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Chapter 4

Polycystic Ovary Syndrome

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Additional information is available at the end of the chapter

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1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinophaty disorder that affecting reproductive aged women [1]; it becomes frequently manifest during early reproductive age [2]. It is a heterogeneous disorder, with multiple reproductive, cosmetic and metabolic complexities which is characterized by dysfunction in ovulation and clinical or biochemical hyperandrogenism and the presence of polycystic ovarian morphology. It is the most common endocrine cause of infertility and increased the risk of adverse pregnancy outcome, metabolic syndrome, type 2 diabetes mellitus, and some carcinoma [2-5]. However, there is not a consensus on its definition [6]. At the first time, PCOS was described by Stein and Leventhal in 1935 [6] as the presence of bilaterally enlarged ovaries with multiple cysts in seven women with infertility, menstrual irregularity and hyperandrogenism [7]. The National Institutes of Health (NIH) in 1990 introduced NIH standard criteria in PCOS for applying in researches and clinics [3]. This definition relied on clinical or biochemical evidence of hyperandrogenaemia (in the absence of adrenal hyperplasia and hyperprolactinemia and thyroid dysfunction) in combination of oligomenorrhoea or amenorrhea. Therefore, PCOS was diagnosed in the absence of an ultrasound appearance of polycystic ovaries morphology [8]. In 2003, a consensus workshop in Rotterdam in the Netherlands presented new diagnostic criteria [3]. Rotterdam criteria describe PCOS as persistence of PCO and hyperandrogenism in women with normal menstrual cycles and especially women presenting with PCO and ovulatory disturbance without hyperandrogenism [9].

In 2009, the Androgen Excess and PCOS Society (AE-PCOS Society) introduced criteria for PCOS. Based on AE-PCOS Society criteria, PCOS should be define by the presence of hyperandrogenism (clinical and /or biochemical), ovarian dysfunction (ovulation disturbance and or polycystic ovary morphology), and the exclusion of other androgen excess or related

disorders [10]. These criteria reflected differences in defining PCOS which could affect reporting, diagnosis and treatment of it.

1.1. Epidemiology

Despite PCOS being considered the most common endocrine disorder, the estimation of its prevalence is highly variable, ranging from 2.2% to 26.7% [11-13], due to differences in the presentation of PCOS phenotype methods [12]. In a study in Iran, a total of 646 reproductive-age women were assessed by Rotterdam, Androgen Excess Society, and NIH criteria, the prevalence of PCOS were 14.1%, 12%, and 4.8% respectively [14]. In a study from china, levels of luteinizing hormone and higher luteinizing hormone/follicle-stimulating hormone ratios were used for defining PCOS for 915 women in reproductive age, the results demonstrated 2.2 % prevalence [14]. In a study from china, levels of luteinizing hormone and higher luteinizing hormone/follicle-stimulating hormone ratios were used for defining PCOS for 915 women in reproductive age, the results demonstrated 2.2 % prevalence [11]. The prevalence based on NIH criteria in an unselected population black and white women in the southeastern United States were 3.4% and 4.7% respectively [15]. Using same criteria, the prevalence of PCOS was almost 6.5% between Caucasian and Greek women [16, 17].

2. Pathogenesis

The pathogenesis of PCOS are not fully understood, it seems that there are many different factors are associated with PCOS.

2.1. Gene's role

Some studies suggest that genetic plays an important role in pathogenesis of PCOS. The high prevalence of women with PCOS and the wide range of phenotypes can be explained by the interaction of key genes with environmental factors [18, 19]. There are some evidences showed that there are association between cytochrome P450 17-hydroxylase/17, 20-desmolase (CYP17) and PCOS. Cytochrome P450 side-chain cleavage enzyme (CYP11A) is another candidate gene that some studies find a role for it in PCOS. This gene encodes the cholesterol side-chain cleavage enzyme. Mutation in cytochrome P450 21-hydroxylase (CYP21) gene has found to have a role in PCOS in studies. This gene encodes 21-hydroxylase, which is responsible for most cases of congenital adrenal hyperplasia (CAH) [20].

2.2. Obesity-insulin

Approximately 50% of women with PCOS are overweight or obese and most of them have the android obesity. Obesity may play a pathogenetic role in the development of the PCOS in women through disturbances in insulin and androgenesis.

Accumulation of adipose tissue mass around abdomen increases the availability of metabolites, which are able to affect the secretion, the metabolism, and peripheral action of insulin.

Insulin, together with liver, adipose tissue and muscles, plays a role in the regulation of ovary. At ovarian level, insulin stimulates ovarian steroidogenesis by interacting with insulin and insulin growth factor type I receptors, in granulosa, thecal and stromal cells. Insulin increases 17-hydroxylase and 17-20 lyase activity and stimulates the expression of 3-hydroxysteroid dehydrogenase in granulosa cells. In addition, insulin seems to increase the sensitivity of pituitary cells to gonadotropin releasing hormone (GnRH) action and by increase the number of the luteinizing hormone (LH) receptor, increase the ovarian steroidogenic response to gonadotropins. Also, insulin is able to reduce sex hormone binding globulin (SHBG) synthesis in liver and ovary. IGFBP-1 regulates ovarian growth and cyst formation and adrenal steroidogenesis [21].

