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Achieving Euglycaemia in Women with Gestational Diabetes Mellitus

Current Options for Screening, Diagnosis and Treatment

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Abstract

Gestational diabetes mellitus is one of the major medical complications of pregnancy. Untreated, the mother and the unborn child may experience morbidity and fetal death may even occur. It is important to diagnose and treat all hyperglycaemia appearing during pregnancy. Ideally, a screening and diagnostic test that identified all women at risk for hyperglycaemia-associated complications would be employed in all pregnant women. Unfortunately, there is no such test available currently. The best alternative is to administer an oral glucose challenge test to all pregnant women and then apply the best strategies for interpretation. This article discusses the limitations of our present diagnostic tools and suggests an option for the clinician until the definitive test has been elucidated.

In addition, this article outlines one dietary and management strategy that has been associated with an outcome of pregnancy that is similar to the outcome of pregnancies in healthy women. This strategy includes starting with a 'euglycaemic' diet (comprising <40% carbohydrates and ≥40% fat), which can then be individualised according to the patient's glucose levels. Appropriate exercise, such as arm ergometer training, may enhance the benefits of diet control. For patients who require insulin, if the fasting glucose level is >90 mg/dL or 5 mmol/L

(whole blood capillary) then NPH insulin (insulin suspension isophane) should be given before bed, beginning with dosages of 0.2 U/kg/day. If the postprandial glucose level is elevated, pre-meal rapid-acting insulin should be prescribed, beginning with a dose of 1U per 10g of carbohydrates in the meal. If both the fasting and postprandial glucose levels are elevated, or if a woman's postprandial glucose levels can only be blunted if starvation ketosis occurs, a four-injections-per-day regimen should be prescribed. The latter can be based on combinations of NPH insulin and regular human insulin, timed to provide basal and meal-related insulin boluses. The total daily insulin dose for the four-injection regimen should be adjusted according to pregnant bodyweight and gestational week (0.7–1 U/kg/day); doses may need to be increased for the morbidly obese or when there is twin gestation.

There is now some evidence that insulin lispro, other insulin analogues and oral antihyperglycaemic drugs may be beneficial in gestational diabetes, and more data on these agents are awaited with interest.

Gestational diabetes mellitus is a diagnosis to be applied only to women in whom glucose intolerance is first detected during pregnancy.[1] The definition applies regardless of whether insulin is used for treatment or whether the condition persists after the pregnancy. It does not exclude the possibility that unrecognised glucose intolerance may have antedated the pregnancy.[2]

There is general agreement on the basic underlying concepts of this disorder, but here the accord ends. The blood glucose level at which the diagnosis should be made, the number of tests and abnormal values needed for diagnosis, and the need for screening procedures to detect unsuspected disease are all subjects for continuing discussion and disagreement. The aim of this article is to overview these issues and to review strategies for attaining euglycaemia in the patient with gestational diabetes.

1. Issues Surrounding Diagnosis

A number of groups have developed protocols for diagnosing gestational diabetes,[1-9] but two are in particularly wide use and were developed at about the same time (approximately 25 years ago). These are: (i) the criteria of the WHO;[1,7,8] and (ii) the criteria endorsed by the US National Diabetes Data Group (NDDG)[3] and the American Diabetes Association (ADA).[9] Both groups define gestational diabetes as glucose intolerance occurring during pregnancy. While agreeing that the best definition has yet to be found, advocates of each of these criteria steadfastly refuse to accept the criteria of the other. Perhaps a historical look at the origin of these two sets of criteria will clarify why neither set of criteria has enjoyed universal acceptance.

1.1 WHO Criteria

The WHO definition of gestational diabetes was first published as such in a Technical Report of a WHO Study Group on diabetes in 1980.[7] At that time, the committee recommended that the procedures and criteria for pregnant women should be the same as those proposed for all adults being assessed for diabetes, but that the diagnosis and management of gestational impaired glucose tolerance be the same as for diabetes.[8] Thus, they labelled a woman as having 'gestational diabetes' if her results on the glucose tolerance test were in the ranges considered to be 'impaired glucose tolerance' for non-pregnant adults.

The WHO procedure for diagnosis consists of an oral glucose tolerance test (OGTT) with a glucose

Table I. WHO criteria for gestational impaired glucose tolerance and diabetes mellitus.[1,7,8] Based on an oral glucose tolerance test with a 75g glucose load after an overnight fast

Timepoint	Plasma glucose level	
	gestational impaired glucose tolerance	gestational diabetes
Fasting	<7.8 mmol/L (<140 mg/dL)	≥7.8 mmol/L (≥140 mg/dL)
	and	*or*
2-Hour	7.8–11.0 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)

load of 75g in the morning after an overnight fast. Diabetes, whether gestational or not, is diagnosed if the fasting plasma glucose level is at least 7.8 mmol/L or the 2-hour plasma glucose level is at least 11.1 mmol/L (table I; 1 mmol/L = 18 mg/dL). However, it was generally recognised that an OGTT 2-hour plasma glucose level of 11.1 mmol/L, the level diagnostic of diabetes in nonpregnant adults, was too high for safety during pregnancy, so gestational impaired glucose tolerance was arbitrarily included in the definition of gestational diabetes. Thus, impaired glucose tolerance is diagnosed if the fasting glucose is <7.8 mmol/L and the 2-hour glucose is at least 7.8 mmol/L but <11.1 mmol/L; however, to all intents and purposes pregnant women meeting these criteria are considered to have gestational diabetes. The WHO criteria for the diagnosis of gestational diabetes have the advantage of employing a test that is identical to the test used in women when they are not pregnant, making the results directly comparable.

No data on complications of the pregnancy or on its outcome were considered in selecting the WHO glucose level criteria for use in pregnant women.

1.2 US Criteria

The NDDG criteria, first published in 1979,[3] have not added to the recommendations put forth by the WHO. The NDDG criteria are based, with later modifications, entirely on a system developed by O'Sullivan and Mahan[10] in the late 1950s. Their approach was purely statistical.

