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COMPARISON OF INSULIN WITH ORAL ANTIDIABETICS IN GESTATIONAL DIABETES

Obstetrics & Gynaecology

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ABSTRACT

Diabetes mellitus is a chronic metabolic condition marked by insulin resistance, glucose and lipid metabolism issues, and several chronic consequences. The major disorder commonly seen during pregnancy is gestational diabetes, in which women without previously diagnosed diabetes develop hyperglycaemia during their gestational period. The pathogenesis is related to insulin resistance and pancreatic beta-cell function during pregnancy. The therapy for gestational diabetes is pointed towards maintaining adequate blood sugar levels. Along with the dietary and lifestyle modifications, most patients require anti-diabetic medications. Oral hypoglycemic drugs are the first choice, but a combination strategy or insulin therapy may be required as the illness progresses. In this review, we have compared different medication and insulin treatments, including the advantages and disadvantages of both, in patients with gestational diabetes. **Conclusion:** Despite many side effects, insulin continues to be the treatment for gestational diabetes. Newer OHAs need to be developed as an alternative, which can be used safely during pregnancy.

KEYWORDS

Type 2 Diabetes Mellitus, Insulin, Gestational Diabetes Mellitus, Oral Hypoglycemic Agents

INTRODUCTION

Diabetes mellitus refers to a series of metabolic illnesses characterized by persistent hyperglycemia. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins. If untreated, uncontrolled diabetes can cause coma, stupor, and, in rare cases, death from nonketotic hyperosmolar syndrome or ketoacidosis.[1,2,3]

Diabetes can affect a wide range of people from low-income to high socioeconomic status, pregnant women, and elderly people. Black, Asian, and Hispanic persons have a higher incidence of type 2 diabetes than non-Hispanic white people.[4] These disparities are multifaceted and include biological variations, such as enhanced insulin resistance and elevated beta cell activity in African Americans compared to Whites, or a higher risk of impaired glucose metabolism at lower BMI levels in South Asians compared to other groups.[5]The beta cell function can be related to genetic and environmental conditions, hence can be attributed to the variation of insulin production and resistance in different areas of the world.[6]

The American Diabetes Association (ADA) first recommended the traditional classification of diabetes in 1997 as endorsed by ADA. Type 1, Type 2, other forms, and gestational diabetes mellitus (GDM). [1]

Gestational Diabetes

The most pregnancy-related medical emergency, gestational diabetes, is described as glucose intolerance with a varied degree that initially manifests itself during pregnancy.[7] This definition leaves open the potential that undiagnosed glucose intolerance existed before conception, making the phrase hyperglycemia in pregnancy, more acceptable, as recently proposed by the Endocrine Society.[8]

According to population-based research, gestational diabetes affects around 200,000 (7 percent) of the more than 4 million births that take place yearly in the United States and is linked to difficulties for both the mother and the baby and carries a major risk of developing T2DM to the mother and fetus later in life. [9,10] In addition, it also has been linked with lipid abnormalities, hypertensive disorders and hyperinsulinemia which are the major cardiometabolic risk factors. [11]

The wide range of physiological and genetic abnormalities that characterize diabetes outside of pregnancy appears to be the cause of GDM.[12] Pancreatic beta cell dysfunction is the major etiology behind increased blood glucose levels. Inadequate cell function can have a wide range of unrecognized causes. The recognized causes of beta cell malfunction are autoimmune and monogenic, happening on a background of insulin resistance.[13]

In general, insulin delivery is insufficient to meet tissue requirements for normal blood glucose regulation, which leads to hyperglycemia.[14-20] Insulin resistance (IR) and hyperinsulinemia are linked to pregnancy and may increase the risk of developing diabetes in some women in the later stage of their lives. While insulin sensitivity remains constant, declines, or even rises during the early stages of pregnancy, insulin output increases. The reduction in insulin sensitivity begins about mid-pregnancy and worsens during the pregnancy, peaking in the late third trimester. GDM often emerges in the late second trimester and disappears completely after birth with the placenta delivery.[16]

