Maturitas 139 (2020) 12–19

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Polycystic ovary syndrome and aging: Health implications after menopause

Nafiye Helvaci[a], Bulent Okan Yildiz[b,*]

[a] Hitit University School of Medicine, Division of Endocrinology and Metabolism, Corum, Turkey
[b] Hacettepe University School of Medicine, Division of Endocrinology and Metabolism, Ankara, Turkey

ARTICLE INFO

Keywords:
PCOS
Obesity
Hypertension
Cardiovascular disease
Cancer
Depression

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine disorder with heterogenous clinical manifestations. The evidence indicates that PCOS is associated with long-term health risks including type 2 diabetes, metabolic syndrome, obstructive sleep apnea, endometrial cancer, and mood disorders. Although cardiometabolic risk factors are more common among women with PCOS, currently there is no strong evidence for increased cardiovascular morbidity and mortality in these patients. The effect of menopausal transition on the long-term health consequences of PCOS is mostly uncertain. The PCOS phenotype improves with aging in affected women. Accordingly, the differences in the cardiometabolic risk profiles of PCOS patients and of the general population seem to disappear after menopause. However, it is not clear whether this phenotype amelioration is associated with changes in other long-term health risks after the menopause. There are also gaps in our knowledge about the impact of long-term use of oral contraceptives on the prevalence of PCOS-related comorbidities. This review summarizes the current knowledge regarding the long-term health consequences of PCOS and their clinical implications in peri- and postmenopause, and highlights areas for future research.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. Depending on the diagnostic criteria used and the population studied, its prevalence ranges between 4–21% [1,2]. According to the widely accepted 2003 Rotterdam criteria, PCOS diagnosis requires at least two of the following three features: oligo-anovulation (OA), clinical/biochemical hyperandrogenism (HA) and presence of polycystic ovarian morphology (PCOM) on ultrasonography [3]. Based on the presence and/ or absence of these diagnostic features, different phenotypes have been identified (Table 1). Phenotypic presentation of PCOS differs between referral and unselected populations [4] and varies within an individual over time and between individuals of different ethnic and geographic regions [5].

PCOS is a life-long condition and is associated with a number of metabolic and non-metabolic long-term health risks that may transcend well beyond the reproductive age including obesity, glucose intolerance and type 2 diabetes, hypertension (HTN), dyslipidemia, metabolic syndrome (MetS), obstructive sleep apnea (OSA), endometrial cancer, depression and anxiety. Nevertheless, few data are available concerning long-term health implications of PCOS after menopause. The aim of this review is to outline the available data about the impact of PCOS on long-term health in aging women and consider the current evidence that is valid for the postmenopausal period.

2. Methods

A thorough literature search was conducted on PubMed database for clinical studies, review articles, and meta-analyses written in English between 1990 and January 2020. MeSH terms, alone or in combination, for the search included ‘polycystic ovary syndrome’, ‘menopause’, ‘cardiometabolic’, ‘cardiovascular disease’, ‘metabolic syndrome’, ‘diabetes’, ‘obstructive sleep apnea’, ‘endometrial cancer’, ‘breast cancer’, ‘ovarian cancer’, ‘mood disorders’, ‘depression’, ‘anxiety’, and ‘oral contraceptives’. In addition, reference lists of identified papers were manually checked for additional related articles.

3. PCOS phenotype and menopausal transition

PCOS phenotype ameliorates with aging, indicated by the increase in regular menstrual cycles, decrease in ovarian volume and follicle number, and decrease in serum androgen levels [6,7]. Confirming this, a longitudinal study with a follow-up of 20 years, demonstrated that the prevalence of more severe phenotypes (phenotypes A and B) were

* Corresponding author at: Hacettepe University School of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Hacettepe 06100 Ankara, Turkey.
E-mail address: yildizbo@yahoo.com (B.O. Yildiz).

https://doi.org/10.1016/j.maturitas.2020.05.013
Received 31 March 2020; Received in revised form 18 May 2020; Accepted 21 May 2020

Table 1
PCOS phenotypes according to the 2003 Rotterdam Criteria.

	Phenotypes			
PCOS features	A	B	C	D
HA	+	+	+	–
OA	+	+	–	+
PCOM	+	–	+	+

Abbreviations: HA, hyperandrogenism; OA, oligo-anovulation; PCOM, polycystic ovarian morphology.

reduced by the fourth decade of life in women with PCOS. In many patients, the diagnosis of PCOS could no longer be made; and in others, the phenotype was less severe during this age period [8]. However, it is not clear whether the improvement in PCOS phenotype during peri- and postmenopause is associated with reduction in long-term health risks associated with PCOS.

4. PCOS and long-term complications

PCOS affects multiple aspects of a woman's health that can change throughout the life (Fig. 1). The health and economic burden due to the high prevalence of PCOS requires greater recognition of its long-term health implications. Accordingly, the new international evidence-based guideline in PCOS emphasizes screening for these PCOS-related complications [9].

4.1. Obesity

Obesity, in particular of visceral origin, is a common feature of PCOS and significantly influences the severity of both reproductive and cardiometabolic features in these patients. In a large meta-analysis, including 35 studies, the risk ratios for obesity and central obesity in reproductive-aged women with PCOS were 2.8 [95% confidence interval (CI): 1.9–4.1] and 1.7 [95% CI: 1.3–2.3), respectively [10]. However, in most of the studies investigating the association between PCOS and obesity, women with PCOS were recruited from clinic populations. Referral PCOS subjects seem to have a greater BMI than non-PCOS women, a difference that is not immediately apparent or less severe in unselected PCOS [4].

