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Review Article

Management of Gestational Diabetes Mellitus – A Review

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Abstract: Gestational Diabetes Mellitus (GDM) is a controversial entity, with conflicting guidelines and treatment protocols. There are various types of diagnostic methods of GDM; each country has got their own. However, 75-gm 2-hour oral glucose tolerance test is widely practiced. Recent studies show that diagnosis and management of this disorder have got additional beneficial effects on the mother and the fetus including reduced rates of preeclampsia, shoulder dystocia, birth trauma, and neonatal hypoglycemia. There is also less incidence of development of obesity and metabolic syndrome in later life of the mother and child. Treatment consists of glucose monitoring, dietary modification, exercise, and when necessary pharmacotherapy to maintain euglycemia. Insulin therapy is the mainstay of treatment, though glyburide and metformin are also used in selected cases. Use of insulin analogue including basal-bolus therapy is a recent addition in the management. Fructosamine as a measure of glycemic control is not widely used due to lack of standardization. In women receiving pharmacotherapy, antenatal testing with non-stress tests and amniotic fluid indices are started in the third trimester to monitor fetal well-being. The method and timing of delivery are controversial. Following delivery follow up is needed. Women with gestational diabetes are at high risk of subsequent development of type 2 diabetes. Lifestyle modification should therefore be encouraged, along with regular screening for diabetes.
Keywords: Gestational diabetes mellitus, antidiabetic pharmacotherapy, pregnancy.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common medical complications of pregnancy; gestational diabetes mellitus (GDM) accounts for approximately 90-95% of all cases [1]. GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The prevalence of GDM varies from 1 to 14%, in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group [2]. The incidence of gestational diabetes is also increasing as a result of higher rates of obesity in the general population and more pregnancies in older women. The concerns of diabetes are mainly due to the maternal and fetal complications if the glycemic control during pregnancy is not adequate. There is a linear relationship between maternal hyperglycemia and adverse fetal outcomes. Two types of risk factors are identified in GDM. Unmodifiable risk factors are age, genetic background, ethnicity, number of previous pregnancies and recently a short stature has been identified as an independent variable. Modifiable known risk factors are obesity, lack of exercise, dietary fat and lifestyle habits like smoking and certain drugs.

GDM is a major cause of maternal, fetal and neonatal morbidities like pre-eclampsia, birth trauma, cesarean section, stillbirth, respiratory distress, hypoglycemia, hyperbilirubinemia, polycythemia, hypocalcemia, increased neonatal intensive care unit admissions and neonatal adiposity with its long-term sequelae including childhood obesity and diabetes [3]. Both Type 2 diabetes and GDM are heterogeneous disorders but their pathophysiology is the same like peripheral insulin resistance. So we can conclude that they are the same disease with different names, representing a continuum of glucose tolerance deterioration.

The strategies and techniques for the diagnosis and management of GDM have greatly improved through the past two decades; new insulin therapies are now available and the diabetic patient's self-monitoring of blood glucose is widely incorporated in care plans. The aim of this review is to evaluate international guidelines regarding the diagnosis and management of GDM and to propose possible new therapies.

Methodology

PubMed, other electronic databases and relevant guidelines were searched to identify articles

that included the keywords 'pregnancy', 'gestational diabetes mellitus' and 'anti-diabetic therapy'. The relevant papers were searched manually for further information.

