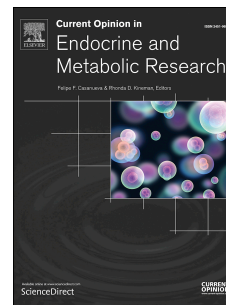


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Ageing women with PCOS:

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

Meri-Maija Ollila¹, Terhi T. Piltonen¹, Juha S. Tapanainen^{1,2}, Laure Morin-Papunen¹

¹Department of Obstetrics and Gynaecology, University of Oulu and Oulu University Hospital, Medical Research Centre, PEDEGO Research Unit, P.O. BOX 23, FI-90029, Oulu, Finland

²Department of Obstetrics and Gynaecology, University of Helsinki and Helsinki University Hospital, P.O. BOX 63, FI-00014, Helsinki, Finland

Corresponding author: Meri-Maija Ollila, Department of Obstetrics and Gynecology, Oulu University Hospital, P.O. BOX 23 90029 OYS, Finland, Tel: +358405365260, E-mail: meri-maija.ollila(a)student.oulu.fi

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16 **ABSTRACT**

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

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

28 INTRODUCTION

29

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

38

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

48 **MAIN TEXT OF REVIEW**49 **Reproductive life span and age at menopause**

50 Women with PCOS have higher number of ovarian antral follicles and possibly greater ovarian reserve than
51 non-PCOS women (14). A previous study reported that women with PCOS may gain regular menstrual
52 cycles with aging (11), however, only a few studies have investigated ovarian aging or age at menopause in
53 the affected women. A longitudinal study of 31 women with PCOS and 266 controls, recruited from a
54 tertiary academic centre, reported women with PCOS and control women having a similar decline rate of
55 antral follicles, after adjusting for baseline antral follicle count and age (15). In our previous study assessing
56 109 women (44 controls and 65 women with PCOS), the decline in AMH levels was comparable in both
57 study groups, although AMH levels were always 2- to 3-fold higher and remained elevated until 40 years of
58 age in women with PCOS (9). As for menopausal age, a cohort study with a 24-year follow up found that
59 women with PCOS diagnosed by having oligomenorrhea and hyperandrogenism (n=27) reached menopause
60 four years later than control women (n=94) (16). In line with this result, another Swedish study found that
61 PCOS was associated with a later age at menopause (Hazard ratio: 0.44 [0.28 – 0.71]) (13). Similarly, the
62 Tehran Lipid and Glucose Cohort study using a prediction model based on AMH levels, estimated the age at
63 menopause to be 51.4 years in women with PCOS and 49.7 years in the controls (17). Interestingly, women
64 with PCOS have also been suggested to have earlier menopause than their non-PCOS counterparts (18).

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

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

77 **Excess weight**

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

98 **Abnormal glucose metabolism**

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

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

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

126 **Other common CVD risk factors in PCOS**

127 A recent systematic review and meta-analysis reported increased prevalence of metabolic syndrome (MetS)
128 in overweight or obese women with PCOS but not in lean ones (34). In the Tehran Lipid and Glucose Study,
129 the incidence of hypertension, MetS, dyslipidemia and obesity were comparable between PCOS women aged
130 > 40 years and similar aged controls, whereas among women < 40 years, women with PCOS had higher
131 incidence of hypertension and MetS than control women (35). A Nordic cross-sectional multicenter case-
132 control study found that in women over 39 years of age, the prevalence of MetS was twofold higher in the
133 hyperandrogenic-PCOS (HA-PCOS) group compared with the normoandrogenic-PCOS (NA-PCOS) or
134 control groups (36). Moreover, the women over 39 years with the HA-PCOS had higher serum levels of low
135 density lipoprotein (LDL) and triglycerides compared with controls, and higher serum levels of LDL
136 compared with the NA-PCOS population (36).

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

144 **Cardiovascular disease events**

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

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

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

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

169 Health related quality of life (HRQoL)

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

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

188 CONCLUSION

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

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

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

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

210

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