FETAL METABOLIC PROGRAMMING IN THE ETIOLOGY OF POLYCYSTIC OVARIAN SYNDROME

A PROGRAMAÇÃO METABÓLICA FETAL NA ETIOLOGIA DA SÍNDROME DOS OVÁRIOS POLICÍSTICOS

ABSTRACT: Polycystic ovary syndrome (PCOS) is an endocrine dysfunction, which can be characterized by hyperandrogenism and chronic anovulation. The main signs of PCOS are amenorrhea and polycystic forms in the ovaries, being the most common disorder in women in menacme and very commonly associated with other metabolic syndromes. Studies suggest that one of the etiological factors of the syndrome is related to fetal metabolic programming, maternal, nutritional, genetic and environmental influences are determinant in the emergence of diseases, including PCOS. The objective of this work is to relate the fetal metabolic programming with the development of PCOS. The study methodology consists in a literature review, through research in PubMed and Scielo databases. It is concluded that factors such as placental pathologies and maternal metabolism, fetal hypoxia, intrauterine growth restriction, low birth weight, maternal hyperandrogenism state and pathologies that corroborate this, hyperinsulinemia, and insulin resistance (IR), in addition to maternal exposure to plastic components, such as
bisphenol A, are factors associated with the etiology of PCOS. Thus, during pregnancy, care must be taken to minimize the chances of future adolescents developing the syndrome and the various comorbidities that are associated with it.

**KEYWORDS:** Metabolic Syndrome, Fetal Development, Hyperandrogenis.

**RESUMO:** A síndrome dos ovários policísticos, a SOP, é uma disfunção endócrina, podendo ser caracterizada por hiperandrogenismo e anovulação crônica, em que os principais sinais são amenorreia e forma policísticas nos ovários, sendo o distúrbio mais comum em mulheres na menacme e muito comumente associada às outras síndromes metabólicas. Estudos sugerem que um dos fatores etiológicos da síndrome está relacionado à programação metabólica fetal, influências maternas, nutricionais, genéticas e ambientais são determinantes no surgimento de doenças, entre elas, a SOP. O objetivo deste trabalho busca relacionar a programação metabólica fetal e o desenvolvimento da SOP. A metodologia do estudo consiste em uma revisão da literatura por meio de pesquisa nas bases de dados do PubMed e Scielo. Conclui-se que fatores como patologias placentárias e do metabolismo materno, hipóxia fetal, restrição de crescimento intraútero, baixo peso ao nascer, estado de hiperandrogenismo materno e patologias que corroboram com este, hiperinsulinemia e resistência à insulina (RI), além de exposição materna a componentes de plástico, como o bisfenol A, são fatores associados a etiologia da SOP. Desta forma, durante a gestação, cuidados devem ser tomados a fim de minimizar as chances de as futuras adolescentes desenvolverem a síndrome e também as diversas comorbidades que se associam a ela.

**PALAVRAS-CHAVE:** Síndrome Metabólica, Desenvolvimento Fetal, Hiperandrogenismo.

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**1. Introduction**

Polycystic Ovarian Syndrome, PCOS, is the most common endocrine dysfunction in women of childbearing age and is responsible for the most frequent cause of chronic anovulation and infertility. Its main symptoms are
hyperandrogenism, amenorrhea and polycystic ovarian forms.\(^{(1)}\) This syndrome has no clear origin. However, fetal metabolic programming is related, i.e., nutritional alterations in the maternal metabolism, associated to genetic predisposition and environmental factors, may favor the appearance of PCOS, since they cause changes in the gene expression of nuclear proteins\(^{(2)}\), altering the normal metabolism.

The diagnosis of PCOS is based on the Rotterdam criteria, characterized with hyperandrogenism, chronic anovulation and polycystic ovaries on ultrasound.\(^{(3)}\) Excess androgen alters the regulation of female hormones, resulting in menstrual irregularity and infertility. Among its main manifestations are hirsutism, acne, seborrhea, and alopecia.\(^{(4)}\) In addition, PCOS can lead to high degrees of insulin resistance and compensatory hyperinsulinemia\(^{(2)}\), which can be especially determinant in the perinatal period.

