Association of polycystic ovary syndrome with metabolic syndrome and gestational diabetes: Aggravated complication of pregnancy (Review)

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Abstract. Polycystic ovary syndrome (PCOS) affects 5-20% of the reproductive age women globally. PCOS is diagnosed by the presence of hyperandrogenism, oligo-anovulation, and polycystic morphology of at least one ovary. Insulin resistance (IR), hyperinsulinemia and associated metabolic abnormalities including metabolic syndrome play a significant role in the development of PCOS. The chances of developing MS in PCOS women was shown to increase by almost 14-fold in patients with increasing body mass index. Even in the absence of overt obesity, a preferential deposition of intra-abdominal fat is noted in PCOS women and this intra-abdominal fat leads to impaired insulin action and functional IR and hyperandrogenism. Functional ovarian hyperandrogenism of ovaries was suggested to be a consequence of IR, which activates androgen synthesizing enzyme, cytochrome p450-c17α-hydroxylase, in ovarian theca cells and causes elevated oxidative stress accompanied by lower antioxidant status in ovaries, which contribute to PCOS pathogenesis. The elevated levels of luteinizing hormone that accompany the early stages of hyperandrogenemia, accelerate ovarian functional deterioration, which is further aggravated by hyperinsulinemia, in PCOS women. The risk of developing gestational diabetes in PCOS women is approximately three times greater, as compared to non-PCOS women, due to IR and hyperinsulinemia. Typical insulin-sensitizing drugs such as metformin, have been used to curtail IR and hyperinsulinemia in pregnant PCOS women, with varying results indicating the complexity of the disease and the need for better controlled studies and additional efforts for PCOS-specific drug discovery.

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Contents

1. Introduction

Polycystic ovary syndrome (PCOS) is a very common reproductive endocrinological disorder seen in women, affecting 5-20% of the reproductive age women globally (1). Insulin resistance (IR) and associated metabolic abnormalities appear to play a significant role in the development of PCOS and in sustaining this disorder (2,3). A vast majority of the affected women also show hyperinsulinemia, developed as a compensatory physiological body need, which in itself contributes to several problems including overweight. Hyperinsulinemia in these patients contributes to the development of metabolic syndrome (MetS), which is a composite of type 2 diabetes, atherosclerosis, obesity and cardiovascular disorders (4,5). The precise etiology of PCOS remains unclear. However, it is suggested that the primary defect lies at the ovarian level or may be a manifestation of hyperinsulinemia that drives elevated androgen production (6). Hyperandrogenism in association with ovulatory dysfunction and polycystic ovarian morphology (PCOM) are common features of PCOS, with the ovaries producing large quantities of androgens (1). This is also accompanied by menstrual disorders (oligo-amenorrhea) (5). The following criteria have been established by several health agencies across the world (National Institutes of Health, European Society of Human Reproduction and Embryology, and American Society of Reproduction Medicine) for the proper diagnosis of PCOS, after eliminating the possibility of other diseases. On the basis of these recommendations, at least two of the following three diagnostic criteria are required for diagnosing PCOS: hyperandrogenism, oligo-anovulation, and polycystic morphology of at least one ovary, as ascertained by ultrasound (minimum 12 follicles of 2-9 mm in diameter

or ≥10 cm^3 ovarian volume). Depending on the presence or absence of ovulation disorders, the phenotypes of PCOS have been separated as the classic PCOS (hyperandrogenism and chronic anovulation, and presence or absence of PCOS) and PCOS with ovulation disorders and polycystic morphology, with IR being evident in both phenotypes (1,5,7).

Apparently, the incidence of MS among PCOS patients seems to be affected also by the geographical region as well as the habits of the patients as it has been recently shown that in Iran the incidence of MS in the Iranian PCOS patients (19.7%) is less than that seen in United States (33-46%) (8), India (9) and Brazil (10) and its incidence increases with age and body mass index (BMI), with the most prevalent condition being low/high density lipoprotein-cholesterol (11). On the other hand, the incidence of MS was reported to be lower among European women with PCOS (12,13). It has been suggested that these differences may be due to differences in the criteria used to diagnose MS in these studies. In this review, we have summarized the current knowledge regarding the association of MetS and PCOS and the resulting complications in pregnancy.

