemic events (most of them asymptomatic) in ~60% of insulin-treated GDM patients and in 28% of glyburide-treated patients. No hypoglycemic events were identified in patients with GDM treated by diet alone or in nondiabetic subjects. The mean recorded hypoglycemic episodes per day were significantly higher in insulin-treated patients. Our data suggest that asymptomatic hypoglycemic events are common during pharmacological treatment in gestational diabetic pregnancies. We speculate that this finding may be explained by treatment modality rather than by the disease pathophysiology itself. Clinical implications of these findings on pregnancy outcome are still a matter of further study.

MANAGEMENT RATIONALE FOR GDM: WHICH MEASURES SHOULD WE USE?

— As was discussed earlier, lack of treatment even in mild forms of GDM is associated with increased perinatal morbidity (3,4). Thus, little controversy exists concerning the need for treatment for GDM. The main issue in treating GDM still remains: what glycemic target should be used? Confusing this issue, different approaches for glycemic profile characteristics for treatment assessment are used by different diabetic management pro-

Table 3—*Comparison in glycemic profile between obese and nonobese nondiabetic subjects during the second half of pregnancy*

	Nonobese	Obese	*P*
BMI (kg/m^2)	23.7 ± 1.8	31.2 ± 1.9	0.002
Mean blood glucose (mg/dl)	83.6 ± 18	84.2 ± 16	NS
Fasting glucose (mg/dl)	72.1 ± 13	73.2 ± 9	NS
Preprandial glucose (mg/dl)	81.2 ± 14	90.3 ± 19	0.04
Peak postprandial glucose value (mg/dl)	106.2 ± 16	117.6 ± 8	0.04
Postprandial peak time (min)	71.4 ± 30	88.0 ± 31	0.03
1-h postprandial glucose value (mg/dl)	103.2 ± 13	112.1 ± 13	0.04
2-h postprandial glucose value (mg/dl)	96.8 ± 12	107.4 ± 14	0.02
3-h postprandial glucose value (mg/dl)	85.9 ± 17	102 ± 16	0.03
Mean blood glucose of 3-h postprandial measurements (mg/dl)	95.4 ± 16	106.2 ± 13	0.02
Mean blood glucose at nighttime (mg/dl)	72.2 ± 7	58.9 ± 5	0.01

Data are means ± 1 SD. From Yogev et al. (14).

grams (i.e., fasting, preprandial, postprandial, and mean 24-h blood glucose concentrations [1,5,6]). Additionally, several authors have emphasized the importance of postprandial glucose determinations and pregnancy outcome, especially macrosomia (8,9). Moreover, testing methods of glucose levels are not uniform, ranging from venous plasma to self-monitoring of capillary blood glucose.

THE ROLE OF A1C IN THE MANAGEMENT OF GDM —Some diabetic programs use levels of glycosylated hemoglobin as a glycemic goal in the management of GDM. Levels of A1C are related to the rate of congenital anomalies and spontaneous early abortions in preexisting diabetes, but the use of this measure, which retrospectively reflects glycemic profile in the last 10 weeks, for treatment evaluation in GDM is questionable. Moreover, most studies found poor to low correlation between glycosylated hemoglobin and mean, fasting, premeal, and postmeal blood glucose values (27,28). In addition, the association between glycosylated hemoglobin and pregnancy outcome in GDM or prediction of macrosomia is poor (29–33). Furthermore, the lack of uniformity among different laboratories has resulted in multiple thresholds of normality obscuring A1C efficiency for routine use. Therefore, from our point of view, using A1C as a tool for monitoring glycemic goal and treatment adjustment in managing GDM is not effective.

USE OF ANTHROPOMETRIC MEASUREMENTS FOR ASSESSMENT OF FETAL GROWTH IN GDM — Ultrasound assessment of the fetus has become a common procedure in the evaluation of all pregnancies and in GDM. Because other techniques for glycemic monitoring were found to have low positive predictive value for pregnancy outcome and especially macrosomia, some investigators have evaluated the use of anthropometric measurements by ultrasound for both treatment assessment and prediction of deviant fetal growth.

