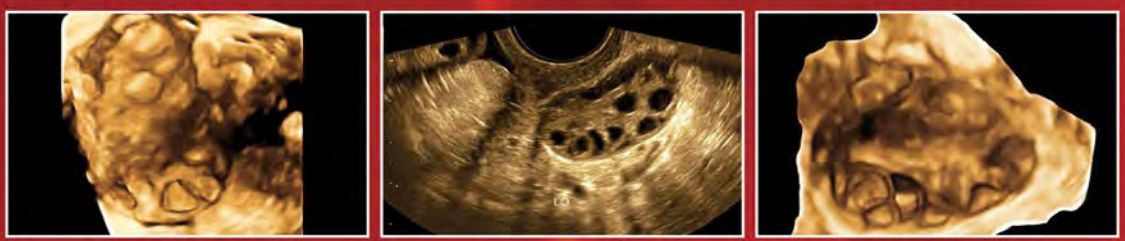
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Polycystic Ovary Syndrome



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Pathophysiology

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ABSTRACT

The etiology is unknown though many speculations have been made. Basic dysfunction lies within the ovary, and the clinical expression and severity of symptoms is dependent on extra ovarian factors. Evidence supports that decreased peripheral insulin sensitivity and consequent hyperinsulinemia are pivotal in pathogenesis of polycystic ovary syndrome. Possibly there could also be a hypothalamic defect. Granulosa cell dysfunction results in Hyper-responsive to FSH in terms of E2 production and impaired maturation of antral follicles due to suppressed activity of enzyme cytochrome P450. Hyperandrogenism, which reflects an intrinsic abnormality of theca cell function. Androgens and intermediate steroids in the androgen biosynthetic pathway are increased, suggesting upregulation of steroidogenic enzymes. Evidence of autosomal transmission related to strong familial clustering-involving a few or many genes is also suggested. Altered expression of genes related to obesity, insulin resistance, inflammation, and steroidogenesis are also seen. It has also been observed that epigenetic modification is linked to metabolic disease.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous and complex disorder with varied collection of signs and symptoms so as no single test is diagnostic. It is a genetically determined, primary ovarian disorder resulting in excess androgen production.

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It has both adverse reproductive and metabolic implications for affected women. It is a complex genetic disorder and may be familial. Polycystic ovary syndrome is seen to cluster in families, and both female and male relatives can show stigmata of the syndrome, including metabolic abnormalities. It is a multigene environmental interaction resulting in the signs and symptoms, most of them related to abnormal gonadotropin secretion, hyperandrogenemia, and insulin resistance (IR) with hyperinsulinism.

Polycystic ovary syndrome is characterized by anovulation with clinical (hirsutism/acne) and/or biochemical evidence of androgen excess. It typically presents during adolescence and affects more than 5% women of reproductive age. It is the commonest cause of menstrual dysfunction (>80% cases of anovulatory infertility) and hirsutism. Typical endocrine features are raised testosterone and luteinizing hormone (LH) and is also associated with metabolic abnormalities and increased risk of type 2 diabetes mellitus (T2DM).

Consequences of PCOS spectrum is seen across the lifespan of a woman and thus requires a multidisciplinary approach involving a pediatrician, dermatologist, gynecologist, endocrinologist, dialectologist, cardiologist, and geriatrics physician.

It is known that diagnosing a woman with PCOS implies an increased risk for infertility, dysfunctional bleeding, endometrial carcinoma, obesity, T2DM, hypertension, dyslipidemia, and cardiovascular disease.

Several authors have shown ethnic variations in presentation of PCOS, though the prevalence is similar in populations worldwide. There are differences in the clinical presentation (degree of hirsutism, ovarian dysfunction), endocrine features, and metabolic abnormalities (body fat distribution, lipid profile, degree of glucose intolerance, and incidence of metabolic syndrome).[1-4]

PREVALENCE

The overall incidence of PCOS varies from 8 to 10%.[4-11] The incidence is higher in South Asian population and is about 50% PCOS as against the Caucasian population, where the incidence is 5–25% PCOS.