2.3. IGFs

IGF-I and IGF-II may be involved in the pathogenesis of the hyperandrogenism in the women with PCOS. IGFs are able to stimulate ovarian progesterone and estrogen secretion and increase the aromatase activity. In normal weight PCOS women, IGF bioavailability seems to be increased. But, in obese women with PCOS, IGF-1 bioavailability has been reduced. It could be suggested that insulin resistance and hyperinsulinemia may play a central role in obese PCOS patients; however disturbance of the IGF-IGFBP system may be important in normal-weight PCOS women [21-23].

2.4. SHBG

Sex hormone binding globulin (SHBG) is a glycoprotein that regulate circulating concentrations of free sexual steroid hormones and their transport to target tissues [24]. The concentrations of SHBG are regulated by a number of factors such as cortisol, estrogens, iodothyronines and growth factors, and decreased by androgens, insulin, prolactin and IGF-I [25]. SHBG concentration reduced specially in women with PCOS influence by hyperinsulinemia. Therefore, the free androgens increase at the level of peripheral tissues [21].

3. Androgens-estrogens-pituitary secretion

Hyperandrogenism play an important role in process of anovulation. In in-vitro study, the ovarian theca cells could increase steroidogenic activity in women with PCOS. Androgens levels originate from both ovarian and adrenal glands in PCOS. LH, ACTH, insulin and IGFs regulate production of androgen by affecting P450c17 enzyme at ovarian theca-interstitial cells and in the adrenal gland. Therefore, hyperactivity of the P450c17 enzyme represents the main mechanism resulting to ovarian hyperandrogenism that manifest in the great majority of women with PCOS. However, it is not cleared that hyperactivity of the P450c17 enzyme is a primary event or secondary to peripheral or central factors [21, 26]. Insulin is involved in hyperandrogenism from three ways. First, insulin in association with free IGF stimulates ovarian androgenesis. Second, hyperinsulinemia lead to reduce production of SHBG from

liver, as a result lead to increase in free androgen level. Third, insulin may affect ovarian follicle maturation, lead to ateresia, and increase level of androgen [22].

Decrease in SHBG level affected the concentration of estron and free estradiol in women with PCOS. Due to none fluctuated production of estrogen, pituitary receive both positive feedback for LH secretion and negative feedback for secretion of FSH. As a result, the LH-FSH ratio increases. LH has pulsatile pattern. In women with PCOS, the frequency of LH secretion is increase. This change happens in response to receiving stmilution by GnRH and increase bioavailabilty of LH. The high level of LH, lead to ovarian hyperplasia and production of androgen from ovarian stromal and tecal cells. This condition fixes the chronic anovulation. It is not clear that the impairment in hypothalamic-pituitary-ovarian axis leads to PCOS or this disturbance happen as an outcome of PCOS [21, 22, 27-29].

4. Metabolic syndrome and polycystic ovary syndrome

The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors, including impaired fasting glucose, central obesity, dyslipidaemia and raised blood pressure [30]. Ever since the metabolic syndrome was described by Reaven in 1988 [31], at least six diagnostic definitions have been published by different organizations. In this respect, although there is a general agreement regarding the main components of the MetS including abnormalities in glucose metabolism (insulin resistance, hyperinsulinemia, glucose intolerance, diabetes mellitus), central obesity, and cardiovascular risk factors (hypertension, increased triglyceride, decreased HDL cholesterol), this variation requires different cut-off points and inclusion criteria [30]. Table 1 shows most important definition of MetS according to World Health Organization (WHO) [32], and International Diabetes Federation (IDF) [33] criteria.

It has been shown that the combination of different components of MetS may predict a higher risk for cardiovascular than individuals and insulin resistance plays as a common link between these coexisting abnormalities [34].

The MetS affects roughly 25% of adults over the age of 20 y and up to 45% over age 50 y [35-37]. Some studies reported that during the last decade, the prevalence of MetS has increased in the general population, especially among young women [38]. However, this incremental trend may be attributable not only to anthropometric differences between diverse ethnicity, but also to differences in the criteria used for MetS diagnosis. Mechanisms underlying the metabolic syndrome are not completely clear. There is no single etiology of the MetS. Hyperinsulinemia, the most accepted and unifying hypothesis and a cornerstone of the syndrome [30],, results from interplay between environmental and genetic factors. Excess caloric intake and lack of physical exercise, combined with a predisposition to visceral adiposity, play a key role in the development of a pro-inflammatory insulin-resistant state that generates the clinical features of the MetS [37, 39]. However, the relationship between PCOS and MS is possibly mutual [34]. Majority of women with PCOS present clinically with at least one component of the metabolic syndrome [40]. In this respect, the prevalence of MetS among PCOS women is 43%-53%; approximately 2-fold higher that general women population [40]. However, the pathophysi-

ology that may link are not fully understood. Possible hypothesis regarding the association include: (I) insulin resistance underlies the pathogenesis of both the metabolic syndrome and PCOS; (II) obesity and related adipose tissue factors, independently of insulin resistance, are the major pathogenic contributors to both conditions; and (III) vascular and coagulation abnormalities are the primary pathogenic contributors to both conditions.

