



## Review article

## A new look at the polycystic ovary syndrome

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## ABSTRACT

**Introduction:** Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age. Currently, the occurrence of PCOS is estimated at 6%–25% depending on the recognition criteria used.

**Aim:** The aim of the study is to discuss the clinical picture and PCOS diagnosis criteria, which are a constant subject of debate among scientists and clinicians.

**Material and methods:** The paper was based on the available literature of the subject, magazines and the latest guidelines.

**Results and discussion:** The crucial criterion for the diagnosis of PCOS is hyperandrogenization, as well as ovulation and infertility disorders. The most common clinical manifestation of hyperandrogenisation in PCOS is hirsutism, and more rarely, acne and androgenetic alopecia. Patients with PCOS also have metabolic disorders such as overweight, obesity, hyperinsulinism, insulin resistance, increased risk of: glucose intolerance and type 2 diabetes, hypertension, dyslipidemia, atherosclerosis and cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, additionally symptoms of depression and anxiety, eating disorders and reduced quality of life. The Rotterdam criteria from 2003 are the most widely accepted (two of the three criteria have to be met): hyperandrogenism (clinical and/or biochemical); oligoovulation or lack of ovulation; presence of polycystic ovaries in ultrasound examination.

**Conclusions:** Patients have hormonal and metabolic disorders what causes problems with the standardized definition of PCOS. Various phenotypes are found in PCOS. The exact pathogenesis of PCOS has not yet been clarified. Diagnosis, prophylaxis and treatment of PCOS should be the primary task of endocrinologists, gynecologists and psychologists.

## 1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most frequently diagnosed endocrinopathies in women of reproductive age. Different criteria are used to recognize PCOS, depending on used, the occurrence of PCOS is estimated currently at 6%–25%. In 1935 it was defined as the Stein–Leventhal syndrome in 7 women with menstrual irregularities, hirsutism, obesity and significantly enlarged, cystic ovaries.<sup>1</sup> In 1958 the elevated concentration of luteinizing hormone (LH) in women urine with changes in both ovaries was described for the first time.<sup>2</sup> Over time, this led to the emergence of crucial criterion for the PCOS diagnosis, detection of hyperandrogenisation in patients.<sup>3</sup> The main abnormalities in PCOS in addition to the excess androgens include ovulation disorders and metabolic disorders (overweight and obesity), hyperinsulinism, insulin resistance and increased risk of glucose intolerance and type 2 diabetes, hypertension, dyslipidemia, atherosclerosis and cardiovascular disease, additionally obstructive sleep apnea, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Nowadays, more and more attention is being paid to the occurrence of symptoms of depression and anxiety, eating disorders and reduced quality of life in women suffering from PCOS.<sup>1,4</sup>

## 2. AIM

The aim of the study is to discuss the clinical picture and PCOS diagnosis criteria.

## 3. MATERIAL AND METHODS

The paper was based on the available literature of the subject, magazines and the latest guidelines.

## 4. DISCUSSION

Various clinical symptoms in patients result in a variety of clinical features:

- hirsutism,
- acne and androgenetic alopecia,
- menstrual disorders and infertility,
- metabolic disorders,
- nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH),
- obstructive sleep apnea (OSA),
- depression and symptoms of anxiety,
- eating disorders,
- reduced quality of life (QoL).

### 4.1. Hirsutism

Hirsutism (the occurrence of male hair overgrowth in women) is the most common clinical manifestation of hyperandrogenisation in women with PCOS (facial hair,

chest, nipples, abdomen, cross section, vulvar area). It is rated that the incidence of hirsutism is 7 times more frequent in the PCOS population than in the general population.<sup>5</sup> Hirsutism is caused by either the increased formation of androgens or increased sensitivity of hair follicles to androgens. For quantitative clinical assessment of hirsutism the scale was developed by Ferriman and Gallwey. It is a subjective scale, assessing the density of hair in nine androgen-dependent areas of the body from 0 (lack of hair) to 4 (extensive hair growth).<sup>6</sup> In Caucasian women, identifying 8 or more points on this scale allows for a diagnosis of hirsutism, and according to the 2008 recommendations of the Endocrine Society requires further diagnostic tests.<sup>7</sup> Currently the most successful method of assessing hirsutism is the Ferriman–Gallwey scale.<sup>6</sup> The results of studies on hirsutism in women with PCOS demonstrated that its presence does not correlate with ovulation disorders, but it can predict the manifestation of infertility and metabolic disorders in this group of women.<sup>8,9</sup> It seems interesting that, in women with abdominal obesity more intense hirsutism is commonly observed.<sup>10</sup>

### 3.2. Acne and androgenetic alopecia.

In addition to hirsutism, there are other clinical manifestations of hyperandrogenisation in women with PCOS. However, acne and androgenetic alopecia and virilization symptoms such as increased muscle mass, lowering of the voice or enlargement of the clitoris are more often caused by ovarian or adrenal tumors and severe insulin resistance.<sup>11</sup> It is estimated, that acne depending on ethnicity and age, is recognized from 14% to 25% women with PCOS.<sup>12</sup> The severity of androgenetic alopecia in women can be evaluated using the Ludwig scale.<sup>13</sup> However, some studies have shown that hirsutism is a better marker of hyperandrogenisation in PCOS, compared to acne and androgenetic alopecia.<sup>14</sup> A correct diagnosis of these abnormalities is very important, it is necessary to have a subjective and objective examination of patients, including age in which symptoms appeared, their rate of accumulation, previous use of drugs (anabolic agents) and fluctuations in body weight and family occurrence of ailments.

