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Review Article

A review of hyperandrogenism state in polycystic ovarian syndrome

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ABSTRACT

Polycystic ovary syndrome is one of the most prevalent endocrinopathy in premenopausal women. The pathophysiology of PCOS is not clear, howeverdisturbance in the hypothalamic-pituitary-ovarian axis and abnormal steroidogenesis along with genetic and environmental factors act as main contributors to this disorder. The steroidogenic pathway is affected by the overexpression of the CYP11A, CYP17, and CYP19 genes in PCOS, which results in a hyperandrogenic condition. The initial effect of too much androgen in PCOS is impaired folliculogenesis. The most frequent clinical manifestations of hyperandrogenism in women with PCOS include hirsutism, acne, and androgenic alopecia. Women with PCOS may have an excess of androgen during foetal life due to the elevated expression of P450c17a during the whole pregnancy. PCOS is believed to be formed in utero by the influence of androgen excess on gene expression in adolescence and adulthood, which offers more solid evidence that real PCOS can be induced by prenatal androgenization. A prenatal androgen excess-induced epigenetic phenomena is suggested by the current theory of PCOS's developmental genesis. It is currently believed that the many tiny follicles seen in polycystic ovaries and the considerable irregularity in the very early stages of folliculogenesis are associated to the formation of anovulation in PCOS.

Keywords: PCOS, Androgen, Hyperandrogenic state, CYP11A, CYP17, CYP19

INTRODUCTION

In premenopausal women, polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies) affecting 4-20% of women globally who are of reproductive age. It is typically characterized by polycystic shape of the ovaries, ovulatory dysfunction, and clinical and biochemical hyperandrogenism. It is also frequently linked to insulin resistance and obesity. Androgens, generally known as "Male hormones," are also found in females, albeit in less amounts. Moreover, androgens serve as the building blocks for oestrogen in both men and women. Male testicles, adrenal glands, and female ovaries are where androgen hormones are largely made. Hyperandrogenism is the term used to describe the overproduction of androgens, the male sex hormones, in the ovaries and adrenals. There are two ways to determine whether there are excessive levels of androgens present. In clinical hyperandrogenism, the presence of high amounts of male sex hormones in the blood is manifested by observable symptoms or signs. Male pattern baldness,

acne, virilization, and excessive hair growth are a few of these. In biochemical hyperandrogenism, the blood test findings reveal elevated amounts of androgen hormones. Measuring free testosterone, total testosterone, or a free androgen index can be used to detect excessive amounts of androgen. A high level of free testosterone implies hyperandrogenism.[1]

Steroid metabolism in a normal state

Since PCOS is characterized by irregularities in steroid synthesis, resulting in a hyperandrogenic state, defining the steroid metabolism in the normal state (Figure 1). Steroids are low molecular weight, lipophilic compounds, and derivatives ofcholesterol that are known to control several cellular physiological processes including metabolism, development, and various signaling pathways. Numerous proteins and enzymes work together in the steroidogenic pathway in humans to convert cholesterol into biologically active steroid hormones. Steroidogenic acute regulatory protein (StAR) is responsible for moving cholesterol from the outer to inner mitochondrial membrane.[2]

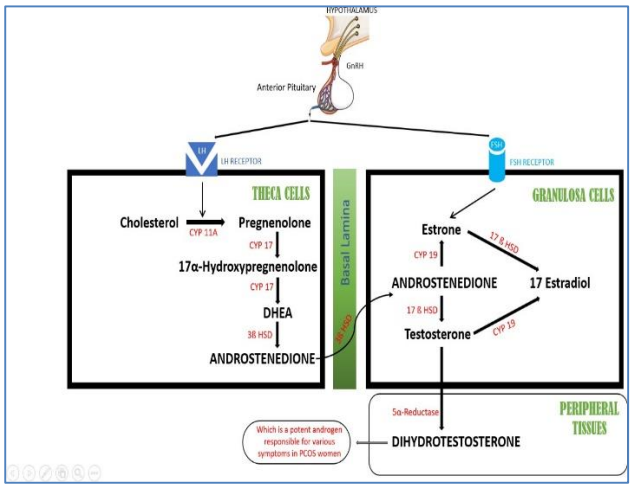

Figure 1: Pathway of hypothalamus pituitary ovarian axisinvolved in steroid metabolism.