PATHOPHYSIOLOGY

Exact pathophysiology and its initiating event have yet to be elucidated. However, various biochemical abnormalities are described, and associations and linkages of one to another have been established. Many abnormalities reinforce each other in vicious circles. However, there is generally poor understanding of its etiology. It is a multifactorial disease with full clinical expression being the result of synergistic pathological interaction of genetic, epigenetic, and environmental factors. The capacity to hypersecrete androgens begins in fetal life and the typical clinical and

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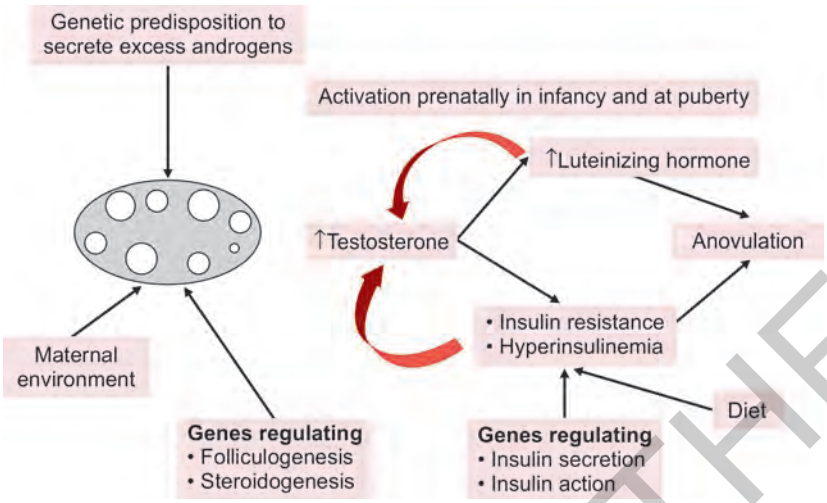


Figure 1: Developmental origin of polycystic ovary syndrome.

biochemical features of PCOS are "downstream" effects of exposure to androgen excess at or before puberty. Phenotype may be influenced by other genes and by nutrients, physical activity, pollutants, psychological stress, and androgen excess that can program and modify epigenome and lead to PCOS (Figure 1).

PATHOGENESIS

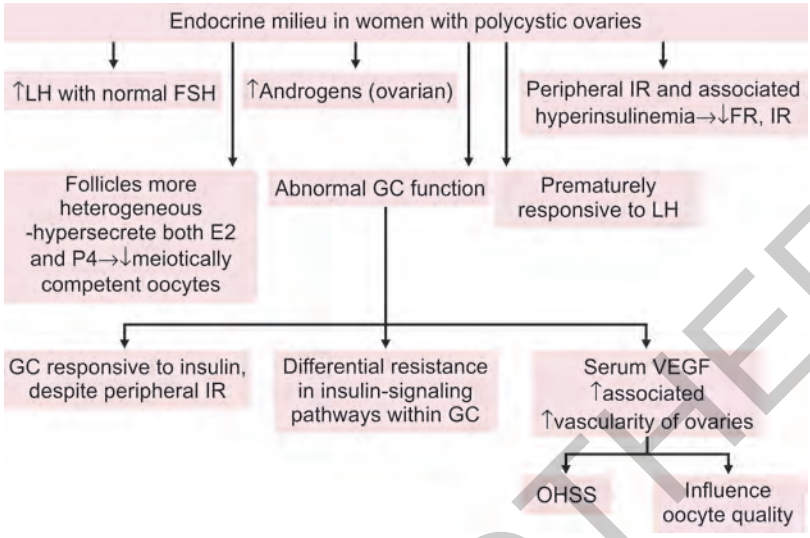
Hyperandrogenism, abnormal feedback of gonadotropins [higher mean concentration of LH, low or low-normal follicle stimulating hormone (FSH), increased circulating estrone levels], IR, and dysregulation of genes encoding enzymes in androgen biosynthesis pathway, and insulin secretion and action (INS VNTR, CYP11a, CYP17-P450c17alpha) are responsible for this metabolic disorder (Figure 2).

Hypothalamic-pituitary Abnormalities

Elevated Luteinizing Hormone and Low-normal Follicle Stimulating Hormone

Hypersecretion of LH is a result of increased gonadotropin releasing hormone (GnRH) pulse frequency that affects ovarian androgen synthesis, folliculogenesis, and oocyte development. There is increase in both the pulse frequency and amplitude of LH secretion. The production of FSH is usually unchanged with decreased production of estradiol and excessive production of testosterone and estrone. Excessive production of LH and unchanged

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OHSS, ovarian hyperstimulation syndrome; IR, insulin resistance; VEGF, vascular endothelial growth factor; FSH, follicle stimulating hormone; LH, luteinizing hormone; GC, granulosa cells; FR, Fertilization rate.