Diagnosis

For diagnosis of GDM, there is variation of concept. American Diabetic Association (ADA) prefers to do screening and diagnostic tests. The most utilized screening test is 50-g non-fasting one-hour glucose challenge test. Screening cutoffs are 130 mg/dL (7.20 mmol/ L; 90 percent sensitivity) or 140 mg/ dL (7.75 mmol/ L; 80 percent sensitivity) [4]. The most recent ADA and American College of Obstetrics & Gynecology (ACOG) guidelines recommend the same cutoff values [5]. Random or fasting glucose measurement is not recommended for screening because of poor specificity [6]. The diagnostic test for GDM is the 100-g 3- hour oral glucose tolerance test (OGTT). Gestational diabetes is diagnosed if two or more plasma glucose measurements meet or exceed the following thresholds: fasting level of 95 mg/ dL (5.25 mmol/ L), one-hour level of 180 mg / dL (10.00 mmol/ L), two-hour level of 155 mg/ dL (8.60 mmol/ L), or three-hour level of 140 mg/ dL [5]. In general, screening and diagnostic tests are performed between 24 and 28 weeks, because at this point in gestation the diabetogenic effect of pregnancy is manifested. In contrast, women at high risk of gestational diabetes should be screened at their first antepartum visit [7]. In Australia universal testing for hyperglycemia at the first pregnancy visit is encouraged [8]. At present, the most commonly used internationally used test is the 2-hour 75 g OGTT. This is the test recommended by WHO and it is used in Europe. Screening cutoffs are if any one of the measurements exceeds these levels i.e. fasting 5.1 mmol/L or above and 2-hour plasma glucose level of 8.5 mmol/L or above [9].

Management

Recent data provide strong evidence that proper treatment of GDM reduces adverse maternal and perinatal outcomes. The Australian Carbohydrate Intolerance Study in Pregnant Women randomized women to receive routine care or treatment for gestational diabetes [10]. Primary fetal outcomes included death, shoulder dystocia, bone fracture, and nerve palsy. Primary maternal outcomes were induction of labor and caesarean delivery. Infants of women in the treatment group had significantly fewer perinatal complications (relative risk [RR] = 0.33; 95% confidence interval [CI], 0.14 to 0.75). There were more labor inductions in the treatment group (RR = 1.36; 95% CI, 1.15 to 1.62), but the number of cesarean deliveries was similar in both groups. The results of this trial offer strong evidence that treatment of gestational diabetes improves fetal outcomes [10].

Further evidence of possible adverse effects associated with even mild maternal hyperglycemia comes from the Hyperglycemia and Adverse Pregnancy Outcomes trial [11]. In this study, investigators followed a group of 23,316 pregnant women at 24 to 32 weeks gestation with fasting glucose levels of up to 105 mg/dL (5.85 mmol /L), and with levels of up to 200 mg/dL (11.1 mmol/ L) after 2-hour 75-g glucose load. This cohort included women with glucose levels at the upper end of the normal range, as well as women with mild gestational diabetes. The investigators found a linear correlation between increasing maternal glucose levels and increasing birth weight, first-time cesarean delivery, fetal C peptide levels, and neonatal hypoglycemia.

a. Diet

First-line therapy for women with gestational diabetes is dietary modification, often referred to as medical nutritional therapy (MNT). This is best done in consultation with an experienced nutritionist, and should take cultural preferences into account. The ADA also recommends nutritional counseling, if possible by a registered dietitian, with individualization of the nutrition plan based on height and weight [12]. For normal-weight women (BMI: 20-24 kg/m^2) 30 kcal/kg should be prescribed; for overweight and obese women (BMI > 24-34 kg/m^2) calories should be restricted to 25 kcal/kg, and for morbidly obese women (BMI > 34 kg/m^2) calories should be restricted to 20 kcal/kg or less [13]. In normal pregnancy expected weight gain varies according to the pre pregnancy weight. The Fifth International Workshop-Conference on GDM recommends a relatively small gain during pregnancy of 7 kg (15 lb.) for obese women (BMI $\geq$ 30 kg/m^2) and a proportionally greater weight gain (up to 18 kg or 40 lb.) for underweight women (BMI < 18.5 kg/m^2). However, there are no data on optimal weight gain for women with GDM [7]. Caloric composition includes 40-50% from complex, high-fiber carbohydrates, 20% from protein, and 30-40% from primarily unsaturated fats. The calories may be distributed 10-20% at breakfast, 20-30% at lunch, 30-40% at dinner and 30% with snacks, especially a bed time snack in order to reduce nocturnal hypoglycemia [14].

