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ETIOLOGY OF POLYCYSTIC OVARIAN SYNDROME

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Abstract

Polycystic ovarian syndrome is a heterogeneous multi system endocrinopathy in woman of reproductive age with ovarian expression of various metabolic disturbances and a wide spectrum of clinical features such as obesity, menstrual abnormalities and hyperandrogenism. It affects approximately 4 -12% of reproductive age women. Among infertile women, about 20% is attributed to anovulation caused by PCOS. The current definition of PCOS is based on the Rotterdam consensus workshop on PCOS in 2003.

Key words: Polycystic ovarian syndrome, insulin resistance, hyperandrogenism

Introduction

Polycystic ovarian syndrome is a heterogeneous multi system endocrinopathy in woman of reproductive age with ovarian expression of various metabolic disturbances and a wide spectrum of clinical features such as obesity, menstrual abnormalities and hyperandrogenism.[1] It affects approximately 4 -12% of reproductive age women. Among infertile women, about 20% is attributed to anovulation caused by PCOS.

It was originally described in 1935 by Stein and Levnethal as a syndrome manifested by amenorrhoea, hirsutism and obesity associated with enlarged poly cystic ovaries. This heterogeneous disorder is characterised by excessive androgen production by the ovaries mainly which interferes with the reproductive, endocrine and metabolic functions. It is a multifactorial and polygenic condition.[2]

Definition

Polycystic ovarian syndrome is a common endocrinopathy typified by oligoovulation or anovulation, signs of androgen excess and multiple small ovarian cysts. These signs and symptoms may vary widely between women as well as individuals over time.

The current definition of PCOS is based on the Rotterdam consensus workshop on PCOS in 2003. It defines the syndrome of PCOS as presence of any two of the following three criteria:

i. Oligoovulation / or anovulation
ii. Hyper androgenism (clinical/biochemical)
iii. Polycystic ovaries identified sonographically with the exclusion of other etiologies

Incidence

Polycystic ovarian syndrome is the most common endocrine disorder of reproductive aged women and affects approximately 4 – 12%. Amongst infertile about 20 %is attributed to anovulation caused by Polycystic ovarian syndrome. Based on ultrasound findings (USG) the incidence seems to be between 21 to 22 %. Approximately 20 – 25 % of women with normal ovulation demonstrate ultrasound findings typical of Poly Cystic Ovaries. Based on symptomatology incidence varies between 4 – 5 % to 21 % (menstrual abnormalities) and 3.5 – 9% (hyperandrogenism). It is important to remember that 40% of women with oligomenorrhoea, 84 % of women with hirsutism and 100% of women with severe acne have PCOS as their etiology. [3]

Causative Factors

Polycystic ovarian syndrome is a heterogeneous disorder of uncertain cause. No single inciting factor triggers the expression of the syndrome. The causes may be:

- Genetic inheritance
- Insulin resistance
- Hyperandrogenism
- Obesity
- Altered Hypothalamo–Pituitary–Ovarian axis.
- Lifestyle changes
- Environmental factors

1. Genetic Inheritance

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but with variable expressivity in females. This means that each child has 50% chance of inheriting the predisposing genetic variants from a parent, and if a daughter receives the variants, then she will have the disease to some extent. The genetic variants can be inherited either from the father or from the mother, and can be passed along to both sons (who may be asymptomatic carriers or may have symptoms such as early baldness or excessive hair) and daughters, who will show signs of PCOS. The phenotype appears to manifest itself atleast partially via heightened androgen levels secreted by ovarian theca cells from women with the allele. [4]

Clinical and invitro studies of human ovarian theca cells have suggested dysregulation of the CYP11a gene in patients with PCOS.[5] This gene encode cholesterol side chain cleavage enzyme, which is the enzyme that performs the rate limiting step in the steroid biosynthesis. In addition, the insulin receptor gene on chromosomen19p13.2 may be involved. Further investigations, however is needed to determine the roles of these gene products in the pathogenesis of PCOS.

2. Insulin Resistance

Insulin resistance, defined as reduced glucose response to a given amount of insulin, is a characteristic metabolic disturbance associated with PCOS. The mechanism of this decreased insulin sensitivity appears to be due to postbinding abnormality in insulin–receptor mediated signal transduction. Due to this peripheral insulin resistance there is a compensatory increase in pancreatic insulin secretion resulting in hyperinsulinaemic state.

