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# Polycystic Ovary Syndrome: Menopause and Malignancy

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KARINE MATEVOSSIAN, DO,\*  
and OLIVIA CARPINELLO, MD†

\**Advocate Aurora Lutheran General Hospital, Chicago, Illinois;*  
and †*Program in Reproductive Endocrinology and Gynecology,*  
*Eunice Kennedy Shriver NICHD, National Institutes of Health,*  
*Bethesda, Maryland*

**Abstract:** Polycystic ovary syndrome (PCOS) has been extensively studied in reproductive-aged women. However, accumulating research shows that PCOS can have lifelong effects on multiple aspects of women's health. PCOS can affect the onset and course of menopause and cardiovascular health in perimenopausal and postmenopausal patients. Moreover, PCOS may increase a woman's risk for both gynecologic and nongynecologic malignancies. When treating older PCOS patients, physicians should be cognizant of the syndrome's long-term effects and consider the unique needs of these women.

**Key words:** PCOS, menopause, malignancy

## Introduction

Polycystic ovary syndrome (PCOS) has been extensively studied in reproductive-aged women. However, accumulating research shows that PCOS can have lifelong effects on multiple aspects of women's health. PCOS can affect the onset and

*Correspondence: Olivia Carpinello, MD, 38 Maryland Avenue, Unit 225, Rockville, MD. E-mail: olivia.carpinello@nih.gov*

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course of menopause and cardiovascular health in perimenopausal and postmenopausal patients. Moreover, PCOS may increase a woman's risk for both gynecologic and nongynecologic malignancies. When treating older PCOS patients, physicians should be cognizant of the syndrome's long-term effects and consider the unique needs of these women.

## Age of Menopause in PCOS Patients

A key component of PCOS is oligomenorrhea or amenorrhea, which is theorized to lead to less follicular depletion from month to month. This, in turn, may lead to a later age of menopause in PCOS women. Research in this area shows that, while the rate of follicle attrition is actually the same for PCOS patients and controls, PCOS patients may start their reproductive years with a larger ovarian reserve due to either an

increased number of germ cells at birth or a decrease in germ cell loss. Ultimately, this larger follicular pool may lead to a later onset of menopause in PCOS patients.<sup>1</sup> While the exact age of menopause in these women has not been extensively studied, available studies suggest that PCOS women, on average, undergo menopause 2 years later than normo-ovulatory women.<sup>2</sup> This finding correlates with the higher levels of anti-Müllerian hormone seen in PCOS women compared with age-matched and body mass index (BMI)-matched controls.<sup>2</sup> While it is not recommended to use follicle-stimulating hormone (FSH) levels to determine menopausal status due to significant day-to-day fluctuation, lower FSH values are seen in menopausal PCOS patients compared with age-matched controls. Postmenopausal PCOS women have also been shown to have higher levels of free androgens and total testosterone, while sex hormone-binding globulin levels are significantly lower in postmenopausal PCOS patients.<sup>3</sup>

As PCOS patients approach menopause, their cycles tend to normalize and become regular with overall shortened intermenstrual intervals.<sup>4</sup> This most likely occurs due to the decreased number of follicles in older PCOS women compared with reproductive-aged PCOS patients with oligomenorrhea or amenorrhea.<sup>5</sup> As the number of follicles decreases, so does the production of inhibin B. Lower serum inhibin B levels prevent the suppression of FSH and allow FSH levels to return to normal. Normalized FSH levels promote follicular growth and spontaneous ovulation. Thus, older PCOS women are more likely to have regular, ovulatory menstrual cycles.<sup>4</sup>

### ***Menopausal Symptoms in PCOS Women***

There is a limited amount of research on menopausal symptoms in PCOS

patients. Previous studies on menopausal women, not specifically those with PCOS, have shown that higher FSH levels, independent of estradiol levels, are associated with increased prevalence and frequency of hot flashes.<sup>6</sup> Therefore, some theorize that PCOS women may have decreased hot flashes because of their lower FSH levels. Similarly, PCOS patients have higher circulating androgens which are ultimately aromatized to estrogens, which may also help decrease vasomotor symptoms. However, studies focusing specifically on PCOS patients have had conflicting results. One study found that PCOS women self-reported hot flushes and night sweats less frequently than controls,<sup>3</sup> while another study showed that PCOS did not affect the incidence, duration, or severity of hot flashes.<sup>7</sup> Postmenopausal PCOS women did self-report higher rates of vaginal dryness than non-PCOS postmenopausal controls. Perhaps this does not reflect a higher prevalence of vaginal dryness, but instead, PCOS patients may be more aware of vaginal dryness because of a potentially increased libido from higher levels of androgens versus control patients.<sup>3</sup>

