POLYCYSTIC OVARY SYNDROME (PCOS) AND RELATED DISEASES

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REVIEW

HIGHLIGHTS

- Management of PCOS is in itself a challenging scenario owing to the complexity of syndrome and varied presentation.
- Insulin resistance in PCOS has paradoxical expression as Insulin mediated glucose regulation is impaired but at the same time Insulin mediated Androgen production continues.
- Hyperandrogenism, ovarian dysfunction and Infertility being fundamental features of PCOS, the situation is further exacerbated by IR and obesity mediated dyslipidemia, early IGT to DM2 conversion, CVD and cancer risk.
- PCOS challenges feminine identity, body image and the affected female in addition has to struggle with depression, anxiety and other psychological effects.

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, with an estimated prevalence of about 10%. The exact pathophysiology of PCOS is complex and still remains largely unclear. It has significant and diverse clinical implications and is associated with numerous reproductive and metabolic alterations. It is characterized by clinical and/or biochemical hyperandrogenism, oligo or anovulation and polycystic ovary morphology. Although it is diagnosed exclusively based on reproductive criteria, but it is furthermore a metabolic disorder. Insulin resistance, impaired glucose tolerance, obesity, dyslipidemia, subclinical inflammation and endothelial dysfunction are more common features in women with PCOS. These metabolic perturbations in PCOS women result in chronic low grade inflammation, Type 2 Diabetes (DM2) and cardiovascular impairments that threaten the risk of developing cardiovascular diseases (CVD). Type 2 diabetes, cardiovascular disease, infertility and endometrial cancer are some of the important issues regarding syndrome's influence on well being of these women. Other than reproductive and metabolic manifestations of PCOS, there are also serious mental health consequences such as increased anxiety, depression and worsened quality of life. This review summarises PCOS features and focuses primarily on the possible outcomes of the syndrome.

KEY WORDS *PCOS; hyperandrogenism; insulin resistance; obesity; dyslipidemia; diabetes mellitus;CVD*

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common heterogenous female endocrine disorder, affecting as many as 10% of women of reproductive age and may account for anovulatory infertility and threaten long term health [1, 2]. The exact etiology of PCOS is uncertain, but there is strong evidence that complex interactions between genetic, environmental, and behavioral factors contribute to this syndrome [3]. Although the diagnosis of PCOS is based exclusively on reproductive criteria (hyperandrogenism, oligo/anovulation, and/or PCO on ultrasound), but it is also a metabolic disorder [3]. Women with PCOS have an increased risk of presenting with metabolic issues such as insulin resistance (IR), impaired glucose tolerance (IGT), obesity and dyslipidemia [4]. Consequently there is an increase in the risk factors for cardiovascular disease including hyperandrogenism, impaired fibrinolysis, an elevated prevalence of clinical and subclinical atherosclerosis, systemic low grade inflammation and type 2 diabetes mellitus [5]. PCOS is also associated with neurological and psychological problems (including anxiety and depression) [6], and chronic anovulation predisposes PCOS women to endometrial carcinoma [7]. As PCOS seems to be dominated by metabolic consequences and other threatened health complications, it is evident that research on the metabolic and cardiometabolic features of PCOS is needed. To date, most attention has been paid to the management of symptoms related to PCOS, but due to the complexity of syndrome a number of metabolic and other implications of women's health have to be dealt with in the near future. This review will provide clear and up to date information, in order to advise clinicians about the possible consequences of the syndrome.

