Section: Physiology

Original Research Article

PATHOPHYSIOLOGY OF ENDOCRINE AND METABOLIC DISORDERS AMONG PATIENTS WITH POLY CYSTIC OVARIAN SYNDROME

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Received : 02/02/2024
Received in revised form : 04/04/2024
Accepted : 20/04/2024

Keywords:
Endocrine Disorders, Poly Cystic Ovarian Syndrome.

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DOI: 10.47009/jamp.2025.7.1.93

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (1); 481-484

Abstract

In this study, that was conducted from August 2019 to march 2020. I discuss the pathophysiology of PCOS. Polycystic ovary syndrome (PCOS) is a very common reproductive endocrinological disorder seen in women, affecting 5–20% of the reproductive age women globally. Given the pivotal role IR and obesity play in the etiopathogenesis and progression of PCOS and its potential subsequent metabolic and cardiovascular complications, both should be considered essential therapeutic targets. Lifestyle modifications in the treatment of PCOS do not escape criticism and controversy despite being widely accepted recommendations. Physical activity (PA) has been reported to ameliorate anovulation, IR, blood pressure, and lipid profiles in women with PCOS, sometimes independently of weight loss. In addition, novel perspectives into the pathophysiology of PCOS, such as the role of ovarian AGE deposition, suggest avoidance of Glycotoxin-rich diets as an added recommendation.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a very common reproductive endocrinological disorder seen in women, affecting 5–20% of the reproductive age women globally.[1]

Insulin resistance (IR) and associated metabolic abnormalities appear to play a significant role in the development of PCOS and in sustaining this disorder.[2,3] Avast majority of the affected women also show hyperinsulinemia, developed as a compensatory physiological body need, which in itself contributes to several problems including overweight. Hyperinsulinemia in these patients contributes to the development of metabolic syndrome, which is a composite of type 2 diabetes, atherosclerosis, obesity and cardiovascular disorders.[4,5] The primary defect lies at the ovarian level or may be a manifestation of hyperinsulinemia that drives elevated androgen production.[6] Hyperandrogenism in association with ovulatory dysfunction and polycystic ovarian morphology (PCOM) are common features of PCOS, with the ovaries producing large quantities of androgens.[1] This is also accompanied by menstrual disorders (oligo-amenorrhea).[5] The manifestations of PCOS are not confined to the gynecological sphere; women affected by this disease show an increased prevalence of several co morbidities, including obesity, dyslipidemia, hypertension, metabolic syndrome (MS), and type 2 diabetes mellitus (DM2) in comparison with women without PCOS. These features, along with other alterations such as endothelial dysfunction and a chronic low-grade inflammatory state, underlie the greater risk of developing cardiovascular disease and increased all-cause mortality observed in these subjects.[7]

MATERIALS AND METHODS

In this study, that was conducted from August 2019 to march 2020. I discuss the pathophysiology of PCOS. First, I summarize our current understanding of the etiology and pathology of PCOS, then; discuss details of two representative environmental factors involved in the pathogenesis of PCOS. Finally, I present perspectives regarding the directions of future research.

PCOS and endocrine manifestations

In contrast to the characteristic picture of fluctuating hormone levels in the normal cycle, a "steady state" of gonadotropins and sex steroids in women with PCOS is due to the persistent anovulation in which the production of estrogen and androgens are both increased.[8,9] Anovulatory women with PCOS also have a higher luteinizing hormone (LH) and gonadotropins-releasing hormone (GnRH) pulse

ISSN (O): 2687-5365; ISSN (P): 2753-6556

frequency and amplitude when compared to the normal midfollicular phase.[10] This enhanced pulsatile secretion of GnRH can be attributed to a reduction in hypothalamic opioid inhibition because of the chronic absence of progesterone.[11] The increased LH secretion, as expressed by the LH: FSH (follicle-stimulating hormone) ratio, is positively correlated with the increased free estradoiol.[12] A sensitive assay for inhibin-B has detected high levels in women with PCO, suggesting that multiple small follicles can suppress FSH by increasing the circulating levels of inhibin-B.[13] However, FSH levels are not totally depressed. Hence new follicular growth is continuously stimulated but not to the point of full maturation and ovulation.[14] Therefore, multiple follicular cysts develop 2-10 mm in diameter, which are theca cells, often luteinized in response to high LH levels. Hyperthecosis refers to patches of luteinized theca-like cells scattered throughout the ovarian stroma. It is characterized by the same histological findings as seen in polycystic (PCOS) syndrome.[15] The clinical picture of more intense androgenization is a result of greater androgen production. This condition is associated with lower LH levels, which is a possible consequence of the higher testosterone levels blocking estrogen action at the hypothalamic pituitary level. It seems appropriate to view Hyperthecosis as a manifestation of the same process of persistent anovulation, but with greater intensity. A greater degree of insulin resistance is correlated with the degree of Hyperthecosis.[16] Because, insulin and insulin-like growth factor 1 (IGF-1) stimulate proliferation of thecal interstitial cells, hyperinsulinemia may be an important factor contributing to Hyperthecosis.[17]