Figure 2: Endocrine milieu in polycystic ovary syndrome.

production of FSH can result in increased LH-FSH ratio of more than 2.5 both in ovulatory and anovulatory cycles. Normal values are seen in about 10–20% of women with PCOS.[12]

Elevated Gonadotropin Releasing Hormone

Metabolic genotype that slows apoptosis and aging, thereby promoting mitosis, is seen in PCOS. This results in more GnRH neurons and/or greater GnRH neuronal connectivity leading to increased GnRH drive that manifests as increased LH pulse frequency and amplitude as well as decreased FSH with resultant anovulation. It is a matter of debate whether the hypothalamic defect is primary or secondary.

Luteinizing hormone pulsatility in young girls at puberty is seen in the late afternoon instead of night, which indicates disruption of GnRH pulse generator providing evidence that this could be a primary defect in pubertal girls with family history of PCOS. [13,14]

Adrenally derived androgens may also contribute to the pathogenesis of PCOS, but their role is less defined. Exposure to anabolic steroids, or androgen producing tumors, which increase the androgens, can also give rise to PCOS like symptoms. Treatment of these conditions usually reduce the symptoms, thus providing very less evidence that abnormality of GnRH pulse generation is secondary defect in women with PCOS.

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Moreover, it has also been observed that disturbed ovarian-pituitary and hypothalamic feedback accentuates the gonadotropin abnormalities via the dysfunction of the Kiss 1 system. Kiss 1 neurons located in the brain are supposed to play an important and indispensable role in the control of gonadotropin secretion and ovulation. The exact role is still to be determined.

Elevated Prolactin

Women with PCOS could have an associated elevated prolactin level in 25% of cases. This elevated prolactin level in turn then can increase the adrenal androgen level, especially dehydroepiandrosterone sulfate (DHEA-S).

Role of Melatonin in Polycystic Ovary Syndrome

Even if there are high concentrations of melatonin in serum, women with PCOS have a deficiency of this indoleamine in their ovarian follicles resulting in low intrafollicular melatonin concentrations as compared to non-PCOS women. These low levels can affect the follicle growth, ovulation, and oocyte quality.[15]

Melatonin can also affect the occurrence of PCOS by its ability to alter the leptin levels. Melatonin acts directly on adipocytes through specific G protein-coupled receptors, MT1 and MT2[16] and the activation of these receptors might exert a modulatory effect on leptin production by lowering cyclic adenosine monophosphate (cAMP) levels.

Ovarian Abnormalities

As mentioned earlier, metabolic genotype that slows apoptosis and aging, thereby promoting mitosis, can also affect the anatomy in the ovaries with increased oocyte endowment and/or slowed atresia that manifests as polycystic ovarian morphology. Within the follicle subunit itself, there are intraovarian paracrine modulators, cytokines, and growth factors, which appear to play a role.

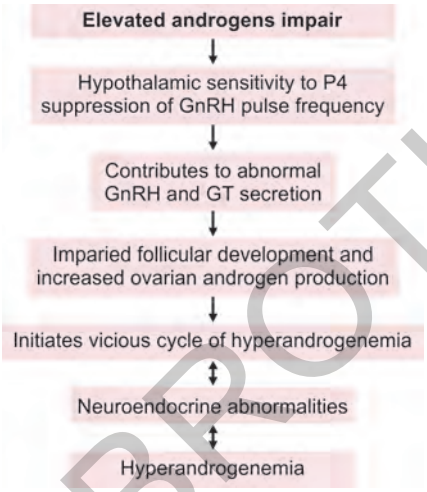
Hyperandrogenism

Elevated androgen levels are a common feature in women with PCOS and seen in about 70% of cases. The remaining 30% though have normal levels, it is on the higher side of normal. In women with PCOS, all the three main androgens—androstenedione (of which >90% is produced in the ovaries), DHEA-S (mainly produced in the adrenal glands), and testosterone (produced from the ovaries and adrenal glands in equal amounts) could be elevated. High androstenedione levels in the ovary are as a result of elevated LH levels. The elevated androgen levels contribute to abnormal GnRH and gonadotropin secretion resulting in impaired