WHO	T2D or IFG or IGT or insulin resistance plus ≥ 2 of the following: • BMI > 30 kg/m^2 or WHR > 0.85 • HDL < 1.0 mmol/L (< 40 mg/dL) • TG ≥ 1.7 mmol/L (150 mg/dL) • BP ≥ 140/90 mmHg or use of blood pressure medication • microalbuminuria > 20 pg/min • Alb/Crea ratio ≥ 30 mg/g
rNCEP ATP III	≥ 3 of the following: • WC ≥ 88 cm • HDL < 1.3 mmol/L (< 50 mg/dL), or on drug treatment for lipid abnormality • TG ≥ 1.7 mmol/L (≥150 mg/dL), or on drug treatment for this lipid abnormality • FBS ≥100 mg/dl (≥5.6mmol/L) • systemic hypertension ≥ 135/85 mmHg or use of blood pressure medication
IDF	Central obesity defined as WC above the ethnicity-specific cut-off plus ≥ 2 of the following: • TG ≥ 1.7 mmol/L (150 mg/dL) or specific treatment • HDL < 1.3 mmol/L (< 50 mg/dL) or specific treatment • BP ≥ 135/85 mmHg or use of blood pressure medication f• asting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed T2D

Table 1. Definitions of MBS for women, according to WHO, NCEP ATP III and IDF criteria

Insulin resistance is the major underlying pathophysiologic abnormality linking the metabolic syndrome and PCOS. Indeed, the co-morbidities associated with insulin resistance are well-known to be common to both conditions [41, 42]. Nevertheless, it is likely that a combination of various factors interacts with or results from insulin resistance to manifest the metabolic abnormalities of the metabolic syndrome and PCOS. In addition, genetic susceptibilities and genetic polymorphisms or mutations likely contribute to the expression of these manifestations [43].

Although PCOS and MetS often coexist, several factors have been shown to predict the risk of metabolic syndrome among women with PCOS. Among these factors fasting insulin, obesity and family history of diabetes have the capacity for prediction of metabolic syndrome in women with PCOS [44, 45].

It seems that it is reasonable to assess the components of MetS in women with PCOS; however there is no consensus on the methods and interval of these assessments [43]. Assessments of blood pressure, waist circumference and/ BMI, fasting lipid profile, Fasting glucose and

glucose tolerance by a 2-hour oral glucose tolerance test have been suggested and aboratory studies for cardiovascular risk markers such as C-reactive protein and homocysteine are recommend [46, 47]. There were therapeutic overlap between PCOS and MetS. *Weight loss with life-style modification* is the safest and cheapest therapy that has shown benefit both in MetS and PCOS.

Reduction of insulin resistance is the primary goal for Weight loss in women with PCOS. Life-style modification through increased physical activity and reduction in body weight, especially waist circumference, represents the first-line therapy for MetS in PCOS. Successful maintenance of exercise and weight loss can lower blood pressure, central adiposity, and very low density lipoprotein cholesterol while improving lipid profile and insulin sensitivity [21, 48]. *Medical therapies for insulin resistance* with pharmacological approaches like metformin improve insulin sensitivity, glucose control and even reproductive abnormalities. Also metformin could decreases weight and BMI, blood pressure and LDL cholesterol [49, 50].

However, evidence has demonstrated that a combination of metformin and lifestyle modification improves the metabolic profile in women with PCOS to a greater degree than either measure alone [51].

5. Obesity and PCOS

The prevalence of obesity has increased worldwide in the last few decades [52]. Obesity status is defined according to the body mass index (BMI=body weight in kilograms divided by height in meters ^{2}) of 30 kg/m^2 or more. BMI of 25 to 29.9 kg/m^2 is defined as 'overweight', while BMI of less than 25 kg/m^2 is considered normal [53]. This had significant impact on the development of chronic diseases such as the metabolic syndrome, coronary heart disease and type 2 diabetes. Also, central obesity can be diagnosed clinically by measuring the waist circumference (WC) larger than 88 cm or waist-to-hip circumference ratio (WHR) greater than 0.85, confer high risk for metabolic complications in obese individuals with BMI between 25.0 and 34.9 kg/m^2.

However, obesity is a common finding in women with PCOS and between 40–80% of women with this condition is reported to be overweight, obese or centrally obese depending on the setting of the study and the ethnical background of the subjects [53-55]. Obesity has a worse additive effect on features of PCOS such as insulin resistance, hyperandrogenism, infertility, hirsutism and pregnancy complications [56].

