

Polycystic ovary syndrome: A component of metabolic syndrome?

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ABSTRACT

In 1935, Stein and Leventhal first described the polycystic ovary (PCO) as a frequent cause of irregular ovulation in women seeking treatment for subfertility. Although the initial management was surgical with wedge resection of ovary, the availability of radioimmunoassay and increased clinical use of ultrasound made it clear that many women had the ultrasound characteristics of PCO with or without the biochemical or clinical features of PCOS and therefore that PCO were not associated with a single syndrome. The association between increased insulin resistance and PCOS is a consistent finding in all ethnic groups. Obesity is a common factor in the majority of women with PCOS. It is postulated that a woman may be genetically predisposed to developing PCOS but it is only the interaction of environmental factors (obesity) with the genetic factors that results in the characteristic metabolic and menstrual disturbances. Weight loss, altered diet and exercise have been shown to be effective in the management of PCOS. Importance of early recognition, proper intervention, long-term monitoring and health implications needs more concern.

KEY WORDS: Diagnosis and intervention, insulin resistance, metabolic syndrome, polycystic ovarian syndrome

Polycystic ovary syndrome (PCOS) is one of the most common reproductive health problems of women.^[1] It is associated with obesity, hyperinsulinemia, elevated luteinizing hormone levels (associated with ovulation), elevated androgen levels (virilization), hirsutism (male hair growth), follicular atresia (ovarian growth failure), ovarian growth and cyst formation, anovulation (failure to ovulate) and amenorrhea (absence of menstruation or irregular periods). Insulin resistance or hyperinsulinemia is associated with excess abdominal fat, glucose intolerance, hypertension and dyslipidemia (increased triglycerides, decreased HDL and increased small dense LDL). This clustering of metabolic characteristics was earlier referred to as "Syndrome X" and now as the metabolic syndrome. Initially called the Stein–Leventhal syndrome after its researchers in the 1930s, PCOS is now recognized to be a metabolic syndrome.^[2] Thus PCOS is not just a gynecological or dermatological disorder, but part of a metabolic syndrome that affects multiple systems and whose key pathogenic element is hyperinsulinemia.

Endocrinology of PCOS

In contrast to the characteristic picture of fluctuating hormone levels in the normal cycle, a "steady state" of gonadotropins and sex steroids in women with PCOS is due to the persistent

anovulation in which the production of estrogen and androgens are both increased.^[3,4] Anovulatory women with PCOS also have a higher luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) pulse frequency and amplitude when compared to the normal midfollicular phase.^[5] This enhanced pulsatile secretion of GnRH can be attributed to a reduction in hypothalamic opioid inhibition because of the chronic absence of progesterone.^[6]

The increased LH secretion, as expressed by the LH: FSH (follicle-stimulating hormone) ratio, is positively correlated with the increased free estradiol.^[7] A sensitive assay for inhibin-B has detected high levels in women with PCO, suggesting that multiple small follicles can suppress FSH by increasing the circulating levels of inhibin-B.^[8] However, FSH levels are not totally depressed. Hence new follicular growth is continuously stimulated but not to the point of full maturation and ovulation.^[9] Therefore, multiple follicular cysts develop 2-10 mm in diameter, which are theca cells, often luteinized in response to high LH levels.

Hyperthecosis refers to patches of luteinized theca-like cells scattered throughout the ovarian stroma. It is characterized by the same histological findings as seen in polycystic (PCOS) syndrome.^[10] The clinical picture of more intense androgenization is a result of greater androgen production. This

condition is associated with lower LH levels, which is a possible consequence of the higher testosterone levels blocking estrogen action at the hypothalamic pituitary level. It seems appropriate to view hyperthecosis as a manifestation of the same process of persistent anovulation, but with greater intensity. A greater degree of insulin resistance is correlated with the degree of hyperthecosis.^[11] Because, insulin and insulin-like growth factor 1 (IGF-1) stimulate proliferation of thecal interstitial cells, hyperinsulinemia may be an important factor contributing to hyperthecosis.^[12]

