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A COMPREHENSIVE OVER VIEW OF POLYCYSTIC OVARIAN SYNDROME (PCOS)

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder characterized by irregular menses, hyperandrogenism&polycystic ovaries. The incidence varies between 0.5 – 4 % more common amongst infertile women. It is prevalent in young reproductive age group (20 – 30 %). The prevalence of PCOS varies depending on which criteria are used to make the diagnosis, but is as high as 15%–20% when the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine criteria are used. Clinical manifestations include oligomenorrhea or amenorrhea, hirsutism & frequently infertility. Risk factor for PCOS in adults includes type I & II diabetes and gestational diabetes. Insulin resistance affects 50%–70% of women with PCOS leading to a number of comorbidities including metabolic syndrome, hypertension, dyslipidemia, glucose intolerance &diabetes. Studies show that women with PCOS are more likely to have increased coronary artery calcium scores and increased carotid intima-media thickness. Mental health disorders including depression, anxiety, bipolar disorder and binge eating disorder also occur more frequently in women with PCOS. Weight loss improves menstrual irregularities, symptoms of androgen excess and infertility. Management of clinical manifestations of PCOS includes Oral Contraceptives for menstrual irregularities and hirsutism. Spironolactone &Finasterideare used to treat symptoms of androgen excess. Treatment options for Infertility include Clomiphene, Laparoscopic Ovarian Drilling, Gonadotropins&Assisted Reproductive Technology. Recent data suggest that Metformin, Letrozole (Femara)andAnastrozole (Arimidex)may play an important role in ovulation induction. Proper diagnosis and management of PCOS is essential to address patient concerns butalso to prevent future metabolic, endocrine, psychiatric andcardiovascular complications.

Key Words: Polycystic Ovary Syndrome (PCOS), Endocrinopathy (Hyperandrogenism), HAIR-AN syndrome, Weight reduction; Ovulation induction& Infertility

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) was originally described in 1935 by American gynaecologists**Irving F. Stein& Michael L. Leventhal** from whom the original name of **Stein-Leventhal Syndrome** is taken, as a syndrome manifested by amenorrhoea, hirsutism and obesity associated with enlarged polycystic ovaries.[1]

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PCOS is one of the most common syndromes in the modern world in women during their reproductive age. It is now recognized as a common, heterogeneous, heritable disorder affecting women throughout their lifetime. PCOS is characterized by hyperandrogenism, ovulatory dysfunction& polycystic ovaries. However, there is considerable interindividual variation in presentation. Although not required for diagnosis, the presence of insulin resistance and hyper insulinaemia is common and places those affected at increased risk of diabetes and cardiovascular disease.[2] PCOS is a condition in which a woman has an imbalance of sex hormones. This may lead to menstrual cycle changes, cysts in the ovaries, leads to anovulation and infertility other metabolic disorders in the body. In PCOS, mature eggs are not released from the ovaries. Instead, they can form very small cysts in the ovary. These changes can

contribute to infertility. Common symptoms of PCOS include menstrual disorders, Infertility, High levels of testosterone and Metabolic syndrome. Obesity, sedentary life style with inadequate physical activity, stress and junk food consumption is thought to be contributing factors in addition to genetic origin. In recent years many of the girls and women are suffering from PCOS because of wrong eating habits, stressful living conditions and lack of physical activity.[3]

PCOS is a multifactorial and polygenic condition. This heterogeneous endocrine disorder is characterized by excessive androgen production by the ovaries mainly, which interferes with the reproductive, endocrine, metabolic functions and cardiovascular dysfunctions.[4]

According to Ojaneimi, PCOS in teenagers is characterized by irregular menstrual cycles (generally less than 6 menses/year) and clinical or biochemical features of hyperandrogenism. PCOS typically presents during adolescence and is a heterogeneous syndrome classically characterized by features of anovulation (amenorrhoea, oligomenorrhoea, irregular cycles) combined with symptoms of androgen excess (hirsutism, acne and alopecia).[5]Hyperandrogenism, most particularly in women with PCOS, that does not virilize, yet is above normal limits.[6] Some rely on the clinical presentation of peripheral androgen excess in women to make the diagnosis of hyperandrogenism as part of the PCOS phenotype that includes midline hirsutism, acne and androgenic alopecia.[7] This syndrome is a common problem affecting approximately **5%** of women of reproductive age when defined by the clinical features of anovulation and hyperandrogenism.[8]

Epidemiology& Risk factors:PCOS is the most common endocrinopathy in women and the most common cause of anovulatory infertility, affecting 5 – 10% of the female population in India. The incidence varies between 0.5 – 4 % more common amongst infertile women. It is prevalent in young reproductive age group (20 – 30 %).[9]