PCOS and metabolic syndrome

It has been suggested that women with PCOS could reduce their risk of Type 2 diabetes and cardiovascular disease through weight reduction and exercise and that the use of medications that reduce insulin resistance might also be warranted.[18] Some studies have demonstrated the benefits of weight reduction and exercise programs for infertile women with PCOS. There is very little evidence that women with PCOS are at increased risk of cardiovascular disease independent of Type 2 diabetes.[19] This may be due to the action of unopposed estrogen in anovulatory cycles, which might protect women with PCOS, despite the presence of other cardiovascular risk factors. The extent to which Type 2 diabetes contributes to premature morbidity and mortality for women with PCOS remains unclear at present. It is also debated whether it is the PCOS per se or the obesity that is a frequent attribute of the condition or both that is the principal contributor to the observed excess of Type 2 diabetes among women with histologically proven PCOS.[20] An Indian study which shows that dyslipidemia in PCOS is associated with obesity rather than raised testosterone.[21]

RESULTS

The results of studies that have considered the relationship between PCOS and lipid levels are inconsistent. The HDL levels are a possible exception as the majority of studies report lower HDL levels among women with PCOS than among controls, regardless of the selection criteria for either cases or controls.[22]

Table 1. Diagnostic Criteria for PCOS (Adult Diagnostic Criteria (Rotterdam)

1. Phenotype 1 (classic PCOS)a
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligo-anovulation
   c. Ultrasonographic evidence of a polycystic ovary
2. Phenotype 2 (Essential NIH Criteria)a
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligo-anovulation
3. Phenotype 3 (ovulatory PCOS)a
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Ultrasonographic evidence of a polycystic ovary
4. Phenotype 4 (nonhyperandrogenic PCOS)
   a. Evidence of oligo-anovulation
   b. Ultrasonographic evidence of a polycystic ovary]]

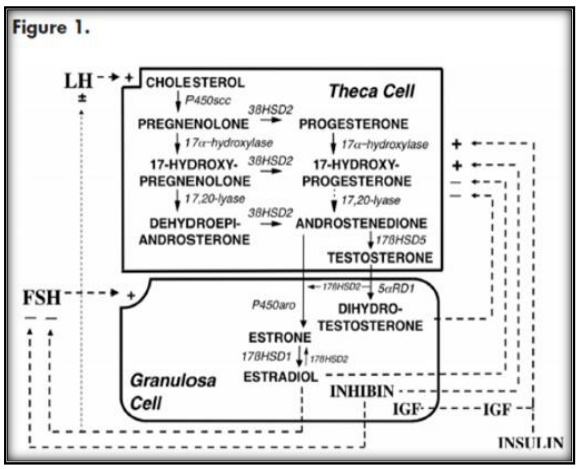
Adolescent Diagnostic Criteria

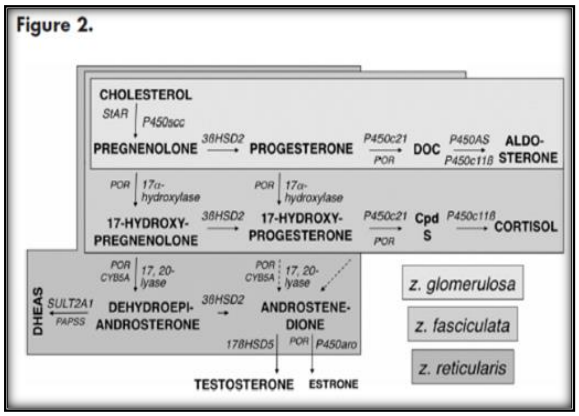
1. Abnormal uterine bleeding pattern
   a. Abnormal for age or gynecologic age
   b. Persistent symptoms for 1–2 y
2. Evidence of hyperandrogenism
   a. Persistent testosterone elevation above adult norms in a reliable reference laboratory is the best evidence
   b. Moderate-severe hirsutism is clinical evidence of Hyperandrogenism