At that time, an OGTT with glucose 100g was in widespread use in much of the US for diagnosis of glucose intolerance, so it was natural that the 100g load was used for testing during pregnancy as well. The criteria were developed by finding the mean plus two standard deviations for each of four timepoints during the OGTT – fasting and 1, 2 and 3 hours after the oral load. The diagnosis of gestational diabetes is made if the glucose level at any two of these four timepoints exceeds the mean by at least two standard deviations.

The original glucose concentrations reported by O'Sullivan and Mahan[10] were measured in whole blood using the Somogi-Nelson method, whereas glucose is currently measured in serum or plasma using a glucose oxidase method. The NDDG converted the original whole blood levels into comparable plasma levels (table II). Almost immediately, Carpenter and Coustan[11] pointed out that the NDDG conversion did not take into account the fact that enzymatically derived plasma levels, which do not measure other reducing substances in the blood, had been shown to be about 5 mg/dL (or 0.28 mmol/L) lower than the Somogi-Nelson levels. Therefore, they proposed a new set of numbers based on conversion after subtracting 5 mg/dL (0.277 mmol/L) from the original data (see table II). These numbers, which are lower than those originally reported by

Table II. National Diabetes Data Group (NDDG) criteria for gestational diabetes: variation in reported glucose levels values obtained during a 100g-load oral glucose tolerance test with different methods of measurement

Timepoint	O'Sullivan and Mahan[10]	NDDG[3]	Carpenter and Coustan[11]	Sacks et al.[12]
Blood sample	Whole blood	Plasma	Plasma	Plasma
Fasting	90 mg/dL	105 mg/dL	95 mg/dL	96 mg/dL
	5.0 mmol/L	5.8 mmol/L	5.3 mmol/L	5.3 mmol/L
1-Hour	165 mg/dL	190 mg/dL	180 mg/dL	172 mg/dL
	9.2 mmol/L	10.6 mmol/L	10.0 mmol/L	9.5 mmol/L
2-Hour	145 mg/dL	165 mg/dL	155 mg/dL	152 mg/dL
	8.1 mmol/L	9.2 mmol/L	8.6 mmol/L	8.4 mmol/L
3-Hour	125 mg/dL	145 mg/dL	140 mg/dL	131 mg/dL
	6.9 mmol/L	8.1 mmol/L	7.8 mmol/L	7.3 mmol/L

the NDDG, have been endorsed by the Fourth International Workshop-Conference on Gestational Diabetes.[2] Sacks et al.[12] refined the numbers by actually measuring 995 duplicate samples both by the Somogi-Nelson method and by the current glucose oxidase method, and developed an empirical formula by linear regression. This procedure avoided the biases introduced by both the NDDG[3] and the Carpenter and Coustan[11] conversions (table II).

Regardless of the glucose levels used to make the diagnosis, there are a number of inherent problems with the O'Sullivan and Mahan[10] criteria. First, there is no biological rationale for defining a disease based purely on a statistical distribution of laboratory values. These statistics simply describe the distribution of glucose levels in the population, regardless of disease presence. There is no reason to assume that exactly 2.5% of the population has a disease. Correlation of glucose levels with an outcome of interest is needed. Secondly, if a statistical cut-off point is to be used, the population studied must be without the disease rather than an 'unselected' population, as chosen for this analysis. Including individuals with abnormally high glucose values does two things: it shifts the mean to the right, which is toward higher glucose levels; and, by increasing the spread of the glucose levels, it increases the standard deviation. The greater the number of abnormally high values and the greater the magnitude of the abnormality, the higher this number will be. By excluding women who clearly had diabetes, albeit previously undiagnosed, O'Sullivan and Mahan[10] stated that they would have seen a 5 mg/dL drop in each of the post-load glucose levels they reported.

Thirdly, even if populations without disease were used and the validity of using a statistical cut-off point to define disease was accepted, there is no rationale for requiring a cut-off point to be met at two timepoints during the test. This arbitrary definition of an abnormal test completely invalidates any attempt at rationalising the statistical approach. The authors abandoned their purely statistical approach because it was considered 'expedient' to do so.[10]

The use and interpretation of the NDDG criteria are further complicated by the custom of screening with an oral glucose challenge test (GCT) using a 50g load under uncontrolled conditions and only further testing those women with a 1-hour post-load level of at least 140 mg/dL (7.8 mmol/L). Carpenter and Coustan[11] have found a sufficient number of women with gestational diabetes with screening levels between 130 and 140 mg/dL (7.2 and 7.8 mmol/L) that they recommend the lower number of 130 mg/dL be used for screening.

In 1988, the changes in the recommendations proposed at the Fourth International Workshop-Conference on Gestational Diabetes Mellitus, in addition to adopting the Carpenter and Coustan[11] modification of the O'Sullivan and Mahan[10] criteria, included omitting all testing and screening on low-risk women and the option of using a 75g glucose load for the OGTT.[2] The former recommendation has met with opposition[13,14] because the criteria proposed for the 75g-load OGTT require extremely high glucose levels to be present at two of the three timepoints during the OGTT for a diagnosis of gestational diabetes to be made.

Although some controversy still continues, the ADA guidelines published in 2004[15] continue to suggest diagnosis of gestational diabetes when two or more of the plasma glucose threshold levels proposed by Carpenter and Coustan[11] are met or exceeded after a 100g-load OGTT (table II).

Several direct comparisons of outcomes using both sets of criteria have shown that the WHO criteria identify more adverse outcomes than the NDDG criteria, but have done little to argue in favour of one or the other set of criteria.[16-18]

2. Screening Strategies

Ideally, a screening and diagnostic test that identified all women at risk for hyperglycaemia-associated complications would be employed in all pregnant women. Unfortunately, there is no such test

available currently. The best alternative is to administer an oral GCT to all pregnant women and then apply the best strategies for interpretation.

The Toronto Tri-Hospital Gestational Diabetes Project[19] was initiated as a study intent on defining a low-risk population in which there would be no need for screening for gestational diabetes. To test the hypothesis that the efficiency of screening could be enhanced by considering a woman's risk of gestational diabetes on the basis of their clinical characteristics, they studied 3131 pregnant women who underwent both screening with a 50g-load GCT at 26 weeks' gestation and a diagnostic test with a 100g-load OGTT at 28 weeks' gestation. Data on half the women were randomly selected and used to derive new screening strategies, and data from the remaining half of the women were used to validate the screening strategies.

