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Polycystic Ovarian Syndrome: Leading Cause of Female Infertility.

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ABSTRACT

The new millennium has brought intense focus of interest on the risk of infertility in women. Polycystic ovary syndrome (PCOS) is a complex disorder with heterogeneity of clinical and endocrine features which is one of the major causes. The polycystic ovary syndrome (PCOS) is a common endocrine disorder in women characterised by hyperandrogenism and oligomenorrhea. It is difficult to diagnose & manage it because of its heterogenecity. Most females with PCOS also exhibit features of metabolic syndrome, including insulin resistance, obesity and dyslipidaemia. This review article focuses on epidemiology, clinical features, pathophysiology, complications & management of this leading cause of female infertility.

Keywords: infertility, polycystic ovary, hyperandrogenism, oligomenorrhea

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a very common disorder affecting 4% to 12% of women of reproductive age [1, 2]. Though very heterogeneous in nature, but the hallmarks of the disease are hyperandrogenism and chronic anovulation. In the past the polycystic ovary syndrome has been diagnosed if a woman has two out of three sets of conditions:

- The first is increased levels of male hormone noticed by the effects such as acne, excess body hair growth or accelerated loss of hair from the scalp.
- The second condition is called **anovulation**. Lack of regular ovulation results in irregular and, usually, infrequent menstrual periods. However, a few women who are not ovulating, will still have regular periods.
- The third condition is the finding of polycystic ovaries on an ultrasound examination of the ovaries or at laparoscopy.

At the US National Institutes of Health Conference in 1990, three key features of PCOS were generally agreed; oligomenorrhea, hyperandrogenism (clinical or laboratory evidence), and the absence of other endocrine disorders (congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, and androgen-secreting tumours)[3]. Despite the high prevalence of PCOS, the diagnosis and differential diagnosis remains confusing. This is due to the lack of a specific diagnostic test for the disorder. Usually there are four issues which arise in the management of PCOS patients: regulation of menses, control of hirsutism, fertility issues, the management of the Insulin Resistance syndrome and its associated risks (type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease).

Symptoms

PCOS is most simply defined as the presence of clinical or biochemical hyperandrogenism and/or chronic anovulation in the absence of specific adrenal and/or pituitary disease[4]. It is characterized by oligomenorrhea, amenorrhea, infertility and hirsutism, occasionally but not invariably in association with enlarged cystic ovaries, PCOS was first described in 1935 by Stein and Leventhal[5]. It is seen that up to 10% of patients presenting with primary amenorrhea and 75% of those with secondary amenorrhea fulfil the criteria for PCOS. Menarche may be normal or delayed and either amenorrhea, oligomenorrhea or dysfunctional uterine bleeding may occur[6]. The clinical features of PCOS are enlisted below. Hyperandrogenism may present clinically as hirsutism, acne, and/or male pattern alopecia. Hirsutism can be defined as the growth of coarse terminal, medullated & pigmented hair in a woman in male pattern i.e. in the region of upper lip, chin, chest, upper abdomen, back etc. Alopecia is a much rarer manifestation of PCOS. Acne related to hyperandrogenism is difficult to distinguish from normal pubertal acne in an adolescent with PCOS though pubertal acne in general is twice as prevalent in adolescent males versus females[7]. Thus, an adolescent female with moderate to severe acne should be investigated for PCOS. Chronic anovulation often presents as oligomenorrhea, amenorrhea, dysfunctional uterine bleeding, and/or infertility. However, around 20% of patients with PCOS may have normal menstrual cycles[8].

Often, menstrual abnormalities are long-standing, even since menarche. It is also important to search for signs of Insulin Resistance. Upper-body obesity is a key component of this[9]. However, obesity is not required for the diagnosis of PCOS because only 35% to 50% of these patients being obese[1, 10]. Most obese patients of PCOS are insulin resistant. [4]Virilization is usually mild. More severe signs such as clitoromegaly, deepening of the voice and increased muscle mass are usually rare; if they are present, then some other diseases of the adrenal and pituitary glands, including congenital adrenal hyperplasia, hyperprolactinemia or androgen-secreting tumours, should be excluded. Rapid, severe virilization with clitoromegaly and muscle changes suggestive of a male habitus usually indicates a virilising tumour. Acanthosis nigricans on physical examination is also a sign of IR.

