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Polycystic Ovarian Syndrome: An awareness guide for women

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ABSTRACT

Polycystic ovary syndrome (PCOS) was originally identified as a reproductive disorder characterized by enlarged, sclerocystic ovaries, menstrual disturbances, obesity, infertility and hirsutism. PCOS is now recognized to be a metabolic syndrome which may include hyperinsulinaemia, hyperlipidaemia, diabetes mellitus, and possibly cardiac disease, as well as the more conventionally recognized increase in androgen levels, cosmetic problems, anovulation, infertility, endometrial cancer and obesity. The high prevalence of adverse metabolic features in women with PCOS translates into significantly increased risks for the development of type 2 diabetes mellitus and other indicators of susceptibility to cardiovascular disease. The prevalence of PCOS in women of reproductive age has been reported to be about 6-10%, although a prevalence of 12.5-50 % has been reported in women with diabetes. It is now very well known that there is an epidemic of diabetes in Indian population and onset of Type 2 diabetes occurs at early age in Indian population. The correction or insulin resistance in PCOS not only helps in restoration of menstrual cycle and ovulation in PCOS but also, reduces overall risk of developing type 2 diabetes, obesity, dyslipidemia, hypertension, and possibly cardiovascular disease. These findings can emphasize the need to begin awareness for effective treatment of insulin resistance by preventing associated lifestyle factors along with insulin sensitizing agents.

KEY WORDS: Hyperinsulinemia, obesity, dyslipidemia, type 2 diabetes, life style modification, metformin.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) or Stein-Leventhal syndrome, also known as PCOD (polycystic ovarian disease) is among the most common endocrinopathies in current practice, affecting 6 - 10% of women of reproductive age. [1,2] Originally labeled as problem of oligomenorrhea, hirsutism, obesity, and infertility by Stein and Leventhal in 1935, the true pathophysiology of the syndrome has been unfolded by the subsequent appreciation of its endocrine, metabolic, and cardiovascular complications. PCOS is a condition characterized by disruption of the regular process leading to ovulation and associated with hyperandrogenemia, normal or elevated oestrogen levels, raised luteinizing hormone (LH) secretion with alteration of the normal relationship between LH and follicle stimulating hormone (FSH) leading to a raised LH:FSH ratio. Macroscopically the ovaries are usually, although not always, enlarged and lobular. On histological examination the ovaries contain atretic follicles, theca cell hyperplasia and a generalized increase in stroma. On ultrasound examination the ovaries are characterized by peripheral distribution of multiple subcapsular cysts.[3] In the last 2 decades, insulin resistance has been identified as a significant contributor to the reproductive as well as metabolic abnormalities associated with PCOS. But to the Gynecologist, PCOS is the single most important cause of infrequent or anovulation, which constitutes 40% of cases of female infertility.[4] Not only fertility but women affected adversely by obesity and a high body mass index (BMI).[5] It is also associated with increase rate of miscarriages and late obstetric complications.[6] Based on the current knowledge of PCOS, important aim is that management should not only focus on improving the often troublesome hirsutism and infertility but also should focus on the long-term risks associated with insulin resistance (IR). Indeed, the management of the PCOS patient often will vary over time as the patient enters different stages of life with different goals. In contrast, because of the long-term health implications of insulin resistance, the importance of lifestyle modification toward weight management and maintaining adequate physical activity should be the one constant in the management of these patients. There has long been debate about the definition of PCOS. Three

