



PATHOGENESIS AND MANAGEMENT OF POLY CYSTIC OVARIAN DISEASE: A REVIEW

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ABSTRACT

PCOS, an abbreviation for Polycystic Ovary Syndrome is the most common endocrine disorder in women reproductive age. Women diagnosed with PCOS exhibit multiple symptoms like irregular menstrual periods, acne, excessive hair on the body and the face, heavy periods, pelvic pain, infertility and patches of dark and thick skin. The criteria for the diagnosis of PCOS, stated that presence of any two of the following three conditions are present, Excess androgen activity, Oligo-ovulation/anovulation, and Polycystic ovaries. Approximately 2-20 % women between the ages of 18 and 44 years are affected. Majority of women that have PCOS are either obese or have insulin resistance. The irregularity of menstrual periods, excess hair on the face and body, heavy menstrual periods, pelvic pain, acne, infertility and thick patches of dark and velvety skin are some of the most profound symptoms of PCOS. Other conditions that are linked with PCOS are obesity, obstructive sleep apnea, type II diabetes, mood disorders, heart disease and endometrial cancer. Obesity, lack of exercise and a family history of the condition are major risk factors leading to PCOS. Pelvic ultrasound, although is a major diagnostic means, apart from that GTT and other blood tests can also be performed. As of now, PCOS doesn't have a cure. Treatment is more of management and involves lifestyle changes like exercise and weight loss. Birth control pills and other hormone therapies can help as improvement in the regularity of periods, acne and excessive hair growth. Anti-androgens and metformin also help.

KEYWORDS: Cysts, Lifestyle, Obesity, PCOS, Rotterdam.

1. INTRODUCTION

PCOS, an abbreviation for Polycystic Ovary Syndrome is the most common endocrine disorder in women reproductive age.^[1] The characteristic cysts are responsible for the naming of the condition, that may develop on the ovaries, albeit it is a sign of the disease and not the underlying cause.^[2] Women diagnosed with PCOS exhibit multiple symptoms like irregular menstrual periods, acne, excessive hair on the body and the face, heavy periods, pelvic pain, infertility and patches of dark and thick skin.^[3] Primary characteristics include, but are not limited to; neuroendocrine disruption, anovulation, hyperandrogenism and insulin resistance.^[4] An international evidence review found that PCOS prevalence can be as high as 26 % among certain populations, although it ranges between 4-18 % in general populations reportedly.^[5] There are multiple names for the syndrome, such as polycystic ovary disease, polycystic ovarian syndrome, ovarian hyperthecosis, functional ovarian hyperandrogenism, sclerocystic ovary syndrome and stein-leventhal syndrome.^[3]

2. DEFINITION

PCOS is defined commonly by the use of the following two common definitions: NIH, 1990, and Rotterdam. In a consensus workshop that NIH/NICHD sponsored, it was suggested that a person can be said to have PCOS if they show all of the following symptoms^[3]:

- Clinical or biochemical signs of androgen excess,
- Oligo-ovulation, and
- Exclusion of other disorders that can cause hyperandrogenism and oligo-ovulation

Another consensus workshop conducted in 2003 by ESHRE/ASRM in Rotterdam revised the criteria for the diagnosis of PCOS, stating that the disease can be confirmed if two of the following three conditions are present^[6]:

- Excess androgen activity
- Oligo-ovulation/anovulation
- Polycystic ovaries

The Rotterdam definition covers more women as it is a wider one, especially those without excess androgen. It is acclaimed that obtained findings from studies of women

with excessive androgen cannot necessarily apply to those without androgen excess.^[7]

3. EPIDEMIOLOGY

Approximately 2-20 % women between the ages of 18 and 44 years are affected, depending on the definition.^[8] WHO estimates that 116 million women are affected by PCOS according to 2010 research, i.e., 3.4 % of all women.^[9] Another study conducted on women of reproductive age estimates a total of 7 % women being affected by the condition.^[10] Another study that used the Rotterdam criteria estimated 18 % women as having PCOS, of which 70 % were undiagnosed^[6]. India, reports a rate of 1 in 5 women having the condition. Racial differences were examined in a study that discovered notable racial differences in the risk factors for cardiovascular disease. Afro-American women were significantly obese and had significantly higher prevalence of the metabolic syndrome when compared with white women diagnosed with PCOS.^[11] Polycystic ovaries are observed in 14 % women on oral contraceptives. Cysts are a common side effect in IUDs that release levonorgestrel.^[12]

4. PATHOGENESIS

Polycystic ovaries are a developed condition that occurs when the ovaries receive stimulus to produce excessive amounts of androgenic hormones, especially testosterone by one or more of the following conditions^[13]: through high levels of insulin in the blood in women whose ovaries show sensitivity to the stimulus, known as hyperinsulinemia, and excessive release of the luteinizing hormone (LH), done by the anterior pituitary gland. Women diagnosed with PCOS show increased frequency of the GnRH pulses of the hypothalamus that results in the increase in ratio of LH/FSH.^[14]