Clinical features of polycystic ovary syndrome.

Oligomenorrhea/amenorrhea
Infertility/first trimester miscarriage
Hirsutism
Obesity
Acne
Acanthosis nigricans
Male pattern alopecia

Risks

Estimates suggest that between 5 percent and 10 percent of females age 18 to 44 are affected by PCOS in some way [11]. This prevalence is higher in women with menstrual irregularities in presence of certain diseases.

Standard Diagnostic Assessment & Differential Diagnosis

The first step in diagnosing PCOS is to rule out other conditions that cause similar symptoms. The diagnosis of PCOS is mainly based on chronic hyperandrogenism or chronic anovulation in the absence of specific pituitary and/or adrenal disease. If the NIH clinical criteria are present, the patient should undergo laboratory evaluation to exclude hyperprolactinemia, late-onset congenital adrenal hyperplasia, and androgen secreting tumours of the ovary or adrenal gland.

Normal serum levels of the following hormones can exclude these disorders:

- Prolactin
- Testosterone
- DHEA-S
- Corticotropin-stimulated 17-alpha-hydroxyprogesterone.

Fasting blood glucose and insulin levels should be measured to evaluate for hyperinsulinemia.

The differential diagnoses of PCOS & the differential laboratory tests are listed in the following table.

Diagnosis	Laboratory test
Pregnancy	Pregnancy test
Hypothyroidism	TSH
Hyperprolactinemia	Prolactin
Late-onset CAH	17-hydroxyprogesteronea
Ovarian tumour	Total testosterone
Hyperthecosis	Total testosterone
Adrenal tumour	DHEA-S
Cushing's syndrome	24-hour urine free cortisol

Symptoms like cold intolerance, dry skin and increased fatigue may signify hypothyroidism, as would the presence of goitre. Galactorrhea may or may not be present in women with hyperprolactinemia. Signs of virilization signify more significantly elevated androgen levels than those seen in PCOS and may indicate an ovarian or adrenal tumour. Patients with Cushing's syndrome may be more prone to have hypertension, purple abdominal striae, prominent dorsal cervical fat pads and rounded, plethoric face. Congenital adrenal hyperplasia occurs due to a variety of enzymatic defects in adrenal steroidogenesis (which leads to increased levels of precursor hormones that have androgenic properties). The classic forms of these disorders show complete enzymatic defects and presence of ambiguous genitalia in newborn girls. The most common form of late-onset congenital adrenal hyperplasia is due to 21-hydroxylase deficiency and is often the only type tested for in the differential diagnosis of PCOS.

Pathogenesis

The exact pathophysiology of PCOS and its initiating event is yet to be elucidated. However, various biochemical abnormalities have been proposed.

Hypothalamic-pituitary abnormalitiesElevated LH, low-normal FSH.

In PCOS, the normal pulsatile secretion of luteinizing hormone (LH) is increased due to increased frequency and amplitude of pulses, while that of follicle-stimulating hormone (FSH) is unchanged. Thus, LH values may be elevated as a result, the LH: FSH ratio can be increased to more than 2.5, even in ovulatory cycles. However, these values may be normal in as many as 10% to 20% of women with PCOS [12].

Elevated GnRH

The inappropriate secretion of gonadotropin is believed to be due to an abnormality of the gonadotropin releasing hormone (GnRH) pulse generator in the hypothalamus.

Elevated Prolactin

In about 25% of patients with PCOS, prolactin levels are elevated. Extreme elevations of prolactin may stimulate adrenal production of dehydroepiandrosterone sulfate (DHEA-S).

Hyperandrogenism

All patients with PCOS have an increased sensitivity to androgens. Androgens are carried in the circulation bound with high affinity to sex-hormone-binding globulin (SHBG). It is found that, up to 70% have elevated androgen levels and the other 30% are in the high-normal range.

Ovarian abnormalities

Androstenedione is produced by the ovarian stromal and thecal cells in response to LH. Normally, it is converted to estradiol by an FSH-dependent aromatase. Excess androstenedione in the circulation is converted to oestrone, which exerts a tonic effect on LH production while contributing to a relative suppression of FSH production. In case of high LH: FSH ratio, like in PCOS, more androstenedione is synthesized but is not aromatized, thus perpetuating a vicious cycle driving LH production and some prolactin production.