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different diagnostic classifications have been proposed to define this disease. The first one, published in 1990, known as the "NIH (National Institute of Health) criteria" requires the simultaneous presence of hyperandrogenism and menstrual dysfunction in order to diagnose PCOS. Later on, in 2003, an expert panel met in Rotterdam and added to the previous criteria the presence of polycystic ovarian morphology detected by transvaginal ultrasonography. The later classification broadened the spectrum of PCOS and also included women with oligomenorrhea and PCO without hyperandrogenism or hyperandrogenism and PCO without menstrual dysfunction. Finally, the Androgen Excess Society, published in 2006 new diagnostic criteria which required the presence of clinical or biochemical hyperandrogenism, with either PCO or menstrual dysfunction to diagnose PCOS.[7] It has recently been accepted that PCOS is defined by the new Rotterdam Criteria formulated by the American Society for Reproductive Medicine (ASRM) and the European Society for Human Reproduction and Embryology (ESHRE) as a condition where two of the following three criteria are present: (1) oligo - or anovulation, (2) hyperandrogenism (clinical or biochemical or both) and (3) polycystic ovarian morphology on ultrasound examination (a polycystic ovary is one which has 12 or more immature follicles measuring 2 - 9 mm in diameter, often described as a string of pearls) with the exclusion of other related disorders.[8,9] It is important to exclude other causes of such presentations. The differential diagnosis of PCOS includes:[10,11] (1) hyperprolactinaemia, (2) congenital adrenal hyperplasia (21-hydroxylase deficiency), (3) primary hypothyroidism, (4) Cushing's syndrome (abdominal adiposity, striae, raised cortisol levels, low K+), (5) acromegaly, (6) adrenal carcinoma or other androgen secreting tumours, (7) musculinising tumours of the adrenal or ovary (rapid onset of signs of virilisation), (8) simple obesity, (9) drugs (e.g., Androgenic drugs, including testosterone, danazol, gestrinone, adrenocorticotropic hormone, high-dose corticosteroids, androgenic progestogens in oral contraceptives, anabolic steroids and Non-androgenic drugs, including ciclosporin, diazoxide, minoxidil, and phenytoin; rarely, carbamazepine, sodium valproate, and acetazolamide), (10) patients with menstrual disturbances and signs of hyperandrogenism and (11) idiopathic or familial hirsutism (12) Hypogonadotropic hypogonadism (that is central origin of ovarian dysfunction). (13) Hyperandrogenic-insulin resistant-acanthosis nigricans (HAIRAN) syndrome.

EPIDEMIOLOGY

The heterogeneous nature of the disease, along with the lack of precise diagnostic criteria, has made the determination of the true epidemiology of PCOS difficult. The prevalence of infertility in PCOS has been reported to be 74%. Evidence from prospective and cross-sectional studies indicates that the general prevalence of polycystic ovary syndrome is probably about 6–7%; the prevalence is higher in women of South Asian origin, who have more severe symptoms and present at a younger age.[12] PCOS is diagnosed in 90-95% of patients attending an infertility clinic with anovulation.[13] Various studies shows PCOS is more prevalent in obese women than those who are lean, affecting around 28% obese and 5% lean women.[14,15] Ninty percent of PCOS patients presented with infertility are overwight.[16]

PATHOPHYSIOLOGY

The cause of polycystic ovary syndrome (PCOS) is unknown. It is one of the most common endocrinopathies and likely to be multifactorial, with both genetic and environmental factors playing a part.

Insulin resistance and endocrinological changes:

"Insulin Resistance", defined as the diminution in the biological responses to a given level of insulin in the body,[17] which results in compensatory hyperinsulinemia in PCOS patients. In women with PCOS, the theca cells of the ovary produce excess androgens, which may be due to hyperinsulinaemia or increased serum levels of luteinizing hormone (LH).

Insulin and LH acts synergistically that increase androgen production in the theca cells of the ovary and in the adrenal gland. This hyperandrogenemia stops follicular development and therefore causes anovulation (failure of the ovaries to produce eggs) and menstrual disturbance.[18,19] PCOS women show lower serum FSH levels as compared to normal cycles and which results in accumulation of antral follicles between 2 mm and 8 mm in large numbers, due to lack of adequate and timely stimulation.[20]

