REVIEW ARTICLE

Polycystic Ovary Syndrome: Its Genetics and Treatments

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Abstract

Polycystic ovary syndrome (PCOS) is an endocrinopathy common among women of reproductive age. Some women with PCOS have cysts on their ovaries. That's why it's called "polycystic." But the name is misleading because many women with PCOS don't have cysts. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. It is characterized by anovulation, infertility, hyperandrogenism, and frequently insulin resistance. Although the role of genetic factors in PCOS is strongly supported, the genes that are involved in the etiology of the syndrome have not been fully investigated until now, as well as the environmental contribution in their expression. Some genes have shown altered expression suggesting that the genetic abnormality in PCOS affects signal transduction pathways controlling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation, and others. Because the primary cause of PCOS is unknown, treatment is directed at the symptoms. Insulin-sensitizing agents are indicated for most women with polycystic ovary syndrome because they have positive effects on insulin resistance, menstrual irregularities, anovulation, hirsutism, and obesity. Metformin has the most data supporting its effectiveness. Rosiglitazone and pioglitazone are also effective for ameliorating hirsutism and insulin resistance. Metformin and clomiphene, alone or in combination, are first-line agents for ovulation induction. Insulin-sensitizing agents, oral contraceptives, spironolactone, and topical eflornithine can be used in patients with hirsutism.

Keywords: Anovulation, Clomiphene, Hirsutism, Hyperandrogenism, Infertility, Metformin, Polycystic ovary syndrome (PCOS).

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Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrinopathy in females,[1] characterized by chronic oligo-anovulation, hyperandrogenism (HA), and polycystic ovaries,[2] all of which can result in worsening of quality of life for these patients.[3,4] This endocrine disorder affects females under 18–44 age.[5] Hyperandrogenaemia is also an important marker of polycystic ovary syndrome (PCOS), a common heterogeneous endocrine disorder affecting 5–10% of women of reproductive age, depending on the population and the diagnostic criteria applied.[6] Menstrual irregularity in adolescence has been shown to be a good marker of hyperandrogenaemia and it has been proposed to lead to the development of PCOS in adulthood.[7,8] In addition, adolescent girls with irregular menstrual cycles have higher androgen levels than girls with regular menstrual cycle.[8-11]

This multi-system, polygenic, multi-factorial disorder is associated with an increased risk for metabolic abnormalities such as type 2 diabetes mellitus.[12]

Pathophysiology

The pathophysiology of PCOS involves primary defects in the hypothalamic–pituitary axis, insulin secretion and action, and ovarian function.[13,14] Clinical signs (neuroendocrine abnormalities) include increased gonadotropin-releasing hormone [GnRH] and luteinizing hormone [LH] levels whereas follicle stimulating hormone [FSH] levels are muted or unchanged.[15,16] As a result of the increase in GnRH, stimulation of the ovarian thecal cells, in turn, produces more androgens.[17] Follicular arrest can be corrected by elevating endogenous FSH levels or by providing exogenous FSH. Elevation of LH level leads to an increase in androgen level that gives rise to the progression of PCOS.[18] Approximately 25% of patients with PCOS have elevated prolactin levels.[19]

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Sign and Symptoms

The clinical presentation of PCOS is variable. Patients may be asymptomatic, or they may have multiple gynaecologic, dermatologic, or metabolic manifestations. Patients with PCOS most commonly present with signs of hyperandrogenism and a constellation of oligomenorrhea, amenorrhea, or infertility.[20,21] It also continues to be a common cause of infertility among women.[22] However, signs and symptoms vary, the three most common factors associated with PCOS include ovulation irregularities, increased androgen levels, and cystic ovaries.[22,23] Problems with ovulation and elevated androgen levels occur in the majority of women with PCOS. Twice as many women with PCOS have metabolic syndrome as in the general population, and about one-half of women with PCOS are obese.[24,25]

There is a fourfold increase in the risk of type 2 diabetes mellitus in patients with PCOS.[26] There is an increased prevalence of non-alcoholic fatty liver disease,[27,28] sleep apnea,[29] and dyslipidemia[30] in patients with PCOS, even when

controlled for body mass index. Finally, there is evidence to suggest an increased risk of mood disorders among patients with PCOS.[31,32] Moreover, hirsutism, acne, and alopecia are directly associated with elevated androgen levels, and the prevalence of polycystic ovaries on pelvic ultrasound exceeds 70% in patients with PCOS.

Diagnosis

This condition can be diagnosed on the basis of Rotterdam criteria i.e. irregular menstrual cycle, elevated androgen level, the presence of cysts.[33]

Genetics of PCOS

Many genes presented altered expression suggesting thus that the genetic abnormality in PCOS affects signal transduction ruling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others. PCOS has a strong genetic association. Genes like CAPN10, CYP11A, Cytochrome family p450, Insulin gene, AR, FTO, FSHR have been discussed.

