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Review Article

OBESITY & PCOS

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ABSTRACTS

Polycystic ovarian syndrome (PCOS) begin at puberty overall (5-10%) women is affected. PCOS is a sign, not a diagnosis which was named by Stean –leventhal in 1935 according to Rotterdam in 2003, the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology agreed that two of the following criteria must be met once other endocrinopathies have been ruled out (i.e., Cushing disease, adrenal hyperplasia or adrenal tumors).[CITATION 1 \l 1033]

- Oligoamenorrhea
- Clinical and or biochemical evidence for hyperandrogenemia
- Polycystic-appearing ovaries on ultrasound[CITATION 2 \l 1033][CITATION 3 \l 1033] [CITATION 4 \l 1033]

The polycystic ovary may result from a virilizing ovarian or adrenal neoplasm or from congenital adrenal hyperplasia, or it may result from suboptimal hypothalamic-pituitary function at puberty. The exact mechanism for the development of ovulatory failure has been attributed to androgen overproduction and its effect on the hypothalamic-pituitary ovarian axis. Stein and Leventhal, during the period 1902 to 1935, noted that a group of women had evidence for what is currently called polycystic ovaries at the time of laparotomy. Specifically, in 1935, Stein and Leventhal reported seven patients with the hallmarks of PCOS.[CITATION 5 \l 1033][CITATION 6 \l 1033]

Key Words: PCOS

INTRODUCTION

Polycystic ovarian disease is a heterogeneous, multisystem endocrinopathy in women of reproductive age with the ovarian expression of various metabolic disturbances and a wide spectrum of clinical features such as obesity, menstrual abnormalities and hyperandrogenism. This disease was discovered by and named as Stein-Leventhal syndrome in 1935.By far the most common, although the least understood, cause of androgen excess is polycystic ovary syndrome (PCOS), accounting for a vast majority of patients seen. PCOS affects 5 to 10 % of women, the full blown syndrome of hyperandrogenism, chronic an ovulation and polycystic ovaries. Approximately 75 % of anovulatory women of any cause have polycystic ovaries and 20 to 25 % of women with normal ovulation demonstrate ultrasound findings typical of polycystic ovaries**.**

[CITATION 7 \l 1033]

Since there are so many clinical and biochemical features in PCOS, the exact definition of PCOS can be confusing. At the 2003, joint European society of human reproduction and Embryology/American Society for reproductive medicine (ESHRE/ASRM) consensus meeting (Rotterdam criteria), a Refined definition of PCOS was agreed: namely the Presence of two out of following the 3 criteria:

1. Oligomenorrhoea and/or an ovulation
2. Hyperandrogenism (clinical and/or biochemical)
3. Polycystic ovaries, with the exclusion of other etiologies (adrenal gland)[CITATION 8 \l 1033][CITATION 9 \l 1033]

Current incidence of PCOS (5-10 %) is fast increasing lately due to change in the lifestyle and stress. It is also becoming a common problem amongst adolescents, developing soon after puberty. Amongst infertile women, about 20% is attributed to an ovulation caused by PCOS. Some of the women who develop cardiovascular disease, hypertension, and endometrial cancer and type 2 diabetes later in life appear to have suffered from PCOS in earlier years.

HISTOPATHOLOGY:

Histological:

There is thickening of tunica albuginea,the cysts are follicles at varying stages of maturation and atresia and theca cell hypertrophy (stromal hyperthecosis).the patient present with features of diabetes type 2 (insulin resistance).

Macroscopically: ovaries in women with PCOS are in enlarged 2to 5 times the normal size.overian volume is increased >10cm3 .stroma is increased with capsule is thickened and pearly white, thickened cortex with multiple more than 12 cysts measuring about 2- 9 mm in diameter.

