Narrative Review

Polycystic Ovarian Syndrome and Menopause in Forty Plus Women

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age group, but it affects women's health and quality of life across the life course. During different stages of life, the PCOS phenotype can change, which requires a personalized diagnostic approach and treatment. With increasing age, the syndrome evolves from a reproductive disease to a more metabolic disorder. Along with various metabolic disturbances like insulin resistance and abnormalities of energy expenditure, PCOS is recognized as a major risk factor for the development of type 2 diabetes and cardiovascular disease (CVD) in later life. The aim of the current review was to conduct a nonsystematic review of published literature and research that has been presented so far regarding menopausal women with PCOS as well as the associated changes in hormone profile, their lipid profile, and various metabolic changes that occur. The current review may also contribute to raise awareness about the risk of hypertension and CVDs in postmenopausal women with PCOS.

Keywords: *Cardiovascular risk, diabetes mellitus, dyslipidemia, menopause, metabolic syndrome, plus forty women, polycystic ovary syndrome, subclinical atherosclerosis*

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Introduction

Polycystic ovary syndrome (PCOS) is one of the multifaceted diseases with a broad spectrum of manifestations affecting not only women of reproductive age but also the adolescents and the postmenopausal women.[1] It is the most common endocrine disorder in women which presents with various signs and symptoms and has a broad range of phenotypes, which may include reproductive, endocrine, and metabolic alterations.[2,3] PCOS generally is characterized by oligo-ovulation, anovulation, hyperandrogenism, and polycystic ovaries.[4] It is a hypothalamic–pituitary–ovary axis dysfunction along with anovulation, but unlike other causes of ovulatory failure that feature insufficient ovarian follicle growth or suppressed gonadotropin secretion (or both), PCOS typically has androgen excess and subtle alterations (not detected by routine tests) in serum levels of gonadotropins and estrogens.[2]

Although the first clinical manifestations of PCOS are present in adolescent females, there is a clear evidence that the disease has its origin in the intrauterine environment, indicating the genetic involvement.[5] Some studies have demonstrated a definite influence of interleukin-6 and interleukin-10 gene polymorphisms, interferon-c, and transforming growth factor-beta 1 in the development of PCOS, although no clear pattern of inheritance has been identified so far.[6] Other causal factors for PCOS are epigenetic exposures, highlighting the association between intrauterine exposure and maternal androgens, and phenotypes related to the syndrome.[7] Ethnic variations in PCOS may be associated with environmental factors, such as socioeconomic conditions and lifestyle.[8]

Insulin resistance (IR) has also been listed as the key pathophysiological element for the development of PCOS. Hyperandrogenism seen in PCOS women persists after the menopausal transition. Insulin acts synergistically with the luteinizing hormone to increase androgen production in the theca cell of the ovary.[9] Another site for androgen production

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is the adrenal cortex because of abnormalities in cortical steroidogenesis promoted by stimulation of adrenocorticotropic hormone.[10] The excess androgen levels in PCOS, mainly testosterone, androstenedione, and dehydroepiandrosterone sulfate, cause premature atresia of the ovarian follicles, forming multiple cysts and anovulation with persistent estrogen levels resulting from aromatization of androgens to estrogens without opposition of progesterone leading to an increased risk of endometrial hyperplasia and neoplasia.[11]

The extrareproductive manifestations of PCOS are IR, metabolic syndrome (MS), and low-grade chronic inflammation.[12-16] The variety of metabolic disturbances in PCOS may be related to a higher risk of developing cardiovascular disease (CVD).[17] This increased risk of CVD is linked directly to PCOS and the exact cause though not known, young women with PCOS may have to undergo many investigations to rule out these diseases.[18]

This fact may explain a predisposition to arterial hypertension in women suffering from PCOS.[19] No doubt, the association between PCOS and changes in arterial blood pressure has still not been fully elucidated, the increased risk of hypertensive state may be explained by IR and hyperandrogenism, even when adjusted for age, body mass index (BMI), and other anthropometric parameters.[20]