Abnormalities of estrogen

Estrogen secretion is usually disturbed in PCOS. **Estradiol** levels may be low to normal and in the anovulatory cycle, there is tonic production without the increase before ovulation or in the midluteal phase as in normal women[13, 14]. **Estrone** levels increase due to extra glandular conversion of androstenedione in adipose tissue, which further stimulates LH and inhibits FSH secretion.

Adrenal abnormalities

Excess adrenal androgen generation takes place during stress or adolescence or due to congenital adrenal hyperplasia because of enzyme defects which might initiate the cycle of abnormal LH/FSH stimulation and lead to PCOS.

DHEA-S

Though pituitary gonadotropin does not directly stimulate adrenal androgens, but prolactin can stimulate DHEA-S. In the adrenal glands, DHEA-S is co-secreted with cortisol. Thus, most excess cortisol secretion, as in stress or in adolescence, is accompanied by an elevation of DHEA-S secretion.

Peripheral abnormalities

Decreased SHBG. When level of circulatory androgen is elevated, especially testosterone, it inhibit production of hepatic sex hormone-binding globulin (SHBG). With less SHBG in circulation, more androgens are left free or unbound and therefore produce a greater clinical response in the form of hirsutism, acne and other manifestations of androgen excess. Thus, hyperandrogenism begets more.

Insulin resistance and hyperinsulinemia

Because hyperandrogenism and hyperinsulinemia coexist in PCOS, it is important to determine whether one causes the other. Exogenous or tumorous hyperandrogenism never result in glucose intolerance and elevated insulin levels[15, 16]. Lowering such hyperandrogenism improves insulin resistance and acanthosis. Numerous mechanisms might explain such a link[17–19]. Plenty of evidence are there which indicates that hyperinsulinemia begets hyperandrogenism [20, 21, 22]. Giving insulin to women with PCOS increases their circulating androgen levels[20] and lowering insulin by administration of diazoxide lowers their androgen levels[23, 24]. Also, insulin sensitizers like metformin[25] and thiazolidinediones[26] have been shown to reduce androgen levels and facilitate follicular maturation, normal menses, and pregnancy. Insulin amplifies the LH response of granulosa cells, thereby causing an abnormal differentiation of these cells, premature arrest of follicular growth, and, so, anovulation.

It is also proposed that the post receptor binding defect is an increase in insulin receptor-mediated serine phosphorylation with a concomitant decrease in protein kinase activity and necessary tyrosine kinase activity, which interferes with transduction of the insulin signal and causing it to be defective [27]. Insulin may increase androgen synthesis by various mechanisms. It may directly increase ovarian androgen synthesis by interacting with its own receptor or with the receptor for insulin-like growth factor-1, thereby increasing P450c17-alpha enzyme activity. In women with a genetic susceptibility, high levels of insulin in the blood stimulate an enzyme called **cytochrome P450c 17-α** in both the ovaries and the adrenal glands to produce excess amounts of male hormones. The excess of male hormones in the polycystic ovary syndrome therefore comes from both the ovaries and the adrenal glands. This is why oophorectomy does not solve the problem of excess body hair and acne. Many other metabolic abnormalities also commonly linked to insulin resistance which are evident in patients with PCOS like dyslipidaemia[28], increased concentrations of tissue plasminogen activator[29] and low-grade chronic inflammation[30].

Diagnostic criteria for the insulin resistance syndrome in women

Any three or more of the following:

Waist circumference >88 cm
Triglycerides > 150 mg/dL

HDL-cholesterol <50 mg/dL
Blood pressure >130/85
Fasting glucose >110 mg/dL

TREATMENT

The traditional treatment of PCOS is based on the clinical features and depends on the manifestations that are most bothersome to the patient. Response to therapy is slow; with biochemical reversal preceding clinical change may occur by as much as 6 to 9 months. The medical management of PCOS can be divided into four components, three of which are "acute" issues (control of irregular menses, treatment of hirsutism and management of infertility) and one is more "chronic."

