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A Review on the Management of Gestational Diabetes Mellitus (GDM): Pharmacological and Non-Pharmacological Interventions

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Abstract: Gestational diabetes mellitus (GDM) is defined as any degree of glucose or carbohydrate intolerance mainly during pregnancy. About 10% to 15% of pregnancies are affected and complicated by gestational diabetes. Due to hormonal changes during pregnancy, the requirement for insulin increases, and thus the usual concentration of insulin previously catered for glycemic control is ineffective. In order to meet the body's demand, the islet cells secrete a higher amount of insulin. GDM occurs when this higher concentration is also unable to control blood glucose. This increased resistance toward insulin is most noticeable during the third trimester of pregnancy, which gradually normalizes after the termination of pregnancy. Various complications do arise, which affect both the mother and her developing fetus. In the mother, miscarriages, delivery of baby via caesarian section, and other complications may result, whereas the fetus may be affected with congenital abnormalities, neonatal hypoglycemia, and even death. Treatment of GDM includes both non-pharmacological and pharmacological interventions. Pharmacological agents are employed when non-pharmacological interventions fail to achieve the desired target. Glyburide, insulin, and metformin are the commonly used pharmacological agents.

Keywords: Gestational diabetes mellitus; Postprandial glucose; Macrosomia; OHA; Neonatal; Pre-eclampsia

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1. Introduction

Gestational diabetes is defined as impaired carbohydrate metabolism during pregnancy. With the progress of pregnancy, there is a steady rise in insulin resistance [1]. IR (insulin resistance) reaches a peak in the third trimester. As pregnancy comes to an end, IR decreases in line with that. Due to hormonal changes during pregnancy, there is an imbalance between glucose and insulin levels, leading to an increase in glucose levels with a decline in insulin sensitivity [2]. In order to compensate for the latter, the pancreas begins doubling the secretion of insulin [3]. Gestational diabetes occurs when this compensated cannot cater to the body's needs. Pregnancies are complicated with congenital malformations, neonatal deaths, miscarriages, macrosomia, and other conditions due to gestational diabetes [4]. The interventions in curtailing GDM and its associated complications are eventually required either via a change in lifestyle or the use of medications, in which drugs that have low transplacental transfer are preferred. Glyburide, a sulfonylurea, is considered a safe drug compared to other pharmacotherapeutic agents, as it has very low transplacental diffusion capacity [5].

This review highlights various interventions including pharmacological and non-pharmacological interventions in managing gestational diabetes along with its complications.

2. Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disease, detected by increased blood glucose level (hyperglycemia), which is the end result of impaired insulin secretion, its activity, or occasionally both. It has become a global health issue, affecting people with its increasing rates of morbidity and mortality. Moreover, health-related expenses are also increasing due to this metabolic disorder [1-3]. By 2030, the number of adult diabetic patients all around the globe will increase from 366 million to 552 million [2].

3. Gestational diabetes mellitus

GDM can be defined as any degree of intolerance towards glucose or carbohydrate with an onset or first recognition during pregnancy [4-6]. GDM is a common medical issue during pregnancy that affects both, mother and fetus with undesirable outcomes, complicating 5% to 12% of pregnancies [4,7]. A good glycemic control decreases morbidity rates in both, mother and fetus [8]. Gestational diabetes is seen in almost 90% to 95% of all cases and yet the incidence of GDM is rising, affecting millions of women around the world [9].

4. Pathophysiology

During pregnancy, placental hormones, such as human placental lactogen, TNF-α, along with increased levels of estrogen, progesterone, and cortisol cause an imbalance between glucose and insulin levels [4], as well as insulin resistance [6]. Hence, in order to recoup the metabolic stress and peripheral insulin resistance, the pancreas has double its secretion of insulin [4]. Gestational diabetes occurs when the increased insulin fails to compensate the body's needs [6]. The insulin resistance (IR) reaches a peak in the third trimester [4,6]. Therefore, the screening of gestational diabetes is usually done in the 24th to 28th week of pregnancy. Insulin sensitivity begins to decline in mid pregnancy and continues to deteriorate until it reaches its final stage in the late third trimester. Insulin resistance and sensitivity resolve after delivery.

