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Clinical Focus on

Polycystic Ovary Syndrome

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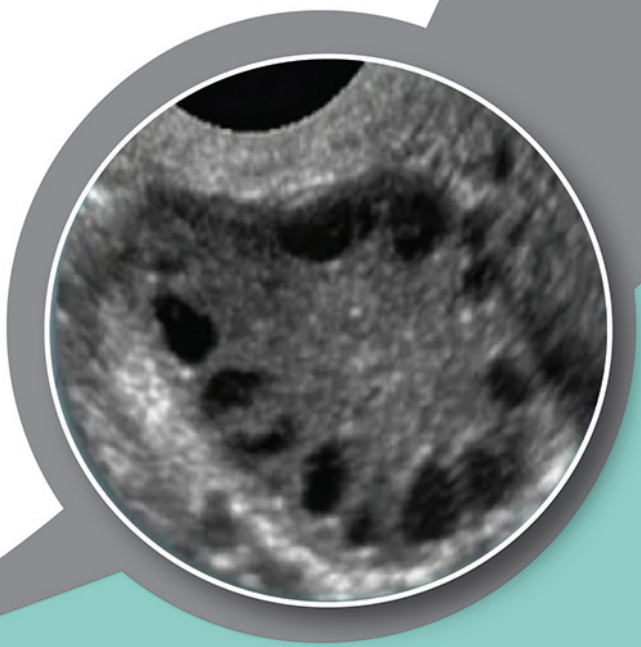

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CHAPTER 2

Pathophysiology in PCOS

Aruna Verma, Mohita Agarwal

INTRODUCTION

Approximately 90% of individuals with polycystic ovary syndrome (PCOS) have abnormal ovarian androgenic effects,[1] and the common denominator of PCOS is ovarian hyperandrogenism. Insulin-resistant hyperinsulinemia is a minor but common complicating factor in pathophysiology. The propensity for luteinizing hormone (LH) excess and obesity appears to accompany underlying ovarian hyperandrogenism and hyperinsulinemia.

So, a unified minimal model of PCOS pathophysiology is given, which incorporated the major features of the syndrome[1] and is as follows:

- Functional ovarian hyperandrogenism (FOH)
- Insulin resistance
- LH excess.

PRIMARY FUNCTIONAL OVARIAN HYPERANDROGENISM

According to ovarian androgenic dynamic testing, approximately 90% of PCOS patients have FOH.[1] Excess circulating androgens act on the skin's pilosebaceous units, causing cutaneous manifestations such as hirsutism and acne. Granulosa cell dysfunction results from an excessive intraovarian androgenic milieu, which manifests as oligo-anovulation and, in some cases, polycystic ovarian morphology (PCOM) **(Figs. 1A and B)**.

Polycystic ovary syndrome is classified into several functional groups, each representing a different source of androgen excess **(Table 1 and Fig. 2)**:

- *Functionally typical PCOS/FOH:* Two-thirds of PCOS/FOH cases are considered "functionally typical" because they show an exaggerated increase in 17-hydroxyprogesterone (17-OHP) in response to LH receptor stimulation achieved clinically with either gonadotropin-releasing hormone agonist (GnRHa) or human chorionic gonadotropin (hCG). The increased 17-OHP response appears to be an indicator of dysregulated cytochrome P450c17 function. Furthermore, these patients have an abnormal response to the dexamethasone androgen-suppression test (DAST): dexamethasone suppresses adrenocortical steroidogenesis but is unable to suppress serum testosterone, indicating an ovarian origin.
- *Functionally atypical PCOS/FOH:* PCOS is classified as "functionally atypical" if the remaining one-third of cases have a normal 17-OHP response to GnRHa or hCG but an abnormal response to DAST. Some patients have isolated primary functional adrenal hyperandrogenism (FAH), as shown by adrenocorticotropic hormone (ACTH) stimulation, or PCOS without FOH or FAH. The majority of the latter group has obesity-related atypical PCOS, while a small percentage has