Increasing body mass index (BMI) is an important finding in women after menopause. Current evidence indicate that weight gain at midlife is primarily influenced by aging, but the changes in the hormonal milieu during menopausal transition are significantly associated with changes in body composition in favor of abdominal obesity [11]. Accordingly, it is suspected that women with PCOS who have transitioned through menopause will have increased rates of obesity, in particular of visceral origin. However, available data regarding the prevalence of obesity and central adiposity in older women with PCOS are very limited. In a previous cross-sectional study where 190 women with PCOS and 99 controls were distributed into 3 stages of reproductive life, BMI and waist to hip ratio (WHR) values, which were found to be higher in the early and late reproductive periods in PCOS patients, did not differ between the patients and controls in the perimenopausal period (mean age 47 years) [12]. On the other hand, Meun et al., in a very recent cross-sectional study including 200 women with PCOS aged > 45 years (mean age 50.5 years; 12.6% were postmenopausal) and 200 age-matched controls (40.5% were postmenopausal), observed a higher BMI and increased waist circumference (WC) in women with PCOS [13]. There are only a few studies reporting on anthropometrics which include mainly postmenopausal women with PCOS [14–16]. In a 21-year follow-up study of a small cohort of women with PCOS aged 61–79 years (n = 25), there were no differences regarding BMI or WHR between patients and age-matched controls (n = 68) [14]. The higher WHR found in women with PCOS at the initial assessment had disappeared during follow-up because of the weight gain among controls [14]. On the contrary, in a 31-year follow-up study of 319 women with PCOS and 1060 age-matched controls (mean age of participants 56.7 years; approximately 80% of women with PCOS and controls were postmenopausal), Wild et al., reported that BMI and self-reported WHR were significantly higher in the PCOS group [15]. Similarly, in the Rotterdam Study, a population-based prospective cohort study including only postmenopausal women, patients with PCOS (n = 106) had higher BMI and WHR compared to age-matched controls (n = 171) [16]. Overall, most, but not all, evidence indicate that women with PCOS remain more obese than controls after menopause.

4.2. Glucose intolerance/Type 2 diabetes

Insulin resistance (IR) is a prominent and intrinsic feature of PCOS [17]. Accordingly, dysglycemia is more often encountered in women with PCOS. In a recent meta-analysis including 40 studies, women with PCOS (mean age was around 30 years in most of the included studies) had approximately three times higher risk for impaired glucose tolerance (IGT) [Odds ratio (OR): 3.3, 95% CI: 2.2–4.9] and type 2 diabetes mellitus (T2DM) (OR: 2.9, 95% CI: 1.4–5.7), compared to controls.

Menopause is associated with increased insulin resistance and a propensity to develop glucose intolerance and T2DM [18]. Therefore, it is reasonable to assume that the prevalences of IGT and T2DM would remain higher in PCOS women making transition into menopause. However, there are limited studies that have assessed the association of PCOS and IGT/T2DM in older women and the results are conflicting. In a cross-sectional study by Meun et al., no difference was observed in the prevalence of T2DM between women with PCOS around the age of 50 and age-matched controls, despite a higher BMI and increased WC [13]. On the other hand, in a previous retrospective cohort study including 28 women with PCOS aged 45–59 years (mean age, 51.9 years) and 752 age- and BMI-matched controls, the prevalence of T2DM was

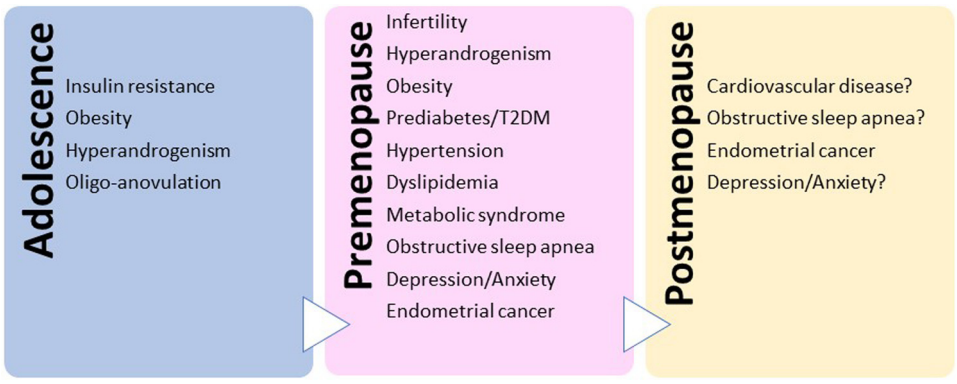

Fig. 1. PCOS and health outcomes across the life course. T2DM, type 2 diabetes mellitus.

significantly higher in PCOS patients (32% vs. 8%; $p < 0.001$) [19]. Similarly, a very recent 24-year follow-up study including 27 women with PCOS with an age range of 42–63 years (mean age 52.4 years, 37% postmenopausal) and 94 age-matched controls (57% postmenopausal), women with PCOS had a higher prevalence of T2DM than controls (19% vs. 1%; $p < 0.01$) [20]. However in this study, women with PCOS, initially recruited from a hospital setting, had significantly higher BMI and WHR both at baseline and during follow-up, and risk of T2DM was not adjusted for these parameters [20].

There are four studies reporting risk of T2DM in postmenopausal women with PCOS. In the 21-year follow-up study by Schmidt et al., the statistically significant increase in the prevalence of T2DM in women with PCOS found at the initial assessment had disappeared at late menopause [21]. Similarly, Merz et al., in a long-term follow-up study including 25 postmenopausal women with PCOS (mean age 62.6 years) and 270 age- and BMI-matched controls, did not find a significant difference in the prevalence of T2DM between the groups [22]. In the study by Wild et al., aforementioned above, BMI-adjusted prevalence rates of T2DM were not significantly different between women with PCOS and controls after an average follow-up of 31 years [15]. On the other hand, in the Rotterdam study, a higher rate of T2DM was reported in postmenopausal women with PCOS ($n = 106$; mean age, 69.6 years) compared with age-matched controls ($n = 171$) (18.9 vs. 7%, respectively; $p < 0.01$) [16]. However, rate of T2DM was not adjusted for BMI and WHR which were significantly higher in women with PCOS in this study [16]. Thus, most of the available data, although limited, do not indicate a substantial increase in risk of T2DM in postmenopausal women with PCOS.

4.3. Hypertension

There have been inconsistent findings so far among studies regarding the prevalence of HTN in women with PCOS. Recently, a meta-analysis including 30 studies reported that the prevalence of HTN was higher in patients with PCOS compared to control population [23]. Subgroup analysis based on the age groups revealed that the pooled relative risk of HTN was higher in reproductive-aged PCOS, while no significant difference was observed for menopausal/aging group. The same results were obtained when only population-based studies were included in the meta-analysis [23]. However, there was a considerable heterogeneity among studies included in this meta-analysis which requires caution for interpretation of the results. Overall, available evidence indicates that the increased risk of HTN in women with PCOS during reproductive years ameliorates with aging and become similar with healthy women after menopause.