The maintenance of adequate glycemic levels is the only treatment for any type of diabetes and there is no cure for the disease as such, once diagnosed. Pregnancy-related hyperglycemia increases the risk of bad outcomes for the mother, the fetus, and the newborn. This risk is present whether the hyperglycemia takes the form of type 2 diabetes diagnosed before or during pregnancy or gestational diabetes. The increased risk of macrosomia (birth weight 4.5 kg), preeclampsia, premature birth, and cesarean delivery owing to large newborns is caused by hyperglycemia throughout pregnancy.[21]

Insulin therapy should be initiated if the medical nutrition therapy and exercise fail to achieve glycemic goals for a woman with GDM.[22]

Achieving Ideal Blood Glucose Levels:

To prevent macro and microvascular complications in diabetes, maintaining adequate glycemic control (GC) is the primary therapeutic objective.[23]

Four categories were used to categorize the factors that affect glycemic control: personal or body-related, therapeutic, medication-related, and behavioral aspects. The glycemic control was linked to several variables; some related to the patient or their health, while some to the medications.[24]

Insufficient glycemic management results in uncontrolled sugar levels, which causes several pregnancy complications.[25,26]

Lifestyle measures, regular exercise, and nutritional therapy are the first line of treatment for GDM. To ensure that the glycemic targets are met, patients must periodically check their blood glucose levels at home. Medical therapy should be started if the glycemic targets are not met.[27]

Three variables are used to assess glucose control clinically: fasting blood glucose (FBG), postprandial glucose (PPG), and glycosylated hemoglobin (HbA1c).

American Diabetes Association has set a recommended range for fasting blood glucose of 70-130mg/dL (3.9-7.2mmol/l), while the American College of Endocrinologists and the International Diabetes Federation have set their respective recommendations <110 mg/dL

(6.1 mmol/l) and 100 mg/dl (5.5mmol/l).[28]

Glycosylated hemoglobin is the gold standard for measuring glycemic control.36 According to the American College of Endocrinologists, good diabetes management indicates 6.5%, whereas the American Diabetes Association (ADA) defined it as 7%.

While dietary adjustments and increased physical activity can greatly improve glycemic control, most people with gestational diabetes will need to take drugs over the term to attain and maintain glycemic control.[29]

Hypoglycemic Agents

Ten kinds of pharmaceuticals are currently available orally to achieve glycemic control and additionally, injections are available for glycemic control for the patients who can't take oral drugs. (Table 1)

Table 1. Hypoglycemic drugs

Sl no:	Oral hypoglycemic agents	Injectable hypoglycemic agents
1)	Sulfonylureas	Amylin,
2)	Meglitinides	Dual GLP-1 receptor agonists
3)	Metformin (biguanide)	GIP receptor agonists
4)	Thiazolidinediones (TZDs)	Glucagon-like peptide 1 (GLP-1) receptor agonists
5)	Alpha glucosidase inhibitors	
6)	Dipeptidyl peptidase IV (DPP-4) inhibitors	
7)	Bile acid sequestrants	
8)	Dopamine agonists	
9)	Sodium-glucose transport protein 2 (SGLT2) inhibitors	
10)	Oral glucagon like peptide 1 (GLP-1) receptor agonists.	

Each of these drugs have a different pharmacokinetics and mechanism of action. Thus, there are several possible combinations of drugs used to reduce the glucose levels. [30]

The oral therapy used one drug alone (monotherapy) or in combination with two or more medications with different modes of action depending on the case. [31-33]

Insulin

A commonly used method to control hyperglycemia in gestational diabetes is intradermal insulin injections. There are different types of insulin used and the most used one is the typical human insulin. Drawbacks of insulin use are related to the standard mealtime and basal insulin formulations for insulin treatment.

First, typical human insulin is slowly absorbed from the subcutaneous tissue; the metabolic response begins by 30 to 60 minutes after injection and peaks 2 to 3 hours later. As a result, frequent insulin therapy increases the risk of late-postprandial hypoglycemia and post meal hyperglycemia.

