

## Blood pressure in postmenopausal women with a history of polycystic ovary syndrome

Katarzyna Doroszevska<sup>1</sup>, Tomasz Milewicz<sup>1</sup>, Sandra Mrozińska<sup>2</sup>, Jarosław Janeczko<sup>3</sup>, Radosław Rokicki<sup>3</sup>, Marek Janeczko<sup>3</sup>, Damian Warzecha<sup>4</sup>, Piotr Marianowski<sup>4</sup>

<sup>1</sup>Department of Gynaecological Endocrinology and Gynaecology, Jagiellonian University Medical College, Cracow, Poland

<sup>2</sup>Department of Metabolic Diseases, Jagiellonian University Medical College, Cracow, Poland

<sup>3</sup>Infertility Treatment Centre PARENS, Cracow, Poland

<sup>4</sup>1<sup>st</sup> Department of Obstetrics and Gynaecology, Medical University of Warsaw, Warsaw, Poland

### Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder at reproductive age, affecting 6-10% of females in this group. The aetiology of this syndrome is not fully understood. Genetics, endocrinology factors, and the influence of the environment are possible causes of this syndrome. PCOS is characterised by menstrual disorders, hyperandrogenism, and abnormalities in ovarian morphology as well as metabolic disorders. PCOS increases the risk of overweight and obesity, diabetes, endometrial cancer, and cardiovascular diseases such as hypertension along with all its long-term consequences. There are limited studies about cardiovascular disorders, especially hypertension, in postmenopausal women with a history of PCOS. The presented paper is an attempt to briefly summarise literature data concerning the influence of this disease on the incidence of hypertension and blood pressure control in postmenopausal women. Women with PCOS more often present features of metabolic syndrome and have increased cardiovascular risk factors including hypertension. The prevalence of hypertension is 2.5 times higher than in corresponding healthy peers. Furthermore, hyperandrogenaemia is associated with elevated blood pressure independent of the patient's age, insulin resistance, obesity, and dyslipidaemia. In view of this, these patients should be thoroughly screened for hypertensive disorders and educated about the lifestyle modifications that could prevent hypertension later in life.

**Key words:** polycystic ovary syndrome, menopause, blood pressure, hyperandrogenaemia, hypertension.

### Introduction

Polycystic ovary syndrome (PCOS) is one of the commonest female endocrinopathies. PCOS is a highly prevalent disorder affecting about 6-10% of women of reproductive age [1-3] and has long-term fallout that goes beyond reproductive age [4]. Its aetiopathogenesis is complex, multifactorial, and heterogeneous, including the interaction of genetic, epigenetic, and environmental factors [5]. The common clinical manifestations of this syndrome are oligo-anovulation, hyperandrogenism, and/or hyperandrogenaemia and polycystic ovary morphology [2, 6, 7]. PCOS is established as a metabolic disorder [6]. Cardiovascular risk factors such as hypertension, dyslipidaemia, metabolic syndrome, and obesity are more frequent among women with PCOS compared to non-PCOS women [6, 9]. This has led to the assumption that women with PCOS have

a higher risk of developing cardiovascular diseases in later life [6, 10, 11].

There are limited studies about cardiovascular disorders, especially hypertension, in postmenopausal women with a history of PCOS. Most authors suggest that PCOS in postmenopausal women increases the risk of hypertension with all its consequences.

### Material and methods

The authors searched the PubMed database with different combinations of the key words: "polycystic ovary syndrome", "menopause", "blood pressure", and "hypertension". The established inclusion criteria for the following review were: an original prospective, cross-sectional or retrospective study with at least five years of follow-up, and a study group of at least 30 participants. Only six trials met the inclusion criteria. All of them are summarised in Table 1.

