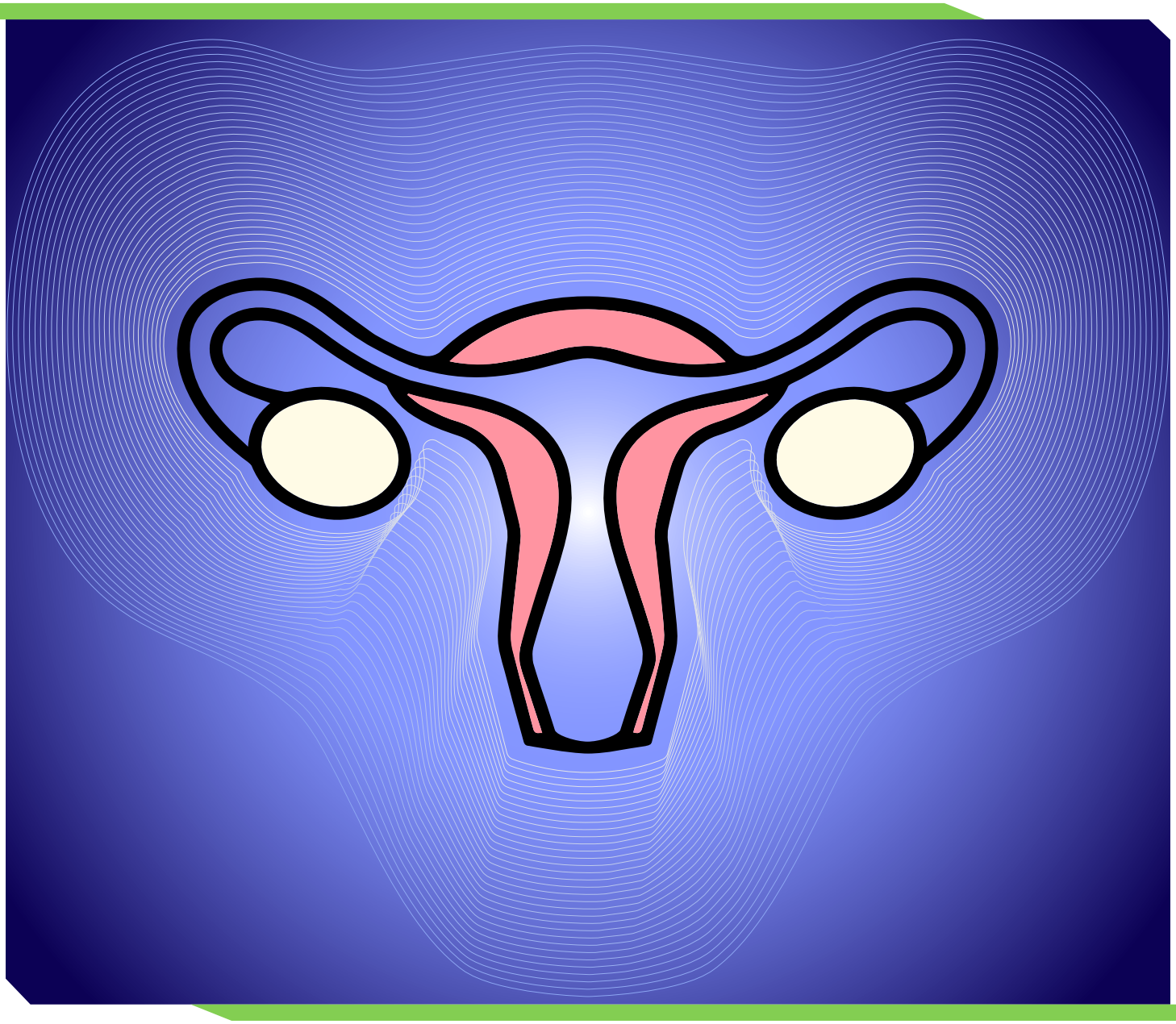
POLYCYSTIC OVARIAN SYNDROME:

Identifying the treatment targets of a disrupting ovarian physiology



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Polycystic Ovarian Syndrome

Identifying the treatment targets of a disrupting ovarian physiology

ANCC Accredited NCPD Hours: 2.3hrs

Target Audience: RN/APRN

Need Assessment

This article is relevant at present times because it addresses the current knowledge of the genetic and developmental contributions to the etiology of PCOS. It also address the ovarian and extra-ovarian mediators of PCOS and the gaps and key challenges in the diagnosis, treatment and prevention of PCOS. ***Innovation in lifestyle modification, including diet, exercise, with and without dedicated stress reduction techniques is the future in treatment of metabolic syndrome associated with PCOS.*** Application of novel interventions, such as group medical care may improve future adherence to lifestyle modification in combination with pharmaceutical therapeutics.

Objectives

- Discuss the origin of Poly Cystic Ovarian Syndrome (PCOS)
- Describe the pathophysiologic concept of PCOS
- Identify the mediators of PCOS
- Discuss the classic therapeutic options for PCOS
- Describe the metabolic abnormalities in PCOS

Goal

The goal of this article is to discuss the importance of developing strategic interventions to increase the compliance to lifestyle and dietary modification, in addition to appreciation of the emerging pharmaceutical therapeutics available for the management of Polycystic Ovarian Syndrome

Introduction

The female hypothalamic–pituitary–ovarian (HPO) axis is a meticulously synchronized and tightly regulated network ultimately responsible for reproductive competence and survival of the species. The HPO axis responds to internal signals (i.e., hormonal and neuronal) and external factors (i.e., environment influences). During gestation, these factors impact future generations through epigenetic factors affecting the brain and the developing germ cells.

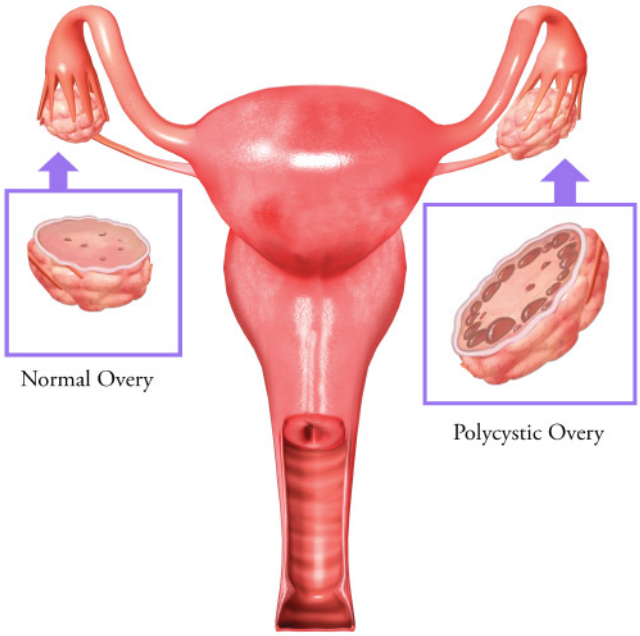

Figure 1 : Anatomical view of Poly Cystic Ovary Syndrome

Polycystic ovary syndrome (PCOS), a disorder primarily characterized by signs and symptoms of androgen excess and ovulatory dysfunction, that disrupts HPO axis function. Depending on the diagnostic criteria, this disorder affects ~6% to 20% of reproductive aged women. Typical clinical features (as shown in fig: 2) include hirsutism, irregular menses, chronic anovulation, and infertility.

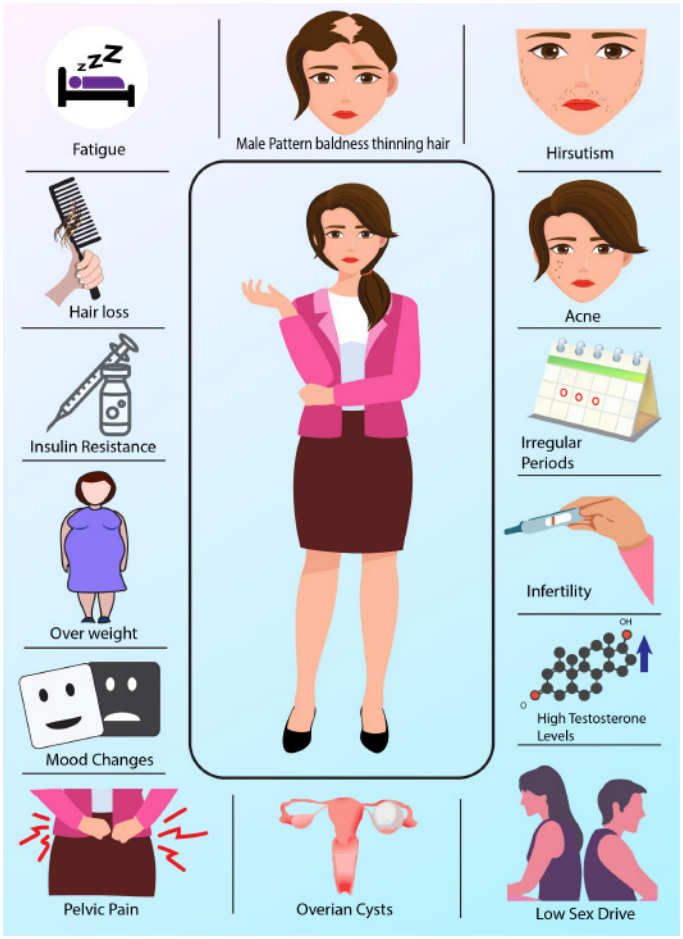

Figure 2: Clinical features of Poly Cystic Ovary Syndrome

The persistent hyperandrogenism is associated with impaired hypothalamic–pituitary feedback, LH hypersecretion, premature granulosa cell luteinization, aberrant oocyte maturation, and premature arrest of activated primary follicles. [1, Rank 5]

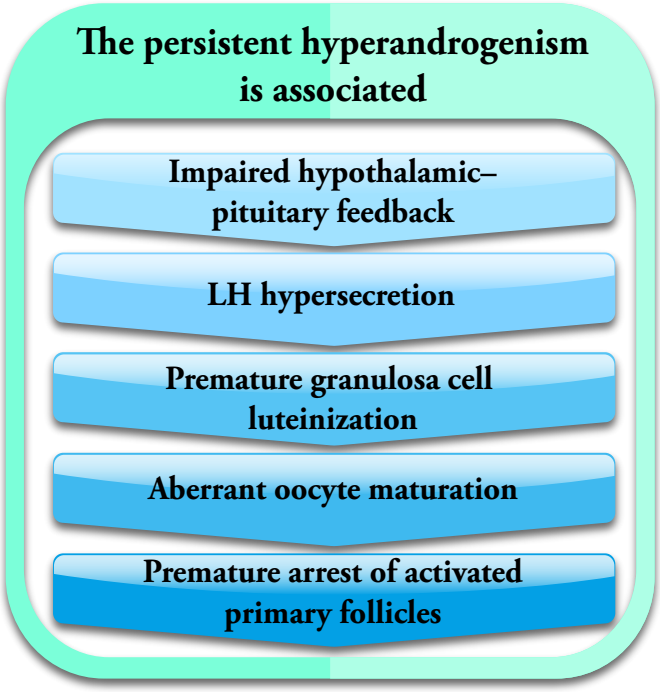

Figure 3: Persistent hyperandrogenism and Poly Cystic Ovary Syndrome

Origin of Poly Cystic Ovarian Syndrome (PCOS)

Because of the heterogeneous nature of this condition, the etiopathology of PCOS is still not clearly identified. Factors ranging from genetic to environmental and/ or the interaction between them have been proposed to have a role in the origin of PCOS.

Genetic basis in the origin of PCOS

The observations of a high amount of familial aggregation among first degree female relatives of women with PCOS coupled with heritability score of 0.79 for PCOS phenotype in a study provide support for the notion that PCOS is heritable.

Among the diagnostic characteristics of PCOS, evidence for heritability is strongest for hyperandrogenism. Considering the heterogeneity in PCOS and the varying attributes it is now not believed to be a monogenic disease. In support of this, mutations or polymorphism in several genes have been identified.