Research on hirsutism in postmenopausal PCOS patients is limited. One study did show that menopausal women with PCOS reported higher rates of hirsutism than control patients. This correlated with the higher androgen levels of these patients.<sup>3</sup> This finding is not surprising due to the up to 70% incidence of hirsutism in premenopausal PCOS patients.<sup>8</sup>

### ***Bone Health***

The relationship between bone density and PCOS in postmenopausal women is not well studied. It is theorized that the higher androgen levels in these patients would be protective for bone health and thus be associated with higher bone

mass. Obese PCOS women with larger amounts of adipose tissue have increased peripheral conversion of androgens to estrogens that should have a protective effect.<sup>9</sup> Low body weight of <127 pounds has been recognized as a risk factor for osteoporosis,<sup>10</sup> and since PCOS women are more likely to be overweight or obese, one would expect a decreased prevalence of osteoporosis in postmenopausal PCOS women.

Only one study focused specifically on postmenopausal PCOS patients and bone health. Schmidt and colleagues investigated the bone mineral density (BMD) of PCOS patients aged 61 to 78 years old. They found that, despite a persistently higher free androgen index in the PCOS patients, there was no difference in muscle mass, BMD, or fracture incidence when compared with controls.<sup>11</sup> This study had a median BMI of 25.7 kg/m<sup>2</sup> in controls versus 27.7 kg/m<sup>2</sup> in PCOS patients and did not address BMD and fractures in younger postmenopausal women, such as those in their 50s. It is unclear whether there is an initial protective effect on BMD that declines over time. Several studies of PCOS patients in adolescence and young adulthood have shown that BMD is comparable to age-matched controls, while studies in PCOS patients who have a mean age of 27 to 28 years old show higher BMD.<sup>12</sup> A study by Kassanos and colleagues compared 15 lean PCOS women and 15 obese PCOS women to 15 controls. The subjects were between 17 and 35 years old with a mean age of 26.5 years in the lean PCOS group, 28.5 years in the obese PCOS women, and 26.7 years in the controls. This study showed that both lean and obese PCOS patients had higher BMD. Interestingly, this effect was more profound in lean PCOS women.<sup>12</sup> Ultimately, more extensive research is needed to determine the effect of PCOS on bone health in postmenopausal patients.

## ***Cardiovascular Disease (CVD) in Perimenopausal and Postmenopausal PCOS Women***

Extensive research has shown that reproductive-aged women with PCOS have higher rates of obesity, insulin resistance, dyslipidemia, and hypertension. Reproductive-aged PCOS women also have increased rates of metabolic syndrome.<sup>13</sup> The studies in perimenopausal and menopausal women, however, are more limited.

The most used criteria for the diagnosis of metabolic syndrome is the National Cholesterol Education Program (NCEP) Adult Treatment Panel III.<sup>14</sup> Three of the 5 criteria are required to meet the diagnosis of having metabolic syndrome. These include: waist circumference > 35 inches, elevated triglycerides ( $\geq 150$  mg/dL), high density lipoprotein (HDL) < 50 mg/dL, elevated blood pressure ( $\geq 130/85$  mm Hg) or receiving antihypertensive treatment, and elevated fasting glucose ( $\geq 100$  mg/dL) or receiving treatment for elevated blood glucose.<sup>14</sup>

Studies suggest that perimenopausal women with PCOS have a similar risk of CVD and stroke when compared with controls.<sup>15</sup> Similarly, despite having a higher BMI,<sup>16</sup> there seems to be no difference in the rate of development of metabolic syndrome in perimenopausal PCOS patients compared with controls.<sup>15</sup>