Corresponding author:

**Damian Warzecha**, MD, 1<sup>st</sup> Department of Obstetrics and Gynaecology, Medical University of Warsaw, 1/3 Starynkiewicza Sq., 02-015 Warsaw, Poland, e-mail: [damwarzecha@gmail.com](mailto:damwarzecha@gmail.com)

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**Table 1.** Studies on cardiovascular disease risk in women with polycystic ovarian syndrome (PCOS)

Study	Type of study	PCOS vs. control (n)	Mean or median age at follow-up (years)	Conclusions
Dahlgren [17] 1992	Cross-sectional	33 vs. 132	40-59	Perimenopausal women with PCOS have increased morbidity in hypertension and diabetes mellitus
Wild [16] 2000	Retrospective	319 vs. 1060	56.7 (31 years follow up)	Increased prevalence of hypertension in menopausal-PCOS women compared to a cohort of control women
Elting [15] 2001	Retrospective	32 vs. 2372	45-54	2.5-times higher prevalence of hypertension than the corresponding age group of the Dutch female population
Schmidt [12] 2011	Cross-sectional	32 vs. 120	61-79 (after 21 years of follow up)	High prevalence of hypertension and high triglyceride levels in postmenopausal PCOS women
Armeni [13] 2013	Cross-sectional	43 vs. 286	55.6 ±7.8	Higher systolic blood pressure and triglycerides and lower high-density lipoprotein (HDL) cholesterol than controls
Merz [20] 2016	Cross-sectional	25 vs. 270	62.6 ±11.6	Clinical features of PCOS were not a significant predictor in prognostic models including hypertension, diabetes, waist circumference, and angiographic coronary artery disease

## Results

Schmidt *et al.* carried out long-term, prospective follow-up research of 35 postmenopausal women with PCOS and 120 age-matched controls. The population participated in a study in 1987 and was reinvestigated 21 years later. The aim of their study was to examine whether postmenopausal PCOS women differ from the control group with regard to cardiovascular risk factors, myocardial infarction, stroke, and mortality. They studied parameters such as blood pressure, insulin, triglycerides, total cholesterol, and fibrinogen as well as incidences of myocardial infarction, stroke, hypertension, and diabetes. They found that menopausal patients with PCOS had a higher prevalence of hypertension and higher triglyceride levels than controls. The well-described cardiovascular profile in pre- and perimenopausal PCOS women does not entail an evident increase in cardiovascular events during the postmenopausal period [12].

Armeni *et al.* conducted a study to evaluate the effect of PCOS on markers of subclinical atherosclerosis in nondiabetic postmenopausal women. They examined blood pressure, blood samples, and arterial structure (intima-media thickness, atheromatous plaque presence) and function (flow-mediated dilation, pulse wave velocity, augmentation index) by ultrasound. They obtained similar results to Schmidt's study. Armeni *et al.* ascertained that postmenopausal women with PCOS had higher systolic blood pressure and triglycerides and lower high-density lipoprotein (HDL) cholesterol than controls. The values of pulse wave velocity differed significantly between PCOS participants and controls. According to the authors, arterial stiffness is increased

in asymptomatic, nondiabetic women with PCOS independently of age, BMI, or blood pressure [13].

Another study, carried out in PCOS women of reproductive age, gave evidence that the insulin resistance of arterial endothelial cells is associated with reduced synthesis of nitric oxide and increased synthesis of vasoconstricting agents. This leads to increased vascular stiffness and consequent hypertension. The authors also found elevated levels of tissue plasminogen activator in such patients, which correlated with body mass index (BMI) and insulin resistance [14].

Elting *et al.* investigated the prevalence of diabetes mellitus, hypertension, and cardiac diseases in a Dutch population with PCOS, comparing these conditions in the healthy Dutch female population. In PCOS women aged 45-54 years ( $n = 32$ ) the prevalence of hypertension was 2.5 times higher than the corresponding age group of the Dutch female population. The strongest predictor of hypertension was elevated BMI [15].

Wild *et al.* conducted a retrospective study of women diagnosed with PCOS an average of 31 years previously and found an increased prevalence of hypertension compared to a cohort of control women [16]. Dahlgren *et al.* studied if the hormonal imbalance in women with polycystic ovary syndrome continues into and after menopause and analysed factors constituting an increased risk for developing metabolic disorders. Blood pressure was examined in menopausal women with PCOS, who had undergone ovarian wedge resection. It was a long-term follow-up study that showed that menopausal women post ovarian wedge resection were three times more likely to have hypertension compared to non-PCOS women [17].