Both individual gene analysis and genome-wide association studies have identified mutations or polymorphisms in follicle stimulating hormone receptor, luteinizing hormone receptor, domain containing 1A, member RAS oncogene family, and thyroid adenoma associated gene loci in individuals with PCOS. While mutations, polymorphisms and splice variants in genes such as follistatin, fibrilin 3, cytochrome p450 side-chain cleavage, insulin receptor (INSR), hydroxysteroid dehydrogenase and androgen receptor have also been linked to PCOS, such observations have not been confirmed in large populations or in multi-

" Offspring exposed to excess androgen in utero, which occur in conditions such as congenital adrenal hyperplasia, congenital virilizing tumors and loss of function mutations in aromatase or sex hormone-binding globulin gene (SHBG) "

ple ethnicities. The degree to which each of these genes contributes to the final reproductive and metabolic phenotype of PCOS women remains unclear. [2, Rank 2]

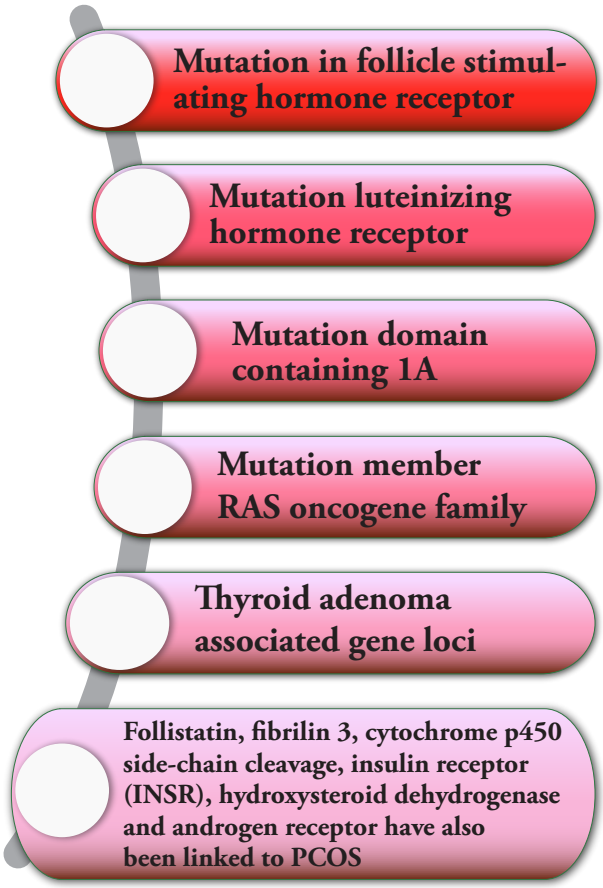

Figure 4: Genetic basis and Poly Cystic Ovary Syndrome

Genetic models involving many of the gene variants linked to PCOS are limited. A transgenic overexpressing the variant identified in PCOS patients resulted in a hyperandrogenic state with no impact on fertility. Detailed phenotypic assessment of PCOS characteristics is not available for this model. Transgenic models overexpressing LH beta subunit produced a cystic, tumorogenic ovarian phenotype.

While FSH deficiency and polymorphism in FSHR has been linked to PCOS, models of FSH deficiency although infertile fail to manifest a hyperandrogenic or multifollicular ovarian phenotype. These findings from transgenic models combined with the <10% heritability estimate of PCOS-linked loci identified suggest involvement of additional loci and factors. Several transgenic models are available that link other loci (nerve growth factor, plasminogen activator inhibitor 1, estrogen receptor alpha) to PCOS characteristics. However these loci have not been substantiated in large PCOS cohort studies. [3, Rank 4]

Developmental basis in the origin of PCOS

The observation that individuals born with low birth weight are at high risk for manifestation of cardiometabolic disorders during adulthood led to the developmental origin of health and disease hypothesis. According to this hypothesis, early fetal exposure to stressors can induce physiological adaptations and manifest as disease during adulthood. The findings that girls born either small or large for their gestational age are at increased risk for developing PCOS during reproductive life, suggests PCOS could also have developmental basis. Additional support for this premise comes

from reports of PCOS in offspring exposed to excess androgen in utero, which occur in conditions such as congenital adrenal hyperplasia, congenital virilizing tumors and loss of function mutations in aromatase or sex hormone-binding globulin gene (SHBG). PCOS characteristics are also seen in individuals exposed to elevated second trimester amniotic fluid testosterone levels and prenatal androgen exposure.

The developmental origins of PCOS theory are also supported by several studies, which show that ***administration of steroids such as testosterone, dihydrotestosterone or estradiol valerate or steroid synthesis inhibitors during the perinatal period induce the development of PCOS. For instance, the prenatal testosterone-treated female, manifests fetal growth restriction and those children are born with low birth weight.*** As these individuals progress in age, they manifest disruptions in physiologic functions like neuroendocrine steroid feedback, increased pituitary sensitivity to gonadotropin-releasing hormone, LH hyper-secretion, functional hyperandrogenism, multifollicular ovarian morphology, oligo- / an-ovulation and insulin resistance. [5, Rank 1]

In addition to meeting the diagnostic criteria proposed for PCOS by all agencies, these patients manifest cardiometabolic

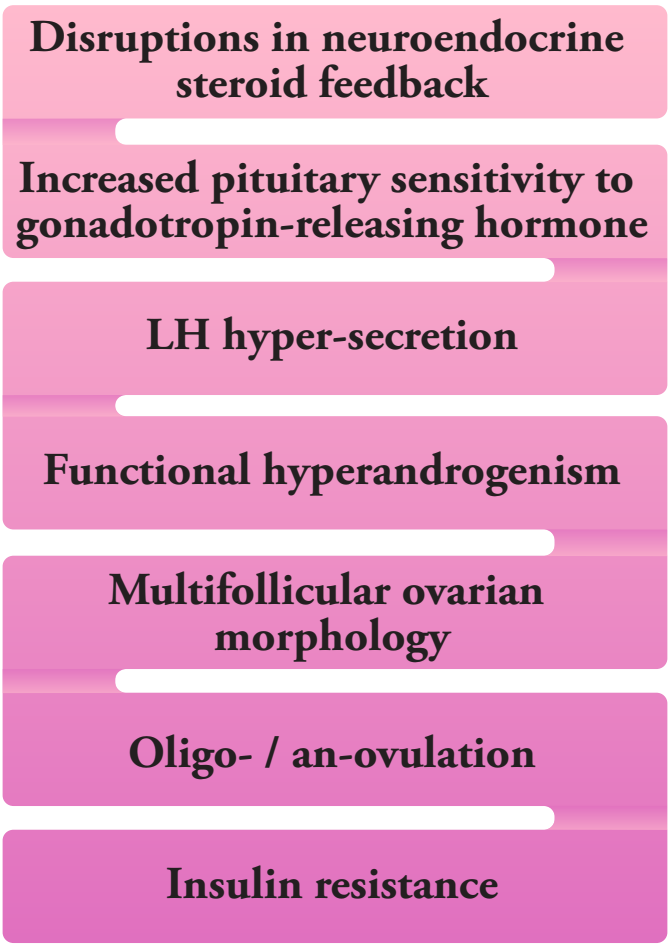

Figure 5: Disruptions in physiologic functions in Poly Cystic Ovary Syndrome

disruptions. Similarly, in animal study subjects, ***developmental exposure of sheep to bisphenol A (BPA), an environmental endocrine disrupting compound (EDC), results in low birth weight offspring. During adulthood, these lab experiment animals manifest hypothalamic, pituitary and ovarian changes that mimic the PCOS phenotype.*** Human studies also point to an association between BPA and hyperandrogenism. [4, Rank 3]

Gene-environment interaction

The evidence accumulated so far suggests that the pathogenesis of PCOS is likely complex and quite possibly involve gene x environment interaction. Such an interaction explain the prevalence estimate of PCOS and its differing phenotypic manifestation. Phenotypic differences in neuroendocrine, ovarian, and metabolic defects can be influenced by differences in the timing, duration, and degree of androgen exposure. Individual genetic susceptibility also influence the effect of androgen exposure. Such gene x environment interactions is likely mediated by epigenetic mechanisms, involving changes in DNA methylation, histone acetylation, and non-coding RNA expression. The epigenome provides a means to translate the information captured from the environment by turning on or off gene expression patterns.

Epigenetic changes in the androgen receptor gene and subsequent modifications in the whole blood, ovarian and adipose tissues have been reported in PCOS. Epigenetic modifications have also been observed in prenatal androgenized models of PCOS. In this context it is important to recognize that sex hormones (estrogens and androgens) are known activators of epigenetic mechanisms. [7, Rank 4]

Mediators of PCOS

PCOS patients manifest disruptions at both ovarian and extra-ovarian levels. Ovarian changes that contribute to the diagnostic criteria of PCOS include multifollicular appearance, hyperandrogenism, oligo/an-ovulation and luteal defects. The extra-ovarian changes, although not part of diagnostic criteria, include LH hypersecretion with increased LH/FSH ratio at the neuroendocrine level and hyperinsulinemia, hyperglycemia, dyslipidemia and altered adipokine secretion at the metabolic level.

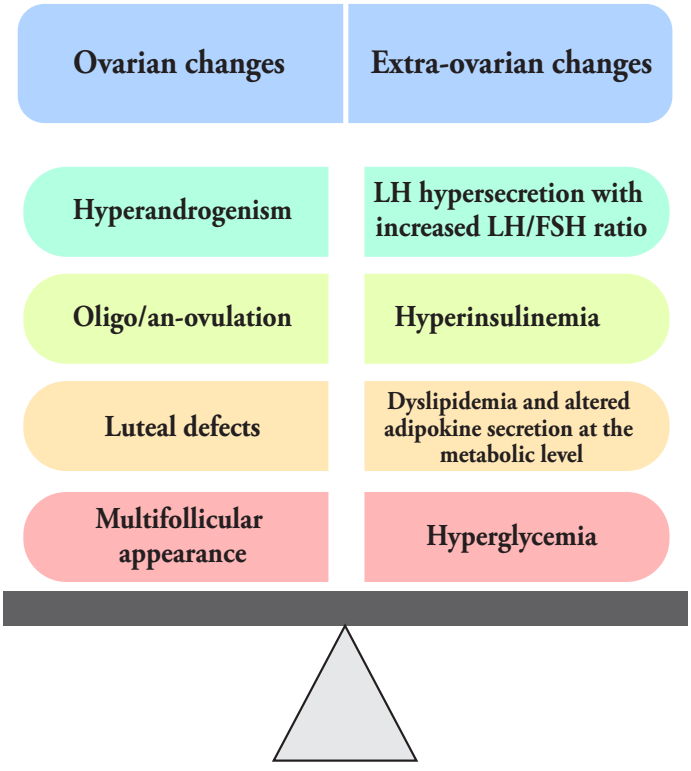

Figure 6: Ovarian and extra ovarian changes in Poly Cystic Ovary Syndrome

Ovarian mediators of PCOS

Women with PCOS are characterized by multifollicular ovarian morphology and ovarian enlargement (an increase in ovarian area and volume). Polycystic (multifollicular) ovarian morphology (PCOM) is a diagnostic criterion for the diagnosis of PCOS as defined by the Rotterdam consensus and the Androgen Excess & PCOS Society criteria and recent NIH consensus meeting. Earlier ovarian studies in humans were confined to wedge resection or post-mortem tissues. These studies have shown that the polycystic ovary appearance results from presence of 10–12 growing follicles that measure < 10mm in size along with increase in stromal hypertrophy. ***With advance in non-invasive imaging tools such as transvaginal ultrasound, follicle count thresholds for distinguishing PCOM ovaries from normal ovaries have changed over time. The most recent recommendation by the task force of the Androgen Excess and the Polycystic Ovary Syndrome Society (AE-PCOS) is a threshold setting of >25 follicles, when scanned with transducer frequency ≥8 MHz.*** [6, Rank 3]

> **" Ovaries of PCOS women are characterized by increased number of follicles , reduction in number of primordial follicles and follicular arrest "**

Most studies addressing follicular number and distribution involved single time point scanning or histological observations with post-mortem ovaries. These studies have concluded that ovaries of PCOS women are characterized by increased number of follicles , reduction in number of primordial follicles and follicular arrest. The PCOM charecteristics in PCOS women can therefore arise from arrest in follicular development, premature luteinization, and reduced state of atresia. Additionally, women with PCOS undergoing in vitro fertilization have been found to produce more number of oocytes, which are often of poor quality, leading to reduced fertilization, cleavage and implantation rates.

