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PCOS AND ITS LONG TERM HEALTH IMPLICATION: FROM INFERTILITY TO METABOLIC SYNDROME

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ABSTRACT

The most common endocrine condition affecting women of reproductive age worldwide is polycystic ovarian syndrome, or PCOS. From the original 1990 NIH criteria to the 2003 Rotterdam criteria, which call for two of three markers—oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology (PCOM)—this complicated disorder is marked by diagnostic variability. Due to ultrasound's limits and inconsistency, serum anti-Müllerian Hormone (AMH) has recently become a possible objective measure for diagnosis. A "central nexus" of insulin resistance, obesity (particularly visceral adiposity), and hyperandrogenism underlies the pathogenesis of PCOS. These elements produce a vicious cycle: Insulin resistance: Causes compensatory hyperinsulinemia, which exacerbates androgen excess by increasing ovarian testosterone synthesis and lowering sex hormone-binding protein (SHBG). Hyperandrogenism: Inhibits normal follicular growth and encourages the formation of belly fat. Metabolic risks include cardiovascular disease, metabolic syndrome, and type 2 diabetes. Malignancies: PCOS-related infertility and endometrial cancer are strongly correlated, and

new studies are looking into possible connections with ovarian and breast cancers. Intergenerational Impact: Obesity, metabolic abnormalities, and neurodevelopmental or psychiatric problems are more common in children of PCOS-affected women. Although early detection is essential to avoiding these dire outcomes, many cases go undetected, impeding timely management**.** According to recent studies on the gut microbiome, dysbiosis may contribute to pathogenesis, opening up novel treatment options with probiotics and prebiotics.

KEYWORDS: polycystic ovarian syndrome, infertility, Metabolic Syndrome, endocrine conditions.

INTRODUCTION

Defining Polycystic Ovary Syndrome: Undiagnosed Burden and Diagnostic Heterogeneity the most prevalent endocrine condition in women of reproductive age globally is polycystic ovarian syndrome, or PCOS. Insulin resistance and a high incidence of visceral adiposity, regardless of obesity, are the main pathophysiological factors of PCOS. These factors lead to mistakes in hormonal cross-talk between the brain, pituitary gland, and ovaries. Infertility, metabolic syndrome, obesity, type 2 diabetes, cardiovascular risks, depression, obstructive sleep apnea, endometrial cancer, and metabolic dysfunction-associated steatotic liver disease (MASLD) are among the several comorbidities linked to PCOS.[1] Information regarding potential long-term health effects for children of PCOS-affected women is also becoming available. Their offspring have a higher risk of developing neurodevelopmental or psychiatric illnesses as well as obesity and metabolic issues.[2] The emergence of dire long-term repercussions.

Infertility

PCOS is the first cause of anovulatory infertility nowadays and infertility is found in 70 to 80% of affected women.[11] PCOS is the first cause of female infertility but the definite diagnosis should be given after exclusion of other etiologies of infertility such as other endocrine disorders (thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome premature ovarian insufficiency) anatomical dysfunctions (endometriosis, pelvic inflammatory diseases, or iatrogenic causes (surgery, chemotherapy, radiation Evaluation of infertility (or subfertility) is recommended after 12 months without pregnancy in couples having regular sexual intercourse (2 or 3 times/week).[12]

SECONDARY EFFECTS OF INFERTILITY

Effect on mental health

While causation cannot be confirmed in any of these studies, it is important to note that a correlation exists between infertility/PCOS and mental health disorders, with some presentations near the time of the infertility diagnosis and others years later. An awareness of this correlation can help clinicians understand the unique challenges faced by women with infertility. Whether a specific biologic or environmental link between infertility and mental health exists remains unclear.[13]

Effect on gynecologic malignancy

Breast cancer: The connection between female infertility and gynecologic malignancy is one of the most studied aspects of the impact of infertility on somatic health. A possible link between infertility and the BRCA-1 mutation, which is a well-documented risk factor for the development of breast cancer. It was shown in three separate studies that BRCA-1 mutations were associated with low anti-mullerian hormone (AMH) levels and low ovarian response rates. This subset of women, as expected, is at higher risk to develop breast cancer in the future. These studies were not included in the review itself because at this point, it may be premature to state that BRCA-1 mutations are an independent predictor of infertility. One key factor that may be confounding all of these studies is the demonstrated increase in breast cancer risk among nulliparous women, as infertile women are more likely to remain nulliparous.