Most of the available literature data suggest an increased prevalence of elevated blood pressure in

women with PCOS compared to the healthy population. However, obesity is also a factor complicating the interpretation of these studies, as a well-known risk factor for hypertension [18].

Dalmasso *et al.* tried to ascertain whether chronic hyperandrogenaemia would result in a more harmful effect on metabolic function, blood pressure, and renal function than normo-androgenaemic age-matched females. They applied an animal model using rats. Female rats were implanted with dihydrotestosterone and were studied at 13 months. In this group it was observed that their blood pressure was significantly higher, heart rate was lower, and renal function (GFR) was reduced by 40%. They also observed that insulin resistance was more significant in rats with higher plasma insulin, normal fasting blood glucose, abnormal oral glucose tolerance test, and higher non-fasting blood glucose. Thus, the chronically hyperandrogenic female rat is a model of postmenopausal PCOS, which exhibits insulin resistance and visceral obesity, hypertension, and debility in renal function [19].

On the other hand, Merz *et al.* claimed that clinical features of PCOS were not significant predictors in prognostic models for hypertension, diabetes, waist circumference, and angiographic coronary artery disease. However, these data should be interpreted with caution because of the small cohort of participants (295 postmenopausal women, only 25% with clinical features of PCOS defined by a premenopausal history of irregular menses and current biochemical evidence of hyperandrogenaemia). Their findings question whether identification of clinical features of PCOS in postmenopausal women who already have known cardiovascular disease provides any additional opportunity for risk factor intervention [20].

## Discussion

Why are postmenopausal women with a history of PCOS more prone to develop hypertension compared to postmenopausal non-PCOS women?

Generally, long-term risk of cardiovascular complications has been linked to an increase in oxidative stress and inflammatory markers.

Some studies have shown that in women with PCOS endothelial dysfunction goes together with, and is influenced by, the presence of increased serum levels of cytokines and endothelial activation markers. These parameters appear to be correlated with hyperandrogenaemia in this insulin-resistant population [21].

Endothelial dysfunction is the starting point of developing cardiovascular disease [22].

Hypertension develops because of decreased vascular compliance and endothelial dysfunction in women with PCOS [23]. Endothelial dysfunction is proportional to the level of androgens and insulin resistance [21].

Hyperinsulinaemia influences the hypertrophic effect on vascular endothelial and smooth muscle cells; it also advocates endothelin 1 (ET-1) production [23]. ET-1 is a vasoactive substance involved in regulating endothelial function, which is commonly chronically increased in women with PCOS. ET-1 is a product of oxidative stress and also a marker of endothelial dysfunction [24].

It has also been proven that androgens may influence microcirculatory regulation with effects on both vascular smooth muscle and the endothelium through actions on substances in the blood such as endothelin 1 [24].

Moreover, intensification of expression of sICAM-1 and sVCAM-1 molecules was observed in PCOS women, which play an important role in focal leukocyte accumulation in subendothelial regions of atheroma [21, 25]. In addition, there is correlation between sVCAM-1 and hyperandrogenaemia. High testosterone levels have been found to induce VCAM expression. Androgens might promote monocyte adhesion to endothelial cells in the development of atherosclerosis [25]. A proatherogenic process might be indicated in PCOS-women by extended CRP levels – another cardiovascular risk factor – and endothelial dysfunction [26]. Data suggest that increased levels of CRP are consistent with the severity of endothelial dysfunction, which supports the hypothesis that chronic inflammation contributes to endothelial dysfunction [21]. Elevated serum levels of ET-1 have been shown to cooperate with other markers of endothelial activation, endothelial dysfunction, and low-grade chronic inflammation molecules. It was found that there is a relationship between ET-1 and hyperandrogenaemia [27].

Advanced glycation end products (AGEs) are pro-inflammatory molecules that trigger a state of intracellular oxidative stress and inflammation after binding to their cell membrane receptors RAGE [28]. In women with PCOS, the concentration of AGEs is increased, and it has a pathogenic significance in many complications. Reason for pathological changes of AGEs include activating oxidative stress and inflammation [29]. PCOS women have elevated serum/ovarian AGEs and ovarian RAGE women with PCOS have a systemic chronic inflammatory condition even at the ovarian level, as represented by elevated levels of serum/ovarian AGEs and increased expression of the pro-inflammatory RAGE in ovarian tissue [30].