4.4. Dyslipidemia

Atherogenic dyslipidemia defined as low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and lower low-density lipoprotein (LDL) particle size is highly prevalent in reproductive-aged PCOS women, encountered in up to 70% of patients with the syndrome [24]. This lipid pattern is also common in general women population after menopause and it is mainly the consequence of IR [25]. The impact of PCOS on the severity of dyslipidemia in women making the transition into menopause is not clear. No differences were found in serum lipid levels in perimenopausal women with PCOS compared with controls in studies by Echiburu et al. [12], Meun et al. [13], and Cibula et al. [19]. In the Rotterdam study, lower HDL and higher triglyceride levels were observed among postmenopausal women with PCOS [16]. Similarly, in the study by Schmidt et al., the only persistent lipid abnormality in postmenopausal women with PCOS compared to controls was higher TG levels [21]. On the other hand, Merz et al. [22] reported similar prevalences of dyslipidemia between postmenopausal women with PCOS and controls. Nevertheless, the small sample size of some of these studies should be kept in mind while interpreting the results. In summary, more data are needed to determine the risk of dyslipidemia in women with PCOS across and beyond menopause.

4.5. Metabolic syndrome

IR plays a pivotal role in the pathogenesis of MetS which is a cluster of common cardiovascular (CV) risk factors, including abdominal obesity, HTN, low HDL-C, elevated triglyceride concentration, and hyperglycemia. Consistent with the high prevalence of individual components in women with PCOS, MetS is reported to be more common in this population. A recent meta-analysis including only good and fair quality studies, demonstrated that the prevalence of MetS was three times higher in reproductive-aged PCOS women compared with controls (OR: 3.4; 95% CI: 2.4–4.6), which remained significantly higher in the subgroup analysis of BMI-matched studies, but not in studies solely assessing lean women [26].

Menopause increases the incidence of MetS in aging women [27]. However, there are only a few studies examining the prevalence of MetS in women with PCOS during menopausal transition. In the cross-sectional study by Meun et al., the prevalence of MetS was not significantly different between women with PCOS and controls at the age of 50 [13]. Similarly, the SWAN study, a 12-year prospective cohort study of 1929 women between the ages of 42–52 years at screening, reported that the BMI-adjusted incidence of MetS was not significantly higher in women with presumed PCOS (defined by the presence of high androgens and a history of menstrual irregularity) compared with their counterparts [28]. Consequently, limited available data do not seem to suggest a continued risk of MetS in women with PCOS transitioning to menopause.

4.6. Cardiovascular disease

The high prevalence of cardiometabolic risk factors in women with PCOS is assumed to be associated with accelerated cardiovascular disease (CVD) in this population (Fig. 2). Indeed, there is substantial data reporting that surrogate markers of early subclinical arterial disease such as increased carotid intima media thickness and coronary artery calcification or decreased flow-mediated dilatation are more prevalent in PCOS patients [29]. However, studies published so far have controversial results on the association between PCOS and actual CVD events. Most of the studies on this topic suffer from several limitations, including retrospective or cross-sectional design, different study populations (community- or hospital-based), small sample sizes, incomplete diagnostic criteria, limited follow-up, suboptimal measurement of CVD events, and inappropriate control of confounders, all of which make it difficult to interpret the reported results [30].

In the recent International Evidence-Based Guideline [9], meta-analyses were conducted with two or more observational studies [15,19,21,31,32] to examine the association between PCOS and CV outcomes. Among the included studies in these meta-analyses, two did not report on menopausal status of the participants [31,32], one included only postmenopausal women [21], other two included both pre- and postmenopausal women [15,19]. The results showed that there was no statistical difference between PCOS and non-PCOS groups in terms of myocardial infarction [3 studies; 472 PCOS and 1161 controls; risk ratio (RR), 1.2; 95%CI, 0.7–2.1], stroke (4 studies; 791 PCOS and 2221 controls; RR, 1.6; 95%CI, 0.9–2.9), coronary heart disease (CHD)/coronary artery disease (CAD) (2 studies; 349 PCOS and 1812 controls; RR, 2.4; 95% CI, 0.9–6.7), or CVD-related death (2 studies; 341 PCOS and 438 controls; RR, 1.8; 95% CI, 0.6–5.9) [33]. A recent meta-analysis reported that on subgroup analysis of 12 population-based studies, the HR of CV events was increased in reproductive-aged patients with PCOS (HR, 1.4; 95% CI, 1.3–1.6), whereas the difference was not statistically significant in menopausal/aging PCOS women compared to healthy controls (HR, 1.0; 95% CI, 0.4–2.6) [34]. Nevertheless, given the abovementioned limitations of these studies, these findings should be

