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PCOS in obesity: Indian scenario

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Abstract
Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinopathy affecting women. It has an unknown etiology and is recognized as a heterogeneous disorder that results in overproduction of androgens, primarily from the ovary, and is associated with insulin resistance (IR). Polycystic Ovary Syndrome (PCOS) has become commonplace in today's world. PCOS must be considered a serious issue because of its implication on long term health regardless of a woman's age. It needs to be seen as a lifelong condition, not one tied only to pregnancy. Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine-metabolic disorder that implies various severe consequences to female health, including alarming rates of infertility. Although its exact etiology remains elusive, it is known to feature several hormonal disturbances, including hyperandrogenemia, insulin resistance (IR), and hyperinsulinemia. Insulin appears to disrupt all components of the hypothalamus-hypophysis-ovary axis, and ovarian tissue insulin resistance results in impaired metabolic signaling but intact mitogenic and steroidogenic activity, favoring hyperandrogenemia, which appears to be the main culprit of the clinical picture in PCOS. This Article analyzes the Related Literature on PCOS in obesity in Indian Scenario in detail.

Keywords: Polycystic ovary syndrome, obesity, ovaries, inflammatory markers, etc

Introduction
Polycystic ovary syndrome (PCOS) is a common reproductive and endocrinologic disorder found in 6-10% of the female population. The three main phenotype characteristics of this condition are hyperandrogenism, polycystic ovaries, and ovulatory dysfunction. This syndrome can also be associated with metabolic issues including obesity, insulin resistance (found in 60-80% of women with PCOS), hyperinsulinemia, and type 2 diabetes mellitus (T2DM). PCOS is associated with cardiovascular problems, neurological and psychological effects on quality of life (Including anxiety and depression), and breast and endometrial cancers. As many as 20% of women with infertility problems (Including fecundability and early pregnancy loss) have been diagnosed with PCOS. It is often called the most common cause of anovulatory infertility in women. There is no known cause of PCOS, however there has been evidence that shows both environmental as well as genetic factors play a role in the etiology.
The biggest problem faced by women in the current scenario is the Polycystic Ovary Syndrome (PCOS) a kind of disease found common in women. It is clearly understood that the complexity of the syndrome is crucial because it will be creating a number of metabolic and other implications among women's health in the near future. The entire life cycle of the PCOS among the affected women shows to have an extended prodromal phase with detectable abnormalities. PCOS classification by medical practitioners is purely based on the hormonal blood test, ultrasound, personal and family histories and so on. In the current scenario, this syndrome seems to be a great scientific challenge among researchers. With the speedy progress in research, the evidence can easily be translated to knowledge and can be implemented as action among the women "Prevention is better than cure".

Polycystic ovary syndrome
Angela *et al* (2013) polycystic ovary syndrome is the commonest hormonal disturbance to affect women. The main problems that women with PCOS experience are menstrual cycle disturbances (irregular or absent periods), difficulty in controlling body weight and skin problems (acne and unwanted hair growth on the face or body). Women with PCOS won't experience all the symptoms and further the problem may change over time. PCOS presenting signs and symptoms are heterogeneous and vary over time; in addition, a precise and uniform definition of the

syndrome has been lacking [6].

Jonard & Robert (2013) have reported that follicles of 2 to 5 mm in size were significantly higher in polycystic ovaries than in normal, while it was similar within 6 to 9 mm range. Setting the threshold of 12 follicles in the range of 2 to 9 mm, the mean Follicle Number per Ovary (FNPO) offered the best compromise between specificity (99%) and sensitivity (75%). Within 2 to 5 mm of follicular range, they found significant positive relationships between FNPO and androgens. The FNPO for the range of 6 to 9 mm range was significant and negatively related to body mass index and fasting insulin serum level [7].

Balen *et al* (2015) published new criteria based on Trans-abdominal ultrasound. They reported that 10 or more cysts of 2–8 mm in diameter are arranged peripherally around an echo dense stroma. These criteria remained in widespread use even after the introduction of transvaginal a decade later [8].

Polycystic ovaries are endowed with an abnormally rich pool of growing follicles. The number is 2 to 3 fold more than normal ovaries, except the pool of primordial follicles, which is normal.

Webber *et al* (2013) examined the cortical biopsies of normal and PCOS ovaries and found that an even greater (6-fold) increase in the number of primary growing follicles in anovulatory women [9].

