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Ageing women with PCOS:

Menstrual cycles, metabolic health and health related quality of life (HRQoL)

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) in their reproductive years age present with metabolic dysfunction and thus increased likelihood of long-term health consequences and diminished well-being in later life. Due to their larger ovarian reserve, however, they may experience menopause at later age and protection from metabolic and cardiovascular diseases. Moreover, previous studies have indicated that late reproductive aged, normal-weight women with PCOS do not seem to have the expected high risk for type 2 diabetes (T2D), as previously thought. Health related quality of life (HRQoL), nevertheless, is decreased in women with PCOS up until late fertile age, warranting attention and actions from the health care personnel. Given conflicting reports regarding the risk of cardiovascular diseases, future research with well characterized and adequately sized PCOS populations are needed as well as studies aiming to improve their HRQoL.

Keywords: PCOS, obesity, metabolic, cardiovascular disease, quality of life

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women in their reproductive years with life-long adverse health impact reflected by decreased health related quality of life (HRQoL) (1, 2). PCOS is characterized by the presence of hyperandrogenism, oligo- or anovulation, and polycystic ovary morphology, and the syndrome associates with high risk of obesity and metabolic derangements (3). Prior studies have reported that severity of PCOS phenotype diminishes with age (4), with aging-related decreases in ovarian and adrenal androgen levels (5-8), ovarian volume and follicle numbers, accompanying increasingly regular menstrual cycles (9-11). Testosterone levels, however, remain higher than in non-PCOS women (5-8).

Given that women with PCOS have higher anti-Müllerian hormone (AMH) levels and ovarian antral follicle count (9, 12), it has also been speculated that they might have a longer reproductive life span and later menopause (13). As the number of ovarian antral follicles decline, menstrual cycles become more regular, and androgen levels decrease over time, it has led to an idea that the metabolic derangements might also resolve. Long-term studies in women with PCOS reaching beyond menopause are, however, scarce and the hormonal and metabolic changes during the late reproductive years and beyond menopause are poorly understood. This mini review aims to provide a brief insight into the literature regarding the effects of ageing and menopause on reproductive and metabolic features, and long-term HRQoL outcomes, in women with PCOS.

MAIN TEXT OF REVIEW

Reproductive life span and age at menopause

Women with PCOS have higher number of ovarian antral follicles and possibly greater ovarian reserve than non-PCOS women (14). A previous study reported that women with PCOS may gain regular menstrual cycles with aging (11), however, only a few studies have investigated ovarian aging or age at menopause in the affected women. A longitudinal study of 31 women with PCOS and 266 controls, recruited from a tertiary academic centre, reported women with PCOS and control women having a similar decline rate of antral follicles, after adjusting for baseline antral follicle count and age (15). In our previous study assessing 109 women (44 controls and 65 women with PCOS), the decline in AMH levels was comparable in both study groups, although AMH levels were always 2- to 3-fold higher and remained elevated until 40 years of age in in women with PCOS (9). As for menopausal age, a cohort study with a 24-year follow up found that women with PCOS diagnosed by having oligomenorrhea and hyperandrogenism (n=27) reached menopause four years later than control women (n=94) (16). In line with this result, another Swedish study found that PCOS was associated with a later age at menopause (Hazard ratio: 0.44 [0.28 – 0.71]) (13). Similarly, the Tehran Lipid and Glucose Cohort study using a prediction model based on AMH levels, estimated the age at menopause to be 51.4 years in women with PCOS and 49.7 years in the controls (17). Interestingly, women with PCOS have also been suggested to have earlier menopause than their non-PCOS counterparts (18).

Taking together, only a few studies have investigated the age at menopause in women with PCOS, but the available evidence indicates that women with PCOS enter menopause later than their non-PCOS counterparts. In agreement with this, a previous GWAS study demonstrated that genetic variants associated with menopausal age have a robust association with variants associated with PCOS (19). Whether all this translates into fertility in the late reproductive years for women with PCOS and consequently longer estrogen exposure, remains to be determined. As the alleles related to later menopause have also been associated with more effective DNA repair, women with PCOS may not experience increased cardiovascular events as predicted from their metabolic profile during their earlier reproductive years. A recent study, however, reported shorter telomere length in women with PCOS and infertility compared to controls, and thus did not support longer life expectancy in this population (20). Whether diminished telomere length applies to all

women with PCOS and not just those suffering from infertility remains to be investigated. This question warrants larger future studies that employ a longitudinal design of the same individuals.