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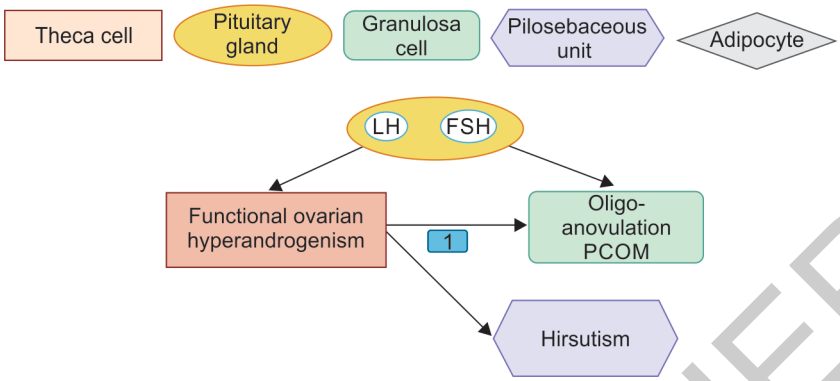

Fig. 1A: Functional ovarian hyperandrogenism in all PCOS.

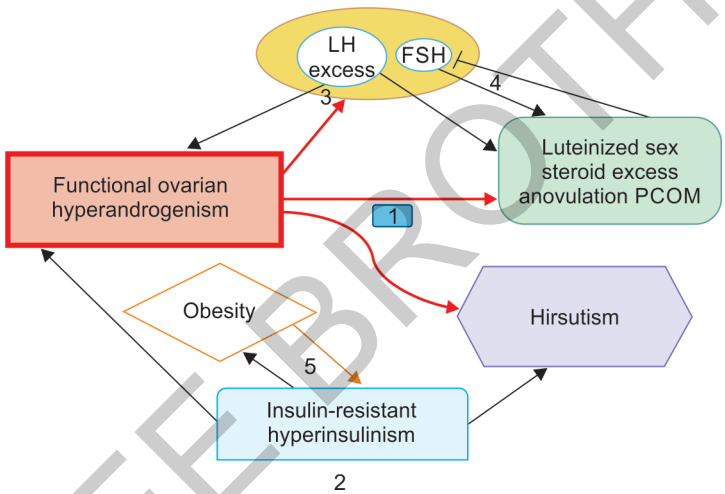

Fig. 1B: Insulin-resistant hyperinsulinism in PCOS.
(FSH: follicle-stimulating hormone; LH: luteinizing hormone; PCOS: polycystic ovary syndrome; PCOM: polycystic ovarian morphology)

idiopathic atypical PCOS **(Table 1 and Fig. 2)**.

The mechanisms for FOH include the following:

- *Dysregulation of theca cell steroidogenesis:* The steroid secretion pattern in PCOS typically indicates generalized over-activity of the whole steroidogenic pathway, from cholesterol to androgens and estrogens, with drastic elevation in 17-OHP stating dysregulation of cytochrome P450c17 activities, which are encoded by the *CYP17A1* gene.[1,2] Cytochrome P450c17 is active in both 17-hydroxylase and 17,20-lyase, the latter being the rate-limiting step in androgen formation.

Androgen production within the ovary is strictly regulated because androgen is a necessary evil in the ovary: androgen serves as the substrate for estrogen formation, and androgen is needed for optimal fertility.[1,3] Excess androgen, on

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TABLE 1: Functional classification of polycystic ovary syndrome according to source of androgen excess.

