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# Review: Gestational Diabetes Mellitus and Its Management

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## ABSTRACT

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of various degrees that is first detected during pregnancy. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As with diabetes mellitus in pregnancy in general, babies born to mothers with gestational diabetes are typically at increased risk of problems such as being large for gestational age (which may lead to delivery complications), low blood sugar, and jaundice. There are 2 subtypes of gestational diabetes. One is Type A1 gestational diabetes where abnormal oral glucose tolerance test (OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels) and other is Type A2 gestational diabetes where abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required. The goal of treatment is to reduce the risks of GDM for mother and child. A repeat OGTT should be carried out 2–4 months after delivery, to confirm the diabetes has disappeared. Afterwards, regular screening for type 2 diabetes is advised. If a diabetic diet or G.I. Diet, exercise, and oral medication are inadequate to control glucose levels, insulin therapy may become necessary. Glyburide and Metformin, a second generation sulfonylurea, has been shown to be an effective alternative to insulin therapy. In one study, 4% of women needed supplemental insulin to reach blood sugar targets.

**Key words:** Gestational diabetes mellitus, etiology, Management, oral hypoglycemic agents.

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# INTRODUCTION

Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy (especially during third trimester of pregnancy) [1, 2]. It is widely accepted as a disease only in the United States, there is some question whether the condition is natural during pregnancy. Gestational diabetes is caused when the body of a pregnant woman does not secrete excess insulin required during pregnancy leading to increased blood sugar levels. Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied, so may be a natural phenomenon.

As with diabetes mellitus in pregnancy in general, babies born to mothers with gestational diabetes are typically at increased risk of problems such as being large for gestational age (which may lead to delivery complications), low blood sugar, and jaundice. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decrease these risks. Women with gestational diabetes are at increased risk of developing type 2 diabetes mellitus (or, very rarely, latent autoimmune diabetes or Type 1) after pregnancy, as well as having a higher incidence of pre-eclampsia and Caesarean section; their offspring are prone to developing childhood obesity, with type 2 diabetes later in life. Most patients are treated only with diet modification and moderate exercise but some take anti-diabetic drugs, including insulin. Women treated for gestational diabetes, generally have smaller birth weight babies, leading to other problems, such as survival rate of premature and early births, particularly male babies.

**History**

For more than a century, it has been known that diabetes antedating pregnancy can have severe adverse effects on foetal and neonatal outcomes. As early as in the 1940s, it was recognized that women who developed diabetes years after pregnancy had experienced abnormally high foetal and neonatal mortality. By the 1950s the term “gestational diabetes” was applied to what was thought to be a transient condition that affected foetal outcomes adversely and then abated after delivery. In the 1960s, O’SullivanB found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy [3]. He proposed criteria for the interpretation of oral glucose tolerance tests (OGTTs) during pregnancy that were

fundamentally statistical, establishing cut-off values — approximately 2 standard deviations— for diagnosing glucose intolerance during pregnancy (4). In the 1980s those cut-off points were adapted to modern methods for measuring glucose and applied to the modern definition of gestational diabetes — glucose intolerance with onset or first recognition during pregnancy (5). While based on O'Sullivan's values for predicting diabetes after pregnancy, the diagnosis of gestational diabetes mellitus (GDM) also identifies pregnancies at increased risk for perinatal morbidity (6–8) and long-term obesity and glucose intolerance in offspring (9–11).

**Definition**

Gestational diabetes mellitus (GDM) is defined as glucose intolerance of various degrees that is first detected during pregnancy. GDM is detected through the screening of pregnant women for clinical risk factors and, among at-risk women, testing for abnormal glucose tolerance that is usually, but not invariably, mild and asymptomatic. GDM appears to result from the same broad spectrum of physiological and genetic abnormalities that characterize diabetes outside of pregnancy. Indeed, women with GDM are at high risk for having or developing diabetes when they are not pregnant. Thus, GDM provides a unique opportunity to study the early pathogenesis of diabetes and to develop interventions to prevent the disease. The current diagnostic criteria in the United States are based on the values of O'Sullivan and Mahan2 [4, 5]. They were derived from the results of 100-g, 3-hour OGTTs administered to 752 unselected gravidas, who represented 76% of individuals registering at a prenatal clinic over a 4-month period. The population was evenly divided among white and black women, and 97% of the tests were administered during the second or third trimesters. Data for each of the four venous whole blood glucose values (fasting, 1 hour, 2 hours, and 3 hours) were normally distributed. The predictive value of the derived thresholds (mean plus two standard deviations) for future diabetes was validated by applying them to a second population of 1,013 Non pregnant women who had been tested during a previous pregnancy and followed for up to 8 years. Using the life table method of analysis, O'Sullivan estimated that 29% of those whose values exceeded two standard deviations above the mean would develop diabetes within 7-8 years. It was concluded that the mean plus two standard deviations (rounded to the nearest 5 mg/dl) would be the most appropriate lower limits for diagnosing gestational diabetes. To avoid reliance on a single laboratory value for diagnosis of gestational diabetes, O'Sullivan and Mahan determined that two of the thresholds should be met or exceeded to make the diagnosis. Since the original publication of the above thresholds for diagnosing gestational diabetes, a number of changes have occurred in the way glucose is analyzed. The most critical change was the switch from whole blood samples to plasma, or