The relationship between PCOS and obesity is complex, and most likely involves interaction of genetic and environmental factors [57]. Obesity in PCOS is usually of the central variety. It is shown that central obesity is associated with increased risk for diabetes, hyperlipidemia, hypertension, atherosclerosis, and insulin resistance [58]. Fat localized in the upper body is correlated with significantly reduced overall clearance of insulin, which contributes to hyperinsulinemia [59]. The mechanisms underlying obesity causes insulin resistance are not fully understood, the 2 main pathogenetic hypotheses that have been proposed focus on the

roles of free fatty acids (FFAs) and tumor necrosis factor-α (TNF-α). FFAs, which are released from adipose tissue triglycerides via lipolysis, as mediators of impaired insulin sensitivity, elevate in PCOS patients. Increased FFA flux into the liver, irrespective of its source, decreases hepatic insulin extraction, increases gluconeogenesis, and produces hyperinsulinemia [60]. Additionally, high circulating FFA concentrations lead to peripheral insulin resistance by reducing glucose uptake by the skeletal muscle [61].

TNF-α is produced by adipose tissue has been increasing in hyperandrogenic PCOS women. It leads to insulin resistance by stimulating the phosphorylation of serine residues of the insulin receptor substrate-1. Consequently, tyrosine kinase activity of the insulin receptor β-subunit, the rate-limiting component of the insulin receptor signaling cascade, is inhibited [62].

However, obese and non-obese PCOS patients may have differences in clinical manifestations. The differences in biochemical and clinical features between obese and non-obese PCOS patients allow determining, to some degree, the contributions of obesity to the clinical manifestations of PCOS. Differences in menstrual function have been reported, with obese patients exhibiting a greater prevalence of oligoamenorrhea and anovulation than non-obese women, And the prevalence of infertility has been increasing in obese PCOS patient [63]. Also, it is known that obesity has a direct relationship with the degree of hirsutism in PCOS patients. Obese women with PCOS had a greater prevalence of hirsutism, acanthosis nigricans, than non-obese patients, reflecting a higher prevalence and magnitude of insulin resistance and hyperinsulinemia among obese PCOS patients [64]. Impaired glucose tolerance, type 2 diabetes mellitus and the dyslipidemia has highest risk in obese PCOS patients. Overall, given the prevalence of risk factors for atherosclerosis in women with PCOS, a higher prevalence of cardiovascular events in these patients can be expected [65]. In addition, obese PCOS patients have higher prevalence of endometrial carcinoma than non-obese PCOS women. Anovulation, unopposed estrogen stimulation, and hyperinsulinemia may play a role in the increased risk of this gynecologic carcinoma in PCOS patients [66]. Also, it is reported that obstructive sleep apnea, pregnancy complications such as preeclampsia, gestational induced hypertension and gestational diabetes are more prevalent in obese PCOS patient [67, 68].

However, the impact of obesity on PCOS therapy is very important. Therapeutic modalities directed at the reduction of hyperinsulinemia (weight loss or insulin-sensitizing agents) appear to ameliorate symptoms of PCOS and restore normal ovarian function in obese women with PCOS.

Weight loss, especially more than 5% of the baseline weight, is the first-line therapy in treatment of these women. It leads to hormonal, menstrual, and metabolic improvement with increased serum concentrations of SHBG and reduced serum concentrations of free testosterone in obese women with PCOS. The mechanism by which weight loss leads to a reduction of hyperandrogenism appears to involve improved insulin sensitivity with a resultant decline in circulating insulin levels [69]. *Metformin* can be suggested as a second-line treatment for most obese women with PCOS [70].

6. Poly cystic ovarian syndrome and cancers

Since 1940s, there is emerging evidence of increased risk of gynecological cancer including endometrial, breast and ovary cancer among women with PCOS [71, 72]. Any association with malignant disease would be highly important from a public health perspective in view of the high prevalence of PCOS. The lack of appropriate recognition of risks takes these patients at highest risk of delayed diagnosis of pre-malignant or malignant disease [70]. At a cellular level there are numerous potential mechanisms which could promote neoplastic disease in women with PCOS, including the prolonged anovulatory state and associated hyperandrogenism with unopposed estrogen action [73]. These could increase the risk of cancer through the effect of these hormones on various tissue and organs [74].