The group created a clinical scoring system incorporating age, race and body mass index prior to pregnancy, and used these scores to assign risk. They then developed strategies that entailed no screening for low-risk women, usual care for intermediate-risk women (plasma glucose threshold for diagnostic testing 140 mg/dL [7.8 mmol/L]) and universal screening with lower thresholds for high-risk women (plasma glucose threshold for diagnostic testing 130 or 128 mg/dL [7.2 or 7.1 mmol/L]). These new strategies of the Toronto Tri-Hospital Gestational Diabetes Project allowed a 34.6% reduction in the number of screening tests performed (95% CI 32.3, 37.0) and detected 81.2–82.6% of the women with gestational diabetes compared with the 78.3% detected through usual care. The percentage of false-positive screening tests was significantly reduced, from 17.9% with usual care to 16.0% ($p = 0.02$) or 15.4% ($p < 0.001$) with the new strategies, depending on the threshold values for high-risk women.[19]

In another report from the Toronto Tri-Hospital Gestational Diabetes Project,[20] they assessed maternal-fetal outcomes in untreated patients with increasing carbohydrate intolerance not meeting the current criteria for the diagnosis of gestational diabetes to further define risk factors for unfavourable maternal-fetal outcomes. The relationship between offspring birthweight and mode of delivery was also investigated among the 3836 women with untreated borderline gestational diabetes, treated overt gestational diabetes and normoglycaemia. A 50g-load GCT was administered to pregnant women at 26 weeks' gestational age and a 100g-load OGTT was administered at 28 weeks' gestation.

Increasing carbohydrate intolerance in women without overt gestational diabetes was associated with a significantly increased incidence of Caesarean section, pre-eclampsia, macrosomia and need for neonatal phototherapy, as well as an increased length of maternal and neonatal hospital stay. Compared with normoglycaemic control individuals, the untreated borderline gestational diabetes group had increased rates of macrosomia (28.7% vs 13.7%, $p < 0.001$) and Caesarean delivery (29.6% vs 20.2%, $p = 0.03$). Usual care of patients with known gestational diabetes normalised offspring birthweights, but the Caesarean delivery rate was about 33%, whether macrosomia was present or absent. An increased risk of Caesarean delivery among treated patients with gestational diabetes compared with normoglycaemic control individuals persisted after adjustment for multiple maternal risk factors.[20]

Receiver operating characteristic curve analysis allowed the selection of the most efficient cut-off points for the GCT based on the time since the last meal. These cut-off points were 8.2, 7.9 and 8.3 mmol/L for elapsed postprandial time of <2, 2–3 and >3 hours, respectively. With this change from the conventional threshold of 7.8 mmol/L, the number of patients with a positive screening test dropped from 18.5% to 13.7%. There was an increase in positive predictive value from 14.4% to 18.7%. The overall rate of patient misclassification fell from 18.0% to 13.1%.[20]

The project team concluded that increasing maternal carbohydrate intolerance in pregnant

women without gestational diabetes is associated with a graded increase in adverse maternal and fetal outcomes. They suggested that the efficiency of screening for gestational diabetes could be enhanced by adjusting the ADA GCT threshold of 7.8 mmol/L to new values related to time since the last meal before screening.[20]

In a recent multicentre Danish study[21] to prospectively evaluate a screening model for gestational diabetes on the basis of clinical risk indications, 5235 consecutive pregnant women (with and without clinical risk factors) underwent diagnostic testing with a 2-hour 75g-load OGTT. The researchers analysed those women with and without risk factors separately. The prevalence of gestational diabetes was 2.4%. They concluded that both screening and diagnostic testing could be avoided in two-thirds of all pregnant women if testing were only performed in women with risk factors.

In an Italian study,[22] the authors compared universal versus selective screening to validate the ADA's recommendation to exclude low-risk women from screening.[23] From 1 June 1995 to 31 December 2001, universal screening for gestational diabetes was performed in 3950 pregnant women with a 50g-load GCT. The GCT was positive (GCT+) in 1389 cases (35.2%). The 1-hour glucose level after GCT enabled the diagnosis of gestational diabetes directly in 24 pregnant women. OGTT was performed in 1221 GCT+ women (144 women with positive GCT tests withdrew from the study); gestational diabetes was diagnosed in 284 of these women (23.2%). OGTT was also performed in 391 randomly chosen women from the GCT-negative (GCT−) group. In this latter group, 25 (6.3%) women had gestational diabetes. Thus, the total number of individuals diagnosed with gestational diabetes was 333 among the 1636 women who underwent OGTT testing or were diagnosed directly. Assuming that the rate of gestational diabetes observed in the random sample of GCT− women is applicable to the whole group of 2561 GCT− women, then 161 GCT− patients could also have gestational diabetes. This makes an estimated prevalence for the whole cohort up to 12.3% (i.e. 469 of 3806 pregnant women).

There were 236 (6%) women with a low risk for gestational diabetes (normal bodyweight, age <25 years and without a family history of diabetes). In this group, they found 34 women with positive screening tests and five women with gestational diabetes. Thus, if low-risk women were excluded from the screening test, as suggested by ADA recommendations, only five women with gestational diabetes would have been missed amongst the almost 4000 women screened. However, about 95% of this population were at medium or high risk for gestational diabetes and, therefore, would have been screened. The rate of gestational diabetes was significantly higher in women with a positive history of diabetes, increasing age, previous pregnancies, pre-pregnancy overweight and short stature. After logistic regression analysis, gestational diabetes diagnosis was significantly correlated with age ($p < 0.0001$), pre-pregnancy body mass index (BMI) [$p < 0.0001$], weight gain during pregnancy ($p < 0.0001$) and family history of diabetes ($p < 0.01$).