Puberty and PCOS

During puberty, insulin resistance develops probably because of the increase in sex steroids and growth hormone, resulting in secondary increase in insulin and IGF-1, which leads to a decrease in the sex hormone binding globulin (SHBG) and would allow greater sex steroid activity for pubertal development. Thus PCOS can be considered as a state of exaggerated puberty or hyperpuberty. After puberty, the insulin and IGF-1 levels progressively decline in most patients, resulting in normalization of the clinical and morphological picture. In subjects with PCOS, the higher levels persist either because hyperinsulinemia persists or because another pathogenic factor has taken over its role in the meantime. In the latter instance, hyperinsulinemia probably only served as an inducing event.

Insulin Resistance and Hyperandrogenism

The association between increased insulin resistance and PCOS is a consistent finding in all ethnic groups.^[13] Hyperandrogenism and insulin resistance are often associated with acanthosis nigricans, which is dependent on the presence and severity of hyperinsulinemia.^[14] Serine phosphorylation of the beta chain of the insulin receptor and of the adrenal and ovarian P450 C17 enzyme would explain both the hyperinsulinemia and hyperandrogenism (serine phosphorylation increases and dephosphorylation decreases 17 20-lyase activity and androgen production).^[15] Serine, instead of tyrosine phosphorylation is an "off" mechanism for glucose transport, but an "on" mechanism for P450 C17 enzyme activity [Figure 1].

If the insulin levels necessary to suppress free fatty acid levels cannot be achieved, then increase in free fatty acids leads to increased hepatic glucose production and hyperglycemia. There are several mechanisms for the state of insulin resistance: peripheral target tissue resistance and decreased hepatic clearance.^[16] Studies with euglycemic clamp technique indicate that hyperandrogenic women and hyperinsulinemia have peripheral insulin resistance and in addition, a reduction in the insulin clearance rate due to decreased hepatic insulin extraction.^[17]

Hyperinsulinemia leads to hypertension and an increased risk of coronary artery disease^[18] and is further associated with increased triglycerides small dense LDL and decreased HDL cholesterol levels. It is also associated with increased

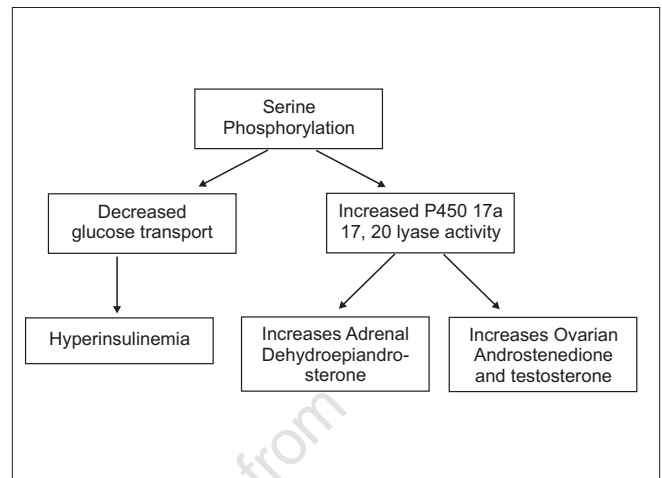


Figure 1: Effects of serine phosphorylation instead of tyrosine phosphorylation

plasminogen activator inhibitor-1 (PAI-1) which is correlated with increased risk of coronary events and impaired fibrinolysis.^[19] Leptin and inflammatory markers were acting at paracrine and endocrine levels in PCOS subjects.^[20]

Overweight anovulatory women with hyperandrogenism have a characteristic distribution of body fat known as android obesity.^[21] Android obesity is the result of visceral mesenteric locations of adiposites. This fat is more and more active metabolically. This type of fat distribution is associated with hyperinsulinemia, diabetes mellitus and an increase in androgen production rates resulting in decreased levels of sex hormone binding globulins and increased levels of testosterone and estradiol.^[22]

How does hyperinsulinemia produce hyperandrogenism?