6.1. Endometrial carcinoma and PCOS

Endometrial carcinoma (EC) is the second most frequent gynecological malignancy among women [74]. The number of reported cases of EC makes it the leading cause of cancer-related deaths across the globe [75]. Major EC-related symptoms include dysfunctional uterine bleeding, hyper-menorrhea, irregular menstruation, and sterility. The two main types of EC are estrogen-dependent type I (the most prevalent type) and estrogen-independent type II carcinomas. Among numerous risk factors, PCOS is commonly considered to be a significant and causative risk factor for the development and progression of type I EC [76]. The prevalence of endometrial hyperplasia with and without atypia in women with PCOS varies from 1 to 48.8% [77]. The prevalence of EC is three times higher among women with PCOS than among women without PCOS [71]. The mechanisms underlying EC and PCOS are also unclear, but it is widely assumed that chronic anovulation, which results in continuous estrogen stimulation of the endometrium unopposed by progesterone, is a major factor. Obesity, hyperinsulinemia, and hyperandrogenism state in PCOS, results in increased bioavailability of unopposed estrogens by progesterone due to the increased peripheral conversion of endogenous androgens such as testosterone and androstenedione into estrogen. Also, Insulin up-regulates aromatase activity in endometrial glands and stroma, endogenous estrogen production is enhanced in women with high circulating insulin. Estrogens act as proliferative factors in the endometrial tissue. Continuous exposure of the endometrium to estrogens with persistent progesterone deficiency, lead to endometrial overgrowth and hyperplasia or cancer [78]. The exact molecular mechanisms linking hyperinsulinaemia as found in PCOS and EC are uncertain. It is however thought that it may be modulated by a direct effect of insulin and IGF on endometrial cells or alterations in the P13K-mTOR-AKT signaling pathway with the loss of PTEN expression which have mitogenic effect on endometrial cells [79] and activation of insulin/IGF-1 signaling through overexpression of INSR and/or IGF-1R.

Overlay, the evidences suggest that interplay between hyperinsulinaemia and estrogen may mediate the mitogenic effect of the hyperinsulinaemia in PCOS.

Other potential risk factors for EC such as androgens and LH are also present in PCOS. Hypersecretion of luteinising hormone, a feature of PCOS, has also been implicated in the development of endometrial cancer in women with PCOS. Receptors for luteinising hormone and

human chorionic gonadotropin are over expressed at both mRNA and protein levels in endometrial adenocarcinomas. Over expression of receptors for both these hormones in endometrial hyperplasia (with stronger staining in complex or atypical hyperplasia), and endometrial carcinoma were detected [80]. Insulin levels reduce the amount of IGFBP which in turn increases the amount of circulating IGF. IGF has been shown to induce LH receptors increasing LH levels, again suggesting an interaction between insulin resistance, LH and EC [81]. It should be noted that the triad of obesity, insulin resistance and diabetes in metabolic syndrome carried significant risks of EC [82]. However, the evidence for impact of PCOS on prognosis of endometrial carcinoma is incomplete and contradictory. Jafari et al. suggested that the presence of PCOS was associated with a favorable prognosis [83]. Insulin has also been found to accelerate the proliferation of cancer cell in the endometrium in an in-vitro study [82], and the concentration of IGF-1 was correlated well to the malignant cells differentiation [79], but, There is not enough knowledge supporting that mortality from endometrial cancer is differ in women with the syndrome.

However, it has been clearly shown in both animal and human studies that *metformin* is valuable insulin sensitizer agent in reversing endometrial hyperplasia. Metformin has exerted a chemo-protective and anti-proliferative effect on EC. It does this by a reduction in cell growth, which is modulated partly via insulin and non-insulin relevant path-ways. In the context of the links between EC and hyperproloferation of endometrium in PCOS, Metformin may therefore prevent EC in PCOS or treatment of EC.

6.2. Ovarian carcinoma and PCOS

Ovarian cancer accounts for 5% of all cancers among women and is the fourth most common cause of cancer deaths in developed countries, causing more deaths than any other female genital tract cancer [84]. Ovarian cancer typically presents late, with symptoms such as pelvic pain, abnormal vaginal bleeding, or involuntary weight loss, and has an overall 5-year survival of 30% after diagnosis. However, if detected early, at stage I, the 5-year survival is as high as 90%. It is, therefore, imperative that high-risk groups are identified so that appropriate screening is undertaken to detect early ovarian malignancy [85].

The majority of malignant ovarian tumors including epithelial malignancies appear to have steroid receptors for estrogen, progesterone and androgen. Cytokines may also play a role in malignant transformation. The various interactions of altered local ovarian factors and environmental factors have been associated with OC, as many of these factors are altered in PCOS.

Epidemiology studies showed that women with PCOS had a 2.5-fold increased risk of developing ovarian cancer, with a 95% confidence interval of 1.1–5.9 [86]. Also, clomiphene citrate and gonadotropin therapy or ovulation induction was found to increase the relative risk of ovarian tumors in women with PCOS around 4.1 [87]. The pathophysiological mechanisms that may be involved in ovarian oncogenesis in women with PCOS are not completely understood. Perhaps the high local steroid and growth factor concentrations that are frequently observed in women with PCOS may be implicated [88]. In addition, ovulation inducing drugs potentially which are used for infertility treatment, may have effect on ovarian cancer

[89]. Some researchers suggest that oral contraceptive use in some anovulatory women with PCOS may protect against ovarian cancer through gonadotropin suppression rather than the prevention of ''incessant ovulation'', with its putative dangers of inclusion cyst formation, epithelial proliferation, genetic damage and ovarian carcinogenesis [89].