Excess weight

Women with PCOS are commonly overweight or obese (21), with the rate of obesity depending on ethnicity and cultural background (22). Recent studies have identified a causal link between PCOS and BMI-related genes (19, 23), although the susceptibility to obesity in affected women is complex, with environmental factors also playing a role. Increased body weight occurs early in girls who ultimately manifest PCOS phenotypes as shown in our previous population based birth cohort (The Northern Finland Birth Cohort, NFBC66) data assessing BMI trajectories from birth until 18 years in women with and without PCOS (24). Interestingly, the rise in BMI around the age of 5 years in children, termed adiposity rebound (AR), occurs almost 5 months earlier on average in girls later diagnosed with PCOS. Given that the early timing of AR was also associated with a PCOS diagnosis independently of BMI (24), precocious AR could be a sign of increased PCOS risk. Recently published longitudinal studies have also indicated that rapid weight gain during adolescence or the early reproductive years is common in PCOS (25, 26). Furthermore, the NFBC66 study with an ongoing follow-up up until 46 years of age, found that women with self-reported PCOS had greater weight gain between the ages of 14 and 31 years, while they exhibited comparable degrees of BMI increase between the ages of 31 and 46 years (25). Interestingly, an Australian longitudinal population-based study assessed three BMI trajectories (low-stable, moderately-rising and high-rising) and found that compared with controls, women with PCOS were 1.6 times more likely to belong to the moderately-rising trajectory and 4.7 times more likely to belong to the high-rising trajectory (27). Taken together, these studies indicate that young women with PCOS have higher BMI and weight gain than similarly aged women without PCOS, which might expose the women with PCOS to increased risk for abnormal glucose metabolism, dyslipidemia, hypertension and cardiovascular diseases (CVD).

Abnormal glucose metabolism

A systematic review and meta-analysis recently concluded that women with PCOS have an increased risk of prediabetes and T2D and that the risk differed by ethnicity and BMI (28). Interestingly, among European

women, the prevalence of T2D did not differ between women with and without PCOS (28), however, the effect of aging was not investigated. In general, aging and hypoestrogenism promote obesity and insulin resistance in all women, increasing the risk for disturbances in glucose metabolism later in life. Even though women with PCOS present with impaired glucose metabolism at an earlier age than women without PCOS, it seems that beyond menopause women without PCOS "catch up" with the risk for T2D found in women with PCOS and consequently exhibit comparable rates of T2D (29). Indeed, the NFBC66 study showed that by age 46, the normal weight women with PCOS do not have an increased risk of pre-diabetes or T2D when compared to normal-weight controls (30). Overweight/obese women with PCOS, however, demonstrated higher risk of T2D compared to controls in the same BMI category (30).

Likewise, a prospective population-based cohort study (Tehran Lipid and Glucose Study) reported that among women over 40 years, the incidence of pre-diabetes and T2D was similar in PCOS (based on NIH criteria) and control women (31), whereas among women aged less than 40 years, the women with PCOS had significantly higher incidence of prediabetes and T2D than controls. Unfortunately, it was not reported whether PCOS women developing abnormal glucose metabolism after the age of 40 years experience greater weight gain or whether they are more obese than controls. Moreover, a large Danish nationwide register study reported that women with PCOS were diagnosed as having T2D at a younger age than controls and that a higher proportion of PCOS women with T2D were < 40 years than found in controls with T2D (32). The opposite was found in a cross-sectional Nordic multicenter study of 876 women with PCOS, which reported the prevalence of T2D and prediabetes as comparable between women < 40 years and > 40 years. Women with prediabetes and T2D, however, were older compared to women with normal glucose tolerance (33). Interestingly, in the latter study, none of the normal-weight women with PCOS had T2D. Considered together, these studies suggest that while ethnicity impacts the risk of T2D, the prevalence of T2D does not increase with aging in women with PCOS. Long-term follow up studies are needed, however, with adequate sample sizes and well characterized PCOS populations (with adjustments for BMI and weight gain) to confirm these findings.

Other common CVD risk factors in PCOS

A recent systematic review and meta-analysis reported increased prevalence of metabolic syndrome (MetS) in overweight or obese women with PCOS but not in lean ones (34). In the Tehran Lipid and Glucose Study, the incidence of hypertension, MetS, dyslipidemia and obesity were comparable between PCOS women aged > 40 years and similar aged controls, whereas among women < 40 years, women with PCOS had higher incidence of hypertension and MetS than control women (35). A Nordic cross-sectional multicenter case-control study found that in women over 39 years of age, the prevalence of MetS was twofold higher in the hyperandrogenic-PCOS (HA-PCOS) group compared with the normoandrogenic-PCOS (NA-PCOS) or control groups (36). Moreover, the women over 39 years with the HA-PCOS had higher serum levels of low density lipoprotein (LDL) and triglycerides compared with controls, and higher serum levels of LDL compared with the NA-PCOS population (36).

A longitudinal study of 38 PCOS and 296 control women recruited from an academic medical center demonstrated that triglyceride levels and HOMA-IR value increased more in the PCOS group than in the control group (37). In line with this, in a 11-year follow-up study, women with PCOS-like status (the presence of two of the following three features: history of irregular menstrual cycles, high free androgen index or high AMH-level) developed MetS almost three years than controls (38). Moreover, the NFBC66 study found that PCOS was associated with elevated blood pressure at age 31 and hypertension at age 46 independently of overweight/obesity (39).