There is an impressive correlation between the degree of hyperinsulinemia and hyperandrogenism.^[23] At higher concentrations, insulin receptors are blocked or deficient in numbers and it is to be expected that insulin would bind to the Type 1 IGF receptors.^[24] In view of the known actions of IGF-1 in augmenting the thecal androgen response to LH, activation of Type 1 IGF receptors by insulin would lead to increased androgen production in thecal cells.^[25,26] Both IGF-1 and IGF-2 activities can be mediated by the Type 1 IGF receptor, which is structurally similar to the insulin receptor. The mechanism by which hyperinsulinemia causes hyperandrogenism is illustrated in Figure 2.

There are two other important actions of insulin which contribute to hyperandrogenism in the presence of hyperinsulinemia: inhibition of hepatic synthesis of SHBG and inhibition of hepatic production of insulin-like growth factor binding protein-1 (IGF BP-1) which in turn increases the circulating level of sex hormone and IGF-1 and greater local activity of IGF-1 and/or IGF-2 in the ovary. Why are not all female patients with hyperinsulinemia, hyperandrogenic having Type 2 diabetes? The answer to this question is not known but a logical speculation is that an ovarian genetic susceptibility factor is required.^[27]

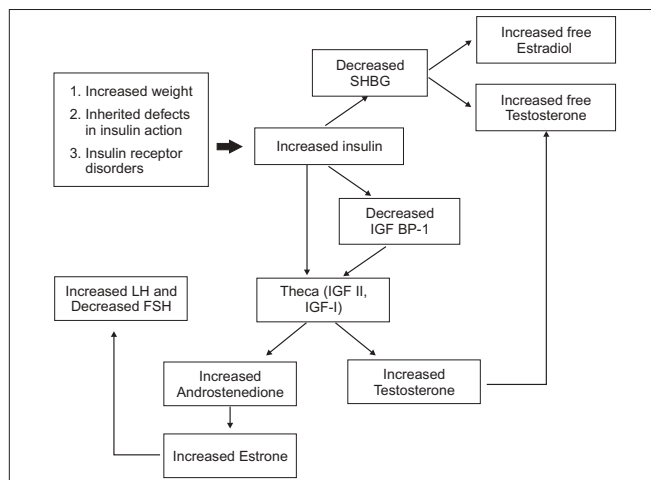


Figure 2: Mechanism of hyperinsulinemia causing hyperandrogenism

Clinical Presentation

The clinical features are heterogeneous but anovulation is the key feature which presents as amenorrhea in 50% of cases and with irregular, heavy bleeding (dysfunctional uterine bleeding) in 30%.^[28] It is usually present from menarche and is due to the unopposed estrogen stimulation of the endometrium and endometrial hyperplasia and in some instances, adenocarcinoma may develop.^[29] Chronic anovulation results in abnormal folliculogenesis resulting in infertility. True virilization is rare, but 70% of anovulatory patients complain of cosmetically disturbing hirsutism. Alopecia and acne can also be consequences of hyperandrogenism.

Obesity has been classically regarded as an important feature, but its presence is variable. However, the higher the body mass index, the greater the insulin resistance and hyperandrogenism. Therefore it follows that hirsutism is more common in overweight anovulatory women i.e., as an anovulatory woman gains weight, the underlying problem is more easily detected.

Acanthosis nigricans has been associated with several metabolic and endocrine disorders, including diseases of adrenal glands, obesity and insulin resistance. An example of these associations has been the HAIR-AN syndrome: hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN).

Although the elevated androgens and anovulation offer some protection against osteoporosis, the adverse impact on the risk for cardiovascular disease is a more important consideration.^[30] Women with PCOS have more extensive coronary atherosclerosis on coronary angiography.^[31] Patients with PCOS are at greater risk for Type 2 diabetes, are more likely to develop glucose intolerance during gestation^[32] and may demonstrate the full blown metabolic syndrome later in life.^[33]

The expression of PCOS is variable within the same family with some members presenting with the full-blown syndrome, others only with mild hirsutism and yet others being completely normal. Diabetes mellitus, obesity, hypertension,

hyperlipidemia and ischemic heart disease are frequently found within the same family. Insulin resistance could probably be the underlying factor that links all these entities.