However, there should not be excessive calorie restriction. Two studies have reported a relationship between elevated maternal serum ketone levels and reduced psychomotor development and IQ from the third to the ninth year of age in the offspring of mothers with GDM [15, 16]. Even when investigators re-evaluated their findings by taking into account socioeconomic status, race or ethnicity and the presence of gestational or pre-existing diabetes, this association persisted. Although the correlation between IQ and ketone levels was weak, it was statistically significant; therefore, it would be prudent to avoid excessive ketonemia or ketonuria during pregnancy [17].

b. Exercise

In the management of Type 2 DM in non-pregnant condition, physical exercise is advocated. Very few studies or reports on the effects of physical activity for the prevention or treatment of gestational diabetes are available at present. Dempsey *et al.;* in a prospective study and in a case-control study showed that lean as well as overweight women who were physically active before and/or during pregnancy experienced statistically significant reduced risks of GDM (48% risk reduction) [18]. In 2006, Zhang *et al.* found that vigorous physical activity before pregnancy and continuation of activity during early pregnancy may reduce the risk of developing abnormal glucose tolerance and GDM [19].

Dietary strategies are the mainstay of therapy for patients with GDM. However, some women suffering from GDM cannot be managed with diet alone and need to use insulin. But insulin corrects hyperglycemia without affecting peripheral insulin resistance. Thus, the most appropriate intervention would be exercise, which affects insulin resistance and, in the absence of either medical or obstetric complications, is certainly the most suitable intervention for GDM women [20]. ADA has endorsed exercise as 'a helpful adjunctive therapy' for GDM when euglycemia is not achieved by diet alone [21].

In 1985 Artal *et al.;* conducted the first pilot study on the efficacy and safety of an exercise program in pregnant patients with GDM. It culminated with the following recommendation by the Second International Workshop-Conference on Gestational Diabetes Mellitus: women with an active lifestyle may continue a program of moderate exercise under medical supervision during pregnancy [22]. In 2001 ACOG suggested that 'women with GDM who lead an active lifestyle should be encouraged to continue a program of exercise approved for pregnancy' [23]. In 2004, Brankston *et al.* found that exercised overweight women were less likely to need insulin compared with overweight women who received only a diet intervention [24]. In 2007 continuation of physical activity in the form of exercise has also been recommended in the Fifth International Workshop-Conference on Gestational Diabetes Mellitus.

The Cochrane Collaboration has recently carried out a meta-analysis on physical activity in pregnant women with GDM. The authors found no significant difference between exercise and no exercise and between exercise and insulin in all the outcomes evaluated (perinatal outcomes, pregnancy complications and maternal morbidity). The conclusion is that there is insufficient evidence to recommend, or advice against, pregnant women with GDM enrolling in exercise programs. Even if exercise is not beneficial during pregnancy, this change in lifestyle may persist after delivery and may help to prevent the onset of Type 2 diabetes and its long-term complications [25].

c. Monitoring Blood Glucose

In non-pregnant individuals, pre-prandial blood glucose is generally monitored. However, the fetus is more sensitive to glucose excesses than to the nadirs of glucose values at different moments of the day. A randomized trial comparing pre-prandial to 1-h postprandial glucose measurements showed that glycohemoglobin levels, macrosomia, neonatal hypoglycemia and cesarean deliveries were significantly lower among those who had postprandial monitoring [26]. Regarding the frequency of glucose monitoring it is stated that pregnant women who are on multiple daily insulin injection, will test their pre-meal, 1-hour post-meal and bedtime blood glucose levels daily [28]. But if they are on diet and exercise or taking oral therapy (with or without diet and exercise therapy) or single-dose intermediate-acting or long-acting insulin, they will test their fasting and 1-hour post-meal blood glucose levels daily [27]. Although daily self-glucose monitoring has not been demonstrated to reduce perinatal mortality in women with GDM, it appears to be useful in reducing potentially adverse outcome such as macrosomia [28].

