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POLYCYSTIC IN OVARIAN SYNDROME AND ITS VARIOUS TREATMENT STRATEGIES

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Abstract:

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder, leading to several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome. Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. PCOS affects as many as 10% of reproductive-age women when using the NIH criteria for diagnosis, and up to 18% of reproductive-age women are diagnosed with PCOS as per the Rotterdam criteria. The exact pathophysiology of PCOS is complex and remains largely unclear. Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the etiology of PCOS. PCOS is a highly prevalent heterogeneous syndrome of clinical and/or biochemical androgen excess, ovulatory dysfunction and polycystic ovaries (PCO). Despite it being one of the most common reproductive health problems of women, its effective treatment remains a significant challenge to medical profession. Further research is needed to find the exact etiology, methods of prevention and proper management of this endocrine disorder.

Keywords: *Polycystic ovary syndrome, Hyperandrogenism, Insulin resistance, obesity.*

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder, leading to several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome [1]. Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries [2]. Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders in premenopausal women. Heterogeneous by nature, PCOS is defined by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses. The etiology of this syndrome remains largely unknown, but mounting evidence suggests that PCOS might be a complex multigenic disorder with strong epigenetic and environmental influences, including diet and lifestyle factors. PCOS is frequently associated with abdominal adiposity, insulin resistance, obesity, metabolic disorders and cardiovascular risk factors [3].

Polycystic ovary syndrome (PCOS) is a hyperandrogenic disorder associated with chronic oligo-anovulation and polycystic ovarian morphology [4, 5]. It is often associated with psychological impairments, including depression and other mood disorders and metabolic derangements, chiefly insulin resistance and compensatory hyperinsulinemia, which is recognized as a major factor responsible for altered androgen production and metabolism [6]. PCOS affects as many as 10% of reproductive-age women when using the NIH criteria for diagnosis, and up to 18% of reproductive-age women are diagnosed with PCOS as per the Rotterdam criteria [7]. Nevertheless, at least 70% of PCOS cases remain undiagnosed in primary care [8]. PCOS can be described as an oligogenic disorder in which the interaction of a number of genetic and environmental factors determine the heterogeneous, clinical, and biochemical phenotype [9]. Although the genetic etiology of PCOS remains unknown, a family history of PCOS is relatively common; however, familial links to PCOS are unclear. A lack of phenotypic information prevents a formal segregation analysis. Nonetheless, the current literature suggests that the clustering of PCOS in families resembles an autosomal dominant pattern [10]. PCOS is a hormonal disorder with a potential to lead to various diseases. It also continues to be a common cause of infertility among women [11]. Although signs and symptoms vary, the three most common factors associated with PCOS include ovulation irregularities, increased androgen levels, and cystic ovaries [11, 12].

Signs and Symptoms of Polycystic Ovary Syndrome [11, 12]

Enlarged ovaries with numerous small cysts
Irregular menstrual cycles
Pelvic pain
Hirsutism
Alopecia
Acne
Acanthosis nigricans
Skin tags

Pathophysiology

The exact pathophysiology of PCOS is complex and remains largely unclear. Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity, ovarian dysfunction and hypothalamic pituitary abnormalities to contribute to the aetiology of PCOS [13, 14]. However, greater understanding of pathophysiological contributors in PCOS have been hampered by a lack of ideal methods to assess either hyperandrogenism or insulin resistance. Hyperandrogenism is a well established contributor to PCOS etiology, detected in around 60% to 80% of cases. Insulin resistance is a pathophysiological contributor in around 50% to 80% of women with PCOS [15], especially in those with more severe PCOS diagnosed on National Institutes of Health (NIH) criteria and in women who are overweight. Conversely, lean women [16] and women with milder PCOS diagnosed on newer European Society for Human Reproduction (ESHRE)/American Society of Reproductive Medicine (ASRM) criteria [17] appear to have less severe hyperinsulinaemia and insulin resistance. , Insulin resistance contributes to metabolic features but also to reproductive features [18]. PCOS is the result of a defect in the hypothalamic pituitary-ovarian circuit which remains unknown. No single causative factor accounts for the various abnormalities that present in a woman with PCOS. Thus, several theories based on identification of the starting defect in the menstrual cycle have been proposed. They include the following:

1. A unique defect in insulin action and secretion leading to hyperinsulinemia and insulin resistance [19].
2. A primary neuroendocrine defect leading to an exaggerated LH pulse frequency and amplitude [19].
3. A defect of androgen synthesis resulting in enhanced ovarian androgen production [19].
4. An alteration in cortisol metabolism resulting in enhanced adrenal androgen production [19].

The following are some of the pathophysiological

mechanisms of PCOS, suggested by King [20]: altered secretion of the gonadotropin-releasing hormone, defect in androgen synthesis, and development of IR]. One of the best-described theories to explain the pathogenesis of PCOS is the disturbance of the hypothalamic-pituitary axis, resulting in disordered secretion of gonadotropin by the hypothalamus leading to raised luteinizing hormone (LH) levels and normal and/or low follicle-stimulating hormone (FSH) levels [21].

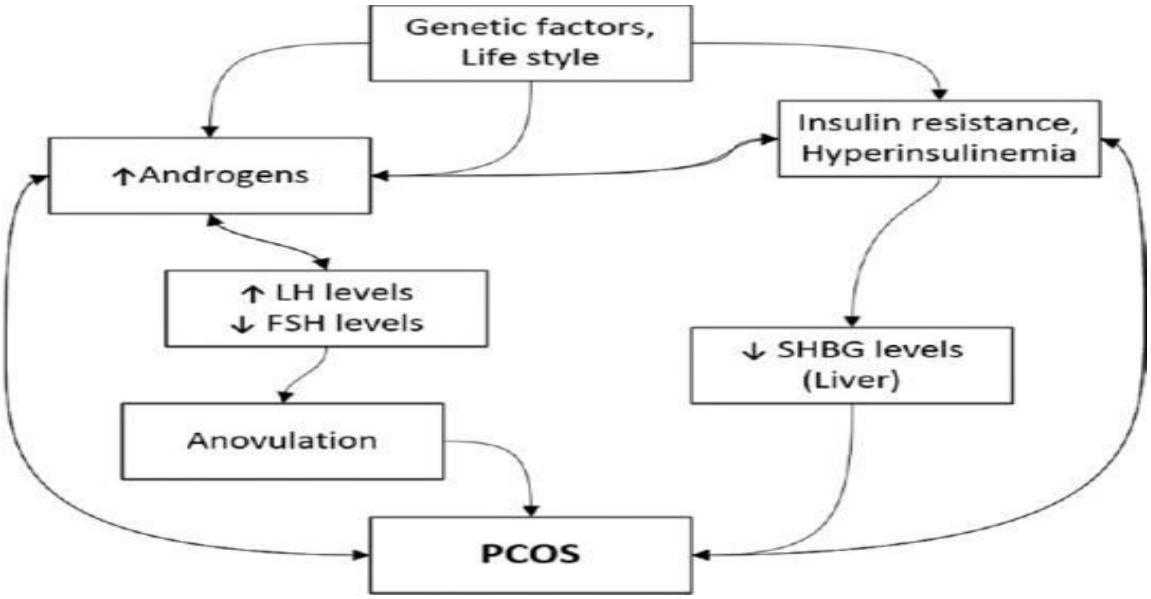

Figure 1: SHBG: Sex Hormone-Binding Globulin. LH- Luteinizing hormone. FSH- Follicle-stimulating hormone [22]

Clinical features and diagnosis of polycystic ovary syndrome

PCOS was first reported in the modern medical literature by Stein and Leventhal, in 1935 [23], who in their original report described PCOS as a variable clinical condition with characteristics such as obesity, hirsutism, acne, and amenorrhea associated with enlarged bilateral polycystic ovaries. Later in 1990, at an international meeting which was held at the U. S. National Institutes of Health, it was recommended that the diagnostic criteria for PCOS should comprise the concomitant presence of anovulation and evidence of hyperandrogenemia – biochemical, clinical (hirsutism/acne), or both – but without reference to ovarian morphology. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group suggested that if two of the three criteria (CA, hyperandrogenism, and polycystic ovaries on ultrasonography) were present, it can be considered as PCOS. In contrast, the Androgen Excess Society states that hyperandrogenism (clinical and/or biochemical) is the key feature and its presence in combination with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) is considered during the diagnosis of PCOS [24-26].