However, when specifically examining postmenopausal women, data on CVD is conflicting. A meta-analysis of 9 studies showed menopausal women with PCOS had higher risks of nonfatal stroke and coronary heart disease (CHD). In women over 45 years old, a total of 28 nonfatal stroke events in 815 PCOS subjects was seen compared with 50 events in 2379 controls. The risk in PCOS women for nonfatal stroke was statistically significantly increased. In the same age group, 43 of 843 PCOS women had nonfatal

CHD compared with 123 of 3131 control patients. This increased risk was not statistically significant but was seen even in lean PCOS patients, indicating that PCOS, independent of BMI, plays a role in CHD.<sup>17</sup> Contrastingly, the Rotterdam study found higher levels of androgens were not associated with a higher incidence of atherosclerosis and CVD. The authors compared postmenopausal PCOS women to controls and found PCOS patients had larger waist/hip ratios, higher BMI, higher rates of type 2 diabetes mellitus, higher triglyceride levels, and lower HDL levels. Despite these findings, PCOS women did not have an increased prevalence of atherosclerosis or risk for CVD. Notably, this study was limited by the small subset of 272 PCOS patients and a retrospective diagnosis of the syndrome using cycle irregularities at the age of 25 as the criteria.<sup>18</sup>

Perimenopausal and menopausal women with PCOS have increased rates of obesity, hyperinsulinemia, hypertension, and hyperlipidemia. Clinicians should be cognizant of these increased risk factors and encourage conservative measures such as lifestyle modifications, weight management, and exercise. Per the American College of Obstetrics and Gynecology (ACOG), universal lipid screening with total cholesterol, LDL-cholesterol, and HDL-cholesterol should occur once between the ages of 17 and 21. Routine screening is not necessary between 22 to 39 years old. Starting at 40, ACOG recommends checking lipid levels every 5 years. After 75 years old, no routine screening is needed but it can be done based on clinical judgment.<sup>19</sup> For PCOS patients ACOG recommends screening for cardiovascular risk by determination of BMI, fasting lipoprotein levels, and metabolic syndrome risk factors. This screening should be repeated periodically as PCOS patients have a higher risk for metabolic syndrome.<sup>20</sup>

## ***Malignancy and PCOS***

### **ENDOMETRIAL CANCER**

There is extensive evidence that PCOS increases a woman's likelihood of having endometrial cancer. The extent of risk varies based on the study, but the risk of endometrial cancer is between 2.7 to 4 times higher in PCOS women than controls.<sup>21</sup> The majority of endometrial cancers in PCOS women are type 1 (endometrioid) and most commonly present with postmenopausal bleeding.<sup>22</sup>

Type 1 tumors are estrogen-dependent and the risk of developing these malignancies increases as unopposed estrogen exposure increases. Women who are obese, nulliparous, or on estrogen replacement therapy have a higher likelihood of developing type 1 endometrial cancer. Of these, obesity is the strongest risk factor.<sup>23</sup>

Age is another significant risk factor for endometrial cancer. The median age of diagnosis for endometrial carcinoma is 61 with most patients falling between 50 and 59 years old. About 5% of cases will be diagnosed before 40 years old and an estimated 25% will be diagnosed before menopause. The younger patients who are diagnosed with endometrial cancer are commonly obese with anovulatory cycles.<sup>24</sup>

The increased rate of endometrial cancer in PCOS patients can be explained by several mechanisms. First, PCOS patients are more likely to be obese. Obese women have increased adipocyte aromatization of androgens to estrogens, which creates unopposed estrogen.<sup>25</sup> Second, many PCOS patients have increased insulin resistance. There is some evidence that insulin increases luteinizing hormone (LH) production from the pituitary,<sup>26</sup> which contributes to the already increased LH due to abnormal gonadotropin-releasing hormone pulsatility. Insulin also directly increases ovarian androgen production

by upregulating 17-alpha-hydroxylase, which promotes the conversion of pregnenolone to androgens instead of progesterone. In addition, hyperinsulinemia leads to decreased insulin-like growth factor-binding protein I, which leads to increased free insulin-like growth factor I (IGF-I). IGF-I further promotes androgen synthesis by theca cells.<sup>9,27</sup> This hyperandrogenic environment in the ovaries, as well as the increased LH:FSH ratio, prevents normal follicular development which leads to anovulation, and thus, unopposed estrogen. Furthermore, androgens, IGF-I, and insulin all decrease sex hormone-binding globulin, which leads to increased free estrogens and, thus, increases the risk of endometrial carcinoma.<sup>9,27</sup>