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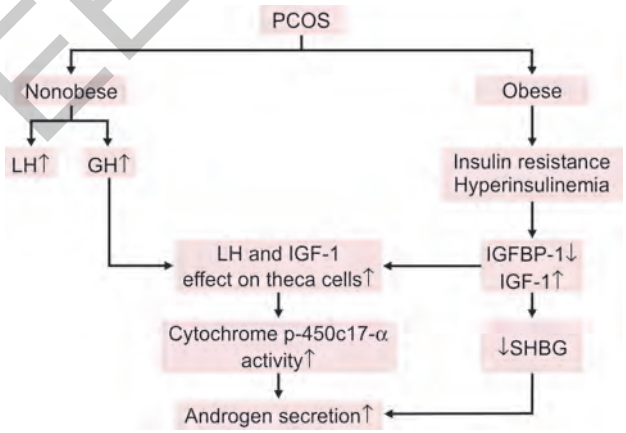
follicular development with resultant increased androgen production perpetuating a vicious cycle of abnormal gonadotropin secretion (Figure 3). The conversion of androstenedione to testosterone in PCOS ovaries is amplified.

Androgen levels are elevated in both the obese as well as nonobese PCOS, but the pathogenesis is different in both the groups. This is clearly explained in figure 4. Amplification of signs and symptoms of PCOS is seen with increasing obesity and IR.



GnRH, gonadotropin releasing hormone; GT, gonadotropins.

Figure 3: Vicious cycle of hyperandrogenemia.



IGFBP-1, insulin-like growth factor-binding protein 1; SHBG, sex hormone-binding globulin; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; GH, growth hormone.

Figure 4: Mechanism of androgen excess in obese and nonobese polycystic ovary syndrome.

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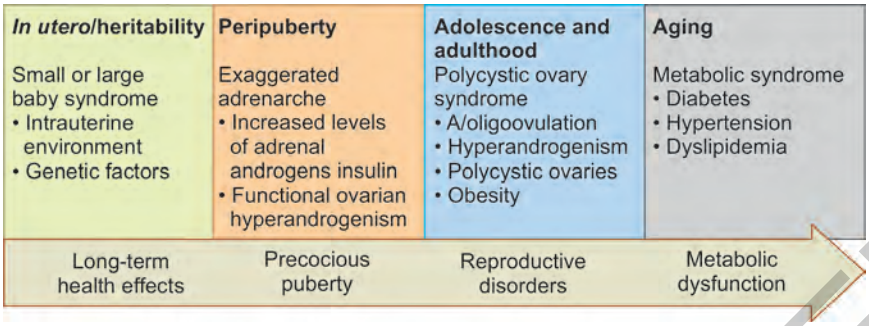


Figure 5: Exposure to androgens. What happens at different stages of life?

Figure 5 is self-explanatory and shows that PCOS can start even *in utero* where intrauterine environment together with genetic predisposition can affect the offspring resulting in large and small baby syndrome. At puberty, there could be exaggerated adrenarche due to prepuberty exposure to androgens. During adolescence and adulthood, reproductive dysfunction is seen in the form of oligo-ovulation, and with aging, these women usually develop metabolic syndrome.[17]

Abnormalities of Estrogen Secretion

Estrogen secretion, especially production of estradiol, is usually abnormal in women with PCOS. Due to arrested folliculogenesis a common feature of PCOS, estradiol levels may be low to normal without midcyclic increase in levels as seen in normal women before ovulation.[18,19]

As mentioned earlier, there is high production of testosterone that results in high estrone levels further increasing abnormal secretion of pituitary gonadotropins with increased levels of LH and low levels of FSH due to inhibition of its secretion. These increased levels of LH in turn result in hyperplasia of the ovarian stroma and theca cells, leading to increased androgens, thus perpetuating the vicious cycle of excessive androgen and LH production.

Moreover, increased theca cell endowment as a result of decreased apoptosis seen in women with PCOS manifests as stromal echogenicity on ultrasound imaging.