Criteria for the diagnosis of polycystic ovary syndrome [24-26]

NIH/NICHD, 1992	Rotterdam criteria, 2004	Androgen Excess Society, 2006
Includes all the following	Includes two of the following	Includes all the following
Hyperandrogenism and/or hyperandrogenemia	Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism
Oligo-ovulation/anovulation	Oligo-ovulation or anovulation	Ovarian dysfunction and/or polycystic ovaries
	Polycystic ovaries	

NIH: National Institutes of Health, NICHD: National Institute of Child Health and Human Disease

Prevalence of polycystic ovary syndrome (PCOS) using different diagnostic criteria [27-30]

Source		NIH/NICHD criteria	Androgen excess and	(Rotterdam) criteria	PCOS society criteria
March et al	728	Australian women	8.7%	17.8%	12.0%
Mehrabian et al	820	Iranian women	7%	15.2%	7.92%
Tehrani et al	929	Iranian women	7.1%	14.6%	11.7%
Yildiz et al	392	Turkish women	6.1%	19.9%	15.3%

Important investigations to be done in suspect cases of PCOS [31]

Name of Investigation	Significance
Lipid profile	May be deranged in metabolic syndrome
Blood sugar (fasting)	May be deranged in metabolic syndrome
Blood sugar (post 75 gm glucose)	May be deranged in metabolic syndrome
Insulin (fasting)	>12 mIU/ml suggestive of insulin resistance
Insulin (Post 75 gm glucose)	>25 mIU/ml suggestive of insulin resistance
TSH	Hypothyroidism may cause oligo/ amenorrhoea
FSH/LH ratio	Normally FSH > 3-4 LH Reversal of ratio significant
Total testosterone	>3.6 ng/ml significant
Androstenedione	Elevated in ovarian pathology
Prolactin	May be raised in PCOS but very high levels indicate a pituitary tumor
17 hydroxy progesterone	Elevated in late-onset CAH
DHEAS	Elevated in adrenal pathology
DHT	Indicative of peripheral conversion of testosterone
Ultrasonography of pelvis	Volume of atleast 1 ovary more than 10 cc with "string of pearl" appearance

PCOS: Polycystic ovarian syndrome

Management of PCOS

PCOS is a highly prevalent heterogeneous syndrome of clinical and/or biochemical androgen excess, ovulatory dysfunction and polycystic ovaries (PCO). Despite it being one of the most common reproductive health problems of women, its effective treatment remains a significant challenge to medical profession.

Lifestyle changes

Guidelines recommend exercise therapy and calorie-restricted diet as a crucial part of the management of obesity in women with PCOS. In fact, lifestyle modifications are considered as a cost-effective first line treatment and as a necessary adjunct to medication [32, 33].

Because the primary cause of PCOS is unknown, treatment is directed at the symptoms. Few treatment approaches improve all aspects of the syndrome, and the patient's desire for fertility may prevent her from seeking treatment despite the presence of symptoms [34]. Treatment goals should include correcting anovulation, inhibiting the action of androgens on target tissues, and reducing insulin resistance.

Weight reduction for obese patients with PCOS is beneficial in many ways. Weight loss helps to decrease androgen, luteinizing hormone (LH), and insulin levels. It also helps to regulate ovulation, thereby improving the potential for pregnancy [35].

