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GESTATIONAL DIABETES MELLITUS: RELATIONSHIP WITH PATHOPHYSIOLOGY, HYPERANDROGENISM AND POLYCYSTIC OVARY SYNDROME

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Abstract: Polycystic ovary syndrome is the most common endocrine disorder among women. It is characterized by the presence of hyperandrogenism and metabolic disorders, with insulin resistance being the most common. Insulin both influences and is influenced by androgens. Pregnant women with diabetes can have complications in pregnancy if they have PCOS, as they may have infertility and high blood pressure.
Keywords: Gestational Diabetes Mellitus; Polycystic ovary syndrome; hyperandrogenism.

INTRODUCTION

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS), according to the Rotterdam criteria, is characterized by the presence of metabolic disorders (hyperandrogenism), ovarian dysfunction, and altered egg morphology. Such variations are prevalent in women of childbearing age, and may also exist in puberty and menopausal women.

Its pathophysiology is mainly described by the hypersecretion of LH (luteinizing hormone), caused by genetic factors, hormonal or metabolic changes. This hypersecretion causes an increase in androgens, which leads to a decrease in hepatic SHBG protein, an increase in estrone production along with a change in the pulse of gonadotropin-releasing hormone (GnRH).

The decrease in SHBG protein, which is responsible for carrying circulating androgens, leads to the appearance of acnes and hirsutism, characteristics present in about 65% to 75% of women with PCOS. In addition, the increase in androgens circulating in the periphery is converted into estrone, which consequently alters the feedback made by estradiol produced in the ovaries, thus modifying the pulsativity of gonadotropins in the pituitary gland, which

may lead to anovulation. This anovulation is due to hyperandrogenism, also resulting from the hypersecretion of IGF-1 (a factor of insulin-like growth 1) and high levels of AMH (anti-Mullerian hormone).

In women with PCOS, insulin resistance is common, but still poorly understood. According to the manuscript Polycystic Ovarian Syndrome: long term metabolic consequences (2017), the development of this resistance is caused by a defect in insulin signaling due to increased serine phosphorylation and decreased insulin receptor and substrate receptor tyrosine phosphorylation. 1 of insulin. Furthermore, it is notorious the ineffective production and transport of insulin, caused by the improper synthesis of GLUT-4, caused, according to the journal Nature, an epigenetic dysfunction of adipocytes, mainly of the micro RNA-93 and micro RNA-223 factors.

Finally, from the perspective of the syndrome and GDM not having a solid relationship, it is conclusive that they are connected, given that 50% of patients with PCOS have some type of metabolic disorder, with higher glucose tolerance being the most common.

HYPERANDROGENISM

The female body produces hormones such as progesterone, estrogen and androgens (testosterone) for reproduction, even though testosterone is a male hormone, the ovary produces it in a smaller and ideal amount in women (Sharma A, et al, 2021). Hyperandrogenism is characterized by an abnormal increase in androgen production in women, which can have consequences such as acne, seborrhea, oily skin, hirsutism, alopecia, anovulation, low fertility and, in the long term, it can develop obesity, type 2 diabetes and cardiovascular diseases such as hypertension and hyperlipidemia (Makrantonaki E, et al, 2020). The most common cause of this hormonal disorder is polycystic ovary syndrome (PCOS), with insulin resistance (IR) an aggravating factor in testosterone secretion (Dadachanji R, et al, 2018). In pregnancy, hyperandrogenism can also be caused by luteoma, congenital adrenal hyperplasia (CAH) or placental aromatase deficiency (Hakim C, et al, 2017).

It is noteworthy that there are two sources of androgens in females: the ovary and the adrenal gland, with the theca cell responsible for 33% of this production (Sharma A, et al, 2021). It has been reported that the lipid profile and IR do not influence the characteristic of the hormonal disorder whether it will be more prevalent in the adrenal or ovarian source (Paschou AS, et al, 2017). Regarding hyperinsulinemia and insulin resistance, studies show that exposure to high concentrations of androgens in mammals alters the morphology of beta cells in the pancreas, which contributes to the development of diabetes (Dadachanji R, et al, 2018).