PCOS DIAGNOSIS

Until recently no universally accepted clinical definition existed for PCOS. Over the past three decades, research has highlighted that PCOS is a heterogeneous condition. Signs and Symptoms related to PCOS have been evaluated and the initial NIH diagnostic criteria which is based on oligomenorrhoea/amenorrhoea and clinical or biochemical hyperandrogenism have been broadened in the 2003 Rotterdam or European society for Human reproduction (ESHRE)/American society of reproductive medicines (ASRM) criteria to include PCO (Polycystic ovaries) at ultrasound in the key diagnostic criteria [8]. It has been found that the inclusion of PCO in diagnostic criteria has increased the prevalence of PCOS. There are reports that the prevalence of PCOS may be doubled on use of the ESHRE/ ASRM criteria, with a prevalence rate of 12% (not imputing presence of polycystic ovaries) to 18% (imputing presence of polycystic ovaries) [9]. In 2006 further modification of the diagnostic criteria was suggested by Androgen Excess PCOS Society to exclude those without symptoms (PCO on ultrasound and oligomenorrhoea/amenorrhoea but no hyperandrogenism). It should be noted that PCOS is a diagnosis of exclusion and conditions such as thyroid dysfunction and hyperprolactinaemia should be excluded biochemically, while other conditions should be excluded clinically (Cushing's syndrome, virilising tumours, and so on). However, insulin resistance and cardiometabolic features are not currently part of the PCOS diagnostic criteria. With the four key diagnostic features, (oligomenorrhoea/amenorrhoea, clinical or biochemical hyperandrogenism and PCO on ultrasound) there are many potential phenotypes and the heterogeneity of the condition is further exacerbated by degree of obesity, insulin resistance, ethnicity and other factors [10]. Therefore, both the heterogeneity of PCOS and the lack of an understanding of its etiology contribute to the evolving diagnostic criteria and ongoing controversy. Although further research is needed, but currently the ESHRE/ASRM or Rotterdam criteria are the agreed International diagnostic criteria for PCOS.

CLINICAL MANIFESTATIONS OF POLYCYSTIC OVARY SYNSROME

Approximately one in 15 women experiences PCOS [11] and an enlarged ovary is observed on ultrasound in 22% of PCOS women during their reproductive years [12]. Clinical manifestations commonly seen in PCOS include hyperandrogenism, oligomenorrhea, acanthosis nigricans, insulin resistance, reproductive aberration and obesity.

Hyperandrogenism

The most widespread biochemical feature of PCOS women is hyperandrogenism. PCOS constitutes 70-80% of hyperandrogenism with an elevated serum total or free testosterone concentrations [13]. Hyperandrogenism usually manifest as hirsutism, acne, and male pattern alopecia.

Hirsutism: In females is defined as male type terminal hair growth and distribution [11]. PCOS is one of the root causes of hirsutism, with hirsutism occurring in approximately 60% of PCOS cases. Hirsutism is assessed with a standardised scoring system (Ferriman-GallweyScore), however the severity of hirsutism varies with race and degree of obesity [10]. Although hyperandrogenemia is the promoter for hirsutism, but the rate of hair growth is not always proportional to the degree of hyperandrogenism [14], supporting the fact that there is a parallel role for androgen receptor localization (keratinocytes,

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sebaceous glands, and hair dermal papilla cells) and sensitivity in the development of hair patterns and various skin manifestations, such as acne, alopecia, or seborrhea.

Acne: One of the androgen-dependent structures are sebaceous glands, with sebocytes being highly sensitive to androgen signaling, which is exacerbated in PCOS and leads to the development of acne [15]. Androgens stimulate proliferation of sebocytes-especially in mid-back, forehead, and chin. Acne affects approximately one third of PCOS cases but this clinical manifestation is not particularly specific for PCOS [11].

Androgenic Alopecia: is a disorder in which hair is miniaturized because of an increased telogen : anagen ratio with telogen hair being at mitotical rest and anagen hair being mitotically active and is also associated with the genetic susceptibility related to an increased activity of 5α-reductase in the hair follicle. An increased activity of 5α-reductase favors the local conversion of testosterone into more powerful androgen known as Dihydrotestosterone DHT [16]. It is reported by Cela et al. that approximately 67% of the women with alopecia areata have PCOS and increased levels of testosterone and androstenedione [17].

Ovarian dysfunction and infertility

Ovarian dysfunction in PCOS is caused by increased androgens, which disturbs the normal menstrual cycle, inhibits folliculogenesis, leads to the development of polyfollicular morphology and ultimately results in anovulation [18]. Prolonged anovulation can lead to dysfunctional uterine bleeding which may mimic more regular menstrual cycles. Ovarian dysfunction is found in majority of PCOS women, and about 70% to 80% of women with PCOS have either oligomenorrhoea or amenorrhoea. Among those women with ovarian dysfunction as oligomenorrhoea 80% to 90% will be diagnosed with PCOS, and among those with amenorrhoea only 40% will be diagnosed with PCOS as hypothalamic dysfunction is a more common cause [19]. PCOS is the most common cause of anovulatory infertility and it accounts for 90% to 95% of women attending infertility clinics with anovulation. However, about 60% of women with PCOS are fertile (defined as the ability to conceive within 12 months), although time to conceive is often increased in these women [19]. In those with both PCOS and infertility, 90% of them are overweight. Obesity is an independent accelerator of infertility, induces a greater risk of miscarriage and also reduces the efficacy of infertility treatment [19]. In addition, pregnancy in PCOS women is more likely to be complicated by gestational diabetes, preeclampsia and pregnancy hypertension [20].