Insulin receptor shares substantial sequence and surface homology with insulin like growth factor-1 (IGF-1).[21] This IGF-1 is produced by the human ovarian tissue and IGF-1 receptors have been detected in the ovary.[22] The basis of the ovarian insulin sensitivity in PCOS may be due to the fact that insulin in hyperinsulinemic state, may inhibits the hepatic production of IGF-1 binding protein.[23,24] This increases the concentration of free IGF-1 in the circulation, which also stimulates theca cells to produce androgen.[24] Thus, changing the microenvironment of the ovarian follicle from estrogenic to androgenic. This intra-ovarian hyperandrogenism induces follicular atresia and prevents the selection of a dominant follicle.[25] At the same time, the granulose cells of these large numbers of viable ovarian follicles maintain an increased sensitivity to FSH and thus retain constant, plateau blood levels of estradiol and inhibin. Due to high level of LH, the physiologic variations of estadiol normally seen during a menstrual cycle which results in the FSH peak and pre-ovulatory LH surge are absent in PCOS women. This finally results in chronic anovulation, formation of ovarian cysts and hirsutism, alongwith a visibly thickened cortex of the typical 'smooth, pearly-white' polycystic ovaries.[26]

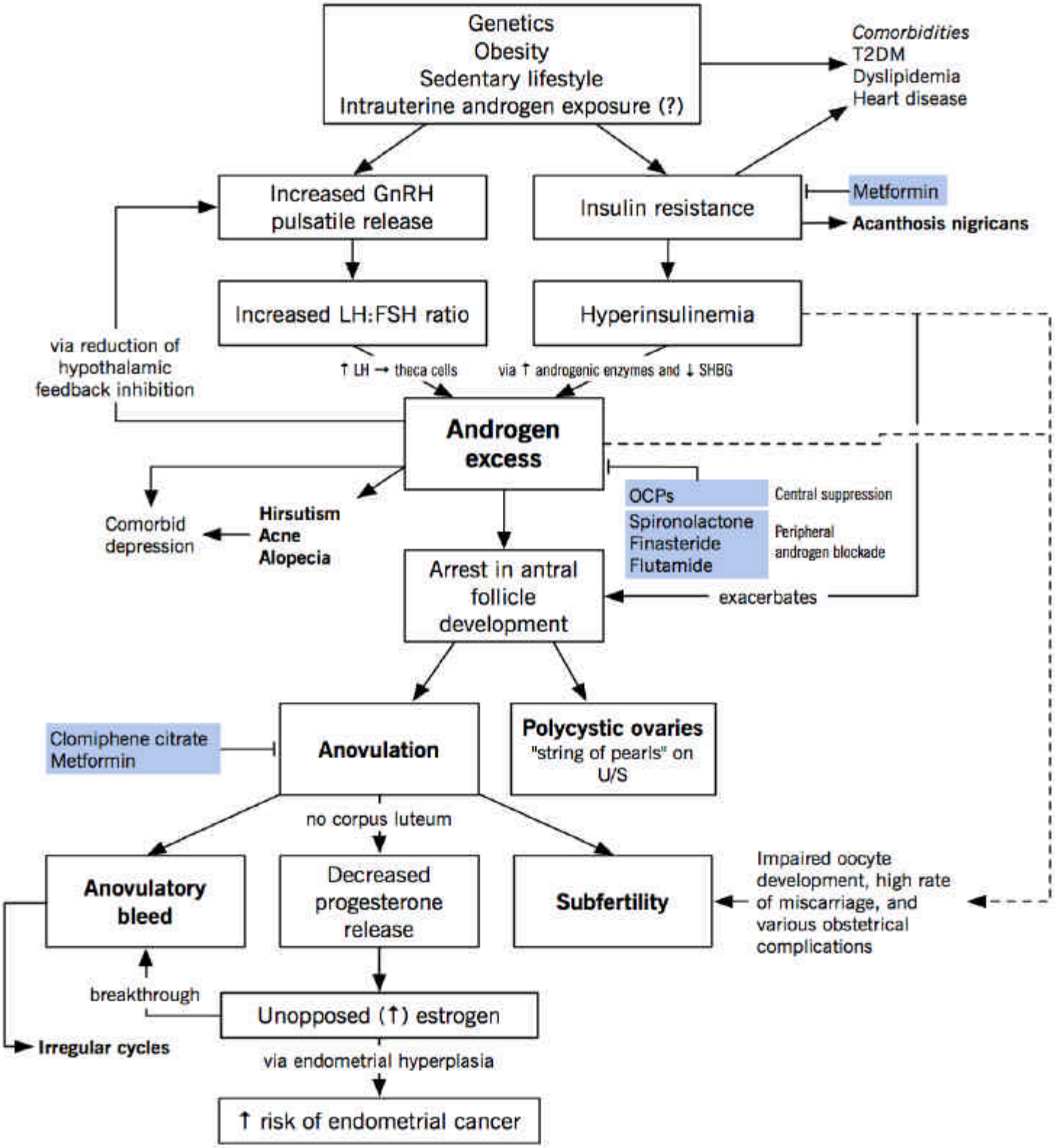

Figure 1: Pathophysiology of PCOS[28]

Insulin acts indirectly to reduce hepatic biosynthesis of sex hormone-binding globulin (SHBG), [27] the key circulating protein which controls the bioavailability of testosterone. With less SHBG in circulation, more androgens are left free or unbound and therefore produces more clinical response in terms of hirsutism, acne and other manifestations of androgen excess. Similarly, IGF binding proteins production reduces in liver and ovary. These actions elevate levels of free IGF-1, up-regulate ovarian IGF type-1 receptor and thus amplify IGF-1 as well as IGF-2 actions in the ovary. Therefore, hyperinsulinemia appears to play a significant role in the pathogenesis of hyperandrogenism that contributes to a full-blown clinical picture of PCOS.[26]

LONG TERM CONSEQUENCES OF PCOS