Diagnosis

A question that has puzzled gynecologists and endocrinologists for many years is what causes polycystic ovaries. The characteristic polycystic ovary emerges when a state of anovulation persists for any length of time. Whether diagnosis is by ultrasonography or by traditional clinical and biochemical criteria, a cross-sectional study of anovulatory women revealed that approximately 75% have polycystic ovaries.^[34] Since the 1990 National Institutes of Health-sponsored conference on PCOS, it has become increasingly clear that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and PCO morphology.^[35] Polycystic ovary syndrome remains a syndrome and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis [Table 1].^[35,36] To label one as having PCO there should be the presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 ml).^[37] This definition does not apply to women taking oral contraceptive pills, since its use modifies ovarian morphology in normal women and putatively in women with PCO.^[38] Only one ovary fitting this definition is sufficient to define PCO. If there is evidence of a dominant follicle (>10 mm) or a corpus luteum, the scan should be repeated during the next cycle. The presence of an abnormal cyst or ovarian asymmetry (which may suggest a homogeneous cyst) necessitates further investigations.

To establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, hyperprolactinoma, Cushing's

Table 1: Revised diagnostic criteria of polycystic ovary syndrome

| Diagnostic criteria proposed by | Year | Criteria |
|--|------|---|
| US National Institutes of Health ^[35] | 1990 | Both 1 and 2 1. Chronic anovulation 2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies |
| European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine ^[34] | 2003 | 2 out of 3 1. Oligo- or anovulation 2. Clinical and/or biochemical signs of hyperandrogenism 3. Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome) |

syndrome and androgen-secreting tumors. Anovulatory women who do not exhibit signs of hyperandrogenism should be evaluated for the presence of a metabolic abnormality by measuring the free testosterone level and LH levels. If elevated, insulin resistance and glucose tolerance should be assessed. However, a fasting glucose / insulin ratio is about one-third the cost of a free testosterone level and hence it may be more economical to measure this ratio in all anovulatory women. Value less than 4.5 is consistent with insulin resistance.^[39] Biochemical features of PCOS are presented in Table 2. The Homeostasis Assessment Model (HOMA IR) can also be used to estimate insulin resistance using the formula: fasting insulin ($\mu\text{U/ml}$) X fasting plasma glucose (mmol/l) / 22.5.^[40]

Early Recognition and Intervention

With the change of emphasis in medical care from disease treatment to illness prevention and health promotion, polycystic ovarian syndrome is an excellent example of a syndrome for which early recognition and intervention, such as weight control, diet modification and lifestyle changes may prevent or delay the development of diabetes and atherosclerosis leading to coronary artery disease.

The great majority of ovulatory women with polycystic ovaries on ultrasonography is endocrinologically normal and only occasionally is an androgen level found to be elevated.^[41] When a mild basic disorder is present, the homeostatic adjustments allow the maintenance of normal physiologic mechanisms and there are no clinical consequences, it is hard to justify medical interventions.

The familial cluster of anovulation and PCO suggests an underlying genetic basis.^[41-44] Family members of women with anovulation, hyperandrogenism and polycystic ovarian have an increased incidence of hyperinsulinemia in females and premature baldness in males.^[45] Initial searches for genes that are associated with a susceptibility to anovulation and PCO have implicated a locus on the insulin gene and the gene encoding P450 (CYP 11A).^[46] These studies imply an autosomal dominant mode of inheritance, directing clinicians to counsel families that theoretically 50% of mothers and sisters

within a family can manifest this disorder. However, the actual expression of the disease is 40% due to modification by both genetic and environmental factors.

There are two aspects of counseling and subsequent management of pregnancy in women with PCO: firstly, the general behavior of the PCO itself and secondly, additional features of PCOS. It is the women with PCOS who will benefit most from preconception counseling. Not only does she have an endocrine disorder, but also a metabolic one of which the insulin resistance in particular has a bearing on pregnancy. Hyperinsulinemia may lead to obesity, which in turn is associated with hypertension, pre-eclampsia and gestational diabetes.^[47] Table 3 summarizes the overall goals of treatment of PCOS.