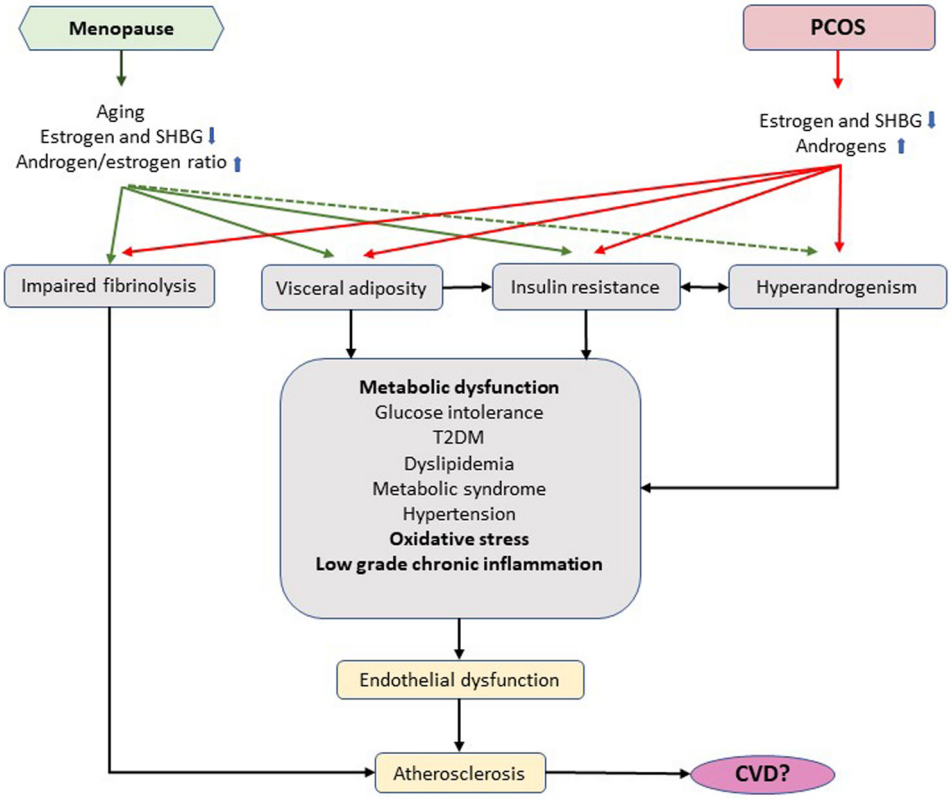

Fig. 2. Postulated mechanisms of increased cardiovascular risk in PCOS. CVD, cardiovascular disease; PCOS, polycystic ovary syndrome; SHBG, sex hormone-binding globulin; T2DM, type 2 diabetes mellitus.

interpreted with caution.

In most of the previous studies, both pre- and postmenopausal women were included where the majority had not reached the ages at which CVD becomes prevalent. However, available prospective cohort studies reporting on advanced aged postmenopausal women with PCOS at follow-up, have also failed to show increased risk for CVD events. In the Rotterdam study, there was not any difference in event-free survival for CHD, stroke, or the composite CVD outcome between a subset of women with PCOS with a mean age of 69.6 years (n = 106) and age-matched controls (n = 171), after adjusting for CV risk factors [16]. Similarly, Schmidt et al. reported no increased risk of MI, stroke, or death caused by CVD in postmenopausal women with PCOS when followed to a mean age of approximately 70 years [21]. Also, Merz et al., demonstrated that, despite a trend toward more frequent angiographic evidence of multivessel CAD, CV mortality rates or non-fatal CV events were not increased in women with PCOS with a mean age of 62.6 years [22]. Although, the latter two studies included small numbers of women with PCOS (35 and 25, respectively), these data suggest that PCOS may not confer additional risk for CVD events in aging women even in late menopause.

4.7. Obstructive sleep apnea

Obstructive sleep apnea (OSA) is a chronic sleep disorder characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstructions during sleep leading to intermittent hypoxia, cortical microarousals, sleep fragmentation, and increased sympathetic neural activity. Numerous studies have suggested an increased risk of OSA in reproductive aged women with PCOS. In the first meta-analysis on this topic, we have reported a pooled prevalence of OSA in adult PCOS patients as 32% (95% CI: 13%–55%; 8 studies) [35]. Confirming our results, in a more recent meta-analysis, the pooled prevalence of OSA in PCOS patients was reported to be 35.0% (95% CI: 22.2–48.9%; 9 studies) [36]. However, most of the studies included in these meta-analyses are limited by cross-sectional study design, small sample sizes, inclusion of mostly obese women, and lack of adequate adjustments for confounding factors [35]. Furthermore, recruitment of women with PCOS who are referred to specialized clinics may have given rise to inclusion bias in these studies. Clinic-based samples are likely to include subjects with more severe symptoms and may not fully represent the women with PCOS in the general population. Nevertheless, evidence for an association between PCOS and OSA has also been confirmed in recent population-based studies [37,38].

The pathophysiological mechanisms leading to increased risk of OSA in PCOS have not yet been fully identified. Findings from population-based studies indicate that older age and obesity are associated with increased risk of OSA in women with PCOS [37,38], in accordance with the data in the general population [39]. However, the persistence of increased risk even in normal weight women with PCOS [38], and after adjustment for age and BMI in the whole cohort [37,38] confirms the presence of other risk factors. Insulin resistance, hyperandrogenemia, and low levels of estrogen and progesterone associated with PCOS are all proposed to play a role in the development of OSA in these patients (Fig. 3) [35,40].

There is a marked increase in the prevalence of OSA in women during the age period corresponding to menopausal transition in general population [41]. However, among women with PCOS, currently there are no studies that assessed the prevalence of OSA in peri- and postmenopause. Therefore, it is not clear whether the risk of OSA is modified after menopause in this population.

4.8. Cancer

Chronic oligo- or anovulation causing prolonged exposure to

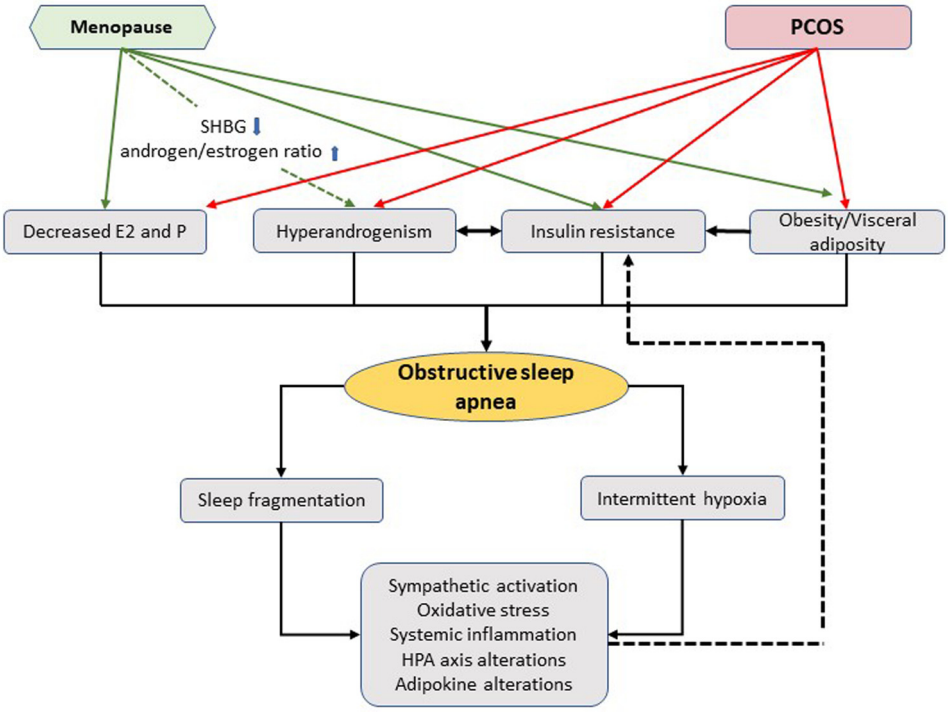

Fig. 3. Proposed interaction between PCOS and obstructive sleep apnea. E2, estradiol; HPA, hypothalamic-pituitary-adrenal; P, progesterone; SHBG, sex hormone-binding globulin; PCOS, polycystic ovary syndrome.

unopposed estrogen may place women with PCOS at increased risk for estrogen-dependent tumors, including endometrial, ovarian, and breast cancers. Other well-known risk factors for these cancers, such as obesity, T2DM, nulliparity, first birth at older age, are also more common among PCOS women [42]. These cancers are age-related and most cases occur in the postmenopausal period [43]; therefore vigilance may be required in the gynecological evaluation of women with PCOS transitioning into menopause.