CAPN10

Calpain-10, encoded by CAPN10 gene, is a cysteine protease which participates in insulin secretion and action,[34] and genetic studies have shown that variation in these gene is associated with type-2 diabetes.[35] Its location is in non-insulin dependent Diabetes Mellitus type 1 region.[36] Any abnormality or polymorphism in CAPN10 leads to PCOS because insulin resistance and type 2 diabetes are associated with PCOS, therefore it is also a candidate gene that is known to be responsible for PCOS.[37]

CYPA1A

It is abbreviated as Cytochrome P450, family 1, subfamily A, member 1 and is located on chromosome 15q24.1. It encodes Cytochrome P450 proteins that are present in the endoplasmic reticulum and its expression is mainly induced by polycyclic aromatic hydrocarbons (PAHs).[38] A study conducted on PCOS patients and healthy individuals which concluded that PCOS patients have a high rate of Isoleucine/valine as compared to normal individuals whereas it was further observed through statistical analysis that isoleucine is replaced by valine in PCOS and they have the genotype for Valine. Hence, they concluded that there was7.8-fold higher frequency of CYP1A1 isoleucine/valine genotype whereas the rate of CYP1A1 of valine genotype was 7.4-fold.[39]

CYP21

CYP21 gene encodes 21-hydroxylase enzyme which is responsible for the conversion of 17-hydroxyprogesterone into 11-deoxycortisol. The deficiency of this enzyme is responsible for most cases of congenital adrenal hyperplasia and increased serum 17- hydroxyprogesterone levels are correlated with its deficiency. It is a common finding among women with functional hyperandrogenism or PCOS an increased serum 17-hydroxyprogesterone response to ACTH stimulation.[40,41] Moreover, patients having both heterozygote CYP21 mutations and clinical symptoms exhibit a PCOS-like phenotype16. Accordingly, mutations of CYP21 have been investigated as a candidate gene in patients with PCOS. Two studies showed that children with premature pubarche and adolescent girls with hyperandrogenism were heterozygous for mutations in CYP21.[42,43] On the other hand, there are other researchers that found no clear concordance between the CYP21 genotype and the functional origin of androgen excess.[44,45] Overall, CYP21 and associated mutations do not seem to play a key role in the development of PCOS.

CYP19

The enzyme complex aromatase, composed of the cytochrome P450 aromatase and the NADPH cytochrome P450 reductase,[46] converts androgens to estrogens and P450arom is encoded by CYP19 located at 15p21.1.[47] It has been reported that several hyperandrogenic patients show Aromatase deficiency.[48,49] It has been observed that granulosa cells obtained from medium-sized follicles of women with PCOS have little aromatase activity.[50] Similarly, it has been showed that when compared to the control follicles, all PCOS follicles contained low levels of P450arom mRNA, estradiol, and lower aromatase stimulating bioactivity.[51] These findings indicate that the aromatase activity might be decreased in PCOS follicles, and that the possible androgen excess resulting might contribute to abnormal follicle development. Association studies utilizing SNPs and haplotypes showed association with PCOS symptoms and serum testosterone levels.[52,53]

CYP17

CYP17, which codes for the cytochrome P450 enzyme that catalyzes the addition of a hydroxyl group at carbon 17 of the steroid D ring of pregnenolone and progesterone to produce 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively.[54]

The conversion of pregnenolone and progesterone into 17-hydroxypregnenolone and 17- hydroxyprogesterone, respectively, and of these steroids into dehydro-hepiandrosterone (DHEA) and Δ4-Androstendione (Δ4A) is catalyzed by the P450c17α enzyme. This enzyme has both 17α-hydroxylase and 17,20-lyase activities and is encoded by CYP17 located at 10q24.3.[55] It was reported increased P450c17α expression and enzymatic activity in ovarian theca cells from women with PCOS as well as increased transactivation of the CYP17 promoter. Moreover, it was showed that CYP17 expression is dysregulated at the level of mRNA stability in PCOS theca cells. Another study identified a rare T/C single nucleotide polymorphism (SNP) in the promoter region of CYP17 increasing the susceptibility to develop PCOS. Subsequently, more comprehensive studies have failed to detect a significant linkage between CYP17 and PCOS.[56-59] Although CYP17 gene does not seem to be a candidate gene in the pathophysiology of PCOS, it should be

noted that post-translational regulation of this gene product might play a role in the pathophysiology of PCOS7.