Family history of PCOS is a risk factor for PCOS. Based on the clustering of cases in families, PCOS is considered to be a heritable disorder.[10,11] A high prevalence of PCOS or its features among first-degree relatives is suggestive of genetic influences.[12, 13] In addition, greater concordance has been reported in monozygotic twins versus dizygotic twins.[14] However, the mode of inheritance remains elusive. Issues that hamper progress in this area include the heterogeneity of PCOS phenotypes, difficulty in assigning a phenotype to men, postmenopausal women, and prepubertal girls, and difficulties in obtaining large enough sample sizes to allow for adequate statistical power.[15] A genome wide association study conducted amongst Han Chinese has identified loci on chromosomes 2p16.3, 2p21, and 9q33.3.[16] Some of these results were replicated in European cohorts, namely the chromosome 2p21 THADA and chromosome 9p33.3 DENND1A susceptibility loci. The sharing of the same susceptibility genes suggests that PCOS is an ancient disorder originating before humans migrated out of Africa.[17] An increased prevalence of PCOS is associated with a number of conditions.[18] A history of weight gain often precedes the development of the clinical features of PCOS,[19]and following a healthy lifestyle has been shown to reduce body weight, abdominal fat, reduce testosterone, improve insulin resistance, and decrease hirsutism in women with PCOS.[20]Obese women referred for assistance with weight loss had a prevalence of PCOS of 28.3%.[21]However, in an unselected population, prevalence of PCOS did not vary significantly based on obesity class.[22]PCOS prevalence rates for underweight, normal-weight, overweight, mildly obese, moderately obese, and severely obese women were 8.2%, 9.8%, 9.9%, 5.2%, 12.4%, and 11.5%, respectively. The authors concluded that obesity may increase the risk of PCOS but that the effect was modest.[23]

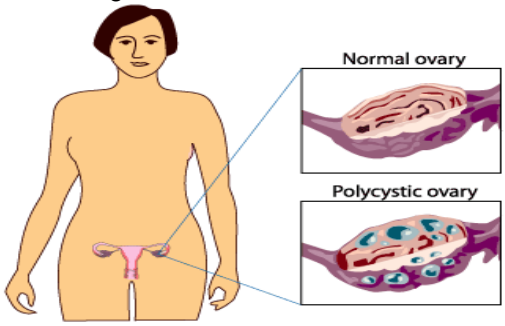
An increased frequency of reproductive disorders, including PCOS, has been reported in women with epilepsy.[24] Using NIH criteria for diagnosis, Biloet al[25] identified PCOS in 13 of 50 women (26%) with epilepsy. Among the 16 patients who were not treated for epilepsy at presentation, five (31%) were diagnosed with PCOS, supporting the contention that epilepsy, independent of antiepileptic drugs, increases the risk of PCOS.[26]Valproic acid, an antiepileptic drug widely used to treat epilepsy, bipolar disorder, and migraine, is associated with features of polycystic ovary syndrome when used to treat women with epilepsy.[27] These features include menstrual disturbances, polycystic ovarian morphology, and elevated serum testosterone.[28] Substitution of lamotrigine for valproic acid in women with epilepsy resulted in reductions in body mass index, fasting serum insulin, and testosterone concentrations.[29] Thus, the confounding effects of medication must be considered when evaluating the literature that probes the relationship between epilepsy, bipolar disorder, and PCOS.[30]

Type 1, Type 2, and gestational diabetes have been associated with an increased prevalence of PCOS. Escobar-Morreale et al screened 85 Caucasian women with type 1 diabetes mellitus for PCOS using the NIH/NICHD criteria.[31] PCOS was diagnosed in 16 of these women (18.8%). Subsequently, Codner et al screened 42 women with type 1 diabetes mellitus and 38 age and body mass index (BMI) matched controls for PCOS using the ESHRE/ASRM criteria.[32] The prevalence of PCOS was 40.5% in the type 1 diabetes group and 2.6% in the control group, yielding a relative risk of PCOS of 15.4 (95% confidence interval [CI] 2.2–110.2; *P*,0.0001) in the type 1 diabetes group. In type 2

diabetes, PCO are extremely common, occurring in 82% of women.[22] The prevalence of PCOS in type 2 diabetes using the NIH/NICHD criteria has been estimated to be 26.7%.[33] A diagnosis of PCOS was verified in 15 of 94 women (16%) with gestational diabetes and in six of 94 (6.4%) of those without gestational diabetes (P=0.03).[34]A number of factors that are associated with an increased risk of PCOS have been identified in children.[34]Prenatal factors include high birth weight in girls born to overweight mothers, congenital virilization, and low birth weight. Risk factors apparent later in childhood include premature pubarche, atypical central precocious puberty, obesity syndromes, acanthosisnigricans, and metabolic syndrome. A high index of suspicion for the diagnosis of PCOS is warranted in adolescents with persistently irregular menses and this risk factors.[35]