Nonpharmacologic measures

Nonpharmacologic measures are universally recommended; which include diet, exercise and weight reduction if obese or to re-establish some degree of insulin sensitivity. Studies have shown a significant reduction in androgens and reestablishments of ovulatory cycles occur with a loss of 10 to 15 pounds over 6 months[31]. Hirsutism can improve in the first 6 to 9 months, concomitant with weight loss and regular menstrual cycles occur at the same time as lowering of androgen levels.

CONTROL OF IRREGULAR MENSES

This cardinal feature of PCOS can be both a significant health risk to patients. Irregular menses can be embarrassing because of unpredictability and painful. Also, it often leads to increased cramping with the heavier flow. Infrequent menstrual cycles also have a 3-fold increased risk of endometrial carcinoma[31]. In general, four menses per year are required to control this increased risk. The mainstay of treatment has been oral contraceptives, which are nearly always effective. The newer formulations are generally safer, although recently their use in PCOS is coming under greater scrutiny in regard to their potentially detrimental effect on insulin sensitivity[32]. Oral contraceptives should not be used in persons with a history of hypercoagulable state or deep venous thrombosis or in women over the age of 35 who smoke. A fasting lipid profile should be assessed before initiating therapy as oral contraceptives may worsen hypertriglyceridemia. For those women who might prefer not to cycle every month, periodic progesterone withdrawal is an option. A 7- to 10-day course of medroxyprogesterone 10 mg daily every 3 months often result in four menses annually. Weight loss result in improvement in menses. Kiddy et al. described improvement in menstrual cycle in 9 of 11 patients with oligomenorrhea who lost >5% initial body weight on a 1000 kcal/day, low-fat diet over 6 to 7 months, whereas only 1 of 11 patients (9%) losing <5% body weight demonstrated such improvement[33]. Metformin therapy is shown to induce resumption of normal ovulatory menstrual cycles in 40% to 90% of patients studied [34-37]. However, doses varied from 500 to 1000 mg twice daily. Overall, the treatment option chosen to regulate menses should depend on factors such as the degree of weight excess or glucose intolerance, the presence of other

PCOS issues requiring management. However, recent data have shown that lean PCOS patients also respond to metformin[38]. Metformin alone does not restore normal menstrual cyclicity in every woman with PCOS. Achievement of normal ovarian function occurs in less than 50% of women. Thus, in women not wishing to become pregnant, oral contraceptives may be a better way to regulate cycles. However, women with PCOS tend to show insulin resistance, which is exacerbated by oral contraceptives[39]. Thats why, use of combined oral contraceptives is cautioned in obese women (BMI more than 30 kg/m^2) and contraindicated in morbidly obese women (BMI more than 39 kg/m^2).

TREATMENT OF HIRSUTISM

Hirsutism is measured and quantified by a variety of methods. However, the decision to treat should be based on the patient's perception of the excess terminal hair growth.

Decreasing testosterone production

Excess testosterone production is predominantly ovarian in nature. It is caused by both increased luteinizing hormone stimulation from the pituitary and the effect of hyperinsulinemia at the ovary. By decreasing gonadotropin production and increasing sex hormone binding globulin (SHBG), oral contraceptives decrease bio available testosterone levels by 40% to 60%[40]. But only 50% of patients respond to oral contraceptives[41].

Decreasing testosterone action

Since the above therapies do not fully suppress testosterone levels, additional method of blocking testosterone action is useful. There are several anti-androgens available, but only spironolactone will be discussed further as many of the others have poor side effect profiles. Spironolactone is an aldosterone antagonist that was initially introduced as an antihypertensive agent. It also has a 67% relative affinity for the testosterone receptor (versus dihydrotestosterone) [42]. It reduces hirsutism scores by ~40%[43, 44] and is effective in ~50% of patients when used alone[45]. When combined with oral contraceptives, the response rate increases upto 75%[45] with a reduction in hirsutism scores of about 45%[46]. 50 mg twice daily is a reasonable starting dose which can be increased up to 100 mg twice daily if needed after 6 to 12 months. The most common side effect is menstrual irregularity, but nausea may also occur. So, the use of spironolactone in combination with oral contraceptives is preferred. For monitoring, potassium should be checked 1 to 2 weeks after initiation or after a dose increase. The effect of metformin and lifestyle modification/weight loss on testosterone action helps in increase in SHBG that occurs with improvement in insulin sensitivity. With an increase in SHBG, bio available testosterone decreases, thus lowering testosterone action. Kiddy et al., showed that >5% weight loss resulted in a 40% reduction in hirsutism[33].