Diamanti *et al* (2009) has clinically examined the presence of PCOS and hyperandrogenism. The clinical manifestations of hyperandrogenism excess hormone are hirsutism, alopecia and acne. The presence of hirsutism is the key feature, but this is a relatively subjective diagnosis and few physicians in clinical practice actually use standardized scoring methods. Testosterone is bound to both sex hormone binding globulin and albumin. The measurement of total testosterone is probably all that is required in order to exclude the presence of an androgen-secreting tumor. In other words the value of testosterone is primarily to exclude other causes of androgen excess. The measurement of free testosterone or the free androgen index may also be used for assessing for hyper-androgenemia [10].

Hiremath & Jyothi (2010) used C-V method to segment single dominant follicle. The negative transformed image is segmented by active contour without edge method by removing spurious regions due to noise and regions in the segmented image having a smaller area than the threshold [11].

Palak & Biswanath (2011) recognized the follicles using scan line thresholding and extracted the contours of the follicles. Speckle noise is suppressed by multi-scale morphological approach [12].

Yinhui & Yuanyuan (2011) proposed the labeled watershed transform segmentation method. The speckle noise is removed by an adaptive morphological filter and contours of objects are extracted. The region of interest is automatically selected using object growing algorithm for follicle identification [13].

Symptoms and signs of polycystic ovary syndrome

Farquar (2007) The history of polycystic ovaries (PCO) starts from 1721 when Vallisneri examined a young married woman, moderately obese and infertile with two ovaries larger in size than normal ovaries, having shiny eggs [1]. In 1921 there was a report published referring something like “bearded diabetic women” pointing towards the association between glucose intolerance and hyperandrogenism. After this report glucose intolerance and insulin resistance has been intensively studied among the metabolic abnormalities. This was followed by case series of seven women with amenorrhea, infertility and enlarged cystic ovaries by Stein and Leventhal's in 1935 and the syndrome was first described by I.F. Stein and M.L. Leventhal in 1935. Polycystic ovaries (PCO) since then are the center of attention of debates in many specialities of modern medicine. Later it was stated that several patients with clinically diagnosed PCOS might not show cysts within the ovaries (Polson *et al*., 1988). Menstrual disturbances in the form of irregular and uncertain uterine bleed attributed to unchallenged estrogen mediated proliferation of endometrium are common in PCOS. 30-40% of females with amenorrhea may very well have PCOS.

Kahn *et al* (2016) Severe insulin resistance along with acanthosis nigricans in three lean adolescent women was reported and this type of insulin resistance soon became known as type A syndrome-similar to what is called as HAIR-AN syndrome (hyperandrogenism, insulin resistance and acanthosis nigricans) [2]. Women with PCOS have basal and glucose-stimulated hyperinsulinemia compared to weight-matched (control) women and significant positive linear correlation was observed between insulin and androgen levels in plasma. Insulin resistance, glucose intolerance and atherogenic lipid profile in PCOS associated with android type obesity was attributed to hyperandrogenism. 20% obese PCOS women showed impaired glucose tolerance or frank type 2 DM by National Diabetes Data Group (NDDG) criteria. Mathews D R *et al* in 1985 devised model for quantitating insulin resistance by homeostatic model assessment for insulin resistance (HOMA-IR).

Ferriman and Gallwey (2011) did evaluation of unwanted hair growth in females in a systematic manner first time when they scored density (0-4) of hair in 11 body areas (upper lip, chest, upper back, sacrum, upper abdomen, lower abdomen, arm, forearm, thigh and lower leg) in 161 women who belonged to age group of 18-38 years and 430 control women who belonged to age group of 15-74 years. They concluded that forearm and lower leg areas were less sensitive and these two sites must be excluded to obtain androgen score [3]. Later simplified scoring system was suggested by Hatch R *et al* that included only four important areas of assessment viz. sideburn area, lower jaw, upper neck, and buttocks and the common areas affected are face and chin with a tendency towards male escutcheon. This is related to high levels of serum androgens or increased local skin 5-α reductase activity or both.