It was suggested (34–36) that sonographic evaluation of soft tissue thickness by measuring cheek-to-cheek diameter may predict abnormal fetal growth. In comparison to estimated fetal weight, this measure was found to have higher sensitivity but less specificity. However, this approach has not been confirmed by others and has not gained wide popularity. Others suggested that measuring subcutaneous fetal fat tissue (e.g., width/femur length ratio) achieves increased sensitivity and specificity (37–41). Moreover, assessment of sonographic markers for deviant fetal growth as the width of fetal fat layers, assessment of intraventricular septum width, and abdominal circumference were tested (42). The width of fetal fat layers was found to be the most accurate measure in predicting macrosomia.

CAN ULTRASOUND BE USED TO GUIDE MANAGEMENT IN GDM?—Principally, management choice (diet treatment versus combined diet and pharmacological treatment) in GDM is based on severity of diabetes (as reflected in fasting and postprandial glucose values), capability to achieve desired level of glycemic control by diet treatment alone, and gestational age of diagnosis. It was postulated that a single ultrasonographic assessment of fetal abdominal circumference between 28 and 33 weeks of gestation can differentiate those who need pharmacological treatment from those who can be managed by diet treatment alone (43–46). It has been suggested that a combination of fasting blood glucose >105 mg/dl and fetuses with estimated abdominal circumference higher than the 70–75th percentile are at high risk for deviant fetal growth and macrosomia; thus, pharmacological treatment is advocated. One major weakness in these studies is related to the fact that only one examination rather than serial is recommended. Moreover, achieving the desired level of glycemic control during 28–33 weeks of gestation does not guarantee having the desired level of glycemic control later in pregnancy. Finally, this method of assessment does not take into consideration those fetuses whose large size is due to genetic rather than environmental factors. Nevertheless, randomized trials have demonstrated efficacy of this approach.

LEVEL OF GLYCEMIA AND PERINATAL MORTALITY —Studies have shown that elevated levels of glycemia are associated with increased risk for fetal demise. Pettitt et al. (47) in a study of 811 gravid Pima women without preexisting diabetes demonstrated that perinatal mortality (PNM) rates increased proportionally with an increase in third trimester 2-h post–75-g glucose challenge blood glucose values. Women with known diabetes also had a higher rate of PNM than the nondiabetic group. Moreover, GDM women had PNM rates similar to women with preexisting diabetes. In a more recent study, Bartha et al. (48) screened 3,986 consecutive pregnant women between 1996 and 1998 and identified 235 with GDM. The subgroup of 65 women whose GDM was diagnosed at the first antenatal visit had a higher PNM rate (6%) than those in whom diabetes was identified later. The author stressed the heterogeneous nature of GDM, which includes pregnancy-induced glucose intolerance and previously undiagnosed overt diabetes. Their findings clearly showed that glucose intolerance at the beginning of pregnancy carries a higher risk of adverse pregnancy outcome. Beischer et al. (49) demonstrated a higher rate of PNM in untreated GDM patients in comparison to treated GDM (PNM rate of 2.6% for the untreated GDM patients, OR 2.3, 95% CI 1.4–3.9). The authors suggested that reducing postprandial glucose values to <140 mg/dl will decrease PNM by at least 75%. Karlsson and Kjellmer (50) evaluated the association between the degree of glycemic control and PNM in women with preexisting diabetes. They divided their subjects into three groups based on mean glucose: *1*) <100 mg/dl, *2*) 100–150 mg/dl, and *3*) >150 mg/dl. PNM rates were 4, 15, and 24%, respectively, in those three groups. Thus, they suggested a continuous increase in PNM rate when mean blood glucose exceeded 100 mg/dl.

Because glucose intolerance is characterized by a continuum of disordered carbohydrate metabolism, it is reasonable to assume that higher mean blood glucose levels during pregnancy (due either to inadequate treatment or higher severity of GDM) are related to an increase in PNM. The American Diabetes Association position statement suggests that fasting hyperglycemia (which reflects level of disease severity) of >105 mg/dl may be associated with an increased risk of late intrauterine fetal death in women with GDM (19). Additionally, when combining the studies by Pettitt et al. (47) and Karlsson and Kjellmer (50), it appears that mean blood glucose >100–115 mg/dl will be associated with an increase in the PNM rate.