2. PCOS and obesity

It is well-known that there is elevated risk for type 2 diabetes mellitus, gestational diabetes and other pregnancy-related complications including venous thromboembolism, cerebrovascular and cardiovascular events and endometrial cancer in patients with PCOS (1). The chances of developing MS in PCOS women was shown (8) to increase by almost 14-fold in patients with BMI in the highest quartile (≥30) as compared to those with BMI in the lowest quartile (<25). Fasting insulin level was found to be elevated even in PCOS women without evident MS and it was suggested that the elevated insulin contributes to the elevated androgen production by the ovaries and other complications. Several studies indicated that as much as 60-95% of PCOS women show IR, which becomes aggravated if accompanied by increased abdominal fat (14,15). However, IR in PCOS women cannot be completely explained by abdominal adiposity and several other factors such as defective glucose, lipid and steroid metabolism, dysregulated insulin signaling and altered adipokine secretion also likely contribute to IR (16). IR and elevated circulating insulin were found to stimulate the theca cells of ovaries to produce and secrete androgens and also to enhance the responsiveness of ovaries to luteinizing hormone (LH) to produce androgens (5,17). In fact, it has been noted that even in the absence of overt obesity, there can be preferential deposition of fat intra-abdominally in PCOS women with normal body weight. This intra-abdominal fat leads to elevated number of small subcutaneous abdominal adipocytes, which contribute to impaired insulin action and thus functional IR and hyperandrogenism (18). Decreased ability of intra-abdominal subcutaneous adipocytes to store and sequester fat in normal weight PCOS women leads to ectopic fat deposition in other tissues such as muscle and liver, and this exerts lipotoxicity and associated IR, contributing to hyperandrogenism (19,20). On the other hand, in overweight PCOS women, adipocytes in the subcutaneous abdominal adipose are large and are not responsive to insulin regulated glucose utilization and also to catecholamine controlled lipolysis and these changes are thought to be androgen-mediated (21).

3. Hyperandrogenism and IR in PCOS

The association between hyperandrogenism and PCOS stemmed from the observations that elevated levels of free testosterone in plasma of hirsute amenorrheic women actually originate from ovaries (22) and that administration of testosterone resulted in polycystic ovaries in female-to-male transsexuals (23). Those findings led to the hypothesis that hyperandrogenism leads to PCOS. In addition, evidence was presented in some studies that IR is related to hyperandrogenism (24) and that insulin addition to ovaries, *in vitro*, stimulates them to produce androgens (25) as well as LH (26). These results led to the proposal that hyperinsulinemia as seen in IR conditions contributes to excess androgen production by ovaries. Many of the hyperandrogenic women with classic PCOS display ovarian steroid hyper-responsiveness without any steroidogenic block and also dysregulation of cytochrome p450-c17α-hydroxylase (27). This type of ovarian dysfunction is known as 'functional ovarian hyperandrogenism', as the steroidogenic response is gonadotropin-dependent (28). Notably, even though the peripheral tissues such as muscle and liver are insulin resistant in PCOS women, the ovaries are very much responsive to both hyperinsulinemia and LH to produce androgens.

Functional ovarian hyperandrogenism was suggested to be a consequence of IR, which causes elevated oxidative stress accompanied by lower antioxidant status in ovaries (29). Increased oxidative stress was found to correlate directly with IR as well as serum testosterone and androstenedione levels (30). IR appears to activate the critical enzyme responsible for the synthesis of androgens, cytochrome p450-c17α-hydroxylase, in ovarian theca cells (Fig. 1), resulting in hyperandrogenism, despite elevated or normal LH secretion (31). Theca cells isolated from polycystic ovaries of classic PCOS patients display elevated expression of several steroidogenic enzymes, specifically, cytochrome P450c17 following long-term cell culture, and also show, that it is characteristic of functional ovarian hyperandrogenism (32). Formation of androgens is controlled by the cytochrome P450c17 enzyme in gonads and also adrenal cortex and its expression is dependent on LH stimulation in ovaries and ACTH in adrenal cortex. Cytochrome P450c17 possesses two activities essential for the generation of androgens: 17-hydroxylase, which converts pregnenolone to 17-hydroxypregnenolone, which is then converted by the 17,20 lyase activity to dehydroepiandrosterone. Dehydroepiandrosterone in turn gives rise to androstenodione and sex steroids. In the theca cells of ovary, cytochrome P450c17 can also convert progesterone to androstenodione and sex steroids (32). A recent study indicated that in PCOS women with functional ovarian hyperandrogenism, elevated LH:FSH ratio, enhanced oxidative stress and increased levels of free (not total) testosterone correlate with each other positively and that the elevated LH:FSH ratio is a better predictive biomarker for the onset of PCOS in women with functional ovarian hyperandrogenism (30). Elevated levels of androgens cause an inhibition of folliculogenesis that in turn leads to polyfollicular morphology, disturbing menstrual cycle and anovulatory infertility (33). Apparently, androgens have complex effects