PCOS functional type	*Source of androgen*	*GnRHa test: 17-OHP response*	*DAST testosterone response*	*ACTH test: DHEA response*	*Prevalence among PCOS*
Typical PCOS (PCOS-T)	Primary FOH (typical FOH)	High	High in 92.5%	High in 28% (associated FAH)	67%
Atypical PCOS (PCOS-A)	Primary FOH (atypical FOH)	Normal	High	High in 30% (associated FAH)	20%
	Isolated primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (atypical PCOS of obesity or idiopathic atypical PCOS)	Normal	Normal	Normal	8%

(ACTH: adrenocorticotropic hormone; DAST: dexamethasone androgen suppression test; DHEA: dehydroepiandrosterone; FAH: functional adrenal hyperandrogenism; FOH: functional ovarian hyperandrogenism; GnRHa: gonadotropin-releasing hormone agonist; 17-OHP: 17-hydroxyprogesterone; PCOS: polycystic ovary syndrome)

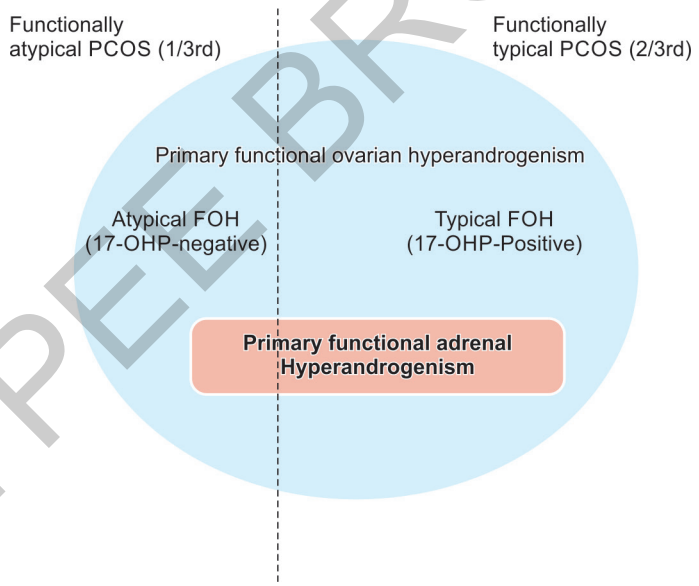

Fig. 2: Atypical PCOS of obesity.
(FOH: functional ovarian hyperandrogenism; 17-OHP: 17-hydroxyprogesterone; PCOS: polycystic ovary syndrome)

the other hand, disrupts the development of ovarian follicles. LH stimulates ovarian theca cells to form androgen and follicle-stimulating hormone (FSH) stimulates granulosa cells to form estrogen during the small antral follicle stage of development.

Intraovarian (paracrine/autocrine) mechanisms, rather than endocrine

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negative feedback loops, normally coordinate theca cell androgen production with granulosa cell estrogen production. The balance of downregulation and upregulation processes within the ovary modulates the response to LH.

Desensitization of LH receptor-binding sites in the presence of elevated LH levels ("homologous desensitization") and inhibition of P450c17 activities by local androgens and estrogens cause downregulation. Granulosa cell factors that upregulate P450c17 activities, particularly insulin-like growth factors (IGFs) and inhibin, balance out the downregulation.

Extraovarian factors such as insulin and proinflammatory cytokines [e.g., tumor necrosis factor α (TNF-α), transforming growth factor β (TGF-β), interleukin 1 (IL-1) and IL-6, and lipopolysaccharide] produced by specialized monocytic cells of adipose tissue and the gut microbiome can disrupt this synchronized intraovarian regulation. These also increase P450c17 activity, whereas other cytokines (e.g., IL-22) suppress androgenic enzymes.[4,5]

Downregulation of thecal androgen production is completely misguided in PCOS because PCOS ovaries are hyperresponsive to LH stimulation **(Figs. 1A and B)**.[1] Clinical evidence suggested that steroidogenesis dysregulation in PCOS is primarily of ovarian origin.[1]