occasionally serum. Plasma or serum glucose levels are, on average, 14% higher than simultaneously measured levels in whole blood10. In 1979, the NDDG8 published conversions of the O'Sullivan and Mahan criteria that were intended to apply to plasma. The resulting values are shown in (Table-1). Although no explanation was provided, it seems that the NDDG changed the 1-hour whole blood value of O'Sullivan and Mahan from 165 mg/dl to 170 mg/dl. Then, it appears; the NDDG added 14% to each of the whole blood values and rounded off to the nearest 5 mg/dl.

**Table 1: O'Sullivan and Mahan Diagnostic Criteria for Gestational Diabetes Based on Whole Blood Glucose**

| Time | Venous blood | Venous plasma |
|---|---|---|
| 1 hour | 165mg/dl | 165mg/dl |
| 2hour | 143mg/dl | 145mg/dl |
| 3 hour | 127mg/dl | 125mg/dl |

If any two threshold values for whole blood glucose after a 100-g oral glucose challenge are met or exceeded, gestational diabetes is diagnosed.

## CLASSIFICATION

There are 2 subtypes of gestational diabetes (diabetes which began during pregnancy):

1. Type A1: abnormal oral glucose tolerance test (OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels.
2. Type A2: abnormal OGTT compounded by abnormal glucose levels during fasting and/or after meals; additional therapy with insulin or other medications is required.

The second group of diabetes which existed prior to pregnancy is also split up into several subtypes.

### Risk Factors

Classical risk factors for developing gestational diabetes are the following [7, 8]

- a previous diagnosis of gestational diabetes or pre-diabetes, impaired glucose tolerance, or impaired fasting glycaemia
- a family history revealing a first degree relative with type 2 diabetes
- maternal age - a woman's risk factor increases as she gets older (especially for women over 35 years of age)
- ethnic background (those with higher risk factors include African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and people originating from South Asia)
- Being overweight, obese or severely obese increases the risk by a factor 2.1, 3.6 and 8.6, respectively.
- a previous pregnancy which resulted in a child with a high birth weight (>90th centile, or >4000 g

(8 lbs 12.8 oz))

- previous poor obstetric history

In addition to this, statistics show a double risk of GDM in smokers. Polycystic ovarian syndrome is also a risk factor, although relevant evidence remains controversial. Some studies have looked at more controversial potential risk factors, such as short stature [4]. About 40-60% of women with GDM have no demonstrable risk factor; for this reason many advocate to screen all women. Typically women with gestational diabetes exhibit no symptoms but some women may demonstrate increased thirst increased urination, fatigue, nausea and vomiting, bladder infection, yeast infections and blurred vision.

**Etiology**

**Normal pregnancy**

A detailed discussion of glucose regulation in pregnancy is beyond the scope of this paper. However, 2 points are important for the discussion that follows. First, pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in individuals with type 2 diabetes. The insulin resistance appears to result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta. The fact that insulin resistance rapidly abates following delivery suggests that the major contributors to this state of resistance are placental hormones. The second point is that pancreatic β cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy. As a result, changes in circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity. Robust plasticity of β cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy.