Microscopically: the cortex is fibrotic and hypo cellular and contain prominent blood vessels .to small atretic

follicles ,there is an increase in the number of follicles with luteinsed theca interna.the stroma may contain luteinised stromal.**[CITATION 10 \l 1033][CITATION 11 \l 1033]**

PATHOPHYSIOLOGY:

Exact path physiology of the polycystic ovary syndrome (PCOS) is clear inspite of that, encompasses inherent ovarian dysfunction that is strongly influenced by external factors, such as disturbances of the hypothalamic-pituitary-ovarian axis and hyperinsulinaemia. Exaggerated gonadotrophin releasing hormone (GnRH) pulsatility results in hyper secretion of luteinizing hormone (LH), which has effects both on ovarian[CITATION 2 \l 1033] androgen production and oocyte development. Disturbed ovarian-pituitary and hypothalamic feedback accentuates the 0gonadotrophin abnormalities. Hyperinsulinaemia is secondary both to insulin resistance at the periphery and to abnormal pancreatic beta cell function. PCOS runs in families and a number of genetic abnormalities appear to result in features of the syndrome and account for the heterogeneity of the symptoms. Environmental influences, such as nutrition and lifestyle, further influence expression of the syndrome.[CITATION 10 \l 1033][CITATION 11 \l 1033] [CITATION 12 \l 1033]

CLINICAL EVALUATION:

Young women of reproductive age most frequently seek attention initially because of irregular menses, hirsutism, or infertility, but PCOS has a long prodrome with detectable abnormalities throughout the life cycle of affected women. The earliest manifestations of PCOS are discernible in the per pubertal years.Ovarian hyperandrogenism and insulin resistance develop with increased frequency in adolescent girls who have premature pubarche. In the early reproductive period, chronic anovulation results in reduced rates of conception. When pregnancy is achieved, it frequently terminates in spontaneous, first-trimester loss or is associated with gestational diabetes. Approximately 25 to 30 % of these women show impaired glucose tolerance by the age of 30, and 8 % of women with PCOS develop frank type 2 diabetes mellitus annually. [CITATION 13 \l 1033][CITATION 14 \l 1033]

Markers of premature coronary artery and cerebrovascular disease are prevalent. Women with polycystic ovaries are seen to have more extensive coronary artery disease by angiography. In two case-control studies, women in their 40s had greater intima-medial thickness of the carotid vessels, and more atherogenic lipid profiles: increased total and low-density lipoprotein (LDL) cholesterol and triglyceride levels, and decreased high-density lipoprotein (HDL) cholesterol levels. These metabolic abnormalities are compounded by the prevalence of obesity, which occurs in more than 65 % of women with PCOS. Abnormal androgen production declines as menopause approaches (as it does in women without PCOS), and menstrual patterns somewhat normalize. However, in retrospective cohort studies, perimenopausal and postmenopausal women with a history of PCOS had increased rates of type 2 diabetes, hypertension, and coronary artery disease compared with control patients. PCOS appears to follow a familial distribution; 40 %

of the sisters and 20 % of the mothers of affected women also have the syndrome to varying degrees.[CITATION 14 \l 1033][CITATION 15 \l 1033] [CITATION 16 \l 1033]

CLINICAL FEATURE:

In many women the symptoms are easily recognizable, but ethnicity influences the extent of symptoms, especially with regard to hirsutism and obesity. Therefore, taking a diligent history with regard to menstrual patterns is crucial to help establish the diagnosis. The National Institute of Child Health and Development held a consensus meeting to develop the following diagnostic criteria for PCOS

- clinical or biochemical evidence of hyperandrogenism
- oligo-ovulation;
- Exclusion of other known disorders, such as congenital adrenal hyperplasia or hyperprolactinemia.[CITATION 4 \l 1033][CITATION 14 \l 1033][CITATION 15 \l 1033] [CITATION 17 \l 1033]

HYPERANDROGENISM:

The wide spectrum of manifestations ranges from mild acne and increased terminal (coarse) hair growth in midline structures (face, neck, abdomen), to android changes in body habitus, with waist-to-hip ratios of more than 1. Variations are influenced by ethnicity, as well as coexisting conditions (such as hyperthyroidism) that alter androgen biosynthesis. For example, Asian women with PCOS are rarely hirsute, but hirsutism is a frequent finding in black women with PCOS. Yet the actual incidences of hyperandrogenemia and insulin resistance do not show a racial predilection.[CITATION 15 \l 1033][CITATION 17 \l 1033][CITATION 18 \l 1033]