6.3. Breast cancer and PCOS

Obesity, hyperandrogenism and infertility occur frequently in PCOS, and are feature known to be associated with the development of breast carcinoma [89]. In this respect, meta analysis about the association between PCOS and breast cancer showed that the risk of breast cancer was not significantly increased overall [90]. However, some studies showed that women with PCOS independently of age, age at menarche or menopause, parity, using oral contraceptive pill, BMI and family history of breast cancer, have 1.8 times as likely to report benign breast disease [91]. In this regard there is a need for more research.

7. Polycystic ovary syndrome and pregnancy

Normal pregnancy is characterized by induction of insulin resistance associated with compensatory hyperinsulinemia in second and third trimesters [49]. This insulin resistance of normal pregnancy is a physiologically advantageous adaptation designed to restrict maternal glucose uptake and to ensure shunting of nutrients to the growing fetus. It is probably mediated by increases in hormonal levels of estradiol, progesterone, prolactin, cortisol, human chorionic gonadotropin, placental growth hormone (PGH), and human placental lactogen (HPL) [33]. HPL and PGH are the hormones mainly responsible for insulin resistance in pregnancy. HPL is responsible for adaptive increase in insulin secretion necessary for pregnancy and for diversion of maternal carbohydrate metabolism to fat metabolism in the third trimester. PGH seems to be a paracrine growth factor probably regulating the metabolic and growth needs of the fetus partially [92]. There is approximately 200 to 250% increase in insulin secretion in lean women with normal glucose tolerance with advancing gestation [93]. However, there is comparatively less robust increase in insulin levels of obese women with normal glucose tolerance.

As we state before, hyperandrogenism and insulin resistance are the metabolic hallmark of PCOS women. In these patients, the baseline insulin resistance seems to be exacerbated with entry into pregnancy. There is an increased risk of pregnancy complications in PCOS women [94]. Nowadays a growing body of evidence points to a high prevalence of pregnancy complications in PCOS women. PCOS was strongly associated increased risk of early pregnancy loss, gestational diabetes (GDM), pregnancy-induced hypertension, preeclampsia, preterm birth, small for gestational age, large for gestational age, caesarean section, operative vaginal delivery, neonatal meconium aspiration and having a low Apgar score (<7) at five minutes and admission to an NICU [95-98].

It should be noted that there were the close link between PCOS and obesity and the association of obesity with poor pregnancy outcome, so, it might be possible that possible confounding effect of BMI play a role in adverse effect of PCOS on pregnancies.

7.1. PCOS and abortion

Abortion is the spontaneous loss of a fetus before the 20th week of pregnancy. Women with PCOS most probably have an increased risk of spontaneous Abortion [95]. It occurs in 30 to 50% of PCOS women compared with 10 to 15% of normal women [99]. Several mechanisms underlying the increased risk of abortion in women with PCOS have been proposed. Treatment with ovulation-inducing agents is associated with a higher incidence of abortion in PCOS women [95]. Obesity has been conclusively associated with an increased prevalence of miscarriage and obesity is obviously more common in PCOS patients than in the normal population. Also, elevated LH levels in women with PCOS and hyperandrogenemia play important role in increased risk of abortion. High androgen levels antagonize estrogen, which may adversely affect endometrial development and implantation [100]. Researchers showed that sex steroids regulate uterine receptivity for embryo implantation by controlling the expression of HOXA10 gene, which is spatially and temporally regulated during embryonic development. Elevated testosterone in PCOS down-regulates the expression of HOXA10 gene, thereby decreasing the uterine receptivity and implantation [100]. In addition high plasminogen activator inhibitor-1(PAI-1) activity which has been found to be associated with unexplained recurrent abortion, is significantly higher in women with PCOS, possibly due to impaired fibrinolysis, which results in placental insufficiency through increased thrombosis of the placental bed [101]. It is suggested that *metformin* therapies before and throughout pregnancy, could decrease the risk of early abortion, but more studies are needed [102].

7.2. PCOS and gestational diabetes mellitus

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance at onset of pregnancy (or first recognition), affects 4–7% of pregnancies overall [103]. There are 2.4-fold increased risks of GDM among PCOS women, independent of age, race/ethnicity, and multiple gestations. It means that GDM complicates 40 to 50% of PCOS pregnancies. The increased odds of GDM among women with PCOS symptoms are consistent with the overlap of metabolic perturbation and reproductive abnormalities and the possibility that some women actually had PCOS. It intervenes in pregnancy when pancreatic β cells cannot overcome the superimposed insulin resistance of pregnancy on intrinsic insulin resistance of PCOS women. It is too suggested that metformin may decrease of GDM among GDM, but recent meta-analysis, strictly, showed that metformin did not significantly effect on GDM with PCOS, though more multi-centers RCTs still need to be investigated [104].