Polycystic ovary syndrome inflammatory markers

Rourke *et al* (2006) Obesity present in varying degree in women with PCOS is associated with chronic systemic inflammation which is manifested by increased serum levels of inflammatory cytokines as well as changes in peripheral blood lymphocyte frequencies and function in adipose tissue, liver, and other tissue. All these processes are the underlying cause of obesity related comorbidities, including atherosclerosis, type 2 diabetes and steatohepatosis. At the molecular level, the intracellular signaling pathways that govern inflammation and glucose homeostasis demonstrate significant crosstalk and share multiple signaling mediators. At the cellular level, adipocytes and macrophages are closely related and likely evolved from the mediators of inflammation common primordial precursor cell, further evidence of the parallel evolution of inflammation and metabolic systems. Approximately 60%–70% of PCOS patients are obese with a central body fat distribution pattern described as visceral obesity that is highly accepted to be related with insulin resistance. However, there are evidences suggesting that insulin resistance is present in PCOS patients independent of obesity.

Orio *et al* (2015) Significant increases in lymphocytes and monocytes in women with PCOS compared with controls might have been expected to play a key role in the pathophysiological

mechanism of atherosclerosis. Increased leukocyte count is directly related with increased incidence of coronary heart disease, ischemic stroke, and mortality from cardiovascular disease. Again circulating levels of tumour necrosis factor-α (TNF-α), interleukin (IL-6), hs-CRP, as well as white blood count (WBC) and neutrophil count have been reported to be elevated in patients with PCOS compared with age and BMI matched controls [4]. Significantly a higher level of ICAM-1 in PCOS than in healthy women is documented. ICAM-1 showed positive correlation with body composition, lipids and insulin secretion. In other study higher plasma levels of hs-CRP, ICAM-1, and E-selectin were seen in PCOS women compared to the controls. These findings imply the presence of chronic inflammation in women with PCOS. Another proinflammatory cytokine IL-18, was reported to be increased in PCOS. IL-18 induces the production of TNF-α which promotes the synthesis of IL-6, is also considered a strong risk marker for cardiovascular disease. Collectively, low-grade chronic inflammation could be a novel mechanism contributing to increased risk of coronary heart disease in PCOS. Obese PCOS women exhibits lower levels of adiponectin, increased levels of PAI-1, increased activity of the angiotensin-renin system and increased cytokines and inflammatory markers compared with normal weight controls are well documented in women with PCOS.

Legro *et al* (2013) Insulin sensitivity is reduced by 35%–40% in PCOS women, independent of obesity, this decrease is of same extent as observed in patients with T2DM however, any increase in degree of obesity further destroys insulin action. Insulin resistance to some extent is present in about 50%–70% of all women with PCOS. Correlative as well as causative relationship between insulin resistance and inflammation has been demonstrated [5]. Subclinical inflammation and insulin resistance are important predictors of cardiovascular disease. Furthermore, in view of the role of insulin resistance in PCOS and of the increased cardiovascular risk of these women, a relationship between inflammation and hormonal-metabolic features of women with PCOS has been demonstrated and significantly increased hs-CRP levels, an inflammatory marker has been reported in PCOS women also hsCRP was found to be independently related to insulin resistance, suggesting hsCRP a marker of low-grade inflammation, as a predictor of coronary heart disease in women with PCOS. Also leukocyte count was found to be significantly higher in women with PCOS compared with healthy controls.

PCOS in obesity

Pasquali *et al* (2016) menstrual irregularities and anovulation appear to be more prevalent and severe in obese women with PCOS than in their non-obese counterparts, and weight loss of at least 5% tends to be associated with improvement of these conditions. Furthermore, obese women with PCOS have greater long term difficulty for conception [14]. Nevertheless, despite the close association between IR and obesity, the latter neither requires IR to influence aspects of PCOS pathophysiology, nor is a sine qua non of quality for this entity. Indeed, obesity is a powerful magnifying factor of several aspects of PCOS, which are not limited to favoring the development of IR and hyperinsulinemia.

Stocco (2013) Aside from disturbances in insulin physiology, obesity implies thorough alterations in steroid hormone metabolism, essentially summarized as increased concentrations of nearly all of these messengers. To this end, hyperestrogenemia is a paramount alteration, stemming from extra ovarian estrogen production in VAT and subcutaneous adipose tissue (SAT), due to expression of aromatase in these adipocytes. Estrogens stimulate LH and inhibit FSH secretion, contributing to GC and TC hyperplasia. In turn, this would increase androgen synthesis, which not only cause the typical manifestations of PCOS, but also serve as substrates for extraovarian aromatization, reinforcing this cycle of hyperestrogenemia-hyperandrogenemia in obese women with this pathology [15].