MECHANICAL

Plucking/shaving/electrolysis/laser

Many women use one or a combination of methods to control hirsutism. Plucking should be avoided, as it can lead to folliculitis and scarring. Shaving is the cheapest and simplest way to remove unwanted hair, but may not be acceptable to some women. Laser treatment of hirsutism works best in fair-skinned patients with darker unwanted hairs as it involves selective thermal damage to the hair follicle [47]. But it may lead to erythema, edema, blistering and/or temporary hyper or hypopigmentation [48].

Eflornithine hydrochloride 13.9% cream Vaniqa is approved for the treatment of unwanted facial hair. It acts by inhibiting the enzyme L-ornithine decarboxylase, which is involved in hair growth. So, Vaniqa slows the growth of, but does not remove hair. It should be used continuously as hair growth rates returned to baseline after 8 weeks off therapy.

MANAGEMENT OF INFERTILITY

Many women with PCOS are infertile [49]. The American Society for Reproductive Medicine defines infertility as the inability of a woman younger than age 30 to get pregnant after 12 months of having unprotected intercourse or the inability of a woman older than age 30 to get pregnant after 6 months of having unprotected intercourse or the inability to carry a pregnancy to delivery [50]. PCOS accounts for 75% of anovulatory infertility and if pregnancies do occur, the first trimester miscarriage rate is as high as 30% to 50% [51].

CLOMIPHENE CITRATE

Obese women with PCOS often do not respond to low doses of clomiphene. Only 20% ovulation rate is seen at the 50 mg dose in women weighing more than 91 kg [52]. Indeed, the degree of obesity correlates with the dose of clomiphene needed to induce ovulation [53]. In two different studies, it is found that when clomiphene citrate was used after metformin pretreatment [54,55], ovulation rates were higher by 82% and 64%. Metformin as pre-treatment and co treatment with clomiphene citrate helps by sensitising follicles to follicle-stimulating hormone (FSH). Therefore, metformin alone and later in combination with clomiphene citrate should be used as a sequential treatment programme before the use of gonadotropin therapy for ovulation induction in infertile women with PCOS [56,57]. The higher doses of clomiphene when used, may cause side effects and can increase the rate of multiple gestations [58].

ORAL CONTRACEPTIVES IN PCOS

Oral contraceptives (OCPs) have been widely used in the treatment of PCOS. OCPs generally give predictable and consistent withdrawal bleeding which remove an important source of frustration. Along with that they reduce ovarian male hormone secretion, improving acne and excess hair, although they do not reduce adrenal gland male hormone secretion. But there is controversy about the short and long term safety of OCP treatment of PCOS [32]. OCPs make insulin resistance worse and further increase the tendency for clots in PCOS. The OCP **Yasmin** elevates blood glucose levels by 19% [59]. Therefore, women with PCOS must be

warned about the risks of deteriorating glucose tolerance and diabetes with OCP use. Before a woman with PCOS starts an OCP, a glucose tolerance test (GTT) should be performed and then repeated after six months of treatment. If a woman has impaired glucose tolerance or diabetes, OCPs should be avoided. If glucose tolerance deteriorates on an OCP, it should be stopped.

Antiandrogen

Many patients show a better benefit from the addition of an antiandrogen to an oral contraceptive. Spironolactone acts mainly by blocking the androgen receptor from "seeing" dihydrotestosterone. It may also suppress 17- hydroxylase and 17, 20-lyase activity, thereby blocking androgen biosynthesis. A 40% to 80% reduction in sexual hair growth is seen with spironolactone [60]. When used for alopecia, it reduces hair loss, but has a minimal effect on hair regrowth. Spironolactone requires 8 to 14 months before its clinical effects can be seen. The side effects of spironolactone include headache, mood swings, fatigue, reduced libido, mastodynia, hyperkalemia, gastrointestinal discomfort, and irregular menstrual bleeding. The dosage is 50 to 100 mg per day in divided doses, but up to 200 mg can be used. Cimetidine and ketoconazole have a very limited role to play in the treatment of PCOS, mainly because their side effects. Finasteride, a 5-alpha reductase inhibitor, has been used because it blocks the conversion of testosterone to dihydrotestosterone and decreases androgen-receptor binding [61]. It is as effective as spironolactone.

