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Review article

THEORETICAL BASIS OF PERINATOLOGY THERAPY IN PREGNANT WOMEN WITH DIABETES MELLITUS

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Abstract: Diabetes mellitus is a metabolic disorder that can occur before pregnancy, be detected during pregnancy, or develop during pregnancy. Therapeutic modalities available today significantly facilitate glycoregulation during pregnancy and childbirth. This review presents different insulin regimens, as well as the advantages and disadvantages of oral antidiabetic agents use with a special focus on hypoglycemia. The importance of maintaining optimal glycemic levels and educating patients in blood glucose self-measurement is explained.

Keywords*:* diabetes mellitus, pregnancy, insulin.

INTRODUCTION

Diabetes during pregnancy is complicated by sudden hormonal changes that affect the entire organism (1). During pregnancy, maternal glucose passes through the placenta by facilitated diffusion, while amino acids are actively transported. As pregnancy progresses, its diabetogenic effects are conditioned by the following factors:

1. Increased production of placental hormones that antagonize the effect of insulin
2. Placental enzymes break down the mother's insulin
3. Increased production of glucose in the mother's organism during starvation.

The diabetogenic effect is primarily made by human placental lactogen (hPL). Circulating levels of this hormone increase in parallel with placental growth. hPL increases the production of higher fatty acids by stimulating lipolysis. More fatty acids lead to peripheral insulin resistance through the down-regulation of insulin receptors and thus to compensatory hyperinsulinemia (2).

Frequency of measurement and standard values of glycemia

To achieve a state of euglycemia, frequent measurement of blood glucose is necessary. The introduction of mobile devices for measuring blood glucose levels has made it possible for people with diabetes to control their glycemia several times during the day. The first report on glycemia measurement performed by patients themselves (SMBG - Self-Monitoring of Blood Glucose) confirmed that SMBG is flexible, practical, and affordable for patients; that the glucose values obtained in this way are suitable for clinical analysis; and that glycemic control may be improved if SMBG is used as part of a standard therapeutic protocol. As a result, SMBG has become the main method of ambulatory control of gestational diabetes. However, some metabolic and physiological changes during pregnancy interfere with the accuracy of measurements and affect the results obtained. During pregnancy, glucose and hematocrit values are lower, while triglycerides and cholesterol are increased. These changes can affect the accuracy of the measurement (3).

Langer et al. (4) conducted a large prospective study to determine the optimal glycemia of women with gestational diabetes mellitus (GDM). Their data, collected from 246 women with GDM, show that

women who achieve optimal glycoregulation have a lower incidence of macrosomia and children who are large for gestational age (LGA - Large for Gestational Age). The incidence of LGA babies increases from 9% to 24% if glycemia exceeds 105 mg/dL. In a subsequent study (5) on the same group of women, it was shown that if the average glycemia is below 100 mg/dL, the incidence of LGA and macrosomia is the same as in the general population. Then, average glycemia below 110 mg/dL has a protective effect on the fetus's metabolism and respiratory system, preventing complications. These data suggest that it is possible to compare the glycemia needed to prevent perinatal morbidity between women with pregestational and gestational diabetes.

Postprandial glycemia was found to correlate better with fetal macrosomia compared to fasting glucose values. DeVeciana et al. (6) obtained similar results when they compared the effect of pre-and postprandial glycemia on the incidence of pregnancy complications in women with insulin-dependent diabetes. Macrosomia was more common in the group of women who measured glycemia before meals compared to the other group of women. Then, in the group of women who measured postprandial glycemia, a greater drop in glycosylated hemoglobin was recorded. Therefore, it was concluded that insulin therapy in women with diabetes during pregnancy should be adapted to postprandial glycemia because this achieves better glycemic control and reduces the risk of macrosomia and other complications. It is recommended to measure blood glucose levels after a meal instead of in a fasting state.