The current recommendations for screening from the ADA,[15] published in 2004, reflect many of the findings of these studies. According to these recommendations, all pregnant women at high risk of gestational diabetes should undergo glucose testing; high risk is defined by marked obesity, glycosuria, personal history of gestational diabetes or strong family history of diabetes. High-risk women with a negative GCT should be retested at 24–28 weeks' gestation. For women at average risk, glucose testing at 24–28 weeks' gestation is recommended. Glucose testing is not required for low-risk women meeting the following criteria: age <25 years; normal bodyweight prior to pregnancy; ethnicity associated with a low prevalence of gestational diabetes; no personal history of abnormal glucose tolerance or first-degree relative history of diabetes; no history of poor obstetric outcome. Glucose testing can be con-

ducted either directly by a 100g-load OGTT, or by a screening test with a 50g-load GCT with subsequent diagnostic OGTT for women with elevated glucose levels. Rather than specifying a glucose threshold value for screening with the two-step process, the ADA states that values of >7.8 mmol/L (>140 mg/dL) and >7.2 mmol/L (130 mg/dL) will identify approximately 80% and 90%, respectively, of women with gestational diabetes. The ADA notes that a 75-load OGTT can be conducted but they consider this test to be less well validated.

The American College of Obstetricians and Gynecologists (ACOG) in their 2001 guidance[24] note that the optimal method of screening is still controversial and data are not sufficient to allow firm conclusions to be drawn. Where screening is undertaken, they recommend the two-step approach with a 50g-load GCT at weeks 24–28 weeks' gestation, and they note that either of the glucose level thresholds outlined by the ADA[23] are acceptable for screening. Although more women with gestational diabetes are identified at the lower threshold, more false-positive results will also occur, the ACOG recommendations note.

In the future, we hope to see more rational criteria for screening for gestational diabetes become available. There is currently a multicentre international trial (the Hyperglycemia and Adverse Pregnancy Outcomes [HAPO] study)[25] underway to correlate the results of the 75g-load OGTT with pregnancy outcomes. These data should provide a basis for the development of international agreements on the best criteria for diagnosing gestational diabetes and the best protocol for identifying women at risk.

3. Does Active Management Affect Outcome?

Gestational diabetes is a common obstetrical complication, with fetal macrosomia affecting up to 40% of the offspring of these pregnancies.[26] Macrosomia is associated with increased rates of secondary complications such as operative delivery, shoulder dystocia and birth trauma. In addition, other neonatal complications attributed to gestational diabetes included respiratory distress syndrome, hypocalcaemia, hyperbilirubinaemia and hypoglycaemia.

The cause of fetal macrosomia associated with gestational diabetes is the subject of current controversy. Classically, the Pedersen[27] hypothesis claims that macrosomia is due to fetal hyperinsulinaemia, a consequence of maternal hyperglycaemia. Early studies by O'Sullivan and Mahan[10] supported this hypothesis in that insulin therapy to normalise maternal blood glucose levels was found to reduce the frequency of macrosomia compared with routine prenatal care or treatment with diet therapy alone. Numerous studies[26,28-30] that followed also reported decreased rates of macrosomia, Caesarean section and neonatal complications with vigourous efforts to optimise maternal glycaemic control. However, other studies have continued to report increased rates of macrosomia and perinatal morbidity associated with gestational diabetes despite 'tight' maternal glycaemic control.[26,31]

Conflicting reports on the efficacy of glycaemic control in reducing perinatal morbidity have led to suggestions that other causes are more important than hyperglycaemia in the pathogenesis of diabetic fetopathy morbidity. Nevertheless, if normalisation of maternal glycaemia does prevent fetal complications, then treatment programmes designed to achieve strict euglycaemia should be the standard of care. In the author's opinion, a sequential management scheme, starting with diet and moving on to insulin treatment, to sustain normoglycaemia is the best approach to prevent adverse pregnancy outcomes associated with gestational diabetes. The strategies for this approach are outlined in the following sections.

4. Dietary Strategies

4.1 Dietary Strategies to Achieve Euglycaemia

The vast majority of women with gestational diabetes will achieve optimisation of blood glucose control with diet and/or diet plus exercise. However, the ADA has not issued specific dietary guidelines for women with gestational diabetes. For those women with gestational diabetes who are obese there is even less of a consensus. In the ADA clinical practice recommendations of 1999,[32] the only advice is "Nutritional recommendations for women with pre-existing and gestational diabetes should be based on a nutrition assessment. Monitoring blood glucose levels, urine ketones, appetite, and weight gain can be a guide to developing an evaluation and appropriate individualised nutritional prescription and meal plan and to making adjustments to the meal plan throughout pregnancy to ensure desired outcomes".[32] Obviously, this statement does not provide advice on the optimal diet for the woman with gestational diabetes.

The optimal dietary prescription would be a diet that provides the caloric and nutrient needs to sustain pregnancy, but does not cause postprandial hyperglycaemia. The search for a 'euglycaemic diet' began when it became clear that the ADA did not have specific recommendations for pregnancy. Furthermore, the meal plan that the ADA supported for use in gestational diabetes, which was composed of >55% carbohydrates and aimed to produce 35 kcal/kg of present pregnant weight, not only caused excessive weight gain but also resulted in severe postprandial hyperglycaemia, which necessitated insulin therapy in 50% of patients with gestational diabetes.[33] The logical step would be to restrict calories below this recommendation; thus an alternative 'euglycaemic' diet has been proposed (table III; 1 kcal = 4.2kJ).

Hypocaloric diets have been advocated for use in pregnancy since the 19th century for prevention of eclampsia and pre-eclampsia, as well as in women with diabetes.[36] The recommendations for caloric needs during pregnancy had not changed dramatically over the years until the recent 1990 recommendation of the National Academy of Science.[37] There are no specific guidelines in the National Academy of Science report for lean, pregnant healthy individuals with diabetes, nor are there prescriptions for the obese woman with gestational diabetes. However, there is reference to the caloric needs during pregnancy of obese, healthy women. In their summary and recommendations it is suggested that no more than 6.8kg (15 pounds) needs to be gained during pregnancy if a woman is >150% of her ideal bodyweight or has a BMI >30 (defined as obese). However, a closer look at the outcome of pregnancies in these morbidly obese women revealed that the subsequent infant birthweight was optimal if the maternal weight gain was minimised to <3kg or no weight was gained.[37]

Caution needs to be stressed when attempting to limit the calories in obese women with gestational diabetes. Of note is that women with diabetes may be more vulnerable to protein malnutrition than women without diabetes during gestation.