Steroids

Glucocorticoids have been known long before to be helpful if oral contraceptives and spironolactone do not suppress DHEA-S or testosterone adequately. Dexamethasone 0.125 to 0.25 mg or prednisone 2.5 to 5.0 mg can be used; the dose should be given in the evening to blunt corticotrophin stimulation of the adrenal glands [62]. Ovulatory cycles can be established, but the response of hirsutism is variable and limited. Higher doses may be associated with adrenal suppression and the development of cushingoid features. Once pregnancy is established, it is a conservative recommendation to continue low dose steroids through the first trimester to offset the luteotropic effect of androgens and prevent early miscarriage.

LIFESTYLE MODIFICATION/WEIGHT LOSS

Weight loss reduces hyperinsulinemia and subsequently hyperandrogenism. In the study by Kiddy et al. discussed earlier, about 40% of obese women with PCOS (mean body mass index [BMI] ~34 kg/m^2) who lost >5% of initial body weight with caloric restriction achieved spontaneous pregnancy [33]. With an average weight loss of 7.5%, 3 of the 20 subjects actively trying to conceive did so for a rate of 15%. Thus, lifestyle modification needs to be stressed in the treatment of infertility.

Insulin-sensitising agents

These agents increase tissue sensitivity to insulin action in vivo & have been used in type 2 diabetes for many years. The most commonly used agent in clinical practice is metformin, a biguanide ant hyperglycaemic drug that can be taken orally. Newer agents include the thiazolidinedione group of drugs, of which the most widely used is troglitazone. Hepatotoxicity of this drug has led to its withdrawal, but newer agents are now available, including rosiglitazone and pioglitazone. D-chiro-inositol has been used with some success as an insulin sensitizer in women with PCOS [63].

METFORMIN

A study by Heard et al. was done which involved 48 anovulatory PCOS patients having mean age of 29.9 years and BMI of 28.7 kg/m^2 enrolled for 15 months [36]. Metformin was started at 500 mg twice daily and increased to three times daily if ovulation did not occur by 6 weeks and clomiphene was added 6 weeks later as needed. It is found that normal menstrual cycles and ovulation occurred in 19/48 subjects (40%) on metformin alone and 15 of them (79%) became pregnant. Nearly 75% of these pregnancies on metformin alone occurred within 3 months of starting the medication. The addition of low dose clomiphene (50 mg) resulted in five additional pregnancies [36]. The rate of ovulation (40%) was seen with metformin alone in obese subjects (mean BMI ~32 kg/m2), while the addition of clomiphene the rate was increased upto 89%[34]. When used for 1 month prior to ovulation induction with FSH, metformin reduced the risk of ovarian hyperstimulation [64]. It is also seen that metformin improves fertilization and pregnancy rates in women with PCOS undergoing in vitro fertilization [65]. Thus, if infertility is the main issue, metformin therapy should be continued for as long as fertility efforts are ongoing, even if it “fails” initially. The first-trimester miscarriage rate in women with PCOS is 3-fold higher than that of normal women [51]. Metformin therapy continued throughout pregnancy has been shown to reduce this risk of early pregnancy loss. In a study by Glueck et al. on 19 women receiving metformin during their pregnancy to date 58% have had normal live births, 32% have ongoing pregnancies beyond the first trimester, and 10.5% had first-trimester miscarriages. No birth defects occurred [66].

Metformin commonly causes nausea and diarrhoea, with occasional vomiting. So, it should be introduced slowly over 4 to 6 weeks to a dose of 1500 mg/day. GIT side-effects are more commonly associated with the lunch dose or with poor dietary compliance as metformin partially blocks glucose absorption from the gut.

Metformin and ovulation: who will benefit

Metformin should have best results on ovulation rates in infertile women who are most insulin resistant. However, the picture is not very clear. Moghetti and colleagues [67] found that higher body-mass index and plasma insulin concentration, lower serum androstenedione concentration, and less severe menstrual abnormalities were baseline predictors of clinical efficacy measured by improved menstrual cyclicity.