A rate-limiting step in the conversion of cholesterol to pregnenolone is catalysed by cytochrome P450 side-chain cleavage, which is encoded by the CYP11A gene.[3] Pregnenolone can then be converted to 17-hydroxypregnenolone by the cytochrome P450 17-hydroxylase process. Together with hydroxylation activity, P450c17 also has lyase activity, which is used to change 17-hydroxypregnenolone into dehydro-epiandrosterone. Ovarian theca cells express P450c17, and this regulation functions as a branchpoint in the steroid production pathway that regulates whether androgens or progestins are generated.[4] Pregnenolone can also be converted into progesterone by type II 3-hydroxysteroid-5-steroid dehydrogenase. P450c17 has the ability to hydroxylate progesterone to create 17-hydroxyprogesterone, which is then converted to androstenedione by P450c17's 20-lyase activity. Instead, 3HSDII acts on DHEA to change it into androstenedione, which is then changed into testosterone by the action of 17-hydroxysteroid dehydrogenase. Granulosa cells absorb testosterone and androstenedione produced in theca cells of the ovaries, which are then converted into oestrogen by the P450arom enzyme under the supervision of FSH With the action of the enzyme 5-reductase in the peripheral tissue, testosterone is transformed into a more potent form known as 5'- dihydrotestosterone. Numerous signs and symptoms, including hirsutism, acne, and androgenic alopecia, are brought on by this powerful androgen. Increased androgen excess also demonstrates other symptoms like weight gain, irregular menstruation, acanthosis nigricans, and insulin resistance.[5]

CYP genes in PCOS

Heterogeneity in clinical features, as well as genetic variations observed in PCOS, is associated with hyperandrogenic conditions indicating the possible involvement of abnormalities associated with the steroidogenic pathway.[6] Genes that code for enzymes involved in the steroidogenic pathway are considered contenders for PCOS. Among those, the most broadly studied genes are theCYP11A gene (cytochrome P450 side-chain cleavage enzyme gene), the CYP17 gene (cytochrome P450 17 hydroxylase/17, 20-desmolase gene), and CYP19 gene (aromatase). Studies have revealed that ovarian theca cells of PCOS women overexpress enzymes involved in androgen biosynthesis[7] resulting in an increased production of 17-hydroxyprogesterone, testosterone, and androstenedione compared with theca cells from non-hyperandrogenic women.[8] Moreover, there is decreased activity of aromatase enzyme, further increasing the androgens. Therefore, abnormalities in androgen productionprime to hyperandrogenism in PCOS.

CYP11 gene

The cytochrome side-chain cleavage enzyme is responsible for catalysing the first step in the production of steroid hormones. The CYP11 gene, which is located at 15q24, codes for the enzyme. The rate-limiting step in the transformation of cholesterol into progesterone is catalysed by CYPscc.[9] According to research, steroid production is abolished in rabbits when the CYP11 gene is deleted, indicating that this enzyme is the first to operate throughout the process of steroidogenesis.[10] According to some theories, polymorphisms in the CYP11 gene either up- or downregulate CYP11 expression, which in turn affects how much androgen is produced. The CYP11 gene has been the subject of numerous polymorphism research in relation to PCOS.

CYP17 gene

This gene, found on chromosome 10q24-q25, produces the endoplasmic reticulum enzyme cytochrome P450 17-

hydroxylase-17, 20- lyase. Via its hydroxylase and lyase activity, this enzyme is crucial to the production of steroid hormones. Pregnenolone and progesterone are transformed into 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, by the action of the enzymes 7-hydroxylase and 17, 20-lyase.[11] These steroids are then transformed into dehydroepiandrosterone and 4-androstenedione. One of the causes of the ovarian hyperandrogenism associated with PCOS is thought to be dysregulated P450 CYP17 enzyme.[12] According to other research, higher expression of P450c17enzyme causes an increase in androgen production in PCOS.[13,14]