The mechanism that leads to hyperandrogenism begins when there is a dysregulation in the hypothalamic-pituitary-ovarian axis (HHO axis) increasing the pulsation of gonadotropin-releasing hormone (GnRH) that stimulates the release of luteinizing hormone (LH). In this sense, the theca cells in the follicle induce the steroidogenesis pathway, which is exacerbated by hyperinsulinemia and insulin-like growth factor 1 (IGF-1). Thus, both act synergistically with LH, increasing androgen synthesis and decreasing the production of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein (IGFBP-1) in the liver, which lead to high concentrations. of free testosterone. However, due to the high pulsatile frequency of GnRH, there is a deficit in the release of follicle stimulating hormone

(FSH) in the granulosa cell., which reduces the activity of the aromatase enzyme - which has the function of converting androstenedione to estrone and testosterone to estradiol - resulting in excess accumulation of androgens in women (Dadachanji R, et al, 2018).

Another mechanism that leads to endocrine disturbance is the high level of production of dehydroepiandrosterone (DHEA-S) in the zona reticularis of the adrenal gland. This androgen is under the influence of adrenocorticotropic hormone (ACTH) which is produced by the anterior pituitary. It is important to point out that DHEA-S has an influence on insulin physiology and that it undergoes intervention by prolactin and IGF-1 (Paschou AS, et al, 2017). There are no studies that elucidate whether there is hyperplasia or any other morphological change in the adrenal cortex to increase the synthesis of DHEA-S.

Therefore, PCOS causes hyperandrogenism, but it is not yet known what leads to dysregulation of the adrenal gland and the HHO axis. Androgens both influence and are influenced by insulin, playing an important role in the development of gestational diabetes.

GESTATIONAL DIABETES MELLITUS

It is an insulin resistance and pancreatic β-cell deficiency in pregnancy, and it can influence the health of the mother and baby. ''According to data, 9 to 25% of pregnancies are affected by GDM" (Alejandro et al., 2020).

During pregnancy, glucose intolerance can occur causing hyperglycemia (GDM), which results in insulin insufficiency to regulate glycosidic homeostasis during pregnancy.

Maternal beta cells do not adapt to metabolic changes and, as a result, DMG hyperglycemia occurs.

Risk factors:

- Excess weight;
- Obesity and pre-gestational body mass index (BMI);
- Deposition and hypertrophy of adipocytes in maternal adipose tissue;
- Increase in triglycerides;
- Systemic arterial hypertension;
- Preterm birth or stillbirth;
- Metabolic syndrome and nutritional diet (sweets, fats, processed foods);
- Vitamin D deficiency;
- Preeclampsia;
- Prolonged exposure to psychological stress;
- Use of antidepressants and psychotropics;
- Smoking;
- Advanced maternal age;
- Number of pregnancies;
- Ethnicity (Hispanic, African American and Asian, Korean, Chinese and Filipino);
- Family history of DM and GDM (in previous pregnancies), in addition to climate, education and socioeconomic status.

During pregnancy, the biochemical and pathophysiological aspects change, due to the production of placental hormones (placental hormone, cortisol, prolactin), which are against insulin, but for the fetus it is beneficial, but in large quantities it will cause hyperinsulinemia.

In 1998, the Ministry of Health published guidelines on the main risk factors for the development of gestational diabetes, such as: age over 25 years, obesity or excessive weight gain during pregnancy, excessive central deposition of body fat, family history of diabetes in first-degree relatives and short stature (≤ 1.51 m). These risk factors also include some ethnic groups, such as African, Hispanic and Asian descent (MARZE, 2002). Among the risk factors, high body mass index increases threefold the risk of developing gestational diabetes (EVANS, 2009). The

World Health Organization (WHO) and the Ministry of Health recommend that screening for diabetes mellitus be universal, regardless of risk factors.