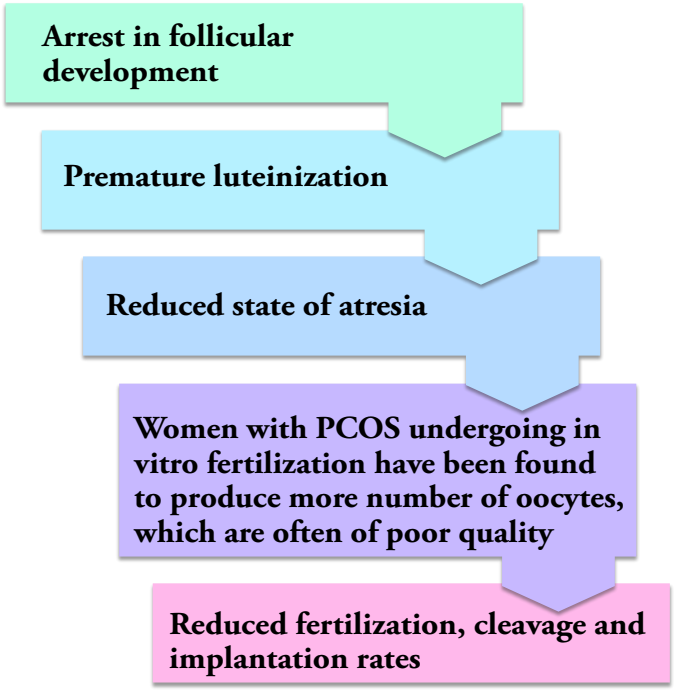

Figure 7: The PCOM charecteristics in Poly Cystic Ovary Syndrome

Follicular activation/recruitment

Ovaries have finite number of primordial follicles at birth that form the ovarian follicular pool or reserve where they remain in a quiescent state. The transition of quiescent primordial follicles in the ovary to primary follicles that initiates the growing phase is referred to as follicular activation or recruitment. [8, Rank 3]

During each reproductive cycle, a few follicles from the primordial pool undergo either activation / recruitment. Out of these, only a few undergo further follicular development into preantral follicles, with others undergoing atresia through programmed cell death. The follicular activation process is tightly controlled by paracrine and autocrine factors such as transforming growth factor (TGF) family members TGFα, TGFβ, bone morphogenetic protein 4 (BMP4), and anti-Mullerian hormone (ANTI-MULLERIAN HORMONE (AMH)), growth factors or cytokines such as kit ligand (KITL), fibroblast growth factor (FGF), and leukemia inhibitory factor (LIF) and steroid hormones.

These growth factors either activate (KITL, FGF, TGFα, LIF, and BMP4) or inhibit (ANTI-MULLERIAN HORMONE (AMH) and TGFβ) the activation process. The balance between these accelerating and inhibitory factors determine the direction of the activation process. Additionally, presence of factors that regulate the bioavailability of these growth factors, for example fibrillins that sequester TGF family members, can also govern the follicular activation process. Androgens can also induce follicular activation via stimulation of AKT signaling and inhibition of FOXO3A protein. [10, Rank 3]

Pathophysiologic concept of polycystic ovary syndrome and metabolic syndrome

Though the exact etiology of PCOS syndrome is unknown, it has a complex evolving pathophysiology with genetic, environmental, hormonal and metabolic components. Hypothalamic function is altered, with notable increased pulse frequency of luteinizing hormone (LH) secretion, and a diminished sensitivity to estrogen feedback inhibition. At the level of the ovary, dysregulated folliculogenesis arrests follicular growth. Additionally, there is granulosa cell dysfunction. There is hypertrophy of the theca cells, which are stimulated by LH. These cells are responsible for production of ovarian androgens.

Both of these findings predispose to polycystic ovarian morphology with multiple peripheral follicles in a string of pearls appearance. ***Granulosa cell function under***

> **"Hypothalamic function is altered, with notable increased pulse frequency of luteinizing hormone (LH) secretion, and a diminished sensitivity to estrogen feedback inhibition."**

the stimulation of follicle stimulating hormone (FSH) is altered due to relatively lower FSH concentrations in women with PCOS. This in combination with increased theca cell function, stimulated by increased LH, promotes increased production of the ovarian androgens, testosterone and androstenedione. Adrenal androgen production is also increased in PCOS with elevated dehydroepiandrosterone and adrenal hyper-responsiveness to corticotropin (ACTH). Aspects of metabolic syndrome like obesity and hyperinsulinemia may increase the severity of biochemical or clinical androgen excess. Hyperinsulinemia also directly stimulates ovarian androgen production. [9, Rank 4]

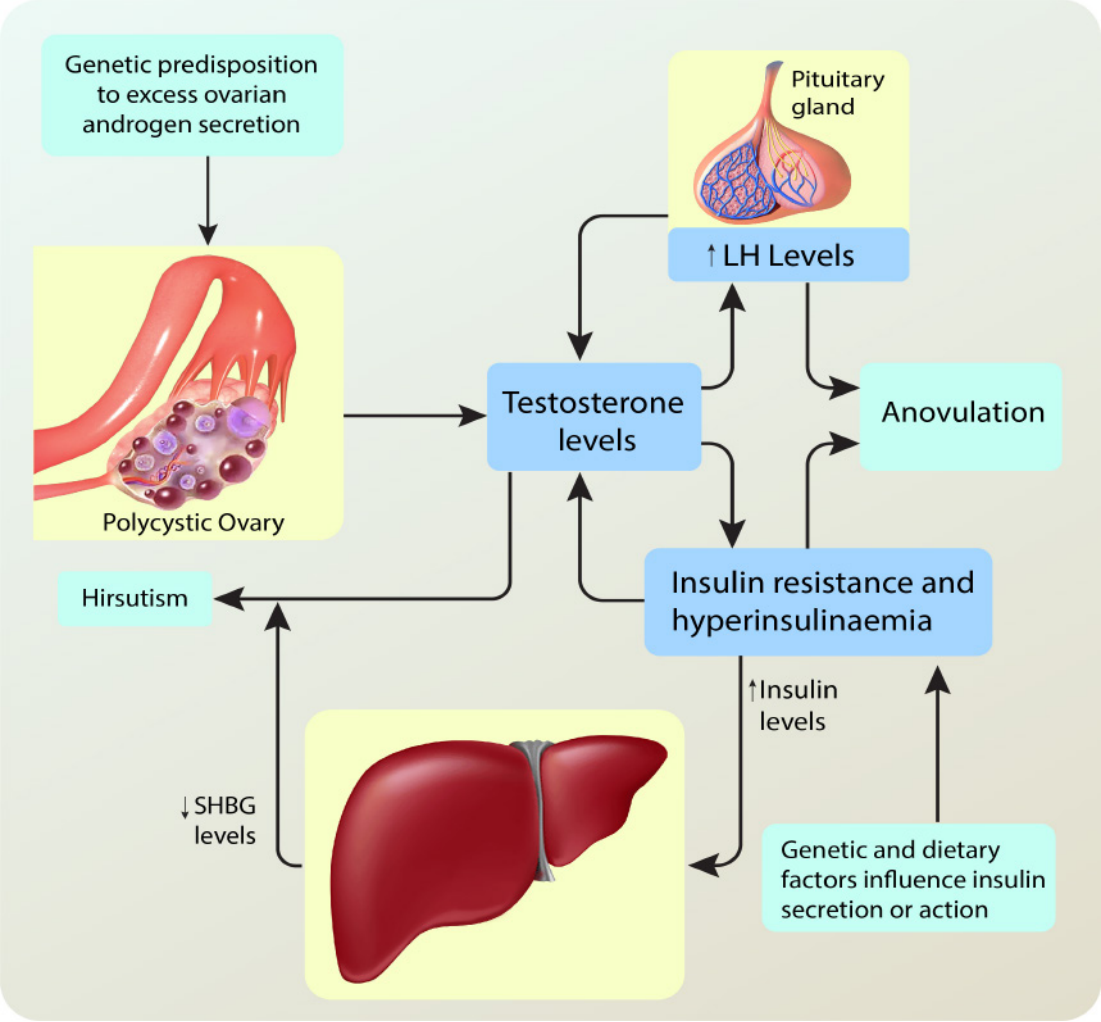

Figure 8: Pathophysiologic concept of polycystic ovary syndrome and physiology of metabolic changes

Pathophysiologic concept of metabolic syndrome in PCOS

Metabolic Syndrome (METABOLIC SYNDROME) is defined as a constellation of cardiovascular risks and insulin resistance, with altered values of serum lipids, abdominal adiposity, blood pressure and blood glucose. It is estimated that obesity is common in approximately 49% of women with PCOS. Abdominal obesity and insulin resistance, has prevalence of between 20 and 40% in these individuals. However, insulin resistance is also present in one-third of lean women with PCOS. ***PCOS is also associated with an increased lifetime risk of dyslipidemia, cardiovascular disease, and type 2 diabetes. Cardiovascular risk seems to be elevated in women with PCOS with obesity, insulin resistance and dyslipidemia.***(as shown in fig:9) [11, Rank 4]

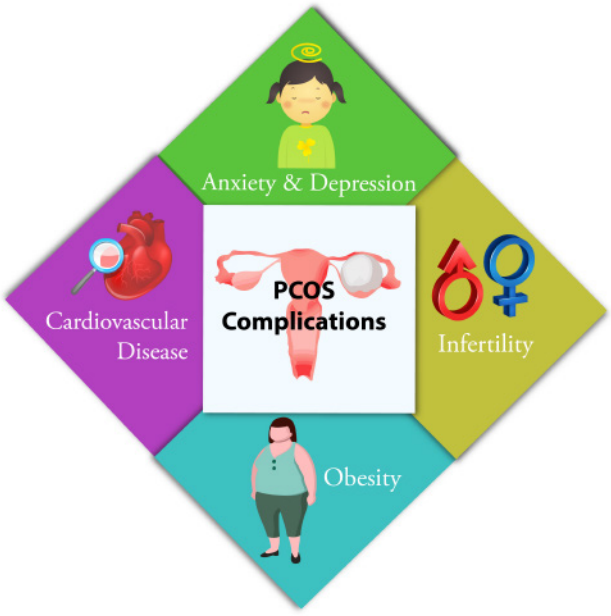

Figure 9: Complications of Poly Cystic Ovary Syndrome

Classic therapeutic options for PCOS and implications for METABOLIC SYNDROME

Combined oral contraceptives (OCPs) and antiandrogens have been used as first-line treatments to target androgen excess in women with PCOS. These treatments have effects at multiple sites.

Traditional use of OCPs has been considered first-line therapy in women with PCOS who are not attempting pregnancy and who do not have contraindications to the use of OCPs. The estrogen component in OCPs stimulates increased hepatic production of binding globulins, of which increased production of sex hormone-binding globulin gene (SHBG). A limitation of OCPs is that this may not be an acceptable therapeutic in PCOS with METABOLIC SYNDROME comprised of hypertension and obesity due to the risk of deep-vein thrombosis and worsening hypertension.