Hyperandrogenism plays a central role in the pathophysiology of PCOS and is associated with anovulation, infertility, altered body fat distribution, dyslipidemia, and hyperinsulinemia as a result of IR.[21] On the other hand, IR itself may worsen the hyperandrogenism *per* SE because the results of some *in vitro* studies have suggested that IR directly contributes to the androgenic potential of ovarian theca cells.[22,23] In addition to impaired carbohydrate and lipid metabolism, chronic inflammation, reflected by elevated levels of inflammatory markers, has been shown to be present, adding to the risk of CVD.[24] Women with the polycystic ovarian disease have higher risk of obesity. The results of a few recent studies are in line with this, which suggest that women with PCOS more frequently have CVD as well as related events along with obesity.[25-27]

Although majority of studies on PCOS have examined only the reproductive and metabolic disturbances of women of reproductive age, as we know, PCOS is a chronic condition which must be managed throughout a woman's life. Nonetheless, few longitudinal studies have been conducted with postmenopausal women who were initially studied 20–30 years ago to examine changes in PCOS presentation associated with age. Till date, various studies have attempted to answer questions about PCOS and menopause such as, what happens in menopausal transition in PCOS, what is the age of menopause in women with PCOS, whether the syndrome gets worse or improves after menopause, or whether it can be cured or it simply disappears. Fortunately, these studies have successfully answered many such questions.

Materials and Methods

We had searched the database focusing the publications related to the polycystic ovaries, including pathogenesis, clinical manifestations, diagnosis, and therapeutic aspects of PCOS, as well as the association of PCOS with cardiovascular and arterial hypertensive disorders in menopausal women with different combinations of the keywords: "polycystic ovary syndrome", "menopause", "blood pressure" "hypertension", "Cardiovascular risk", "diabetes mellitus", "dyslipidemia" "menopause", "metabolic syndrome", "subclinical atherosclerosis: etc. The established inclusion criteria for our review were: original prospective articles, cross-sectional or retrospective studies with at least five years of follow-up, and with study groups of at least 30 participants.

Menopausal transition

During the menopausal transition, several hormonal and metabolic changes take place in women. Androgen levels are known to remain stable or even to increase as women enter menopause, while at the same time, estrogen levels decrease dramatically.[28,29] As women become more androgenic, several features such as IR, chronic inflammation, abdominal adiposity, and dyslipidemia tend to worsen.[30,31] Although ovarian androgen secretion capacity declines with age in both healthy women and in women with PCOS, it remains enhanced until the late reproductive years in PCOS.[32,33] The adrenal androgen secretion also remains pronounced up to menopause in women with PCOS, indicating that exposure to hyperandrogenism persists for a long time in these women.[34] Thus, it seems probable that long-lasting hyperandrogenism may magnify the unfavorable hormonal and metabolic changes related to menopause and expose these women to increased health risks.

Impaired glucose metabolism, enhanced ovarian androgen secretion, and chronic inflammation observed in premenopausal women with PCOS persist after menopause emphasizing life-long health risks related to this syndrome.[35]

The women with PCOS exhibited higher insulin levels as well as increased insulin responses in oral glucose tolerance test before and after menopause, indicating a greater degree of IR than in the control women. Similarly, they had increased Homeostatic Model

Assessment for IR (HOMA-IR) values when compared with control women.[36]

Age of menopause

The age of menopause varies between women and it is unclear whether this difference is due to the original number of follicles or differences in the depletion of the follicles with aging. Women with PCOS have higher anti-Müllerian hormone (AMH) levels as compared with the controls,[37] and the AMH levels are highly correlated with antral follicle count on ultrasound and can be used as a surrogate for follicle number.[38] Forslund *et al*.[39] demonstrated that women with PCOS reached menopause 4 years later than their age-matched controls. S-follicle-stimulating hormone (S-FSH) levels and the proportion of women with S-FSH >50 IU/L were also lower in women with PCOS. Neither parity nor nulliparity differed between PCOS and controls.[39] There have been attempts to calculate the menopausal age of women with and without PCOS based on AMH levels earlier in life and the postulated menopausal age of women with PCOS, based on AMH, was approximately 2 years later than that of controls.[40]

