

# Current aspects of polycystic ovary syndrome: A literature review

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## SUMMARY

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder with variable prevalence, affecting about one in every 15 women worldwide. The diagnosis of polycystic ovary syndrome requires at least two of the following criteria: oligoovulation and/or anovulation, clinical and/or biochemical evidence of hyperandrogenism and morphology of polycystic ovaries. Women with PCOS appear to have a higher risk of developing metabolic disorders, hypertension and cardiovascular disorders. The aim of this article was to present a review of the literature by searching the databases Pubmed and Scielo, focusing on publications related to polycystic ovaries, including its pathogenesis, clinical manifestations, diagnosis and therapeutic aspects, as well as its association with cardiovascular and arterial hypertensive disorders.

**Keywords:** polycystic ovary syndrome, hyperandrogenism, cardiovascular disorders, arterial hypertension.

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## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common gynecological endocrine disorder of unknown etiology, with a prevalence ranging from 8.7 to 17.8% in women of reproductive age.<sup>1</sup> Evidence suggests that PCOS phenotype may vary widely and is most commonly observed in the post-pubertal period.<sup>2</sup> Despite a diversity of phenotypes, women with PCOS are characterized by polycystic ovaries, chronic anovulation, hyperandrogenism and gonadotropin abnormalities.<sup>3,4</sup>

In addition to the characteristics that are inherent in PCOS, it is a common occurrence of metabolic and hormonal abnormalities associated with obesity, type 2 *diabetes mellitus* and dyslipidemia.<sup>5</sup> A combination of these characteristics lead to metabolic syndrome.<sup>6</sup> The variety of metabolic disturbances in PCOS may be related to a higher risk of developing cardiovascular disease.<sup>7</sup> This fact may explain a predisposition to arterial hypertension in women suffering from the syndrome.<sup>8</sup> Although the association between changes in arterial blood pressure and PCOS has still not been fully elucidated, the increased risk of hypertensive state may be explained by insulin resistance and

hyperandrogenism, even when adjusted for age, body mass index and other anthropometric parameters.<sup>9</sup>

The study of PCOS is one of the most important topics in female reproductive endocrinology, subject that has the experience of our research group with studies in rats in persistent estrus mimicking state of chronic anovulation.<sup>3</sup> Although the syndrome has been widely investigated, its definition and pathophysiological aspects are still highly controversial. Therefore, the aim of the current study was to conduct a non-systematic review of published literature through PubMed and SciELO search. Publications were related to polycystic ovaries, including the pathogenesis, clinical manifestations, diagnosis and therapeutic aspects of the disease, as well as its association with cardiovascular disease and arterial hypertension. The current study may also contribute to raise awareness about the risk of hypertension in patients with polycystic ovary syndrome.

## ETIOLOGY AND PATHOPHYSIOLOGY

Polycystic ovary syndrome is a chronic disorder with unknown etiology that was first described in 1935 by Stein

and Leventhal. It is a reproductive, heterogeneous and metabolic disorder.<sup>10</sup> The prevalence of the disorder ranges from 8.7 to 17.8% in women of reproductive age.<sup>1</sup> The first clinical manifestations of PCOS are present in adolescence. However, there is evidence that the disease has its origin in the intrauterine environment, indicating genetic involvement.<sup>11</sup> Some studies including a study by Soter et al.,<sup>12</sup> have demonstrated a definite influence of interleukin-6 and interleukin-10 gene polymorphisms, interferon- $\gamma$  and transforming growth factor- $\beta$ 1 in the development of PCOS, although no clear pattern of inheritance has been identified.<sup>12</sup> Other causal factors are epigenetic exposures, highlighting the association between intrauterine exposure and maternal androgens and phenotypes related to the syndrome.<sup>13</sup> Ethnic variations in PCOS may be associated with environmental factors, such as socioeconomic conditions and lifestyle.<sup>14</sup>

Despite a large number of research studies, pathogenesis of PCOS still needs further elucidation.<sup>15</sup> However, some pathophysiological mechanisms are known, e.g. alterations in the secretion of gonadotropin-releasing hormone, defect in androgen synthesis and development of insulin resistance.<sup>16</sup> One of the numerous theories proposed to explain pathogenesis of the syndrome is the disturbance of the hypothalamic-pituitary axis, resulting in disarranged gonadotropin secretion by the hypothalamus with a consequent elevation of luteinizing hormone (LH) levels and normal and/or low follicle-stimulating hormone (FSH) levels.<sup>14</sup>