Furthermore, physical inactivity, deposition of adipose tissues, and increased caloric intake, all lead to glucose intolerance [4].

5. Complications of GDM

Gestational diabetes mellitus causes various pathophysiological conditions in pregnant mothers, such as miscarriages, pre-eclampsia, and preterm labor [10]. The risk of developing hypertensive disorders, such as gestational hypertension, increases with GDM. It also affects the developing fetus and baby by causing congenital malformations, macrosomia, birth injuries, and even perinatal mortality. The excessive fetal growth (macrosomia) results in birth trauma, maternal mortality during C-section deliveries, and shoulder dystocia [5]. Other neonatal complications that may affect the fetus include neonatal hypoglycemia, jaundice, hyperbilirubinemia [5], hypoglycemia, erythema, and respiratory distress syndrome [4,6,10]. Appropriate management is provided to avoid adverse pregnancy outcomes [6]. As GDM usually occurs in the late second trimester, congenital abnormalities are rare since embryogenesis has already completed [11]. Maternal and fetal complications can be minimized if good metabolic monitoring is done during pregnancy [8].

6. Treatment and management of GDM

6.1. Non-pharmacological interventions

Lifestyle modification should be considered the initial treatment for GDM. Lifestyle modification includes

medical nutrition therapy and daily exercise [4,5]. Patients should monitor their glycemic levels at home, so that they can achieve their glycemic targets.

An oral glucose tolerance test (OGTT) should be done for pregnant women with risk factors, such as high BMI, previous macrosomic baby, a history of GDM, and familial history of DM. They should be evaluated based on the proposed diagnostic criteria for GDM by the World Health Organization (WHO). Women who previously had GDM should perform early self-monitoring or an oral glucose tolerance test at 16 to 18 weeks and at 28 weeks if results found normal during the first test. Women with other risk factors for GDM should have an OGTT at 24 to 28 weeks. Fasting plasma glucose, random blood glucose, glucose challenge test, or urine test for glucose should not be used for screening [12].

6.1.1. Dietary therapy

Healthy diet favors weight reduction, which improves insulin sensitivity and normalizes blood pressure [13]. Almost all types of diabetes can be tackled by adhering to good diet control. In order to maintain optimal glucose level, the diet should contain a low percentage of carbohydrate (~40%) [11]. All women with gestational diabetes should consult a dietitian. The main purpose of dietary therapy is to achieve normoglycemic conditions while consuming the required nutrients necessary for fetal growth and maternal health maintenance. It also helps in controlling excessive weight gain, particularly for those who are already obese or overweight. Various trials have been conducted to validate the efficacy of dietary therapy for GDM patients, and in 2004, the American Diabetes Association (ADA) recommended medical nutrition therapy (MNT) [1]. In a study, 215 patients suffering from GDM were randomly given either MNT or standard care. The study found that fewer subjects in the MNT group needed insulin (24.6% versus 31.7%, $p = 0.05$) and there was a trend to lesser women having glycated hemoglobin (HbA1c) of more than 6% (8.1% versus 13.6%, $p = 0.25$) [3]. ADA recommends that all pregnant women should receive individual counseling on adequate calorie and nutrient consumption to achieve optimal glycemic levels (fasting ≤ 105 mg/dL [5.8 mmol/L], 1 hour ≤ 155 mg/dL [8.6 mmol/L], and 2 hours ≤ 130 mg/dL [7.2 mmol/L]). As far as obese women are concerned, there is a 30 to 33 percent calorie restriction to 25 kcal/kg actual weight per day. A decrease in carbohydrate intake results in decreased post-prandial glucose level and ultimately the requirement for insulin. A non-randomized study found that women with GDM having carbohydrate intake of less than 42% of their total daily calorie intake had lower postprandial glycemic level and required lesser insulin; additionally, they study also found that the incidence of large for gestational age pregnancies was also lower [5]. In a comparative randomized study, in which pregnant women were initiated on low glycemic and high glycemic index diets, with both containing 55% carbohydrate, those receiving low glycemic index diet showed a decrease in pregnancy-related insulin resistance (IR) and lowered weights of born babies (3,408 ± 78 g versus 3,644 ± 90 g) as compared to their higher carbohydrate index diet counterparts [6]. This suggests that the concept of glycemic index (GI) is applicable in pregnancy, and it is necessary that low carbohydrate index diets should be given to GDM affected women. The general recommendations for dietary control are same as for diabetes mellitus. It is obligatory that the intake of carbohydrate and fat should be reduced. Non-caloric sweeteners may be moderately substituted in order to avoid carbohydrate overload [6].