Majority of women that have PCOS are either obese or have insulin resistance. The elevated levels of insulin result in abnormalities of the hypothalamic pituitary ovarian axis, leading to PCOS in turn. Hyperinsulinemia results in the increment of GnRH pulse frequency, increased ovarian production, decreased SHBG binding and decreased follicle maturation. Excessive insulin furthermore acts through the cognate receptor in presence of cAMP component signaling, upregulates the activity of 17 alpha hydroxylase via P13K, wherein the activity of 17 alpha hydroxylase is responsible for the synthesis of androgen precursors. An increased risk of PCOS is contributed to by the combined effects of hyperinsulinemia.^[15] Women of normal as well as higher than normal body weight commonly display insulin resistance.^[16]

Aromatase, an enzyme that converts androstenedione to estrone and testosterone to estradiol is possessed by adipose tissue. Thus, excessive adipose tissue in overweight women creates a paradoxical situation where androgens are in excess (resulting in virilization and hirsutism) along with higher levels of estrogens that

inhibits FSH by negative feedback mechanism.^[17]

Chronic inflammation is also linked with PCOS. Many investigators have correlated inflammatory mediators with anovulation and symptoms of PCOS.^[18] There seems to be a relation between PCOS and increased levels of oxidative stress in a similar manner.^[19] Previously, it was suggested that excessive production of androgen in PCOS could be because of the decreased level of a serum IGFBP-1 which would increase the level of free IGF-1 that would stimulate androgen production, however recent data refutes this mechanism.^[20] Association of PCOS has also been made to a specific FMR1 sub genotype. Research suggests that women with heterozygous or normal FMR1 exhibit polycystic like symptoms of follicle activity in excess and also hyperactive function of the ovaries.^[21]

5. SIGNS AND SYMPTOMS

The irregularity of menstrual periods, excess hair on the face and body, heavy menstrual periods, pelvic pain, acne, infertility and thick patches of dark and velvety skin are some of the most profound symptoms of PCOS. Other conditions that are linked with PCOS are obesity, obstructive sleep apnea, type II diabetes, mood disorders, heart disease and endometrial cancer^[3]. PCOS patients can exhibit the following signs and symptoms commonly^[6]:

- **Infertility:** It is usually a result of prolonged anovulation, i.e., lack of ovulation.
- **Menstrual disorders:** Among other types of menstrual disorders, oligomenorrhea (less than nine periods in a year) or amenorrhea (no menstrual periods for 3 consecutive months or more) are commonly seen.
- **Metabolic syndrome:** It is associated with central obesity and symptoms that link with insulin resistance, including food cravings and low energy levels. Homocysteine, insulin resistance and serum insulin levels are higher in patients of PCOS.^[16]
- **Hyperandrogenism:** Hyperandrogenism, or high levels of male hormones, shows symptoms like hirsutism (male pattern hair growth on body and face) and acne. However, it may also exhibit symptoms like hypermenorrhea (prolonged and heavy menstrual bleeding) and androgenic alopecia (hair loss and increased hair thinning) among others.^[22]

Associating obesity to PCOS indicates that 80 % women diagnosed with PCOS are obese, whereas only 20 % have a healthy weight, or are considered "lean"^[23]. Obese women that also have PCOS are at a higher risk of outcomes like hypertension, metabolic syndrome, insulin resistance and endometrial hyperplasia.^[24]

6. RELATED METABOLIC DISORDERS OF PCOS

Diagnosis of polycystic ovarian syndrome point towards an increased risk of the following conditions

- Type II diabetes/Insulin resistance: A published review of the year 2010 showed that women with PCOS have higher levels of insulin resistance as well as type II diabetes, while even controlling for BMI.^[25] PCOS thus results in a woman's risk of having type II diabetes being higher than that of those without PCOS.^[26]
- Endometrial hyperplasia: Along with endometrial cancer, it is possible due to increased accumulation of uterine lining due to non-shedding because of anovulation. Lack of progesterone also results in a stimulation of the uterine cells due to estrogen.^[26]
- Depression and anxiety can be factors too, due to hormonal imbalance as well as disease related stress that comes along with factors like infertility.^[27]
- Cardiovascular disease, particularly arterial disease can be at a higher risk of occurring at nearly 2-fold, using meta-analysis, for women with PCOS irrespective of the body mass index.^[28]
- Dyslipidemia, a group of disorders related to lipid metabolism, especially triglycerides and cholesterol is another condition related closely with PCOS. Women with PCOS show slow reduction of atherosclerosis, which includes remnants and the condition is independent of type II diabetes and insulin resistance.^[29]
- Gaining weight, fatty liver, strokes, sleep apnea, especially in obese patients, miscarriage & infertility.