Acanthosis Nigricans

Acanthosis nigricans a disorder seen as dark and velvety skin with hyperpigmentation and papillomatosis, normally manifest in the areas such as axillae, skin flexures and nape of the neck. These dark velvety raised skin deposits in intertriginous areas are associated with insulin resistance and result from insulin mediated stimulation of the basal layers of the epidermis. In conjunction with hyperandrogenism, acanthosis nigricans constitute a condition termed as HAIR-AN syndrome (hyperandrogenic-insulin resistant–acanthosis nigricans) which occurs in 2 to 5 percent of hirsute women. Only 3% of women with PCOS express acanthosis nigricans, which is associated with insulin resistance and consequently hyperinsulinemia [21].

Insulin Resistance

Around 50% to 80% of women with PCOS have insulin resistance [22]. Mechanisms involved in insulin resistance together with genetic and environmental contributors are likely to be complex. Reductions in insulin secretion, reduced hepatic extraction, impaired suppression of hepatic gluconeogenesis and abnormalities in insulin receptor signalling, are some of the specific abnormalities of insulin metabolism identified in PCOS women [23, 24]. Interestingly, there is a paradoxical expression of insulin resistance in PCOS where insulin-mediated androgen production continues while as its role in regulating glucose metabolism is impaired [24]. Therefore, insulin resistance in PCOS women generates hyperinsulinaemia which modulates androgen production with diverse and complex effects on regulation of lipid metabolism and protein synthesis. Lean women with PCOS compared to weight-matched control subjects often but not always have abnormalities of insulin secretion and action [25]. Obesity enhances insulin resistance and women with PCOS may also present an extrinsic insulin resistance associated with adiposity, which is potentially distinct from the insulin resistance as seen in lean women with PCOS. Women with PCOS are at a greater risk of developing IGT and DM2 with prevalence rates of 31.3% and 7.5%, respectively, compared to 14% for IGT and 0% for DM2 in age-matched and weight-matched non-PCOS control women [26].

Obesity

In USA the prevalence of obesity among women with PCOS is 70 to 80%, almost double as much as in the general US female population [27]. An elevated BMI >25 is infact known to be the most influential factor in endocrinologic and metabolic disturbances in women with PCOS. Obesity plays an important role in the

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expression of metabolic features and other clinical manifestations of PCOS [27]. Although insulin resistance also appears in normal weight PCOS women, but the frequency and magnitude of insulin resistance increases with obesity [28]. Hepatic insulin resistance which is associated with reduced sensitivity to insulin mediated suppression of endogenous glucose production only occurs in obese PCOS women [28]. Obese PCOS women have a 7-fold increased risk of conversion to IGT and a 10-fold risk of developing DM2 compared with normal weight (BMI < 25 kg/m2) PCOS women. Obesity also increases the risk of developing cardiovascular disease by inducing chronic low-grade inflammation and an elevation of inflammatory markers (such as CRP, TNF-α, and IL-6) that increases the risk of cardiovascular disease, which is more pronounced in PCOS women [29]. Although the levels of inflammatory mediators such as TNF-α, IL-6, and CRP directly correlate with BMI in PCOS and non-PCOS women [30] but in some studies an overweight and obese PCOS women have presented with increased levels of these inflammatory markers than their BMI-matched non-PCOS counterparts increasing their risk to cardiovascular disease [30].

POSSIBLE OUTCOMES OF PCOS

Dyslipidemia

One of the most common metabolic abnormalities in PCOS is dyslipidemia, and PCOS itself is considered as the leading cause of dyslipidemia in reproductive-age women [31]. Results obtained from PCOS affected women and their relatives have revealed that the probability of developing dyslipidemia is 1.8-fold greater in the PCOS individuals. PCOS women display the lipid profile as seen in insulin resistant states such as DM2 with elevated levels of TG, VLDL-C, LDL-C, and decreased levels of cardioprotective HDL-C. Total cholesterol (TC) to HDL-C ratio is the main determinant of heart disease, and this ratio is also found to be slightly elevated in PCOS women [31, 32]. Although dyslipidaemia occurs independent of body mass index (BMI), but there is a synergistic deleterious effect of obesity and insulin resistance in PCOS analogous to that seen in DM2. Besides BMI, other factors such as age, ethnicity, genetic influences, and environment also modulate lipid profiles of women with PCOS. Insulin resistance appears to have a pivotal role mediated in part by stimulation of lipolysis and altered expression of lipoprotein lipase and hepatic lipase [33].