Current data regarding the relationship between PCOS and cancer is most convincing for endometrial cancer (EC). The most recent systematic review and meta-analysis of observational studies revealed that the risk of EC was 2.8 times higher in women with PCOS compared to controls (OR: 2.8; 95% CI: 1.3–5.9; $p = 0.008$]. When studies including women aged over 54 years were excluded from the analysis, the risk of EC increased further in PCOS women (OR, 4.1; 95% CI, 2.4–6.8, $p < 0.001$) [44]. However, studies in this meta-analysis were limited by small number of exposed cases, case-control study design, self-report of PCOS diagnosis, and lack of control for confounders including obesity, T2DM, and PCOS treatment which may influence the risk of EC. There are only a few cohort studies assessing the risk of cancer in women with PCOS. A long-term retrospective cohort study including 319 women with PCOS (mean age 56.7 years) and 1060 age-matched controls who were followed for an average of 31 years, reported a 5.3-fold increased odds of endometrial cancer in PCOS subjects (OR, 5.3; 95% CI, 1.5–18.6, $p = 0.009$) [45]. Similarly, in a recent registry-based Danish cohort study comprising more than 12,000 women with PCOS, authors found an overall 4-fold increased risk for EC [standardized incidence ratio (SIR) = 3.9; 95% CI = 2.2–6.3]. In this study, when the analysis was restricted to women aged over 50 years, the risk of EC was no longer significantly increased in PCOS women (SIR = 2.0; 95% CI = 0.5–5.1) [46]. These studies support an evidence for increased risk of EC in women with PCOS. The increased risk for this malignancy may be attenuated after menopause, but further studies are needed to clarify this issue.

Although some inconsistent findings exist regarding ovarian cancer, collective data coming from recent meta-analyses [44,47] and the recent Danish cohort study [46] suggest that there is no significant elevation in risk for ovarian or breast cancer in women with PCOS.

4.9. Mood disorders

There is growing data that women with PCOS are more likely to suffer from mood disorders. A recent systematic review and meta-analysis by Cooney et al., reported significantly increased odds of depressive (OR: 3.8; 95% CI: 3.0–4.7; 18 studies) and anxiety symptoms (OR: 5.6; 95% CI: 3.2–9.8; 9 studies) in women with well-defined PCOS compared with controls [48]. The association remained significant when the analysis was restricted to the prevalence of moderate and severe depression and anxiety scores. This meta-analysis also confirmed that the increased risk of depressive and anxiety symptoms was independent of BMI and seen in both clinic and community recruits [48].

The underlying causes of the association between PCOS, depression and anxiety are not clear. Obesity, infertility, hyperandrogenism, IR are all proposed to have a potential role [49]. However, current evidence on the interaction of these PCOS associated conditions and depression and anxiety scores are very limited and have conflicting results [50]. In the meta-analysis by Cooney et al., women with PCOS and depressive or anxiety symptoms had a higher mean BMI and higher odds of hirsutism and/or increased Ferriman-Gallwey scores than those without depression or anxiety. Women with PCOS and depressive symptoms also had a higher mean value of homeostatic model assessment–insulin resistance (HOMA-IR). However, the effects sizes of all these associations were small, thus may not fully explain the strong link between PCOS and these emotional disorders [48].

The menopausal transition constitutes a critical phase for mood disorders in the general population. Data from longitudinal studies have suggested an increased risk for depressive and anxiety symptoms during perimenopausal years [51,52]. Increased vulnerability to depression and anxiety during this life stage has been attributed to hormone variations, somatic symptoms of menopausal transition (vasomotor symptoms, sleep problems), health factors (increased BMI, chronic medical conditions), psychosocial stressors, and history of anxiety or

previous episode of depression [51,52]. Regarding the impact of aging on prevalence of depressive and anxiety symptoms in women with PCOS, a few longitudinal studies have demonstrated that the risk remains high during follow-up in this population [53,54]. In the population-based Northern Finland Birth Cohort 1966 (NFBC66) study [55], depression and anxiety scores were significantly increased in both 31 and 46 years in women with PCOS compared with controls, suggesting that symptoms of mood disorders persist up until premenopausal age in these women. However, currently there is no data concerning the prevalence of depressive and anxiety symptoms in PCOS throughout menopausal transition and during postmenopause. Risk of negative mood and depressive symptoms seem to decrease in the postmenopausal years in general population [56]. Considering the improvement in PCOS phenotype and attenuation of the differences between women with PCOS and age-matched controls regarding cardiometabolic risk profile with aging, it is reasonable to assume that the risk of depression and anxiety may decrease during postmenopause also in PCOS women.

5. Oral contraceptive use and its consequences after menopause in aging women with PCOS

Oral contraceptives (OCs) are recommended as first-line medical treatment for the management of menstrual abnormalities and clinical signs of hyperandrogenism in women with PCOS who do not desire pregnancy. Potential risks of OCs including weight gain, mood changes, and adverse CV and metabolic effects have raised some concerns about the long-term use of these drugs in PCOS. However, current data do not endorse the idea that OCs would bring additional harm to women with PCOS [57].

In most of the available studies, OC use in women with POCS did not significantly influence BMI, anthropometric parameters, blood pressure, or surrogate markers of carbohydrate metabolism [58,59]. Long-term observational data also did not demonstrate a significant impact of prolonged use of OCs on the development of T2DM in either PCOS patients or healthy women [60,61]. OC use was found to be significantly associated with an increase in HDL-C, triglycerides [59], and high-sensitivity C-reactive protein in women with PCOS [62], but clinical implications of these changes need further investigation.