Methods of self-measurement of blood glucose

Although self-measurement of glycemia has revolutionized the control of diabetes, it still has certain limitations and does not show the most accurate variations of glycemia that occur during the day. Therefore, devices that constantly measure glycemia have been sought for a long time to ensure better control of diabetes. The Continuous Glucose Monitoring System (CGMS) is marketed by Medtronic. MiniMed was the first meter of this group to become available for use. It is a holter that works with the help of sensors and automatically and continuously measures glucose from the subcutaneous tissue. The monitor is connected to a small sensor (microelectrode) that is implanted under the skin and measures the glucose level. The sensor generates electrical impulses whose strength corresponds to the concentration of glucose in the subcutaneous tissue. The signal travels to the monitor, a pager-sized mobile device that records signals every 5 minutes and converts them to glycemic values, providing 288 readings during the day over three days. Data is entered into the computer; The software then creates graphs and pies that represent glycemic changes. Although CGMS has been proven to be a useful method for normalizing HbA1c levels outside of pregnancy with poorly controlled type 1 diabetes, a large number of unexpected asymptomatic hypoglycemias during the night have been reported (7).

To reduce complications, the executive committee of the American Diabetes Association (8) recommends that the blood pressure of people with diabetes should be up to 130/80 mmHg. Patients with DM type 2 have a lipid metabolism disorder that results in a higher rate of cardiovascular disease. Diabetics usually have increased triglycerides and decreased high-density lipoproteins (HDL). Lipidemia control is aimed at reducing low-density lipoprotein (LDL), cholesterol, and triglycerides and increasing high-density lipoprotein (HDL).

Insulin therapy

During pregnancy, conventional insulin therapy is replaced by intensive therapy to achieve better disease control. Patients are transferred to an appropriate dietary regimen, informed about the action of insulin, and trained to recognize and react to hypoglycemia, then to adjust insulin doses to daily activities and accompanying diseases, as well as to monitor hyperglycemia and the eventual appearance of ketosis.

Insulin is given in a dose that meets basal and mealtime needs, with rapid adjustment to blood glucose levels. The therapeutic regimen includes three or four daily doses of insulin or continuous application using a pump. Regardless of the regimen used, frequent self-monitoring of glycemia is necessary to establish physiological control (9). Patients are trained to dose insulin according to the meals taken, as well as during the night. Meal-adjusted insulin doses depend on its composition, pre-meal glycemia, and physical activity.

In patients with poor disease control, a short hospitalization is often required to initiate therapy. This way, the recommended therapy is adapted to individual needs. For many patients, being able to take control of their disease is of great importance (9, 10).

Therapeutic regimen with multiple daily doses

Insulin is most often given in two to three doses, more often in three doses, although many patients prefer a combination of intermediate-acting and short-acting insulin before dinner and breakfast. The

general rule is that the amount of intermediate-acting insulin exceeds the value of natural insulin by one to two units. Patients usually receive two-thirds of the required dose of insulin before breakfast and the rest in the evening as a combined dose during dinner or divided into two smaller doses. In this case, a combination of short-acting insulin before dinner and intermediate-acting insulin at bedtime is given to prevent nocturnal hypoglycemia. These episodes of hypoglycemia occur when the mother is in a state of starvation, so the placenta continues to use glucose (9, 10).

Continuous subcutaneous insulin infusion

Literature data (9, 11) show that the use of a pump for CSII (Continuous Subcutaneous Insulin Infusion) during pregnancy is still very significant today. This pump is battery operated and attached to the anterior abdominal wall, and can be worn during normal daily activities. This system provides a constant supply of short-acting insulin that is administered subcutaneously. Doses covering basal needs, as well as boluses given before meals, are determined based on blood glucose values. Pregnant women often have to be hospitalized before starting therapy. They are trained on standard continuous insulin therapies and manage to stabilize glycemia within a few days. This means that numerous measures must be taken to prevent episodes of hypoglycemia and hyperglycemia.

Insulin requirements

It is well known that the need for insulin increases significantly during pregnancy due to the increase in the concentration of antagonistic hormones. Several studies (12) have attempted to document the changes in insulin doses required to maintain glycemic control during pregnancy. As these data provide insight into the characteristics of certain populations, control must be carried out at the individual level because insulin dosing is based on the algorithm of glycemic values reported by each patient individually.

An increase in the need for insulin is expected during the second trimester of pregnancy, and it depends in part on the current body weight as well as the pre-pregnancy weight. The significant reduction in insulin requirements remains unexplained and may not be associated with fetal death. Also, it is considered that this phenomenon does not affect the outcome of the pregnancy (13).