Diagnosing polycystic ovary syndrome in menopause

It is not possible to diagnose a woman with PCOS when she has already reached menopause because the cardinal features disappear, i.e., menses cease. Testosterone levels may no longer be higher than in control women, although less conventional measures of androgen excess such as the free androgen index (FAI) and human chorionic gonadotropin-stimulated androstenedione and 17-hydroxyprogesterone levels remain higher.[36,41,42] Although it has been suggested that PCO morphology persists into menopause, the hypoechoic structures found on ultrasound in postmenopausal women with PCOS correspond to inclusion cysts and vascular structures rather than follicles, and pathology studies also do not demonstrate secondary follicles in postmenopausal ovaries.[41] Thus, we are able to make the diagnosis of PCOS only during the reproductive years.

Metabolic syndrome in aging polycystic ovary syndrome women

The lipid metabolism worsens as women with PCOS age, especially with regard to triglyceride and high-density lipoprotein (HDL) concentrations. In a study, LDL cholesterol levels were found to be similar for middle-aged women with and without PCOS, although HDL was reduced and triglyceride levels were higher.[43] These findings support those of other researchers who demonstrated an unfavorable lipid profile (e.g., elevated triglycerides and reduced HDL concentrations) in postmenopausal women with the syndrome.[36,44]

Longitudinal and cross-sectional studies including women with PCOS >40 years of age are limited in number and design, but many demonstrate that some of these comorbidities persist.[18]

Longitudinal studies which were done in women with PCOS suggest that waist circumference, cholesterol, and triglyceride levels increase in women with PCOS as they reach 40–50 years of age,[36,45,46] whereas BMI increased in some women, but not in all as per many studies,[41,45] whereas in various cross-sectional studies done on women with PCOS over the age of 35 years have demonstrated higher BMI, HOMA, glucose, and triglyceride levels compared with age-matched controls.[41,47-49] A large longitudinal study of women with PCOS demonstrated a prevalence of type 2 diabetes of 39%, exceeding the prevalence of 5.8% in the general population.[50] However, the high prevalence of type 2 diabetes is likely related to the very high BMI in those women[50] because other studies do not demonstrate an increase in diabetes prevalence in this age group.[51] Consistently, cross-sectional studies of menopausal women with PCOS compared with menopausal controls demonstrate that only the insulin area under the curve remained significantly higher in women with PCOS when controlled for the higher BMI.[36]

Despite the longer exposure to these cardiovascular risk factors, it is difficult to demonstrate an increased risk of morbidity and mortality in menopausal women with PCOS. There has been only one small longitudinal study and one retrospective cohort study in menopausal women diagnosed with PCOS in their reproductive years and controls to assess the risk of mortality and cardiovascular morbidity into menopause, up to age 70 years.[52,53] These studies have not demonstrated an increased risk of myocardial infarction or death from CVD or increased total mortality from any cause in women with PCOS.[52] Only the retrospective cohort study demonstrated an increased risk of stroke,[53] but the group also had a higher BMI, more diabetes, and more cardiovascular risk factors overall. Taken together, further studies are needed to determine whether the increased cardiovascular risk in reproductive life translates into an increased cardiovascular morbidity and mortality in later life for women with PCOS. However, it is possible that in most of the women with PCOS the cardiovascular risk normalizes with age, whereas in a subgroup where PCOS women maintain high androgen levels also after menopause, the cardiovascular risk remains increased and affects the morbidity. Patients with MS have a higher incidence of CVD.[35]