Magee et al.[38] designed a study to evaluate strict caloric restriction as a treatment for obese women with gestational diabetes. They compared a 2400 kcal/day with a 1200 kcal/day diet (50% calo-

Table III. Comparison of American Diabetes Association (ADA)-supported and 'euglycaemic' diets for use by women with gestational diabetes[30,33-35]

Criteria	Total daily calories[a]	
	ADA diet	'euglycaemic' diet
BMI = 80–120% IBW	35 kcal/kg PPW	30 kcal/kg PPW
BMI = 121–150% IBW	35 kcal/kg PPW	24 kcal/kg PPW
BMI ≥151% IBW	35 kcal/kg PPW	12 kcal/kg PPW
Calories as fat	<25% of total	≥40% of total
Calories as carbohydrate	>55% of total	<40% of total
Calories as protein	20% of total	20% of total
Dietary cholesterol	<25% of total	>40% of total
	<300 mg/day	<800 mg/day

a 1 kcal = 4.2kJ.

BMI = body mass index; **IBW** = ideal bodyweight; **PPW** = present pregnant weight.

rie restricted). After more than 6 weeks of the assigned diet, the two groups differed significantly in average glucose and fasting insulin levels, but fasting glucose and post-glucose challenge levels were not significantly different. Ketonaemia and ketonuria developed in the calorie restricted group after 1 week on the 50% calorie restricted diet and the investigators concluded that the 1200 kcal diet may have an impact on the well being of the fetuses and, therefore, was not recommended. The same investigators then went on to study a 33% calorie restricted diet.[39] With this mildly calorie restricted diet, glycaemia improved (fasting and mean 24-hour glucose levels) by 22% after 1 week compared with the full calorie diet group. Ketonaemia did not develop with this 33% calorie restricted diet.

The role of ketones in pregnancy complicated by diabetes has remained controversial.[40] The initial evaluation of the offspring of mothers with ketonuria suggested these children might have lower IQ scores than expected;[41] however, this study has been questioned because of the methodology used and concern that chorioamnionitis might have caused the intellectual impairment.[39] Rizzo et al.[42] studied 223 pregnant women and their offspring; 89 women with type 1 diabetes, 99 with gestational diabetes and 35 with normal glucose tolerance. No relationship was found between maternal hypoglycaemia and intellectual function of the offspring. However, scores on the Stanford-Binet tests correlated inversely with the third trimester β-hydroxybutyrate and free fatty acid plasma level. The level of acetonuria did not correlate with test scores. Thus, there may be a difference between starvation ketosis and the ketosis that develops with poorly controlled diabetes.[40] Ketonuria develops in 10–20% of normal pregnancies after an overnight fast[43] and may in fact protect the fetus from starvation in the mother without diabetes. Concurrent studies by others[39] have shown improvement in glycaemic control without producing ketonuria with 1500–1800 kcal/day diets in obese women with gestational diabetes.

Buchanan et al.[31] compared the glucose, insulin, free fatty acid and β-hydroxybutyrate responses to a briefly extended overnight fast during the third trimester of pregnancy between two groups: obese women with normal glucose tolerance, and age- and weight-matched women with gestational diabetes. After a 12-hour fast, plasma glucose, insulin and free fatty acid levels were higher in the women with gestational diabetes. β-Hydroxybutyrate levels were similar in the two groups. When the fast was extended to 18 hours, glucose levels fell more rapidly in the group with gestational diabetes, but remained elevated compared with the obese nondiabetic women. Insulin levels declined equally in both groups. In contrast, free fatty acid levels increased 44% in the obese nondiabetic women, whereas the free fatty acids did not continue to increase beyond the levels seen in the 12-hour fast in the women with gestational diabetes. In addition, β-hydroxybutyrate levels remained virtually equal in the two groups. Therefore, brief periods of fasting are well tolerated by women with gestational diabetes. Thus, mild carbohydrate restriction, coupled with longer spacing between meals, may be useful for the treatment of obese women with gestational diabetes.

The Diabetes in Early Pregnancy Study showed that the risk of macrosomia increases with increased maternal postprandial glucose levels,[28] and have revealed that β-hydroxybutyrate levels in the first trimester are an independent predictor of macrosomia and can be used to assess the importance of intermediate metabolites in the aetiology of abnormal fetal growth, spontaneous abortion and malformations,[43-45] although this study was only in women with type 1 diabetes. Interestingly, in the control group of women who did not have diabetes, β-hydroxybutyrate levels were negatively correlated with fasting glucose levels and, thus, most probably reflect ketones of starvation. There was also evidence that the β-hydroxybutyrate level in the first trimester may be a prognostic indicator of subsequent macrosomia of the newborn in the offspring of

both the women with diabetes and control nondiabetic women.[44]

Further studies of β-hydroxybutyrate levels throughout pregnancy and in women with gestational diabetes are warranted to definitively show a relationship between β-hydroxybutyrate levels and birthweight.

4.2 Diets Designed to Minimise the Postprandial Glucose Levels

Diabetic fetopathy resulting from maternal postprandial hyperglycaemia can be minimised when the peak postprandial response is blunted. Gestational diabetes is a disease of carbohydrate intolerance. Thus, the peak postprandial response is minimised in the woman with gestational diabetes if her meal plan has attention toward carbohydrate restriction. Therefore, a caloric prescription can be designed to achieve postprandial normoglycaemia by minimising carbohydrates in the meal plan.

To date, there are no randomised controlled trials specially focusing on the optimal diet for either the lean or obese woman with gestational diabetes. One diet which has proven to provide the needs of pregnancy and not result in excessive weight gain or hyperglycaemia consists of 30 kcal/kg of present pregnant weight for normal weight women, 24 kcal/kg for overweight women and 12 kcal/kg for morbidly obese women (table III).[30,33-35] The overall carbohydrate content of the diet is 40% of the total calories and is distributed throughout the day as described in table IV. As can be seen in table III, compared with the recommended ADA diet, the 'euglycaemic diet' has less carbohydrate and more fat.