Adrenal Abnormalities

Pituitary gonadotropin does not directly stimulate adrenal androgens, but prolactin (elevated prolactin, seen in 25% of patients with PCOS), can stimulate DHEA-S production.

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Peripheral Abnormalities

Decreased Sex Hormone-binding Globulin

Insulin resistance and hyperinsulinemia results in hyperandrogenemia and increased production of insulin-like growth factor 1 (5α-reductase activity is stimulated). All these together inhibit production of hepatic sex hormone-binding globulin (SHBG) in the liver. Decreased levels of SHBG in circulation result in high levels of free or unbound androgens resulting in hyperandrogenemia. Increased free androgen index produces greater clinical symptoms with more hirsutism, acne, and other manifestations of androgen excess. Thus, hyperandrogenism results in more hyperandrogenism and its action on tissues gets more amplified.

Insulin Resistance and Compensatory Hyperinsulinemia

Evidence supports that decreased peripheral insulin sensitivity and consequent hyperinsulinemia are pivotal in pathogenesis of PCOS.[20] Insulin resistance is intrinsic to PCOS and is independent of obesity (30% of PCOS women are not obese). It plays a central role in the pathogenesis of PCOS as insulin-induced hyperandrogenemia is the underlying biochemical abnormality seen. Obesity when present (*de novo* or as a result of intrinsic insulin resistance) is an extrinsic cause of insulin resistance in PCOS. Thus, insulin resistance in PCOS is both intrinsic and extrinsic.

Insulin resistance and hyperinsulinemia are the major causes of metabolic syndrome, which compromises cardiometabolic risk factors that include obesity, insulin resistance, hypertension, and dyslipidemia.

Insulin resistance results in impaired glucose metabolism and high androgen levels which contribute to increased visceral adiposity. This then contributes to hypertension, T2DM, and atherosclerosis resulting in higher incidence of cardiovascular disease. Hyperinsulinemia results in increased lipid storage and altered lipoprotein and cholesterol metabolism resulting in dyslipidemia.

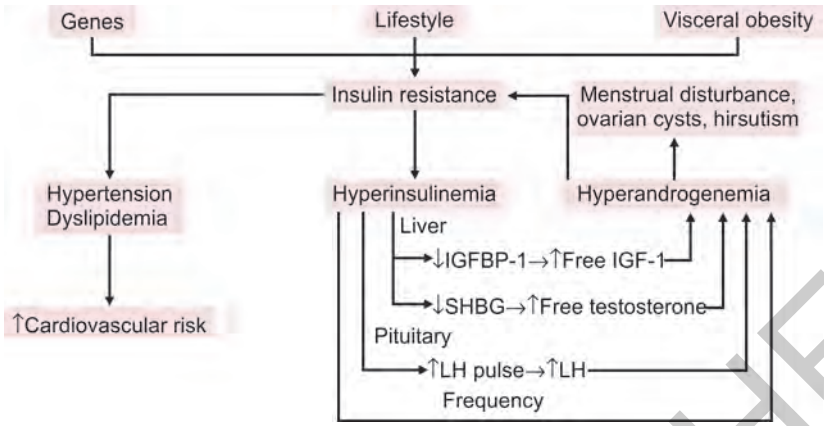
Increased number of adipocytes can amplify IR and hyperandrogenism, thus making adipose tissue dysfunction a major contributing factor to IR.

Hyperinsulinemia and Hyperandrogenemia Link (Figure 6)

Because hyperandrogenism and hyperinsulinemia coexist in PCOS, the important question is whether one causes the other.

Though several studies have shown that exogenous androgens and androgen producing tumors resulting in hyperandrogenism, can result in glucose intolerance and elevated insulin levels, and lowering androgen levels in these cases can improve IR and symptoms related to it.[20-24]

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IGFBP-1, insulin-like growth factor-binding protein 1; SHBG, sex hormone-binding globulin; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; CV, cardiovascular.

Figure 6: Hyperinsulinemia and hyperandrogenemia link.