PCOSa complex syndrome of unclear etiopathogenesis appears to involve genetic & environmental components.[34] It has also been associated with coronary heart disease, diabetes & other metabolic syndromes & hence the estimation of high PCOS prevalence rates appears in the countries where obesity & type - II diabetes are more common.In the past 2 decades, developing countries began relying on westernized diets & lifestyles.[35] It is predicted that they may see up to 6 - fold increase in the obesity prevalence in the next 10 years, especially from **India** who already has the highest rates of diabetes in the world.[36]Though genetic predisposition plays an important role, many studies also show that dietary habits & exercise can also influence the causation of the disease.[37]

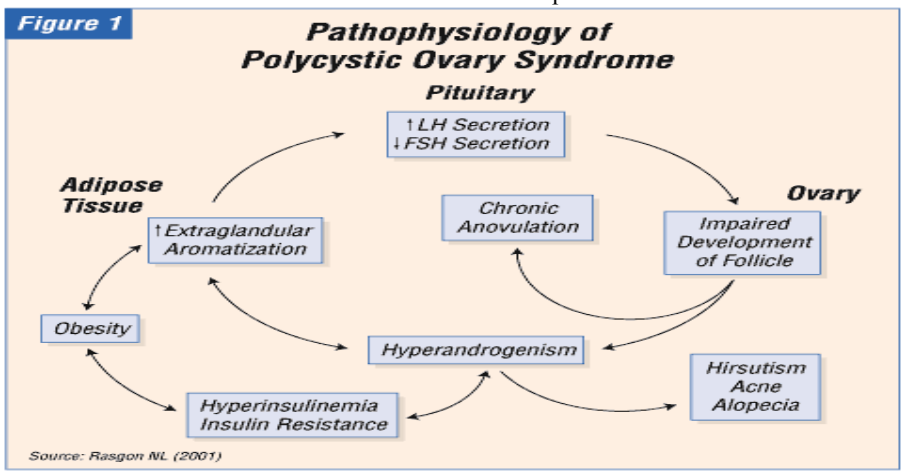
Pathology: Typically the ovaries are enlarged. Ovarian volume is increased ≥ 10 cm3. Stroma is increased. The capsule is thickened and pearly white in colour. Presence of multiple (≥ 12) follicular cysts measuring about 2 - 9 mm in diameter is crowded around the cortex.[4]



Histologically, there is thickening of tunica albuginea. The cysts are follicles at varying stages of maturation and atresia. There is theca cell hypertrophy (Stromal hyperthecosis). Patient may present with features of diabetes mellitus (DM)[Insulin resistance (IR)].[4]

Pathophysiology: Exact pathophysiology of PCOS is not clearly understood.[4]Presence of IL-18 gene polymorphisms had no direct relationship with the pathogenesis of PCOS, but the carriage of the C allele at position -137 in the promoter of the IL-18 gene may play a protective role from the development of PCOS IR.

Figure 1



The pathophysiology of PCOS may be discussed under the following heads;[4]

1. Hypothalamic – pituitary compartment abnormality –

- Increased pulse frequency of GnRH leads to increased pulse frequency of LH.
- GnRH is preferential to LH rather than FSH.
- FSH level not increased it may be due to negative feedback effect of chronically elevated oestrogen and the follicular inhibin.
- Increased free oestradiol due to reduced SHBG bears positive feedback relationship to LH.
- The LH: FSH ratio is increased.

2.Androgen excess – production from the ovaries and adrenals may be due to abnormal regulation of the androgen forming enzyme (P450 C 17). The principal sources of androgens are;

A. Ovary produces excess androgens due to,

i) Stimulation of theca cells by high LH

ii) P450 C17 enzyme hyperfunction

iii) Defective aromatization of androgens to oestrogen

iv) Stimulation of theca cells by IGF-1 (insulin growth factor-1)

B. Adrenals are stimulated to produce excess androgens by, i) Stress ii) P450 C17 enzyme hyperfunction iii) Associated high prolactin level (20%).

C. Systemic metabolic alteration:

(i)Hyperinsulinaemia causes:

a. Stimulation of theca cells to produce more androgens.

b. Insulin results in more free IGF-1. By autocrine action, IGF-1 stimulates theca cells to produce more androgens.

c. Insulin inhibits hepatic synthesis of SHBG, resulting in more free level of androgens.