In addition, no hirsute women with oligo-ovulation may have laboratory evidence of hyperandrogenism. Frank or rapid “virilization” involving clitoromegaly, vocal cord thickening, or male-pattern baldness is rare in patients with PCOS and, when present, suggests another cause of hyperandrogenism, such as adrenal disorders or androgen-producing tumors.

OLIGO-OVULATION:

Oligo-ovulation manifests as menstrual irregularity and occurs in 70 % of women with PCOS. Among women with more regular menses, many have variable degrees of ovulatory dysfunction. Often the menstrual formula (i.e., 3 to 5 days of menstrual flow every 28 to 35 days) occurs for the first one to two years after menarche (which occurs at the normal age), but menses then become less frequent, occurring every 45 to 365 days. Because the estrogen from ovarian and adipose tissues stimulates proliferation of endometrial that is not stabilized by post-adulatory progesterone, bleeding can be unpredictable, heavy, and prolonged. Chronic endometrial proliferation can result in carcinoma.[CITATION 14 \l 1033][CITATION 17 \l 1033] [CITATION 19 \l 1033]

SYMPTOMS WITH VARIABLE FREQUENCY:

Obesity:

More than 65 % of women with PCOS have a body mass index exceeding 27. The fat distribution often is abdominal/visceral, similar to that frequently associated with metabolic abnormalities (e.g., hypertension, dyslipidemia, insulin resistance, glucose intolerance). Most women deny childhood obesity and describe normal weight until after menarche. Significant weight gain appears in the mid-teens and accelerates in the later teens and early 20s.

The presence of obesity also is influenced by ethnicity. It is most common in Hispanic, black, and white women, less striking in women of Mediterranean descent, and rare in Asian women. Obesity is likely to facilitate the metabolic abnormalities of PCOS, as evidenced by the reduction in insulin resistance and restoration of cyclic menses following weight loss. A 1982 study, which has been confirmed by later research, showed that a 10 to 15 % weight reduction resulted in spontaneous conception in more than 75 % of obese patients with PCOS.

Acanthosis Nigricans:

These velvety, raised skin deposits in intertriginous areas are associated with insulin resistance and result from insulin stimulation of the basal layers of the epidermis. When found in conjunction with hyperandrogenism, the condition is termed HAIR-AN syndrome (hyper androgenic-insulin resistant–acanthosis nigricans); it occurs in 2 to 5 % of hirsute women. The majority of women with PCOS (70%) are insulin resistant, but hyperinsulinemia is far more severe in women with HAIR- AN syndrome.

Polycystic ovaries:

Ovaries with multiple, small (less than 10 mm) follicular cysts surrounding the ovarian stroma are found in 16 to 25 % of normal women and in female patients with amenorrhea caused by other etiologies. Nearly 80 % of women with hyperandrogenism have polycystic ovaries, but these may not be present at the time of evaluation in women who have used oral contraceptive pills (OCPs), insulin-sensitizing agents, or other forms of ovarian suppression. Therefore, the presence of polycystic ovaries on ultrasonography is not a diagnostic essential.[CITATION 16 \l 1033][CITATION 17 \l 1033][CITATION 19 \l 1033][CITATION 20 \l 1033]

DIAGNOSIS /INVESTIGATION

A. Laboratory Investigation:

1. Serum value-LH level is elevated and /or the ratio LH:FSH is >3:1 (raised level of the oestradiol and oestrone. The estrone level is markedly elevated and SGBG level is reduced
2. Raised serum testosterone >150 ng/dl and DHES-Smay be marginally elevated. Insulin resistance IR; raised insulin levels >25uIU/ml and level of serum insulin response >300Uiu/ml at 2 hours post

glucose 75gm load suggests IR.[CITATION 3 \l 1033] [CITATION 14 \l 1033][CITATION 21 \l 1033]