Insulin and IGFs I and II bind to receptors in the endometrium and regulate endometrial proliferation through proliferative, differentiative, and metabolic effects.<sup>25</sup> Moreover, hypersecretion of LH in and of itself may be associated with increased endometrial malignancy. Research has shown an increased expression of LH and human chorionic gonadotropin receptors in human endometrial carcinoma and hyperplasia compared with normal endometrium.<sup>25</sup>

Restoring the hormone balance of estrogen and progesterone in PCOS patients can reduce the risk of endometrial cancer. Treatment with oral contraceptives (OCPs) can provide consistent exposure to progesterone and regulate menses in younger PCOS patients. For postmenopausal women or women who are poor candidates for OCPs, progesterone-only regimens including medroxyprogesterone acetate, megestrol acetate, and the levonorgestrel-releasing intrauterine device can be utilized to counteract unopposed estrogen and decrease the risk of malignancy.<sup>28</sup> In women who already have a low-grade disease or who are poor surgical candidates, malignancy may be treated with progesterone-only options in select cases.

Metformin and other pharmaceuticals can be used to decrease hyperinsulinemia, which can help decrease androgen synthesis and promote the resumption of ovulation and normal menses.<sup>27</sup> However, studies investigating metformin's direct effects on endometrial carcinoma have generally suggested no decreased risk.<sup>29</sup> One recent study, however, did find a protective effect against endometrial cancer with the use of metformin in women with type II diabetes mellitus.<sup>30</sup>

PCOS patients do not require routine screening for endometrial hyperplasia or carcinoma. However, premenopausal PCOS patients who have prolonged amenorrhea, irregular bleeding, or unopposed estrogen exposure may require further evaluation with transvaginal ultrasound, endometrial biopsy, or both per the clinician's discretion.<sup>31</sup> Any woman with postmenopausal vaginal bleeding should be evaluated with either a transvaginal ultrasound or endometrial biopsy.<sup>28</sup>

## **BREAST CANCER**

Estrogen exposure is a well-established risk factor for breast cancer. Factors which increase lifetime estrogen exposure include early menarche, late menopause, and nulliparity. While pregnancy decreases the overall risk of breast cancer, there is a temporarily increased risk in the immediate postpartum period with a peak at 5 years postpartum.<sup>32</sup> One possible explanation for this finding is increased access to medical care during pregnancy and the postpartum period. Obesity seems to increase the risk of breast cancer in postmenopausal women but potentially decreases the risk in premenopausal women.<sup>25</sup> Infertility has also been associated with increased breast cancer risk.<sup>26</sup>

Since PCOS patients struggle with obesity, infertility, and increased estrogen exposure from anovulation, there is a hypothetical increased risk of breast cancer among these patients. However, the available research to date has not shown

an association between PCOS and an increased incidence of breast cancer.<sup>22,25</sup> A study by Kim and colleagues focused on women with newly diagnosed breast cancer and compared them to age-matched controls. This study found that women with breast cancer and PCOS were more likely to have used OCPs, to have a history of infertility, and to have irregular menstrual cycles, none of which are surprising. There was a 3-fold increase in the rate of breast cancer in premenopausal women with PCOS but a 33% decrease in breast cancer incidence in postmenopausal PCOS patients.<sup>33</sup> Overall, there is not enough data to confirm that PCOS increases the risk of breast cancer, and larger, confirmatory studies are needed.

#### OVARIAN CANCER

The risk of epithelial ovarian cancer also increases with nulliparity and infertility.<sup>25</sup> Studies have found evidence that LH, estrogens, and androgens may all be part of the pathophysiology of ovarian cancer. Progesterone may have a protective effect against ovarian cancer by promoting apoptosis of abnormal cells.