PCOS women reported hot flushes and sweating less frequently than the control women. The possible

explanation for this may be the persistent androgenicity among PCOS women could ameliorate these menopausal symptoms, in accordance with effects on sexuality, mood, and well-being.[54] Vaginal dryness was more often reported in postmenopausal PCOS women than in controls, possibly implicating differences in sexual activity with experience of vaginal dryness secondary to the higher FAI and thereby libido.[42] The climacteric symptoms (apart from vaginal dryness) and hypothyroidism were less prevalent in the PCOS group than in the controls groups. BMI was still similar in both groups. The previously higher WHR in women with PCOS had disappeared, mainly due to weight gain in the controls.[42]

Constant long-term exposure to elevated androgen levels in women with PCOS can have a lasting effect on excessive facial and body hair, hair loss, and even balding that extends past menopause.[42] These dermatological effects can be detrimental to a woman's self-esteem and body image.

Conclusion

It is now evident that PCOS does not disappear as women get into menopause. Reproductive hormones and the lipid profile in women with PCOS differ from those in women without PCOS after menopause. Women with PCOS reach menopause a few years later and have lower serum FSH compared with age-matched controls. Moreover, the inflammatory and the metabolic parameters worsen with age, putting women with PCOS at increased risk of life-long health issues beyond menopause, especially the risk of developing CVD, arterial hypertension, and type 2 diabetes. All providers involved in the multidimensional care of women with PCOS should be aware of these long-term health risks to provide appropriate counseling, screening, and management options. This supports the need for treatment involving dietary and lifestyle modifications and insulin sensitizers in older women with PCOS who have metabolic complications.

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Conflicts of interest

There are no conflicts of interest.

References

1. Azziz R, Dumesic DA, Goodarzi MO. Polycystic ovary syndrome: An ancient disorder? Fertil Steril 2011;95:1544-8.
2. Rocha AL, Oliveira FR, Azevedo RC, Silva VA, Peres TM, Candido AL, *et al*. Recent advances in the understanding and management of polycystic ovary syndrome. F1000Res 2019;8:F1000.
3. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update 2014;20:748-58.
4. Shah D, Bansal S. Polycystic ovaries – Beyond menopause. Climacteric 2014;17:109-15.
5. de Melo AS, Dias SV, Cavalli Rde C, Cardoso VC, Bettiol H, Barbieri MA, *et al*. Pathogenesis of polycystic ovary syndrome: Multifactorial assessment from the foetal stage to menopause. Reproduction 2015;150:R11-24.
6. Sóter MO, Ferreira CN, Sales MF, Candido AL, Reis FM, Milagres KS, *et al*. Peripheral blood-derived cytokine gene polymorphisms and metabolic profile in women with polycystic ovary syndrome. Cytokine 2015;76:227-35.
7. Demissie M, Lazic M, Foecking EM, Aird F, Dunaif A, Levine JE. Transient prenatal androgen exposure produces metabolic syndrome in adult female rats. Am J Physiol Endocrinol Metab 2008;295:E262-8.
8. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36:487-525.
9. Erhmann DA. Polycystic ovary syndrome. N Engl J Med 2005;352:1223-36.
10. da Silva BB, Lopes-Costa PV, Rosal MA, Pires CG, dos Santos LG, Gontijo JA, *et al*. Morphological and morphometric analysis of the adrenal cortex of androgenized female rats. Gynecol Obstet Invest 2007;64:44-8.
11. Dumitrescu R, Mehedintu C, Briceag I, Purcarea VL, Hudita D. The polycystic ovary syndrome: An update on metabolic and hormonal mechanisms. J Med Life 2015;8:142-5.
12. Çakıroğlu Y, Vural F, Vural B. The inflammatory markers in polycystic ovary syndrome: Association with obesity and IVF outcomes. J Endocrinol Invest 2016;39:899-907.
13. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia F. Genetic, hormonal and metabolic aspects of PCOS: An update. Reprod Biol Endocrinol 2016;14:38.
14. Durmus U, Duran C, Ecirli S. Visceral adiposity index levels in overweight and/or obese, and non-obese patients with polycystic ovary syndrome and its relationship with metabolic and inflammatory parameters. J Endocrinol Invest 2017;40:487-97.
15. McCartney CR, Marshall JC. Clinical practice. Polycystic ovary syndrome. N Engl J Med 2016;375:54-64.
16. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. Reproduction 2015;149:R219-27.
17. Chen MJ, Yang WS, Yang JH, Chen CL, Ho HN, Yang YS. Relationship between androgen levels and blood pressure in young women with polycystic ovary syndrome. Hypertension 2007;49:1442-7.
18. Krishnan A, Muthusami S. Hormonal alterations in PCOS and its influence on bone metabolism. J Endocrinol 2017;232:R99-R113.
19. Rocha Gontijo JA, Gui DC, Boer PA, Dos Santos AR, Ferreira-Filho CP, Nery Aguiar AR, *et al*. Evaluation of arterial blood pressure and renal sodium handling in a model of female rats in persistent estrus. Clin Exp Hypertens 2010;32:385-9.
20. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: Current perspectives. Int J Womens Health 2015;7:745-63.
21. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001;111:607-13.
22. Qu J, Wang Y, Wu X, Gao L, Hou L, Erkkola R. Insulin resistance directly contributes to androgenic potential within ovarian theca cells. Fertil Steril 2009;91:1990-7.