Impaired glucose tolerance and diabetes

PCOS commonly associated with impaired glucose metabolism is an independent risk factor for the development of diabetes. Insulin resistance appears to be the key underlying abnormality that leads to the development of impaired glucose tolerance (IGT) [34]. Insulin resistance with abdominal obesity accounts for the higher prevalence of type 2 diabetes in PCOS women. Although there is a risk of developing type 2 diabetes in non-obese women with PCOS, but it is reported that more than 20% of obese women with PCOS will have impaired glucose tolerance after the age of 30 [35]. There are evidences which demonstrate that women diagnosed with PCOS are 7 times at a higher risk of developing type 2 diabetes than controls (15% to 2% respectively) [36]. Most of the women with type 2 diabetes under the age of 45 are also diagnosed with PCOS and these women are at an increased risk of developing gestational diabetes [35]. The risk of developing gestational diabetes is much greater in obese women with PCOS and also in those who need ovulation induction in order to conceive [26]. IGT is an independent predictor of developing DM2 and it is also reported from various studies that the rate of conversion from normal glucose tolerance (NGT) to IGT and from IGT to DM2 is much greater in PCOS women [37]. Lifestyle intervention and medications such as metformin and glitazones can prevent the progression of IGT to DM2, and strengthening the argument for early detection of IGT in high-risk PCOS women [38].

Cardiovascular disease

A major concern for women with PCOS is their risk to cardiovascular disease (CVD), but a clear cause and effect relationship has not been established. Hyperinsulinemia appears to be the main reason for an increased risk of PCOS women to cardiovascular disease. Insulin resistance and consequently hyperinsulinemia contributes to higher incidence of cardiovascular disease in PCOS women by two mechanisms, one being the direct atherogenic action and the other is the adverse affect on the lipoprotein profile [39]. The lipoprotein profile in PCOS women is significantly distorted, showing elevated concentrations of serum triglycerides and total and low-density lipoprotein cholesterol [37], whereas the levels of high density lipoprotein (HDL) and particularly HDL2 subfraction are decreased in these women [40]. In addition the levels of serum plasminogen activator inhibitor-I are also elevated in PCOS women, which could lead to impaired fibrinolysis thereby causing changes associated with coronary heart disease by directly affecting vascular tissues. Women with PCOS are seen to have more extensive coronary artery disease by angiography, and are known to have increased novel cardiovascular risk factors such as inflammation and oxidative stress [41]. Also, increased early clinical and subclinical markers of atherosclerosis such as endothelial dysfunction, impaired pulse wave velocity, increased carotid intima media wall thickness, presence of carotid plaque and increased coronary artery calcification are seen in PCOS women, which are further exacerbated by obesity [42]. Currently, there is a lack of long-term studies in PCOS to appropriately address CVD risk. A recent meta-analysis reported that women with PCOS are at a 2-fold increased risk of developing coronary heart disease (CHD) and stroke compared

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to women without PCOS [43]. The Women's Ischemia Syndrome Evaluation study reported that the cumulative 5-year event-free survival for women without a history of PCOS is 88.4% and it is only 78.9% for those with a premenopausal history of PCOS. Some studies are in consistent with the above findings suggesting an increased risk to CVD in PCOS, but these findings are not universal, and further research is needed [44].

Psychological Problems

Most of the attention in terms of research has been paid on the biological and physiological aspects of the syndrome. The challenges to feminine identity and body image due to obesity, acne and excess hair, as well as infertility and long-term health related concerns compromise quality of life and adversely impact on mood and psychological well-being [6]. Limited studies to date have reported that women with PCOS are much susceptible to depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction. Since the foremost phenotypes of this syndrome (obesity, infertility, hirsutism) are major issues that would undoubtedly cause psychological stress on any patient, it is therefore recommended that women who have PCOS should undergo psychological screening and take appropriate interventions where required. All these issues need to be explored and addressed properly as a part of PCOS assessment and management.