"However, in 3-14% of pregnant women, glucose intolerance develops. Gestational diabetes mellitus (GDM) is characterized by a further decrease in insulin sensitivity and an inability to compensate with increased insulin secretion. Insulin is primarily an anabolic hormone, it causes the growth and development of the fetus, causing macrosomia and visceromegaly of the liver and heart" (NORTH; MAZUMDAR; LOGRILLO, 1977).

"In addition to contributing to the emergence of chronic noncommunicable diseases, it occurs in approximately 14% globally, ranging from 9% in Africa, 12.6% in North America and 21% in Asia in 2017" (Juan, J., & Yang, H et al., 2020).

The relationship of SOP with DMG:

Polycystic ovary syndrome (PCOS) is an endocrine disruption with chronic oligomenorrhea, hyperandrogenism and insulin resistance. The risk of GDM increases in who have PCOS, due to altered insulin resistance, in addition to obesity and advanced maternal age. A 1.5-fold increased risk for GDM in women with PCOS in early pregnancy.

It is considerable that women with PCOS are at a higher risk of pregnancy complications. They have an increased risk of metabolic disorders such as insulin resistance (IR) (50% to 70%), altered fasting glucose (IFG), type 2 diabetes (DM) and obesity.

"Pregnant women with PCOS have a higher risk of pregnancy-induced hypertension compared with controls in the present study, which is in agreement with other studies. Furthermore, to clarify the effect of PCOS itself on the risk of IPH (pregnancy-induced hypertension)." (Wang Y et al., 2013).

"PCOS has reproductive (hyperandrogenism, oligo/anovulation and infertility), metabolic [dyslipidemia and type 2 diabetes mellitus (DM2)] and psychological (depression, anxiety and low self-esteem) characteristics. The etiology of PCOS is underpinned by both insulin resistance (IR) and hyperandrogenism, with IR increasing hyperandrogenism). IR occurs in approximately 80% of women with PCOS and occurs independently of obesity." (Joham AE et al., 2013).

Screening and diagnosis:

To diagnose gestational diabetes, it is recommended to perform fasting blood glucose tests and after a 2-hour period of a simplified oral glucose tolerance test (OGTT) with a 75g overload. After the patient is submitted to glucose overload, the cut-off point for fasting glucose must be 95 mg/dl; and for blood glucose after 2 hours, glucose tolerance is 140 mg/dl (WHO, 2006; GOLBERT, 2008; BOLOGNANI; SOUZA; CALDERON; 2011; BRASIL, 2013).

Diagnostic criteria vary according to: American Diabetes Association (ADA); WHO; International Association of Diabetes and Pregnancy Study Group (IADPSG); Australasian Diabetes in Pregnancy Society (ADIPS); Diabetes Canada]; German Association of Gynecology and Obstetrics (DGGG]; Istituto Superiore di Sanità (ISS); Cooperative Research Group of the Study of Hyperglycemia and Adverse Pregnancy Outcomes (HAPO); and The Swiss Society of Endocrinology and Diabetes.

Insulin therapy is considered the first-line pharmacological therapy.

For GDM, as it does not cross the placenta to a significant degree. Fasting hyperglycemia is treated with basal (long- or intermediate-acting) insulin, and postprandial hyperglycemia is treated with prandial (rapid-acting) insulin.

It must be noted that the second and third trimesters of pregnancy are characterized by a progressive increase in insulin resistance and also in insulin requirements due to the gradual increase in diabetogenic hormones throughout pregnancy.