**Gestational diabetes**

GDM is a form of hyperglycemia. In general, hyperglycemia results from an insulin supply that is inadequate to meet tissue demands for normal blood glucose regulation. Studies conducted during late pregnancy, when, as discussed below, insulin requirements are high and differ only slightly between normal and gestational diabetic women, consistently reveal reduced insulin responses to nutrients in women with GDM .Studies conducted before or after pregnancy, when women with prior GDM are usually more insulin resistant than normal women (also discussed below), often reveal insulin responses that are similar in the 2 groups or reduced only slightly in women with prior GDM [9]. However, when insulin levels and responses are expressed relative to each individual's degree of insulin resistance, a large defect in pancreatic β cell function is a consistent finding in women with prior GDM. Potential causes of inadequate β cell function are myriad and not fully described. Outside of pregnancy, there are 3 general settings that are recognized — through classification as distinct forms of diabetes mellitus — as separate

categories of β cell dysfunction: (a) autoimmune; (b) monogenic; and (c) occurring on a background of insulin resistance. There is evidence that β cell dysfunction in GDM can occur in all 3 major settings, a fact that is not surprising given that GDM is detected by what is, in essence, population screening for elevated glucose levels among pregnant women.

**Auto-immune Diabetes and GDM**

Type 1 diabetes results from autoimmune destruction of pancreatic β cells. It accounts for approximately 5–10% of diabetes in the general population (12). Prevalence rates vary by ethnicity, with the highest rates in Scandinavians and the lowest rates (i.e., 0%) in full-blooded Native Americans. Type 1 diabetes is characterized by circulating immune markers directed against pancreatic islets (anti–islet cell antibodies) or β cell antigens (such as glutamic acid decarboxylase [GAD]). A small minority (less than 10% in most studies) of women with GDM have the same markers present in their circulation [10, 11, 12]. Although detailed physiological studies of these women are lacking, they most likely have inadequate insulin secretion resulting from autoimmune damage to and destruction of pancreatic β cells. They appear to have evolving type 1 diabetes, which comes to clinical attention through routine glucose screening during pregnancy. The frequency of anti–islet cell and anti-GAD antibodies detected in GDM tends to parallel ethnic trends in the prevalence of type 1 diabetes outside of pregnancy. Patients with anti–islet cell or anti-GAD antibodies often, but not invariably, are lean, and they can rapidly develop overt diabetes after pregnancy.

**Monogenic Diabetes and GDM**

Monogenic diabetes mellitus has been identified outside of pregnancy in 2 general forms. Some patients have mutations in autosomes (autosomal dominant inheritance pattern, commonly referred to as maturity-onset diabetes of the young [MODY], with genetic subtypes denoted as MODY 1, MODY 2, etc.). Others have mutations in mitochondrial DNA, often with distinct clinical syndromes such as deafness. In both instances, onset tends to occur at an early age relative to other forms of no immune diabetes (e.g., type 2 diabetes, described below), and patients tend not to be obese or insulin resistant. Both features point to abnormalities in the regulation of β cell mass and/or function. Indeed, detailed metabolic studies have revealed abnormalities in glucose-mediated insulin secretion in some forms of MODY (32). Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes coding for: (a) glucokinase (MODY 2); (b) hepatocyte nuclear factor 1α (MODY 3); (c) and insulin promoter factor 1 (MODY 4). Together, these monogenic forms of GDM account for less than 10% of GDM cases[5, 13, 14].

**Prognosis**

Gestational diabetes generally resolves once the baby is born. Based on different studies, the chances of developing GDM in a second pregnancy are between 30 and 84%, depending on ethnic background. A second pregnancy within 1 year of the previous pregnancy has a high rate of recurrence.

Women diagnosed with gestational diabetes have an increased risk of developing diabetes mellitus in the future [15, 16.] The risk is highest in women who needed insulin treatment, had antibodies associated with diabetes (such as antibodies against glutamate decarboxylase, islet cell antibodies and/or insulinoma antigen-2), women with more than two previous pregnancies, and women who were obese (in order of importance). Women requiring insulin to manage gestational diabetes have a 50% risk of developing diabetes within the next five years. Depending on the population studied, the diagnostic criteria and the length of follow-up, the risk can vary enormously. The risk appears to be highest in the first 5 years, reaching a plateau thereafter. One of the longest studies followed a group of women from Boston, Massachusetts; half of them developed diabetes after 6 years, and more than 70% had diabetes after 28 years. In a retrospective study in Navajo women, the risk of diabetes after GDM was estimated to be 50 to 70% after 11 years. Another study found a risk of diabetes after GDM of more than 25% after 15 years. In populations with a low risk for type 2 diabetes, in lean subjects and in patients with auto-antibodies, there is a higher rate of women developing type 1 diabetes.