CYP19 gene

The CYP19 gene, found at 15p21, encodes the P450 aromatase enzyme. Nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome P450 reductase, and cytochrome P450 aromatase make up the enzyme complex. It facilitates the transformation of androgens into oestrogens. Many patients with hyperandrogenism have shown decreased aromatase activity. In granulosa cells taken from PCOS-afflicted women, Erickson et Al found decreased expression of the aromatase enzyme.[15] Similar findings were reached by Jakimiuk et al who found that aromatase mRNA expression was present in both PCOS and control women's follicles.[16] They came to the conclusion that PCOS follicles had decreased aromatase activity and contained low levels of P450arom mRNA, which led to low levels of estradiol. Because of the reduction in aromatase activity, androgen overproduction is likely to be a factor in aberrant follicular development. According to Ito et al, Zhang et al decreased aromatase activity in granulosa cells of the ovaries causes hyperandrogenemia in PCOS women.[17,18]

ORIGIN OF EXCESS ANDROGEN IN PCOS

One distinctive characteristic of PCOS-afflicted women is hyperandrogenism. It results from abnormal ovarian or adrenal function, which leads to the overproduction of androgens. In PCOS, poor folliculogenesis is the initial effect of excess androgen. At the early gonadotropin-independent stage, increased androgens encourage the development of primordial follicles and boost the quantity of tiny antral follicles.[19] The hypothalamus normally secretes the gonadotropin-releasing hormone in a pulsatile manner, which encourages the pituitary gland to release the gonadotropins LH and FSH. Luteinizing hormone promotes the generation of androgens by acting predominantly on ovarian theca cells that contain LH receptors. FSH also affects ovarian granulosa cells, converting androgens produced in theca cells into oestrogens, primarily estradiol, which is essential for follicle formation. However, it has been proposed that in PCOS patients, dysregulation of the neuroendocrine system results in an imbalance of the hypothalamic-pituitary-ovarian axis, which in turn causes an excess of gonadotrophins to be produced. The conventional hormonal signature of raised LH/FSH ratio in PCOS is caused by an increase in hypothalamic GnRH, which favours the production of the -subunit of LH over the -subunit of FSH, which in turn favours the production of LH over FSH.[20,21] Theca cells hyperplasia and the subsequent accumulation of follicular fluid, which form cyst-like structures along the periphery of the ovary and give it a string of pearls appearance, are caused by increased LH stimulation, which also causes numerous follicles in the ovaries to get arrested, mostly in the preantral and antral stages.[22] As seen in (Figure 2) an excessive amount of androgens are produced as a result of an increase in the number of follicles and the expression of key enzymes involved in androgen production. Moreover, it appears that insulin action is related to the hyperandrogenic condition in PCOS. According to Wu et al, the increased insulin secretion may imitate the luteinizing hormone's tropic effect on ovarian theca cells, which further raises androgen levels (Figure 2).[23] This is further supported by the finding that decreasing levels of hyperandrogenism are seen in PCOS women with improved insulin sensitivity. [24]

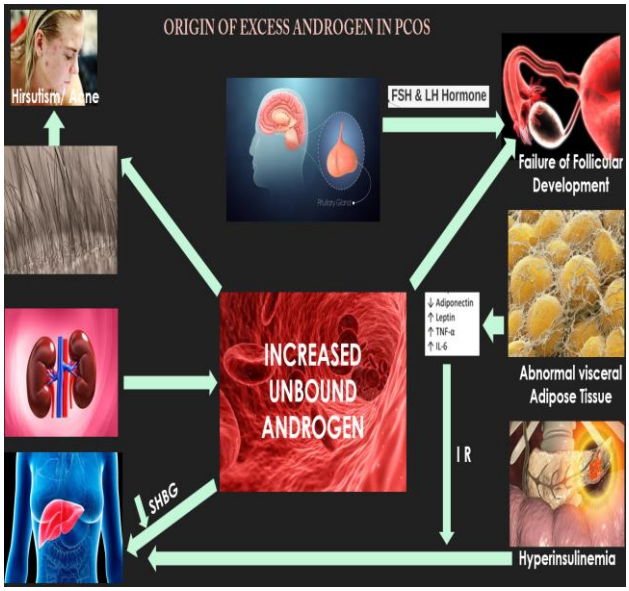

Figure 2: schematic representation of origin of excess androgen in PCOS.