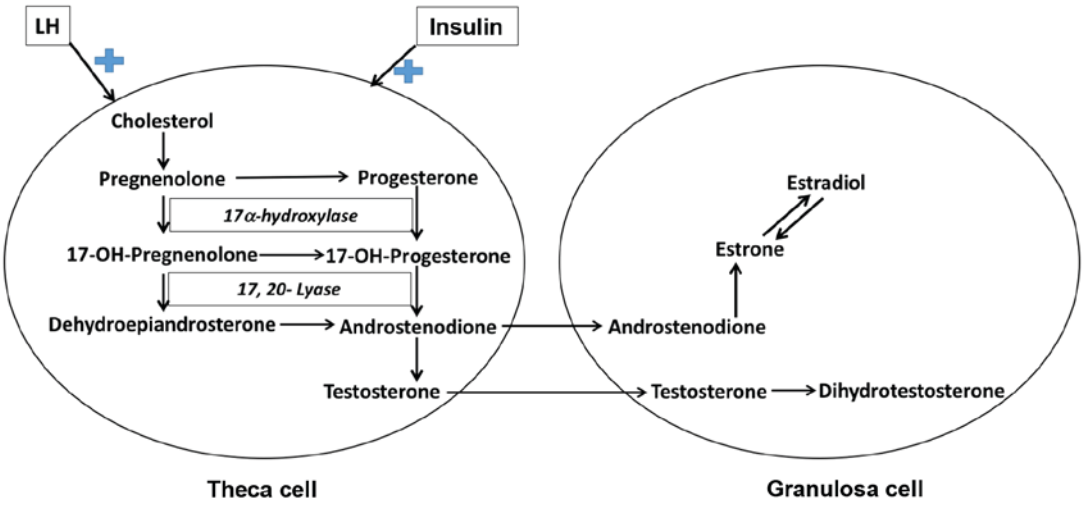

Figure 1. Steroid hormone biosynthetic pathways in ovary. In the ovarian theca cells androgen formation is stimulated by LH via the steroidogenic pathway. Androgen biosynthesis following stimulation by LH is modulated by cytochrome P450c17, which possesses both 17-hydroxylase and 17,20-lyase activities in theca cells. Androstenedione formed in theca cells is also taken up by granulosa cells, where it can contribute to the formation of estrogens. Androstenodione in theca cells is converted to testosterone, which leads to hyperandrogenism. Insulin also stimulates androgen production by theca cells. LH, luteinizing hormone.