Children of women with GDM have an increased risk for childhood and adult obesity and an increased risk of glucose intolerance and type 2 diabetes later in life. This risk relates to increased maternal glucose values. It is currently unclear how much genetic susceptibility and environmental factors each contribute to this risk, and if treatment of GDM can influence this outcome.

## PATHOPHYSIOLOGY

**Effect of insulin on glucose uptake and metabolism.**

Insulin binds to its receptor on the cell membrane which in turn starts many protein activation cascades. These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose, glycogen synthesis, glycolysis and fatty acid synthesis.

The precise mechanisms underlying gestational diabetes remain unknown. The hallmark of GDM is increased insulin resistance [17]. Pregnancy hormones and other factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signalling pathway behind the insulin receptor. Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in the bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance; about 1.5-2.5 times more insulin is produced than in a normal pregnancy.

Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which progresses thereafter to levels seen in non-pregnant patients with type 2 diabetes. It is thought to secure

glucose supply to the growing foetus. Women with GDM have an insulin resistance they cannot compensate with increased production in the β-cells of the pancreas. Placental hormones, and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Cortisol and progesterone are the main culprits, but human placental lactogen, prolactin and estradiol contribute too. It is unclear why some patients are unable to balance insulin needs and develop GDM, however a number of explanations have been given, similar to those in type 2 diabetes: autoimmunity, single gene mutations, obesity, and other mechanisms [18]. Because glucose travels across the placenta (through diffusion facilitated by GLUT3 carriers), the foetus is exposed to higher glucose levels. This leads to increased foetal levels of insulin (insulin itself cannot cross the placenta). The growth-stimulating effects of insulin can lead to excessive growth and a large body (macrosomia). After birth, the high glucose environment disappears, leaving these newborns with ongoing high insulin production and susceptibility to low blood glucose levels (hypoglycaemia) (Figure 1).

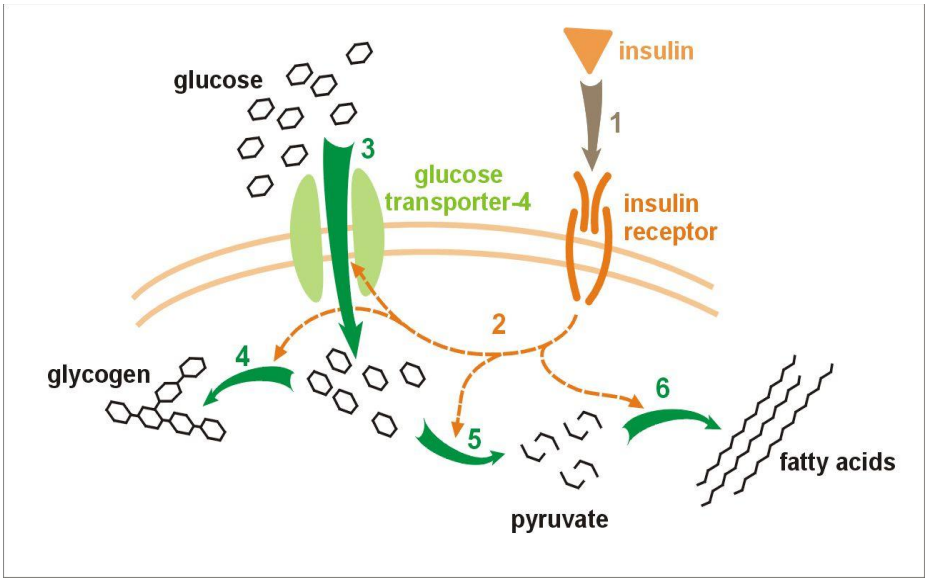


**Figure 1: Picture representing Glucose uptake into the Cells.**

**Hypothesis**

It is possible that GDM develops in response to an‘antigenic load’ and ‘individuals’ capacity to express HLA-G and the interaction between the HLA-G expression and NF-jB activity are the main determinants in this process. Adipose tissue itself may serve as an antigenic source, but the foetus is the major source of the antigenic load here. In this sense, there is an analogy between the development of DM in some transplant patients and GDM development in some pregnancies. The antigenic load is represented by the transplanted organ in transplant patients and by the foetus in GDM patients. Tolerance to both pregnancy and organ transplantation may be generated via similar immunologic mechanisms. Thus, HLA-G may play similar roles in the

development of diabetes in both conditions. For the sake of convenience, this novel hypothesis will be referred as ‘‘antigenic load hypothesis’’ within this text[20, 22, 25].