CLINICAL FEATURES OF HYPERANDROGENISM

Clinical manifestations of hyperandrogenism in women with PCOS include hirsutism, acne, and androgenic alopecia. Increased androgen excess also demonstrates other symptoms like weight gain, irregular menstruation, acanthosis nigricans, and insulin resistance.

Hirsutism

Hirsutism is the presence of terminal hair on the face and/or body in a masculine pattern. It is one of the primary characteristics of PCOS hyperandrogenism. According to research studies, between 60 and 80% of PCOS women exhibit hirsutism.[25-28] The ethnic makeup of the population

has an impact on the degree of hirsutism as well. The formation of dihydrotestosterone, a more active form of testosterone, by the action of 5 reductase on testosterone in the pilosebaceous gland is thought to be the cause of hirsutism in PCOS women. When evaluating clinical hyperandrogenism, hirsutism is the most consistent and reliable symptom. A visual scoring system known as the Ferriman-Gallwey (FG) score was developed to evaluate the degree of hirsutism clinically.[29]

Acne vulgaris

The second most typical manifestation of hyper-androgenism is acne. Acne incidence varies by ethnicity; Pacific Islanders have the lowest reported incidence while Indo-Asian women have the highest. 48% of Kashmiri women with PCOS get acne.[28,29] According to Grover et al 17.7% of people in Allahabad have acne on a regular basis.[30] According to certain additional research, patients with PCOS experience acne 9.8-34% of the time on average.[31,32] Pilosebaceous gland irritation leads to acne. A higher concentration of dihydrotestosterone is produced when testosterone levels are higher, which leads to increased sebum production in the sebaceous glands and aberrant desquamation in the follicular epithelial cells. Acne is caused by the bacterium Propionibacterium acnes taking control of this buildup of sebum and epithelial cell debris. In the face, upper back, neck, and pectoral areas, acne is usually seen. The severity of acne varies from person to person.

Alopecia

Another sign of the hyperandrogenic disease affecting PCOS women is androgenic alopecia, or male pattern baldness. According to numerous studies, the incidence of alopecia in PCOS ranges considerably between 3.2 and 34.8%.[33-35] The adult terminal hair on the scalp region shortens the anagen (growth) phase and gradually transforms into less, finer vellus hair, which is one of its hallmarks.[36] The issue of thinning scalp hair affects women with PCOS in contrast to their difficulty managing excessive facial hair development. This is due to the fact that testosterone, which causes hair loss in both men and women with PCOS, is present in high quantities in PCOS women. Yet, the hair follicle is still alive in PCOS women with androgenic alopecia, increasing the likelihood that these women's hair will regrow after receiving hair therapy.

In PCOS women, the front hairline typically does not suffer damage, and hair loss is typically noticed in the front mid-vertex region with posterolateral extension to the crown as a "triangular" patch. For hyperandrogenic women, losing hair around the scalp has a substantial psychological effect. In conclusion, it is important to look for signs of hyperandrogenism in the endocrine system in premenopausal women who have alopecia.