- *Granulosa cell dysfunction:* Granulosa cells synthesize estrogens from androgens (via aromatase expression) and secrete peptides and growth factors that control follicle and oocyte development.[6] Androgens normally stimulate the transformation of dormant primordial follicles into primary follicles ("recruitment"), the first step in their growth and development into small antral follicles.[7] Androgens then normally synergize with FSH to induce LH receptor expression on granulosa cells, resulting in "luteinization," which allows granulosa cells to produce progesterone in response to LH and initiates the formation of the preovulatory follicle.[1]

Excess intraovarian androgen causes granulosa cell dysfunction in PCOS, which leads to anovulation and PCOM **(Figs. 1A and B)**.[1] High androgen levels promote the growth of an abnormally large number of small follicles which is primarily due to increased granulosa cell proliferation, and responsible for the increased anti-müllerian hormone (AMH) levels in women with PCOS (AMH is a product of the granulosa cells of small growing follicles that normally restrain the growth of primordial follicle). Androgens also contribute to follicular luteinization occurring in the mid- rather than a late follicular phase, which appears to be the basis for the follicular maturation arrest that prevents the emergence of a dominant follicle and prevents ovulation.[8]

Alternatively, granulosa cell dysfunction in PCOS could be the result of an intrinsic defect in the intraovarian (paracrine) regulation of follicle dynamics. Excessive granulosa cell secretion of factors that stimulate androgens, such as inhibin B, may reflect intrinsic granulosa cell dysfunction. Indeed, a subset of women with PCOS has deleterious variants in the genes encoding AMH or its receptor that impairs the restraint of follicular growth and granulosa cell aromatase activity.[8]

INSULIN-RESISTANT HYPERINSULINISM

Insulin resistance is a contributing factor in roughly half of PCOS cases: insulin resistance

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is disproportionately high for the severity of their obesity [body mass index (BMI)].[1,9] Insulin resistance is thus thought to be intrinsic in these women.

Compensatory hyperinsulinemia is a mechanism by which insulin resistance aggravates PCOS. Excess insulin action in some tissues, most notably the ovary, is paradoxically caused by hyperinsulinemia, which compensates for resistance to insulin's glucose-metabolic effect. This "insulin-resistant hyperinsulinism" is a major extra-ovarian factor in the pathophysiology of roughly half of all PCOS cases.

Polycystic ovary syndrome with insulin resistance is remarkable because resistance to insulin's metabolic effects is tissue-specific.[1] While skeletal muscle is resistant to insulin action on glucose metabolism due to mitochondrial gene dysfunction,[7] compensatory hyperinsulinemia causes excess insulin action in the ovary, liver, and adipocytes. As a result, signaling pathways that mediate insulin's mitogenic, growth factor-like, protein-anabolic, and lipogenic actions remain insulin sensitive. These insulin actions aggravate steroidogenic dysregulation and contribute to obesity and acanthosis nigricans, which are common PCOS comorbidities.

This insulin-resistant hyperinsulinism is an important aggravating factor in PCOS pathogenesis because it promotes FOH.

Hyperinsulinemia sensitizes the intrinsically dysregulated ovarian theca cells to secrete excess androgen in response to LH[1] (**Fig. 1B**, step 2). It does this by reversing the LH-induced homologous desensitization of LH-binding sites, which then upregulates cytochrome P450c17 activities. Insulin also upregulates testosterone formation by type 5 17-beta-hydroxysteroid dehydrogenase via a transcription factor (*KLF15*) that stimulates adipogenesis.

Insulin excess also synergizes with androgen excess and FSH to prematurely induce LH receptors on granulosa cells, leading to their premature luteinization and follicle maturation arrest.[1]

The severity of insulin resistance correlates with the severity of hyperandrogenism, the severity of anovulatory symptomatology, and the prevalence of PCOM. Any treatment that lowers insulin levels, therefore, improves hyperandrogenism (including in experimental models of PCOS[10]), though the hyperandrogenism of typical PCOS is seldom fully corrected by such treatments alone in most populations.