Fetal development is the most dynamic phase of human development. If during this period of development there is intrauterine exposure to high concentrations of androgens by a catabolic process of dietary restriction, maternal and placental diseases, the fetus may enter a state of chronic fetal hypoxemia.\(^{(5)}\) For their survival, there is an adaptive response of the fetus, called fetal metabolic programming. This adaptation can promote metabolic and hormonal changes that favor the appearance of metabolic syndromes in the future, such as PCOS.\(^{(5)}\)

Thus, this review will relate the various insults during the perinatal period that may contribute to the development of PCOS in adulthood. In addition, the relationship of the presence of other syndromes, such as obesity, with the establishment of PCOS will be investigated.
2. Discussion

2.1 Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the endocrinopathy that most affects women of reproductive age. It is characterized by chronic oligovulation or anovulation, clinical or laboratory hyperandrogenism, and the presence of at least 12 ovarian cysts and/or ovarian volume greater than 10 cm³, observed on ultrasound.²⁻⁵

The Rotterdam criteria (2003), used for diagnosis, require 2 of the 3 aforementioned criteria, being facultative ovarian cysts.¹⁻³ Its diagnosis is of exclusion. Pathologies such as ovarian or adrenal tumors, hyperprolactinemia, hypo- or hyperthyroidism and Cushing syndrome can cause the same androgenic and anovulation symptoms and can mask the syndrome.⁸⁻¹⁰

The etiology of PCOS is still not defined. It is believed to be multifactorial, with genetic, maternal and environmental influence.⁷,¹¹ The pathophysiology surrounds a modification in ovarian steroidogenesis.⁶,¹¹ An alteration occurs in the pulses of GnRH (Gonadotrophin Releasing Hormone), produced in and released by the arcuate nucleus of the hypothalamus.¹²,¹³ In the pituitary gland, GnRH stimulates the production of the hormones FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone), which act in the ovaries, in the granulosa cells and in the theak cells, respectively, for hormone production during the menstrual cycle.⁷,¹²,¹⁴

The GnRH pulse in women with PCOS shows a predominance of LH synthesis, which stimulates the theca cells to convert cholesterol into androstenedione, one of the androgenic hormones.¹²,¹⁵,¹⁶ As a result, the body enters a stage of hyperandrogenism. Furthermore, FSH will be released in less quantity by the pituitary gland, and the ovary, in turn, will not produce estrogen properly. Thus, the thickening of the endometrium and the
Maturation of the ovarian follicles will not occur, becoming atrophic and leading to anovulation and secondary amenorrhea.

These high serum peaks of androgenic hormones stimulate the secretion of inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-\(\gamma\) (TNF-\(\gamma\)), due to the infiltration of inflammatory cells into the ovarian tissue.\(^{(6,13)}\) Thus, chronic inflammation and oxidative stress are installed, affecting follicle maturation in the ovary, forming the cystic follicles, besides all the metabolic disturbances that PCOS entails.\(^{(15)}\)

This hyperandrogenism manifests itself as hirsutism in 70% of cases, as well as acne and androgenic alopecia.\(^{(9,10)}\) The testosterone produced is converted via the enzyme 5-\(\alpha\)-reductase into dihydrotestosterone, which influences the thickening and growth of the hair follicle. In addition, increased keratosis occurs in the sebaceous glands, producing acne.\(^{(7,12,17)}\) The presence of hirsutism has been related to Insulin Resistance (IR) and a 3-fold increased risk of developing Metabolic Syndrome (MetS).\(^{(9,10)}\)

In the long term, PCOS causes great consequences to women, such as obesity, IR, dyslipidemia, Type 2 Diabetes Mellitus (DM2), cardiovascular diseases (CVD), MS, depression, non-alcoholic fatty liver disease, sleep apnea, among others.\(^{(6,8-11)}\)

Hyperinsulinemia and IR influence disease pathogenesis.\(^{(10)}\) IR in women with PCOS is related to an increase in serine phosphorylation, corroborating with a failure in insulin signaling after binding to the receptor, reducing its sensitivity to the receptor, not mobilizing glucose properly and leading to an increase in compensatory insulin production by pancreatic \(\beta\) cells.\(^{(10,13,18)}\)