Antiandrogen therapy includes use of cyproterone acetate, spironolactone and flutamide. The antiandrogen cyproterone acetate has an untoward side effect of increasing insulin resistance. Spironolactone, another antiandrogen, acting as a competitive inhibitor of the androgen receptor has the additional benefit of increasing HDL and decreasing triglycerides in lean patients on long-term therapy. However, one study

suggested decreased HDL in short-term spironolactone therapy in conjunction with OCPs in lean women with PCOS. Flutamide, a non-FDA-approved non-steroidal selective androgen receptor blocker, does have an additional beneficial effect on lipid profiles including decreased total cholesterol, low density lipoprotein and triglycerides. [14, Rank 5]

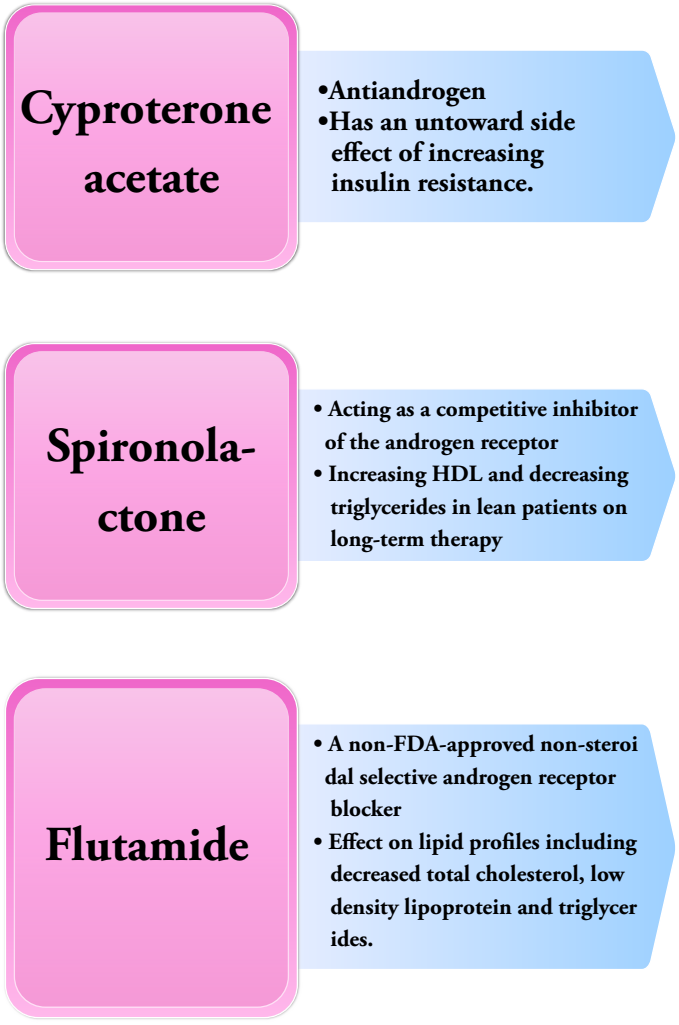

Figure 10: Antiandrogen therapy and Poly Cystic Ovary Syndrome

Metabolic Abnormalities in PCOS

Obesity

Obesity is increasing in incidence and compound the risk of METABOLIC SYNDROME in women with PCOS. The prevalence of central obesity among women with PCOS is estimated to range between 20 and 85.5%. Two large population-based cohort studies showed that body mass index (BMI) was directly correlated with increasing serum total testosterone and inversely correlated with SHBG concentrations in both ovulatory and oligo-ovulatory women. Obesity also appears to modify the characteristics and severity of metabolic dysfunction in women with PCOS. For example, lean women with PCOS are more often present with symptoms consistent with a hyperinsulinemia-driven pathophysiology in the absence of insulin resistance compared to obese women who demonstrate insulin resistance, most likely associated with visceral adiposity.

Several studies comment on the currently available therapeutic agents for METABOLIC SYNDROME in PCOS. Metformin, a biguanide insulin sensitizer, has been proposed as one such drug thought to impact nearly all aspects of

METABOLIC SYNDROME. For some patients with PCOS and METABOLIC SYNDROME, metformin has provided direct treatment of insulin resistance and weight loss. [12, Rank 4]

Insulin Resistance

Insulin activity and glucose metabolism are abnormal in women with PCOS. Insulin resistance has been demonstrated in many target tissues such as skeletal muscle, fibro-blasts and adipose tissue. The prevalence of insulin resistance has been noted in 60–80% of women with PCOS and is compounded by obesity. Earlier studies reported a prevalence of impaired glucose tolerance of 35% and type 2 diabetes of 10% in women presenting with PCOS.

A more recent systematic review reported increased odds of impaired glucose tolerance and type 2 diabetes among women with PCOS. Metabolic profile, more specifically insulin resistance, also appears to depend upon BMI. Severity of insulin resistance has been shown to increase with age in PCOS women who are obese, but not in lean or overweight PCOS women.

Classic treatment for insulin resistance includes peripheral insulin sensitizers, such as metformin. It decreases hepatic gluconeogenesis, increases peripheral glucose uptake and decreases gastrointestinal absorption of glucose. Metformin has beneficial effects on inflammation and cardiovascular risk profile, Further studies are needed to determine whether metformin provides long-term cardiovascular risk reduction in women with PCOS. [13, Rank 5]

> **" Phenotypic differences in neuroendocrine, ovarian, and metabolic defects can be influenced by differences in the timing, duration, and degree of androgen exposure. Individual genetic susceptibility also influence the effect of androgen exposure. "**

Dyslipidemia

Abnormalities in lipid metabolism and fasting lipid profiles in women with PCOS are variable and are due to a combination of insulin resistance, obesity, diet, amount of exercise and genetic predisposition. The general trend is a lowering of HDL, elevation of total cholesterol, low-density lipoproteins and triglycerides. One study reported presence of oxidized LDL as an early marker of altered metabolism in young women.

It is notable that lean women with

PCOS have lipid profile abnormalities compared to normal women of lowered HDL. In another study of obese women with PCOS, there was a slight but statistically significant increase in HDL. Further research is needed to better understand the pathophysiology and early clinical biomarkers of abnormal lipid metabolism in PCOS with Metabolic syndrome. [15, Rank 5]

Liver

Serum sex hormone-binding globulin gene (SHBG), produced by the liver, corresponds with the bioavailable concentration of androgens. ***The level of sex hormone-binding globulin gene is decreased by elevated circulating androgens and obesity.*** Nonalcoholic fatty liver disease has been described occurring in 2–30% of women with PCOS. However,S screening guidelines do not recommend routine screening of liver enzymes or imaging of the liver. Further studies are needed to accurately quantify this risk and guide clinical screening recommendations.

Cardiovascular Risk

Cardiovascular risk seems to be elevated in women with the constellation of PCOS with METABOLIC SYNDROME, or obesity, insulin resistance/impaired glucose tolerance and dyslipidemia. The absolute risk of cardiovascular disease is not well established. ***Cardiovascular risk may depend on the severity of PCOS, as well as individual risk predictors such as BMI, genetic predisposition, diet and lifestyle factors.*** In a study of fatal or non-fatal coronary heart disease (CHD) and stroke, women with PCOS had 1.55 times the risk of CHD or stroke compared to women without PCOS after adjusting for BMI.

> **“ Aspects of metabolic syndrome like obesity and hyperinsulinemia may increase the severity of biochemical or clinical androgen excess. ”**

Additionally, in one large prospective cohort study, menstrual irregularity was associated with an increased risk of non-fatal and fatal CHD. Emerging literature demonstrates that women with PCOS have increased serum markers of inflammation such as CRP and white blood cell count, abnormalities in the renin–angiotensin system and endothelial dysfunction, which may predispose to CHD seen in PCOS. At least two studies have suggested that the cardiovascular risk in women with PCOS may be mediated through early atherosclerotic disease. [16, Rank 5]

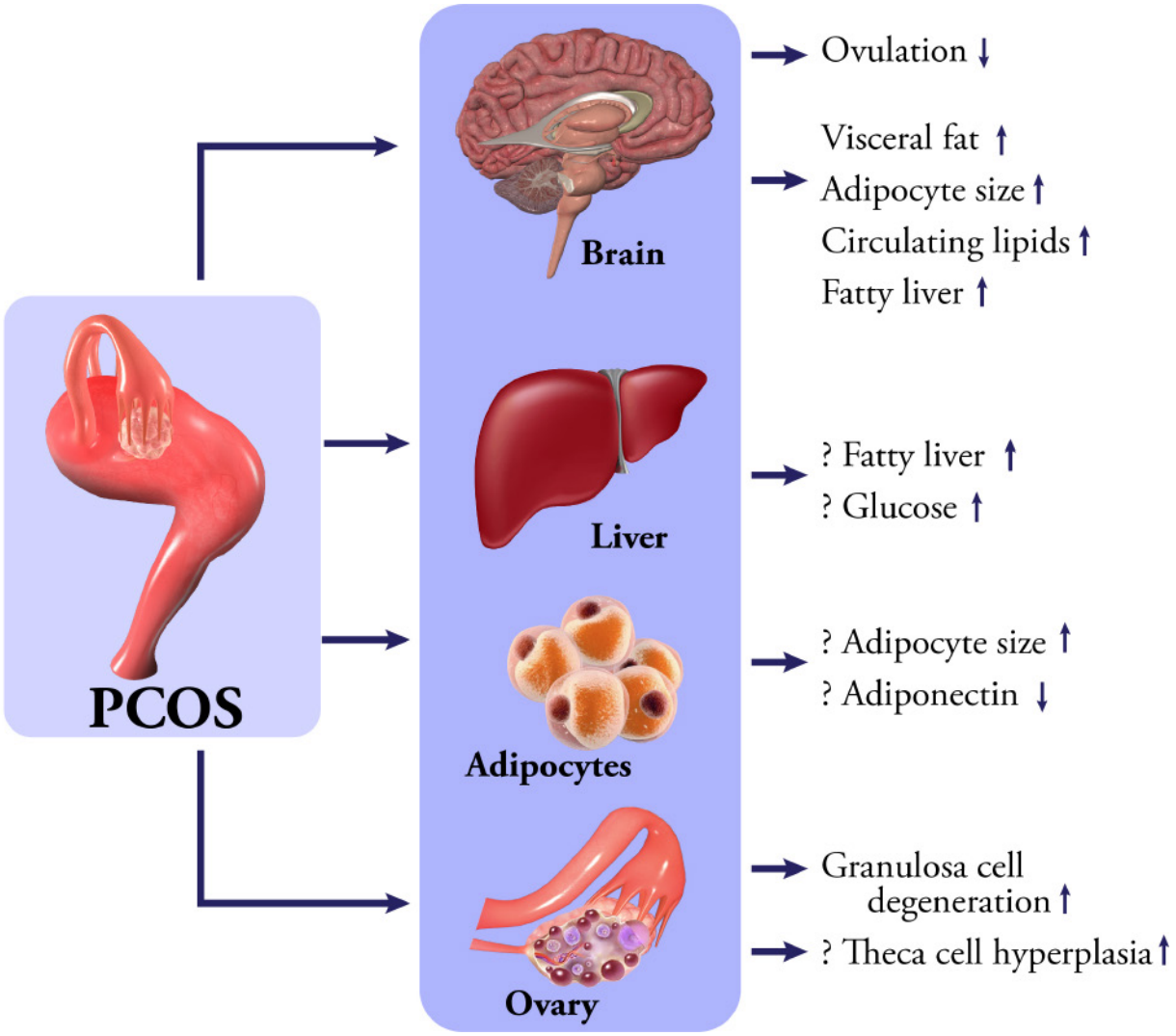

Figure 11: Metabolic Abnormalities in and Poly Cystic Ovary Syndrome

Ovary, Adrenal, and Androgen Excess in Patients with PCOS

PCOS is characterized by excessive ovarian and/or adrenal androgen secretion. Intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to the excessive ovarian androgen production. Characteristic features include more growing follicles in women with PCOS with premature growth arrest of antral follicles at 5 to 8 mm. The classic ovarian phenotype of enlarged ovaries with string-of-pearl morphology and theca interstitial hyperplasia reflects androgen exposure. This morphology has also been observed in women with congenital adrenal hyperplasia (CAH) and female-to-male transgender individuals. Distorted interactions among the endocrine, paracrine, and autocrine factors responsible for follicular maturation may contribute to ovarian dys-

regulation in PCOS.

Ovaries are relatively quiescent until the onset of puberty. Detailed knowledge regarding follicular morphology in prepubertal and early pubertal ovaries is lacking. Ovarian tissue obtained from prepubertal and early pubertal girls shows differences in follicle morphology and growth potential. Specifically, prepubertal ovaries contain a high proportion of abnormal nongrowing follicles, which are not found in pubertal ovaries. The physiologic relevance of this finding is unclear. [17, Rank 4]

Signalling Mechanisms in Patients with PCOS

The precise signalling mechanisms initiating follicular activation are poorly understood. Presumably a balance of factors influences the activation. One such factor appears to be follicle density.

Anti-Müllerian hormone (ANTI-MULLERIAN HORMONE (AMH)), a glycoprotein secreted by granulosa cells, inhibits initial follicular recruitment and indicates follicular reserve. Peak ANTI-MULLERIAN HORMONE (AMH) concentrations are found in antral follicles. Once FSH-stimulated granulosa cell estradiol concentrations achieve the necessary threshold, estradiol suppresses ANTI-MULLERIAN HORMONE (AMH) expression.