Recently the new technology of continuous glucose monitoring (CGM) is available. The CGM measures interstitial glucose levels in subcutaneous tissue within a range of 50-400 mg/dl every 5 min [1]. CGM can accurately detect high postprandial blood glucose levels and nocturnal hypoglycemic events that may go unrecognized by intermittent blood glucose monitoring. However, CGM is not recommended to replace self-monitoring of blood glucose, but the intermittent application of CGM could be used who have problematic severe hypoglycemia (with or without impaired hypoglycemic awareness) or who have unstable blood glucose levels (to minimize variability) or to gain information about variability in blood glucose levels [27].

d. Target Blood Glucose

Pregnant women with pre-gestational or gestational DM are advised to keep their fasting blood glucose level 5.3 mmol/L and 1-hour and 2-hour post-prandial level 7.8 and 6.7 mmol/L respectively [5]. HbA1c levels are measured in all women with gestational diabetes at the time of diagnosis to identify those who may have pre-existing type 2 diabetes [27]. But HbA1c levels are not used routinely to assess a woman's blood glucose control in the second and third trimesters of pregnancy [27]. As due to increased red blood cell turnover, HbA1c is lower in normal pregnancy than in normal non pregnant women. The A1c target in pregnancy is 6–6.5% (42–48 mmol/mol); 6% (42 mmol/mol) may be optimal if this can be achieved without significant hypoglycemia, but the target may be relaxed to 7% (53 mmol/mol) if

necessary to prevent hypoglycemia. (5) Other alternate new measure of glycemic control—fructosamine test has been proposed. The fructosamine measures glycemic levels over a period of 2-3 weeks. However, it is less widely used due to lack of standardization [29].

e. Insulin treatment

Pharmacotherapy is indicated when medical nutrition therapy results in inadequate glucose control, lack of expected weight gain (as a result of calorie restriction), or when patients are consistently hungry. Pharmacotherapy is also indicated in elevated fasting glucose levels, because dietary modification has little effect on these levels.

Expert opinion guides insulin therapy because data from Randomized Controlled Trials are lacking. Insulin is started at a dosage of 0.7 units per kg per day (based on pre-pregnancy weight), given in divided doses. A commonly used dosing regimen includes two thirds of the total insulin dose to be given in the morning, with the remainder before dinner. The morning dose should be two thirds NPH and one third short-acting regular insulin, and the pre-dinner dose should be equal parts NPH and short-acting regular insulin [30]. However, this approach requires modification based on the patient's body mass index, glucose levels, and lifestyle.

Regular insulin, which is often used in pregnancy for the treatment of diabetes, has some drawbacks: it starts its action from 30 to 60 min after subcutaneous injection and it peaks too late (2-3 hour after injection) to be very effective in postprandial control; in addition, its action also lasts about 8-10 hour with an increased risk of postprandial hypoglycemia [31]. For this reason, insulin analogue started to be used in the last few years. Two types of insulin analogues are used, rapid acting like lispro and aspart (bolus) and long acting (basal) like glargine and detemir. Combining these two types of insulin, basal-bolus therapy (BBT) is planned which most closely simulates physiological insulin profiles and already in use in non-pregnant patients. Now this BBT is also used in pregnant patients. Compared to regular insulin, rapid acting insulin analogue is associated with lower rate of 1- and 2- hour postprandial hyperglycemia. [32, 31] This is important for perinatal outcome as post prandial hyperglycemia is more predictive of neonatal complications than is elevated fasting blood glucose level. Rapid acting analogues also reduce the risk of late postprandial hypoglycemia, helping to minimize daily glucose excursion. Use of insulin analogue in pregnancy is associated with decrease in HbA1c, less maternal and neonatal hypoglycemia when compared to conventional insulin (regular and NPH) [33]