- **Role of adipose tissue**:

  Adipose tissue secretes a variety of proteins, called adipocytokines that can potentially impact on glucose metabolism. Among these adipocytokines are adiponectin, leptin, resistin, visfatin and omentin. Adipose tissue also secretes other cytokines such as IL-6, IL-1, TNF-a and certain complement factors [6, 10, and 19]. Thus, it does not function only as an energy store but is now regarded as an endocrine organ. Adiponectin, visfatin and omentin appear as insulin-sensitizing adipocytokines, whereas TNF-a, IL-6 and resistin induce insulin resistance. Hence, it is evident that adipose tissue plays a central role in the development of diabetogenic conditions. According to the antigenic load hypothesis, adipose tissue itself is an antigenic source. Increased adipose tissue (obesity) means an increased antigenic load. The finding of antibody formation to cell membranes of adipocytes in human blood supports this postulation[20].

- **Role of inflammation:**

  Type 2 DM is associated with a chronic low-grade systemic inflammation. Some inflammatory cytokines (mainly adipocytokines), through their ability to interfere with insulin signalling, have been implicated in insulin resistance in type 2 DM [8]. Biomarkers of inflammation such as TNF-a, IL-6 and CRP that are present at increased levels in individuals who are obese and insulin resistant may predict the development of type 2 DM. Development of GDM during pregnancy has been reported to be associated with inflammatory reactions in the maternal circulation, and inflammation was suggested to be a pathophysiological link between GDM and future type 2 diabetes mellitus[20].

- **Role of NF-jB:**

  Identification of the role of NF-jB in the TNF-a induced insulin resistance has been one of the cornerstones for the investigations in diabetes field. NF-jB and its target genes such as TNF-a and IL-6 are involved in the development of insulin resistance. These findings arose increased activity of NF-jB as a chief suspect for the development of insulin resistance and type 2 DM. NF-jB provides a link between inflammation and obesity- induced insulin resistance. Furthermore, it is now advocated that NF-jB is a culprit in the development of insulin resistance and diabetic complications.

- **Role of HLA-G:**

If a relationship between HLA-G and GDM were established, we could find some clues for the answers to the questions above. Actually, the relation between HLA-G and type 2 DM has never been investigated either. During pregnancy, maternal immune system and semi allogenic foetus are in a close interaction [20, 21 and 22]. Why is the foetus not rejected in pregnancy? Non-classical HLA class Ib molecules which are expressed on trophoblast cells in the placenta are supposed to be involved in this process. The trophoblast cells originating from the foetus do not express classical HLA classes Ia and II antigens. A non-classical HLA class Ib molecule, HLA-G, is thought to be responsible for the acceptance of the semiallogenic fetus. Beside its central role in the maternal– foetal tolerance, it is distinguished from other HLA class I genes by its low polymorphism and tissue distribution that is somewhat restricted to normal foetal and adult tissues that display a tolerogenic function towards both innate and acquired immunity. HLA-G may have a role in implantation and in some pregnancy complications like recurrent abortions and preeclampsia. A suggested role of HLA-G in the immunological analogy between allograft rejection, recurrent abortion and preeclampsia has already been proposed. Can HLA-G be a link between organ transplantation and diabetes? Is there an association between organ transplantation and development of type 2 diabetes? It has been a well known observation that development of type 2 DM, a condition known as post-transplant DM, is a frequently seen complication after organ transplantations. It has also been demonstrated that pre-transplant serum adiponectin concentration is an independent predictive factor for post-transplant DM development in kidney-transplanted patients. Expression of HLA-G in the sera of heart, kidney and liver transplant recipients has been associated with a significantly better acceptance and fewer rejections of the transplanted organs. At this point, studies investigating the incidence of post transplant DM with respect to HLA-G expression in transplant patients are needed. On the other hand,\ in a study investigating HLA-G expression after heart transplantation, it was a finding that none of the HLA-G-positive patients had a history of DM when compared with 14.3% incidence in HLAG- negative patients[23,24]. Thus, it seems logical to think that immunological mechanisms generating tolerance to both pregnancy and organ transplantation may share common pathways and the same mechanisms may also be involved in the development of DM. Does HLA-G play a role in autoimmunity? Is there a role of autoimmunity in type 2 DM and GDM? We know that HLA is associated with autoimmune diseases including type 1 DM. Some studies have indicated that HLA-G may have a direct immune-modulatory role during pregnancy. HLA-G also plays a role in autoimmune diseases by protecting tissues from damage by infiltrating cytotoxic T cells. Supporting this idea,