Associated Pathophysiologic Disturbances

Excess gonadotropin secretion, adiposity, and adrenal androgenic dysfunction are inconsistent features of PCOS that seem related to dysregulation of steroidogenesis and/or insulin-resistant hyperinsulinism.

Gonadotropin Abnormalities

Luteinizing hormone is necessary for the expression of steroidogenic enzymes. Thus, PCOS is gonadotropin-dependent, i.e., functional, a form of ovarian hyperandrogenism. Any treatment that suppresses LH levels (e.g., estrogenic–progestin oral contraceptives) suppresses ovarian hyperandrogenism.[1]

Increased LH, often accompanied by decreased FSH, was the first laboratory abnormality identified in classic PCOS and was historically thought to play a role in its pathogenesis by increasing ovarian androgen production. This discrepancy between adolescents and adults suggests that this resistance only becomes apparent when the high sensitivity to sex-steroid negative

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feedback of childhood fully wanes with maturity.

Such data suggest that LH excess in PCOS is the result, rather than the cause, of androgen excess. In more severe cases of PCOS, the moderate testosterone excess stimulates LH secretion (**Fig. 1B**, step 3). Additionally, granulosa cells that have been prematurely luteinized, under the influence of both increased testosterone and insulin levels, begin to secrete estrogenic in response to LH as well as to FSH. The negative feedback effect of the resultant estradiol excess can account for the significantly low FSH levels of PCOS (**Fig. 1B**, step 4).

Obesity

Approximately half of patients with PCOS are obese, and at least one-third of non-obese patients with PCOS have increased intraabdominal fat.[1]

The reason for the high prevalence of obesity in PCOS is not entirely clear. The hyperinsulinism of insulin resistance seems to be an important factor. Insulin signaling is of major importance to the size and function of the white adipose tissue depot. It stimulates adipogenesis and lipogenesis while inhibiting lipolysis.[11] Androgens oppose insulin effects on subcutaneous fat stores, instead favoring a myogenic differentiation. However, mild hyperandrogenemia also promotes visceral fat accumulation, which promotes insulin resistance. There also appear to be inherent differences in the subcutaneous abdominal fat cells of normal-weight and obese women with PCOS; normal-weight women can form small adipocytes in subcutaneous fat depots that retain insulin sensitivity.

Obesity aggravates the clinical severity of FOH by increasing insulin resistance **(Fig. 1B)**. In PCOS, visceral fat contributes more to insulin resistance than subcutaneous abdominal fat because of its enhanced lipolytic response to catecholamines.[1] Enhanced visceral fat lipolysis is unique to PCOS and not attributable to androgen excess; the free fatty acids and diacylglycerol released from visceral fat appear to promote insulin resistance in the liver and muscle, respectively.

The mechanisms by which obesity causes insulin resistance include a deficiency of insulin-sensitizing adipokines that are secreted by a unique population of adipose tissue–derived, monocytic, regulatory T cells[12] and by an altered intestinal microbiome.[4,5] Inflammatory cytokines not only cause insulin resistance but also aggravate ovarian hyperandrogenism. Hyperandrogenism, in turn, sensitizes circulating mononuclear cells to secrete inflammatory cytokines in response to glucose and saturated fat ingestion,[1] which, in a vicious cycle, aggravates hyperandrogenism and insulin resistance.

Obesity also causes low microbial diversity of the intestinal microbiome, which results in a "leaky gut" and resultant endotoxemia.[13] This "leaky gut" leads to increased serum lipopolysaccharide, IL-1β, and TNF-α levels, which directly stimulate thecal androgen production.[4,13] Dysbiosis is also found in nonobese PCOS, indicating that hyperandrogenism is a causative factor.