Evidence which shows that hyperinsulinemia is primary contributing factor to ovarian hyperandrogenemia are as follows:

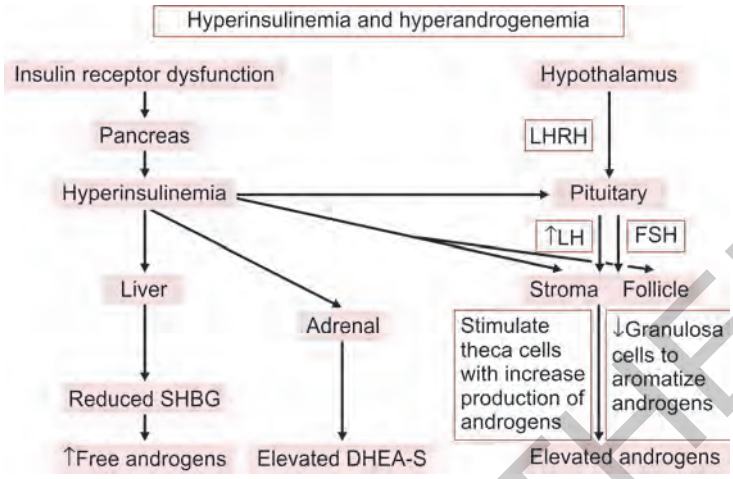
- Pharmacologic reduction of insulin levels in PCOS women improves hyperandrogenemia
- Reduction of androgen levels by bilateral oophorectomy or administration of GnRH agonist or antiandrogenic compounds in PCOS women has no effect on IR or hyperinsulinemia.

Insulin is known to amplify the LH response of granulosa cells, thereby causing an abnormal differentiation of these cells. This is because the ovaries are more insulin resistant as opposed to muscle and liver, and therefore, respond excessively to high insulin levels seen in women with PCOS. There is marked heterogeneity of granulosa cells from antral follicles in anovulatory PCOS with hyper-responsive to FSH in terms of E2 production and impaired maturation of antral follicles due to suppressed activity of enzyme cytochrome P450 (aromatase). This leads to premature follicular growth arrest resulting in anovulation. Upregulation of steroidogenic enzymes in the ovarian theca results in excessive androgen production. This in turn results in uncoupling of hypothalamic estradiol inhibition and estrogen related sensitization of pituitary LH release which further causes increase in LH secretion.

Insulin alters normal folliculogenesis by increasing intraovarian androgens, altering gonadotropin release, or by direct effects on the ovary (Figure 7).

Insulin sensitizers such as metformin[25] and thiazolidinediones[26] have been shown to reduce androgen levels and facilitate follicular maturation, normal menstrual cycle, and pregnancy.

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SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle stimulating hormone; DHEA-S, dehydroepiandrosterone sulfate; LHRH, luteinizing hormone-releasing hormone.

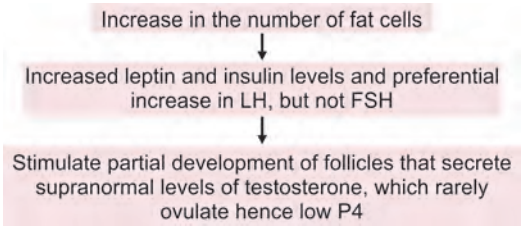
Figure 7: Alteration of normal folliculogenesis.

Adipose Tissue Dysfunction and Polycystic Ovary Syndrome

Adipose tissue dysfunction may be a central factor in the pathogenesis of PCOS contributing to IR and its consequences. There exists a complex interaction between the pituitary gland, pancreas, and ovary that result in a changed hormonal secretion pattern. Women with PCOS have increased abdominal or visceral fat with larger adipocyte volume and lower serum adiponectin values than weight-matched controls. Polycystic ovary syndrome is thought to be mediated by ghrelin (gastric peptide) which is orexigenic and adipogenic. Obesity is known to increase IR with consequent increase in androgen, insulin, and leptin levels. Obesity also decreases SHBG, growth hormone, insulin-like growth factor-binding protein 1, response to controlled ovarian hyperstimulation, thus requiring higher doses of gonadotropin therapy with more duration of stimulation and cycle cancellation rate. It also increases the peak E2 concentrations, number of oocytes retrieved, and can affect the endometrial receptivity and corpus luteum function along with early embryo development. This can further result in higher risk of early pregnancy loss. There is data suggesting the role of degree of abdominal obesity resulting in adipose dysfunction.[27] It was also observed that ovulatory women as compared to anovulatory women with PCOS have lesser visceral obesity and exhibit lesser adipocyte dysfunction.[28]

It is known that adiponectin is protective against IR, diabetes, and cardiovascular disease, and also inhibits androgen production by theca cells. It has

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LH, luteinizing hormone; FSH, follicle stimulating hormone.