The rationale for the distribution of carbohydrates in the euglycaemic diet (table IV) is based on a study that showed that the peak postprandial glucose response is directly related to the carbohydrate content of the meal plan.[46] Fourteen women diagnosed with gestational diabetes according to standard protocol were enrolled during weeks 32–36 of gestation. All patients were >130% of ideal bodyweight and did not require insulin treatment. The patients were put on a 24 kcal/kg/day calorie diet and given 12.5% of the total caloric requirement for breakfast, 28% for both lunch and dinner, and the remaining calories were divided among three snacks. Patients self-monitored blood glucose levels four times daily and kept a diet diary. The 1-hour post postprandial glucose levels showed a significant correlation with percentage carbohydrate in the meal. This relationship was most striking at dinner and more variable at breakfast and lunch. To maintain a 1-hour postprandial capillary whole blood glucose level <140 mg/dL (7.8 mmol/L) requires ≤45% carbohydrates at breakfast, ≤55% at lunch and 50% at dinner. For better control (postprandial ≤120 mg/dL or 6.7 mmol/L) respective values of 33%, 45% and 40% are required. Although this is a small study, the authors clearly showed that glycaemic response to a mixed meal is highly correlated to the percentage of carbohydrates ingested and that high carbohydrate diets do not facilitate glycaemic control.

Table IV. The 'euglycaemic diet' for women with gestational diabetes. Calorie distribution to maintain normoglycaemia[30,35]

Diet calculation for women			
time	meal	fraction (kcal/24h)	daily carbohydrate allowance (%)
8:00am	Breakfast	2/18	10
10:30am	Snack	1/18	5
12:00 noon	Lunch	5/18	30
3:00pm	Snack	2/18	10
5:00pm	Dinner	5/18	30
8:00pm	Snack	2/18	5
11:00pm	Snack	1/18	10

Thus, the optimal diet for the woman with gestational diabetes is based on maternal glucose levels as the variable upon which the success or failure of a dietary prescription is based. The caloric and percentage carbohydrate prescription of the 'euglycaemic diet' should only be the starting point, and invariably the medical nutritional therapy needs to be tailored according to the postprandial glucose results recorded in the woman's diary of glucose measurements.

5. Exercise as Adjunctive Treatment for Gestational Diabetes

Intuitively, one would think that exercise should be safe for a pregnant woman. How did the human species survive if the fetus died whenever the mother fled from an enemy, worked in a field, sought out food or contributed to the workload of her community? However, it has been very hard to prove scientifically that exercise is safe for a pregnant woman.

In a study of three Pacific Island countries, Taylor et al.[47] have demonstrated that exercise as well as diet has a significant effect on rural/urban differentials in obesity and diabetes. They found that rural individuals had higher levels of physical activity, were leaner, were less likely to have diabetes and hypertension, and had greater total energy intake than urban dwellers. In addition, the US National Institutes of Health recently announced that their multicentre trial that studied the utility of lifestyle intervention to prevent the progression to diabetes succeeded in decreasing the prevalence of progression to overt diabetes by 58%.[48]

The animal studies on the safety of exercise in pregnancy have been difficult to apply to human pregnancy. Many of the studies exercised the animals to exhaustion; other studies were of pregnancies in animals that carry multiple fetuses.[49-51] The overall conclusion that can be made of these experiments is that moderate maternal exercise does not seem to harm the fetus(es), and strenuous exercise decreases litter size and weight of the fetuses.

Human studies also do not completely answer the question of safety of exercise during pregnancy. Limitations include ethical constraints and difficulties with assessing fetal well being. Most research of this issue has used fetal heart rate as an indicator of fetal distress. Fetal heart rate is also used as a measurement criteria for disturbances in fetal gas exchange. Maternal heart rate and blood pressure are used as indicators of maternal well being. However, while some researchers have observed marked fetal bradycardia during maternal exercise, others have not.[52-60] In addition, there is still controversy over the analysis and interpretation of fetal bradycardia, including that the change in fetal heart rate during maternal exercise may be an artefact inherent in the monitoring technique.[61]

Another area of controversy in the literature is whether or not exercise causes uterine activity. Many studies suggest that exercise may trigger premature labour that is mediated through uterine activity precipitated by exercise.[62,63] Of concern, an increased incidence of prematurity, growth restriction and/or lower birthweight has been reported for infants born to mothers who stand during the workday as opposed to those who remained sedentary.[63,64] However, other studies have produced conflicting results regarding whether or not rigourous exercise programmes cause intrauterine growth restriction.[65,66]

Therefore, it appears that the safest form of exercise would be that type of exercise which does not cause: (i) fetal distress; (ii) low infant birthweight; and (iii) uterine contractions. In addition, it would also be logical to avoid exercise that produces maternal hypertension (blood pressure >l40/90mm Hg). Therefore, we designed a study to elucidate a type of exercise that would meet these criteria. We recruited healthy pregnant women to exercise on five types of equipment while we monitored maternal blood pressure, fetal heart rate and uterine activity. Uterine contractions were observed with use of an exercise bicycle (50% of 25 sessions) and walking on a treadmill at jog pace (40% of l0 sessions) but slower paces on the treadmill were not problematic. A rowing machine was associated with fewer problems if the seat was fixed and the arms did most of the work (l0% of 68 sessions). The recumbent bicycle did not cause contractions (0% of 20 sessions). The upper arm ergometer proved to be the safest and most accepted mode of exercise; in 95 sessions of at least 20 minutes of a cardiovascular workout (target heart rate = [220 − age] × 70%), no maternal hypertension, fetal distress or uterine ac-

tivity was observed. None of the 95 infants born to these mothers were growth retarded.[67]

Therefore, exercises that do not cause uterine activity are those that utilise the upper body muscles or place little mechanical stress on the trunk region during exercise. When the lower body is kept from an excessive weight-bearing load the workload can be increased safely, permitting a cardiovascular workout without fear of fetal distress. Women may be taught to palpate their own uterus during exercise and stop the exercise if they detect a contraction. In addition to proper frequency, intensity, duration and modality of exercise, self-uterine activity monitoring may be a means of surveillance that allows the safe prescription of exercise during the third trimester.