Ovulation induction in PCOS

For ovulation induction, synthetic forms of LH and FSH (known as gonadotropin) have been used and it has a high success rate in PCOS [68] but carries an increased risk of multiple pregnancies. Also, women with PCOS are susceptible to the ovarian hyper stimulation syndrome (OHSS) by gonadotropin. The risk of the ovarian hyper stimulation syndrome can be reduced by treatment with metformin.

Laparoscopic ovarian diathermy (LOD) in PCOS

Laparoscopic ovarian diathermy is indicated when a female fails to conceive with the above treatments and has ovulation and pregnancy rates of 70% and 55% [69,70]. LOD releases male hormones stored in the cysts and reduces the number of male hormone-producing theca cells. Each ovary is punctured 6-10 times. Excessive punctures can destroy too many eggs and cause of ovarian failure.

IVF in PCOS

IVF is now reserved as a last option in the treatment of infertility in PCOS, particularly in those insulin resistant women with high oestrogen levels because of the risk of ovarian hyperstimulation.

THIAZOLIDINEDIONES (TZDS)

Many studies regarding ovulation induction with troglitazone were completed before it was removed from the market in 2000 [71-73]. Troglitazone alone resulted in ovulation rates of >40% and troglitazone pre-treatment, the success rate of clomiphene increased from 35% to 75% [72]. In a clinical trial involving a TZD, Azziz et al. evaluated the effect of troglitazone in 305 obese PCOS patients [72]. They found, at the highest dose of troglitazone (600 mg daily), 57% of the patients ovulated compared with just 12% of the placebo group. Although pregnancy was not an outcome measure of the study, troglitazone-treated subjects had a 4-fold greater fertility rate compared to the placebo group (18% versus 4%) [71].

COMPLICATIONS ASSOCIATED WITH PCOD

Insulin resistance

A connection between disturbed insulin action and PCOS was first indicated in 1980[74]. Subsequent studies have convincingly shown that insulin resistance is a key feature of PCOS, particularly in obese women [75-76]. Insulin resistance plays an important role in the pathogenesis of PCOS and is often exacerbated by co-existent obesity [77]. It is seen that both lean and obese women with PCOS have increased rates of insulin resistance and type 2 diabetes mellitus compared with body mass index (BMI) matched controls [77-79]. PCOS and obesity have synergistic effects on the incidence and severity of insulin resistance. There is also a strong

positive correlation between hyperandrogenaemia and insulin resistance in PCOS [72]. Hyperandrogenaemia may also lead to insulin resistance [80]. However, although insulin resistance has been associated with endothelial dysfunction and increased cardiovascular risk [81,82], there is no evidence that hyperandrogenaemia is a risk factor for cardiovascular disease in women [83].

Hyperandrogenaemia

The gender difference in susceptibility to cardiovascular disease has been attributed to the difference in sex steroids. It is found that oestrogen being cardio protective and androgens as a possible cardiovascular risk factor [84]. In pre- and post menopausal women carotid intima-medial thickness (CIMT) has been shown to be inversely correlated with endogenous dehydroepiandrosterone sulphate (DHEAS) and testosterone [84].

Dyslipidaemia

PCOS is classically associated with an atherogenic lipoprotein profile & it is characterised by elevated triglyceride-rich lipoproteins, accumulation of small dense low density lipoprotein (LDL) and depressed high density lipoprotein (HDL).

Metabolic syndrome

The metabolic syndrome is a clustering of factors which increase the risk of diabetes and cardiovascular disease and typically it includes a combination of disorders like insulin resistance, central obesity, dyslipidemia, hypertension and microalbuminuria [9,86]. The prevalence of the metabolic syndrome is probably increased in subjects with PCOS and this is likely to represent the interaction of a genetic predisposition to insulin resistance, dyslipidemia and hypertension with hyperandrogenaemia in the setting of visceral obesity [87-89]. The prevalence of type 2 diabetes which is another manifestation of the metabolic syndrome is increased in PCOS and increases with age, being reported in up to 21% of 35–40- year-old women with PCOS [90].