7.3. PCOS and hypertensive disorders in pregnancy

Hypertensive disorders of pregnancy include: i. new onset of hypertension during pregnancy (or gestational hypertension which is defined as new-onset hypertension in pregnancy after 20 weeks of gestation), ii. Preeclampsia (defined as defined as gestational hypertension with

proteinuria due to endothelial dysfunction and damage), iii. Pre-existing hypertension, and iv. exacerbation of pre-existing hypertension. The etiology of hypertensive pregnancy is uncertain and includes immune, genetic, and placental abnormalities. Three main hypotheses have been proposed regarding the metabolic alterations involved in the etiology of hypertensive disorders in pregnancy, namely endothelial dysfunction and activation, oxidative stress and insulin resistance [105]. Hypertensive disorders occurs in 8% of PCOS pregnancies [106]. Increased levels of androgens in PCOS have been associated with the development of preeclampsia [107]. Various studies have documented hyperinsulinemia and/ or hyperglycemia in early or mid pregnancy, before the development of preeclampsia, gestational hypertension, or both [108]. Hyperinsulinemia may directly predispose to hypertension by increased renal sodium re-absorption and stimulation of the sympathetic nervous system. Insulin resistance and/or associated hyperglycemia may impair endothelial function.

Two other factors, obesity and physical inactivity, are closely associated with insulin resistance, and are predictive of hypertensive pregnancy. A higher body mass index before pregnancy or early in pregnancy is associated with increased risk for both gestational hypertension and preeclampsia. Furthermore, it has been suggested that gestational diabetes, which itself is associated with underlying insulin resistance, is a risk factor for the development of hypertensive pregnancy. This association persists even after adjusting for obesity and maternal age. Also, a higher prevalence of preeclampsia and gestational diabetes may account for increased fetal stress leading to preterm birth, low Apgar scores at five minutes, and meconium aspiration.

7.4. PCOS and preterm birth

There was evidence of a significant positive association between PCOS and preterm births (<37weeks) [109]. It complicates 6 to 15% of pregnancies of PCOS women [110]. Although preterm birth may be higher in this group of women, PCOS by itself may not be an independent risk factor. Patients who have received ovulation induction agents are more likely to be at higher risk of preterm births, because these medications, together with the increased chance of multiple pregnancies related to them, will increase the risk of preterm birth or delivery [111]. Preeclampsia itself is a risk factor for preterm deliveries. Also, Obstetric intervention may be responsible for iatrogenic prematurity [110].

7.5. PCOS and Small for Gestational Age (SGA) and Large for Gestational Age (LGA)

There is still some controversy as to whether women diagnosed as having PCOS were more likely to have been born small for SGA and LGA, and whether theses baby is more prone to develop the symptoms of PCOS later in life. Whereas the probable association of higher maternal body weight, increased weight gain during pregnancy, and increased prevalence of gestational diabetes in women with PCOS would be expected to produce birth weights higher than the mean. Also, the prevalence of SGA offspring seems to be increased in women with PCOS. Insulin resistance resulting in impaired insulin-mediated growth and the fetal programming hypothesis are the possible explanations for this higher prevalence of SGA infants in mothers with PCOS [33].

8. Management of women with PCOS

The medical management of PCOS can be broken down into four components, three of which are "acute" issues (control of irregular menses, treatment of hirsutism and management of infertility) and one that is more "chronic." This latter issue may be the most important but least remembered by patients and providers alike–management of the IR syndrome. "Acute" issues that need management may change; however, a continuous life-long management approach is important for the IR of PCOS.

8.1. Weight reduction

As mentioned above the central obesity related to PCOS hyperandrogenism and anovulation. Also, obesity reduces the treatment effect in women with PCOS [112]. Weight lose can modified the hormonal profile, and androgen level therefore has good effect on ovulation and treatment of infertility. It is showed that 5 % weight reduction can modify menstruation cycle and ovulation. However, weight reduction is effective for women, who are overweight, a BMI 25-27 kg/m2. It includes change in life style with diet, exercise and surgery. Low carbohydrate and fat diets is recommended for obese PCOS women. Bariatric surgery may be recommended for morbidly obese women [112].

8.2. Induction ovulation

In PCOS, patient complaints of menstrual disturbance, that often related to chronic anovulation. It can increase risk of endometrial hyerplegisa and carcinoma. Therefore, this complication needs treatment. Low FSH concentration, high LH, androgen and insulin have roles in anovulation. Medications and another option apply for correct these underlying disturbance [112]. Treatments options are explained further in the following sections.

8.3. Clomiphene citrate

The first line medication for treatment of anovulation is clomiphene citrate (CC). CC is a nonsteroidal triphenylethylene with both estrogenic agonist and antagonist properties. CC bind to estrogen receptors by structural similarity with it. Improvement in ovulation happens with the CC effect at hypothalamic level. Reduction of hypothalamic estrogen receptor leads to mis interpretation of blood level estrogen. Therefore, estrogen feedback reduces and pulsatile GnRH secretion modify. As a result, FSH and LH secretion from pituitary normalized, in turn, improve follicular activity in ovarian. CC is administered for 5 days with doses of 50–150 mg, starting on days third or fifth days of mensural cycle or a progestin-induced menss. Most pregnancies occurred within the first six cycles with ovulation following the application of 50 mg CC. Higher doses may be required in patients with greater BMI. The rates of multiple pregnancies are under 10%, and ovaraian hyper stimulation syndrome is rare [112].