HYPERANDROGENISM IN PCOS THROUGHOUT THE LIFE CYCLE

In long-term culture of PCOS theca cells, enhanced androgen biosynthesis is a stable phenotype, suggesting that higher androgen secretion is a key feature of these women.[37] Given that p450c17a, a crucial enzyme for the synthesis of dehydroepiandrosterone and androstenedione, is expressed in the primary and theca interstitial cells of the foetal primordial follicle at three months of foetal life in humans and increases throughout pregnancy, androgen excess may be present in the foetus of affected women.[38] Patients with PCOS frequently experience adrenal hyperandrogenism as well. The causes of increased androgen release by the adrenals, however, are still unknown. This is perhaps because it would be unethical to take adrenal samples from PCOS patients because the adrenals are vital to life. Studies on the molecular genetics of adrenal steroidogenesis failed to find mutations and polymorphisms in the genes encoding for the enzymes responsible for androgen synthesis.[39-43] However, irregularities in peripheral cortisol metabolism may stimulate adrenal androgen secretion secondarily to a slight reduction in cortisol levels. Increased cortisol clearance, compensatory activation of the hypothalamic-pituitary-adrenal axis, and adrenocorticotropin-mediated adrenal hyperandrogenism can all occur in cortisone-reductase deficiency due to impaired regeneration of active cortisol from inactive cortisone by 11b-hydroxysteroid dehydrogenase (11b-HSD1; HSD11B1 gene). Hexose-6-phosphate dehydrogenase (H6PDH; H6PD gene) is necessary for the endoplasmic reticulum to have a high NADPH/NADP+ ratio, which is needed by 11b-HSD1 to function as an oxoreductase catalysing the activation of glucocorticoids.[44] Mutations in either HSD11B1 or H6PD (Lavery et al., 2008) result in cortisone reductase insufficiency.[45] According to preliminary research, PCOS patients' metabolic function and adrenal hyperandrogenism may be affected by polymorphisms in the genes HSD11B1 and H6PD, respectively.[46,47]

Hypothetical consequences of exposure to excess androgens in utero resultingin excess androgen production in later life

Nowadays, there is little doubt that the intrauterine environment can affect how genes behave when they are programmed to in adults.[48] There is growing evidence that links prenatal maternal testosterone concentrations to gender role behaviour in preschool girls and that this relationship is dose-related, specifically in relation to the effects of testosterone (T) on the female foetus.[49] In addition, girls with CAH, a congenital adrenal hyperplasia, who were exposed to high amounts of T during pregnancy, displayed some behaviours that are more typical of men.[50] There is additional evidence that the developmental effects of T on the brain and behaviour are correlated with the levels of T in amniotic fluid. [51] The defeminization of sexual function would then seem to be proof of the impact

of androgen levels on brain function, whereas prenatal androgen levels may, in the extreme, result in the virilization of the female foetus. The increased prevalence of PCOS in women with foetal androgen excess illnesses such classical CAH (21-hydroxylase deficiency) and congenital adrenal virilizing tumours provides clinical evidence of the ability of foetal androgen excess to re-program numerous organ systems. The story of a female foetus who had an androgen-secreting tumour removed shortly after birth and later developed PCOS in adulthood is particularly instructive.[52-55]. Abbott and colleagues have performed a spectacular set of tests utilizing female rhesus monkeys who have been prenatally androgenized to simulate the signs and symptoms of PCOS.[56-59] Beginning at different gestational ages, mothers were given T injections, bringing circulation levels of T in the female foetus to levels comparable to those reported in foetal males.[60] It's crucial to consider when androgenization begins because an early prenatal injection could disrupt the development of reproductive and metabolic organ systems, whereas a late treatment that causes an excess of androgen could affect functional maturation. Female children of both early and late androgenized moms exhibited significant PCOS symptoms. According to the date of the beginning of androgenization, the PCOS phenotype changed. In both phenotypes, oligo-amenorrhea, a sign of ovulatory failure, was prevalent. In comparison to controls, female kids from androgenized moms had larger ovaries and ovarian morphology that was notably similar to PCOS. Furthermore, leuteinizing hormone (LH) hypersecretion was only observed in early treated monkeys, indicating that the programming of hypothalamic activity is amplified at this point in the pregnancy. This LH hypersecretion is believed to be the result of enhanced pituitary reactivity to GnRH, greater pituitary priming, and maybe related to lessened ovarian hormone negative feedback control.[22,61] Surprisingly, prenatally treated females who were treated early had impaired insulin secretion, whereas those who were treated late had impaired insulin sensitivity and increased adiposity.[62] This is more convincing proof that "true" PCOS can result from prenatal androgenization and offers a very solid foundation for the idea that PCOS is "born" in the womb due to the effects of excess androgen on gene expression in adolescence and adulthood. In prenatal, testosterone-treated sheep, very identical outcomes were obtained, simulating the reproductive phenotype of women with PCOS.[63]