Screening women with polycystic ovarian syndrome for glucose intolerance should become a part of normal practice. Ultrasonographic prevalence of PCO was higher in women with diabetes than in nondiabetic subjects.^[48] Women with endometrial hyperplasia and carcinoma are traditionally obese with hypertension and diabetes and they are likely to have PCO. Thus, preconception counseling is important not only to advise short-term weight loss in order to reduce maternal and neonatal morbidity, but also to prevent later morbidity by encouraging obese women to lose weight and nonobese women to stay slim.^[49] It is appropriate and indeed essential to monitor glucose tolerance with periodic glucose tolerance testing.

A variety of pharmacologic agents are available to reduce insulin levels. Diazoxide and octreotide, the long-acting analogue of somatostatin, both inhibit insulin secretion but are accompanied by worsening of glucose intolerance.^[50,51] The best approach is to improve peripheral insulin sensitivity, thus achieving reductions in insulin secretion and stability of glucose intolerance. Metformin enhances weight reduction and improves lipid profile and vascular integrity. It is the preferred drug for reducing insulin resistance. It works well in both overweight and normal weight individuals and is now considered the drug of choice for PCOS.^[52] A recent systematic review and meta-analysis which included 13 trials concluded that metformin is an effective treatment for anovulation in women with PCOS and that there is some evidence of benefit on variables of the metabolic syndrome.^[53] It is suggested that metformin should always be used as an adjuvant to lifestyle changes and not as a replacement for increased exercise and improved diet.^[54]

Thiazolidinediones are insulin-sensitizing drugs that increase the disposal of glucose in peripheral tissues and act by

Table 2: Biochemical features of polycystic ovarian syndrome

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|--|
| <ul style="list-style-type: none"> Increased androgen levels in blood (testosterone and androstenedione) Increased LH levels, exaggerated surge Serum LH to FSH ratio (exceeds 2) Increased fasting insulin or fasting glucose insulin Increased estradiol and oestrone levels Decreased SHBG levels Atherogenic lipid profile Increased ALT levels Increased prolactin levels Microalbuminuria, hyperuricemia, increased PAI-1, fibrinogen and CRP levels |
|--|

LH- Luteinizing hormone, FSH- Follicle-stimulating hormone, SHBG- Sex hormone, binding globulin, ALT- Alanine aminotransferase, PAI-1- Plasminogen activator inhibitor -1, CRP- C-reactive protein

Table 3: Overall goals of treatment of polycystic ovarian syndrome

| |
|--|
| <ul style="list-style-type: none"> Reduce the production and circulating levels of androgens Protect the endometrium against the effects of unopposed estrogens Support lifestyle changes to achieve normal body weight Lower the risk of cardiovascular disease Avoid the effects of hyperinsulinemia on the risk of cardiovascular disease and diabetes mellitus Induction of ovulation to achieve pregnancy |
|--|

activating specific nuclear receptors. They have been found to be effective in the treatment of PCOS.^[55] Medical treatment of hirsutism (antiandrogens) is often combined with cosmetic methods (bleaching, electrolytes, waxing, shaving) gonadotropin, GnRH analogue). Ovarian diathermy has replaced wedge resection.

The best therapy for women with PCOS is weight loss. Both the hyperinsulinemia and the hyperandrogenism can be reduced with weight loss. Increased PAI-1 levels associated with hyperinsulinemia also improve with weight loss.^[56] These metabolic improvements are associated with resumption of ovulation and can help women to conceive.^[57] Modest increase in exercise can improve insulin effectiveness. High-fiber diet and low-fat diets with increase in monounsaturated fats may also help. Low-sodium foods are also recommended. Smoking should be stopped, because it stimulates adrenal androgens.