Androgen Receptor Gene (AR)

This gene is present on chromosome Xq11-12 and is composed of three functional domains: the transactivation domain, the DNA binding domain, and the ligand-binding domain.[60] It has 11 exons. Androgen receptor AR is also linked with PCOS. X Inactivation disrupts androgen signaling pathway and elevated. AR is an X linked gene and a single copy of X chromosome perturbs the whole pathway. It is possible to conduct Genome- Wide Association for PCOS to identify the novel mutations and other genetic variants that is associated with the cause of PCOS.

LH Gene

It hasbeen shown that LH and LHR gene mutations may alter the structure or function of the LH and LH receptor (LHR), either activating or inactivating their bioactivity, which cause anovulation, amenorrhea and polycystic ovary in women.[61,62] Two missense point mutations in the LH gene (Trp 8 Arg and Ile 15 Thr) were reported to associate with PCOS in Japan and obese PCOS women in UK. However, a study of obese PCOS from north European found LH gene (Trp 8 Arg and Ile 15 Thr) were in lower frequency. Another LH gene variant G1502A in exon 3 (Gly102Ser) was found to be higher in Singapore Chinese women who had menstrual disorders.[63] Yet a Korean research found no difference of LH gene Gly102Ser in PCOS patients.[64] Women with LHR mutations often show amenorrhea and infertility.[65] Besides this, these mutations produced structural changes in the variant LH molecules (v-LH) and caused v-LH to have an increased in vitro activity and a decreased in vivo half-life compared to that of non-mutant form. It has been reported that the occurrence of these mutations in LH β-subunit gene was not higher in PCOS compared with healthy women. However, other studies failed to find any association with PCOS.

Treatment

Infertility

Lifestyle modification is first-line therapy for women those are overweight. A calorie-restricted diet is recommended for all patients with PCOS who are over weight. Weight loss has been shown to have a positive effect on fertility and metabolic profile.

First-line agents for ovulation induction and treatment of infertility in patients with PCOS include metformin[66-71] and clomiphene (Clomid),[72] alone or in combination, as well as rosiglitazone[73]

Recently it has been reported that letrozole is associated with higher live-birth rates and ovulation rates compared with clomiphene in patients with PCOS[74] The impact of metformin on fer¬tility is controversial; although it was once believed to improve infertility, a 2012 Cochrane review concluded that it does not.[75]

Hirsutism

According to a 2015 Cochrane review, the most effective first-line therapy for mild hirsutism is oral contraceptives.[76] First-line agents include spironolactone (Aldactone)[77] and metformin,[78] as well as eflornithine (Vaniqa) for facial hirsutism.[69] Insulin-sensitizing agents, including metformin, acarbose (Precose), and rosiglitazone (Avandia), may be used to treat hirsutism in women with PCOS. Spironolactone and rosiglitazone have been shown to be more effective than metformin, based on Ferriman-Gallwey hirsutism scores.

Other therapies include eflorni¬thine (Vaniqa), electrolysis, or light-based therapies such as lasers and intense pulsed light. Any of these can be used as monotherapy in mild cases or as adjunctive therapy in more severe cases.[79]

Menstrual Irregularity

In a patient not seeking pregnancy, the Endocrine Society recommends hormonal contraception (i.e., oral contraceptive, dermal patch, or vaginal ring) as the initial medication for treatment of irregular menses and hyperandrogenism manifesting as acne or hirsutism.[20,80] It has been suggested that the following agents may improve menstrual irregularities (e.g., oligomenorrhea): spironolactone (in an open-label study), acarbose, rosigli-tazone, and metformin.[81] Metformin is possibly the best choice as it may improve insulin resistance along with irregular menstruation. It has shown that metformin can restore regular menses in up to 50% to 70% of women with PCOS,[82] but oral contraceptives have been shown to be superior to metformin for regulating menses and declining androgen levels.

ACNE

Acne is common in the general popula¬tion and in polycystic ovarian patients. Hormonal contraceptives are first-line medications for treating acne associated with PCOS and can be used in conjunction with standard topi¬cal acne therapy (e.g., retinoids, antibiotics, benzoyl peroxide) or as monotherapy. Antiandrogens, spironolactone being the most common, can be added as second-line medications.[80]

Conclusion

Polycystic ovary syndrome is a complex endocrine disorder for which multiple treatment approaches are essential, depending on the reason a patient seeks treatment. Metformin and clomiphene, alone or in combination, as well as rosiglitazone can be used to treat infertility, whereas data are limited regarding the pharmacological treatment of androgenic symptoms. Insulin-sensitizing agents, including metformin, acarbose (Precose), and rosiglitazone (Avandia), may be used to treat hirsutism in women with PCOS. Spironolactone and rosiglitazone have been shown to be more effective than metformin, based on Ferriman-Gallwey hirsutism scores.

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