Diabetes risk and long-term management of in PCOS

Most PCOS patients are inherently IR with the obesity seen in many of them. As compared to the lean patients, obese patients had a 31% rate of impaired glucose tolerance and 7.5% met the criteria for type 2 diabetes mellitus [90]. In the United States, non-obese PCOS patients have a prevalence of these disorders 3 times that of the general population (10.3% impaired glucose tolerance and 1.5% type 2 diabetes mellitus) [90]. Cibula et al. noted a 4-fold increased prevalence of type 2 diabetes mellitus in women with PCOS who had undergone ovarian wedge resection for polycystic ovaries compared to a closely matched control population [91]. Metformin is perhaps the most widely studied agent so far and most [92,93] but not all [95] uncontrolled studies have shown a significant improvement in insulin sensitivity. A review of controlled trials showed similar findings with 5 of 7 other studies

showing improvements in insulin sensitivity [96].Troglitazone has similar effects in PCOS patients[97, 98]. Also, it is seen that metformin use throughout pregnancy in women with PCOS decreases the rate of gestational diabetes mellitus from ~30% to ~3%. [99] Metformin resulted in a 31% reduction in the development of type 2 diabetes mellitus over 2.8 years versus placebo, while lifestyle modification reduced the risk to a greater extent (58%) [100]. The lifestyle modification intervention was modest which involves approximately a 7% weight loss and 20 minutes of brisk walking daily.

Cardiovascular risk factors and disease in PCOS

Apart from increased risk of type 2 diabetes mellitus, there are multiple other metabolic abnormalities that put PCOS at higher risk for cardiovascular disease. The pattern of dyslipidemia in PCOS is increased triglycerides, and low HDL-cholesterol [101-104]. Women with PCOS may also have other disturbances like higher levels of small, dense LDL-cholesterol [105], homocysteine [106], plasminogen activator inhibitor type 1 [107], decreased insulin induced vascular relaxation [108], and endothelial dysfunction [109]. Also, women with polycystic ovaries on ultrasound had more extensive coronary artery disease at catheterization than those without such ultrasound findings [110]. Lastly, PCOS patients also have been shown to have increased carotid intimal thickness [111] and an almost 6-fold increased prevalence of coronary artery calcification [112]. Based on the increased prevalence of risk factors in patients with PCOS, Dahlgren and colleagues estimated a 7-fold increased risk of myocardial infarction [113]. Wild et al. found a significantly increased risk of stroke (odds ratio, 2.8) but no difference in coronary artery disease in a retrospective cohort of PCOS patients [114], while Cibula et al. reported a 4-fold increased risk of coronary artery disease in PCOS patients followed 20 to 40 years [91].

PCOS in adolescents

Premature pubarche (appearance of pubic hair before the age of 8year) may be an early indication of PCOS and is associated with ovarian hyperandrogenism [115] and the development of chronic anovulation [116]. Increased awareness by physicians about PCOS will lead to diagnosis at an earlier age. The incidence of type 2 diabetes mellitus in children is increasing dramatically [117]. Palmert and colleagues performed oral glucose tolerance tests in adolescents with PCOS (mean age 16.7 years) and found the prevalence of impaired glucose tolerance to be 30% and that of type 2 diabetes mellitus 3.7% [118]. A glucose-to-insulin ratio may also be helpful in adolescents to determine insulin resistance.

PCOS, seizure disorders and valproic acid

There is an increased prevalence of reproductive endocrine disorders in patients with epilepsy. The reason for this overrepresentation is likely to be multifactorial, ranging from the influence of epilepsy itself on the hypothalamic-pituitary axis to various effects of antiepileptic drugs on hormone secretion and action, Valproate has received particular attention in this

regard. Some evidence suggests that some women on this therapy have higher levels of insulin, testosterone, and triglycerides than those on another agent like lamotrigine [116].

CONCLUSION

The variable clinical presentations of PCOS require a comprehensive approach to patient management. The clustering of cardiovascular & metabolic risk factors needs the importance of management of PCOS as a chronic disease. Usually, women with PCOS consult a physician for infertility, androgen excess or menstrual abnormality. So, treatment strategy is focused on managing these complaints. However, treatment should also cover the long term complications. Treatment of insulin resistance constitutes a vital component of long term treatment policy. Non pharmacologic measures like diet restriction, exercise & weight reduction should also be implemented whenever necessary.

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