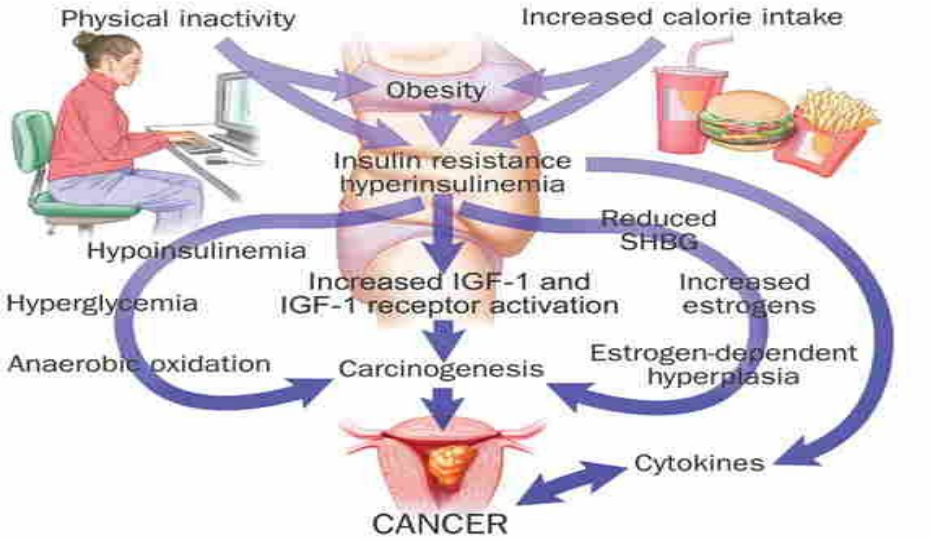
Features suggestive of insulin resistance are: BMI > 25 kg/m2, **Acanthosisnigricans** and waist to hip ratio > 0.85.

(ii) Hyperprolactinaemia: In about 20 % cases, there may be mild elevation of prolactin level due to increased pulsitivity of GnRH or due to dopamine deficiency or both. The prolactin further stimulates adrenal androgen production.

3. Anovulation: Because of low FSH level, follicular growth is arrested at different phases of maturation (2-10 mm diameter). The net effect is diminished oestradiol and increased inhibin production. Due to elevated LH, there is hypertrophy of theca cells and more androgens are produced either from theca cells or stroma. There is defective FSH induced aromatization of androgens to oestrogens. Follicular microenvironment is therefore more androgenic rather than oestrogenic. Unless there is oestrogenic follicular microenvironment, follicular growth, maturation and ovulation cannot occur. There is huge number of atretic follicles that contribute to increased ovarian stroma (Hyperthecosis). LH level is tonically elevated without any surge. LH surge is essential for ovulation to occur.

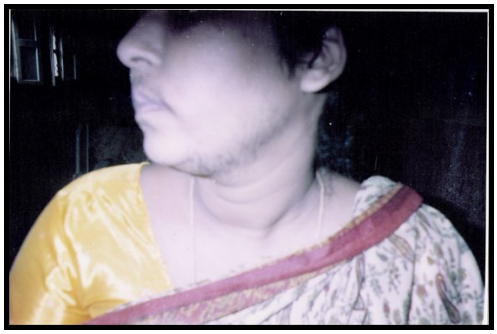
4. Obesity and Insulin resistance (IR): Obesity (Central) is recognized as an important contributory factor. Apart from excess production of androgens, obesity is also associated with reduced SHBG. It also induces insulin resistance and **hyperinsulinaemia** which in turn increases the gonadal androgen production. PCOS is thought to have a dominant mode of inheritance as about 50% of 1st degree relatives have PCOS.

The prevalence of insulin resistance in PCOS ranges from 50%–70%57–60 and occurs independently of obesity.The effect of obesity on insulin resistance is additive to that of PCOS.[38]



5. Long-term consequences in a patient suffering from PCOS includes: The excess androgens (mainly androstenedione) either from the ovaries or adrenals are peripherally aromatized to oestrone (E1). There is concomitant diminished SHBG. Cumulative excess unbound E2 and oestrone results in a tonic hyperoestrogenic state. There is endometrial hyperplasia.[39]

Possible late sequelae are:



Diabete des femmes a barbe (*"Diabetes of the bearded lady"*)