The association between obesity and ovarian cancer is not well understood. Some studies have shown increased risk with obesity, while others have shown that obesity is inversely associated with ovarian carcinoma.<sup>25</sup>

It is now widely recognized that the use of OCPs can decrease the risk of ovarian cancer. One potential explanation is that recurrent ovulatory events may lead to the malignant transformation of the epithelium, and OCPs decrease the number of lifetime ovulations.<sup>34</sup> Therefore, it can be expected that PCOS would decrease the risk of ovarian cancer since it leads to anovulation. However, there is minimal evidence addressing PCOS and the risk of ovarian carcinoma. A study by Schildkraut et al<sup>35</sup> showed a 2.5-fold increased risk of ovarian cancer in PCOS patients but was limited by small sample size.

Conversely, a cross-sectional study by Atiomo and colleagues, a Danish cohort study, and a meta-analysis by Barry and colleagues showed no association between PCOS and ovarian cancer.<sup>21,36,37</sup> Interestingly, when the meta-analysis excluded women older than 54 years old, PCOS patients had a significantly increased risk of ovarian cancer with an odds ratio of 2.52.<sup>37</sup>

Two studies have focused on the association of PCOS with specific subtypes of ovarian carcinoma. Both investigated the association between PCOS and borderline serous ovarian carcinoma and found an increased incidence in PCOS patients who were overweight or obese. This finding may be due to the fact that serous borderline ovarian tumors have higher androgen receptor levels than serous invasive tumors. In addition, higher levels of androgens have been shown to increase the risk of low-grade tumors and decrease the risk of high-grade tumors. These studies are limited, and further research is needed to confirm the relationship between PCOS and serous borderline ovarian tumors.<sup>29</sup>

#### OTHER MALIGNANCIES

There is some research suggesting uterine sarcomas, such as leiomyosarcoma, are hormone-sensitive and there may be an increased risk with prolonged unopposed estrogen. While most of these cancers occur in postmenopausal women, there are a limited number of case reports of uterine sarcomas occurring in premenopausal PCOS women.<sup>25</sup> Ultimately, more data is needed to conclusively say whether or not PCOS increases the risk of leiomyosarcoma.

There is currently insufficient data to make any conclusions about the association of PCOS with vaginal, vulvar, or cervical cancer.<sup>22</sup>

Limited data exists on the association between PCOS and other nongynecologic malignancies. However, a study that analyzed the Danish Cancer Registry found that PCOS increases the risk for kidney, colon, and brain cancer by 2- to

**TABLE 1. Summary of Conditions and Risk in PCOS Patients**

Condition	Risk for PCOS Patients
Osteoporosis	May have higher bone mineral density, more data needed
CVD	Perimenopausal—higher risk Postmenopausal—possibly higher risk, more data needed
Stroke	Perimenopausal—higher risk Postmenopausal—possibly higher risk, more data needed
Endometrial cancer	Increased risk by 2.7 to 4 times
Breast cancer	More data needed
Ovarian cancer	Limited research showing higher risk, more data needed
Kidney, colon, brain cancer	Limited research showing higher risk, more data needed

CVD indicates cardiovascular disease; PCOS, polycystic ovary syndrome.

4-fold. For patients with brain cancer, the majority had a pituitary gland tumor. Of the pituitary tumors, 8 were diagnosed within 4 years of the diagnosis of PCOS, and 4 patients were diagnosed 5 or more years after their PCOS diagnosis. The authors did not find an obvious pattern between the age of PCOS diagnosis or age of cancer diagnosis for patients with colon or kidney cancer.<sup>21</sup> A study by Brinton et al,<sup>38</sup> found a significantly increased incidence of melanoma among women with infertility and androgen excess or menstrual cycle disorders compared with the general United States population. These findings are all limited and need further research to be confirmed.

## Conclusions

PCOS is a disorder with lifelong implications. PCOS affects the age of menopause and metabolic health in older women. PCOS patients also have a higher likelihood of being diagnosed with endometrial cancer. However, as summarized in Table 1, further research is needed to elucidate the effects of this syndrome during the perimenopausal/postmenopausal period as well

as the relationship between this condition and other cancers.

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