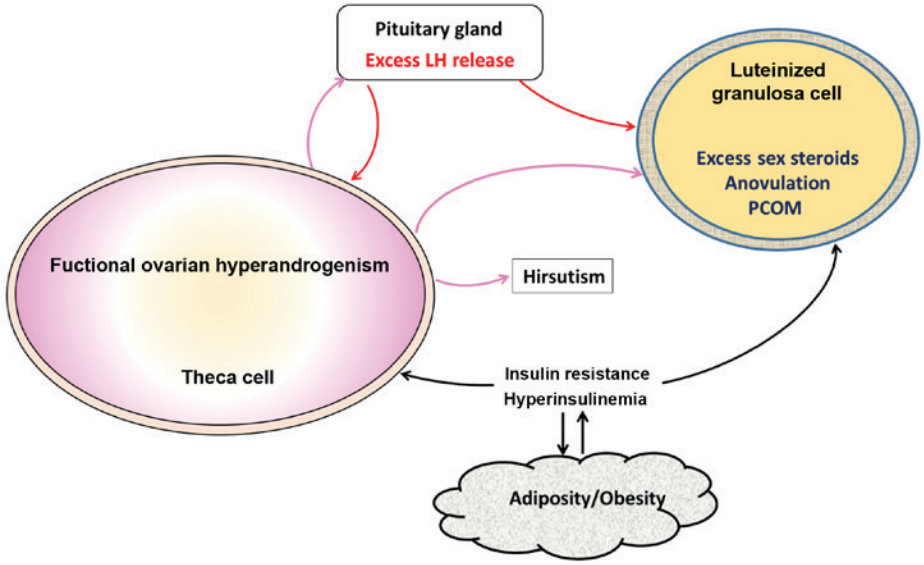

Figure 2. Pathological events in PCOS. Ovarian hyperandrogenism is very common in PCOS and contributes to several abnormalities including hirsutism, oligo-anovulation, and PCOM. LH secretion from pituitary gland is needed for the ovarian androgen production, but other factors such as hyperinsulinism and obesity are also necessary for full-blown pathogenesis of PCOS. Insulin resistance, which is very common in PCOS leads to hyperinsulinemia, which stimulates theca cells and aggravates hyperandrogenism. Excess insulin along with androgen, luteinize granulosa cells prematurely. Adipogenesis is another abnormality resulting from hyperinsulinism. Elevated androgens coming from theca cells in turn stimulate pituitary and cause LH excess, which worsens hyperandrogenism. These changes in granulosa cells further exacerbate PCOM and lead to oligo-anovulation. PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; LH, luteinizing hormone.

on folliculogenesis at a concentration of 10 ng/ml, testosterone positively affects preantral follicle growth, whereas, when testosterone concentration is elevated to 50 ng/ml, levels seen in the hyperandrogenemia conditions, there is a strong blockade of the follicle growth (34). Testosterone and other androgens can also be synthesized by adrenal cortex, under the stimulation of ACTH and approximately 25% of the functional ovarian hyperandrogenism cases are actually due to primary functional adrenal hyperandrogenism and contribute to PCOS (35). Thus overall evidence suggests that functional ovarian hyperandrogenism is the underlying causative factor for PCOS and accounts for many of the clinical features of PCOS such as anovulation, hirsutism and polycystic ovaries. IR and associated hyperinsulinemia aggravate the pathogenic effects of hyperandrogenism. The elevated levels of LH, during the early stages of hyperandrogenemia, accelerate the ovarian functional deterioration, which is further aggravated by accompanying hyperinsulinemia (Fig. 2) (32).

4. PCOS and gestational diabetes

Inasmuch as significant populations of PCOS women are insulin resistant and hyperinsulinemic, they are highly prone to develop type 2 diabetes. In fact, a major complication of

PCOS diagnosis in pregnancy is gestational diabetes (36) and several studies demonstrated increased incidence of gestational diabetes in PCOS women (37,38) and vice versa (39). However, few studies suggested increased BMI to be a better predictor of gestational diabetes than PCOS, raising questions on cause and effect relationship between PCOS and gestational diabetes (40). The risk of developing gestational diabetes in PCOS women is approximately three times greater, as compared to non-PCOS women (41). Treatment of pregnant PCOS women with metformin, an insulin sensitizer drug, commonly used in type 2 diabetic patients, was found to be beneficial as it reduced the high rates of miscarriage usually seen in PCOS women and also the incidence of gestational diabetes (42,43). Although its continuous use is controversial (44), metformin is prescribed to pregnant PCOS women to correct not only the metabolic abnormalities and hyperinsulinemia, but also endocrine disturbances, such as lowering LH and sex-hormone binding globulin levels (45). Metformin is useful as the first-line therapy in PCOS women for inducing ovulation (46). Metformin was suggested to protect against early pregnancy loss in PCOS women, by lowering plasma androgen levels, probably secondary to reduction in insulin levels (47). There is a need to conduct randomized clinical trials with appropriate placebo controls and blinding, with large cohorts, in order to ascertain the beneficial effects of metformin in PCOS women, particularly because this drug does not have any teratogenic effects and has no adverse effects (45,46). It has been suggested that PCOS be considered as a 'prediabetic' condition that is associated with impaired glucose tolerance (with a prevalence of approximately 33%) and because PCOS women with impaired glucose tolerance develop type 2 diabetes at 5- to 10-fold higher rate than women without PCOS (48).