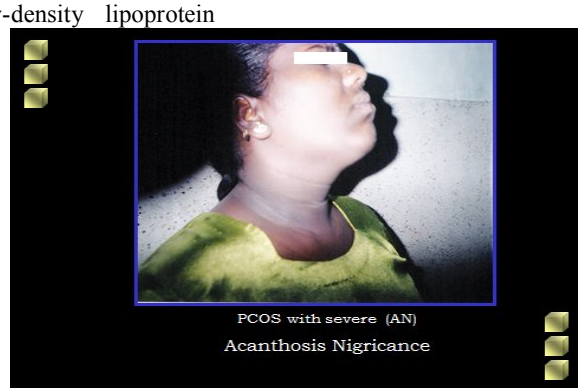
2. Risk of developing **endometrial carcinoma** due to persistently elevated level of oestrogens.Oestrogens effects are not opposed by progesterone because of chronic anovulatory state.
3. Risk of **hypertension** and **cardiovascular disease** due to abnormal lipid profile (Dyslipidaemia).
4. Breast cancer. Women suffering from PCOS are considered to be at high risk for **dyslipidemia** due to elevatedandrogen levels and frequent association of this syndrome with obesity.[40] Furthermore, since these patients are often hyperinsulinemic and insulin resistant, it would also be expected to be at increased risk for the dyslipidemia associated with insulin resistance.[41] A number of studies have shown that women with PCOS have lower high-density lipoprotein (HDL) and/or HDL2 levels, as well as higher triglyceride and low-density lipoprotein

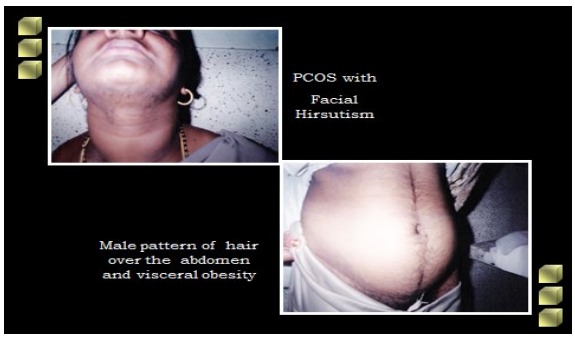
1. Risk of developing **Diabetes mellitus (15%)** due to insulin resistance

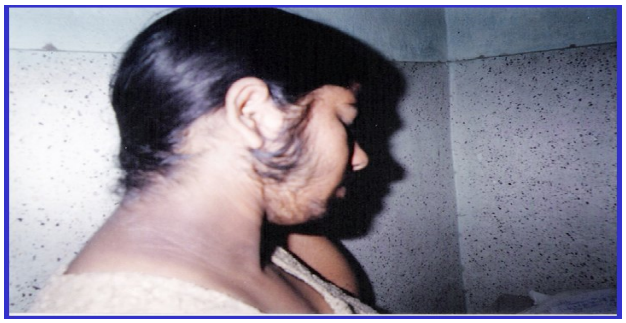
(LDL) levels than age, sex, and weight matched control women.[42] **Hypertriglyceridemia,** increased levels of very low-density lipoprotein (VLDL) and LDL cholesterol and decreased levels of HDL–cholesterol[42] predispose patients to vascular disease in the PCOS. Both insulin resistance and hyperandrogenemia contribute to this atherogenic lipid profile. Testosterone decreases lipoprotein lipase activity in abdominal fat cells, and insulin resistance impairs the ability of insulin to exert its antilipolytic effects.[43] Cardiovascular risk factors are usually present even in younger age and this suggests that the chronic disturbances in hormonal and metabolic status typical for the syndrome predispose the patients to development of early atherosclerosis and premature clinical presentation of cardiovascular disease.[44]

Clinical features:[4] The patient complains of increasing **obesity** (abdominal), **menstrual abnormalities** in the form of **oligomenorrhoea, amenorrhoea** or **DUB** and **infertility.** There may be **hirsutism** and **acne.Virilism** is a rare complaint. The patient may not always be obese.

1. Acanthosisnigricans -[4] is characterized by specific skin changes due to insulin resistance. The skin is thickened and pigmented. Commonly affected sites are nape of the neck, inner thighs and axilla.