In contrast with energy-storing white adipose tissue, women with PCOS have been shown to have less energy-consuming brown adipose tissue. The study of the regulation of brown fat development is in its infancy.[14]

In addition to aggravating PCOS via insulin resistance, obesity seems to be the sole cause of most functionally atypical PCOS (sometimes termed "atypical PCOS of obesity") **(*see* Table 1 and Fig. 2)**.[1] Both androgen and estrogen are formed in excess by the adipose tissue of obese women. Obesity

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also suppresses gonadotropin levels by accelerating their metabolism. Thus, obesity should be suspected as the cause of menstrual irregularity when dehydroepiandrosterone sulfate (DHEAS) and LH are normal in obese PCOS women with marginally elevated testosterone levels.

FUNCTIONAL ADRENAL HYPERANDROGENISM

In 25–50% of cases, primary FOH is accompanied by primary FAH. In another 5% of cases of PCOS, FAH is the only detectable source of androgen excess **(Table 1 and Fig. 2)**.[1] Isolated primary FAH usually occurs in hirsute women without menstrual abnormalities, i.e., without PCOS.

Primary FAH is defined as 17-ketosteroid hyper-responsiveness to ACTH that is otherwise unexplained. This FAH has been postulated to result from a dysregulation of adrenal zona reticularis steroidogenesis that parallels the dysregulation of ovarian theca cell steroidogenesis.[1] This FAH has been associated not only with mild adrenal enlargement in some cases but also with slightly smaller adrenal volumes and a marginal degree of autonomous adrenocortical function in others. Hyperinsulinism seems to aggravate FAH as it does FOH.

External Factors

Genetics

Multiple population-wide genome-wide association studies (GWAS) have revealed numerous pathogenic variants of PCOS. Out of the several culprit genes, *LHCGR*, *THADA*, and *DENND1A* promoter genes are most important.[15] Polymorphism of LH/chorionic gonadotropic receptors (LHCGR) found in theca and mature granulosa cells of the adult ovary drives excess androgen production.[16] Overexpression of *DENND1A* which encodes for DENN proteins drives excess ovarian steroidogenesis.[17] Altered expression of thyroid adenoma-associated gene (*THADA*) modifies insulin secretion and subsequent insulin resistance by interfering with pancreatic beta-cell function.

Epigenetics

Epigenetics studies inheritable alterations in the gene expression and genomes that take place without any changes in DNA sequences. Due to lack of any single gene defect that could explain the various systemic manifestations of PCOS, scientists have been looking for factors that could change the characteristics of gene expression. Environmental factors, specifically increased exposure to in utero androgens, is one of the most important theories in fetal programming for development of PCOS in later life.[18]

Some genes which undergo reprogramming in PCOS are:

- *LHCGR* gene encoding for LH receptor, present on the theca cell surface
- *FST*—encodes for follistatin
- *LMNA*—encodes for Lamin A/C
- *PPARGC1A*—encodes for peroxisome proliferation
- *EPHX1*—encodes for epoxide hydrolase which degrades aromatic compounds.

Changes in the methylation status of these genes are the precursors which encode for the physiologic processes of steroidogenesis, follicular development, inflammatory mediation, insulin regulation, and glucose metabolism. Xu et al. found that serum global methylation was higher in obese PCOS patients than in nonobese PCOS patients. This indicates that obesity may play a role within the disease process itself, not

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only as a phenotypic expression but also as an epigenetic modifier itself.[19]

Histone epigenetic modifications, via methylation or acetylation, complements the direct methylation changes in DNA. Proper gene expression requires the presence of the correct pattern of both histone epigenetic modifiers and DNA. Hosseini et al. confirmed that increased serum levels of acetylation in histone H3 and methylation of H3K9 were found in PCOS patients, reducing the expression of *CYP19A1*, ultimately reducing cytochrome P450 aromatase activity, thus contributing to the hyperandrogenic phenotype.[20]

Another epigenetic modification influencing gene expression involves the presence of noncoding single-stranded RNA molecules called microRNA (miRNA). Several miRNAs such as mi222 linked with type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM) and mi93 linked with cellular glucose and lipid metabolism have been associated with disease pathogenesis.