Drugs used in PCOS

1. Clomiphene citrate

CC remains the treatment of first choice for medical ovulation induction in PCOS women owing to its simplicity of use, low cost, relative safety and efficacy. It is a nonsteroidal synthetic oestrogen, which is related to the synthetic oestrogen, diethylstilboestrol and is known for its anti-oestrogenic and weak oestrogenic properties. By binding to oestrogen receptors at the hypothalamic-pituitary level, clomiphene blocks the negative feedback effect of oestradiol on GnRH secretion, thus resulting in an increase in the GnRH pulse amplitude leading to an increased gonadotropin secretion from the pituitary. The resultant increase of FSH triggers an ovulatory cycle [36]. Initially, a dose of 50 mg/day for 5 days is given. If ovulation occurs but no pregnancy results, 50 mg/day for 5 days is continued for the subsequent cycles. However, if ovulation does not occur after the first cycle, the dose may be increased to 100 mg daily for 5 days at least 30 days after the previous course of therapy.

Further treatment is not usually recommended after three courses of therapy; however, up to six cycles may be attempted before further therapy is considered. Clomiphene results in successful pregnancies approximately 30% of the time; however, 20% of these pregnancies result in spontaneous abortions or stillbirths [37].

Antidiabetic agents.

Metformin is the most commonly used insulin sensitising agent and is the only available biguanide drug with a UK license for use in type II diabetes. For several years, metformin has been increasingly used worldwide in PCOS women. However, recent data from large randomised trials have shown that metformin is not as effective as initially thought to be. Metformin alone is much less effective than CC when used for ovulation induction in women with PCOS. Furthermore, adding metformin to CC does not seem to increase live-birth rates above those observed with CC alone. The incidence of miscarriage in women receiving CC is not lowered by the addition of metformin. The Thessaloniki ESHRE/ASRM consensus has, therefore, recommended that metformin should not be used as a first-choice or as an adjuvant to CC for induction of ovulation in women with PCOS. It should only be considered in PCOS patients with glucose intolerance. The role of metformin in anovulatory women with PCOS who have insulin resistance remains to be established [36].

In its 2008 consensus statement, the ESHRE/ASRM concluded that metformin is less effective than clomiphene in inducing ovulation and that there was no advantage to adding metformin to clomiphene [38]. In a meta-analysis of randomized controlled trials, metformin improved ovulation rate and clinical pregnancy rate but not live birth rate when compared to placebo or no treatment [39]. However, in a recent multicenter, randomized, double-blind, placebo-controlled study, metformin increased live-birth rates compared to placebo (41.9% versus 28.8%, P=0.014) with the most beneficial effect seen in obese women [40]. These results are consistent with another study that evaluated pretreatment with metformin for 3 months before in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) [41].

Gonadotropins.

Human menopausal gonadotropin (HMG) and FSH can also be used to induce ovulation if clomiphene and/or metformin therapy fails. In one study of 302 women, 132 received low-dose FSH (50 units subcutaneously) on cycle day 4 with weekly incremental increases of 25 units, and 123 patients received clomiphene 50 mg for 5 days starting on day 4 with the dose titrated upward to 150 mg/day

[42].Pregnancy rates were higher with FSH than with clomiphene (58% vs. 44%, respectively; $P = 0.03$), and there were more live births with FSH (52% vs. 39%, respectively; $P = 0.04$). Although gonadotropins might be more effective than clomiphene for inducing ovulation, the comparative expense and ease of administration of clomiphene favored clomiphene as a first-line therapy for fertility in PCOS. Of note, low-dose FSH was used in this study, because high doses are associated with an increased risk of multiple pregnancies and OHSS [43].