23. Zhao L, Li W, Han F, Hou L, Baillargeon JP, Kuang H, *et al*. Berberine reduces insulin resistance induced by dexamethasone in theca cells *in vitro*. Fertil Steril 2011;95:461-3.
24. Orio F Jr., Palomba S, Cascella T, Di Biase S, Manguso F, Tauchmanovà L, *et al*. The increase of leukocytes as a new putative marker of low-grade chronic inflammation and early cardiovascular risk in polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:2-5.
25. Cooney LG, Dokras A. Beyond fertility: Polycystic ovary syndrome and long-term health. Fertil Steril 2018;110:794-809.
26. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, *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 Metab 2008;93:1276-84.
27. Patel SM, Ratcliffe SJ, Reilly MP, Weinstein R, Bhasin S, Blackman MR, *et al*. Higher serum testosterone concentration in older women is associated with insulin resistance, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 2009;94:4776-84.
28. Burger HG, Dudley EC, Cui J, Dennerstein L, Hopper JL. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. J Clin Endocrinol Metab 2000;85:2832-8.
29. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: Focus on findings from the Melbourne Women's Midlife Health Project. Hum Reprod Update 2007;13:559-65.
30. Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, *et al*. Adipokines, inflammation, and visceral adiposity across the menopausal transition: A prospective study. J Clin Endocrinol Metab 2009;94:1104-10.
31. Matthews KA, Crawford SL, Chae CU, EversonRose SA, Sowers MF, Sternfeld B, *et al*. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366-73.
32. Piltonen T, Koivunen R, Ruokonen A, Tapanainen JS. Ovarian age-related responsiveness to human chorionic gonadotropin. J Clin Endocrinol Metab 2003;88:3327-32.
33. Piltonen T, Koivunen R, Perheentupa A, Morin-Papunen L, Ruokonen A, Tapanainen JS. Ovarian age-related responsiveness to human chorionic gonadotropin in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2004;89:3769-75.
34. Puurunen J, Piltonen T, Jaakkola P, Ruokonen A, Morin-Papunen L, Tapanainen JS. Adrenal androgen production capacity remains high up to menopause in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2009;94:1973-8.
35. Mumusoglu S, Yildiz BO. Metabolic syndrome during menopause. Curr Vasc Pharmacol 2019;17:595-603.
36. Puurunen J, Piltonen T, Morin-Papunen L, Perheentupa A, Järvelä I, Ruokonen A, *et al*. Unfavorable hormonal, metabolic, and inflammatory alterations persist after menopause in women with PCOS. J Clin Endocrinol Metab 2011;96:1827-34.
37. Tehrani FR, Solaymani-Dodaran M, Hedayati M, Azizi F. Is polycystic ovary syndrome an exception for reproductive aging? Hum Reprod 2010;25:1775-81.
38. Visser JA, Themmen AP. Anti-Müllerian hormone and folliculogenesis. Mol Cell Endocrinol 2005;234:81-6.
39. Forslund M, Landin-Wilhelmsen K, Schmidt J, Brännström M, Trimpou P, Dahlgren E. Higher menopausal age but no differences in parity in women with polycystic ovary syndrome compared with controls. Acta Obstet Gynecol Scand 2019;98:320-6.