Epidemiologic data suggest that, in general population, current use of OCs is associated with an increased risk of arterial thrombosis, particularly in women who smoke and are over the age of 35 years, although that risk does not continue once OCs are stopped [63]. However, in the Women's Ischemia Syndrome Evaluation study, which evaluated the association between past OC use and angiographic coronary artery disease in postmenopausal women, past OC use was found to be a significant independent negative predictor of coronary artery disease severity after adjustments for several coronary risk factors [64]. Furthermore, a prospective cohort study demonstrated a significantly lower rate of death from circulatory disease among OC users compared with never users [65]. Although, there are no longitudinal follow-up studies assessing the potential association of OC use and CVD outcome in PCOS, available evidence do not suggest an increased risk of CV events with OC treatment in PCOS [66]. In fact, based on the findings of studies assessing OCs and CVD in general population, as mentioned above, OC use in reproductive years might potentially be protective against CV morbidity and mortality later in life.

Prolonged use of OCs is associated with decreased risk of endometrial and ovarian cancers in general population. The protective effect of OCs against these cancers increases with longer duration of use and persists for more than 20 years after ceasing [67]. In contrast, OC use may result in a slight increase in breast cancer risk in short-term; however 10 years after cessation the risk becomes similar to those who never used OCs [68]. Although there are very limited data assessing potential association between the use of OCs and cancer in PCOS, reduced risk of endometrial and ovarian cancers with OC use in general population might also be valid for women with PCOS.

Early community-based, observational studies suggested a protective effect of hormone replacement therapy on sleep disordered breathing [69]. However, to date, no studies have evaluated the impact of OC use on the prevalence of OSA in PCOS.

There is some evidence that estradiol improves depressive symptoms in perimenopausal women. However, most studies have examined the effects of unopposed transdermal estradiol. Available data on oral estrogens and menopausal hormonal therapy are limited and inconclusive [70]. Among women with PCOS, only a few studies are available regarding the effects of OCs on depressive and anxiety symptoms. These studies, although limited by small number of subjects and relatively short follow-up, indicate either a beneficial or no adverse effect of short-term OC use on depressive and anxiety symptoms in this population [50,71].

6. Conclusions

PCOS is a lifelong endocrine, metabolic, and reproductive disorder affecting millions of women worldwide. Current evidence indicates that reproductive-aged women with PCOS have increased cardiometabolic risk factors and are at increased risk for developing T2DM, MetS, OSA, endometrial cancer, and mood disorders. Despite of a worse cardiometabolic profile and increased prevalence of surrogate markers of subclinical arterial disease at a younger age, available evidence does not strongly suggest an increased or premature CV morbidity and mortality in women with PCOS. However, data in older age group are very limited and come from studies with serious limitations.

Consistent with the improvement in the phenotypic features of PCOS, cardiometabolic health does not appear to deteriorate after menopause in women with PCOS. Moreover, the differences in some cardiometabolic risk factors between PCOS patients and general population seem to lose their significance in peri- and postmenopause. On the other hand, the impact of menopausal transition and menopause on long-term health consequences of PCOS including OSA, endometrial cancer, and anxiety/depression is uncertain (Table 2).

The clinical heterogeneity of the syndrome might indicate that not all PCOS patients are exposed to the same long-term complications. Nevertheless, data are lacking regarding the effects of PCOS phenotypes, race, and ethnicity on long-term health. Considering the confounding factors such as obesity, insulin resistance, hyperandrogenemia, anovulation, infertility, and long-term use of OCs, it also remains to be clarified to what extent PCOS *per se* is responsible for the associated long-term health consequences.

In order to answer the questions on the issues mentioned above, further studies on large community-based cohorts free from clinical referral bias, where both healthy controls and well-phenotyped PCOS patients are followed from early reproductive age into late menopause are needed. The findings of these future studies may facilitate to determine optimal screening, counseling, and management strategies in this population.

Contributors

Nafiye Helvaci performed the literature search and drafted the manuscript.

Bulent Okan Yildiz edited and revised the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for the preparation of this article.

Table 2
Comparison of the modifications in the health outcomes between general population and PCOS patients after menopause.

	Changes after menopause	
Characteristic	General population	PCOS
Obesity	Increased prevalence	Unaltered or increased prevalence [14,15,16]
Glucose intolerance/T2DM	Increased prevalence	Increased prevalence in premenopausal women becomes similar to controls [15,21,22]
Hypertension	Increased prevalence	Increased prevalence in premenopausal women becomes similar to controls [23]
Dyslipidemia	Increased prevalence	Unaltered or increased prevalence [16,21,22]
Metabolic syndrome	Increased prevalence	Increased prevalence in premenopausal women becomes similar to controls [28]
CVD events	Increased risk	No apparent increase in risk [15,16,21,22]
CV mortality	Increased risk	No apparent increase in risk [15,21]
OSA	Increased risk	No direct comparative studies
Endometrial cancer	Increased prevalence	No direct comparative studies
Anxiety/Depression	Increased risk during menopausal transition that declines in postmenopause	No direct comparative studies

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

Provenance and peer review

This article was commissioned and externally peer reviewed.

