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Maha Yousef Soliman Omran

Obstetrics & Gynecology Department, Cairo University

Abstract

The polycystic ovary syndrome (PCOS), one of the most common causes of infertility due to anovulation, affects 4-7% of women). Etiology of PCOS remains largely unknown, familial aggregation of cases suggests genetic susceptibility to the disorder. Though genes involved remain unknown, recent evidence points to a gene of the insulin receptor. Genes implicated in ovarian follicular development may also play a role. A fundamental aspect of the syndrome seems to be a defect in insulin metabolism. There is consistent evidence that increase of body weight may favour a more severe hyperandrogenism. Treatment of PCOS has been mostly symptomatic. Only recently has the use of insulinomimetic or insulin sensitizing agents provided an option to treat the presumed underlying cause of this disorder, which is insulin resistance. Metformin appears to improve risk factors for cardiovascular disease in diabetic and non-diabetic patients, indicating that its use could be associated with a reduction in coronary heart disease in patients with PCOS. The use of metformin in hyperinsulinemic women with PCOS improved the lipid profile, including decreases in total cholesterol, low density lipoprotein cholesterol, and triglyceride concentration.

Correspondence

Dr. Maha Yousef Soliman Omran

Obstetrics & Gynecology Department

Cairo University, Egypt.

The polycystic ovary syndrome (PCOS), one of the most common causes of infertility due to anovulation, affects 4-7% of women.⁽¹⁾ According to the national institutes of health, basic diagnostic criteria should be the presence of hyperandrogenism and chronic oligo-anovulation, with the exclusion of other causes of hyperandrogenism such as adult-onset congenital adrenal hyperplasia, hyperprolactinaemia and androgen-secreting neoplasms. A consensus conference held in Rotterdam⁽²⁾ agreed on the appropriateness of including ultrasound morphology of the ovaries as further potential criteria to define the PCOS but also established that at least two of the following criteria are sufficient for the diagnosis: oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries at ultrasound.

Etiology of PCOS remains largely unknown, familial aggregation of cases suggests genetic susceptibility to the disorder.⁽³⁾ Though genes involved remain unknown, recent evidence points to a gene of the insulin receptor. Genes implicated in ovarian follicular development may also play a role. A fundamental aspect of the syndrome seems to be a defect in insulin metabolism. There is peripheral insulin resistance in adipose tissue and skeletal muscle which, in turn, leads to hyperinsulinaemia, though the ovaries remain sensitive to insulin. Insulin, insulin-like growth factor-1 and luteinizing hormone cause thecal cell hyperplasia, increased circulating levels of androgen and estrogen and arrest of follicular development. There is consistent evidence that increase of body weight may favour a more severe hyperandrogenism. Higher proportions of obese women with PCOS complain of androgenic abnormalities in comparison with normal weight women. Despite the fact that ovarian hyperandrogenism is considered the mainstay of PCOS, 40%-50% of the patients also exhibit elevated adrenal androgens and it is possible that this feature is also clusters in families with this disorder. There is a significant correlation between the DHEAS levels of PCOS patients and their sisters, suggesting that adrenal androgen secretion is partially determined by inherited factors.⁽⁴⁾

Determination of insulin resistance (IR) in women with PCOS depends on baseline fasting blood measurement of glucose and

insulin e.g. fasting insulin level, glucose / insulin ratio (G/I) and the calculated indices of the homeostasis model assessment (HOMA), quantitative sensitivity check index (QUI CKI), as well as Kitt (kinetic disappearance of glucose) values after insulin tolerance test (ITT). Normal insulin sensitivity was diagnosed by insulin level < 12mU ml, G/I ratio > 6.4, HOMA values < 47, and QUIKI values of > 0.333. By using G/I ratio, IR was diagnosed in 65.4% of women of PCOS and in 76.7% in obese women. HOMA and QUIKI are more sensitive methods for detecting IR in PCOS, suggesting that the prevalence of IR is approximately 80% of women of PCOS and 95% of obese women.⁽⁵⁾