Ovarian cancer: A link between ovarian cancer and infertility has also yielded conflicting results.[13] Nine studies relating to ovarian cancer showed a clear increase in ovarian cancer risk for women with an infertility-associated diagnosis. This study by Cirillo et al. published in 2016 showed a positive link between irregular menses and subsequent risk of developing ovarian cancer.[14] While Cirillo's study looked at irregular menses rather than a specific diagnosis of infertility, many women with infertility caused by PCOS have irregular menstrual cycles, which makes this finding noteworthy. However, it must be noted that Cirillo's study included women who had previously given birth, indicating that despite a history of irregular menses, the women in the study may not have been infertile. The remaining eight studies showed conflicting data about whether women with infertility were at a higher risk to develop ovarian cancer. Specific subgroups of women did appear to be at higher risk for subsequent ovarian cancer. These subgroups included women with unexplained infertility, parous women with only one delivery as opposed to multiple

deliveries following reproductive technology, women with PCOS, and women who had used progesterone therapy as part of their fertility treatment.[15,16,17,18] In a meta-analysis of 21 studies by Kvaskoff et al., 20 studies showed an elevated ovarian cancer risk in women with endometriosis, while one study failed to show this association.[19] Evaluating women with a general diagnosis of infertility appears to yield conflicting results, but certain subgroups of infertile women may benefit from additional testing or counseling related to the topic of ovarian cancer. It is also important to note that the studies above were inconsistent in controlling for nulliparity, which is a known risk factor for ovarian cancer.

Endometrial cancer: Women with unexplained infertility or women diagnosed with PCOS at a young age showed substantial elevations in endometrial cancer risk.[15,16] Endometrial cancer risk was found to be elevated in women receiving natural cycle IVF as well as women who began using Clomid therapy at less than 30 years of age.[20,21] Overall, infertility related to PCOS seems to show a strong relationship with subsequent endometrial cancer risk. Many of the statistical risks published were significantly elevated, which makes this area of study highly relevant for clinical practice. PCOS is intrinsically linked to infertility, but whether the primary cause of remains unclear. (endometrial cancer in these women stems from PCOS, obesity, their infertility diagnosis, or a combination of these factors.[13]

Metabolic dysfunction due to infertility: PCOS seems to play a prominent role in the development of overall health problems, likely due to its intrinsic relationship to metabolic syndrome. Endometriosis also seems to elevate an individual's cardiovascular risk.[19]

Metabolic syndromes in PCOS: Central pathophysiological nexus-insulin resistance and hyperandrogenism issues Insulin acts as a regulator of glucose homeostasis by stimulating glucose uptake by insulin-sensitive tissues, such as adipose tissue, skeletal muscle, liver, and heart, but also by suppressing hepatic glucose production. Insulin is also able to suppress lipolysis, leading to a decrease in free fatty acid levels, which may mediate insulin's action on hepatic glucose production. Insulin resistance is defined as a decreased ability of insulin to carry out these metabolic actions inherent in glucose uptake and production and lipolysis, thus leading to compensatory high insulin levels, both at baseline and after glucose loading, if pancreatic function is normal. There is still no consensus on the exact mechanism that leads to insulin resistance in PCOS, regardless of body mass index (BMI). An old study argued that in PCOS, the mechanism underlying insulin resistance decreased autophosphorylation of the insulin receptor following insulin binding. The mechanisms by which insulin resistance

exerts its effects have only recently been well described. At a liver and skeletal muscle level, insulin resistance increases lipolysis with the accumulation of non-esterified fatty acids. The accumulation of intrahepatic lipids activates the diacylglycerol/protein kinase C axis and inhibits the insulin receptor, also affecting insulin signalling and subsequent gluconeogenesis. In skeletal muscle, the inhibition of phosphoinositide-3 kinase and phosphorylation of insulin receptor substrate 1 leads to impaired insulin signalling by altering the GLUT-4 expression and glucose uptake.[5]