Impaired glucose tolerance and PCOS:

The presence of a defect in insulin action which amplifies LH stimulated androgen secretion from thecal cells, has been well established. Insulin resistance in PCOS has been linked to later development of impaired glucose tolerance and type-2 diabetes.[29.30] Risk of type 2 diabetes in middle age of 10–20% is evident from small long-term cohort studies, case–control studies and case series, [31-33] with a high rate of impaired glucose tolerance, suggesting that further cases of diabetes will develop later. Evidence demonstrates that the prevalence of type 2 diabetes in women diagnosed with PCOS is 7 times higher than controls (15% to 2% respectively).[34,35]

It is well known that obesity is observed in about 60% of women with PCOS. Studies reported that more than 20% of obese women with PCOS will have impaired glucose tolerance after the age of 30.[34,36] The central distribution of fat though is not dependent to BMI and actually is associated with higher insulin concentrations. Increased body mass, particularly abdominal obesity, and a strong family history of diabetes (up to 83% in one study) increase the risk of developing type 2 diabetes in the presence of polycystic ovary.[33] However, studies says that the frequency of type 2 diabetes is also increased in women with PCOS who are not obese (body mass index less than 27 kg/m^2),[29,32,33,37] suggesting that PCOS is an independent risk factor for type 2 diabetes in middle age.[38,39]

Cardiovascular disease and hypertension:

Evidence is limited; women with PCOS have more risk factors for cardiovascular disease than other women of the same age, and may be at increased risk of cardiovascular events and death.[40] PCOS women have increased cardiovascular risk factors such as obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia. Hyperinsulinemia appears to be the main reason for the increased cardiovascular risk of women with PCOS. In the absence of impaired glucose tolerance, pancreatic b-cell fails to function properly, which is inversely correlated to SHBG (sex hormone binding globulin) concentration, leading to hyperandrogenism and chronic unopposed estrogen secretion.