linkage disequilibrium between HLA-G and HLA class II genes has been found. It is well known that type 1 DM has an autoimmune origin and type 2 DM is due to an insulin resistance. But increasing data show that there is an overlap between these two conditions and autoimmunity is a factor in type 2 DM. Anti-CD38 auto-antibodies have been found in some patients with type 2 DM and shown to stimulate insulin secretion by cultured human islets . It is now accepted that while some degree of insulin resistance is present in type 1 DM, markers of autoimmunity are often associated with type 2 DM [20,25].

**Complications**

GDM poses a risk to mother and child. This risk is largely related to high blood glucose levels and its consequences. The risk increases with higher blood glucose levels. Treatment resulting in better control of these levels can reduce some of the risks of GDM considerably.

The two main risks GDM imposes on the baby are growth abnormalities and chemical imbalances after birth, which may require admission to a neonatal intensive care unit. Infants born to mothers with GDM are at risk of being both large for gestational age (macrosomic) and small for gestational age. Macrosomia in turn increases the risk of instrumental deliveries (e.g. forceps, ventouse and caesarean section) or problems during vaginal delivery (such as shoulder dystocia). Macrosomia may affect 12% of normal women compared to 20% of patients with GDM [26, 27, 28]. However, the evidence for each of these complications is not equally strong; in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study for example, there was an increased risk for babies to be large but not small for gestational age. Research into complications for GDM is difficult because of the many confounding factors (such as obesity). Labelling a woman as having GDM may in itself increase the risk of having a caesarean section. Neonates are also at an increased risk of low blood glucose (hypoglycaemia), jaundice, high red blood cell mass (polycythemia) and low blood calcium (hypocalcaemia) and magnesium (hypomagnesaemia). GDM also interferes with maturation, causing dysmature babies prone to respiratory distress syndrome due to incomplete lung maturation and impaired surfactant synthesis. Unlike pre-gestational diabetes, gestational diabetes has not been clearly shown to be an independent risk factor for birth defects. Birth defects usually originate sometime during the first trimester (before the 13th week) of pregnancy, whereas GDM gradually develops and is least pronounced during the first trimester. Studies have shown that the offspring of women with GDM are at a higher risk for congenital malformations. A large case-control study found that gestational diabetes was linked with a limited group of birth defects, and that this association was generally limited to women with a higher body mass index ($\geq 25$ kg/m$^2$). It is difficult to make sure that this is not partially due to the inclusion of women with pre-existent type 2 diabetes who were not diagnosed before pregnancy [20, 29, 30]. Because of conflicting studies, it is unclear at the moment whether women with GDM have a higher risk of preeclampsia. In the HAPO study, the risk of

preeclampsia was between 13% and 37% higher, although not all possible confounding factors were corrected. (Table 2)

**Table 2: Tests and Screening 2006 WHO Diabetes criteria**

| Condition | 2 hour glucose | Fasting glucose |
|---|---|---|
| | mmol/l(mg/dl) | mmol/l(mg/dl) |
| Normal | <7.8 (<140) | <6.1 (<110) |
| Impaired fasting glycaemia | <7.8 (<140) | ≥ 6.1(≥110) & <7.0(<126) |
| Impaired glucose tolerance | ≥7.8 (≥140) | <7.0 (<126) |
| Diabetes mellitus | ≥11.1 (≥200) | ≥7.0 (≥126) |

A number of screening and diagnostic tests have been used to look for high levels of glucose in plasma or serum in defined circumstances. One method is a stepwise approach where a suspicious result on a screening test is followed by diagnostic test. Alternatively, a more involved diagnostic test can be used directly at the first antenatal visit in high-risk patients (for example in those with polycystic ovarian syndrome or acanthosis nigricans)

**Tests for gestational diabetes**

Non-challenge blood glucose tests

- Fasting glucose test
- 2-hour postprandial (after a meal) glucose test
- Random glucose test
- Screening glucose challenge test