The clinical features of PCOS are heterogeneous and may change throughout the lifespan, starting from adolescence to postmenopausal age.⁽⁶⁾ Hyperandrogenism (i.e., hirsutism and acne), menstrual irregularities and infertility from chronic anovulation represent the major complains in young women. PCOS is of paramount importance due to the increased risk for metabolic syndrome⁽⁷⁾ impaired glucose tolerance, type 2 diabetes mellitus, hypertension and atherogenic lipid profile. Subclinical atherosclerosis has been demonstrated by carotid ultrasound in premenopausal women with PCOS. In women undergoing coronary angiography; those with history of PCOS have more extensive coronary artery disease. It has been estimated that women with PCOS are at a higher risk for complications of cardiovascular disease with a seven fold increased risk for myocardial infarction.

Treatment of PCOS has been mostly symptomatic. Only recently has the use of insulinomimetic or insulin sensitizing agents provided an option to treat the presumed underlying cause of this disorder, which is insulin resistance. Metformin is not a true insulin sensitizer, but it improves peripheral insulin sensitivity. Metformin is an oral, biguanide, antihyperglycemic agent that is chemically and pharmacologically unrelated to the sulfonylureas. Its mechanism of action is thought to include decreased hepatic glucose production, decreased intestinal absorption of glucose, and increased peripheral uptake of glucose and utilization, resulting in improved insulin sensitivity.⁽⁸⁾ Metformin is highly water-

soluble drug. It is not metabolized but is eliminated through the kidneys by tubular secretion. The most common side effects of metformin are nausea and diarrhea. Ingestion of metformin along with food decreases these side effects. Other untoward effects are bloating, flatulence, and vomiting. These symptoms are dose dependent. Hypoglycemia does not usually occur. A rare but potentially dangerous side effect is lactic acidosis.

Initial studies of the effects of metformin on women with PCOS have shown an increase in insulin sensitivity accompanied by decreasing insulin and androgen levels. Most studies have demonstrated a pronounced decline of free circulating testosterone and androstenedione levels, modulation of adrenal androgen production and a decrease in intraovarian androgen production. Metformin may have a direct inhibitory effect on the expression of various enzymes involved in thecal cell steroidogenesis and thecal cells; androgen production.⁽⁹⁾ Beata et al⁽¹⁰⁾ evaluated the effects of 12 weeks of metformin therapy (500 mg three times per day) on hormonal and clinical indices in women with PCOS and elevated fasting insulin levels (more than 17 $\mu\text{U/l}$). Metformin significantly reduced levels of fasting insulin by more than 30%. Most of the decline of insulin was observed at 4 weeks of treatment, however, insulin also declined thereafter. Concurrent decreases of serum testosterone and increase in SHBG concentrations resulted in a decline of free testosterone index by almost 40%. Level of testosterone stabilized within 4 weeks of therapy and did not vary significantly thereafter. The greatest decline in testosterone and free testosterone index in response to metformin was observed among patients with the most pronounced hyperandrogenemia. In women with normal baseline concentration of DHEAS, metformin result in significantly increase of DHEAS by 13%. In contrast in women with high baseline DHEAS, metformin resulted in statistically significant decrease of DHEAS by 12%. Thus the adrenal response to declining levels of insulin may be dependent on the baseline adrenal function. In that study, improvements of acne and hirsutism were statistically significant; however only the decrease in acne appeared to be clinically meaningful. In view of the duration of the hair growth, one would

anticipate that the full effect of metformin on hirsutism would require therapy for more than 6 months. The study has demonstrated that responses to metformin are related to the severity of hyperandrogenemia and to adrenal function.⁽¹⁰⁾

It is well known that PCOS patients have a distinctive abnormal LH pulsatile secretion, with normal (sometimes higher) pulse frequency and higher pulse amplitude. The exaggerated GnRH-induced LH response is reduced by metformin. After 6 months of metformin administration, LH plasma level is reduced as a result of decreased pulse amplitude and becomes similar to that of eumenorrheic women. Significant restoration of the menstrual cyclicity in amenorrheic and oligomenorrheic PCOS patients occurs after 4-6 months. Metformin administration improves reproductive axis functioning in hyperandrogenic nonobese PCOS patients by restoring normal ovarian activity and modulating the reproductive axis (namely GnRH-LH episodic release.). It improves menstrual cyclicity through the normalization of the gonadotrophin pulsatile release.⁽¹¹⁾