References

[1] D. Lizneva, L. Suturina, W. Walker, et al., Criteria, prevalence, and phenotypes of polycystic ovary syndrome, Fertil. Steril. 106 (2016) 6–15.
[2] B.O. Yildiz, G. Bozdag, Z. Yapici, et al., Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria, Hum. Reprod. 27 (2012) 3067–3073.
[3] Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, Fertil. Steril. 81 (2004) 19–25.
[4] D. Lizneva, R. Kirubakaran, K. Mykhalchenko, et al., Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis, Fertil. Steril. 106 (2016) 1510–1520 e2.
[5] G. Bozdag, S. Mumusoglu, D. Zengin, et al., The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. 31 (2016) 2841–2855.
[6] Z.A. Brown, Y.V. Louwers, S.L. Fong, et al., The phenotype of polycystic ovary syndrome ameliorates with aging, Fertil. Steril. 96 (2011) 1259–1265.
[7] S. Alsamarai, J.M. Adams, M.K. Murphy, et al., Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age, J. Clin. Endocrinol. Metab. 94 (2009) 4961–4970.
[8] E. Carmina, A.M. Campagna, R.A. Lobo, A 20-year follow-up of young women with polycystic ovary syndrome, Obstet. Gynecol. 119 (2012) 263–269.
[9] Teede Helena, Misso Marie, Costello Michael, Dokras Anuja, Laven Joop, P.T. Moran Lisa, NR, International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome, Available from: (2018) https://www.monash.edu/_data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf.
[10] S.S. Lim, M.J. Davies, R.J. Norman, et al., Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. Update 18 (2012) 618–637.
[11] S.R. Davis, C. Castelo-Branco, P. Chedraui, et al., Understanding weight gain at menopause, Climacteric. 15 (2012) 419–429.
[12] B. Echiburú, N. Crisosto, M. Maliqueo, et al., Metabolic profile in women with polycystic ovary syndrome across adult life, Metabolism. 65 (2016) 776–782.
[13] C. Meun, M.N. Gunning, Y.V. Louwers, et al., The cardiovascular risk profile of middle-aged women with polycystic ovary syndrome, Clin. Endocrinol. (Oxf). 92 (2020) 150–158.
[14] J. Schmidt, M. Brännström, K. Landin-Wilhelmsen, et al., Reproductive hormone levels and anthropometry in postmenopausal women with polycystic ovary syndrome (PCOS): a 21-year follow-up study of women diagnosed with PCOS around 50 years ago and their age-matched controls, J. Clin. Endocrinol. Metab. 96 (2011) 2178–2185.
[15] S. Wild, T. Pierpoint, P. McKeigue, et al., Cardiovascular disease in women with polycystic ovary syndrome at long- term follow-up: a retrospective cohort study, Clin. Endocrinol. (Oxf). 52 (2000) 595–600.
[16] C. Meun, O.H. Franco, K. Dhana, et al., High androgens in postmenopausal women and the risk for atherosclerosis and cardiovascular disease: the rotterdam study, J. Clin. Endocrinol. Metab. 103 (2018) 1622–1630.
[17] S. Cassar, M.L. Misso, W.G. Hopkins, et al., Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies, Hum. Reprod. 31 (2016) 2619–2631.
[18] R. Slopien, E. Wender-Ozegowska, A. Rogowicz-Frontczak, et al., Menopause and diabetes: EMAS clinical guide, Maturitas. 117 (2018) 6–10.
[19] D. Cibula, R. Cífková, M. Fanta, et al., Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome, Hum. Reprod. 15 (2000) 785–789.
[20] M. Forslund, K. Wilhelmsen, P. Trimpou, et al., Type 2 diabetes mellitus in women with polycystic ovary syndrome during a 24-year period: importance of obesity and abdominal fat distribution, Hum. Reprod. open. 2020 (2020) hoz042.
[21] J. Schmidt, K. Landin-Wilhelmsen, M. Brännström, et al., Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-Year controlled follow-up study, J. Clin. Endocrinol. Metab. 96 (2011) 3794–3803.
[22] C.N.B. Merz, L.J. Shaw, R. Azziz, et al., Cardiovascular disease and 10-Year mortality in postmenopausal women with clinical features of polycystic ovary syndrome, J. Womens. Health (Larchmt). 25 (2016) 875–881.
[23] M. Amiri, F. Ramezani Tehrani, S. Behboudi-Gandevani, et al., Risk of hypertension in women with polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression, Reprod. Biol. Endocrinol. (2020) 23 202018.
[24] R.S. Legro, A.R. Kunselman, A. Dunaif, Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome, Am. J. Med. 111 (2001) 607–613.
[25] S.R. Davis, I. Lambrinoudaki, M. Lumsden, et al., Menopause, Nat. Rev. Dis. Prim. 1 (2015) 15004.
[26] S.S. Lim, N.S. Kakoly, J.W.J. Tan, et al., Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression, Obes. Rev. 20 (2019) 339–352.
[27] S. Mumusoglu, B.O. Yildiz, Metabolic syndrome during menopause, Curr. Vasc. Pharmacol. (2018) 16.
[28] A.J. Polotsky, A.A. Allshouse, S.L. Crawford, et al., Hyperandrogenic oligomenorrhea and metabolic risks across menopausal transition, J. Clin. Endocrinol. Metab. 99 (2014) 2120–2127.
[29] N.S. Kakoly, L.J. Moran, H.J. Teede, et al., Cardiometabolic risks in PCOS: a review of the current state of knowledge, Expert Rev. Endocrinol. Metab. 14 (2019) 23–33.
[30] N. Helvaci, B.O. Yildiz, Cardiovascular health and menopause in aging women with polycystic ovary syndrome, Expert Rev. Endocrinol. Metab. 15 (2020) 29–39.
[31] S. Iftikhar, M.L. Collazo-Clavell, V.L. Roger, et al., Risk of cardiovascular events in patients with polycystic ovary syndrome, Neth. J. Med. 70 (2012) 74–80.
[32] O. Lunde, T. Tanbo, Polycystic ovary syndrome: a follow-up study on diabetes mellitus, cardiovascular disease and malignancy 15-25 years after ovarian wedge resection, Gynecol. Endocrinol. 23 (2007) 704–709.
[33] Teede Helena, Misso Marie, Costello Michael, Dokras Anuja, M.L.P. Laven Joop, N, Technical Report for: International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome, Available from: (2018) https://www.monash.edu/_data/assets/pdf_file/0020/1412282/PCOS-Guideline_Technical-report.pdf.
[34] F. Ramezani Tehrani, M. Amiri, S. Behboudi-Gandevani, et al., Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis, Gynecol. Endocrinol. 36 (2020) 12–23.
[35] N. Helvaci, E. Karabulut, A.U. Demir, et al., Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature, Endocr. Connect. 6 (2017) 437–445.
[36] H. Kahal, I. Kyrou, O.A. Uthman, et al., The prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome: a systematic review and meta-analysis, Sleep Breath. 24 (2020) 339–350.
[37] T.Y. Lin, P.Y. Lin, T.P. Su, et al., Risk of developing obstructive sleep apnea among women with polycystic ovarian syndrome: a nationwide longitudinal follow-up study, Sleep Med. 36 (2017) 165–169.
[38] B. Kumarendran, D. Sumilo, M.W. O'Reilly, et al., Increased risk of obstructive sleep apnoea in women with polycystic ovary syndrome: a population-based cohort study, Eur. J. Endocrinol. 180 (2019) 265–272.
[39] C.V. Senaratna, J.L. Perret, C.J. Lodge, et al., Prevalence of obstructive sleep apnea in the general population: a systematic review, Sleep Med. Rev. 34 (2017) 70–81.
[40] S. Sam, D.A. Ehrmann, Pathogenesis and consequences of disordered sleep in PCOS,