Cancer

It has been suggested that there is an increased risk for endometrial, ovarian and breast cancer in PCOS women. Many factors such as obesity, hyperglycemia and anovulation (unopposed estrogen) with infertility make it difficult to define the absolute risk of these neoplasms attributed to PCOS alone. This is especially true in case of ovarian and breast cancer where specific conclusions cannot be drawn due to paucity of data. However, the link between PCOS and endometrial cancer is supported by the evidences which suggest a 2 -3 fold increased risk of endometrial cancer in the setting of anovulation, menstrual irregularity and PCOS [7]. An excess risk of endometrial cancer was identified to be 3.1(95% CI, 1.1-7.3) from a big study in which 1270 women with chronic anovulation participated [45]. Proper endometrial surveillance (ultrasound and/or sampling) and periodic induction of uterine bleeding with progesterone withdrawal may reduce the risk of endometrial cancer. Also, a significant reduction in the risk of endometrial and ovarian cancer is found with the use of Oral contraceptives [46]. In those desiring fertility, it is seen that pregnancy reduces one's risk of all three cancer types [47]. The use of a progesterone releasing IUD in women with PCOS has not been investigated, but recent evidences support its use in the prevention and treatment of uterine hyperplasia and early endometrial cancer [48].

CONCLUSION

PCOS, a common complex condition is associated with reproductive and metabolic abnormalities. Insulin resistance is one of the most common findings in PCOS, especially those who are overweight. Altered glucose metabolism including impaired glucose tolerance, insulin resistance and type 2 diabetes are well known co-morbidities of PCOS and also significant confounders of cardiovascular disease in PCOS women. Further prolonged exposure to unopposed estrogen in PCOS, can lead to endometrial hyperplasia and endometrial carcinoma. There is a great need for research into several issues regarding the complexity of PCOS and their true negative late impact on women's health. Prospective longitudinal data is required to improve our understanding of long term heath risks associated with PCOS. Likewise the management of PCOS should focus on support, education, addressing psychological factors and strongly emphasizing healthy lifestyle with targeted medical therapy as required.

CONFLICT OF INTEREST

The author declares no competing interests.

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FINANCIAL DISCLOSURE

None.

REFERENCES

[1] *Dokras A. Cardiovascular disease risk factors in polycystic ovary syndrome. Semin Reprod Med 2008; 26: 39-44.*

[2] *Dhindsa G, Bhatia R, Dhindsa M, Bhatia V. Insulin resistance, insulin sensitization and inflammation in polycystic ovarian syndrome. J Postgrad Med 2004; 50: 140-44.*

[3] *Hoffman LK, Ehrmann DA."Cardiometabolic features of polycystic ovary syndrome. Nat Clin Pract Endocrinol Metab 2008; 4(4): 215-22.*

[4] *Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in the polycystic ovary syndrome. Mol Cell Endocrinol 2011; 335: 30–41.*