Effect of OBESITY in PCOS: Obesity, especially abdominal obesity, is a common manifestation of PCOS, and the prevalence depends on geographic location and ethnicity.[22] Studies have shown that abdominal obesity may be associated with a variety of clinical features of PCOS. For example, due to adipose tissue dysfunction, adipocytes secrete non-physiological levels of adipokines, including IL6, IL8, TNF-α, leptin, adiponectin, resistin, lipocalin 2, monocyte chemoattractant protein-1 (MCP1), retinol binding protein-4 (RBP4), and CXC-chemokine ligand 5 (CXCL5), which may be involved in IR.[23,26] In addition, a recent study has indicated that obesity may function as a better predictor of skeletal muscle mass in PCOS women than hyperandrogenism and IR, which may aggravate PCOS complications.[27] Interestingly, adipose tissue dysfunction can affect follicular development. A recent study showed that IL-10 secreted by adipocytes tampers with VEGF-induced angiogenesis and further disrupts folliculogenesis.[28] Moreover, molecular mechanisms about androgens and adipose function in PCOS were mentioned recently. Lerner et al. revealed that excess androgen can inhibit brown adipogenesis, attenuating the activation of thermogenesis and reducing mitochondrial respiration in brown adipose tissue.[29] Zhou et al. used bioinformatics analysis to identify CHRDL1 gene which may be responsible for obesity of PCOS by inhibiting bone morphogenetic protein 4 signaling or regulating IGF-1.[30]

Hyperandrogenism: One of the PCOS diagnosis criteria is hyperandrogenism. IR, obesity and hyperandrogenism are inseparable in the pathogenesis of PCOS. Hyperinsulinaemia caused by IR exerts a cogonadotropin effect on the ovaries and decreases the expression of sex hormone-binding protein (SHBG), leading to the onset of hyperandrogenism.[31,32] Androgens can induce the accumulation of adipose tissue, especially abdominal fat tissue, and cause IR in subcutaneous adipose tissue.[33,34] In humans, androgen plays a dual role in folliculogenesis: a low dose of androgens promotes follicle growth, while a high level of androgens could augment the secretion of anti-Müllerian hormone (AMH) in granulosa cells,

thus inhibiting follicular development.[35] Several studies have also reported other potential mechanisms of hyperandrogenism-induced PCOS, such as dihydrotestosterone (DHT), which could contribute to mitochondrial fission in granulosa cells of PCOS patients, and excess androgens induce ER stress, which may damage oocyte quality.[36,37] Besides, Wang et al. found that hyperandrogenism may contribute to chronic low-grade inflammation in ovary and granulosa cells of PCOS by generating NLRP3 inflammasome, which further promotes granulosa cells pyroptotic death and ovarian fibrosis.[38] Therefore, hyperandrogenism plays a complicated role in PCOS.

Recent studies have hypothesized the role of the gut microbiome as a cause or effect of BMI, insulin resistance, and inflammation in PCOS. Gut dysbiosis due to poor-quality diet could cause the passage of lipopolysaccharides produced by Gram-negative microorganisms into the circulation. The consequence could be the activation of the immune system, insulin resistance, and hyperandrogenism. A recent revision of 31 studies published in the last 10 years reported reduced alpha diversity and dysbiosis in women with PCOS. Treatment of PCOS with prebiotics, probiotics, and symbiotic could have some beneficial effects on metabolic and biochemical profiles. Further studies should investigate the role of the microbiome in the pathogenesis and management of PCOS.[5]

CONCLUSION

- A complex endocrine condition that affects 70% to 80% of people with anovulatory infertility, polycystic ovarian syndrome (PCOS) is still the most common cause of infertility globally. Insulin resistance, visceral obesity, and hyperandrogenism are all part of a complex "central nexus" that drives its pathogenesis and creates a vicious cycle of hormonal and metabolic dysfunction. Beyond issues with reproduction, PCOS has serious long-term health consequences that include serious risks for.
- Metabolic diseases include cardiovascular disease, metabolic syndrome, and type 2 diabetes.
- Malignancies: Strong associations with endometrial cancer, as well as possible connections to ovarian and breast cancers in some patient subgroups.
- Mental health: A recognized association with mental illnesses that may manifest years later or at the time of diagnosis.
- Intergenerational Health: Offspring of PCOS-affected mothers are more vulnerable to risks of obesity, metabolic abnormalities, and neurodevelopmental or psychiatric issues.

Advancements in diagnostic tools, such as the use of **Anti-Müllerian Hormone (AMH)** as an objective marker and the exploration of the **gut microbiome**, offer promising avenues for more accurate identification and novel treatment options like probiotics. Ultimately, early detection is vital to breaking the cycle of pathogenesis and implementing timely interventions to mitigate these severe, lifelong health consequences.

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