8.4. Metformin

Metformin is a biguanide, insulin-lowering effects, which are used for treatment of type 2 diabetes mellitus. Metformin has several benefits to manage PCOS complication. It improves ovulation, menstrual irregularity and reduces concentration of androgen. Also metformin help to weight reduction. Metformin has more effect in obese PCOS women [115]. Serious side effects of metformin are rare. Hypoglycemia is a rare side effect. For reducing common complication with metformin, it is start at 500 mg daily after food. The week after increase to achieved 1000 mg daily. After one week, the dose is increase to 1500 mg daily. The target is 1500–2550 mg/day. Usually, treatment effect appears at 1000 mg/day [113].

8.5. Aromatase inhibitors

The third generation aromatase inhibitors available include anastrozole and letrozole. They block production of estrogen from ovarian, conversion of androgen in referral fat cells, and suppress locally estrogen produced in brain. Therefore, this condition acts as positive feedback for hypothalamous to secrete GnRH, in turn, increase gonadotropin secretion. Also, reduction in estrogen concentration leads to increase activin that is a positive stimulation for FSH secretion. This positive feedback helps to growth of ovarian follicles. Usually Letrozole is used as anaromatase inhibitor for ovulation induction in women with PCOS. The administration dose is between 2.5–7.5 mg daily for 5 days starting on third day of the menstrual cycle. The main advantage of letrozole is antiestrogenic effect on endometrium, despite of stimulating follicle growth [113].

8.6. Gonadotropins

After resistance to CC, gonadotropins are another option for induction ovulation. Gonadotropins induce ovulation, and help to achieve a capable follicle for fertilization. The serious side effect of gonadotropins is ovarian hyperstimulation syndrome (OHSS) that result from simultaneous growth of multiple follicles. Several treatment protocols have been developed, one of the low-dose gonadotropin protocols regimen starts with a 37.5–50 IU/day, which increases, if confirm the lack of follicle response. Control is made by ultrasound. HCG is act as LH surge; leading to maturation of the oocyte, rupture of the follicle, and formation of the corpus luteum [112].

8.7. Laparoscopic ovarian diathermy

In clomiphene resistant condition, and when gonadotropin is not useful, laparoscopic ovarian diathermy is an acceptable treatment. The mechanism of action of ovarian diathermy is correction of hypersecretion of LH via modification in ovarian pituitary feedback. To assess the efficacy of unilateral laparoscopic ovarian diathermy in the induction of ovulation, researchers find unilateral ovarian diathermy resulted in ovulation from both ovaries [112, 113].

8.8. Treatment of menstrual dysfunction

In patient complaints of menstrual irregularity, often there is chronic anovulation that associated with risk of endometrial hyperplasia and carcinoma. Thus, treatment of menstrual dysfunction is important. Endometrial biopsy is recommended for PCOS women, who have not menstrual bleeding for a long time (m0re than 6 months). In women, who does not intent to be pregnant, oral contraceptive pills (OCPs) or cyclic progestin are recommended. OCPs increase production of SHBG at liver, thus reduce androgen concentration, and improved LH secretion. It is important to consider the androgenic effect of progestin component of OCPs. New OCPs have less androgenic effects [112].

8.9. Treatment of androgen-related symptoms

Hirsutism, acne, alopecia are the androgen-related symptoms that appeared in patients with PCOS. Antiandrogens such as spironolactone, cyproterone acetate (CPA), or flutamide act by competitive inhibition of androgen-binding receptors or by decreasing androgen production.

Spironolactone is a specific antagonist of aldosterone, acting through blocks androgen receptors. Its treatment effect is dosage-dependent: low dosages are less effective than other antiandrogens, whereas high dosages (200 mg/day) are very effective but have several adverse effects such as dysfunctional uterine bleeding but the concurrent use of OCPs may prevent from it. Spironolactone have feminizing effect on male fetus, therefore concomitant use of OCPs with spironolactone is useful for sexually active women [112]. Cyproterone acetate (CPA) is a progestin agent. This drug inhibits gonadotropin secretion and suppresses androgen action. CPA is recommended in 50-100mg (high dose) for ten days of cycle with 20-50 μg Ethinyl Estradiol. CPA is effective for management of hirsutism and acne. It may leads to nausea, headaches, and breast tenderness, reduce libido, and weight gain. CPA rarely appears hepatotoxicity effects. This drug has feminizing effect such as Spironolactone. Finasteride restrain 5α-reductase and inhibit androgen production, therefore, it is useful for management of hirsitism. In a study that patients treated with finasteride, reduction in hirsutism occurred after 6 months. Concomitant use of OCPs with 5 mg Finasteride was shown to be more effective than OCPs alone. It has feminizing effect, thus risks and benefits of treatment must be carefully considered and discussed with the patient. In conclusion, at least 6 months is required to see benefit from medication and prolong treatment is often necessary for maintain benefit. Pregnancy must be avoided during treatment with all antiandrogens [112, 113].

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