In addition, the insulin receptor can also be tyrosine phosphorylated, leading to further negative feedback in insulin signaling, affecting metabolic pathways in adipocytes, skeletal muscle, and ovaries,\(^{(13,18,19)}\) promoting complex effects on the regulation of lipid and protein metabolism.
Among the lipid abnormalities that develop from RI can be observed the development of CVD,\(^{(18)}\) due to altered fibrinolysis, compromising lipolysis, inducing hypertension (SAH) and dyslipidemias.\(^{(10)}\)

Some studies have shown that ovaries have insulin receptors.\(^{(20,21)}\) Excess insulin stimulates receptors in the pituitary gland to release LH.\(^{(6)}\) Thus, hyperinsulinemia promotes androgen production in the ovarian tissue cells, leading to the clinical symptoms of hyperandrogenism, and aggravates the chronic ovarian inflammatory response, worsening the pathological process of PCOS.

In PCOS there is an inhibition of hepatic protein synthesis of SHGB (Sex hormone-binding globulin), induced by hyperandrogenism, which results in increased availability of free androgens.\(^{(6,18,22)}\) Chronic exposure to androgens directs macrophages to adipocytes, which induce their hypertrophy, leading to visceral fat accumulation, causing obesity.\(^{(18,23)}\) Obesity is present in 56% of patients with PCOS\(^{(10)}\) and its presence can aggravate metabolic and reproductive disorders associated with it.\(^{(9)}\) Studies have shown that patients with PCOS are 4 times more likely to have MS.\(^{(8,24)}\)

Thus, PCOS brings complex health consequences, in which it affects the quality of life of women in the short and long term. Its etiology is unclear and studies in the area are lacking. Therefore, this present study aims to relate fetal metabolic programming with the factors that can trigger PCOS in their daughters, in order to act early and inhibit the development of this disease.
2.2 Glucose Homeostasis and SOP

As the concentration of glucose in the bloodstream increases, insulin is produced and secreted by pancreatic β-cells. One of its main actions is to carry out glucose uptake by cells in target tissues, regulating carbohydrate, lipid, and protein metabolism, and participating in cell growth and differentiation. For insulin to exert its action it needs to bind to an insulin receptor (IR). The binding of insulin on the α-subunit promotes a tyrosine kinase activity on the β-subunit, performing an autophosphorylation on tyrosine residues. Modifications in this glucose and insulin homeostasis pathway, such as the reduction in IR tyrosine kinase activity and phosphorylation and also in PI3K activity, are determining factors in IR.

In PCOS, phosphorylation of substrates in serine, i.e., tyrosine phosphorylation is impaired, usually associated with reduced insulin action, due to failure of receptor activation. This phosphorylation also affects the Akt and PI3K substrates, which provide feedback inhibition of glucose homeostasis. IR are also present in the ovaries, pituitary, and adrenal glands, which remain sensitive even with IR. Thus, hyperinsulinemia, characteristic of PCOS, stimulates LH production because it increases the activity of the GnRH neuron and thus stimulates the production of androgenic hormones. The excess insulin inhibits the production of proteins that would bind to IGF-1 (free insulin-like growth factor 1), which becomes available in the bloodstream, stimulating the production of more androgenic hormones by the teak cells, exacerbating the inflammatory process.

Hyperandrogenemia has been linked to the secretion of pro-inflammatory cytokines such as TNFα, IL-1β, IL-6 that interfere with intracellular insulin signaling. These cytokines activate the enzyme c-Jun N-terminal kinase (JNK) which has a serine kinase activity acting on substrates including IRS-1 and IRS-2. Thus, if IR is phosphorylated...
at serine by JNK, this causes a failure in the activation of PIK3 and Akt and thus the activation cascade is compromised.\textsuperscript{(32,33)} Insulin does not phosphorylate its receptors, remaining available in the bloodstream, and does not mobilize glucose, since GLUTs are not expressed, leading to the picture of hyperinsulinemia and hyperglycemia, characteristic of IR.

Women with PCOS are more likely to accumulate fat, especially abdominal fat.\textsuperscript{(18,23)} Free fatty acids activate Toll-like receptors (TLRs), especially TLR4, which plays an inhibitory role in the IR β-subunit pathways by increasing the phosphorylation of JNK at serine, making a vicious cycle of IR.\textsuperscript{(26,34)}

2.3 Fetal Metabolic Programming and SOP

Due to the multifactorial causes of PCOS,\textsuperscript{(7,11)} some studies suggest that during fetal development changes occur that increase the chance that offspring will present PCOS as adolescents,\textsuperscript{(1)} a process known as metabolic programming.