There are two mechanisms by which insulin resistance in PCOS contributes significantly to higher incidence of cardiovascular disease in these women. One mechanism is the direct atherogenic action and the other mechanism is the adverse affect of the lipoprotein profile.[37] Obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia caused by PCOS are known risk factors for cardiovascular disease. The abnormal lipoprotein profile in women with polycystic ovaries is significantly noted. That consists of high concentrations of serum triglycerides and total and low-density lipoprotein cholesterol.[41] While the levels of high density lipoprotein (HDL) are suppressed.[42,43] The serum plasminogen activator inhibitor-I concentrations are elevated,[44] which lead to impaired fibrinolysis and therefore directly affect vascular tissue that causes changes associated with coronary heart disease. The evidence is thus indicating that there is indeed an increased risk for women with PCOS of developing cardiovascular disease. The elevation of risk factors in young women with PCOS may therefore put them at increased risk of developing accelerated atherosclerosis resulting in myocardial infarction.[31,41,45] In the Nurses' Health Study, menstrual cycle irregularity was associated with an increased risk of nonfatal and fatal coronary heart disease, although no data were available for confirmation of a diagnosis of PCOS.[46]

There seems to be a direct relationship between insulin plasma levels and blood pressure.[47,48] The prevalence of hypertension is three times higher in women with PCOS between the age of 40-59 years as compared to controls. The incidence of preeclampsia in obese women with PCOS conceiving is four times higher as compared to the general pregnant population.[48] It seems that significant risk factors for developing atherosclerotic conditions, hypertension and myocardial infarction, are present at an earlier age than women without PCOS.[49] As per the Joint British Society Guidelines, the persistent blood pressures greater or equal to 140 mmHg systolic and or 90 mmHg diastolic, not responding to lifestyle measures, need to be considered for drug therapy (women with diabetes or other high risk factors with blood pressure greater than 130 mmHg systolic and or 80 mmHg diastolic may require drug therapy).[49]

Endometrial Cancer:

The recent interest of researchers is in the long term risks of PCOS has focused on its association with endometrial cancer. Severe oligo- and amenorrhoea in the presence of premenopausal levels of estro-

gen can lead to endometrial hyperplasia and carcinoma.[11,50] The risk may be higher in developing endometrial cancer in patients with obesity, longterm use of unopposed oestrogens, nulliparity, infertility, hypertention and diabetes.[11,35,44] In women with PCOS intervals between menstruation of more than three months may be associated with endometrial hyperplasia and later carcinoma.[38,51] Evidence from a Balen's study in which 1270 women with chronic anovulation participated, the excess risk of endometrial cancer was identified to be 3.1.[52] However, the evidence for association between PCOS and endometrial cancer was inconclusive.[53] The true risk of endometrial carcinoma in women diagnosed with PCOS has not been clearly defined yet.

Ovarian Cancer:

A cause-and-effect relationship between induction of ovulation and ovarian cancer has never been established. However, the possibility that fertility drugs may increase a woman's risk of ovarian cancer is distributing, particularly to infertile couples and the professionals who treat them. Several study reports might suggest that there is a connection between PCOS and increased risk of ovarian cancer.

The risk is higher in nulliparous women (multiple ovulations), with early menarche and late menopause. Without any evidence based data to support this theory, it may be that to treat infertility by inducing multiple ovulations in women will increase their risk. So, there will be less chances of developing ovarian cancer in women with PCOS due to their life time reduced ovulation rate, by using ovulation induction treatments and inducing multifollicular ovulations their risk for ovarian cancer will be technically created.