Test	Normal value	Purpose
β-hCG	< 5 mIU per mL (< 5 IU per L)	Exclude pregnancy
TSH	0.5 to 4.5 μU per mL (0.5 to 4.5 mU per L)	Exclude thyroid dysfunction
Prolactin	< 20 ng per mL (< 20 μ g per L)	Exclude hyperprolactinemia
Testosterone (total)	< 20 ng per dL (< 0.7 nmol per L)	Exclude androgensecreting neoplasm
Testosterone (free)	20 to 30 years—0.06 to 2.57 pg per mL (0.20 to 8.90 pmol per L) 40 to 59 years—0.4 to 2.03 pg per mL (1.40 to 7.00 pmol per L)	Establish diagnosis or monitor therapy
DHEAS	600 to 3,400 ng per mL (1.6 to 9.2 μmol per L)	Exclude androgensecreting neoplasm
Androstenedione	0.4 to 2.7 ng per mL (1.4 to 9.4 nmol per L)	Establish diagnosis
17 α-Hydroxyprogesterone	Follicular phase < 2 μg per L (6.1 nmol per L)	Exclude NCAH
Fasting insulin	< 20 μU per mL (< 144 pmol per L)	Exclude Hyperinsulinemia
Fasting glucose	65 to 119 mg per dL (3.6 to 6.6 mmol per L)	Exclude type 2 diabetes or glucose intolerance
Fasting glucose: insulin Ratio	@ 4.5	Exclude insulin resistance
Cholesterol (total)	150 to 200 mg per dL (1.5 to 2 g per L)	Monitor lifestyle changes
HDL cholesterol	35 to 85 mg per dL (0.9 to 2.2 mmol per L)	Monitor lifestyle changes
LDL cholesterol	80 to 130 mg per dL (2.1 to 3.4 mmol per L)	Monitor lifestyle changes
Pelvic ultrasonography		Monitor lifestyle changes
Endometrial biopsy	Negative for hyperplasia/malignancy	Exclude malignancy or hyperplasia

Table 1: Table of several hormonal reference values regarding PCOS test

NOTE: Diagnosis of PCOS established by exclusion of other causes of oligomenorrhea or hyperandrogenism. Other tests may be of benefit in monitoring therapy.**PCOS** = polycystic ovary syndrome; **β-hCG** = beta subunit human chorionic gonadotropin; **TSH** = thyroidstimulating hormone; **DHEAS** = dehydroepiandrosterone sulfate; **NCAH** = nonclassic adrenal hyperplasia; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein.**SHBG** =sex hormonal binding globulin

B. SONOGRAPHY:

Transvaginal /abdominally sonography is especially useful in obese patient. Ovaries are enlarged in volume >10 cm3, increased number > 12 of peripherally cysts 2-9 mm

C. LAPARASCOPY:

Bilateral polycystic ovaries are characteristic of PCOS

TREATMENT:

The purpose of treatment is:

1) to cure a woman with menstrual disorders
2) to treat hirsutism
3) to treat infertility
4) to prevent long-term effects of X syndrome in later life.

The treatment therefore is catered to the requirement of the woman.

Weight loss: Weight loss of more than 5% of previous weight alone is beneficial in mild hirsutism and it restores the hormonal milieu considerably.

Lifestyle: Cigarette smoking should be abandoned. It lowers E2 level and raises DHEA and androgen level.

Hormones to control menstruation are

- Oral combined pills (OC)
- OC and cyproterone acetate

Oestrogen suppresses androgens and adrenal hormones (DHEA). It raises the secretion of SHBG in the liver, which binds with testosterone, thus reduces free testosterone. It also suppresses LH. It is best given as low-dose combined pills, having progestogen with lesser androgenic effect. The Fourth generation of combined pills which contains 30 µg E2 and 2-3 mg drospirenone (progestogen with anti-androgenic action) is best for PCOS (Yasmin, Janya, Tarana). It helps to reduce acne and further development of hirsutism. Progestogen may be required to induce menstruation in amenorrhoeic woman prior to initiating hormonal cyclical therapy. OC with cyproterone is prescribed if the woman has hirsutism.