ISSN: 2456-2254
PRECISION MEDICINE

[5] *Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril 2002; 77: 1095-05.*
[6] *Deeks AA, Gibson-Helm ME, Teede HJ. Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation. Fertil Steril 2010; 93: 2421-23.*
[7] *Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed 2009; 19(3): 398–05.*
[8] *Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group: Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome Society. Fertil Steril 2004; 81: 19-25.*
[9] *March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010; 25: 544-51.*
[10] *Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Androgen Excess Society: Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab 2006; 91: 4237-45.*
[11] *Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007; 370(9588): 685-97.*
[12] *Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004; 18(5): 671-83.*
[13] *Nisenblat V, Norman RJ. Androgens and polycystic ovary syndrome. Curr Opin Endocrinol Diabetes Obes 2009; 16(3): 224-31.*
[14] *Escobar-Morreale HF, Carmina E, Dewailly D. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the androgen excess and polycystic ovary syndrome society. Human Reprod 2012; 18(2): 146-70.*
[15] *Zouboulis CC. Acne and sebaceous gland function. Clinics in Dermatol 2004; 22(5): 360-66.*
[16] *Price VH. Androgenetic alopecia in women. J Invest Dermatol 2003; 8(1): 24-27.*
[17] *Robertson EC, Rush K. Prevalence of polycystic ovaries in women with androgenic alopecia. Europ J Endocrinol 2003; 149(5): 439-42.*
[18] *Schuring AN, Schulte N, Sonntag B, Kiesel L. Androgens and insulin–two key players in polycystic ovary syndrome: recent concepts in the pathophysiology and genetics of polycystic ovary syndrome. Gynakol Geburtshilfliche Rundsch 2008; 48(1): 09-15.*
[19] *Brassard M, AinMelk Y, Baillargeon JP: Basic infertility including polycystic ovary syndrome. Med Clin North Am 2008; 92: 1163-92.*
[20] *Norman RJ CA. Lifestyle factors in aetioloy and management. In:Polycystic Ovary Syndrome. 1st ed Cambridge University Press 2000.*
[21] *Balen AH, Conway GS, Kaltsas G, Techatrasak K, Manning PJ, West C. Polycystic ovary syndrome: The spectrum of the disorder in 1741 patients. Hum Reprod 1995; 10(8): 2107-11.*
[22] *Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 2004; 59: 141-54.*
[23] *Dunaif A, Finegood DT. Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 1996; 81: 942-47.*
[24] *Dunaif A. Insulin resistance and the polycystic ovary syndrome:mechanism and implications for pathogenesis. Endocr Rev 1997; 18: 774-00.*
[25] *Vrbikova J, Cibula D, Dvorakova K, Stanicka S, Sindelka G, Hill M, et al. Insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004; 89: 2942-45.*
[26] *Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999; 84: 165-69.*
[27] *Kandarakis ED, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012; 33(6): 981-30.*
[28] *Moran C, Arriaga M, Rodriguez G, Moran S. Obesity differentially affects phenotypes of polycystic ovary syndrome. Int J Endocrinol 2012; 10(1): 01-07.*
[29] *Attie AD, Scherer PE. Adipocyte metabolism and obesity. J Lipid Res 2009; 50: 95-99*
[30] *Samy N, Hashim M, Sayed M, Said M. Clinical significance of inflammatory markers in polycystic ovary syndrome:their relationship to insulin resistance and body mass index. Dis Markers 2009; 26(4): 163-70.*
[31] *Randeva HS, Tan BK, Weickert MO. Cardiometabolic aspects of the polycystic ovary syndrome. Endocr Rev 2012; 33(5): 812-41.*
[32] *Wild RA, Carmina E, Diamanti-Kandarakis E. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the androgen excess and polycystic ovary syndrome (AE-PCOS) society. J Clin Endocrinol Metabol 2010; 95(5): 2038-49.*
[33] *Joharatnam J, Barber TM, Webber L, Conway GS, McCarthy MI, Franks S. Determinants of dyslipidaemia in probands with polycystic ovary syndrome and their sisters. Clinl Endocrinol 2011; 74(6): 714-19.*
[34] *Cho LW, Jayagopal V, Kilpatrick ES, Atkin SL. The biological variation of C-reactive protein in polycystic ovarian syndrome. Clin Chem 2005; 51: 1905-07*
[35] *Sharma A, Yousef M. Recent development in polycystic ovary syndrome IN: Progress in Obstetrics and Gynecology. Edited by John Studd 2005; 14: 227-39*
[36] *Wijeyaratne CN, Balen AH, Barth J, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference. Clin Endocrinol 2002; 57: 343-50*
[37] *Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001; 111(8): 607-13.*

ISSN: 2456-2254
PRECISION MEDICINE

[38] *Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-03.*
[39] *Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at longterm follow-up. J Clin Epidemiol 1999; 51: 779-86*
[40] *Giallauria F, Orio F, Palomba S, Lombardi G, Colao A, Vigorito C. Cardiovascular risk in women with polycystic ovary syndrome. J Cardiovasc Med 2008; 9: 987-92*
[41] *Cho LW, Jayagopal V, Kilpatrick ES, Atkin SL. The biological variation of C-reactive protein in polycystic ovarian syndrome. Clin Chem. 2005; 51: 1905-07*
[42] *Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. J Clin Endocrinol Metab 2005; 90: 5711-16.*
[43] *DeGroot PCM, Dekkers OM, Romijn JA, Dieben SWM, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and metaanalysis. Hum Reprod 2011; 17(17): 495-00.*
[44] *Shaw LJ, Merz CN, Azziz R, Azziz R, Stanczyk FZ, Sopko G, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health-National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. J Clin Endocrinol Metabol 2008; 93(4): 1276-84*
[45] *Balen A. Rajkhowa R. Health consequences of polycystic ovary syndrome. Reprod endocrinol 2003; 99-07.*
[46] *Cramer DW. The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am 2012; 26(1): 01–12.*
[47] *Adami HO, Hunter D, Trichopoulos D. Textbook of Cancer Epidemiology. Oxford University Press 2008.*
[48] *Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2010; 203(6): 547.*