Despite prior assumptions that androgens negatively impact follicles, androgens synthesized in preantral follicle theca cells promote growth of preantral and antral follicles and induce granulosa cell FSH receptor (FSHR) expression in early antral follicles. [18, Rank 3]

Typically, one follicle is "selected" as the dominant follicle. With increasing estrogen secretion, pituitary FSH secretion declines due to negative feedback. The dominant follicle compensates for this loss of FSH stimulation through increased LHCGR expression and increased responsiveness to LH stimulation. Subordinate follicles undergo atresia, presumably due to relative FSH deficiency and androgen excess. Upon achieving a sufficient estradiol concentration, neuroendocrine mechanisms trigger the LH surge to induce ovulation. [19, Rank 3]

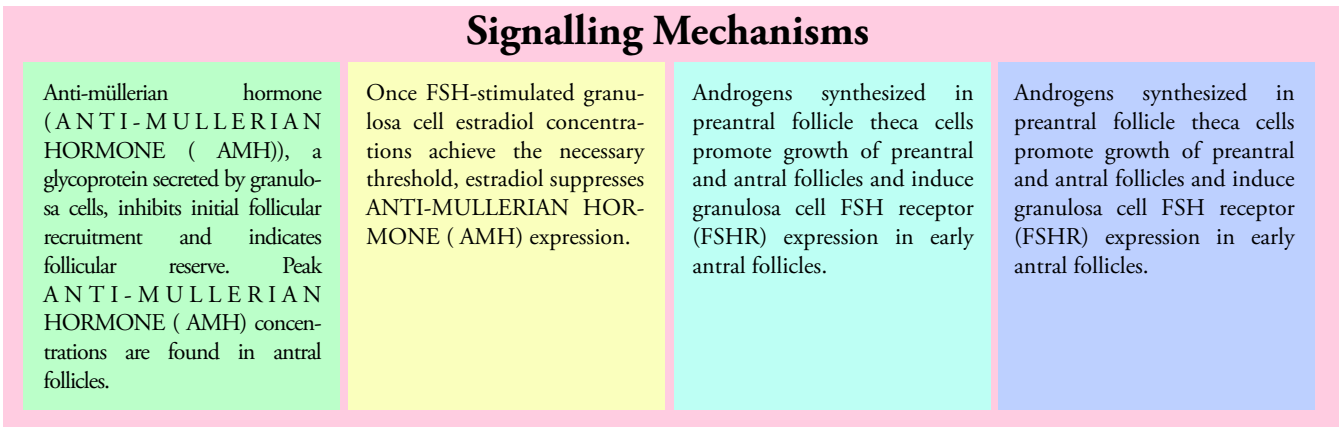

Figure 12: Signalling Mechanisms in Patients with Poly Cystic Ovary Syndrome

Obesity, the Adipocyte, and Nutrient Excess in PCOS

Overweight and obesity are common among adolescent girls and adult women with PCOS. In response to nutrient excess, adipocytes can enlarge (hypertrophy) or form new adipocytes (hyperplasia). According to the adipose tissue expandability hypothesis, adipocyte hypertrophy establishes a microenvironment characterized by hypoxia, proinflammatory cytokine secretion, free fatty acid "spillover," macrophage invasion, and Insulin resistance. Another consequence is increased fat storage in skeletal muscle, liver, and pancreas because the adipose tissue capacity to store lipid is exceeded. In the liver, ectopic fat storage known as hepatic steatosis, which can develop into nonalcoholic fatty liver disease.

White adipose tissue has several distinct locations, that is, visceral and subcutaneous. Partitioning of fat among different storage sites influences metabolic consequences. Increased abdominal fat is associated with greater risk for dysglycemia and cardiovascular disease. Investigation of normal-weight women with PCOS showed increased total abdominal fat mass due to preferential deposition of intra-abdominal fat.

In a study involving normal-weight women with PCOS, subcutaneous adipose IR correlated with serum androgen concentrations and the percentage of small subcutaneous abdominal adipocytes. These data support the hypothesis that expansibility of the subcutaneous abdominal adipose depot is limited and unable to expand sufficiently to meet the metabolic needs for most normal-weight women with PCOS. Emerging data in adolescent girls with PCOS showed that reduction of visceral fat improved menstrual irregularity. [20, Rank 5]

Developmental Hypotheses/ Fetal Origins

The developmental theory of PCOS proposes that exposure of the female fetus to elevated androgen concentrations contributes to the development of PCOS. ***Potential mechanisms include effects on steroidogenesis, insulin signaling, pancreatic β-cell function, hypothalamic–pituitary organization, neuroendocrine secretory patterns, and epigenetic modifications.***

Fetal, neonatal, prepubertal, and/or pubertal ovaries may be genetically predisposed to increased androgen secretion. Women with PCOS typically have higher androgen concentrations than do women without PCOS. One report involving 23 mothers self-reporting PCOS and 277

> **" Exposure of the female fetus to elevated androgen concentrations contributes to the development of PCOS. "**

women reporting no PCOS indicated increased anogenital differences, a marker of prenatal androgen exposure, in daughters of women with PCOS.. [22, Rank 2]

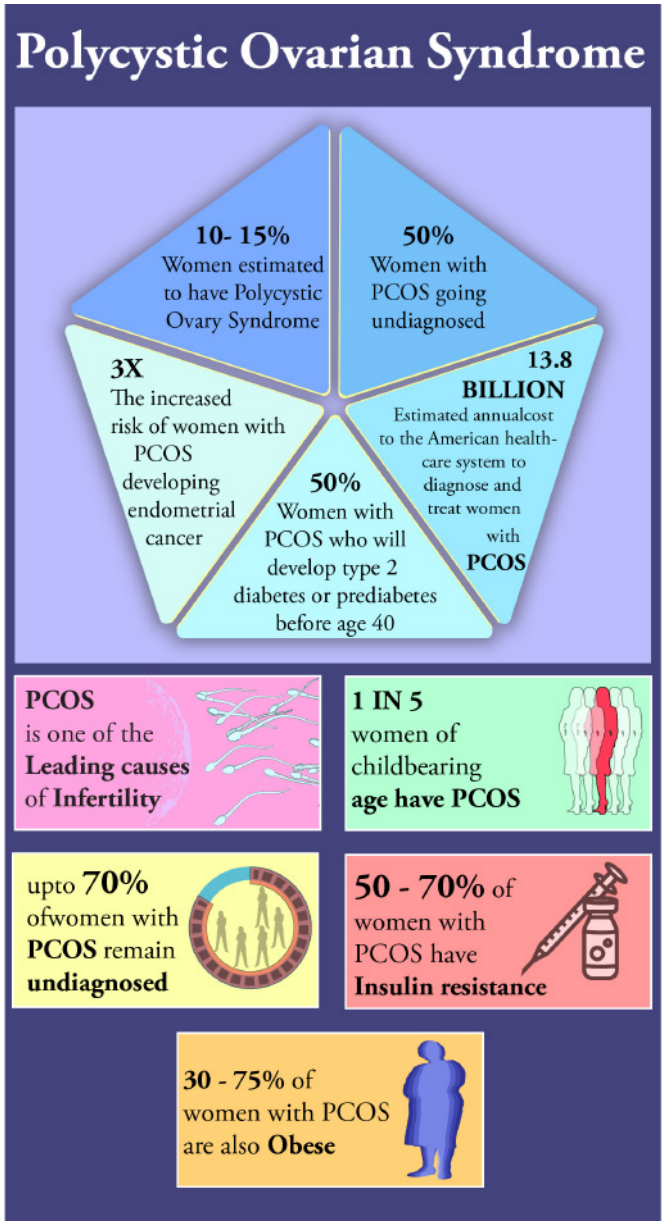

Figure 13: Facts about Poly Cystic Ovary Syndrome

Developmental Hypotheses/ Fetal Origins

Bacteria, archaea, fungi, and viruses comprise the microbial community or microbiome of the gastrointestinal tract. These organisms play roles in fermentation of dietary fiber, bile acid metabolism, host defense, and modulation of metabolism. It has been suggested that the ***gut microbiome influences development of nonalcoholic fatty liver disease and is associated with insulin sensitivity. Sex and sex steroids modulate the composition of the gut microbiome.*** Numerous questions remain to be answered regarding the functional relationships, if any, between sex steroids, metabolic dysregulation, and the gut microbiome.

Twin studies suggest that the heredit-ability is ~70%. The few identified genetic loci explain only a modest proportion of estimated hereditability. Several genetic variants are similar in populations, imply-ing that PCOS is an ancient disease.

Diagnosis of PCOS

The classic features of PCOS include clinical or biochemical hyperandrogenism, oligomenorrhea or amenorrhea associated with chronic anovulation, and polycystic ovary syndrome morphology. The current

consensus is that use of the Rotterdam criteria is appropriate for adult women. ***For diagnosis of PCOS, women must fulfill two of the three characteristics: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovary morphology on ultrasound with exclusion of other disorders.***

The National Institute of Health–sponsored Evidence-Based Methodology PCOS Workshop categorized PCOS into four phenotypes as follows: phenotype A characterized with hyperandrogenism, ovulatory dysfunction, and polycystic ovary morphology; phenotype B with hyperandrogenism and ovulatory dysfunction; phenotype C having hyperandrogenism and polycystic ovary morphology; and phenotype D exhibiting ovulatory dysfunction and polycystic ovary morphology.

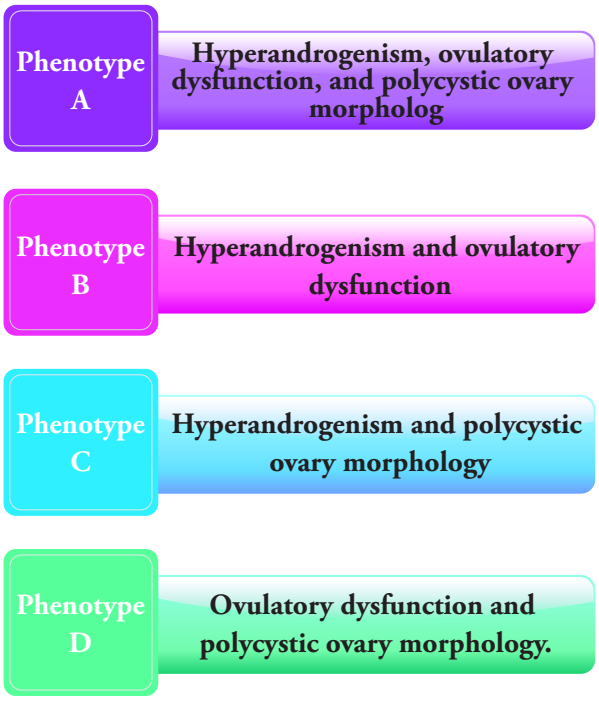

Figure 14: Phenotype and Poly Cystic Ovary Syndrome

Delineating appropriate diagnostic criteria for PCOS among adolescent girls has been problematic because irregular menses, cystic acne, mild hyperandrogenism, and multifollicular ovarian morphology occur during normal pubertal maturation. These similarities between normal pubertal development and the clinical features associated with PCOS confound the diagnosis in adolescent girls. Similar to the evaluation of adult women, other disorders associated with irregular menses and/or hyperandrogenism need to be excluded. These disorders include CAH, typically nonclassic 21-hydroxylase deficiency, androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia, Cushing syndrome, exogenous use of steroid hormones/androgens, or severe IR syndrome. [23, Rank 4]

Menstruation

With reactivation of the GnRH pulse generator, increased gonadotropin secretion stimulates ovarian estrogen secretion and follicular development. Estrogen promotes uterine growth and endometrial proliferation. ***Endometrial estrogen exposure eventually culminates in vaginal withdrawal bleeding and menarche.*** A study found that the median age at menarche for girls was 12.25 years.

> **"Excessive terminal hair growth in male pattern distribution in women, is the primary clinical sign of hyperandrogenism"**

Contemporary understanding is that it takes 3 to 4 years postmenarche for adult menstrual cyclicity to mature. By the third year after menarche, 10 or more menses occur annually in 90% of adolescent girls. Approximately 41% of girls have achieved ovulatory cycles by the fourth gynecologic year. Importantly, ovulation may occur despite irregular menses.

A systematic review of menstrual patterns during the first gynecologic year concluded that menstrual and ovulatory patterns are diverse during this time period. In 22 studies involving >2000 adolescents, frequent menstrual bleeding (<21 days) occurred in 23% and prolonged menstrual bleeding (>30 to 45 days) occurred in at least 33%. A study entailing serial hormone concentrations and ultrasound studies in ovulatory post. menarcheal girls revealed lower steroid (estrogen and progesterone) concentrations, slower dominant follicle growth rate, and longer follicular phases compared with adult women. These data suggest that coordinated development of all components of the HPO axis may take up to 5 years postmenarche.

Oligomenorrheic adolescents tend to have persistent oligomenorrhea. Secondary amenorrhea for >90 days is uncommon and warrants additional consideration. Girls presenting with primary amenorrhea at ages 15 to 16 years merit further evaluation. [28, Rank 3]

Hyperandrogenism

Hirsutism, defined as excessive terminal hair growth in male pattern distribution in women, is the primary clinical sign of hyperandrogenism. The extent of the clinical features of hyperandrogenism represents the interactions between circulating androgen concentrations, local androgen concentrations, and sensitivity of the pilosebaceous unit/hair follicle to androgens. The severity of hirsutism does not correlate with circulating androgen concentrations. Ethnic and genetic variations influence the development of hirsutism. Other cutaneous signs of androgen excess include severe cystic acne and male pattern baldness.