Clin. Med. Insights Reprod. Health 13 (2019) 117955811987126.
[41] T. Young, L. Finn, D. Austin, et al., Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study, Am. J. Respir. Crit. Care Med. 167 (2003) 1181–1185.
[42] D.A. Dumesic, R.A. Lobo, Cancer risk and PCOS, Steroids. 78 (2013) 782–785.
[43] Cancer Research UK. Statitics by Cancer Type, (2020) Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type.
[44] J.A. Barry, M.M. Azizia, P.J. Hardiman, Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. Update 20 (2014) 748–758.
[45] S. Wild, T. Pierpoint, H. Jacobs, et al., Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study, Hum. Fertil. Camb. (Camb) 3 (2000) 101–105.
[46] M. Gottschau, S.K. Kjaer, A. Jensen, et al., Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study, Gynecol. Oncol. 136 (2015) 99–103.
[47] F. Shobeiri, E. Jenabi, The association between polycystic ovary syndrome and breast cancer: a meta-analysis, Obstet. Gynecol. Sci. 59 (2016) 367.
[48] L.G. Cooney, I. Lee, M.D. Sammel, et al., High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis, Hum. Reprod. 32 (2017) 1075–1091.
[49] N. Cinar, M.C. Kizilarslanoglu, A. Harmanci, D.Y. Aksoy, G. Bozdag, B.Y.B. Demir, Depression, anxiety and cardiometabolic risk in polycystic ovary syndrome, Hum. Reprod. 26 (2011) 3339–3345.
[50] A. Dokras, E. Stener-Victorin, B.O. Yildiz, et al., Androgen Excess- Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome, Fertil. Steril. 109 (2018) 888–899.
[51] J.T. Bromberger, H.M. Kravitz, Mood and menopause: findings from the study of women's health across the nation (SWAN) over 10 years, Obstet. Gynecol. Clin. North Am. 38 (2011) 609–625.
[52] C.N. Soares, Mood disorders in midlife women: understanding the critical window and its clinical implications, Menopause 21 (2014) 198–206.
[53] J.H. Hung, L.Y. Hu, S.J. Tsai, et al., Risk of psychiatric disorders following polycystic ovary syndrome: a nationwide population-based cohort study, PLoS One 9 (2014) e97041.
[54] R. Hart, D.A. Doherty, The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage, J. Clin. Endocrinol. Metab. 100 (2015) 911–919.
[55] S. Karjula, L. Morin-Papunen, J. Auvinen, et al., Psychological distress is more prevalent in fertile age and premenopausal women with PCOS symptoms: 15-year follow-up, J. Clin. Endocrinol. Metab. 102 (2017) 1861–1869.
[56] E.W. Freeman, M.D. Sammel, L. Liu, et al., Hormones and menopausal status as predictors of depression in women in transition to menopause, Arch. Gen. Psychiatry 61 (2004) 62–70.
[57] B.O. Yildiz, Oral contraceptives in polycystic ovary syndrome: risk-benefit assessment, Semin. Reprod. Med. 26 (2008) 111–120.
[58] S.F. de Medeiros, Risks, benefits size and clinical implications of combined oral contraceptive use in women with polycystic ovary syndrome, Reprod. Biol. Endocrinol. 15 (2017) 93.
[59] I.J. Halperin, S.S. Kumar, D.F. Stroup, et al., The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: a systematic review and meta-analysis of observational studies, Hum. Reprod. 26 (2011) 191–201.
[60] A. Gambineri, L. Patton, P. Altieri, et al., Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study, Diabetes. 61 (2012) 2369–2374.
[61] L. ChasaTaber, W.C. Willett, M.J. Stampfer, et al., A prospective study of oral contraceptives and NIDDM among U.S. Women, Diabetes Care 20 (1997) 330–335.
[62] S.F. de Medeiros, M.A.S. de Medeiros, Nde S. Santos, et al., Combined oral contraceptive effects on low-grade chronic inflammatory mediators in women with polycystic ovary syndrome: a systematic review and meta-analysis, Int. J. Inflam. 2018 (2018) 9591509.
[63] N. Helvaci, B.O. Yildiz, Oral contraceptives in polycystic ovary syndrome, Minerva Endocrinol. 39 (2014) 175–187.
[64] C.N. Bairey Merz, B.D. Johnson, S. Berga, et al., Past oral contraceptive use and angiographic coronary artery disease in postmenopausal women: data from the National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation, Fertil. Steril. 85 (2006) 1425–1431.
[65] P.C. Hannaford, L. Iversen, T.V. Macfarlane, et al., Mortality among contraceptive pill users: Cohort evidence from Royal College of general practitioners' oral contraception study, BMJ. 340 (2010) 695.
[66] C.T. Tay, A.E. Joham, D.S. Hiam, et al., Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: an overview of systematic reviews, Clin Endocrinol. (Oxf). 89 (2018) 535–553.
[67] G.F. Grimbizis, B.C. Tarlatzis, The use of hormonal contraception and its protective role against endometrial and ovarian cancer, Best Pract. Res. Clin. Obstet. Gynaecol. 24 (2010) 29–38.
[68] J.M. Gierisch, R.R. Coeytaux, R.P. Urrutia, et al., Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review, Cancer Epidemiol. Biomarkers Prev. 22 (2013) 1931–1943.
[69] E. Lindberg, M.R. Bonsignore, P. Polo-Kantola, Role of menopause and hormone replacement therapy in sleep-disordered breathing, Sleep Med. Rev. 49 (2020) 101225.
[70] C.N. Soares, Depression and menopause: an update on current knowledge and clinical management for this critical window, Med. Clin. North Am. 103 (2019) 651–667.
[71] Nese Cinar, Ayla Harmanci, B.O.Y. Basaran Demir, Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study, Hum. Reprod. 27 (2012) 1840–1845.