Cardiovascular disease events

Hyperandrogenemia, a key feature of PCOS, has been thought to be a risk factor for metabolic abnormalities and CVD both in PCOS and in non-PCOS women, although the existing literature is inconsistent. In women with PCOS, hyperandrogenemia is associated with abdominal obesity and insulin resistance and is thought to associate with an increased risk of T2D and MetS, and eventually an increased prevalence of CVD events. This assumption has been challenged by a recent study including both a meta-analysis of previously published prospective studies and a prospective population-based cohort study of 3,117 postmenopausal women with an average follow-up time of 11.1 years (Rotterdam study). That study reported that total testosterone or bioavailable testosterone levels did not associate with T2D, whereas low level of sex-

hormone binding globulin and high levels of total estradiol were associated with increased risk of T2D, implicating obesity rather than hyperandrogenism as the more critical risk factor (40).

Another publication from the Rotterdam Study included a total of 2,578 women with a mean age of 70.2 years and reported that there were no associations between high androgen levels and incidence of stroke, coronary heart disease or CVD (41). The investigators also made a sub-analysis on CVD risk in women with PCOS, in which PCOS was defined based on a reported history of cycle irregularities and current high androgen levels. Women with PCOS (n=160) had a larger waist/hip ratio, a higher BMI, higher prevalence of T2D and dyslipidemia, but no increased risk for incident CVD was observed after adjusting for confounding factors (41). In line with these findings, a follow up of a relatively small cohort (n=25) of postmenopausal women, those with previous PCOS were not associated with angiographic coronary artery disease nor increased 10-year mortality (18).

The exact opposite results, however, have also been found. In the NFBC66 study, compared to controls women with PCOS had higher prevalence of acute myocardial infarction and CVD events, already by the age of 46 years (39). In line with that study, a large nationwide register study from Denmark reported higher CVD event rate in women with PCOS compared to controls (22.6 per 1000 patient years in PCOS *vs*. 13.2 per 1000 patient years in controls) (42).

Health related quality of life (HRQoL)

As PCOS is associated with high morbidity, it is not surprising that women with PCOS have been shown to experience decreased quality of life, although long-term studies are scarce (2). Given that the HRQoL has been shown to decrease with ageing in women in general, the question is whether PCOS has additional effects on the long-term quality of life. During the reproductive years, anxiety and depression (43-45), hirsutism (46), infertility (47, 48) and obesity (49, 50) have all been shown to associate with decreased HRQoL in PCOS, psychological distress being the most commonly reported contributor. As there is a great of individual variation in symptomology, the most bothersome symptoms should be identified and treated effectively, preferably by utilizing a multidisciplinary approach (1).

Given that several of the PCOS features, like menstrual irregularities and hyperandrogenism, decrease along age HRQoL may improve with age in women with PCOS. Our recent publication on age-related HRQoL in women with PCOS showed that decrease in HRQoL persisted between the ages of 31 and 46 years compared to controls after adjusting for BMI, education, marital status and self-reported infertility (51). Interestingly, clinical hyperandrogenism also associated with lower HRQoL, whereas testosterone levels or free androgen index (FAI) did not. This underlines the fact that esthetic aspects should not be underestimated in aging women with PCOS and that hirsutism warrants effective treatments. The research community should assess in the future whether HRQoL remains low in women with PCOS beyond menopause. In addition, the intervention studies should also routinely include HRQoL questionnaire in addition to clinical measures in order to evaluate health outcomes more widely.

CONCLUSION

The long-term follow-up and high-quality studies in large PCOS population are lacking, and the oldest women with reliable PCOS diagnosis are not more than 70-75 years old. Only a few studies have investigated the age at menopause in women with PCOS, but the available evidence indicates women with PCOS have a later age at menopause than women without PCOS. Whether this translates into increased fertility for women with PCOS in their later reproductive years remains to be determined. The recent publications indicate that late reproductive aged women with PCOS have an increased risk for obesity and

that overweight and obese women with PCOS, but not those with normal BMI, seem to present risk for T2D. Later age at menopause and consequently longer estrogen exposure might protect women with PCOS from CVDs.

In most studies, however, the PCOS exhibiting CVD are younger than women without PCOS and exhibiting CVD. Most of the studies have been limited with too small sample sizes to detect a difference between women with PCOS and non-PCOS controls. Moreover, the definitions of PCOS and the CVD events have been very variable.

In conclusion, future research is needed to establish the metabolic and cardiovascular disease profiles in women with PCOS in their late reproductive years as well as beyond menopause. Although there are no long-term data on the morbidity for CVD in PCOS, it is advisable to perform a careful metabolic and cardiovascular assessment in affected women in order to prevent conditions leading to CVD. Those individuals at increased risk (obese, family history) should be identified early during childhood. This means targeted screening of girls at risk for PCOS to enable lifestyle changes and prescription of medication according to generally accepted criteria. In addition, women with PCOS should be systematically screened using HRQoL so that comprehensive improvements in their HRQoL can be achieved.

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