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Invited Commentary

The association between polycystic ovary syndrome and early cardiovascular disease morbidity strengthens

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Significance

It has been debatable for many years whether PCOS is associated with increased risk for cardiovascular disease (CVD) events, and not just the CVD risk factors. The recent publications, including the work by Dwivedi et al. have consistently shown that the accumulation of CVD risk factors translates to an increased risk of CVD events already at a young age. These findings highlight the need for active screening and management of CVD risk factors from early on.

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that predisposes to several comorbidities.[1] The syndrome has vast metabolic sequela that have early onset: early increase in body weight at childhood, central fat accumulation, high risk for dyslipidemia, hypertension, low-grade inflammation, and insulin resistance, all translating into metabolic syndrome (MS) and type 2 diabetes (DMT2).[2–8] Given the early clustering of the metabolic abnormalities, MS, and DMT2, it has been under debate for several years whether the affected women have an elevated risk for developing cardiovascular diseases (CVD), such as coronary artery disease, heart attacks, and stroke.[9,10] The bottleneck in the analysis and available cohorts has been the relatively young age of women with PCOS as well as variable diagnostic criteria. Indeed, as the diagnostics of PCOS were developed after the 1990s, the number of women with reliable diagnosis is still limited to assess more rare events, like cardiovascular outcomes. On the other hand, it has been suggested that the prolonged menopausal age among women with PCOS and adverse metabolic effects in other women due to menopause would even up the risk.

To assess the CVD risk among women with PCOS, Dwivedi et al.[11] performed a cross-sectional study using the National Inpatient Sample database from the United States. Their study included women who were hospitalized and between 15 and 65 years of age. They sought to determine the association of PCOS with multiple CVD outcomes including composite CVD, major cardiovascular events (MACE), coronary heart disease (CHD), stroke, heart failure (HF), arterial fibrillation (AF) or arrhythmia, myocardial infarction (MI), cardiac arrest (CA), pulmonary heart disease (PHD), and diabetes mellitus (DM). They performed sampling weighted logistic regression analysis to investigate the association of PCOS and different cardiovascular disease events, which were identified using the disease codes of the 10th revision of the International Classification of Diseases (ICD-10). Given the interaction of age and PCOS on CVD, the endpoints were separately analyzed for women < 40 and > 40-65 years of age. Important covariates were added in the adjusted analysis. Mediation analyses adjusting for obesity and other components of MS were performed for various CVD outcomes.

The analysis included 2 183 020 hospitalized women with mean age of 40.6 years. The prevalence of PCOS was 0.97% among women aged ≤40 years and 0.24% among women aged >40 years. The low prevalence of PCOS after age 40 years may underline that PCOS is underdiagnosed in middle-aged and older women. Dwivedi et al. found that PCOS was significantly associated with most CVD outcomes including composite CVD, MACE, CHD, stroke/CVA, HF, AF/arrhythmia, and PHD among hospitalized women with age ≤40 years. Interestingly, the association between PCOS and CVD outcomes was mediated through MS or its components like obesity. Contrary, the association was inverse for most of the events among PCOS women over 40 years. However, the absolute number of CVD events in women with PCOS increased with advancing age, as the prevalence of MACE was 1.61% in women with PCOS ≤ 40 years and 8.74% in women with PCOS and > 40 years. Considering the increase in absolute event numbers and the pathology behind CVD (slowly progressing atherosclerosis), it was rather surprising that in the regression analysis, the CVD event risk was increased in

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women aged under 40 years, whereas most of the CVD events were inversely associated with PCOS in women aged above 40 years. However, according to the authors, the rationale for this age cut-off was to account for a strong interaction between age and PCOS on CVD events. These analyses are also of clinical relevance and represent the early CVD morbidity among PCOS women. However, future studies with longitudinal design and time-to-event analysis without age restriction will be needed to gain better understanding on how CVD event risk develops after menopause in women with PCOS.

One of the important novel findings of this study was the previously unreported association between PCOS and atrial fibrillation. Atrial fibrillation is the most frequent arrhythmia requiring management in clinical practice, and it increases the risk of stroke, peripheral embolism, and death.[12] The risk factors of AF, such as hypertension, obesity, inflammation, obstructive sleep apnea, and diabetes, are common among women with PCOS, and thus, it is not surprising that also the risk of AF is increased in women with PCOS. The common presentation of AF—rapid and irregular heartbeat—is easy to recognize, but sometimes, AF can be asymptomatic or present with only mild and misleading symptoms, such as shortness of breath, anxious feeling, tiredness, and declining physical performance calling for an electrocardiogram recording to rule out AF.