Figure 8: Anovulation due to obesity.

been observed that adiponectin circulating concentrations are lower in women with PCOS in body mass index (BMI)-matched controls.[29,30] These reduced circulating adiponectin levels have an effect on ovarian stroma, and thus, the theca cells resulting in increased androgen secretion in obese women with PCOS. This provides an additional and direct link between obesity and increased androgen production in women with PCOS in addition to IR.

How Obesity in Polycystic Ovary Syndrome Results in Anovulation (Figure 8)?

Figure 8 clearly shows the mechanism of anovulation in obese women with PCOS. It has also been observed that abnormalities of leptin secretion predispose to weight gain in women with PCOS. Leptin resistance was seen more commonly in insulin resistant and overweight PCOS women as compared to thin PCOS women. Intake of leptin is associated with decrease in hypothalamic neuropeptide Y and increase in GnRH and sympathetic nervous system activity, which in turn reduces food intake, increases thermogenesis improving the hormonal imbalance, thus also improving the reproductive potential.

Role of Anti-Mullerian Hormone in the Pathogenesis of Polycystic Ovary Syndrome

Women with PCOS have overproduction of anti-Mullerian hormone (AMH), which may be related to abnormally elevated LH, androgens, insulin, advanced glycation end products (AGE), or decreased soluble receptor for AGE (sRAGE).[31-33] Apart from this, genetic factors such as variants of *ACVR1* gene also contribute to AMH overexpression.[34]

Moreover, there is also greater production of AMH by individual granulosa cells. With increased number of follicles, there is increased granulosa cell mass, which may be responsible for high levels of AMH in PCOS. It has been shown by Pellatt et al., that there is a 75-fold increase in AMH production per granulosa cell in women with anovulatory PCOS as compared to those with normal ovaries.[35]

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It is known that AMH plays an important inhibitory role in follicular recruitment and development and high level of AMH contributes to follicular arrest. Anti-Mullerian hormone also has an inhibitory action on FSH-induced aromatase production, which is likely to contribute to hyperandrogenism in these women, which further enhances IR.[36] Anti-Mullerian hormone may also have a paracrine effect on theca interna cells, leading to theca cell dysregulation in PCOS resulting in the excessive production of androgens.[37]

Elevated serum AMH concentrations are predictive of poor response to various treatments of PCOS including weight loss, ovulation induction, and laparoscopic ovarian drilling, while clinical improvement in various parameters following treatment is associated with serum AMH decline, further supporting an important role for AMH in the pathophysiology of this syndrome.[38]

Genetic

Although PCOS can be familial, genetic studies have failed to reveal any specific gene markers or chromosomal abnormalities associated with the disorder. Familial clustering of cases,[39-44] concordance greater incidence in identical than in nonidentical twin pairs,[45] and heritability of endocrine and metabolic features[46-48] provide evidence for genetic basis of PCOS. The mode of inheritance is likely to be oligogenic or polygenic.[49,50] The candidate genes in PCOS have been mentioned in table 1.

Polycystic ovary syndrome is determined in part by inherited factors as a complex trait; however, the genetic basis of this complex disorder remains largely unknown. Gene expression studies from PCOS tissues have identified novel pathways and genes important in PCOS pathophysiology, which may be different in lean and obese women with PCOS.[51-54] Alterations are also seen in expression of genes involved in insulin signaling including cAMP-guanine nucleotide exchange factor II and tribble which regulate the activity of Akt/protein kinase B, a key enzyme in one of the arms of insulin signaling pathway.

Table 1: Candidate Genes in Polycystic Ovary Syndrome

Steroid hormone production and metabolism	• *CYP11a (P450scc)* • *CYP17 (P450c17)* • *CYP19 (P450arom)*
Metabolic: insulin secretion and action; obesity	• β-cell function: *TCF7L2, KCNJ11* • Insulin resistance: *IR, PPARγ* • Obesity: *Fat mass and obesity associated*
Androgen action	• *Androgen receptor*
Ovarian follicle development	• *Follistatin* • *FBN3*

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