f. Oral Anti-diabetic agents

Traditionally insulin is considered as the gold standard for management of GDM due to its unparalleled efficacy and safety. But it can be problematic for some women as it is expensive and invasive. This may lead to poor patient compliance. For this a safe and effective oral agent for the treatment of gestational diabetes is highly desired. Since GDM is characterized by insulin resistance and relatively decreased insulin secretion, a treatment with oral anti-diabetic agents (OAA) could be of potential interest. The sulfonylurea glyburide is close to meeting these goals, with prospective and retrospective studies demonstrating its effectiveness and probable safety [34, 35]. Randomized controlled studies conducted by Langer *et al.;* showed that glyburide does not cross the placenta due to its high protein binding affinity (99.8%) and short elimination half-life (10h) [36]. Glyburide increases insulin secretion, and it decreases insulin resistance. Its onset of action is approximately 4 h, and its duration of action is approximately 10 h. The starting dose is 2.5 mg orally in the morning. If the targeted level of glycemia is not reached, 2.5 mg could be added to the morning dose. If indicated (after 3-7 days), a further 5 mg could be added in the evening. Thereafter, the dose could be increased by 5 mg to a total of 20 mg/day. If patients fail to achieve glycemic objectives, insulin can be added to the regimen [36]. The insulin-treated patients and the glyburide-treated patients obtained comparable results for many outcomes: cord serum insulin concentrations, incidence of macrosomia, increased Ponderal Index, percentage of large for gestational age infants, and prevalence of neonatal metabolic complications, respiratory complications, pre-eclampsia and cesarean delivery [36]. However, there is evidence that glyburide is less successful in obese patients, GDM diagnosed before 25 weeks of gestation and in patients with marked hyperglycemia. Glyburide is found to be associated with a higher rate of neonatal hypoglycemia and macrosomia than insulin or metformin [37].

Metformin is classified as a category B drug, which implies that there is no evidence of animal or fetal toxicity or teratogenicity [38]. It is an insulin sensitizer increasing muscle glucose uptake but inhibiting gluconeogenesis. While many of the studies of the use of metformin in GDM are limited by small numbers, they are similarly encouraging; showing at least equivalent neonatal outcomes for metformin compared with insulin, while reporting reductions in maternal hypoglycemia weight gain and improved treatment satisfaction. There is also less incidence of neonatal hypoglycemia. Metformin is introduced gradually in 500 or 850 mg increments to a maximum of 2000 mg daily [1]. If there is inadequate glycemic control insulin is started and metformin continued [2]. Women with high BMI, prior history of GDM and high baseline glucose level have a high chance of missing their glycemic target. According to the few studies found in the literature, 30% of women treated with metformin required insulin to obtain adequate glycemic control [39]. Regarding the use of other OAA like

thiazolidinediones and acarbose there are only limited data in human pregnancy and so their use in pregnancy is not recommended.

Antenatal care

Management of the pregnant diabetic is a complex issue and a single provider cannot take care of all aspects of the care. It is a team work consisting of obstetrician, diabetologist, nutritionist, perinatologist, nurse and a social worker or counselor. Women with GDM which is well controlled by diet alone, fetal surveillance with non-stress test or biophysical profile may be initiated later in pregnancy. However, women who require medication for control of blood sugar, who are noncompliant or who have GDM that is not well controlled, earlier initiation of fetal surveillance is advised.

Fetal surveillance consists of screening for congenital anomalies, monitoring for fetal well-being, and ultrasound assessment of fetal growth. The ADA recommends screening for congenital anomalies in women with gestational diabetes who present with evidence of preexisting hyperglycemia, such as an HbA1c level greater than 7 percent, a fasting glucose level greater than 120 mg/ dL, or a diagnosis of gestational diabetes in the first trimester [8]. Monitoring for fetal well-being is generally based on local practice. The frequency of antenatal monitoring depends on the patient's degree of metabolic control, the type of therapy she is receiving and the presence of other risk factors (hypertension). ACOG recommends that women with gestational diabetes who are on insulin or who have poor glucose control have the same antenatal monitoring as women with pre gestational diabetes [6]. This typically consists of twice-weekly non stress testing, with amniotic fluid determinations beginning early in the third trimester [40].

Maturity of the fetus must be ensured before delivery, except when continuation of pregnancy is life threatening to the mother or fetus. If ultrasound is available to date the pregnancy, there is no need of doing amniocentesis to assess fetal lung maturity. There are no indications to induce the labor before 40 weeks of gestation in cases of good glycemic control and without maternal or fetal complications [41]. As a general rule, in the presence of good metabolic control and fetal surveillance, insulin-requiring diabetics are delivered between 38 and 39 weeks.