Hirsutism: Anti-androgens is used in idiopathic hirsutism or hyper-androgenic stat

Cyproterone acetate: it inhibits gonadotrophin secretion and interferes with androgen action on the target organs by competing for the androgen receptors. It blocks the action of DHT & T at both the nucleus and cytosol receptor level

Spironolecstone: it is an aldosterone antagonist and acts as a potassium sparing diuretic as well as Anti-androgen effects

- it inhibits ovarian and adrenal androgen biosynthesis
- it competes for the androgen receptors in the hair follicles
- It inhibits 5 α – reductase activity directly

Flutamide: it is a non steroidal anti-androgen.it blocks the androgen receptors as well as its inhibits tetosterone biosynthesis.

Finasteride: it inhibits 5α-reductase activity

Ketoconazole: inhibits the enzyme for androgen synthesis

Cosmetic Treatment:

Removal of hair: the excess hair is to be removed by bleaching, twitching, epilation, waxing, lasers, shaaving or electrolysis .in electrolysis individual hair follicle is destroyed .side effects are pain, scarring and pigmentation.[CITATION 20 \l 1033]

Acne: can be managed by **Clindamycin** lotion 1 % or **Erythromycin** gel 2% if pustules form. For severe acne, isotretinoin is used, but it is teratogenic and pregnancy should be avoided while on this medication. The drugs take 3-6 months before the effect on hirsutism is noted.

Dexamethasone (0.5 mg) at bedtime reduces androgen production, and is used in some infertile women with clomiphene.

Infertility: (1) Clomiphene is the first line of treatment if PCOS woman is to be treated (2)Cyproterone acetate it inhibits gonadotrophin secretion and interferes with androgen action on the target organs by competing for the androgen receptors. It blocks the action of DHT & T at both the nucleus and cyrtosol receptor level. Induces ovulation in 80% and 40-50% conceives, but 25-40% abortion rate is caused by corpus luteal phase defect. Hyper stimulation occurs in 1 0% cases. Clomiphene with dexamethasone improves fertility rate. In a resistant case (3) Tamoxifen 20-40 mg daily for 5 days or off-label(4) Letrozole (2.5 mg daily for 5 days or 20 mg single dose on day3) should be tried. Failure to above therapy calls for FSH, LH or GnRH analogues. A woman with insulin resistance requires metformin in addition. This woman also shows raised level of homocysteine in which case *N*-acetyl-cysteine 1 .2 g may be added to clomiphene therapy. *N*-acetyl-cysteine (NAC) is a mucolytic drug and insulin-sensitizer (5) Metformin treats the root cause of PCOS, rectifies endocrine and metabolic functions, and improves fertility rate, and is used as insulin sensitizer. It reduces insulin level, delays glucose absorption and liver production of glucose (liver neoglycolysis). It also improves peripheral utilization of glucose. Liver function tests should be performed prior to metformin administration. Besides reducing the level of insulin, metformin also reduces the level of

total and free testosterone and increases the sex hormone binding globulin. Ovulation occurs in 70 - 80%, and pregnancy in 30-40%. It does not cause hypoglycemia and does not reduce weight. It is contraindicated in hepatic and renal disease. It causes gastrointestinal disturbances and lactic acidosis. Starting with 500 mg daily, the dose is gradually increased to 500 mg three times a day. One gram tablet is also available to be taken once at night time (Riomet 1 g). If metformin is contraindicated, acarbose 300 mg daily can replace it. Octequitide is a peptide hormone secreted by hypothalamus which inhibits growth hormone and insulin. It enhances ovulation in clomiphene-resistant infertility. It is important to inform the patient that PCOD can recur. Any form of treatment is likely to give temporary relief and maybe required to be repeated and varied at various times during her reproductive years. This will also ensure that in the long term diabetes and endometrial cancer do not develop.