A number of studies have also indicated that insulin resistance is the key pathophysiological element for development of the syndrome. Insulin acts synergistically with LH to increase androgen production in the theca cell of the ovary.<sup>17</sup> Another site for androgen production is the adrenal cortex, due to abnormalities in cortical steroidogenesis promoted by stimulation of adrenocorticotropic hormone.<sup>18</sup> And these excess androgen levels, mainly testosterone, androstenedione and dehydroepiandrosterone sulfate, cause premature atresia of ovarian follicles, forming multiple cysts and anovulation with persistent estrogen levels resulting from aromatization of androgens to estrogens without opposition of progesterone and associated with an increased risk of endometrial carcinoma.<sup>19,20</sup>

## CLINICAL MANIFESTATIONS AND DIAGNOSIS

In the Rotterdam Consensus, it was defined that at least two of the following three findings are required for diagnosis of PCOS: oligoovulation or chronic anovulation, clinical and/or laboratory evidence of hyperandrogenism,

and pelvic ultrasonography indicative of polycystic ovaries.<sup>10</sup> These criteria recognize that PCOS is a diagnosis of exclusion.<sup>21</sup> Therefore, to confirm this syndrome, disorders that mimic the clinical characteristics of PCOS must be excluded, such as thyroid disorders, hyperprolactinemia and non-classical congenital adrenal hyperplasia.<sup>22</sup>

Although PCOS has been traditionally considered a disorder that affects women in their reproductive years, clinical manifestations may be observed at menarche.<sup>23</sup> In addition, clinical complications vary according to different phenotypes, age, ethnicity and body weight.<sup>24</sup>

According to research studies, the classical PCOS phenotype is linked to hyperandrogenism, anovulation and polycystic ovaries. Symptoms usually worsen with time.<sup>25</sup> Among these characteristics, hyperandrogenism is considered a cardinal element for diagnosing this condition and to define a patient as hyperandrogenic may be of major clinical significance.<sup>26</sup> The clinical manifestation of hyperandrogenism in these women varies in different ethnic groups, with external manifestations like oily skin, acne, hirsutism, central obesity, and even androgenetic alopecia.<sup>22,27</sup>

The cardiovascular system of women with PCOS is affected, regardless of obesity, due to metabolic disturbance associated with the respective syndrome.<sup>28</sup> Factors such as dyslipidemia, diabetes and obesity are all potent risk factors for cardiovascular disease, explaining why women with PCOS are more predisposed to hypertension.<sup>8</sup>

## PCOS AND HYPERTENSION

In general, systemic arterial hypertension (SAH) is more common in PCOS patients. A study carried out by Stener-Victorin et al.<sup>28</sup> showed that the prevalence of hypertension was about 40% in this group of women. Insulin resistance is a potential determinant of the association between PCOS and hypertension. It plays a central role not only in the development of PCOS, but also in the development of cardiovascular disease.<sup>29</sup>

Researchers have invested in research studies to discover the underlying relationship between hypertension and endocrine disorder. One of the most well-accepted hypotheses is that such alterations are stimulated by insulin resistance.<sup>28</sup> Some authors demonstrated an inverse association between insulin sensitivity and systolic arterial pressure in the group of women with PCOS.<sup>30</sup>

Insulin resistance leads to hyperinsulinemia and amplification of LH action in theca cells, with a consequent increase in androgen levels (Figure 1).<sup>19,20</sup> In experimental models, some authors have also demonstrated that the

adrenal gland of the rat in persistent estrus resembles PCOS. A higher proliferative activity occurred in the reticular zone of the adrenal gland, producer of androgens in humans, in comparison to controls.<sup>3</sup> Androgen levels may directly regulate the renin-angiotensin system of the proximal renal tubule and increase reabsorption flow rate, thus increasing extracellular volume and blood pressure.<sup>7,31</sup>

A long-term follow-up study carried out by Wild et al.<sup>32</sup> suggested an increased prevalence of hypertension in patients with PCOS. However, it did not evaluate the association between PCOS syndrome and the increased risk of morbidity and mortality from coronary artery disease.<sup>33,34</sup> Nevertheless, these results suggest that women with polycystic ovary syndrome should be screened for hypertension at a younger age.<sup>35</sup>

## ANIMAL MODEL

A study of women with polycystic ovaries has some ethical limitations. Therefore, there has been a search for appropriate experimental models that mimic PCOS.<sup>36</sup> During the last decades, researchers have used diverse animal models, such as rats, mice, hamsters, guinea pigs and subhuman primates to study the reproductive cycle, ovarian morphology and hormonal changes.<sup>37</sup> However, the animal model that has the morphology and endocrinology most similar to humans is the rat.<sup>38</sup>

Rats are polyestrous animals, i.e., these animals have regular and consecutive estrous cycles, manifested by morphological changes in the ovaries, uterus, vagina and mammary glands. These cycles last from 4 to 6 days and