On the basis of our preliminary work to derive a safe mode of exercise for a pregnant woman, we then applied arm ergometer training to a population of women with gestational diabetes women. We randomised 20 women with gestational diabetes into two groups. One group received 6 weeks of intensive dietary therapy.[68] The other group received 6 weeks of the same dietary therapy, but also exercised under supervision three times a week, 20 minutes per time. All women exercised on an arm ergometer that allowed for all the work to be in the form of a pedalling motion with the arms while they remained seated comfortably in a chair. The two groups' glycaemic levels started to diverge by week 4 of the programme. By week 6, the women in the exercise group had normalised their glycosylated haemoglobin level (mean $4.2 \pm 0.2\%$), and their fasting plasma glucose level (3.89 ± 0.37 mmol/L) and the postprandial plasma glucose levels (5.9 ± 1.0 mmol/L) on a 50g-load oral GCT. Glycaemic control in the women in the diet alone group improved, but they still had elevated fasting plasma glucose levels (4.9 ± 0.34 mmol/L) and postprandial hyperglycaemia (10.4 ± 0.16 mmol/L) based on their 50g-load oral GCT at week 6.[68]

These studies have very few patients and need to be confirmed in larger clinical trials. In addition, studies of insulin sensitivity classically incorporate the intravenous glucose tolerance test (IVGTT), not just fasting and postprandial glucose measurements. Thus, at best, the latter report[68] is circumstantial evidence to support the notion that insulin sensitivity improves with exercise in women with gestational diabetes. While confirmation is required, there does appear to be added benefit when arm exercise is added to dietary programmes. Women with gestational diabetes can be taught to do arm exercises at home while sitting comfortably in a chair with good back support and lifting weights while watching the television for at least 20 minutes per session.

One study that looked at the use of exercise to manage diabetes in pregnancy studied a walking exercise programme after dinner in pregnant women with type 1 diabetes.[69] This study found no improvement in the after-dinner glucose levels with this programme, but triglyceride levels were improved; this latter benefit suggests that walking may be useful for the management of gestational diabetes and its associated disordered glucose homeostasis.

Bung and colleagues[70,71] have confirmed the safety and potential utility of exercise for gestational diabetes in two studies. Between the 26th and 32nd week of gestation, 41 pregnant women were randomised into either an exercise and diet group or an insulin and diet group. The exercising patients ($n = 21$) trained at 50% maximum oxygen consumption per session for three sessions of 15 minutes each week on a recumbent bicycle ergometer throughout pregnancy with blood glucose monitoring before and after exercise. Blood glucose metabolism was followed by daily home monitoring and weekly fasting blood glucose sampling. The fasting glucose results were comparable in the study and the control group (<105 mg/dL or 5.8 mmol/L). They concluded that such a medically supervised exercise programme can be safely conducted in women with gestational diabetes, resulting in normoglycaemia for the mother and, thus, preventing the need for insulin therapy. Studies of diet and exercise provide

cost-effective means by which we can begin to achieve these goals.

6. Insulin Treatment for Gestational Diabetes

When dietary strategies fail to achieve the desired glucose goals for the woman with gestational diabetes, insulin therapy needs to be initiated. The type of insulin chosen should be based on the specific pattern and magnitude of blood glucose elevation. A woman with diet-controlled gestational diabetes should monitor her blood glucose levels four times per day (fasting and 1 hour after each meal). A pregnant woman with diabetes who requires insulin should increase her frequency of monitoring of blood glucose levels to at least six times a day (before and 1 hour after each meal).[72]

The frequency of monitoring and the criteria for initiation of insulin in women with gestational diabetes are controversial; however, the Santa Barbara County Health Care Services Program,[73] with which the author is involved, has succeeded in normalising the birthweight of infants born to women with gestational diabetes in our largely Mexican-American patient population in the Santa Barbara area. Furthermore, this programme has been shown to produce cost savings of over $US1000 per pregnancy screened for gestational diabetes.[73] The discussion in this section outlines this programme.

If the fasting glucose level is >90 mg/dL or 5 mmol/L (whole blood capillary) then NPH insulin (insulin suspension isophane) should be given before bed, beginning with doses of 0.2 U/kg/day. If the postprandial glucose level is elevated, pre-meal rapid-acting insulin should be prescribed, beginning with a dose of 1U per 10g of carbohydrates in the meal.

If both the fasting and postprandial glucose levels are elevated, or if a woman's postprandial glucose levels can only be blunted if starvation ketosis occurs, a four-injections-per-day regimen should be prescribed, similar to the protocol for women with type 1 diabetes[35,74] (table V). The insulin is administered to provide the basal and the meal-related insulin bolus. This delivery may be given by four injections a day of combinations of NPH and regular human insulin; however, it is possible to decrease the number of injections to three per day if the patient is willing to time her lunch to coincide with the pre-programmed insulin midday peak if morning NPH insulin is increased and, thus, no pre-lunch insulin is necessary.

Table V. Initial calculation of insulin therapy for a regimen requiring four injections per day[a] for gestational diabetes

Time	Fraction of total insulin dose	
	NPH-insulin[b]	regular human insulin
Pre-breakfast	5/18	4/18 (2/9)
Pre-lunch		3/18 (1/6)
Pre-dinner		3/18 (1/6)
Bedtime	3/18 (1/6)	

a Total daily insulin dose = 0.7 U/kg for weeks 1–18 of gestation; 0.8 U/kg for weeks 18–26; 0.9 U/kg for weeks 26–36; 1.0 U/kg for weeks 36–40, calculated for the present pregnant weight in kg at each timepoint. Doses may need to be increased for morbidly obese women or in the case of twin gestation.

b Insulin suspension isophane.

The total dose of insulin for the day, when both a basal and meal-related insulin is needed should be based on bodyweight and gestational week (table V). In the first trimester the insulin requirement is 0.7 U/kg/day, in the second trimester it is 0.8 U/kg/day and in the third trimester it is 0.9–1.0 U/kg/day. In morbidly obese women, the initial doses of insulin may need to be increased to 1.5–2.0 U/kg to overcome the combined insulin resistance of pregnancy and obesity.[73]

The titration of insulin dosage in response to blood glucose levels is based on frequent monitoring. Six or more glucose measurements each day may be required to optimise therapy and ensure a smooth increase of insulin dose as the pregnancy progresses to a higher insulin requirement. Twin gestations will cause an approximate doubling of the insulin requirement throughout pregnancy. Of note, there is also support for less aggressive dose administration of insulin in women with gestational diabe-

tes when stricter adherence to the meal plan has been documented.