It has also been found that the insulin resistance of the arterial endothelial cells is associated with decreased synthesis of nitric oxide and increased synthesis of vasoconstricting agents. This leads to increased vascular stiffness [14].

Endothelium dysfunction occurs at the beginning of the atherosclerotic process [31]. Measuring carotid intima-media thickness is a non-invasive method for diagnosing atherosclerosis [32]. Carotid intima-media

thickness is a structural change in the vascular system visualised by ultrasonography, and it is a strong predictor of cardiovascular events [33]. According to Armeni *et al.*, arterial stiffness is increased in women with PCOS. It might be a mechanism through which PCOS increases the risk of CVD and hypertension [13].

In other research, which was conducted on young women with PCOS, early markers of atherosclerosis were studied using CVD markers assessed by ultrasonography, including: common carotid artery stiffness index and distensibility, and intima-media thickness. It was found that already in young age, women with PCOS exhibit changes in vascular elasticity even in the absence of classical risk factors for CVD, such as hypertension and obesity [34]. Regarding the contribution of individual PCOS features, hyperandrogenism and insulin resistance are the most significant predictors of arterial stiffness [13]. An attempt to explain the effects of hyperandrogenism on arterial stiffness is based on rats model – testosterone has influence on vascular contraction and interferes with oestradiol-mediated endothelium-dependent vasodilation [35]. Central arterial stiffness is characterised by excessive collagen in the vessel wall, an amount higher than the presence of elastin, induced by the inflammatory state and the increase in luminal pressure. Metal-proteinases also play an important role in degrading the matrix protein. Moreover, the glycation phenomenon makes collagen more rigid, reduces elastin, and stimulates inflammation in vessels [36].

Hyperandrogenaemia in women with PCOS is associated with an elevated blood pressure independently of the patient's age, insulin resistance, obesity, and dyslipidaemia [37]. Furthermore, Markopoulos *et al.* performed a study to examine hyperandrogenism in PCOS after menopause. They found that postmenopausal PCOS women are exposed to higher adrenal and ovarian androgen levels than non-PCOS women [38]. Puurunen *et al.*, based on the results of cross-sectional research, claimed that impaired glucose metabolism, increase ovarian androgen secretion, and chronic inflammation observed in premenopausal women with PCOS continue after their menopause [39]. In conclusion, hyperandrogenaemia might increase the risk of hypertension in postmenopausal women with PCOS.

Ethinylestradiol in combined hormonal contraceptives elevates the production of hepatic angiotensinogen, which causes an elevation of blood pressure via the rennin–angiotensin–aldosterone system, regardless of the route of administration [40]. Despite the evolution of new progestogens, only drospirenone has the antimineralocorticoid activity of endogenous progesterone, regardless of the ethinylestradiol dose present in hormonal contraceptives [41]. Therefore, systolic arterial hypertension is considered an unfavourable effect of contraceptives. That is why the use of hor-

monal contraceptives is not indicated for women with hypertension with or without PCOS, regardless of the route of administration or oestrogen type [42]. In the other hand, in another study, it was found that lowering androgen levels with a combined oral contraceptive resulted in lower arterial stiffness over a period of 12 months in women with PCOS [43]. In postmenopausal women, oestrogen replacement therapy ameliorated hyperandrogenicity, and this was accompanied by marked improvements in glucose homeostasis and lipoprotein profile [44]. In another study, women who took hormone replacement therapy had higher SHBG, and lower FAI levels were noted among postmenopausal women who developed CVD events [45].

## Conclusions

Available studies show that women with PCOS more frequently present features of metabolic syndrome and have increased cardiovascular risk factors, including hypertension. Patients with this syndrome should be screened for these civilisation diseases and educated about the lifestyle modifications that could prevent hypertension later in life [46, 47].

Further studies should broaden the knowledge concerning dependency between PCOS, hypertension, and other civilisation diseases.

## Disclosure

The authors report no conflict of interest.

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