7. CAUSES

PCOS is caused by numerous environmental and genetic factors^[30]. Obesity, lack of exercise and a family history of the condition are major risk factors leading to the development of the condition^[31]. The genetic variations may be inherited from father or mother and can be passed along to male offspring that can be asymptomatic carriers, or show symptoms like early baldness and/or excessive amounts of hair; and daughters who exhibit PCOS.^[32] The expression of the phenotype seems partially due to increased androgen levels secreted by the follicle theca cells of women with the concerned allele.^[33]

8. DIAGNOSIS

Pelvic ultrasound, although is a major diagnostic means, is not the sole one. According to the Rotterdam criteria^[34], 12 or more small follicles must be visible in the ultrasound examination. More research is suggestive that there must be more than 25 follicles in an ovary to determine it as a polycystic morphology in women between the ages of 18 and 35 years. The follicles can be placed along the periphery, rendering a shape of a string of pearls. In case of unavailability of a high-resolution transvaginal ultrasonography machine, ovarian volume of 10 ml or more is acceptable definition of polycystic ovarian morphology instead of the follicle count.^[35]

Levels of androgen in the blood serum including testosterone and androstenedione can be elevated. More

than 700-800 mcg/dL levels of Dehydroepiandrosterone sulphate are nearly confirmative of adrenal dysfunction.^[36] LH to FSH ratio, when measured in international units is elevated in PCOS affected women. Common cut offs to designate abnormally high ratios are 2:1 or 3:1 as tested on 3rd day of the menstrual cycle.^[37]

9. TREATMENT AND MANAGEMENT

As of now, PCOS doesn't have a cure. Treatment is more of management and involves lifestyle changes like exercise and weight loss.^[34] Birth control pills and other hormone therapies can help as improvement in the regularity of periods, acne and excessive hair growth. Anti-androgens and metformin also help. Hair removal techniques and typical acne treatments are also used and efforts to improve fertility include weight loss, clomiphene or metformin.^[38] Goals of the treatment can be understood under the four following categories:

- Restoration of fertility
- Lowering of levels of insulin resistance
- Treatment of acne/hirsutism
- Restoration of normal menstruation along with prevention of endometrial cancer or hyperplasia.^[39]

9.1 DIET

PCOS is associated with overweight or obesity; and successful weight loss is the most efficient method of restoration of normal menstruation and ovulation. Guidelines by the American Association of Clinical Endocrinologists recommend a goal of losing 5-15 % of one's body weight, thus improving hormonal disorders and insulin resistance.^[40] Insulin resistance can lead to increased cravings and hunger and lower levels of energy, making it difficult to lose weight on a normal diet designed for weight loss^[3]. Low GI diet with significant carbohydrate from whole grains, fruits and vegetables resulted in greater menstrual regularity as opposed to a macronutrient matched healthy diet.^[25]

9.2 MEDICATIONS

Metformin and oral contraceptives are medications used in the management of PCOS. Oral contraceptives increase SHBG production and the binding of free testosterone. This causes a reduction in the symptoms of hirsutism and regulates return to normal menstruation. Metformin is commonly used to treat insulin resistance in type II diabetes mellitus and helps treat insulin resistance in PCOS as well^[41]. Evidence from RCTs suggests that metformin may be better than placebo in terms of live birth. Metformin and clomiphene in combination are better than clomiphene alone and women in both cases may be more likely to experience side effects of the GI system, associated with metformin.^[42]

DISCUSSION

As humans approach puberty, both sexes start producing sex hormones that differentiate them from one another. Females release Progesterone, Estrogen, Follicle Stimulating Hormone, Gonadotropin Releasing Hormone and Luteinizing Hormone. A small amount of male

hormone is additionally present in females, called Androgen. When androgen levels in women rise to greater extents, it leads to PCOS, known as Polycystic Ovarian Syndrome. PCOS can be identified by any two among the three, Excess androgen activity, Oligo-ovulation/anovulation, Polycystic ovaries. Polycystic ovaries are a developed condition that occurs when the ovaries receive stimulus to produce excessive amounts of androgenic hormones, especially testosterone. Women diagnosed with PCOS show increased frequency of the GnRH pulses of the hypothalamus that results in the increase in ratio of LH/FSH. Majority of women that have PCOS are either obese or have insulin resistance. The irregularity of menstrual periods, excess hair on the face and body, heavy menstrual periods, pelvic pain, acne, infertility and thick patches of dark and velvety skin are some of the most profound symptoms of PCOS. Diagnosis of polycystic ovarian syndrome point towards an increased risk of the conditions like Type II diabetes/Insulin resistance, Endometrial hyperplasia, Depression and anxiety, Cardiovascular disease, particularly arterial disease, Dyslipidemia, Gaining weight, fatty liver, strokes, sleep apnea, miscarriage & infertility. Obesity, lack of exercise and a family history of the condition are major risk factors leading to the development of the disease. Pelvic ultrasound, levels of androgen in the blood serum including testosterone and androstenedione, and GTT can be used to determine PCOS.

CONCLUSION

PCOS doesn't have a cure. Treatment is more of management and involves lifestyle changes like exercise and weight loss. Goals of the treatment includes, restoration of fertility, lowering of levels of insulin resistance, treatment of acne/hirsutism, and restoration of normal menstruation along with prevention of endometrial cancer or hyperplasia.

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