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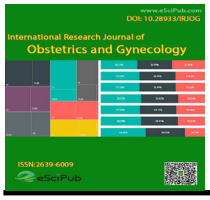

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Treatment of Gestational Diabetes Mellitus and postpartum care

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ABSTRACT

Treatment for Gestational Diabetes Mellitus comprises a series of Clinical-therapeutic protocols, which are necessary for proper attention to the patient with this pathology. In this sense, this chapter will address treatment care and postpartum care for Gestational Diabetes Mellitus, taking into account pharmacotherapeutic protocols and adverse effects of non-recommended treatments.

Keywords: Pharmacotherapy, Treatment, Pregnancy

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Introduction

Women with gestational diabetes mellitus should be referred to secondary care centers. Pregnant women diagnosed with pre-gestational diabetes should be managed in tertiary care centers by a multidisciplinary team composed of an obstetrician, endocrinologist, nutritionist, obstetric nurse and other professionals depending on the need and severity of the case[9].

Regardless of the type of diabetes (pre-gestational or gestational), clinical management aims at maternal euglycemia, that is, maintaining a maternal glycemic average <100 mg / dL, so that the result of pregnancy is a live newborn, term, with adequate weight for gestational age and free of malformationThus, pregnant women are expected to engage in self-care actions aimed at controlling possible complications, such as physical activity, prescribed diet, daily capillary glycemic monitoring and insulin therapy, requiring the guidance and monitoring of a multidisciplinary team with experience in this pathology, avoiding the self-care deficit[10,11].

The nutritional control is the beginning of treatment and aims to maintain the postprandial glucose peak within normal values between 60 and 90 mg / dL, fasting, 60 and 105 mg / dL one hour before and 100 and 130 mg / dL one or two hours after meals. The prescription of the diet must have the participation of a nutrition professional, making it necessary to establish limits in relation to nutrition and the body mass index (weight / height^2), in order to avoid overweight, macrosomia and other complications during pregnancy[15,16].

Physical activity in GDM has the main objective of decreasing glucose intolerance, through cardiovascular conditioning, decreased intra-abdominal fat, increased blood flow in tissues sensitive to insulin and reduced free fatty acids[6,7], that is, exercise can minimize the incidence of cardiovascular risk, reduce blood triglyceride levels, oxidative stress, the risk of obesity in pregnancy and can keep blood glucose within limits without the need for insulin [8]. In addition to these benefits, regular physical activity increases the activity of lecithin, cholesterol acyltransferase, lipoprotein lipase, decreases the luteinizing hormone, changing the hormonal profile[1].

After two weeks of nutritional education and physical therapy if the glycemic index exceeds 90 mg / dL, fasting or 120 mg / dL after meals, insulin use is recommended[2], some authors estimate that up to 60% of patients diagnosed with GDM require insulin therapy, depending on the parameters used for glycemic control. Insulin is an effective therapy to control maternal blood glucose, but it is inconvenient and expensive. In addition, hypoglycemia occurs in approximately 71% of women who use insulin during pregnancy[9,13]

In pregnancy it is recommended to use human insulin (NPH) with a total dose ranging from 0.8 to 2.0 U / kg. One should start with intermediate-acting insulin in a single morning dose (3 U / kg) (Table 1). In cases where fasting blood glucose is high, treatment can be started with an intermediate dose at bedtime (0.5 U / kg) with adjustments for each patient[18]. In more intensive regimens, multiple doses of fast action are used before meals, in addition to intermediate and prolonged action. During follow-up, doses change according to the patient's trimester and current weight, although there are individual variations, and should take into account the glycemic profile and the response to an increase in the previous dose, and may increase regular insulin when postprandial hyperglycemia occurs (Table 1), and alternate NPH at bedtime[12,20].

The total daily dose should be divided into 2/3 in the morning and 1/3 in the evening. The breakfast dose should be divided into 2/3 intermediate and 1/3 regular insulin, at night should be divided in half (1/2) with regular insulin before dinner and NPH at bedtime[13].

The use of oral antidiabetics is not recommended due to the probable risk of congenital malformation and glucose transport through the placenta (prolonged neonatal hypoglycemia), but resistance to the use of oral hypoglycemic

agents by pregnant women is still high[14]. The oral hypoglycemic agents most cited by research are glibenclamide and metformin. Glibenclamide is a second generation sulfonylurea and was approved by the Food and Drug Administration (FDA) for human use in 1984. Metformin does not appear to affect the uptake or placental transport of glucose, being able to reduce the incidence of GDM 10 times in patients with polycystic ovary syndrome, in addition to having insulin-like efficacy and safety in perinatal and neonatal outcomes and maternal glycemic control[22,19,4].

Oral hypoglycemic agents are grouped into larger subdivisions, based on their mechanism of action and chemical structure. Thus, according to the mechanism of action (Table 2), these drugs can be separated into: sulfonylureas and glinides, insulin secretagogues causing pancreatic insulin secretion; alpha-glycosidase inhibitors (delay the absorption of carbohydrates); biguanides (decrease hepatic glucose production); and glitazones or thiazolidinediones (increase the peripheral use of glucose by sensitizing the action of insulin)[26,31], these drugs are effective in reducing blood glucose, its side effects include weight gain, swelling, anemia and hepatotoxicity [21]

Table 1. Example of insulin use in a 60 kg pregnant woman with a dose of 0.3 to 0.5 U / kg / day[12].