**a) Oral glucose tolerance test (OGTT)**

Non-challenge blood glucose tests involve measuring glucose levels in blood samples without challenging the subject with glucose solutions [31.] A blood glucose level is determined when fasting, 2 hours after a meal, or simply at any random time. In contrast, challenge tests involve drinking a glucose solution and measuring glucose concentration thereafter in the blood; in diabetes, they tend to remain high. The glucose solution has a very sweet taste which some women find unpleasant; sometimes, therefore, artificial flavours are added. Some women may experience nausea during the test, and more so with higher glucose levels. There are different opinions about optimal screening and diagnostic measures, in part due to differences in population risks, cost-effectiveness considerations, and lack of an evidence base to support large national screening programs. The most elaborate regime entails a random blood glucose test during a booking visit, a screening glucose challenge test around 24–28 weeks' gestation, followed by an OGTT if the tests are outside normal limits. If there is a high suspicion, women may be tested earlier.

**b) Non-challenge blood glucose tests**

When a plasma glucose level is found to be higher than 126 mg/dl (7.0 mmol/l) after fasting, or over 200 mg/dl (11.1 mmol/l) on any occasion, and if this is confirmed on a subsequent day, the diagnosis of GDM is made, and no further testing is required. These tests are typically performed at the first antenatal visit [32]. They are patient-friendly and inexpensive, but have a lower test performance compared to the other tests, with moderate sensitivity, low specificity and high false positive rates.

**c) Screening glucose challenge test**

The screening glucose challenge test (sometimes called the O'Sullivan test) is performed between 24–28 weeks, and can be seen as a simplified version of the oral glucose tolerance test (OGTT). It involves drinking a solution containing 50 grams of glucose, and measuring blood levels 1 hour later.

If the cut-off point is set at 140 mg/dl (7.8 mmol/l), 80% of women with GDM will be detected. If this threshold for further testing is lowered to 130 mg/dl, 90% of GDM cases will be detected, but there will also be more women who will be subjected to a consequent OGTT unnecessarily.

**d) Oral glucose tolerance test**

The OGTT should be done in the morning after an overnight fast of between 8 and 14 hours. During the three previous days the subject must have an unrestricted diet (containing at least 150 g carbohydrate per day) and unlimited physical activity. The subject should remain seated during the test and should not smoke throughout the test. The test involves drinking a solution containing a certain amount of glucose, and drawing blood to measure glucose levels at the start and on set time intervals thereafter.

The diagnostic criteria from the National Diabetes Data Group (NDDG) have been used most often, but some centers rely on the Carpenter and Coustan criteria, which set the cut off for normal at lower values [33, 34, 35] Compared with the NDDG criteria, the Carpenter and Coustan criteria lead to a diagnosis of gestational diabetes in 54 percent more pregnant women, with an increased cost and no compelling evidence of improved perinatal outcomes [5.]

The following are the values which the American Diabetes Association considers to be abnormal during the 100 g of glucose OGTT:

- Fasting blood glucose level ≥95 mg/dl (5.33 mmol/L)
- 1 hour blood glucose level ≥180 mg/dl (10 mmol/L)
- 2 hour blood glucose level ≥155 mg/dl (8.6 mmol/L)
- 3 hour blood glucose level ≥140 mg/dl (7.8 mmol/L)

An alternative test uses a 75 g glucose load and measures the blood glucose levels before and after 1 and 2 hours, using the same reference values. This test will identify fewer women who are at risk, and there is only a weak concordance (agreement rate) between this test and a 3 hour 100 g test. The glucose values used to detect gestational diabetes were first determined by O'Sullivan and Mahan (1964) in a retrospective cohort study (using 100 grams of glucose OGTT) designed to detect risk of developing type 2 diabetes in the future. The values were set using whole blood and required two values reaching or

exceeding the value to be positive. Subsequent information led to alterations in O'Sullivan's criteria. When methods for blood glucose determination changed from the use of whole blood to venous plasma samples, the criteria for GDM were also changed.

**e) Urinary glucose testing:**

Women with GDM may have high glucose levels in their urine (glucosuria). Although dipstick testing is widely practiced, it performs poorly, and discontinuing routine dipstick testing has not been shown to cause under diagnosis where universal screening is performed [36, 37]. Increased glomerular filtration rates during pregnancy contribute to some 50% of women having glucose in their urine on dipstick tests at some point during their pregnancy. The sensitivity of glucosuria for GDM in the first 2 trimesters is only around 10% and the positive predictive value is around 20%.