40. Minooee S, Ramezani Tehrani F, Rahmati M, Mansournia MA, Azizi F. Prediction of age at menopause in women with polycystic ovary syndrome. Climacteric 2018;21:29-34.
41. Alsamarai S, Adams JM, Murphy MK, Post MD, Hayden DL, Hall JE, *et al*. Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age. J Clin Endocrinol Metab 2009;94:4961-70.
42. Schmidt J, Brännström M, LandinWilhelmsen K, Dahlgren E. Reproductive hormone levels and anthropometry in postmenopausal women with polycystic ovary syndrome (PCOS): A 21-year followup study of women diagnosed with PCOS around 50 years ago and their age-matched controls. J Clin Endocrinol Metab 2011;96:2178-85.
43. Krentz AJ, von Mühlen D, Barrett-Connor E. Searching for polycystic ovary syndrome in postmenopausal women: Evidence of a dose-effect association with prevalent cardiovascular disease. Menopause 2007;14:284-92.
44. Macut D, Micić D, Parapid B, Cvijović G, Sumarac M, Kendereski A, *et al*. Age and body mass related changes of cardiovascular risk factors in women with polycystic ovary syndrome. Vojnosanit Pregl 2002;59:593-9.
45. Carmina E, Campagna AM, Lobo RA. A 20-year follow-up of young women with polycystic ovary syndrome. Obstet Gynecol 2012;119:263-9.
46. Pasquali R, Gambineri A, Anconetani B, Vicennati V, Colitta D, Caramelli E, *et al*. The natural history of the metabolic syndrome in young women with the polycystic ovary syndrome and the effect of long-term oestrogen-progestagen treatment. Clin Endocrinol (Oxf) 1999;50:517-27.
47. Loucks TL, Talbott EO, McHugh KP, Keelan M, Berga SL, Guzick DS. Do polycystic-appearing ovaries affect the risk of cardiovascular disease among women with polycystic ovary syndrome? Fertil Steril 2000;74:547-52.
48. Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, *et al*. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: Results of a case-control study. J Clin Epidemiol 1998;51:415-22.
49. Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: Results of a 31 year follow-up study. Hum Fertil (Camb) 2000;3:101-5.
50. Carmina E, Campagna AM, Lobo RA. Emergence of ovulatory cycles with aging in women with polycystic ovary syndrome (PCOS) alters the trajectory of cardiovascular and metabolic risk factors. Hum Reprod 2013;28:2245-52.
51. Livadas S, Christou M, Economou F, Karachalios A, Xyrafis X, Boutzios G, *et al*. Menstrual irregularities in PCOS. DoeE it matter when it starts? Exp Clin Endocrinol Diabetes 2011;119:334-7.
52. Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: A 21-year controlled follow-up study. J Clin Endocrinol Metab 2011;96:3794-803.
53. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: A retrospective cohort study. Clin Endocrinol (Oxf) 2000;52:595-600.
54. Mathur R, Braunstein GD. Androgen deficiency and therapy in women. Curr Opin Endocrinol Diabetes Obes 2010;17:342-9.