Hyperinsulinaemia increase GnRH pulse frequency and acts synergistically with LH to enhance androgen production in ovarian theca cells. It decreases follicular maturation and decreases SHBG binding thus increasing the amount of free testosterone that is biologically active. In addition, insulin resistance in PCOS has been associated with adinopectin, a hormone that is secreted by adipocytes. Hyperinsulinaemia is

responsible for dyslipidemia and increased levels of plasminogen activator inhibitor-1(PAI-1) which is a risk factor for intravascular thrombosis.[6]

3. Hyperandrogenism

Abnormal regulation of the androgen forming enzymes (P450 C17) is thought to be the main cause for excess production of androgens from the ovaries and adrenals. The principal sources of androgens are

A) Ovary

B) Adrenals

C) Systemic metabolic alteration.

A) Ovary: produces excess androgen due to

- Stimulation of theca cells by high LH
- P450C17 enzyme hyper function
- Defective aromatization of androgens to Oestrogen.
- Stimulation of theca cells by insulin like growth factor

B) Adrenals: are stimulated to produce excess androgens by

- stress
- P450 C17 enzyme hyper function
- associated high prolactin level

C) Systemic metabolic alteration:

1) Hyperinsulinaemia causes

a) Stimulation of theca cells to produce more androgens

b) Insulin results in more free IGF -1, which in turn stimulates theca cells to produce more androgens

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

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

4. Obesity

The exact incidence of obesity in PCOS is not known. But approximately 50% of women are found to be obese. Central obesity is more common and is known to augment the metabolic disorder leading to severe menstrual disturbances, oligo-amenorrhoea, chronic anovulation, lower preganacy rates, higher miscarriage rates and increased obstetric complication. An increased waist to hip ratio is associated with increased androgenesity, increased basal and post glucose load, blood insulin levels and decreased insulin sensitivity. “Nutrient Toxicity” – an excess of nutrition and resulting obesity can also cause insulin resistance by an increase in production of agents that impair insulin action such as TNF alpha and resistin and a decrease in production of insulin sensitizing compound adinopectin.

5. Altered Hypothalamo–Pituitary–Ovarian axis

- Increased pulse frequency of GnRH leads to increased pulse frequency of LH.
- GnRH is preferential to LH rather than FSH.
- Increased pulse frequency and amplitude of LH results in tonically elevated level of LH.
- FSH level is not increased due to negative feedback effect of chronically elevated Oestrogen and follicular inhibin.

- Increased free estradiol due to reduced sex hormone binding globulin bears positive feedback relationship to LH.
- LH:FSH ratio is increased (>3:1).

6. Lifestyle changes

High calorie diet and lack of exercise results in obesity which may intensify the symptoms of PCOS. Recent studies show that women with PCOS exhibited a dietary pattern that was marked by consumption of a greater amount of specific foods with a high glycaemic index and sedentary lifestyle. Stress is also known to disrupt the normal rhythmic process in hypothalamus and pituitary gland resulting in anovulation. Under stress hypothalamus signals the adrenal glands to produce adrenaline and cortisol. Cortisol, a glucocorticoid can reduce or even block the release of LH causing decreased levels of oestrogen and progesterone resulting in anovulation and temporary amenorrhoea.

7. Environmental factors

Origin of PCOS occurs in utero or in early life. Timing of gestational androgen excess is important as different PCOS associated characteristics arise on the hormonal insult administered at various stages of foetal organogenesis. This concept of early origin of PCOS offers a possible mechanism through which environmental conditions during gestation or early life influence gene expression patterns later in life. A recent report released by WHO, suggests that, exposure to Endocrine Disrupting Chemicals (EDCs) during foetal life or puberty plays a role in the proliferation of male and female reproductive problems.

Signs and Symptoms

- ❖ Menstrual dysfunction
- ❖ Hirsuitism
- ❖ Acne
- ❖ Alopecia
- ❖ Acanthosis nigricans
- ❖ Obesity
- ❖ Infertility
- ❖ Pregnancy loss

Management

The purpose of medical treatment of PCOS is:

- ✓ To cure a woman with menstrual disorders.
- ✓ To treat hirsutism.
- ✓ To treat infertility.
- ✓ To prevent long term effects of metabolic X syndrome later in life.

Prevention

With the knowledge that PCOS having long-term adverse effects on health of the woman, such as diabetes, hypertension, cardiovascular disease and hyperlipidaemia, endometrial cancer, it is now suggested that PCOS should be adequately treated at the earliest. These women should be observed for these ailments in later life. Obesity in adolescents needs to be avoided and corrected. Lifestyle changes should be recommended.

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