Insulin-induced hypoglycemia

Hypoglycemia is a limiting factor for intensive insulin therapy in patients with type 1 diabetes. Most patients with DM type 1 are left without any reserve of β - cells within a few years, with a simultaneously weakened response of α - cells (glucagon) to hypoglycemia, which leads to serious hypoglycemic episodes (13). Women with longstanding diabetes may be deficient in epinephrine, cortisol, and growth hormone in response to insulin-induced hypoglycemia. These individuals typically experience 1-2 symptomatic hypoglycemia episodes each week. Transient hypoglycemia progressing to coma or EPI attacks develops in more than 25% of patients with type 1 DM, while the mortality rate exceeds 4% per year. The fear of severe hypoglycemia can cause psychological instability in patients, and the doctor must search within different regimens of insulin therapy until finding the optimal one so that the patient is under control (14).

Cryer and Gerich (15) defined three categories of physiological conditions that can seriously compromise glycoregulation and lead to hyperinsulinemia, i.e. hypoglycemia: (a) unawareness of hypoglycemia: absence of neurogenic (autonomic) symptoms of hypoglycemia; (b) defective counterregulation due to a combined defect of glucagon and the adrenal response to falling glycemia (c) reduced glucose threshold - lower glycemic values are required for symptoms to appear and counterregulatory mechanisms to be triggered; this happens during intensive therapy and reduction of the total amount of circulating glucose. Although hypoglycemia-related conditions have a similar pathophysiological basis including a reduced response of the autonomic nervous system to hypoglycemia, they are still considered separate entities from diabetic autonomic neuropathy.

Research (16, 17) suggests that hypoglycemia lowers the glucose threshold required to elicit a symptomatic and autonomic response in nondiabetic patients. These findings were also confirmed in patients with DM type 1, so it became clear how previous hypoglycemia leads to the “circulus vitisus”, that is, it reduces awareness of the event, as well as the autonomic response to it. It is believed that avoiding hypoglycemic episodes in patients with DM type 1 who are unable to recognize it leads to improvement, primarily by increasing the sensitivity of β-receptors.

The risk of hypoglycemia during pregnancy is increased because the placenta continues to use glucose while the mother is in a state of starvation, and exogenous insulin, on the other hand, limits the use of other substances. There is no clear evidence that hypoglycemia has teratogenic potential during human pregnancy, but caution is advised, given that the results of studies investigating subtle effects on neurobehavioral development are suspect. Notably, the results of a large study, the California Gestational Diabetes Project (18),

failed to show a link between maternal hypoglycemia and neonatal malformations.

Control during childbirth

The goal of diabetes control during labor is to maintain euglycemia. Hyperglycemia during labor significantly increases the risk of neonatal hypoglycemia. This condition may be present at birth despite excellent glycemic control before delivery. Monitoring a pregnant woman with diabetes during childbirth requires special attention to the mother's glycemia value, then the value of the ingested glucose and the dose of insulin. In general, glucose measurement is performed every 1-2 hours with a mobile glucose meter standing next to the bed (19).

There are several approaches used to maintain maternal euglycemia during labor. An infusion solution containing glucose and insulin is most often used. Ten units of natural insulin are added to 1000 ml of 5% dextrose solution. The infusion is given at a dose of 100 – 125 ml/h and usually results in good control. Insulin can also be given in a syringe in a dose that normalizes glucose values. In women who use an insulin pump, insulin can also be administered in this way. If hyperglycemia persists for a long time, the pump can be switched to intravenous administration (20).

Several studies (21, 22) show that the administration of oxytocin did not affect glycemic control. This decrease in the need for insulin can be explained by a decrease in the level of antagonistic hormones produced by the placenta. Well-controlled studies by Jovanovic and Peterson (23) showed a reduced need for insulin and constant glucose monitoring in the first stage of labor. They used a glycemic-controlled insulin infusion system, the Biostator, showing that insulin requirements dropped to zero during the first stage of labor while glucose was administered at a dose of 2.55 mg/kg/min to maintain a glycemia of 70 - 90 mg/dL.

In patients who deliver by caesarean section, the operation is planned for the morning hours to ensure optimal glycemic control. Patients were trained to take their usual evening dose of insulin the day before delivery. They do not take food in the morning, and they keep the usual morning dose of insulin. Before epidural anesthesia, the intravenous line should ensure volemia to prevent hypotension, and intravenous fluids do not contain glucose. Epidural anesthesia is convenient because it allows the anesthesiologist to monitor the mental status of the patient, as well as the development of possible hypoglycemia. After the operation, glucose levels are measured every 2 hours, and a dextrose infusion solution is given (24).