LEVEL OF GLYCEMIA AND FETAL MACROSOMIA —The most common and significant neonatal complication clearly associated with GDM is

macrosomia, an oversized infant with a birth weight greater than the 90th percentile for gestational age and sex or a birth weight >4,000–4,500 g at birth, depending on different definitions (51). The greatest danger of macrosomia lies in its association with increased risk of birth injuries and asphyxia. In untreated GDM, the risk of macrosomia is as high as 40% of neonates (52). In addition, neonatal macrosomia may be associated with the metabolic syndrome of hyperinsulinemia and deposition of fat in the visceral cavity (53). It was even postulated that in utero hyperglycemia/hyperinsulinemia is the strongest predictor of type 2 diabetes, overriding genetic predisposition (54). Intensified management of GDM reduces the rate of neonatal complications and can normalize birth weight (5). Moreover, Langer et al. (51,55) have demonstrated that the optimal ratio of small-for-gestational-age infants (below the 10th percentile) to large-for-gestational-age (LGA) infants (above the 90th percentile) is achieved when mean blood glucose ranges between 87 and 105 mg/dl. Deviation from these thresholds was associated with a greater likelihood of deviant fetal growth. When mean blood glucose decreases to <87 mg/dl, the proportion of small-for-gestational-age infants rises (23%), and vice versa, when mean blood glucose exceeds 105 mg/dl the rate of LGA is increased. These data suggest that management of glycemia within a fairly narrow range may be effective in achieving an LGA rate comparable to that seen in the nondiabetic population while not increasing the rate of small-for-gestational-age babies.

LEVEL OF GLYCEMIA AND FETAL METABOLIC COMPLICATIONS

— It is generally agreed on that fetal metabolic complications (e.g., hypoglycemia, hypocalcemia, hyperbilirubinemia, and erythemia) are directly related to fetal hyperinsulinemia, which in turn, is related to the degree of maternal metabolic control. Thus, it would be logical to assume that level of glycemic control is associated with the rate of these complications. In untreated GDM patients (4), the rate of metabolic complications was two- to fourfold higher in comparison to non-GDM patients. It has been postulated by Langer and colleagues (5,6) that different glycemic thresholds are needed to minimize different complications, and mean blood glucose <100 mg/dl is associated with a complication rate similar to that of the non-GDM population. By achieving this threshold, most adverse pregnancy outcomes related to GDM may be reduced to nearly nondiabetic pregnancy ranges. In practice, even when this threshold is achieved, the rate of these complications remains higher in comparison to non-GDM patients (4).

ADDED IMPACT OF OBESITY ON PREGNANCY OUTCOME AND METABOLIC GOALS IN GDM

— The prevalence of obesity in the U.S. has increased dramatically over the past 20 years (56). The World Health Organization and the National Institutes of Health define normal weight as a BMI of 18.5–24.9 kg/m^2, overweight as a BMI of 25–29.9 kg/m^2, and obesity as a BMI of ≥30 kg/m^2. Maternal overweight and obesity are associated with major health complications and adverse outcomes in nondiabetic pregnant women. Complications include hypertension and increased rates of cesarean delivery, GDM, fetal macrosomia, and stillbirth.

Controversy exists as to whether pregravid obesity alone, GDM, hyperglycemia, and treatment modality are independent risk factors for adverse pregnancy outcome. The majority of studies have not controlled for obesity, parity, or level of glycemic control, and in many studies, sample sizes were too small to allow sufficient statistical power (57–62). Recently, in a prospective study on 4,001 GDM patients (63), it was shown that obese and overweight GDM patients achieving established levels of glucose control with insulin therapy showed no increased risk for composite adverse outcomes, macrosomia, and LGA in comparison to normal-weight GDM patients with good control. In contrast, diet-treated obese patients who achieved established levels of glycemic control experienced worse pregnancy outcomes in comparison to normal-weight patients. Poorly controlled overweight and obese patients, regardless of treatment modality, had significantly higher rates of composite adverse outcomes, metabolic complications, macrosomia, and LGA. Why did well-controlled diet-treated obese patients fail to improve pregnancy outcome? Perhaps the improved outcome in the insulin-treated overweight and obese women may be due to an unidentified effect of insulin itself, or to subtle differences in compliance with diet that accompany initiation of insulin therapy. In addition to achievement of targeted levels of glycemic control, it is also possible that the improvement in outcome is related to yet unaccounted for differences between the groups.

METABOLIC GOALS IN GDM OTHER THAN GLUCOSE METABOLISM

— As presented, it seems that glucose metabolism is the key variable for managing and monitoring GDM. However, the fact that pregnancy outcome is not entirely normalized compared with non-GDM subjects, even when strict glycemic control is achieved, and insulin-treated patients have lower complication rates when compared with diet-treated patients (especially obese patients) despite achievement of the same glycemic goals implies that other factors may be associated with the pathogenesis of adverse outcomes in GDM.