Biochemical hyperandrogenism is confirmed by documentation of elevated serum androgen concentrations. Calculated free testosterone, free androgen index, calculated bioavailable testosterone, androstenedione, and DHEAS may provide helpful information. Testosterone determinations are confounded by several

problems, including inadequate assay sensitivity to accurately measure low concentrations, limited evidence-based normal ranges, assay interference due to other steroid molecules or sex hormone-binding globulin gene (SHBG), and technical aspects of the assay methodology [29, Rank 5]

Evaluation and Diagnosis of PCOS

> **" The diagnosis of PCOS can be considered for the adolescent girl with persistence of oligoamenorrhea for 3 to 4 years postmenarche with clinical and/or biochemical hyperandrogenism after exclusion of other disorders associated with irregular menses or hyperandrogenism. "**

The approach to the evaluation of a girl with signs and symptoms suggestive of PCOS begins with a thorough history, including ***detailed family history and complete physical examination.*** The individualized ***laboratory evaluation typically includes thyroid function studies as well as the determination of prolactin, total testosterone, androstenedione, sex hormone-binding globulin gene, DHEAS, and 17-hydroxyprogesterone concentrations.*** Direct free testosterone assays should be avoided due to inadequate sensitivity, accuracy, and reproducibility of available assays.

Fasting glucose, HbA1c, and lipid concentrations should be determined. Ideally, the blood sample should be obtained prior to 8:30 AM. If CAH is a diagnostic possibility, an ACTH stimulation test can be obtained. The cut point of a basal 17-hydroxyprogesterone >200 ng/dL has been suggested as the threshold for performing ACTH stimulation tests. ***Adrenal and pelvic imaging may be considered depending on the clinical information, physical examination, and initial laboratory data.*** [30, Rank 3]

ANTI-MULLERIAN HORMONE (AMH) concentrations are often elevated in women with PCOS. ANTI-MULLERIAN HORMONEconcentrations reflect ovarian reserve and are correlated with the number of growing follicles. Although it is premature to use ANTI-MULLERIAN HORMONE concentrations to diagnose PCOS, ANTI-MULLERIAN HORMONE concentrations have been found to be elevated in nonobese girls with PCOS. ANTI-MULLERIAN HORMONE concentrations were found to be higher in girls with obesity with PCOS compared to girls with obesity without PCOS of comparable

age and pubertal status.Insulin resistance, hyperinsulinemia, and obesity are commonly identified in women with PCOS.

The diagnosis of PCOS can be considered for the adolescent girl with persistence of oligoamenorrhea for 3 to 4 years postmenarche with clinical and/or biochemical hyperandrogenism after exclusion of other disorders associated with irregular menses or hyperandrogenism. When oligomenorrhea has not persisted for >2 years, these girls can be considered to be "at risk" for PCOS and require longitudinal evaluation to assess for ongoing features of PCOS. Deferred diagnosis attempts to avoid overdiagnosis with its potential for premature labeling, anxiety, and unnecessary interventions. Diagnostic labelling needs to be balanced with the patient's desire for a diagnosis and specific therapeutic interventions. [33, Rank 3]

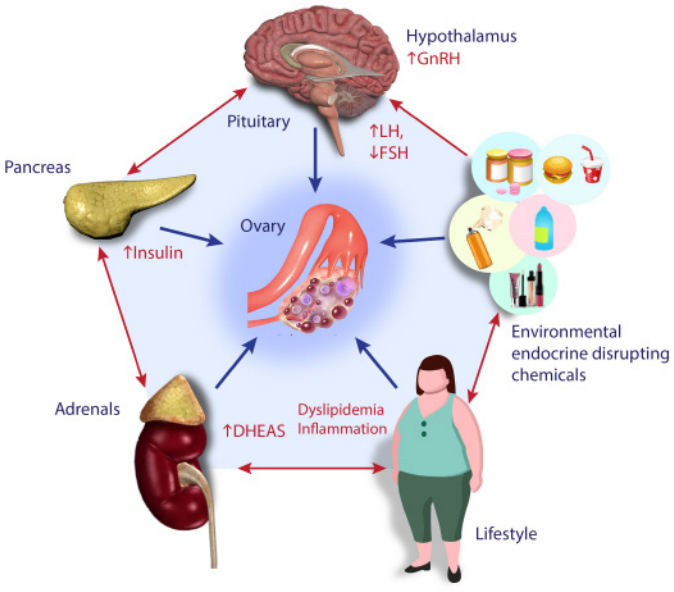

Figure 15: Physiological changes in Poly Cystic Ovary Syndrome

Treatment of Adolescent PCOS

Adolescents presenting with PCOS features, before the diagnosis is confirmed, often require management of their symptoms. The management of adolescents with a clear diagnosis of PCOS should include education about the condition and lifestyle interventions. The interventions can be individualized to target the foremost complaints and symptoms. Interventions include metformin, combined oral contraceptive pills (COCPs), spironolactone, and local treatments for hirsutism and acne. Management should also include management of comorbidities, regular follow-up, and a plan for transition to adult care providers.

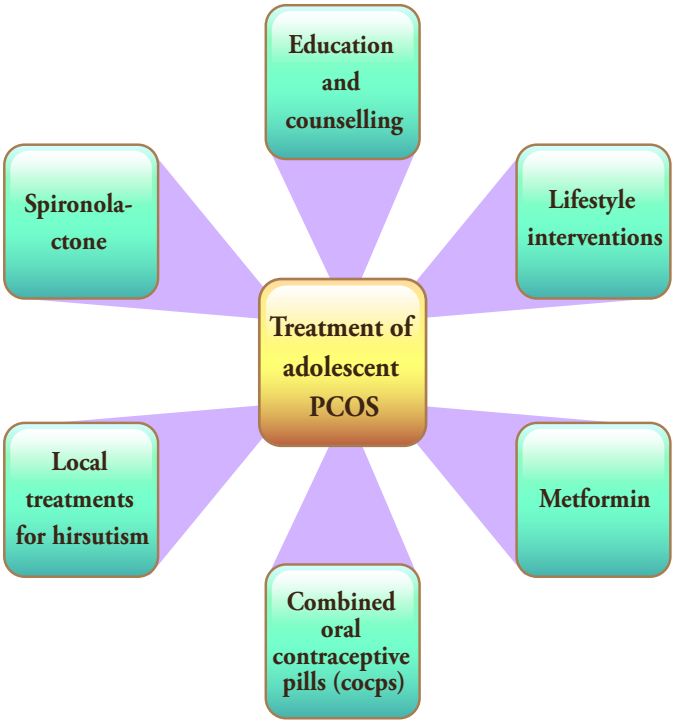

Figure 16: Treatment of adolescent Poly Cystic Ovary Syndrome

Education and Counselling

Education and counselling about the condition is very important. The explanation and discussion of PCOS should be culturally sensitive as well as appropriate, comprehensive, and tailored to the individual. ***This discussion should use an empathetic approach, promote self-care, and highlight peer support groups.*** Counselling about fertility concerns is important, as adolescents with PCOS are more concerned than theirs peers about future fertility after diagnosis. [31, Rank 5]

Lifestyle Interventions

Healthy lifestyle interventions must be incorporated in the management plan of all adolescents with PCOS because ***a large proportion of these adolescents are overweight/obese or are at risk for gaining excessive weight. Lifestyle interventions comprise multiple components, including healthy diets, physical activity, decreased sedentary behaviors, and behavioral strategies.*** The interventions should also include the family, as parents' involvement and their readiness to change affect adolescent outcomes.

Engagement and adherence to lifestyle interventions can be improved by management of psychological factors such as anxiety, body image concerns, and disordered eating, which are common in adolescents. Two systematic reviews of lifestyle interventions in women with PCOS show improvements in weight, hyperandrogenism, and Insulin resistance. Lifestyle interventions in adolescents with PCOS have shown additional improvements in quality of life. [32, Rank 4]

> **" The HPO axis responds to internal signals (i.e., hormonal and neuronal) and external factors (i.e., environment influences). During gestation, these factors impact future generations through epigenetic factors affecting the brain and the developing germ cells . "**

Several studies have evaluated diets in the management of adolescents with overweight/obesity with PCOS, with only three that evaluated diet as a single intervention. A low-carbohydrate diet (20 to 40 g/d) and a hypocaloric diet (<40 g of fat per day) during 12 weeks improved weight and menstrual irregularities with no difference between the diets. Similarly, both low–glycemic load and low-fat diets during 6 months improved weight with no difference between diets. A low-energy diet com-

pared with a healthy diet for 6 months was associated with weight loss, more regular menses, and decreased hirsutism. Nutrition education in addition to exercise training and behavioural therapy for 12 months resulted in weight loss, as well as improvement of menstrual irregularities and androgen levels in adolescents with obesity and PCOS.

Physical activity of longer duration, frequency, and intensity results in better maintenance of health. Importantly, moderate to vigorous physical activity for at least 60 minutes per day is associated with better physical and psychosocial health in children and adolescents. Sixty minutes of moderate to vigorous physical activity at least 3 times a week should be encouraged for the prevention of weight gain and maintenance of health in PCOS. Exercise interventions can also improve cardiometabolic risk factors in women with PCOS. Alternative exercise activities such as yoga for 12 weeks can also improve PCOS symptoms during adolescence. Limiting sedentary behaviors such as watching television and the use of tablets, computers, and/or mobile phones to 2 h/d is advised for adolescents and relates to better health. [35, Rank 2]

Figure 17: Lifestyle and treatment in Poly Cystic Ovary Syndrome

Metformin

Metformin is the single most studied insulin sensitizer in PCOS. It is commonly used in adolescents 15 to 19 years of age despite being "off label" for this indication. Additionally, according to the recent international evidence-based guidelines for assessment and management of PCOS, The use of metformin in addition to lifestyle could be considered in adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made.

A study of metformin use with and without lifestyle changes in PCOS showed beneficial effects on BMI and menstrual cycles. There have been multiple observational studies and six RCTs evaluating the effect of metformin on adolescents with PCOS. These studies have demonstrated short-term beneficial effects mostly in adolescents with overweight/obesity. Metformin doses used ranged from 1000 to 2000 mg daily with the major side effect being mild gastrointestinal distress. Limitations are that the frequency of side effects and adherence to medications have not been fully reported. Side effects can be reduced by starting metformin at a lower dose with slow increments and the use of extended release preparations. RCTs were mostly of 6-month duration; only one study lasted 24 months, and no longer-term studies have been reported. [37, Rank 4]

Metformin at a dose of 1700 to 2000 mg/d is associated with greater improvement of BMI, and are associated with improvement in menstrual irregularity and acne according to a meta-analysis of metformin vs oral contraceptives in adolescents with PCOS. Both metformin and oral contraceptives had similar beneficial effects on hirsutism, triglycerides, and high-density lipoprotein cholesterol, but the estimates of effect were derived from low-quality evidence involving small studies. Meta-analyses including larger number of RCTs in women with PCOS showed limited or no benefit of insulin sensitizers on hirsutism.

Metformin also can be used in addition to COCPs, especially in adolescents with PCOS and BMI ≥25 kg/m2, as well as high–metabolic risk groups such as certain ethnicities and individuals at increased risk of type 2 diabetes. [36, Rank 3]

" Metabolic Syndrome (METABOLIC SYNDROME) is defined as a constellation of cardiovascular risks and insulin resistance, with altered values of serum lipids, abdominal adiposity, blood pressure and blood glucose "

Combined Oral Contraceptives (COCPs)

COCPs (estrogen and progestin preparations) should be considered for management of menstrual irregularity and/or clinical hyperandrogenism in adolescents with a clear diagnosis of PCOS and in adolescents at risk of PCOS before the diagnosis is confirmed according to the recent international evidence-based guidelines. There are limited evidence-based data regarding specific types or doses of progestins, estrogens, or combinations of COCPs for management of PCOS in adolescents and women, but the lowest effective estrogen dose (20 to 30 µg of ethinylestradiol) should be considered. Contraindications such as thromboembolism risk should be assessed when prescribing COCPs by obtaining thorough medical histories of the patient and her family. In most instances, 35 µg of ethinylestradiol plus cyproterone acetate preparations should not be considered first line in PCOS. Duration of treatment has not been evaluated beyond 24 months in adolescents with PCOS. However, COCPs have been used for contraception in longer periods of time.