6.1.2. Physical activity

There is evidence that regular physical activity improves insulin sensitivity, helps in weight reduction, and hence optimizes blood glucose levels and reduces the risk of GDM [5,6,13]. There is an inverse relationship between the levels of physical activity in the year prior to pregnancy with gestational diabetes. Exercise has been shown to lower the risk of GDM by 48% to 51% [5]. Another randomized trial of 29 women with GDM who were instructed to perform 30 minutes of exercise at 70% estimated maximum heart rate, three

to four times a week, showed improved glucose levels [7]. Women with GDM should observe moderate exercise until the end stages of pregnancy. Walking for 20 to 30 minutes daily may improve glycemic control [6]. Exercise has shown to improve glycemic control in GDM and play a role in its prevention [4,5]. Daily moderate exercise for 30 minutes or more is recommended for a woman with GDM, given that she has no medical or obstetric contraindications. Advising GDM patients to walk briskly or perform arm exercises while seated on a chair for at least 10 minutes after each meal facilitates a reduction in postprandial spikes and helps in achieving glycemic targets [4]. Physical activity before and during pregnancy may reduce GDM up to 40% to 69% [5]. The auxiliary benefits of exercise include sympathetic activity and blood pressure reductions.

6.2. Pharmacological interventions

Pharmacotherapy is initiated when normal glycemic levels are not achieved with lifestyle modifications [14]. Medications used during pregnancy that are considered critical for both maternal and fetal health require more attention. Two third of pregnant women use prescribed medications. Due to lack of knowledge of the drugs prescribed, there is a higher risk of congenital abnormalities along with undesired consequences [12]. Insulin has remained as the first line of treatment for GDM [4,13], but its inconvenience in administration has compelled clinicians to opt for oral substitutes of almost equal results [8]. Analogues of insulin are approved for use except for glargine, which is a long-acting insulin analogue. As far as OHAs are concerned, there has been a reluctant behavior while recommending these drugs in the management of GDM induced hyperglycemia [8]. The reason is that they generally cross placental barrier and impose a risk on fetus for neonatal hypoglycemia as in the case of first-generation sulfonylureas, like tolbutamide and chlorpropamide [8,14]. Sulfonylureas do cross blood placental barrier depending upon their molecular weight. The transplacental transfer of tolbutamide and chlorpropamide is 21% and 11%, respectively, while that of glyburide is just 3.9% [15]. Previous experiences with SUs include multiple cases of prolonged neonatal hypoglycemia and major congenital malformations [8,14,15]. In an animal study, metformin was found associated with the delayed closure of neural tube and the reduction in yolk sac proteins. However, recent studies have shown that some OHAs may be safe for use in pregnancy [14]. Drugs like glyburide and metformin have been used in pregnancy as safe and effective medications for years without reported adverse side effects to fetus, and that is the reason the available data on the safety profiles for OHAs in pregnancy focuses on these two drugs. Except for glyburide, nearly all OHAs were shown to be able to induce fetal hyperinsulinism by crossing the placental barrier [4].

6.2.1. Insulin

Insulin has been considered the first choice of pharmacotherapy for GDM [6,7,13], in which 15% to 60% of women with GDM require insulin therapy [9] due to failed non-pharmacological approaches [15]. For many years, regular (rapid acting) insulin and isophane (intermediate acting insulin) have been used to treat gestational diabetes. Human insulin cannot cross placental barrier, and it is considered safe in pregnancy as no such reports of fetal complications have been registered yet [16]. Various analogues such as insulin lispro, aspart, and detemir are administered in pregnancy. The analogues are safer and provide good glycemic control as compared to human insulin. Glargine, a long-acting insulin analogue, is not recommended although no contraindicating studies have been conducted [4,16]. Although insulin provides effective glycemic control, there is reluctance in using it due to several reasons, which include its cost, requirement of special conditions for storage, administration skills, associated hypoglycemia, weight gain, multiple injections, pain at the site of injection, and non-compliance [4,9,13]. Therefore, OHAs, which are user-friendly and effective in achieving glycemic controls similar to insulin, are opted for [9,17]. OHAs are less expensive, more acceptable, less invasive, and equipotent to insulin [18]. Hence, glyburide and