Insulin	Fasting morning	Late afternoon (6 pm)	Evening (10 pm)
NPH	8 – 13 U	-	3 – 5 U
Regular	4 – 7 U	3 – 5 U	-

Addapted dom o Manual Técnico [40]

Tabela 2. Mechanisms of action according to types of drugs.

Medication / class	FDA Category	Mechanism of action	Effects on insulin	Transplacental passage	Adverse effects	Contraindications
Glibenclamide / Sulphonylureas	B/C	↑ Pancreatic insulin secretion	↑ insulin secretion	Irrelevant	Hypoglycemia, weight gain	Renal or hepatic impairment
Metformin / biguanides	B	↓ Hepatic glucose production	There is no insulin secretion	Yes	Abdominal discomfort, nausea, diarrhea	Liver, kidney, heart and lung failure.
Regular insulin, NPH	B	Exogenous insulin supplementation	-	No	Hypoglycemia	-

Source: Author

Metiglinides (Repaglinide and Nateglinide) are insulin secretagogues, like sulfonylureas, act in blocking the pancreatic beta cell KATP channels causing insulin. The difference between the mechanism of action of metiglinides and sulfonylureas is to act on binding sites different from the KATP channels[2,31.]

Dietary measures and exercise are recommended as an initial treatment and it takes around two weeks to give an opinion on a pharmacological intervention starting with insulin therapy and the use of metformin and glibenclamide only if the use of insulin is not possible[32]. However, in cases of uncontrolled GDM

in which there is an emergency with high negative endocrine changes, immediate treatment is necessary[19]. The criteria for adopting a pharmacological therapy vary, but are generally based on one or more blood glucose values in a previously designated period of time, but other parameters must be taken into account, such as high levels of ketone, weight loss and inadequate nutrition-deficient diet[19,32].

Glibenclamide and metformin are the two most frequently reported drugs in studies that subjectively presented an interesting path in GDM therapy, as they point out administration complexity and similar results in parallel with insulin. Glibenclamide and metformin are the two most frequently reported drugs in studies that subjectively presented an interesting path in GDM therapy, as they point out administration complexity and similar results in parallel with insulin[21]. Glibenclamide has shown in studies the lack of transplacental passage of the substance to the fetus, indicating a probable safety of the use of the drug during pregnancy[19]. In addition, there is evidence that glibenclamide has a similar effect on insulin daily concentrations of glucose in the blood[18,32]. In contrast, other studies demonstrate that glibenclamide crosses the placenta and present evidence that it can be harmful to the mother and fetus with risks of developing neonatal hypoglycemia and macrosomia[3,4,25,27]. As studies on the efficacy and safety of glibenclamide demonstrate lower results than metformin and insulin [3] and also controversial[28] its use during pregnancy is not recommended, suggesting metformin in cases where insulin cannot be used.

In studies carried out in recent years, metformin has been shown to be effective and considered an alternative in the treatment of GDM without harmful effects on the mother or fetus during pregnancy compared to other therapeutic alternatives such as insulin[4,36,37]. However, metformin crosses the placental barrier[11,12] being classified by the FDA as safety level B, presenting no harm to the fetus in animal tests, However, its use for the treatment of GDM is not approved by ANVISA in Brazil[24].

Hypoglycemic agents are contraindicated in pregnancy because there is a view that the drugs cause negative effects on fetal development due to placental passage, association with fetal anomalies, the possibility of causing adverse effects on the mother; Safety after childbirth the lactation period due to the presence in breast milk and long-term effects on a child[14,21], however this contraindication is based mainly on studies with small samples and case reports[21].

Pregnant women with excellent metabolic control and without complications can wait for spontaneous evolution to childbirth, which can be anticipated for those with inadequate metabolic control, vasculopathy, nephropathy, or history of stillbirth. In those with difficult control and / or with fetal impairment, it is recommended to use corticosteroids for fetal lung maturation. The mode of delivery is an obstetric decision, and it is necessary to estimate fetal weight by clinical evaluation and ultrasound. If the fetal weight is greater than 4000g, a caesarean section may be considered. Pregnant women using insulin require special attention during delivery and must maintain blood glucose[13].

Fetuses of diabetic pregnant women have excessive intrauterine growth; therefore, at birth, their weight exceeds the normal range. The newborn is called macrosomal, whose weight at birth is ≥ 4,000 g and large for gestational age (weight> 90th percentile of the standard curve at the Service)[17].

Macrososia can favor other complications during delivery, such as tocotrauma, shoulder dystocia and asphyxia[3]. Adequate prenatal care, as well as early detection and treatment of GDM, are limiting to reduce the perinatal complications of this pathology, in addition, high birth weight is a predisposing factor for insulin resistance, obesity and type 2 diabetes in childhood[21].

After pregnancy, a woman should be submitted between the 6th and 8th week postpartum to an oral glucose tolerance test (OGTT), women with

GDM have 17-63% of developing glucose tolerance. Breastfeeding should be encouraged, as it is a way of preventing diabetes for newborns[5].

Conclusion

The criteria for the adoption of a pharmacological therapy vary among several studies. Inmost the criteria are based on one or more blood glucose values for a previously designated period of time. Glucose values alone do not present evidence necessary for the recommendation of a pharmacological therapy and other criteria should be taken in cosideration such as weight loss, positive ketone levels and inadequate nutrient intake. Dietetic and practical measures of exercises are recommendedaround two weeksso that one can give an opinion on a pharmacological intervention. However, some authors note that in cases of lack of control of MGD in which there is some emergency with high negative endocrine changes, immediate treatment is necessary.

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