5. PCOS and MetS

MetS, also known as Syndrome X is a combination of multiple conditions including central abdominal obesity, hypertension, dyslipidemia and hyperglycemia, all of which are the prime risk factors for cardiovascular diseases. People suffering from MetS display varying degrees of these abnormalities, which primarily result from complex multi-organ interactions of IR, obesity and age (49). Inasmuch as IR is almost globally present in PCOS women, it has been reported that nearly 33% of adolescents with PCOS develop MetS and this incidence increase to 50% with age in adults with PCOS (50,51). A recent clinical study with 100 newly diagnosed PCOS women observed that presence of at least two of the following three criteria, *viz,* hyperandrogenism, oligo/anovulation and polycystic ovaries, poses the highest risk for the development of MetS (52). A recent study has proposed that lipid accumulation product and visceral adiposity index are better markers of IR risk for cardiovascular disease than simple lipid ratios (53). There is a school of thought that suggests that the metabolic abnormalities associated with IR and obesity are probably more important, mechanistically, than hyperandrogenemia for the anovulation in PCOS women (54,55). There is some evidence suggesting women with typical PCOS, i.e., associated hyperandrogenemia, have a heritable component for β-cell defect and impaired glucose tolerance (56). In PCOS women the extent of IR is often much higher than what is anticipated on the basis of existing adiposity in them. The tissue selective IR together with hyperinsulinism is a major extraovarian contributory factor for the pathogenic alterations seen in PCOS ovaries. Insulin function is preserved in the ovaries of PCOS women despite a state of IR in the body and insulin signaling via insulin receptor in the theca cells appears to mediate the steroidogenic and androgenic effects of insulin (57).

Besides the known association of type 2 diabetes with PCOS as mentioned above, type 1 diabetes also appears to be associated with PCOS and this is particularly because of the very high doses of insulin administered to these patients systemically, for controlling hyperglycemia (58). Almost all the approaches that are commonly employed to correct insulin homeostasis in MS and obese patients, such as lifestyle modification for weight reduction, bariatric surgery, thiazolidinediones and metformin have beneficial effects on ovulation and also control hyperandrogenemia in PCOS women (32). Besides these drugs, of which thiazolidinediones are seldom used, there are inconsistent reports showing efficacy of myo-inositol in improving ovulation and other ovarian functions in PCOS women (59). An important characteristic of MS, the central abdominal obesity, and also occasionally pseudo-Cushing syndrome are noted in PCOS women and appear to be due to hyperinsulinism and possibly also through stimulation of glucocorticoid action and associated β-cell dysfunction (60). Thus, the overall interrelationship between obesity, IR and hyperandrogenemia together with LH drive the pathogenesis of PCOS.

6. Conclusion

PCOS is a very common endocrine disorder affecting a significant proportion of women worldwide and yet there is no effective treatment for this disease. PCOS poses significant risk to pregnant women for loss of pregnancy and/or other associated disorders such as pre-eclampsia and gestational diabetes. PCOS encompasses disturbances in several hormones, including insulin, androgens, and LH. Functional ovarian hyperandrogenism of ovaries, is a consequence of IR, and develops by the activation of androgen synthesis and contributes to PCOS pathogenesis. Despite several common conditions such as diabetes, IR and MetS, seen in non-PCOS obese women, the treatment options available for non-PCOS women do not always work effectively in PCOS women, because of the complexity of the disease. Typical insulin sensitizing drugs such as metformin, have been tried to curtail IR and hyperinsulinemia in pregnant PCOS women, with varying results indicating the complexity of the disease and the need for better controlled studies and additional efforts for PCOS specific drug discovery.

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