Insulin lispro, an analogue of human insulin, possesses unique properties that facilitate lowering of the postprandial glucose level, and this may make it a valuable therapeutic option in the treatment of gestational diabetes and prevention of neonatal complications. The rapid absorption of insulin lispro from the subcutaneous site allows for a faster peak insulin concentration versus regular human insulin. This effect more closely mimics physiological first-phase insulin release and results in lower postprandial glucose levels. In addition, insulin lispro is known to upregulate insulin receptors.[75]

In a study designed to assess the safety and efficacy of insulin lispro for the treatment of gestational diabetes, Jovanovic et al.[76] randomised 42 women with gestational diabetes in their second trimester who had failed to achieve normoglycaemia with diet alone to treatment arms consisting of either a regimen of NPH and regular human insulin or a regimen of NPH insulin and insulin lispro. After 6 weeks of therapy, the insulin lispro group had significantly lower postprandial glucose levels without an increase in hypoglycaemia events. In addition, no increase in lispro-specific or insulin-specific antibodies was demonstrated in the insulin lispro group.

Since placental transfer of insulin occurs when it is complexed with immunoglobulin, the lack of insulin lispro-induced antibody formation could be expected to result in little, if any, placental transfer of insulin lispro to the neonate, as was demonstrated in the latter study.[76] The overall decrease in circulating insulin as insulin lispro, plus the low immunogenic response to insulin lispro, leads to little maternal antibody formation and, therefore, no insulin transfer to the fetus. During parturition, the subset of mothers who received a continuous infusion of insulin lispro[76] had documented concentrations of insulin lispro at the time of delivery, but no insulin lispro could be detected in the cord blood. This finding lends additional support to the conclusion that insulin lispro does not cross the placenta.

In summary, for the treatment of gestational diabetes, insulin lispro proved to be as safe as regular human insulin in this study and resulted in significantly lower glycaemia. The antibody formation in response to insulin lispro is comparable with regular human insulin. Thus, whether macrosomia is linked to postprandial hyperglycaemia or maternal insulin antibody formation, insulin lispro demonstrated treatment benefits equivalent to those of regular human insulin for patients with gestational diabetes.

Recently, it has also been reported that insulin aspart[77] is efficacious and can be safely used for the treatment of women with gestational diabetes. Studies of the safety and efficacy of other insulin analogues (both rapid- and long-acting insulins) for the treatment of women with pre-gestational type 1 and type 2 diabetes are still in progress.

Of note, drugs that are associated with deterioration in glucose tolerance should be avoided, if possible, in the treatment strategies of women with gestational diabetes. Drugs to be avoided are listed in table VI. A woman who could have been managed by diet alone for her gestational diabetes may need insulin in order to maintain normoglycaemia while taking these drugs.

7. The Use of Oral Antihyperglycaemic Agents for Gestational Diabetes

Although the use of oral antihyperglycaemic agents in pregnancy has long been thought to increase the risk of fetal anomalies, there is now evidence that indicates otherwise.[78] This evidence clearly shows that blood glucose levels rather than

Table VI. Drugs that are commonly used during pregnancy that may cause deterioration in glucose tolerance

Glucocorticoids for asthma or arthritis, or to accelerate fetal lung maturity
Decongestants for asthma, cold or influenza symptoms, other symptomatic treatments such as antihistamines, and other asthma medications such as β-adrenoceptor agonists
Preterm labour drugs, including terbutaline
Ethanol (alcohol)
Blood pressure medications, including diuretics and β-adrenoceptor antagonists

the drugs themselves are responsible for the malformations.[78]

Langer et al.[78] studied 404 women with singleton pregnancies and gestational diabetes that required treatment. The women were randomly assigned between 11 and 33 weeks of gestation to receive glibenclamide (glyburide) or insulin according to an intensified treatment protocol. The study showed that the mean (± SD) pretreatment blood glucose level as measured at home for 1 week was not different between the groups; 114 ± 19 mg/dL (6.4 ± 1.1 mmol/L) in the glibenclamide group and 116 ± 22 mg/dL (6.5 ± 1.2 mmol/L) in the insulin group (p = 0.33). Likewise, the mean glucose levels during treatment were not different between the groups; 105 ± 16 mg/dL (5.9 ± 0.9 mmol/L) in the glibenclamide group and 105 ± 18 mg/dL (5.9 ± 1.0 mmol/L) in the insulin group (p = 0.99). In addition, there were no significant differences between the glibenclamide and insulin groups in the percentage of infants who were large for gestational age (12% and 13%, respectively), had macrosomia defined as a birth weight of ≥4000g (7% and 4%), had lung complications (8% and 6%), had hypoglycaemia (9% and 6%), were admitted to a neonatal intensive care unit (6% and 7%) or had fetal anomalies (2% and 2%). The cord-serum insulin concentrations were similar in the two groups, and glibenclamide was not detected in the cord serum of any infant in the glibenclamide group.

As a result of this study, oral antihyperglycaemic agents are gaining recognition as an effective and safely used alterative to insulin when diet alone fails to optimise the glycaemic profile in women with gestational diabetes.[79]

8. Conclusion

Pregnancy is a time when serial metabolic changes in the mother are carefully regulated to provide optimum substrate to both mother and fetus. Subtle disturbances in maternal metabolism can have implications not only for the index pregnancy but also for future generations. The goal of management during the past century has generally focused on the delivery of a live infant from a live mother. This goal is generally achieved at most centres. The challenge for the 21st century is to develop management strategies that provide not only a normal outcome of the index pregnancy, but also establish a maternal/fetal environment that does not place the mother, infant or subsequent generations at risk for abnormal glucose and insulin homeostasis. The challenge is to derive optimal treatment protocols and then document that these protocols have changed the destiny of the offspring.

Pregnancy represents a window of opportunity for healthcare providers to change lifestyle patterns toward habits that will be healthier for the individual as well as society. The challenge to clinicians is to provide information based on scientific evidence that facilitates the accomplishments of these goals.

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