Mukherjee and Maitra (2010) Both short and long term high-lipid, low-fiber diets have been associated with hyperandrogenemia, possibly acting through intake-induced hyperinsulinemia, which would lower SHBG synthesis, increasing androgen availability. Nevertheless, novel mechanisms suggest a direct effect of diet in ovarian physiology disruption. Advanced glycation end products (AGE) are cytotoxic metabolites derived from disrupted carbohydrate metabolism, which may also be exogenously obtained from a myriad of food typical of Westernized diets. AGE deposition in ovarian tissue induces oxidative stress and aberrant structure modification due to molecule cross-linking, leading to damage of all ovarian cell types and therefore altering all aspects of its functionality. Moreover hyperandrogenemia appears to inhibit glyoxalase-I activity, which is an important enzymatic scavenging system for 2-oxoaldehydes, including major precursors of AGE. Thus, in PCOS, the deleterious effects of AGE deposition may be exacerbated [16].

Dardeno *et al* (2010) Leptin, known as the prototypical adipokine, is a 167 amino acid peptide secreted primarily from white adipose tissue, although it is present at several other sites, including the ovary. Leptin secretion occurs predominantly in SAT over VAT in women and appears to be inversely related to adipocyte size [17]. Leptin can be found circulating freely—its metabolically active form—or bound to soluble leptin receptor (sOB-R), a carrier protein derived from alternative splicing of leptin receptor (OB-R) mRNA or codomain shedding of OB-R trans membrane structures. SOB-R modulates leptin activity by lengthening clearance and half-life, yet limiting its availability to membrane OB-R. Leptin participates in regulation of energy homeostasis and multiple neuroendocrine, immune, and reproductive functions. In the context of PCOS, the role of leptin has been subject to profound controversy, with opposing views regarding its true participation. Because leptin concentrations are consistently found to be strongly correlated with weight, some reports consider the hyperleptinemia seen in PCOS as only a byproduct of this condition. On the other hand, findings linking leptin levels to estradiol, testosterone, and insulin in women with PCOS advocate for a more complex role of leptin in its pathophysiology. Moreover, reports of elevated leptin in nonobese PCOS patients further question quantitative adiposity as the sole origin of hyperleptinemia in this scenario.

Simpson (2014) another common finding in women with PCOS is elevated serum concentrations of adrenal androgens, which suggest dysregulation of the HHAA. Parallel to the effects of insulin in this axis, adrenal hyperandrogenemia may be reinforced by increased amounts of VAT, which displays a high traffic and catabolism of cortisol, triggering a compensatory activation of the HHAA, which results in elevation of adrenal androgen levels. Additionally, progesterone may interact with the glucocorticoid receptor, impairing activity of these hormones. As a consequence, hyperestrogenemia, such as that found in PCOS and the luteal phase of the menstrual cycle, may exacerbate this HHAA compensation, leading to higher adrenal androgen production, which can also be converted back to

estrone in adipose tissue and then into estradiol by 17-β-HSD in extraovarian tissues, restarting the hyperestrogenemia-hyperandrogenemia cycle. Moreover, glucocorticoids, which are elevated due to HHAA hyperactivity, induce expression of aromatase, further fueling this positive feedback circuit [18].

Conclusion

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder characterized by multiple hormonal imbalances, reflecting on a clinical presentation dominated by manifestations of hyperandrogenism, which generate short and long term consequences on female health. The manifestations of PCOS are not confined to the gynecological sphere; women afflicted by this disease show an increased prevalence of several comorbidities, including obesity, dyslipidemia, hypertension, metabolic syndrome (MS), and type 2 diabetes mellitus (DM2) in comparison with women without PCOS. These features, along with other alterations such as endothelial dysfunction and a chronic low-grade inflammatory state, underlie the greater risk of developing cardiovascular disease and increased all-cause mortality observed in these subjects. Given the pivotal role IR and obesity play in the etiopathogenesis and progression of PCOS and its potential subsequent metabolic and cardiovascular complications, both should be considered essential therapeutic targets. Although traditionally metformin is thought of as a hallmark of PCOS treatment as the mainstay insulin sensitizer, the advent of the distinct phenotypes for this syndrome and the broader acceptance of this categorization bring into question its indication in all cases of PCOS.

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