The current theory of PCOS's developmental origin proposes an epigenetic phenomenon brought on by an excess of foetal androgen. A route that could disrupt ovarian differentiation and result in a polycystic phenotype is the amplification of transforming growth factor (TGF)-b-regulated extracellular matrix protein synthesis.[3] This idea is particularly appealing because CYP17, the main androgen-producing enzyme, is controlled by other members of the TGF-b family, including anti-Mullerian hormone (AMH), and androgen exposure promotes the expression of these proteins.[64,65] Regarding the hypothesised developmental aetiology of PCOS, there are still many unanswered concerns. Although it would not ordinarily be expected for maternal testosterone to reach the placenta, experimentally produced maternal hyperandrogenism results in an excess of foetal androgen. Total and free testosterone levels are greater in the serum of expecting PCOS women.[66] Additionally, foetal testosterone levels positively link with maternal T levels.[67,68] Therefore, it's possible that PCOS-positive pregnant women pass on their excess androgen to the foetus's gender. This is connected to the well-known familial PCOS characteristics. [68] Increased foetal adrenal androgen output is the result of experimentally produced foetal hyperandrogenism, which may be caused by an increase in 17, 20 lyase activity.[69] Additionally, foetal plasma testosterone and foetal cortisol concentrations have a positive correlation.[70] The foetal ovaries were previously believed to be virtually completely inert in terms of hormone synthesis, therefore these discoveries connecting the involvement of the foetal adrenals in excess androgen production may be significant. However, temporary expression of the androgen biosynthetic enzyme CYP17 has been found in human foetal ovaries during mid-gestation, suggesting that the foetal ovaries may not be as dormant as originally believed.[38]

Recent research in a sheep model has revealed that aberrant folliculogenesis in polycystic ovary may result from testosterone's conversion to estradiol rather than being a direct result of excess testosterone.[71] In contrast, foetal androgen excess could only come from foetal tissue. The mother's genes that cause hyperandrogenism may have been passed on to the foetus. Whatever the cause of the excess foetal androgen in females, it is currently a very tenable theory that PCOS is preprogrammed during pregnancy. If this programming is carried over into adolescence and adulthood, it may have one or many effects that all serve to promote the overproduction of androgens. First, there would be an improvement in the transition from primordial to primary and small antral follicles, and a decrease in the rate of atresia of these follicles.[72-74] Second, the activity of the enzymes (P450-17a, lyase 17, 20, 17-hydroxylase) in theca cells that make androgen would be increased. Primary cultures of polycystic ovary theca cells establish significantly enhanced androgen production.[13] Thirdly, the physiological trigger for androgen production, LH secretion, will be impaired by higher levels. Fourthly, increasing insulin secretion will promote the creation of too much androgen. An increase in the utilisation of the intracellular signalling route involving serine phosphorylation, which would improve the androgen-producing capacity of the enzyme lyase 17, 20, is one potential outcome of higher insulin output. By directly lowering the formation of sex hormone-binding globulin (SHBG) in the liver, hyperinsulinemia, whether brought on by insulin resistance or pancreatic B cell failure, will also raise the concentrations of free (unbound, physiologically active) testosterone.

CONCLUSION

According to research, PCOS is characterized by a hyper androgenic state caused by irregularities in steroid synthesis and the conversion of testosterone into more potent androgen in peripheral tissue. This condition is also linked to the overexpression of enzymes involved in androgen biosynthesis as well as the decreased activity of the aromatase enzyme, which are primarily seen in the ovarian tissue. The production of LH over FSH is thought to result from a malfunction in the neuroendocrine system, which in turn causes an imbalance in the hypothalamic-pituitary-ovarian axis. A hyper androgenic state is brought on by the elevated LH stimulation in PCOS. But an excess of androgen inside the ovaries causes polycystic ovarian morphology and ovulatory failure.

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