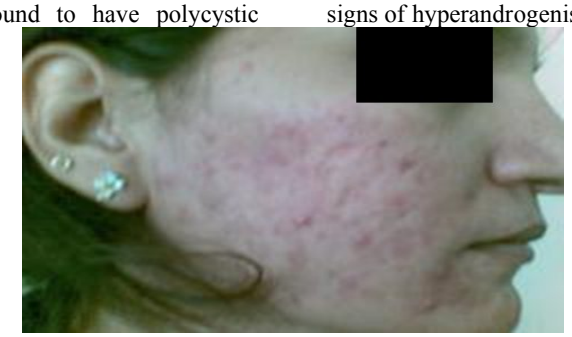






PCOS with exaggerated Hirsutism

Infertility affects 40% of women with PCOS. PCOS is the most common cause of **anovulatory infertility.** Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS.[51]Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased. However, due to derangements in factors involved in normal follicular development, follicular growth becomes arrested as follicles reach a diameter of 4–8 mm. Because a dominant follicle does not develop, ovulation does not ensue.[52]In addition, **spontaneous abortion** occurs more frequently in PCOS with incidences ranging from 42%–73%.[53] Over 90% of normally menstruating women with hirsutism are identified through ultrasound to have polycystic ovaries.In addition, PCOS occurs in 50% of women with less severe distribution of **unwanted hair growth.[54] Acne** can also be a marker of hyperandrogenism but is less prevalent in PCOS and less specific than hirsutism. Approximately 15%–30% of adult women with PCOS present with acne.The difference in prevalence of hirsutism and acne may be attributed to the difference in expression of 5α-reductase in the sebaceous gland and the hair follicle, and resulting higher dihydrotes-tosterone in the hair follicle. Of those women presenting with severe acne, over 40% were diagnosed with PCOS.Some experts recommend that women presenting with acne be asked about their menstrual history and be evaluated for other signs of hyperandrogenism.[55]



PCOS with Severe acne

Diagnosis: Diagnostic criteria for PCOS have been offered by three groups: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD);[56] the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM);[57] While there are certain consistencies between the criteria offered by the different groups, important differences exist. Each issuing group considers PCOS a diagnosis of exclusion, and other diagnoses, such as congenital adrenal hyperplasia, nonclassic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders must be excluded. Because 20%–30% of otherwise normal women have evidence of multiple cysts on their ovaries,the presence of polycystic ovaries (PCO) alone was not considered sufficient by any group. The NIH/NICHD and the Androgen Excess Society require that patients have signs or symptoms of hyperandrogenism such as hirsutism, or hyperandrogenemia, defined as elevated free testosterone, reduced SHBG (sex hormone-binding globulin), elevated free testosterone index, or elevated dehydroepiandrosterone sulfate.[56-58] However, ESHRE/ASRM (Rotterdam) criteria allows for the diagnosis of PCOS without the presence of hyperandrogenemia or clinical hyperandrogenism. Women with ovulatory dysfunc-tion and the presence of polycystic ovaries are considered to have PCOS by the Rotterdam criteria. Another key difference between the criteria is how oligomenorrhea or amenorrhea is viewed. The Rotterdam criteria did not require irregular menses or ovulatory dysfunction for diagnosis citing that women with regular menstrual cycles could be considered to have PCOS in the presence of PCO

and hyperandrogenemia or hyperandrogenism. Subclinical ovulatory dysfunction can occur in women with regular menstrual bleeding. However, NIH/NICHD excludes the diagnosis of PCOS in women with regular menses and subclinical ovulatory dysfunction.

According to **European Society for Human Reproduction and embryology (ESHRE)** and **American Society for Reproductive Medicine (ASRM)(ASRM/ESHRE, 2003);** presence of any 2 of the following 3 criteria can be used for diagnosis:[53-59]

(a) Polycystic ovaries on ultrasound scan;

NIH/NICHD 199218	ESHRE/ASRM (Rotterdam criteria) 200419	Androgen Excess Society 200620
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation	• Ovarian dysfunction and/or polycystic ovaries
	• Polycystic ovaries	

Abbreviations: ESHRE/ASRM, EuropeanSociety for Human Reproduction and Embryology/American Society for Reproductive Medicine; NIH/NICH, National Institutes of Health/National Institute of Child Health and Human Disease.

Table 1 Criteria for the diagnosis of polycystic ovary syndrome[59]

(b) Oligo and/or anovulation; and

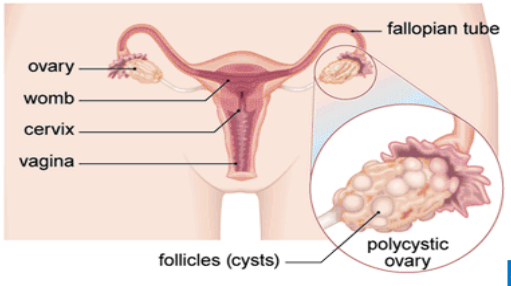
(c) Clinical or biochemical evidence of hyperandrogenism, provided other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome) have been excluded.