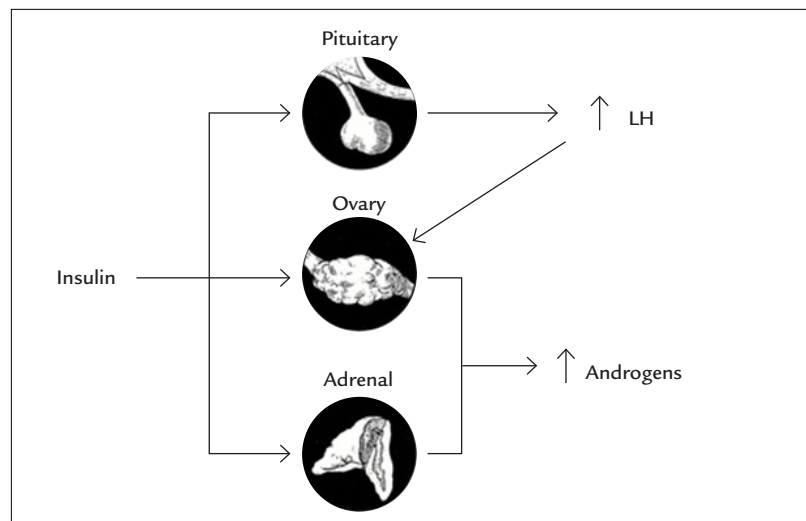
are easily observed, including proestrus, estrus, metaestrus and anestrus, with a mean pregnancy period of 21 days.<sup>39,40</sup>

Nevertheless, interruption of the rat estrous cycle, characterized by persistent vaginal keratinization or persistent estrus, is different from the short period of sexual receptivity named estrus or heat. The rat model was more widely studied by Barraclough in 1961, who characterized the period of most intense hypothalamic sensitivity. That author used only a subcutaneous injection of androgen (testosterone propionate at a dose of 1.25 mg). Thus, a simple s.c. injection of 1.25 mg of testosterone propionate administered to female rats during the first 5 days of life induced persistent estrus in all animals.<sup>39,41,42</sup>

These animals in adulthood present anovulation, higher LH secretion, polycystic ovaries and aggressive behavior when in contact with males, thus there is a resemblance to the human condition of polycystic ovary syndrome.<sup>18,40</sup> Furthermore, rats in persistent estrus may have hypertension, as shown in a study conducted by Gontijo et al.<sup>8</sup> Those authors showed that rats in persistent estrus had a significant increase in arterial pressure, in comparison to rats in the control group.<sup>8</sup>

## TREATMENT

Regarding treatment, it is recommended to start with aggressive diet/lifestyle modifications which may lead to weight loss, improve anovulation and indirectly cause a reduction in systolic arterial pressure.<sup>33</sup> If weight loss is insufficient to correct anovulation and decrease arterial pressure, drug treatment should be administered in order



**FIGURE 1** The influence of insulin in the amplification of LH and increase in androgen levels.

Source: Adapted from Dunaif.<sup>19</sup>

to correct the signs and symptoms. Despite a lack of consensus on the treatment of cardiovascular disease in women with PCOS, target therapy for hypertension in the PCOS population is similar to treatment given to patients without the syndrome.<sup>25</sup>

## CONCLUSION

Women with PCOS, in addition to anovulation and infertility, have an increased risk of developing hypertension and cardiovascular disease in association with metabolic syndrome. The diagnosis of PCOS is fundamentally clinical. Treatment of PCOS is limited to management of signs and symptoms since the etiology of the disorder is unknown. There is a need for further studies to understand the pathophysiology of PCOS and the development of high blood pressure in women suffering from the disorder.

## RESUMO

Aspectos atuais da síndrome do ovário policístico: uma revisão da literatura

A síndrome dos ovários policísticos (SOP) é uma desordem endócrina heterogênea com prevalência variável, que afeta cerca de uma em cada 15 mulheres no mundo. O diagnóstico da SOP requer, pelo menos, dois dos seguintes critérios: oligo-ovulação e/ou anovulação, evidência clínica e/ou bioquímica de hiperandrogenemia e morfologia dos ovários policísticos. As mulheres com SOP parecem ter um risco mais elevado de desenvolver distúrbios metabólicos, hipertensão e doenças cardiovasculares. O objetivo deste artigo foi apresentar uma revisão da literatura por meio de pesquisa nas bases de dados PubMed e Scielo, focada em publicações relacionadas com ovários policísticos, incluindo patogênese, manifestações clínicas, diagnóstico e aspectos terapêuticos, bem como associação com doenças cardiovasculares e hipertensão arterial.

**Palavras-chave:** síndrome do ovário policístico, hiperandrogenismo, distúrbios cardiovasculares, hipertensão arterial.

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