Moreover, another novel finding was that PCOS was significantly associated with PHD among hospitalized women under 40 years of age. Pulmonary heart disease is a wide spectrum of different diseases that cause high blood pressure in the lung arteries and consequently increase the workload of right ventricle and eventually lead to right ventricular failure.[13] This is an interesting new finding and warrants further research to gain deeper understanding of possible mechanisms behind this association.

In conclusion, PCOS is a multifaceted hormonal disorder that extends beyond reproductive health concerns. With the current evidence, the connection between PCOS and cardiovascular disease seems to be strengthening. Since the association between CVD and PCOS was mediated by obesity and components of MS, this emphasizes the importance of prevention and treatment of obesity, hypertension, and dyslipidemia in women with PCOS even under the age of 40 years. Women with PCOS should be aware of their increased risk and take proactive steps to manage it. Like in the general population, lifestyle modifications, including regular exercise, a balanced diet, weight management, and smoking cessation, are the first-line and can help reduce the risk of CVD also in PCOS. Healthcare providers, on the other hand, should also be proactive with early initiation of interventions such as glucose, lipid, and blood pressure–lowering medications as well as implementing effective weight management strategies with GLP-1 analogs or bariatric surgery but also acknowledging the possibility or wish for pregnancy in young fertile women posing restrictions to some of these medical treatments. Increasing the awareness and above actions could reduce the likelihood of cardiovascular complications among women with PCOS. However, longitudinal follow-up studies beyond menopausal years and analysis on specific CVD diagnosis are still warranted to reveal the life-long disease burden.

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References

1. McCartney CR, Marshall JC. CLINICAL PRACTICE. Polycystic ovary syndrome. *N Engl J Med*. 2016;375(1):54-64. https://doi.org/10.1056/NEJMcp1514916
2. Koivuaho E, Laru J, Ojaniemi M, *et al*. Age at adiposity rebound in childhood is associated with PCOS diagnosis and obesity in adulthood-longitudinal analysis of BMI data from birth to age 46 in cases of PCOS. *Int J Obes (London)*. 2019;43(7):1370-1379. https://doi.org/10.1038/s41366-019-0318-z
3. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev*. 2012;33(6):981-1030. https://doi.org/10.1210/er.2011-1034
4. Aboeldalyl S, James C, Seyam E, Ibrahim EM, Shawki HED, Amer S. The role of chronic inflammation in polycystic ovarian syndrome-a systematic review and meta-analysis. *Int J Mol Sci*. 2021;22(5):2734. https://doi.org/10.3390/ijms22052734
5. Amiri M, Ramezani Tehrani F, Behboudi-Gandevani S, Bidhendi-Yarandi R, Carmina E. Risk of hypertension in women with polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Reprod Biol Endocrinol*. 2020;18(1):23. https://doi.org/10.1186/s12958-020-00576-1
6. Macut D, Bjekić-Macut J, Savić-Radojević A. Dyslipidemia and oxidative stress in PCOS. *Front Horm Res*. 2013;40:51-63. https://doi.org/10.1159/000341683
7. Lim SS, Kakoly NS, Tan JWJ, *et al*. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Obes Rev*. 2019;20(2):339-352. https://doi.org/10.1111/obr.12762
8. Ollila MME, West S, Keinänen-Kiukaanniemi S, *et al*. Overweight and obese but not normal weight women with PCOS are at increased risk of type 2 diabetes mellitus—a prospective, population-based cohort study. *Hum Reprod*. 2017;32(2):423-431. https://doi.org/10.1093/humrep/dew329
9. Guan C, Zahid S, Minhas AS, *et al*. Polycystic ovary syndrome: a "risk-enhancing" factor for cardiovascular disease. *Fertil Steril*. 2022;117(5):924-935. https://doi.org/10.1016/j.fertnstert.2022.03.009
10. Wekker V, Van Dammen L, Koning A, *et al*. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. *Hum Reprod Update*. 2020;26(6):942-960. https://doi.org/10.1093/humupd/dmaa029
11. Dwivedi AK, Vishwakarma D, Dubey P, Reddy S. Association of polycystic ovary syndrome with cardiovascular disease among US female hospitalizations. *Eur J Endocrinol*. 2023;188(6):555-563. https://doi.org/10.1093/ejendo/lvad067
12. Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E, Tousoulis D. Atrial fibrillation: pathogenesis, predisposing factors, and genetics. *Int J Mol Sci*. 2021;23(1):6. https://doi.org/10.3390/ijms23010006
13. Hassoun PM. Pulmonary arterial hypertension. *N Engl J Med*. 2021;385(25):2361-76. https://doi:10.1056/NEJMra2000348