There are only a few studies related to the possibility of association of polycystic ovaries and ovarian cancer with conflicting evidence. Study held by Danish suggest that infertility itself increases the risk of borderline and invasive ovarian tumors.[54,55] Another study with clomiphene, an ovulation inducer and ovarian cancer suggests that the relative risk for ovarian cancer for women with PCOS is 4.1 compared to controls.[56]

Breast Cancer:

There are limited data evaluating the risk of breast cancer in women with PCOS. Putative risk factors for breast cancer include obesity and nulliparity which are common in PCOS. A meta-analysis of three studies was performed, of which, one showed a trend to an increased risk, one showed protection, and one showed no risk. In aggregate, no association was found.[57] On the other hand though, it seems that there is a positive association between PCOS and the presence of family history of breast cancer. In a study of 217 women the proportion of women with positive family history of breast cancer was significantly higher in women with PCOS compared with controls.[58]

Obstructive sleep apnoea

Obstructive sleep apnoea (OSA) is an independent risk factor for cardiovascular disease and is more common in PCOS. Women diagnosed with PCOS should be asked about the symptoms of OSA (snoring, daytime fatigue/somnolence) and offered investigation and treatment if indicated.

TREATMENT

Treating PCOS women presenting with infertility has always been a therapeutic challenge for clinicians. The traditional treatment of PCOS aimed at the clinical features and depends on the manifestations that are most bothersome to the patients. Rather than empirical therapy a step-by-step approach should be incorporated to the patient profile, such as age, Body mass index, duration of infertility, history of prior treatment and signs of insulin resistance have been found to be more successful. Recently published Thessaloniki ESHRE/ASRM-sponsored PCOS Consensus Workshop Group's report on consensus in infertility treatment related to PCOS, which has addressed the important questions relating to the efficacy and safety of various treatments available for these women[59] can be used as the guideline while formulating the management of this condition.

Nonpharmacological interventions:

Nonpharmacologic measures are universally recommended that include diet, exercise, and weight reduction if obese or to reestablish insulin sensitivity to the extent. It has been proved that reduction of body mass or even calorie restriction without weight loss can result in improvement of ovulation and regression of hyperandrogenic features.[60] Studies have shown a significant reduction in androgens and reestablishment of ovulatory cycles with a loss of as little as 10 to 15 pounds of weight over 6 months.[61]

Variety of interventions have been proposed for obesity include; behavioral counseling, life style therapy such as diet and exercise, pharmacologic therapy and bariatric surgery, but none have been evaluated for the specific treatment of infertility in PCOS.[62] Diet and exercise simultaneously brings improvement in insulin sensitivity and normalization of plasma insulin levels in obese PCOS patients.[60] The diet should be hypocaloric, reduced by 500kcal/day with less carbohydrate contents or any low-calorie diet which is comfortable to the patients.[59]

Any exercise such as jogging, yoga or brisk walking for some period at a particular time each day, is beneficial, and ideally any physical activity should be clubbed in with a diet control program to help in weight loss and further maintenance of ideal body weight.

On the whole, general lifestyle modification and weight control are

definitely effective and need to be advised as a prudent first step before drug therapy is considered. But still these programs have their limitations. About 10-30% of women with PCOS are lean, and weight loss is not an option for them.

Pharmacological interventions:

Clomiphen Citrate:

Traditionally, Clomiphene citrate is first-line therapy for ovulation induction in normogonadotropic anovulatory women. It is selective estrogen receptor modulator (SERM). It acts by releasing small amounts of FSH from the anterior pituitary through its anti-estrogenic action, indirectly by blocking hypothalamic estrogen receptors, therefore signaling a lack of circulating estrogen to the hypothalamus and inducing a change in the pattern of pulsatile release of GnRH. In many euestrogenic anovulatory women, these minute variations in the circulatory FSH levels is enough to reset the cycles of events leading to ovulation and often pregnancy. It restores ovulation in approximately 80% of patients but it results in pregnancy in only about 35-40% of patients.[63] It has the advantages of being cheap, simple to use, requires little monitoring and hardly any side effects reported in 50 years of clinical practice.[64] Though its long career as one of the most trusted ovulation inducer for PCOS, clomiphene citrate is not the ultimate option in clinical practice. Clomiphene citrate failure may be due to either clomiphene resistance or failed to conceive despite of successful clomiphne citrate induced ovulation. Furthermore, clomiphene citrate treatment should be limited to 12 cycles because longer-term treatment is associated with increased risk of ovarian cancer due to ovarian hyperstimulation.