Table 2: Functional Classification of PCOS According to Source of Androgen Excess

PCOS Functional Type	Source of Androgen	GnRHag Test 17OHP Response	DAST Testosterone Response	ACTH test DHEA Response	Prevalence Among PCOS
PCOS-T	Primary FOH (typical FOH)	High[a]	High in 92.5%	High in 28% (associated FAH)	67%[b]
PCOS-A	Primary FOH (atypical FOH)	Normal[a]	High	High in 30% (associated FAH)	20%
	Primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A)	Normal	Normal	Normal	8%

ISSN (O): 2687-5365; ISSN (P): 2753-6556





Long-term follow-up of women with PCOS treated previously with ovarian wedge resection has shown these women to be at increased risk of developing Type 2 diabetes, independent of obesity [23]. As pregnancy has a diabetogenic effect, all women who are at risk of Type 2 diabetes by virtue of a positive family history of diabetes and/or obesity are also at risk of developing gestational diabetes. Insulin resistance, defined as decreased insulin-mediated glucose utilization, is found in 10-25% when sophisticated dynamic studies of insulin action are performed.[24] However, the criteria for selecting an abnormal cutoff point vary. Insulin resistance in women with PCOS appears to be even more common (up to 50%), both in obese and no obese women.[25] Reports of the prevalence on insulin resistance in women with PCOS vary depending on the sensitivity and specificity of the tests employed and the Heterogeneity of PCOS. Also the criteria of metabolic syndrome itself vary, based on at least three criteria, NCEP,[26] WHO,[27] and IDF,[28] and consequently the prevalence of metabolic syndrome in PCOS would vary depending on the criteria employed. The association between exposure to unopposed estrogens and an increased risk of endometrial cancer has been well established. Obesity has been shown consistently to be an important risk factor for endometrial cancer. Many studies support the hypothesis that reduced exposure to ovulatory menstrual cycles is protective against breast cancer.[29]

DISCUSSION

Given the pivotal role IR and obesity play in the etiopathogenesis and progression of PCOS and its potential subsequent metabolic and cardiovascular complications, both should be considered essential therapeutic targets [30]. Although traditionally metformin is thought of as a hallmark of PCOS treatment as the mainstay insulin sensitizer, the advent of the distinct phenotypes for this syndrome and the broader acceptance of this categorization bring into question its indication in all cases of PCOS.[31] Uncertainties are even more commonplace surrounding other pharmacologic alternatives habitually considered for PCOS management, such as thiazolidinedione's and statins.[32,33] Lifestyle modifications in the treatment of PCOS do not escape criticism and controversy despite being widely accepted recommendations. Physical activity (PA) has been reported to ameliorate anovulation, IR, blood pressure, and lipid profiles in women with PCOS, sometimes independently of weight loss,[34] yet PA alone does not seem to be able to equal these parameters to non-PCOS subjects.[35] Therefore, it should be accompanied by a complementary diet plan in order to fully potentiate the effects of a lifestyle-modification therapeutic program. Standard weight loss programs may be sufficient for ameliorating features of PCOS, in the form of a nutritionally adequate, fiber-rich, low fat, moderate protein, and high carbohydrate intake diet with a 500–1,000kcal/day reduction.[36] On the other hand, more specialized low-carbohydrate ketogenic diets have been reported to significantly reduce weight, LH/FSH ratio, testosterone and fasting insulin ratio, and IR in women with PCOS,[37] although concerns on their safety on lipid profiles and cardiovascular risk call for careful consideration.[38,39]

CONCLUSION

Ultimately, a wide range of dietary programs akin to these general concepts are accepted to similarly improve weight, reproductive and metabolic variables in PCOS so long as they boast nutritional adequacy and long term sustainability.[40] In addition, novel perspectives into the pathophysiology of PCOS, such as the role of ovarian AGE deposition, suggest avoidance of glycotoxin-rich diets as an added recommendation.[41]

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ISSN (O): 2687-5365; ISSN (P): 2753-6556

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ISSN (O): 2687-5365; ISSN (P): 2753-6556