After childbirth, the need for insulin decreases significantly. The requirement to ensure strict glycemic control before delivery is no longer so strict. Patients who gave birth vaginally can eat and receive, under the control of an endocrinologist, half of the prenatal dose of NPH insulin on the first day after delivery in the morning hours. If the insulin doses from the period before pregnancy are not known, usually after delivery, 1/2 or 1/3 of the dose given before delivery is given. A similar reduction in insulin dose is applied to women using an insulin pump. Frequent blood glucose measurements help with insulin dosing. Insulin should be prescribed based on previous and current glucose values, and the same applies to diet. If subsequent natural insulin is given with the morning dose of NPH insulin, the amount of NPH insulin given the next morning is increased by 2/3 of the natural insulin given. In this way, most patients stabilize a few days after giving birth (25).

Patients who have had a caesarean section receive regular doses of insulin over the next 24-48 hours to maintain glycemia. If the diet they follow is successful, NPH insulin is given in a dose that corresponds to their needs during the previous day. For women using an insulin pump, the insulin dose is approximately half of the dose at the end of pregnancy. Similarly, boluses are reduced by a third or half of the dose at the end of pregnancy. All women can breastfeed their children after giving birth. Insulin requirements may be lower in lactating women (26).

Oral antidiabetic therapy

The drugs available today are divided into three groups: insulin secretagogues, drugs that increase the sensitivity of insulin receptors, and α-glucosidase inhibitors (27). Available drugs from the group of insulin secretagogues include sulfonylurea derivatives (glyburide, glipizide, glimepiride) and newer meglitinide preparations (nateglinide, repaglinide). Both groups of drugs act on the potassium channels of β-cells by performing depolarization and thereby stimulating the secretion of insulin, which is independent of glucose intake. The difference between these two classes of drugs is initially the duration of their action, although the latest research shows that these substances have a certain affinity for cardiac receptors (SUR2), which may change the current recommendations on their use. Meglitinides are non-sulfonic drugs with a rapid onset and short duration faction and must be taken before each meal, and their short action results in mild postprandial hypoglycemia (28).

Drugs that increase the sensitivity of insulin receptors include biguanides (metformin) and thiazoli-

dinediones (pioglitazone, rosiglitazone). Biguanides increase the action of insulin by increasing the release of glucose from the liver, while thiazolidinediones act on peripheral tissues by increasing their sensitivity to insulin (29).The good side of both of these groups of drugs is that they do not cause hypoglycemia, since they do not increase the release of insulin. However, gastrointestinal complaints such as diarrhea and dyspepsia can limit its use, as can lactic acidosis, a rare but potentially fatal complication. To reduce the risk of lactic acidosis, metformin should not be given to patients with impaired liver and kidney function, congestive heart failure, and patients who consume large amounts of alcohol (30).

CONCLUSIONS

Diabetes mellitus is characterized by insufficient insulin secretion and/or peripheral insensitivity to insulin. Achieving optimal glycemic control in pregnant women with diabetes mellitus is necessary to avoid adverse pregnancy outcomes. This is usually achieved with a specifically targeted insulin regimen and close monitoring of glucose blood levels. Two main insulin regimens: Basal and meal-dependent secretion are mimicked by either continuous or interval insulin use. Frequent measurement of glycemia can be bypassed by insulin pump use. Hypoglycemia is one of the main concerns of insulin and oral antidiabetic agents, and patients should be advised on how to recognize it. The prevention of micro- and macrovascular complications requires a joint approach that, in addition to normalizing glycemia, includes strict control of lipid status and blood pressure.

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Sažetak

TEORETSKE OSNOVE PRIMENE TERAPIJE U PERINATOLOŠKOM PERIODU KOD TRUDNICA SA DIJABETES MELITUSOM

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Dijabetes melitus je metabolički poremećaj koji se može javiti pre trudnoće, otkriti u trudnoći ili razviti tokom trudnoće. Terapijski modaliteti koji su danas dostupni značajno olakšavaju glikoregulaciju tokom trudnoće i porođaja. U ovom pregledu prikazani su različiti insulinski režimi, kao i prednosti i mane oralne antidijabetične terapije sa posebnim osvrtom na hipoglikemiju. Objašnjen je značaj održavanja optimalnih nivoa glikemije i važnost edukacije pacijentkinja da same mere nivo ešećera u krvi.

***Ključne reči**:* dijabetes melitus, trudnoća, insulin.

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