Metformin is an effective ovulation-inducing agent. When used in conjunction with clomiphene citrate, it acts synergistically and increases ovulation and pregnancy rates. Its use in PCOS patients resulted in an ovulation rate of 40% with metformin therapy alone but 67% when clomiphene citrate was added, and 69% of the ovulating patients conceived. Costello and Eden⁽¹²⁾ found a 34% pregnancy rate after metformin therapy, with or without clomiphene citrate, over 9 months in unselected women with PCOS. Among clomiphene citrate-resistant women with PCOS, a pregnancy rate of 25% after clomiphene citrate plus metformin for 6 months has been reported. Pretreatment with metformin prior to FSH results in lower peak of serum estradiol and more follicular development. Addition of metformin to controlled ovarian stimulation decreases the cycle cancellation and reduces the incidence of multiple pregnancies.

Patients with PCOS undergoing in vitro fertilization (IVF) usually are high responders to gonadotrophins, producing large numbers of follicles with high serum estradiol levels and increasing risk of ovarian hyperstimulation. However, a greater

percentage of these oocytes are immature due to high androgen environment in the ovary. In patients treated with metformin, mean number of oocytes retrieved is not affected. However, the mean number of mature oocytes and embryos cleaved are increased. Fertilization rates and clinical pregnancy rates are also increased. Metformin leads to modulation of preovulatory follicular fluid insulin-like growth factors⁽¹³⁾.

Jonard et al⁽¹⁴⁾ showed that there are important differences in categories of antral follicles definable with their size. The number of smaller visible follicles (Follicle diameter between 2 and 5 mm) is significantly raised in PCOS compared with normal, and they represent the category responsible for the high circulating androgen concentrations, whereas the number in the larger category (Follicle diameter between 6 and 9 mm) reflects the degree of insulin resistance and is closely linked to the frequency to the follicular maturation, ovulation and infertility. These two follicular categories represent later stages of development, before the preovulatory stage, and whose development from the primordial stage requires many weeks' growth. Thus in PCOS, rates of initial recruitment and progress through development stages appear to differ from normal. The raised androgens in the circulation of women in PCOS probably derive from the enlarged cohort of small follicles of androgen-secreting stage as well as increased direct stimulation by insulin, perhaps involving stromal tissue well. Mullerian-inhibiting substance (MIS), known as anti-Mullerian hormone, is believed to regulate granulosa cell and oocyte function and it may be an important regulator of follicle recruitment. It is raised in the circulation of woman with PCOS in humans, MIS is not seen in primordial follicles, but it is expressed from the primary stage through to the small antral follicles, where maximum expression is seen.⁽¹⁵⁾ In this later category of follicle, with maximum granulosa cells, that is likely to be responsible for much of the MIS in the circulation. Metformin treatment of PCOS patients results in significant reduction in circulating MIS. Suppression of MIS occurs only after protracted treatment (after 4 months). The protracted delay suppression of MIS, in contrast to rapid suppression of androgen, may be secondary to the development of a

cohort of follicles that underwent initial recruitment in an environment of reduced insulin stimulation.⁽¹⁶⁾