metformin should be used as an alternative to insulin. However, insulin should be considered when these drugs are unable to achieve optimal glycemic control [19]. Insulin provides effective glycemic control when administered in basal-bolus regimen. The administration of short-acting insulin is to control postprandial hyperglycemia, while basal insulin (morning injection of a long-acting insulin) is used to supplement glycemic control. Low-dose insulin is initiated and gradually increased to achieve the glycemic target. With increased insulin resistance in the third trimester, the insulin dosage increases. However, toward the termination of pregnancy, the need for insulin decreases, but the dosage is reviewed more frequently [20].

6.2.2. Glyburide (glibenclamide)

According to the Americans, glyburide is the first line of treatment for GDM, replacing insulin. This was corroborated on the basis of a randomized controlled trial, in which 404 women with gestational diabetes were enrolled and treated with glyburide and insulin. The results were the same for both, glyburide (5.9 ± 0.9 mmol/L) and insulin (5.9 ± 1.0 mmol/L) as far as mean glucose concentration was concerned; furthermore, the incidence of maternal hypoglycemia was 2% with glyburide as compared to 20% with insulin; only 4% of patients showed inadequate results with glyburide and were switched to insulin [21]. Various non-randomized and retrospective studies reporting the efficacy of glyburide in treating gestational diabetes have been tabulated demonstrating the effectiveness of glyburide in achieving targeted blood glucose levels in a large number of patients. Majority, but not all vote in favor of glyburide as far as the effect on fetus is concerned [6]. Glyburide is favorable owing to its ease of administration and better patient satisfaction and adherence. Furthermore, its comparable efficacy with insulin and minimal placental crossing engender it as a useful drug [22]. Several studies have established that glyburide is safe for fetal development since it crosses the placental barrier in a negligible amount that is not even detected in neonatal cord blood [23]. The rationale for the negligible transplacental transfer of glyburide is owing to its 99.8% protein binding property, which neither allows it to be metabolized nor cross the placenta [24]. Glyburide is a commonly used OHA which potentiates insulin secretion and reduces insulin resistance (IR) by lowering glucotoxicity. The onset of action is approximately 4 hours, lasting for about 10 hours. This means that glyburide covers both, basal and bolus requirements [25]. In a randomized study, 440 women ranging from 11 to 33 weeks of gestation with first time pregnancies, having gestational diabetes, and needing intervention were enrolled. They failed their OGTT, and upon fasting plasma glucose test, their glucose concentrations ranged from 95 mg/dL to 140 mg/dL. The patients were given either glyburide (n=201) or insulin (n=203). Oral glyburide was initiated at 2.5 mg, which was then increased by 5 mg, achieving a maximum dose of 20 mg, whereas the insulin dose was initially set to 0.7 units/kg, subcutaneously, thrice daily, and then increased weekly as necessary for glycemic control. The patients were told to check their glycemic levels seven times a day. Their plasma glycemic profiles were evaluated before and after the therapy. The results showed that 82% of patients under glyburide and 88% of insulin administered patients were able to achieve their targeted glycemic levels. However, a significantly higher rate of hypoglycemia (< 40 mg/dL) was found in patients treated with insulin, while glyburide showed a lower rate of hypoglycemia [11]. In pregnancy, the stipulated initial dose of glyburide is 2.5 mg in the morning. The dose can be increased to 5 mg in the morning or with addition of another 5 mg in the evening if the target glycemic level is not achieved. A total of 20 mg can be administered to achieve glycemic targets [11,12]. If the glycemic targets are not achieved with the latter, insulin should then be administered. In a meta-analysis of 745 pregnant women taking glyburide and 637 insulin treated pregnancies, glyburide did not potentiate the risk of macrosomia, large for gestational age, or neonatal hypoglycemia. However, more serious complications such as perinatal mortality and congenital issue were not examined. Several studies have identified the factors that contribute to the failure of glyburide therapy in achieving glycemic control. Patients with severe gestational diabetes were shown to be more likely to require insulin [26].