## MANAGEMENT OR TREATMENT:

A kit with a glucose meter and diary used by a woman with gestational diabetes. The goal of treatment is to reduce the risks of GDM for mother and child. Scientific evidence is beginning to show that controlling glucose levels can result in less serious foetal complications (such as macrosomia) and increased maternal quality of life. Unfortunately, treatment of GDM is also accompanied by more infants admitted to neonatal wards and more inductions of labour, with no proven decrease in cesarean section rates or perinatal mortality. These findings are still recent and controversial.

A repeat OGTT should be carried out 2–4 months after delivery, to confirm the diabetes has disappeared. Afterwards, regular screening for type 2 diabetes is advised. If a diabetic diet or G.I. Diet, exercise, and oral medication are inadequate to control glucose levels, insulin therapy may become necessary. The development of macrosomia can be evaluated during pregnancy by using sonography. Women who use insulin, with a history of stillbirth, or with hypertension are managed like women with

**Lifestyle**

Counseling before pregnancy (for example, about preventive folic acid supplements) and multidisciplinary management are important for good pregnancy outcomes. Most women can manage their GDM with dietary changes and exercise [38]. Self monitoring of blood glucose levels can guide therapy. Some women will need antidiabetic drugs, most commonly insulin therapy. Any diet needs to provide sufficient calories for pregnancy, typically 2,000 - 2,500 kcal with the exclusion of simple carbohydrates. The main goal of dietary modifications is to avoid peaks in blood sugar levels. This can be done by spreading carbohydrate intake over meals and snacks throughout the day, and using slow-release carbohydrate sources—known as the G.I. Diet. Since insulin resistance is highest in mornings, breakfast carbohydrates need to be restricted more[8] ingesting more fiber in foods with whole grains, or fruit and vegetables can also reduce the risk of gestational diabetes. Regular moderately intense physical exercise is advised,

although there is no consensus on the specific structure of exercise programs for GDM. Self monitoring can be accomplished using a handheld capillary glucose dosage system. Compliance with these glucometer systems can be low. Target ranges advised by the Australasian Diabetes in Pregnancy Society are as follows:

• Fasting capillary blood glucose levels <5.5 mmol/L

• 1 hour postprandial capillary blood glucose levels <8.0 mmol/L

• 2 hour postprandial blood glucose levels <6.7 mmol/L

Regular blood samples can be used to determine HbA1c levels, which give an idea of glucose control over a longer time period. Research suggests a possible benefit of breastfeeding to reduce the risk of diabetes and related risks for both mother and child.

**Medication**

If monitoring reveals failing control of glucose levels with these measures, or if there is evidence of complications like excessive fetal growth, treatment with insulin might become necessary. The most common therapeutic regime involves pre-meal fast-acting insulin to blunt sharp glucose rises after meals [24, 39, 40].Care needs to be taken to avoid low blood sugar levels (hypoglycemia) due to excessive insulin injections. Insulin therapy can be normal or very tight; more injections can result in better control but requires more effort, and there is no consensus that it has large benefits. There is some evidence that certain oral glycaemic agents might be safe in pregnancy, or at least, are significantly less dangerous to the developing fetus than poorly controlled diabetes. Glyburide, a second generation sulfonylurea, has been shown to be an effective alternative to insulin therapy. In one study, 4% of women needed supplemental insulin to reach blood sugar targets. Metformin has shown promising results, with its oral format being much more popular than insulin injections. Treatment of polycystic ovarian syndrome with metformin during pregnancy has been noted to decrease GDM levels. A recent randomized controlled trial of metformin versus insulin showed that women preferred metformin tablets to insulin injections, and that metformin is safe and equally effective as insulin. Severe neonatal hypoglycemia was less common in insulin-treated women, but preterm delivery was more common. Almost half of patients did not reach sufficient control with metformin alone and needed supplemental therapy with insulin; compared to those treated with insulin alone, they required less insulin, and they gained less weight. With no long term studies into children of women treated with the drug, here remains a possibility of long-term complications from metformin therapy, although follow-up at the age of 18 months of children born to women with

polycystic ovarian syndrome and treated with metformin revealed no developmental abnormalities.

## CONCLUSION

Women with DM who are of reproductive age should be identified as members of a high-risk group. Access to specialized pre-pregnancy clinics should be made available where their DM can be intensively managed throughout pregnancy by a combined obstetrical/ endocrine multidisciplinary team. Use of multiple insulin injection regimens, including use of insulin as part during pregnancy, is both well tolerated and effective and may offer some benefits with respect to postprandial glycemic control.

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