Women with PCOS are frequently infertile and most of those who become pregnant miscarry in the first trimester. Hypofibrinolytic and plasminogen activator inhibitor (PAI) activity are usually associated with miscarriage. High PIA activity promotes abortion probably through thrombotic induction of placental insufficiency. Metformin therapy (1.5-2.55 g/day) throughout pregnancy reduces the otherwise high rate of first-trimester spontaneous abortion from a historical value of 73% to 10% as it lowers PAI activity, and does not appear to be teratogenic.⁽¹⁷⁾ Recent studies indicate that metformin throughout pregnancy might reduce pregnancy complications such as gestational diabetes and premature delivery in women with PCOS.⁽¹⁸⁾ Metformin passes freely through the placenta⁽¹⁹⁾ and the fetus is exposed to the therapeutic concentrations. The knowledge on metformin metabolism in the fetus is scarce. In adults, metformin is eliminated by renal tubular secretion. Hence, one may speculate that in the fetus, some of metformin is excreted to the amniotic fluid and reabsorbed to the fetal circulation by swallowing, then eliminate from the fetus by passage through the placenta into maternal circulation. Although no teratogenic effects are reported for metformin, and metformin does not seem to influence pH levels in umbilical artery blood, long term follow up is mandatory in infants of patients with PCOS receiving metformin throughout pregnancy. A recent randomized controlled trial confirmed that both clomiphene citrate (CC) and metformin are similarly effective for ovulation induction in women with PCOS and demonstrated that metformin is superior to CC in term of pregnancy rate after a 6 months follow-up.⁽²⁰⁾ Clomiphene citrate acts on human endometrium with antiestrogenic effect, reducing endometrial thickness and impairing endometrial pattern and vascularization. Large follicle dimensions, such as those obtained in CC administration may reflect delayed ovulation and result in post maturation, aging of oocytes, and defective embryo development. Oocytes produced by CC have low developmental ability due to an alternation of perfollicular vascularization, subsequent hypoxic damage, and cytoplasmic and

chromosomal disorders. Metformin induces not only normalization of ovarian, follicular, and corpus luteum vascularization, but improves several surrogate markers of endometrial receptivity (i.e. uterine, subendometrial, and endometrial blood flow, and endometrial thickness and pattern).⁽²¹⁾

Obesity is strongly associated with PCOS. Although the cause of this association remains unknown, but obesity is present in at least 30% of cases, in some series, the percentage may be as high as 75%.⁽²²⁾ The high prevalence of obesity in PCOS has profound effects on both pathophysiology and clinical manifestation of the disorder. Compared with normal weight women with PCOS, those with obesity are characterized by a worsened hyperandrogenic and metabolic state, poorer menses and ovulatory performance, poorer pregnancy rates, higher abortion rates and a lower live birth rate. Abdominal phenotype of obesity can be defined as a condition of relative functional hyperandrogenic state. Pathophysiological mechanisms by which obesity influences the expression of PCOS are complex and not completely understood. These mechanisms may involve early factors during intrauterine life, leptin, insulin, insulin like growth factors, and potentially the endocannabinoid system. In obese women with PCOS, the presence of obesity in her mother during pregnancy appears to increase the susceptibility to develop hyperandrogenism and PCOS phenotype of the daughter later in time i.e.; in-utero androgen excess may be an important factor programming subsequent PCOS development during puberty. Leptin is considered as one of the major peripheral signals that affect food intake and energy balance and obesity is a classic condition of circulating leptin excess. Leptin may exert inhibitory effect on ovarian function and play a role in determining anovulation in PCOS. Endocannabinoid system has been found to regulate multiple endocrine functions including hypothalamic - pituitary - gonadal axis and it is deeply involved in dynamic and homeostatic regulation of feeding and energy metabolism.⁽²³⁾ Although there are not many reports in the literature on the effect of weight loss in obese women with PCOS, all these studies, nonetheless, clearly demonstrate that the weight loss improves both endocrine and

metabolic abnormalities. Overall, after 8-10 months of lifestyle intervention to achieve weight loss, approximately 80% achieve regular menses, 60% have ovulatory cycles and 40% become pregnant. In a recent study to evaluate the efficacy of weight loss with and without metformin in obese women with PCOS, all women improved indicating that weight loss, rather than metformin treatment, is responsible for the improvement.⁽²⁴⁾

No studies have examined the effect of metformin on cardiovascular morbidity in women with PCOS. However, metformin appears to improve risk factors for cardiovascular disease in diabetic and non-diabetic⁽²⁵⁾ patients, indicating that its use could be associated with a reduction in coronary heart disease in patients with PCOS. The use of metformin in hyperinsulinemic women with PCOS improved the lipid profile, including decreases in total cholesterol, low density lipoprotein cholesterol, and triglyceride concentration.

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