Metabolic programming refers to the response to stimuli, whether environmental, nutritional, or metabolic, during fetal life that will influence the development of health and disease in adulthood.\textsuperscript{(35)} These epigenetic stimuli can alter the expression of certain genes without influencing the DNA sequence,\textsuperscript{(6,36)} but rather influencing the development and metabolism of the normal organism. Such changes relate to the modification of histones, methylation, the insertion, or removal of chemical compounds in the DNA strand, etc.\textsuperscript{(37-39)}

Studies state that SOP can promote hypomethylation of the LH receptor in the teak cells, increasing its expression, as well as hypomethylation of the epoxide enzyme gene hydrolase 1 (EPHX1).\textsuperscript{(40,41)} This enzyme, blocks the conversion of testosterone to estradiol.\textsuperscript{(7,12)} In other words, with increased expression of EPHX1, less estradiol is produced, and a
hyperandrogenic state predominates.\textsuperscript{(40,41)} Maternal hyperandrogenism can have long-term consequences for the fetus, discussed below.

In addition, placental injury can lead to fetal hypoxia,\textsuperscript{(42-44)} which overloads the hypothalamic-pituitary-adrenal (HHA) axis, increasing the concentration of circulating glucocorticoids to compensate for fetal poor circulation.\textsuperscript{(12, 45)} The increased glucocorticoid leads to resistance and alters insulin secretion, promoting hyperinsulinemia, IR, adipocyte changes, childhood visceral obesity, early pubarche and adrenarche, and PCOS.\textsuperscript{(1,12,45)} Moreover, in adulthood, the chances of DM2, SAH, and CVD increase, which becomes more common in patients under 40 years of age.\textsuperscript{(10,18)}

Activation of the HHA axis promotes an increase in androgens, due to hyperactivity of the adrenal gland, mainly dehydroepiandrosterone (DHEA) and androstenedione, precursors of testosterone.\textsuperscript{(12,46)} One study suggests that excess maternal androgens during pregnancy is associated with fetal growth restriction.\textsuperscript{(47)} The compensatory growth that PIG (Small for Gestational Age) babies have in the first two years of life is related to a state of hyperinsulinemia, which is associated with a picture of infantile visceral obesity.\textsuperscript{(35,47)} Adipose tissue dysfunction is associated with increased LH secretion, ovarian hyperandrogenism and hyperinsulinemia,\textsuperscript{(9,10,26,27)} leading to more frequent anovulatory cycles in these women and a greater likelihood of developing PCOS.

Mothers who are born with PIGs are more susceptible to having pregnancies with placental pathologies, babies with fetal growth restriction and a possible birth with low birth weight.\textsuperscript{(1)} Moreover, it is worth remembering that women who were not born with such conditions can also develop PCOS, and the environmental factor is crucial for the development of the condition.\textsuperscript{(6)} Maternal exposure during pregnancy to endocrine disruptors increases the chances of developing PCOS in the fetus, besides DM2, obesity, and other metabolic disorders.\textsuperscript{(41,48)} Bisphenol A, for example,
can increase androgen synthesis and decrease testosterone breakdown, leading to a state of maternal hyperandrogenism.\(^{(47,49)}\)

Therefore, during pregnancy, care must be taken. One should maintain regular physical exercise, control weight gain, eat a healthy diet, avoid processed foods, choose not to heat food in plastic containers, be careful with the dental procedures performed during this period, avoid contact and inhalation of chemicals, etc. Preventions like these, can decrease the chances of a possible metabolic programming and thus the development of diseases in the adult life of this child, such as PCOS.

3. Conclusion

It is known that metabolic programming has major maternal influences on the health and disease process of the baby in its adult life. Thus, it is concluded that fetal hypoxia and the excess glucocorticoids it produces alter insulin secretion, contributing to IR, obesity, precocious puberty and PCOS. Similarly, the hyperactivity of the adrenal gland generates a state of maternal hyperandrogenism, leading to fetal growth restriction and low birth weight. The compensatory growth of these babies is associated with adipose tissue dysfunction, thus increasing the secretion of LH, androgen hormones and hyperinsulinemia, leading to future anovulatory cycles and PCOS.
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