Long-term monitoring of women with PCOS

In order to address this issue, we need to consider the known risks of long-term health problems and the effectiveness of any interventions that might be offered to reduce morbidity and/or mortality. The hope for long-term monitoring of women with PCOS would be to offer effective interventions that reduce morbidity and mortality. Women with PCOS are at increased risk of developing a number of chronic conditions and consequently their health should be monitored with particular emphasis on screening for diabetes, coronary artery disease and endometrial cancer. Advice about exercise and diet is more rational, given the abundant data on the role of lifestyle change in preventing and treating problems of glucose metabolism.

PCOS and Components of Metabolic Syndrome

It has been suggested that women with PCOS could reduce their risk of Type 2 diabetes and cardiovascular disease through weight reduction and exercise and that the use of medications that reduce insulin resistance might also be warranted.^[58] Some studies have demonstrated the benefits of weight reduction and exercise programs for infertile women with PCOS. There is very little evidence that women with PCOS are at increased risk of cardiovascular disease independent of Type 2 diabetes.^[59] This may be due to the action of unopposed estrogen in anovulatory cycles, which might protect women with PCOS, despite the presence of other cardiovascular risk factors. The extent to which Type 2 diabetes contributes to premature morbidity and mortality for women with PCOS remains unclear at present. It is also debated whether it is the PCOS per se or the obesity that is a frequent attribute of the condition or both that is the principal contributor to the observed excess of Type 2 diabetes among women with histologically proven PCOS.^[60] An Indian study which show that dyslipidemia in PCOS is associated with obesity rather than raised testosterone.^[61] The results of studies that have considered the relationship between PCOS and lipid levels are inconsistent. The HDL levels are a possible exception as the majority of studies report lower HDL levels among women with PCOS than among controls, regardless of the selection criteria for either cases or controls.^[62] Long-term follow-up of women with PCOS treated previously with ovarian wedge

resection has shown these women to be at increased risk of developing Type 2 diabetes, independent of obesity.^[63] As pregnancy has a diabetogenic effect, all women who are at risk of Type 2 diabetes by virtue of a positive family history of diabetes and/or obesity are also at risk of developing gestational diabetes. Insulin resistance, defined as decreased insulin-mediated glucose utilization, is found in 10-25% when sophisticated dynamic studies of insulin action are performed.^[64] However, the criteria for selecting an abnormal cutoff point vary. Insulin resistance in women with PCOS appears to be even more common (up to 50%), both in obese and nonobese women.^[65] Reports of the prevalence on insulin resistance in women with PCOS vary depending on the sensitivity and specificity of the tests employed and the heterogeneity of PCOS. Also the criteria of metabolic syndrome itself vary, based on at least three criteria, NCEP,^[66] WHO^[67] and IDF^[68] and consequently the prevalence of metabolic syndrome in PCOS would vary depending on the criteria employed.

The association between exposure to unopposed estrogens and an increased risk of endometrial cancer has been well established. Obesity has been shown consistently to be an important risk factor for endometrial cancer. Many studies support the hypothesis that reduced exposure to ovulatory menstrual cycles is protective against breast cancer.^[69]

Conclusions

PCOS is an excellent example of the importance of clinical research and of how a simple clinical observation can pave the way for new scientific discoveries. PCOS is not just a reproductive disease, easily remedied by the use of ovulation induction, but a systemic condition, the molecular biology of which is still being investigated. Every clinician must recognize the clinical impact of anovulation and undertake therapeutic management of all anovulatory patients to avoid the risks of developing cardiovascular disease and diabetes. If the woman is overweight, an oral glucose tolerance test should be performed since >25% of obese women with PCOS will develop impaired glucose tolerance or Type 2 diabetes mellitus by the age of 30. Furthermore, the comprehensive evaluation of women with PCOS should be performed not only once at the time of diagnosis, but longitudinally thereafter since the risk for developing these associated disorders increases with age. By creating and supporting a preventive healthcare attitude, we not only correct specific clinical consequences of anovulation, but can also reduce the co-morbidities such as obesity, diabetes, hypertension, cardiovascular disease and ovarian cancer linked to this syndrome.

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