COCPs improve menstrual irregularity in adolescents with PCOS. COCPs should be also offered when contraception is required and/or medical treatment of hirsutism or acne is needed. When no contraception is required, menstrual irregularity alone can also be managed with cyclical medroxyprogesterone acetate (10 mg per day for 10 days). This can be offered when there is a desire to have fewer menstrual cycles and/or a preference for not taking daily medications or being on COCPs due to cultural reasons. [37, Rank 3]

> **" The polycystic ovary appearance results from presence of 10–12 growing follicles that measure ‹ 10mm in size along with increase in stromal hypertrophy. "**

Management of Histurism

Acknowledgment of the significance of the hirsutism, irrespective of the severity, for a particular adolescent is important when offering treatment options as well as understanding expectations of the treatment. Long-term commitment is required for any topical and/or medical interventions. ***More severe hirsutism may require a combination of strategies. Current available therapies have been mostly evaluated in women and include physical hair removal methods, topical medications, light-based therapies, COCPs, and antiandrogens.***

Physical hair removal methods include waxing, shaving, chemical epilation, plucking, bleaching, and electrolysis. All but electrolysis are temporary hair removal methods, easily available and commonly used by adolescents even before they are evaluated for PCOS. Topical medications such as 13.9% eflornithine cream, an irreversible inhibitor of ornithine decarboxylase, affects hair follicle growth and differentiation and can improve mild facial hirsutism in women with mild skin irritation. [39, Rank 5]

Professional light-based therapies include lasers (alexandrite, diode, and neodymium-doped yttrium aluminum) and intense pulsed light. These light therapies provide wavelengths of 600 to 1100 nm that are absorbed by the melanin in the hair and destroy the hair. This approach provides a prolonged solution for hirsutism after multiple treatments. The light can also be absorbed by epidermal melanin, which is greater in darker skinned individuals, increasing the risk of blisters, dyspigmentation, and scarring

Light-based therapies should be the first line of treatment of localized hirsutism. Laser treatment was associated with a 50% reduction of hair at 6 months after treatment with mild side effects such as pain, skin redness, and perifollicular edema. Uncommon side effects include burns, blisters,

" The prevalence of depression and anxiety is higher in women with PCOS than in the general population. "

hyperpigmentation/hypopigmentation, and scarring that can be reduced by topical anesthetic creams prior to treatment and by cooling mechanisms after treatment. Sun exposure should be avoided before and after treatment. Improvement of hirsutism with laser has been associated with improvement in quality of life, anxiety, and depression in young women with PCOS.

Hormonal therapies should be considered in moderate or severe forms of hirsutism and include COCPs and antiandrogens. COCPs alone improve hirsutism in adolescents with PCOS. Estrogens in the COCPs decrease free androgens by increasing hepatic production of SHBG and decrease ovarian and adrenal androgen production by suppressing LH levels. [40, Rank 4]

Progestins in the COCPs also have some antiandrogenic properties by blocking the AR and inhibiting 5α-reductase activity. A small RCT involving adolescents with PCOS showed no difference in hirsutism improvement when two COCPs were compared during 12 months (30 μg of

ethinyl estradiol and 0.15 mg of desogestrel vs 35 µg of ethinyl estradiol and 2 mg of cyproterone acetate). However, cyproterone acetate is not available in the United States.

Spironolactone, cyproterone acetate (which can be part of COCPs), and flutamide are antiandrogens that have been evaluated and used to treat hirsutism in women. Spironolactone is an aldosterone antagonist that blocks the AR. It should be used after 6 months of COCPs; monitoring for side effects such as volume depletion and electrolyte disturbances should be explained and performed.

The starting dose for spironolactone is 25 mg/d. Subsequently, doses can range from 100 to 200 mg/d divided in two doses. Flutamide at a dose of 250 to 500 mg/d divided in two doses during 12 months has shown beneficial effects on hirsutism in women, but there are no RCTs evaluating the effect of flutamide alone or in combination with COCPs in adolescents. Low doses of flutamide (125 mg/d) in combination with metformin have been used in adolescents with ovarian hyperandrogenism. Flutamide has been associated with severe side effects such as liver toxicity. Finasteride is a topical medication that inhibits 5α-reductase that should be avoided in adolescents, as data are very limited even among adult women. [43, Rank 3]

SYMPTOMS	TREATMENTS
Polycystic Ovaries	**Fertility Drugs. Weight Reduction in Obese Patients.**
Irregular Periods	If you do not want to be pregnant, **birth control pills** can help regulate the menstrual cycle. If you wish to be pregnant **fertility drugs** may help.
Hirsutism(Facial and Body hair), acne, Alopecia	Oral contraceptives containing Ceproterone Acetate. Progesterone treatment. **Insulin sensitizing medications like Glyciphage (metformin).** Acne can be treated with retinoids and antibacterial creams.
Irregular ovulation, Reduced Fertility	**IVF stimulation drugs can improve fertility and help in conception.**
Obesity, Rapid weight gain, difficult to lose weight.	Lifestyle changes, healthy diet and excersise has shown to improve conception chance in women. Diabetic drugs can help with weight loss.

Figure 18 : Treatments in Poly Cystic Ovary Syndrome

Cancer Risk in Patients with PCOS

Women with PCOS have multiple risk factors for endometrial cancer that include obesity, metabolic abnormalities (such as diabetes and hypertension), and a history of oligomenorrhea with prolonged exposure to unopposed estrogen. Studies have noted a 2.7-fold increased risk for developing endometrial cancer vs the general population. This increased endometrial cancer risk in PCOS likely applies to a subgroup of PCOS women with obesity, because the risk is reduced but not elimi-

nated when adjusted for BMI. ***The increased risk for this malignancy in PCOS is largely from prolonged endometrial exposure to unopposed estrogen due to chronic anovulation, although secretory endometrium in women with PCOS shows progesterone resistance with dysregulated gene expression controlling steroid action and cell proliferation.***

Studies regarding PCOS and ovarian cancer risk are contradictory. In a long-term study of women diagnosed with PCOS through hospital records, mortality from ovarian cancer was not increased over the general population. Conversely, a case-control study of women with histologically confirmed epithelial ovarian cancer showed an increased, age-adjusted, 2.5-fold risk of developing ovarian cancer in women with self-reported PCOS. There is no apparent association of PCOS with breast cancer, and insufficient data exist to evaluate the relationships between PCOS and uterine leiomyosarcoma or vaginal, vulvar, or cervical cancers. [41, Rank 4]

Psychosocial Issues in patients with PCOS

The prevalence of depression and anxiety is higher in women with PCOS than in the general population. Such mood disorders, capable of impairing quality of life, can be prominent in adolescents faced with issues of self-presentation, in young adult women concerned with fertility, and in women of all ages with respect to eating, overweight, and clinical manifestations of androgen excess. A study associated PCOS with bipolar disorder, although the association may be with both the disorder and specific treatments of the disorder. Specifically, studies have associated valproate with weight gain and the development of oligomenorrhea. Administering valproate to normal human thecal cells in vitro has increased thecal androgen production similar to what is seen in polycystic ovary thecal cells. [42, Rank 5]

Bariatric Surgery for PCOS

The first line of treatment for ovulation induction in PCOS is lifestyle intervention, especially in obese patients, which seeks to improve body composition (BMI, body weight, and waist-to-hip ratio), and IR. The objective should be a reduction of at least 5 to 10% of the initial weight. Although controversial, better body-weight control has been reported when metformin has been added to lifestyle modification. Lifestyle therapy consists of a hypocaloric diet (1200–1400 kcal/day for 3 months or a 500–1000 Kcal/day deficit) in combination with physical exercise (120 min of exercise per day, 3 to 5 days/week for 6 months).

The patient's capacity to adhere to diet and exercise programs and to maintain an appropriate weight over time is paramount. In this context, psychological support is essential. Pharmacotherapy for weight reduction has not demonstrated its effectiveness for fertility purposes. Bariatric surgery can be considered in women with BMI ≥ 40 kg/m2 or ≥ 35 kg/m2 with associated comorbidities and who have failed to lose enough weight with other treatments in ≥ 6 months. It shows several benefits, including the improvement or resolution of type 2 diabetes mellitus, IR, and fertility problems. However, surgery is a risky option with important associated complications before and during pregnancy. Moreover, it is not a quick approach to achieve pregnancy, since it should be avoided for at least 12 to 18 months after surgery to reduce fetal complications. Therefore, bariatric surgery should be considered as the last therapeutic option in obese women with fertility problems. [43, Rank 5]

Evidence of Developmental Origins of PCOS

In considering developmental origins for PCOS, maternal–fetal environmental modification of the fetal female epigenome contributes to its transgenerational transmission. ***Amniotic fluid from daughters of women with PCOS exhibit male-similar T levels during mid-gestation, exceeding levels in mid-gestation daughters of women without PCOS. As mid-gestation amniotic fluid T originates from the fetus, elevated T levels suggest hyperandrogenism in fetal daughters of women with PCOS during a crucial developmental window.***

Consistent with these findings and the well-established, androgen receptor-mediated, elongation of the anogenital distance (AGD) as an initial component of genital virilization, newborn daughters of women with PCOS, as well as adult PCOS women, exhibit elongated AGDs. Differential patterns of DNA methylation in newborn girls of PCOS women, as well as in adult PCOS women themselves, implicate epigenetic modifications during a critical developmental window, potentially indicative of changes in degree of individual gene expression.

In addition to such evidence for gestational hyperandrogenism contributing to PCOS etiopathogenesis, gestationally diabetic in utero environments, as well as poor intrauterine nutrition and fetal growth restriction, contribute developmental, likely epigenetic, programming to women with PCOS. Human placentae readily convey maternal glucose to the fetus engaging a progressively maturing fetal pancreat-

ic beta cell response, but preventing transfer of maternal insulin. While the 40% incidence of gestational diabetes in women with PCOS may be driven more by pre-conception BMI and lifestyle than PCOS per se, such metabolically challenged pregnancies contribute not only to fetal female hyperglycemia, but may also contribute to fetal female hyperandrogenism through diminished placental aromatase. [44, Rank 4]

Physiological hypotheses on the prognosis of PCOS

Despite many investigations on PCOS and the expression of different hypotheses about the development of PCOS, the main cause of this syndrome is still unknown. The PCOS is a syndrome with different and completely heterogeneous characteristics. There are different pathways that may be involved in its etiology. For instance, a) hormonal imbalances such as hyperandrogenism increased LH/ follicle stimulating hormone (FSH) ratio, increased estrogen levels, and decreased serum progesterone, b) reproductive disorders such as non-ovulation, and menstrual irregularities, c) metabolic abnormalities such as impaired glucose tolerance and insulin resistance, obesity, cardiovascular disease, and type 2 diabetes, and d) changes in serum lipid parameters, are all components of this complex syndrome. Naturally, the appearance of each of these phenotypic traits follows a special physiological pathway in the body, but which pathway(s) causes the disease and which pathway is affected after the disease, is still in debate.