Second, the typical basal NPH insulin has a varied rate of absorption from the subcutaneous tissue, a duration of action that is significantly less than 24 hours, and a unique peak glucose-lowering impact. These pharmacodynamic restrictions put users at risk for nighttime hypoglycemia and increased glucose levels before breakfast.[34,35]

Oral Diabetic Medicine v/s Insulin

Recommendations vary regarding the start of insulin therapy for people with gestational diabetes.[36-40] Some researchers have indicated that higher baseline Hemoglobin A1c (A1c) values should start insulin therapy. Many individuals refuse to start taking insulin, despite A1c values which can be due to pharmaceutical anxiety (such as a fear of needles), and unfavorable cultural perceptions.[40,41]

Side effects of insulin can be divided into two categories: due to the medication or due to a particular delivery method.

By far, the most frequent side effect of insulin therapy is hypoglycemia.[43] The National Electronic Injury Surveillance System Joint Adverse Drug Event Surveillance Project estimates that each year, insulin-related hypoglycemia, and prescription errors result in close to 100,000 visits to the emergency department (ED).[44]

Weight gain is a common side effect of insulin therapy, which can have an impact on cardiovascular risk. Excess fat deposition acts as a psychological barrier to the introduction or intensification of insulin, and interferes with the functioning of prescribed regimens, increasing diabetic morbidity and death. A reduction in blood sugar to levels below the renal threshold without a corresponding decrease in caloric intake, contribute to insulin-associated weight gain. An increased calorie intake is normally due to fear of hypoglycemia.[44]

Less frequently, electrolyte changes like hypokalemia are another side effect of insulin therapy, especially when combined with other medications that cause hypokalemia.[45]

Glycemic Control Of Gestational Diabetes.

If the glycemic control throughout pregnancy is insufficient, there can be an increased incidence of unfavorable outcomes, for mother and newborn. Medication can be used to attain ideal glycemic control. For managing diabetes during pregnancy, insulin has long been the drug of choice. Due to its unequaled efficacy and safety as well as the lack of a well-researched alternative, this decision was made. 62 But because this therapy calls for many daily insulin injections, patient compliance may suffer. Additionally, some patients may be unable to afford treatment due to its high cost. Due to their affordability and convenience of use, oral anti-diabetic drugs (OAAs) have been researched as an alternative to insulin therapy. Due to this, more OAAs are now being used, during pregnancy. Care for pregnant women with diabetes requires an understanding of the benefits of OAAs, as well as their safety for the mother and fetus.[46]

It is usually challenging to study a drug's safety and effectiveness during pregnancy due to ethical issues. However, several medications, like metformin and glyburide, now have a sufficient amount of data to justify their use in pregnancy, or at the very least to spark a discussion about their use and safety.

Medical nutrition therapy, as it is for all types of diabetes, is the foundation of diabetic treatment during pregnancy. 63 If the medical nutrition therapy and exercise fail to achieve glycaemic goals for a woman with GDM, insulin therapy should be initiated. [47]

Low income is linked to a higher rate of hospitalization for immediate diabetes-related complications in pregnant patients. This can be due to inaccessibility to diabetic care, improper diabetic education, and affordability of anti-diabetic medications, especially insulin therapy.

CONCLUSION:

From this review regarding gestational diabetes and glycemic control during the pregnancy period, the following conclusions can be made. Gestational diabetes is a multifactorial disorder that disappears soon after delivery, and it is a major risk factor for Type II diabetes later in life. Adequate glycemic control is the only therapy for GDM to avoid several complications. Insulin is commonly prescribed despite the many side effects of it, due to the lack of an alternative. Thus, newer OHAs must be developed which should be affordable and can give superior results compared to insulin with minimum complications during pregnancy.

Abbreviations:

GC- Glycemic control
FBG- Fasting blood glucose
PPG- Postprandial glucose
HbA1c- Glycosylated hemoglobin
GDM – Gestational diabetes mellitus
TZD - Thiazolidinediones
DPP-4 - Dipeptidyl peptidase IV inhibitors
SGLT2- Sodium-glucose transport protein 2 inhibitors
GLP-1 - Oral glucagon like peptide 1receptor agonists.

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