The diagnosis of PCOS using the Rotterdam and AES criteria depends on the use of a reliable method to describe polycystic ovarian morphology. The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group includes the presence of 12 or more follicles measuring between 2 and 9 mm in diameter and/or an increased ovarian volume of greater than 10 cm3. This presentation in one ovary sufficiently defines the polycystic ovary.[55]However, since that time, significant advancements in ultrasound image technology have been made, improving resolution and allowing for the detection of smaller follicles.[60]This has prompted calls for revisiting the criteria used to define polycystic ovarian morphology.[61]Also the presence of 12 or more follicles in each ovary, measuring 2 - 9 mm in diameter and or increase ovarian volume (>10 ml) is considered as morphological diagnostic criteria based on ultrasonography.

It is known that in PCOS individual's serum levels of insulin may be elevated. Around 40% of females with PCOS have some degree of glucose intolerance. So, blood glucose level testing for diabetes is usually recommended.[62]

Investigations: Ultrasound measurement of ovarian stroma is useful in predicting hyperandrogenism severity and cardiovascular risk in women affected by PCOS. In particular, the ratio between stroma and total ovarian area is associated with higher androgen serum levels, thus improving the diagnostic accuracy of PCOS, whereas the stroma itself is related to the intima-media thickness of common carotid artery and the plasma levels of important prothrombotic factors such as PAI-1

1. Sonography –[4]Transvaginal sonography is especially useful in obese patient. Ovaries are enlarged in volume (≥ 10 cm3). Increased number (> 12) of peripherally arranged cysts (2-9 mm) are seen.

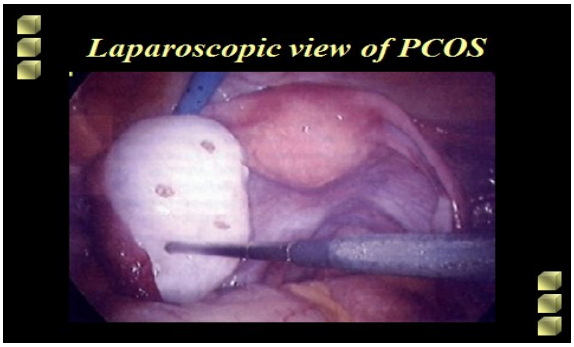


An ovary affected by polycystic ovary syndrome

2. Serum values:[4]

- LH level is elevated and/or the ratio LH: FSH is > 3:1.
- Raised level of oestradiol and oestrone – the oestrone level is markedly elevated.
- SHBG level is reduced.
- Androstenedione is elevated.
- Raised serum testosterone (> 150 ng/dl) and DHEA-S may be marginally elevated.
- Insulin resistance (IR): Raised fasting insulin levels > 25µ IU/ml at 2 hours postglucose (75 gm) load, suggests IR.

3. Laproscopy –[4]Bilateral polycystic ovaries are characteristic of PCOS.



Management of PCOS needs - individualization of the patient. It depends on her presenting symptoms like menstrual disorder, infertility, obesity, hirsutism or combined symptoms. Patient counseling is important.[4]

Treatment of PCOS is mainly aimed at lowering insulin resistance levels, restoration of fertility & regular menstruation, treatment of hirsutism/acne & prevention of endometrial hyperplasia & endometrial cancer though the optimal treatment is still doubtful.[63,64]

Studies have shown that anti-diabetic medications like, metformin, etc., have shown encouraging results, particularly in obese patients who are suffering from chronic anovulation.India having the highest rates of diabetes in the world with an increasing trend towards obesity in this modern era is expected to have a high prevalence of PCOS in the next few years.

Treatment is primarily targeted to correct the biochemical abnormalities associated with PCOS;[4]

- Hyperandrogenism
- Hypersecrection of LH
- High serum oestrogens (Oestradiol, oestrogen)
- Androgenic follicular microenvironment
- Hyperinsulinaemia
- Hyperprolactinaemia
- Low FSH
- Low serum SHBG
- Low serum progesterone
- Hyperlipidaemia

Weight reduction; is the 1st line treatment in obese patients. BMI < 25 improves menstrual abnormalities, hirsutism and infertility. It reduces insulin and androgen levels.[4] In India, nowadays the adolescents & teenagers are more attracted towards the western food habits. The intake exceeds the burning of calories, thus resulting in the accumulation of fats in the adipose tissue.[65]

Obesity, sedentary life style with inadequate physical activity, stress, junk food consumption are thought to be contributing factors in addition to genetic origin. In recent years many of the girls and women are suffering from PCOS because of wrong eating habits, stressful living conditions and lack of physical activity.[66]