6.2.3. Metformin

The use of metformin in gravid women is still doubtful; that is why a meta-analysis using randomized controlled trials was conducted to investigate its safety and efficacy in comparison with insulin. Effects such as glycemic control as well as neonatal and maternal outcomes in GDM were compared. The results showed that metformin is comparable to insulin, and the meta-analysis provides credential information about the benefits and risks of metformin in gestational diabetes [16]. As far as the use of metformin in pregnancy with type 2 diabetes is concerned, there is conflicting information. Some studies have shown no noticeable adverse effects on fetus with the use of metformin during pregnancy for polycystic ovary syndrome [13]. A study randomly selected 751 women with gestational diabetes who were treated with either insulin or metformin although insulin was also administered as a supplement to metformin if the glycemic target was not achieved even with the maximum dose of metformin (2.5 grams daily) [18]. The primary outcomes were neonatal hypoglycemia, respiratory distress, birth trauma, and other complications, excluding fetal death and malformations. There was no difference found in the primary outcomes between the two groups. Metformin was responsible for 116 events, while insulin was responsible for 119 events. However, as far as the effect on fetus was concerned, metformin was responsible for 19 severe events, of which 11 were congenital malformations, whereas insulin was responsible for 18 congenital anomalies out of 23 severe cases, including one death. No such serious adverse effects were found associated with metformin use, and in addition, its priority of use indicated that the treatment is more accepted as compared to insulin. Many researchers have suggested the use of metformin as an effective treatment for GDM [6]. The use of metformin among pregnant women has shown greater weight reduction [9,16,19] as compared to insulin [9]. As obesity is responsible for other metabolic diseases, so a reduction in weight gain confers less risks for complications. Metformin inhibits glucose formation (gluconeogenesis) and absorption. It also stimulates peripheral glucose uptake. On the other hand, a study has revealed a relatively higher occurrence of preterm birth with metformin as compared to insulin, as a result of an unexplained effect on the labor process. In short, metformin is safe for use in women with mild gestational diabetes; however, the risk of preterm birth cannot be ruled out [27].

6.2.4. Acarbose

Acarbose delays the absorption of carbohydrates from the gut and thus reduces postprandial hyperglycemia. Due to its local action on the gastrointestinal tract, there is no transplacental transfer. Its efficacy as compared to glyburide is lower, and it is not usually used with glyburide or metformin [28,29], although its use has not been fully investigated in pregnant women with diabetes. A study in Mexico revealed that six women who were treated with acarbose achieved normal deliveries with normal newborns [30]. Although it has not been proven that acarbose can influence pregnancy via increasing the amount of starch in the bowel, which may be broken down by bacteria into butyrate and in turn increase the secretion of prostaglandin E, the latter could have negative effects on pregnancy.

7. Management of pre-existing GDM

Women with pre-existing diabetes having the intention to be pregnant must control their glycemic levels and measure their HbAc1 levels. However, they should not rely on routine HbA1c for accessing glucose concentration. Their HbA1c levels should be less than 6.1%, and those with Hb1Ac levels of more than 10% should avoid pregnancy altogether. This level assures the reduction of risk of congenital malformations. The risk of hypoglycemia should also be taken into account. Pregnant women should keep their fasting blood sugar between 3.5 mmol/L and 5.9 mmol/L, while the 1-hour postprandial blood glucose should be less than 7.8 mmol/L [31].

8. Conclusion

This review concludes that GDM screening and management at the primary care level may have a positive effect on neonatal birth and weight as well as maternal health and weight. This review comes to a conclusion that GDM is prevalent among European women, thus requiring screening and management approaches (both, pharmacological and non-pharmacological) that enable early interventions at the primary care level.

Disclosure statement

The authors declare no conflict of interest.

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