Complications:

- Hyperglycemia, which may generate a possible vascular dysfunction with SAH;
- Increased risk of developing postpartum DM2;
- Increased fetal insulin production;
- Increase of GLUTs in the placenta;
- Neonatal adiposity or macrosomia;
- Neonatal asphyxia;
- Neonatal hypoglycemia;
- Jaundice;
- Neonatal respiratory distress syndrome (NRDS);
- Consideration must also be given to the risk of children of mothers who have diabetes mellitus who are more likely to develop
    - obesity, hypertension that is systemic arterial disease and dyslipidemia, in addition to cardiovascular disease.
    - Fetal/neonatal:
    - High risk of cesarean delivery;
    - Shoulder dystocia and birth injury;
    - Fetal augmentation;
    - Fetal hyperinsulinemia;
    - Fetal hypoxia;
    - Polycythemia and hyperbilirubinemia;
    - Hypocalcemia.
    - Childhood:
    - Excessive adiposity;
    - Insulin resistance;
    - Decreased tolerance to glucose and DM2;
    - Difficulty in neurodevelopment.
    - Adult:
    - Obesity;
    - Insulin resistance;
    - Glucose intolerance;
    - Type 2 diabetes mellitus.
    - Prevention:
    - Balanced diet according to the pregnant woman and her complications;
    - Change in lifestyle;
    - Regular practice of physical activity.
    - It is important to consider that GDM is increasingly common in today's world. However, it is extremely important to know that it has serious complications for both mother and baby. Research has linked the use of metformin in

Intrauterine exposure may have adverse effects in patients with GDM. Its prevalence is related to maternal obesity, in addition to having genetic and environmental factors involved.

MATERIAL AND METHODS

The methodologies used were digital databases (PubMed and Scielo) and as inclusion criteria, most of the selected articles are from the last 5 years, in English, Portuguese, German and with the keywords: "Polycystic Ovary Syndrome", "Gestational Diabetes ", "Hyperandrogenism", "DHEA-S" among other words.

RESULTS AND DISCUSSION

PCOS is a multifactorial endocrine disorder that is very common in women, affecting 5 to 18%, and which increases the risk of developing Gestational Diabetes Mellitus. Existing studies conclude that there is not a survey that covers all populations, being right only for specific populations of some studies.

According to the "Practical Approach to Hyperandrogenism in Women" (Sharma A, et al, 2021) about 65% to 75% of women with PCOS develop hyperandrogenism,

with hirsutism being considered to be 80% of the most common symptom reported in the study. "Diagnosis of hyperandrogenism: clinical criteria" (Yildiz BO, et al, 2006).

According to data from the article "Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes" (Johns EC., et al 2018), 9 to 25% of pregnancies are affected by GDM, but already according to data from the article '' Prevalence, Prevention and Lifestyle Intervention of Gestational Diabetes Mellitus in China" (Juan, J., & Yang, H. 2020), 4% globally, ranging from 9% in Africa, 12.6% in North America and 21% in Asia in 2017. Thus, it can be concluded that the incidence of GDM varies by continent, ranging from 4% to 21%.

CONCLUSION

In view of the ideas presented, it is concluded that the syndrome is the result of genetic, metabolic and hormonal changes, with hyperandrogenism and insulin resistance as central characteristics. The pathophysiology of the syndrome is mainly described by the hypersecretion of luteinizing hormone, IGF-1 and changes in the gonadotropin pulse.

Most women with PCOS develop hormonal disorders that lead to androgen hypersecretion known as ovarian and adrenal hyperandrogenism. The physiology of Insulin is strongly related to testosterone synthesis, which is evidenced with hyperinsulinemia and insulin resistance in this mechanism, thus causing Diabetes.

Gestational diabetes mellitus is caused by insulin resistance, which can affect both the mother and the baby, having several risk factors. Thus, it is necessary for the pregnant woman to follow the treatment if she is diagnosed with gestational diabetes mellitus so as not to put her own health and that of her baby at risk both during pregnancy and post-pregnancy, which can be aggravated and result in type 2 diabetes mellitus. In addition to being more careful if you have polycystic ovary syndrome, as you may have infertility, oligo/anovulation, hyperandrogenism and a higher risk of hypertension.

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