Environmental Toxicants

The United States Environmental Protection Agency (USEPA) defines endocrine-disrupting chemical (EDC) as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behaviour."[21] EDCs bind to the cellular hormone receptor as hormones' agonists or antagonists. Studies have approved the higher serum concentration of EDCs in PCOS women with prolonged and continuous exposure from prenatal to adolescence. One such EDC is bisphenol A found in polycarbonate plastics, epoxy resins, baby bottles, dental fillings, etc. Its effects are as follows:

- Directly affects oogenesis by interacting with estrogen receptor (ER)
- Overproduction of androgens
- Potent ligand for sex hormone–binding globulin (SHBG) and replaces testosterone; thereby, free testosterone concentration increases.
- Acts as an obesogen
- Can also change glucose homeostasis by directly influencing the pancreatic cells.

Advanced chemical group is advanced glycation end products (AGEs), also called glycotoxins. AGEs are pro-inflammatory molecules[22] which interact with their receptor called RAGE (receptor for AGE) and stimulate pro-inflammatory pathways and oxidative stress. Increased serum concentration of AGEs has been found in patients with PCOS. AGEs interrupt growth of preovulatory follicles and damage follicles by oxidative stress caused by interaction with RAGEs.

Microbiome and Dysbiosis

Rapid human cultural changes and significant dietary modifications have resulted in development of a mismatch between human metabolic genes and bacteria that enhance fat storage. In PCOS women, harboring such microbes increase energy storage, thereby leading to insulin resistance and development of obesity and T2DM. Evidence suggests that microbiome of obese individuals is capable of extracting more energy from the host diet compared with the microbiome of lean individuals. This results from an increase in pro-inflammatory species of bacteria, such as *Escherichia coli*, and a decrease in anti-inflammatory bacteria such as *Faecalibacterium prausnitzii*.[23] Tremellen in 2012[24] proposed that a poor-quality diet and resulting imbalanced microbiome increase

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intestinal permeability and endotoxin production, with resultant hyperinsulinemia. This unleashes the cascade of increased androgen production and disrupted follicular development. The "first hit" inside the uterus combines with vertical transmission of a dysbiotic microbiome from a mother with PCOS, resulting in dysbiosis in the offspring.

Adult diet high in saturated fatty acids has also been linked to PCOS by producing an inflammatory reaction and reducing insulin sensitivity. Vitamin D deficiency exacerbates PCOS and its associated comorbidities by inducing an inflammatory response. Calcitriol upregulates insulin receptors and also increases insulin sensitivity directly and indirectly. It activates the PPAR delta receptor involved in fatty acid metabolism in adipose tissue and skeletal muscle, directly. Indirectly, it regulates intracellular calcium.