Aromatase inhibitors

Aromatase inhibitors block the conversion testosterone and androstenedione to estradiol and estrone, respectively. This decrease in estrogenic activity releases the hypothala-mus from negative feedback, allowing for an increase in the release of FSH [44]. Letrozole, the most commonly used aromatase inhibitor for ovulation induction, is administered in doses between 2.5–7.5 mg per day for 5 days starting on day 3 of the menstrual cycle [45]. Putative advantages of letrozole include its lack of antiestrogenic effects on the endometrium, [46] shorter half-life when compared to clomi-phene and a higher rate of monofollicular ovulation [44]. A recent systematic review and meta-analysis of randomized controlled trials that compared letrozole with clomiphene indicated that letrozole administration was associated with a higher ovulation rate per person. However, letrozole did not increase ovulation per cycle, pregnancy, or live birth rate per person [47]. Since that review, a study comparing clomiphene citrate with letrozole in 103 treatment-naïve infertile women with PCOS demonstrated that letrozole use was associated with a similar ovulation rate (73.08% in the letrozole group versus 60.78% in the clomiphene group, P=0.39) but significantly higher pregnancy rate (21.56% in the letrozole group versus 7.84% in the clomiphene group, P=0.015) [48].

Antiandrogens

Two types of anti-androgens are used in the management of PCOS: androgen receptor blockers like spironolactone, flutamide, and the third generation progestin, cyproterone acetate, and inhibitors of 5-alpha reductase such as finasteride, which prevents the conversion of testosterone to DHT. In adolescents with PCOS, direct comparisons of the various anti-androgens or RCTs are not available [49,50]. Spironolactone is the most commonly used because of its availability and safety profile, with an initial dose of 25 mg/day gradually increasing up to 200 mg/day. At initiation, spironolactone may be associated with transient menstrual irregularity or spotting, breast tenderness, and occasionally fatigue or orthostasis from volume depletion. Flutamide is not available in some countries and is used sparingly because of concerns regarding its potential hepatotoxicity at high doses (>250 mg/day). Evidence indicates that 1 mg/kg/day is effective and not hepatotoxic, even with extended use [51]. Data on efficacy of spironolactone compared to flutamide are limited, and the methodological quality of the studies is low [52]. Anti-androgens significantly reduce hirsutism compared with placebo [53] and normalize menstrual cyclicity and endocrine-metabolic variables better than monotherapy with metformin [52]. The efficacy is enhanced when combined with OCP, metformin, or other anti-androgens [52-55].

Oral contraceptives

Combination OCP containing an estrogen component (typically ethinylestradiol) and a progestin component address multiple concerns in adolescents with PCOS. An increase in SHBG and decreased LH release due to the estrogen component leads to a decreased free androgen index, and the progestin component allows for suppression of endometrial proliferation and regular withdrawal bleeding. As such, there is improvement in acne and hirsutism and reduction in menstrual irregularity with OCP. Unfortunately, there are few RCTs comparing the relative efficacy or metabolic impact of the different formulations of hormonal contraceptives in adolescents. An RCT comparing the progestins desogestrel and cyproterone acetate in combination with ethinylestradiol found equal improvements in hirsutism, but total and LDL cholesterol were increased by both formulations [56]. Additionally, there was evidence for worsening of HOMA-IR and fasting glycemia with both preparations [57]. Metabolic changes overall, however, did not result in significant concentrations outside the normal ranges. In young women with PCOS (aged 20–25 years) treated with an OCP containing drospirenone versus a combined contraceptive vaginal ring, an RCT suggested that both methods worsened the lipid profile, but OCP significantly worsened triglycerides while remaining within the normal range [58]. In adult women, an RCT involving OCP with 3 different progestins (desogestrel, drospirenone, and cyproterone acetate) showed identical metabolic impact [59].

CONCLUSION:

PCOS is one of the most important endocrine

disorders that affects women of the reproductive age and may cause serious complications. Insulin resistance plays a key role in the pathophysiology of this syndrome, and this makes the use of oral antidiabetic drugs most compelling. The majority of studies have shown amelioration of typical symptoms such as hyperandrogenism and cycle irregularities following the use of oral anti-diabetics, and ovulation and pregnancy rates increased. The reproductive and metabolic features of PCOS are sometimes reversible with lifestyle modifications such as weight loss and exercise. Further research is needed to find the exact etiology, methods of prevention and proper management of this endocrine disorder.

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