Intrapartum Management

As women with pre gestational diabetes, the goal of intrapartum management of women with GDM is to avoid maternal hyperglycemia and thus minimize the risk of neonatal hypoglycemia after delivery. Patients controlled by diet will not require intrapartum insulin and may simply need glucose level monitoring on admission for delivery. During labor, patients with insulin-requiring diabetes need capillary hourly monitoring of blood glucose levels. Target values are 80-110 mg/dl [42]. Published protocols recommend low-dose insulin infusion for intrapartum management of patients with insulin requiring diabetes. The only published comparative trial evaluated intravenous insulin versus continuous insulin infusion for the management of patients with insulin requiring diabetes in labor [42]. The study showed the continuous pump to be superior in achieving and maintaining metabolic control. Golde *et al.;* demonstrated that 48% of diabetic patients did not require insulin in labor [43]. A study suggests 5% dextrose infusion in active labor when maternal blood glucose is below 100 mg/dl [48]. For blood glucose concentrations exceeding 100 mg/dl, no dextrose is included in the intravenously administered solution.

Cervical ripening for induction of labor is done in the same manner as nondiabetic patient. Continuous fetal monitoring is used. If fetus is compromised expeditious delivery is done by method depending upon the stage of labor. If fetus is suspected to be macrosomic, operative vaginal delivery should be done with caution. Infant of diabetic mother is at increased risk of shoulder dystocia.

Neonatal Management

Women with GDM should be advised to deliver in hospitals where advanced neonatal resuscitation skills are available 24 hours a day. Newborn should stay with their mothers unless there is a clinical complication or there are abnormal clinical signs that warrant admission for intensive or special care. Blood glucose monitoring should be done routinely 2- 4-hour interval after birth. Mothers should feed their babies as soon as possible after birth (within 30 minutes) and then at frequent intervals (every 2–3 hours) until feeding maintains pre-feed capillary plasma levels at a minimum of 2.0mmol/L [27]. Blood tests for polycythemia, hyperbilirubinemia, hypocalcemia and hypomagnesemia should be done for babies with clinical signs. An echocardiogram for babies of women with GDM can be done if they show clinical signs associated with congenital heart disease or cardiomyopathy, including heart murmur. The timing of the examination will depend on the clinical circumstances. Babies should not be transferred to community care until they are at least 24 hours old, feeding well with maintenance of their blood glucose level.

Postpartum Management

If the patient did not require pharmacotherapy during pregnancy, it is not likely that she will require any further treatment. These patients to be followed by a primary care provider with monitoring of their blood glucose. Studies are underway to evaluate the effect of placing these patients on metformin in an effort to delay the development of overt diabetes. If the patient required pharmacotherapy, generally it is

discontinued as most patients reverts euglycemia and only blood glucose monitoring is done. Medical follow-up of these patients must be more intense as they are more likely to remain or progress to overt diabetes. Breastfeeding has got a protective effect in women with gestational diabetes reducing the risk of developing type 2 diabetes. Contraception should be discussed and a commitment sought to a program of planned pregnancies. Low-dose oral contraceptive (OC) can be prescribed to GDM patients with careful monitoring of their serum lipids and glucose concentrations. If OCs is contraindicated barrier methods can be used. Though there is limited experience with long-acting progesterone in these patients, but in the absence of serum lipid abnormalities, there are good results.

CONCLUSION

The incidence of GDM is increasing and, if not diagnosed, managed and treated adequately, can have unfavorable maternal and fetal outcomes. New methods for assessing glycemic control and fetal development seem promising, but have to be tested for routine use. Dietary restrictions remain the mainstay of GDM management, and suitable physical exercise can help too. Insulin analogues are novel treatments for improving metabolic control by reducing postprandial hyperglycemia. Numerous studies have found glyburide and metformin safe in GDM but more randomized controlled trials are needed in GDM women, with a long-term follow-up of mother and child to confirm these results. GDM patients have got the risk of developing Type 2 diabetes in their later life. They are also at risk of earlier gestational diabetes in subsequent pregnancies. They should be offered lifestyle advices which include weight control, diet and exercise. They should also remain under long term follow up.

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