> **" The elevation of frequency and amplitude of the release of gonadotropin releasing hormone (GnRH) and subsequent LH secretion is the most important pathophysiological feature of PCOS. "**

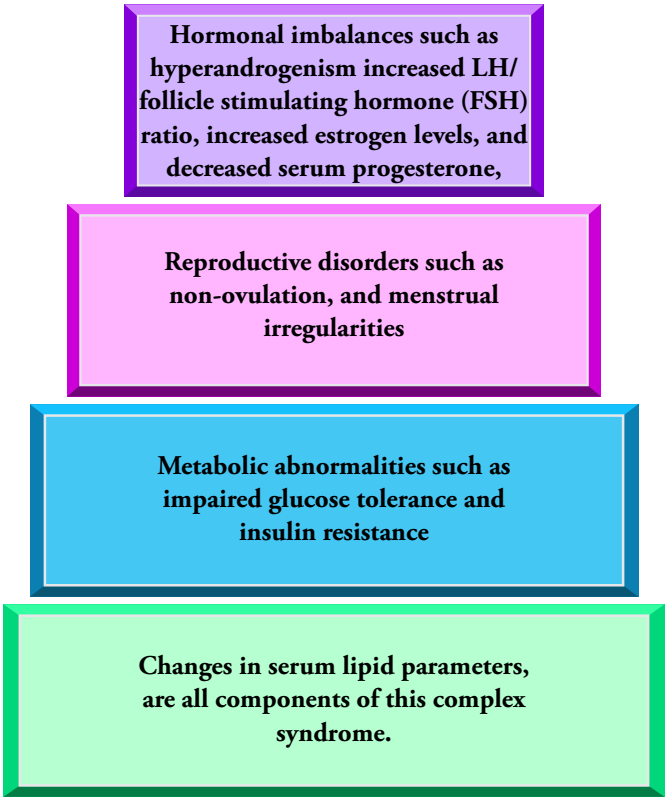

Figure 19 : physiological expressions in the development of Poly Cystic Ovary Syndrome

Hypothalamus-pituitary-ovarian axis

The elevation of frequency and amplitude of the release of gonadotropin releasing hormone (GnRH) and subsequent LH secretion is the most important pathophysiological feature of PCOS. It seems that the most important reason for GnRH secretion impairment is dysfunction of gonadotropin-inhibitory hormone. In PCOS women, this disorder can be examined through regular daily or hourly evaluations of serum samples, and examination of LH pulse secretion. [45, Rank 4]

Hyperandrogenism

Another important endocrine feature of PCOS is the increased level of serum androgens. This hypothesis that PCOS can be due to androgen hypersecretion and eventually hyperandrogenism . Hyperandrogenism can occur for several reasons, and it can disrupt normal activity of ovary and interfere with menstrual cycle. The first reason, based on the above hypothesis, is the disruption of hypothalamic-pituitary axis and increase of LH secretion. LH affects ovarian theca cells and increases synthesis of androgens. The second reason is the metabolic abnormalities in PCOS such as insulin resistance and hyperinsulinemia.

Hyperinsulinemia increases the secretion of androgens with different effects on ovary, adrenal, pituitary, LH receptor, sex hormone-binding globulin (SHBG) protein etc. Another reason for hyperandrogenism is the exposure to androgens during fetal development, which can result in PCOS phenotypes in adulthood. During development of fetus, embryo may receive additional androgens for four reasons, resulting in epigenetic changes leading to PCOS in the future. Firstly, the mother has PCOS and placenta is also unable to perform aromatization and increase the concentration of SHBG, which will result in receiving maternal androgen via the placenta by fetus. Second, the fetus has a genetic disorder, and the fetal undifferentiated ovary is the source of excess androgen production. The third reason is malformation of tissues producing androgens including the adrenal; for example, adrenal hyperplasia can also affect production of additional androgen. The fourth reason is hypothalamic-pituitary axis disorders during embryonic development simultaneously with evolution of this system that may increase androgen production. Therefore, the increase in serum androgen levels in both embryonic and adulthood plays an important role in initiating PCOS. [46, Rank 5]

Gonadotropin secretion and actions

Unlike the name, PCOS is probably due to impaired neuronal pathways in the brain that control the hypothalamic-pituitary-ovarian (HPO) axis. Ovarian functions in most mammalian are regulated by the small group of neurons localized in the preoptic area of hypothalamus, named GnRH neurons. The release of GnRH neuropeptide from the axon terminal of neurons into median eminence and portal vein leads to secretion of gonadotropins from the adenohypophysis gland, which in turn mediates ovarian folliculogenesis and steroidogenesis. FSH is responsible for stimulating the growth of follicles in the ovary, which naturally applies this effect by binding to FSH receptors on granulosa cells. If the release of FSH decreases for a long time, follicular maturation and subsequently ovulation does not occur and leads to subfertility. These immature follicles eventually form small cysts in the ovary.

On the other hand, LH stimulates follicular growth, steroidogenesis, and formation of corpus luteum. Ovulation is the result of LH surge. The LH actions are carried out via binding to high affinity LH receptor and luteinizing hormone/chorionic gonadotropin receptor (LHCGR), which also serves as the receptor of human chorionic gonadotropin (hCG). Unsuitable secretion of gonadotropins is main attribute of PCOS. Women with PCOS showed high concentrations of LH, and have high and low levels of LH and FSH, respectively; the 2/1 to 3/1 ratios usually were expressed for abnormal gonadotropin release. [48, Rank 5]

The prominent neuroendocrine abnormalities involved in PCOS are an elevation of frequency and amplitude of GnRH release, which is reflected by LH secretion and in fact it is the main pathophysiological component of PCOS. Effective mechanisms for increasing pulse frequency and amplitude of LH in PCOS are not well understood, but four hypotheses have been suggested that explain the impact of peripheral hormones on brain function in pathogenesis of PCOS.

The first hypothesis is the increase of circulating insulin level (hyperinsulinemia) that elevates the activity of GnRH neurons or pituitary responsiveness to GnRH. The second hypothesis is the low levels of serum progesterone that is followed by anovulation in PCOS conditions, which eventually removed the influence of negative feedback by progesterone on GnRH release. The third hypothesis is hyperandrogenism that changes the setting up of critical neuronal circuits for negative feedback of steroid hormones.

The recent mentioned hypothesis seems play a serious role on the function of GnRH pulse generator that reduces the activity of GnRH inhibitors such as GnIH or its counterpart in mammals, RFRP-3. RFRP-1 and RFRP-3 neuronal cell bodies are located in the dorsomedial nucleus of the human hypothalamus and axonal projection that reach to preoptic area and median eminence. The mRNA expression of hypothalamic RFRP-3 neuropeptide is reduced in patients after induction of PCOS by continuous light [47, Rank 4]

The Ovarian Cycle in PCOS: When it All Goes Wrong

Because no specific sole cause for PCOS has been determined, the most accepted premise is a multifactorial model, where interactions between environmental cues and factors intrinsic to each individual act in consonance toward a common result, which is the development of hyperandrogenemia, a biochemical hallmark of this pathology. This alteration is the main culprit behind most clinical manifestations of PCOS.

Feedback disturbances in the hypothalamus-hypophysis-ovary axis (HHOA) are a typical feature of PCOS, with increased frequency and amplitude of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) pulsatile secretion. Higher levels of this hormone induce greater androgen synthesis in ovarian theca cells (TC). In turn, hyperandrogenemia induces a decrease in feedback sensitivity to both estradiol and progesterone in gonadotropic hypothalamic cells, reinforcing GnRH and LH hypersecretion. This represents the first of many self-perpetuating pathophysiologic cycles in which hyperandrogenemia plays a pivotal role in the development and progression of PCOS, while simultaneously warranting the presence of the clinical manifestations. The constant growth of follicles, along with nonselection of a dominant unit, leads to the hyperstimulation of several of these structures, hence the alternative proposed denomination of "polyfollicular ovary syndrome", which maintains all the characteristic hormonal imbalances.

Recent evidence describes a central role for certain proinflammatory mediators in the pathophysiology of PCOS, posing a new focus on the etiological considerations for PCOS, which is currently considered a chronic, low-grade inflammatory disorder, independently of the presence of obesity, although these phenomena are indeed exacerbated by adiposity. Reports show that women with PCOS, both with obesity and normal weight, exhibit elevated serum TNF, C-reactive protein (CRP), monocyte

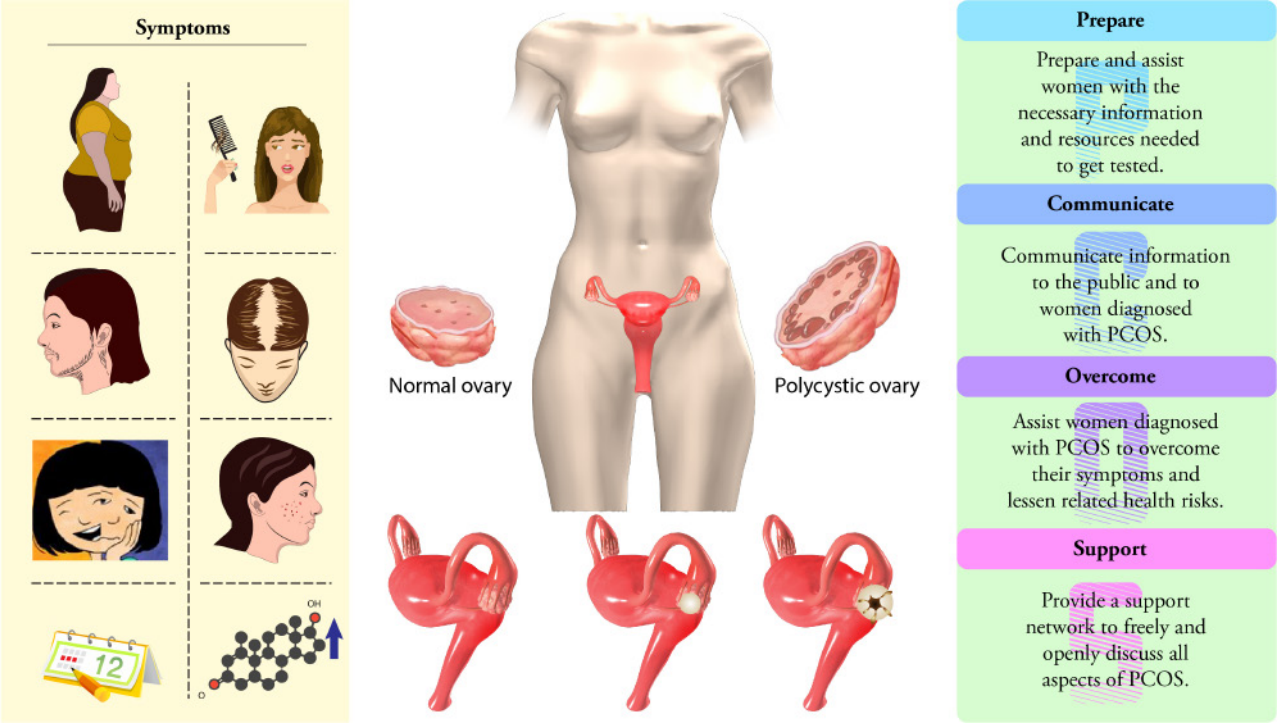

Figure 20: Poly Cystic Ovary Syndrome and management

and lymphocyte circulating levels, and inflammatory infiltration in ovarian tissue [49, Rank 3]

Conclusion

PCOS is a condition that spans the lives of women. Fetal programming may represent the beginning of a syndrome which can have a series of medical consequences in adolescence, adulthood, and old age. Menstrual and fertility problems evolve into metabolic complications as age advances, with early diagnosis being crucial to avoid complications. A precise diagnosis is important, especially at the extreme ends of the reproductive lifespan. Many different phenotypes are included under the same condition. Therefore, it is important to look at these different phenotypes separately, as they may require different treatments and have different consequences.

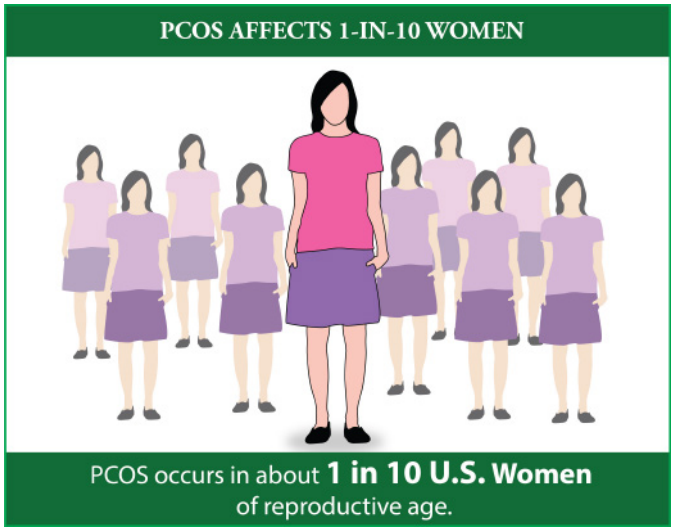

Figure 21: Poly Cystic Ovary Syndrome in women

In this way, PCOS exhibits a great metabolic complexity and its diagnosis should be revised once again according to recent data

obtained by new technologies. Lifestyle therapy tends to be the first step in PCOS management, especially when associated with excess body weight. Pharmacotherapy is frequently used to manage the most predominant manifestations in each age group, such as irregular menses and hirsutism in adolescence, fertility problems in adulthood, and metabolic problems and risk of cancer in old age. New research may change future information once different phenotypes of the syndrome are analysed as complete separate entities. [50, Rank 5]

Figure 22 : Poly Cystic Ovary Syndrome

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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