Insulin-sensitizing agents:

Given the strong association and possible pathophysiologic relationship between insulin resistance and PCOS, insulin sensitizers have begun to play a more significant role in its treatment. Insulin-sensitizing agents not only helps to correct the immediate symptoms related to dysovulation and infertility but also acts on to prevent long term complication arising of it. These drugs have shown to improve insulin sensitivity to non-diabetic women with PCOS and lead to conversion of impaired glucose tolerance to normal glucose tolearance. Normally used drugs are metformin as category B drug, thiazolidinediones (rosiglitazone and pioglitazone) as category C drugs in pregnancy as per FDA.

Metformin is the first-line insulin sensitizer used in clinical practice. It acts by inhibiting hepatic glucose output and, to a lesser extent, enhances muscle glucose uptake, lowering insulin levels. Metformin does not cause any significant improvement in spontaneous ovulation, compared to placebo with lifestyle modification and it is less effective than clomiphene citrate in inducing ovulation. In overweight and hyperandrogenic women, the combination of metformin with clomiphene citrate is more effective as ovulation inducer and improves pregnancy rates than any of these used alone.[65]

However, the recent research and reviews have suggested controversial views regarding use of metformin as part of the treatment for infertility.[66,67] The Thessaloniki Consensus does not recommend meformin routinely for all PCOS.[59] As per the recent Cochrane Review on the use of insulin-sensitizing agents in PCOS for the treatment of subfertility, the role of metformin in the management of infertility in PCOS is limited. There is no proven benefit of metformin either alone or alongwith clomiphene citrate, or when compared to clomiphene citrate.[67] Even other insulin sensitizing drugs like thiazolidonediones do not offer any additional advantage over metformin.

Gonadotropin therapy:

Gonadotropin therapy is usually the second line therapy for induction of ovulation following clomiphene citrate failure and has been used for more than 40 years of clinical practice. It is administered in PCOS patients to increase transient yet sufficient circulatory levels of FSH. The drugs commonly used are FSH and LH or their combinations. Risks associated with gonadotropin therapy are poor oocyte quality, multiple pregnancy especially in PCOS patients with very narrow therapeutic range. [68]

Oral Contraceptives:

Oral contraceptives are useful in patients with PCOS who do not desire pregnancy. They not only establish regular menstrual cycles, but they also reduce gonadotropin stimulation of the ovary and thereby reduce androgen production.[69] They inhibit 5-alpha reductase and androgenreceptor binding, and cause an increase in SHBG. Oral contraceptives mainly used to treat cosmetic problems such as acne and hirsutism.

It is important to choose the appropriate oral contraceptive. Newer progestins such as desogestrel, as well as norgestimate and ethynodiol diacetate, have minimal androgenic potential and are considered to be superior to preparations containing norgestrel or norethindrone, which have more androgenic properties.

CONCLUSION

Polycystic ovary syndrome is a complex disorder of unknown etiology and it involves several specialists for presenting reproductive, endocrinological, dermatological, gynecological, cardiac and psychological manifestations. Hyperinsulinemia seems to be one of the main

factor. The essential problem is anovulation, resulting in infertility. The variable and heterogenous clinical picture makes diagnosis more difficult and tends to delayed management that could avoid late complications. Its treatment should include preventive measure and aim to antagonize the actions of androgens in target-tissues, to reduce insulin resistance and to correct anovulation. Current conservative treatment should emphasize sustainable weight loss through dietary modification and exercise. Modifying additional lifestyle factors, including psychosocial stressors are also crucial in long-term treatment of PCOS. The review will provide evidence that weight loss, psychosocial status and sedentary lifestyle in female influence prevalence of insulin resistance associated with PCOS. Health education should be given to patients regarding dietary habit and sedentary life style and influence of stress on the disease along with treatment attempts by physician should be made to modify each of several factors a little, along with insulin sensitizing agent to prevent this high prevalent condition.

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