AMINO ACIDS AND PROTEIN METABOLISM IN GDM

— In addition to glucose, protein is essential for fetal growth. Nitrogen retention is increased in pregnancy in both maternal and fetal compartments. It is estimated that there is a 500-g increase in protein accumulation by about week 30. A significant decrease occurs in maternal fasting concentrations of most amino acids in early pregnancy before the accumulation of significant maternal or fetal tissue (64). Duggleby and Jackson (65) reported that protein synthesis in the first trimester is similar to that of nonpregnant women; however, there is a 15% increase during the second trimester and a further increase of ~25% in the third trimester.

There is paucity of data on the effects of insulin infusion on amino acid turnover during pregnancy in women with and without GDM. It appears that there may be a slight decrease in the rate of protein breakdown during fasting and a slight increase in protein turnover during the day in GDM patients in comparison to non-GDM subjects (66,67).

Correlation of maternal plasma amino acid levels to fetal birth weight in GDM has been suggested. Kalkhoff et al. (68) demonstrated a direct association between maternal amino acid concentrations and birth weight in infants of diabetic mothers. Thus, it may be that measurements of amino acid fluxes in the maternal extracellular pool are of importance.

Distinct from glucose, the concentrations of amino acids in fetal plasma are

even higher than those found in the mother, because placental transfer of amino acids is carried out by energy-dependent processes. This ensures the appropriate availability of these essential amino acids to the fetus. Importantly, amino acids have a greater effect on insulin secretion than glucose, and therefore changes in their delivery to the fetus may have profound consequences on fetal growth. In GDM, the transport of neutral amino acids has been shown to be either not affected (69), decreased (70), or even increased (71). Most of these changes, however, did not correlate with fetal size, suggesting that they are not the primary cause for deviant fetal growth in GDM.

LIPID METABOLISM AND GDM

— Scarcity of data exists concerning the role of lipid metabolism in GDM. Darmady and Postle (72) measured serum cholesterol and triacylglycerol before, during, and after pregnancy in nondiabetic women and found that cholesterol and triacylglycerol decreased at ~7 weeks of gestation and increased progressively thereafter until term. In the fed state, free fatty acid released from adipose tissue is suppressed by the antilipolytic actions of insulin so that free fatty acid levels are only slightly higher in pregnancy during the first hours postprandial.

Infants of obese women were reported to have not only increased birth weight and skinfold measurements but increased serum free fatty acid levels compared with infants of lean women (73). In GDM, especially during the third trimester, there has been a reported associated increase in triacylglycerol and decrease in HDL concentration (74). It has also been demonstrated that GDM women have an increase in total triacylglycerol but lower LDL cholesterol (75). Studies in nondiabetic pregnant and GDM women (76,77) using the hyperinsulinemic-euglycemic clamp showed a decreased ability of insulin to suppress free fatty acid with advancing gestation in both groups. This ability of insulin to suppress plasma free fatty acid was significantly lower in women with GDM (77).

GDM patients with macrosomic fetuses have been associated with high triacylglycerol, VLDL, and low HDL levels (78). Moreover, macrosomic newborns of poorly controlled GDM patients have higher lipid and lipoprotein concentrations than those found in control subjects (79).

SUMMARY — GDM is characterized by many metabolic changes diverting physiology to pathophysiology. Although the main focus over the years was on research of carbohydrate metabolism, significant changes ensue in lipid and protein metabolism as well.

GDM has been considered an entity for >30 years, but no consensus exists concerning the metabolic goals in managing it or for its diagnosis. General agreement exists that treatment should be aimed to restore normality. However, until recently, only scarce data existed concerning normal glycemic profiles in nondiabetic pregnancies, and treatment goals were settled by different academic societies without the support of evidence-based data. Importantly, as presented in this review, enhanced pregnancy outcome in GDM can be achieved with glycemic thresholds that are higher than found in normal pregnancy. Yet, randomized prospective studies are needed to support the hypothesis that achievement of even tighter glycemic targets will enhance pregnancy outcome in GDM.

Although the metabolic changes in protein and lipid metabolism in GDM in comparison to normal pregnancies is apparent, scarce information exists regarding this issue. It is not clear whether monitoring these changes during diabetic pregnancy and attempting to mimic normality will enhance pregnancy outcome in GDM subjects. Prospective studies are needed to clarify this issue.

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