Surgery:

Surgery is reserved for those in whom:

1) Medical therapy fails
2) Hyper stimulation occurs
3) Infertile women
4) Previous pregnancy losses.

Surgery comprises laparoscopic drilling or puncture of not more than four cysts in each ovary either by laser or by unipolar electrocautery. Surgery restores endocrine milieu and improves fertility for a year or so. Thereafter, pelvic adhesions caused by surgery may again reduce fertility rate. Hydro floatation reduces adhesion formation.[CITATION 17 \l 1033][CITATION 18 \l 1033][CITATION 19 \l 1033][CITATION 20 \l 1033][CITATION 22 \l 1033] [CITATION 23 \l 1033][CITATION 24 \l 1033]

LIFE MODIFICATION:

The most successful but difficult therapy to “administer” is weight loss. Weight loss is most successful because it brings about the greatest global improvement in cardiovascular risks, insulin sensitivity, and menstrual patterns; it is most difficult because of the compliance issue. Weight loss should not be rapid or drastic but should be achieved through consistent lifestyle modification that includes gentle exercise, intake of dietary carbohydrates with a low glycemic index, and a reduced intake of fats and simple sugars. Severe dietary deprivation is uniformly unsuccessful. No single food plan is recommended, but frequent feedings (four to six times per day) are important to avoid hypoglycemia and hunger. Hypoglycemia leads to cravings and poor food choices that, in turn, result in simple sugar intake and reactive hyperinsulinemia. In the experience of the author, most women respond well to the admonition to eat more food more frequently to lose weight. In addition to the metabolic improvements, successful weight loss has the benefit of improving body image, reducing depression, and restoring a sense of control. Programs that have targeted this issue

alone have achieved pregnancy rates as high as 60 % without medical intervention. There are no data to support the use of lipid-lowering drugs in women younger than 40 years, but dietary regulation should be encouraged. Family physicians should monitor blood pressure elevations and smoking cessation for further cardiovascular protection. Knowledge gained over the past 60 years has carried PCOS beyond the realm of gynecology and infertility, and warrants heightened attention from physicians who will focus on the functional abnormalities that have serious long-term consequences. It is important to recognize that PCOS is an entity with a long lifespan, requiring "control" rather than "cure," and that therapies will change with the stage of life that why, life modification plays an important role in controlling it.

CONCLUSION

PCOS is a multi-factorial hormonal related disease which is the constellation of anovulation, oligomenorrhoea, hirsutism, obesity and enlarged polycystic ovaries. The patient with PCOS have anovulation in common but can have any or all of the other findings .chronic anovulation (ovary) adrenal cortex both releases androgen, that converted peripherally in the adipose tissues into estrone, further the increase amount androgens leads to a decrease in the production of sex hormone binding globulin (SHBG) resulting higher levels of free estrogen and androgens. The hyper estrogenic levels lead to an increased LH: FSH ratio, untypical follicular developed anovulation and increased androgen production leading to a cyclical prolongation of the diseases. Many patients with PCOD, who are hyprestrogenic and physically obese also develop insulin resistance and hyperinsulinemia and prone to diabetes mellitus type 2.

Treatment depends on the particular symptoms and desires of patients. If patient desiring for fertility then, ovulation induction (CC) clomiphene citrate should be used or if PCOS causes resist to ovulation and there is evidence of obesity then, the probability of ovulation can be increased by weight loss or combine use of corticosteroids. Likewise, in the patients with hyperinsulinemia and insulin resistance, metformin has been shown to increase spontaneous ovulation. For those who are not currently interested in infertility, either cyclic progesterone or Depot- provera should be used to decrease the risk of endometrial hyperplasia and endometrial cancer. In addition, obese patients should be strongly urged to lose weight and diet controli because this will decrease the risk of break the cycle of anovulation. Obviously, such patient is prone to type 2 diabetes mellitus so; such patient should undergo a screening test for DM 2.

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