Weight loss has been the major recommendation by physicians for women with PCOS. Lifestyle modifications including stress reduction, moderate exercise, and group support, along with a decrease in total calorie intake and avoiding junk food consumption have had positive results. A decrease of only 5% of total body weight is associated with decreased insulin levels, increased fertility, reduced hirsutism and acne and lower testosterone levels. Whole grains, fruits and vegetables with foods containing protein and natural fat along with vitamins and minerals are beneficial.[3] There is in general agreement that, obese women with PCOS are insulin resistant. There are some long term health complications of PCOS like, those with hyper-insulinemia are at a greater risk of developing type-II diabetes & gestational diabetes, hyperandrogenic individuals are more prone towards developing arterial diseases, etc.,[67] For a PCOS patient, it is always advised to have a proper diet rich in fibers, vitamins & a low glycemic index (GI) diet in which a significant part of total carbohydrates are obtained from fruit, vegetables & whole grain sources.[68] It is well known that Vitamin D deficiency may play a significant role in exacerbating PCOS & so, vitamin D supplementation is found to be effective in the management of this syndrome.[69] As we all know, regular exercise is required to keep us healthy, it has been seen that, low-carbohydrate diets& sustained regular exercise may help practically to improve every parameter of PCOS, e.g., in obese, an

ovulating PCOS women, weight loss restores ovulation & pregnancy rates.[70]

A. Fertility not concerned –[4]In case of, **Androgen excess –**

- Combined oral contraceptive pills are effective. Progestin suppresses LH and oestrogen improves SHBG, reducing free testosterone level. **Norgestrel** containing pill is avoided because of its high androgenicity.
- **Newer progestins (Desogestrel 0.15 mg – Ethinyloestradiol)** are best suited.
- **GnRH Agonists** –Leuprolide acetate 3.75 mg IM or Goserelin 3.6 mg SC every 4 weeks can be used to suppress ovarian steroid production.
- **Cyproterone acetate, Spironolactone, Ketoconazole, Flutamide, Finasteride** are the other **antiandrogens** that can be used for the management of **Hirsutism.**
- Hyperinsulinaemia is treated to reduce the risks of cardiovascular diseases and DM.
- Endometrium should be protected against the unopposed effects of oestrogen.

B. Patient wanting pregnancy:[4]

1. Ovulation induction; is usually achieved by **Clomiphere citrate** with or without **Dexamethasone** or **Bromocriptine.** In unresponsive cases pure **FSH** or **HMG** along with **hCG**may be administered backed up with monitoring facilities.

2. Insulin sensitisers: Women with PCOS and hyperinsulinaemia with BMI > 25, ovulate satisfactorily when **Clomiphene** is combined with **Metformin** 500 mg 3-times/day is found to correct the biochemical abnormalities (Hyperinsulinaemia and Hyperandrogenism). Pioglitazone and Rosiglitazone are also being used in cases resistant to metformin.

Metformin administration in anovulatory patients with PCOS exerts a differential action on the ovarian AMH levels on the basis of ovulatory response. Changes in AMH levels in antral follicular fluid during metformin treatment could be involved in the local mechanisms mediating the ovulatory restoration.[71]

3. Surgery:[4] is the alternative procedure for PCOS who are resistant to medical therapy. **Endoscopic cauterisation** or **CO2 laser vapourisation** of multiple cysts has replaced the **conventional wedge resection** of the ovaries. Pregnancy rates following ovarian diathermy are higher. The health impact of infertility has resulted in aggravation of medical, social, psychological and economic burdens in developing countries.[72] Stress of infertility disturbs wellness of a couple in general and women in particular, resulting in emotional instability, distress and anxiety that may end up in depression. The resolution to the issue is provided by "Assisted reproductive clinics" where a number of treatment procedures are offered for the above.[73] Intra Cytoplasmic Sperm Injection (ICSI) is one of the advanced techniques conceded after down regulation of ovaries, Controlled Ovarian Stimulation (COS), Oocyte Pick Up (OPU) and micro injection of spermatozoa followed by Embryo Transfer (ET).[74]

CONCLUSION

Proper diagnosis and management of PCOS is essential as PCOS has many potential metabolic and cardiovascular risks if not managed appropriately.[75]It is clear that eventhough the underlying pathophysiology of PCOS is not fully understood, as a result, treatment is often focused on individual symptoms, not the syndrome itself. However, as the understanding of the pathophysiology of PCOS improves, so does the treatment. Although the treatment is individualized, it should also focus on all metabolic consequences and decreasing future complications.[76]More extensive research and understanding of the pathophysiology of PCOS will improve treatment success and overall management of patients.[77]

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