REFERENCES

1. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): The hypothesis of PCOS as Functional ovarian hyperandrogenism revisited. Endocr Rev. 2016;37:467-520.
2. Ehrmann DA, Barnes RB, Rosenfield RL. Polycystic ovary syndrome as a form of functional ovarian hyperandrogenism due to dysregulation of androgen secretion. Endocr Rev. 1995;16:322-53.
3. Sen A, Hammes SR. Granulosa cell-specific androgen receptors are critical regulators of ovarian development and function. Mol Endocrinol. 2010;24:1393-403.
4. Fox CW, Zhang L, Sohni A, Doblado M, Wilkinson MF, Chang RJ, et al. Inflammatory stimuli trigger increased androgen production and shifts in gene expression in theca-interstitial cells. Endocrinology. 2019;160: 2946-58.
5. Qi X, Yun C, Sun L, Xia J, Wu Q, Wang Y, et al. Gut microbiota-bile acid-interleukin-22 axis orchestrates polycystic ovary syndrome. Nat Med. 2019; 25:1225-33.
6. Hsueh AJ, Kawamura K, Cheng Y, Fauser BC. Intraovarian control of early folliculogenesis. Endocr Rev. 2015;36:1-24.
7. Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA, et al. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest. 1998;101:2622-9.
8. Willis DS, Watson H, Mason HD, Galea R, Brincat M, Franks S. Premature response to luteinizing hormone of granulosa cells from anovulatory women with polycystic ovary syndrome: relevance to mechanism of anovulation. J Clin Endocrinol Metab. 1998;83:3984-91.
9. Kim JY, Tfayli H, Michaliszyn SF, Arslanian S. Impaired lipolysis, diminished fat oxidation, and metabolic inflexibility in obese girls with polycystic ovary syndrome. J Clin Endocrinol Metab. 2018;103:546-54.
10. Yuan X, Hu T, Zhao H, Huang Y, Ye R, Lin J, et al. Brown adipose tissue transplantation ameliorates polycystic ovary syndrome. Proc Natl Acad Sci U S A 2016;113:2708-13.
11. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell. 2014; 156:20-44.
12. Semple RK. EJE PRIZE 2015: How does insulin resistance arise, and how does it cause disease? Human genetic lessons. Eur J Endocrinol. 2016;174:R209-23.
13. Banaszewska B, Siakowska M, Chudzicka-Strugala I, Chang RJ, Pawelczyk L, Zwozdziak B, et al. Elevation of markers of endotoxemia in women with polycystic ovary syndrome. Hum Reprod. 2020;35:2303-11.
14. Hussain MF, Roesler A, Kazak L. Regulation of adipocyte thermogenesis: mechanisms controlling obesity. FEBS J. 2020;287:3370-85.
15. Combs JC, Hill MJ, Decherney AH. Polycystic ovarian syndrome genetics and epigenetics. Clin Obstet Gynecol. 2021;64(1):20-5.
16. Narayan P. Genetic models for the study of luteinizing hormone receptor function. Front Endocrinol (Lausanne). 2015;6:152.
17. McAllister JM, Modi B, Miller BA, Biegler J, Bruggeman R, Legro RS, et al. Over-expression of a DENND1A isoform produces a polycystic ovary syndrome theca

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phenotype. Proc Natl Acad Sci USA. 2014; 111(15):E1519-27.
18. Dumesic DA, Hoyos LR, Chazenbalk GD, Naik R, Padmanabhan V, Abbott DH. Mechanisms of intergenerational transmission of polycystic ovary syndrome. Reproduction. 2020;159(1):R1-R13.
19. Xu J, Bao X, Peng Z, Wang L, Du L, Niu W, et al. Comprehensive analysis of genome-wide DNA methylation across human polycystic ovary syndrome ovary granulosa cell. Oncotarget. 2016;7(19):27899-909.
20. Hosseini E, Shahhoseini M, Afsharian P, Karimian L, Ashrafi M, Mehraein F. Role of epigenetic modifications in the aberrant *CYP19A1* gene expression in polycystic ovary syndrome. Arch Med Sci. 2019;15(4): 887-95.
21. Rocha AL, Oliveira FR, Azevedo RC, Silva VA, Peres TM, Candido AL, et al. Recent advances in the understanding and management of polycystic ovary syndrome. F1000Research. 2019;8:565.
22. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, et al. Polycystic ovary syndrome: A comprehensive review of pathogenesis, management, and drug repurposing. Int J Mol Sci. 2022;23:583.
23. Ridaura VK, Faith JJ, Rey FF, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013;341: 1241214
24. Tremellen K, Pearce K. Dysbiosis of gut microbiota (DOGMA)—a novel theory for the development of polycystic ovarian syndrome. Med Hypotheses. 2012;79:104-12.

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Sonia Malik

The book *"Clinical Focus on Polycystic Ovary Syndrome"* is a ready reckoner for undergraduates, postgraduates and practitioners for better understanding of the so-called modern Era endemic-PCOS. This book has a targeted approach towards every little detail of the syndrome, proper for rejuvenating our existing knowledge.

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