### 3.3. Menstrual disorders and infertility

One of the basic symptoms of PCOS, which for the first time described Stein and Leventhal was infertility.<sup>15</sup> It is estimated that PCOS is the most frequent cause of ovulation and anovulation disorders, accounting for 90%–95%, and epidemiological studies on infertility in women have shown that infertility caused by anovulation accounts for up to 40% of cases.<sup>1,16</sup> Studies on women with PCOS have shown that in this group almost 50% of them demonstrate primary infertility, and 25% secondary infertility.<sup>17</sup> The basic mechanism of infertility in PCOS is considered to be a prolonged term of oligo- or anovulation, significant is also reduced egg cell competence and metabolic disorders.<sup>18,19</sup> Among the causes of infertility one should also take into account the cervical factor, uterine infertility and endome-

triosis, obstruction of the fallopian tubes, pelvic inflammatory disease (PID) and male factor.<sup>20</sup>

### 3.4. Metabolic disorders

Overweight or obesity are the frequent clinical features of the syndrome and occur in 30%–70% of patients with PCOS.<sup>21</sup> There is now a gradual increase in obesity worldwide, especially ventral, which is influenced by hereditary factors (multigenetic inheritance) and environmental factors, mainly related to low physical activity, poor quality and quantity of diet and cultural factors (in around 70%).<sup>22</sup> With increasing obesity, there is a gradual increase in the prevalence of PCOS, and adult women with PCOS, overweight and obesity have more often menstrual disorders than women with normal body weight.<sup>23,24</sup> The occurrence of obesity in PCOS is associated with the fertility disorders (difficulty in getting pregnant, more often miscarriages).<sup>25</sup> Abdominal obesity affects the PCOS phenotype, causes hyperandrogenemia with increased production of testosterone and other androgens and with reduced SHBG concentration and increased bioavailability of androgens in target tissues.<sup>24,26</sup> Women with overweight and obesity are more exposed to the development of insulin resistance, in other words the condition in which tissues are less sensitive to the influence of endogenous and exogenous insulin, often despite hyperinsulinaemia and the biological reaction to insulin is inadequate in the metabolism of carbohydrates, proteins and lipids. The increased concentration of free fatty acids released from adipose tissue into the circulation leads to increased storage of lipids in the liver, skeletal muscles and  $\beta$ -cells of the pancreas.<sup>27,28</sup> In the group of women with PCOS increasing BMI causes the risk of developing insulin resistance increases from 11%–50% in women with BMI below 25 kg/m<sup>2</sup> to 62%–80% in women with BMI over 30 kg/m<sup>2</sup>.<sup>29</sup> Obesity in adolescents and adult women with PCOS increases the risk of impaired glucose tolerance (IGT) and type 2 diabetes (type 2 diabetes mellitus – T2DM) and is associated with a higher incidence of metabolic syndrome (MS) in this group of patients.<sup>30,31</sup> It is estimated, that the risk of T2DM in PCOS is 3–7 times higher than in a group of healthy women appropriately selected in terms of age and weight.<sup>32,33</sup> Women with PCOS are at risk of cardiovascular complications in older age.<sup>34</sup> In the group of patients with PCOS occurs abnormal lipid profile – the growth of triglycerides, low density lipoproteins (LDL) and the decrease of high density lipoproteins (HDL), and in women with insulin resistance as well as obesity, these changes are more intense. By some scientists, PCOS is called a variant of the MS. Epidemiological studies have not shown an increased mortality in women with PCOS.<sup>35</sup>

### 3.5. Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

NAFLD and NASH are chronic liver diseases, which appears in 17%–33% in the Western world population. In NAFLD infiltration of the liver cell with excess fat is observed (steatosis), NASH is developed in a subgroup of pa-

tients with NAFLD, in which appears to hepatic steatosis and inflammation and damage to hepatocytes (after excluding other causes of liver diseases, it means toxic, virus infection, autoimmune and genetic diseases, etc.). In patients with the primary NAFLD/NASH insulin resistance is observed more often.<sup>36</sup> In the pathogenesis of PCOS, insulin resistance and compensatory hyperinsulinemia are also important. The prevalence of NAFLD in the population of women with PCOS is approximately 40%. Excess androgens may be an additional factor contributing to the development of NAFLD in PCOS.<sup>37,38</sup> Studies show that PCOS may increase the risk of developing NAFLD, and fatty liver disease may be a PCOS risk factor.<sup>39,40</sup>

### 3.6. Obstructive sleep apnea

OSA in the general population occurs at a frequency of approximately 17%–26% in men and 9%–28% in women, while in overweight persons (BMI  $\geq$  25 kg/m<sup>2</sup>) the risk of mild and moderate OSA increases from 41% to 58%.<sup>41,42</sup> The risk of developing OSA in women with PCOS increases to similar frequency as in men. A higher incidence of OSA may depend on hyperandrogenism, which is the main feature of PCOS.<sup>43,44</sup> OSA and PCOS are associated with the co-occurrence of MS (obesity, hypertension, dyslipidemia, insulin resistance, IGT, T2DM) and impairment of quality of life (depression, fatigue, memory impairment). If undiagnosed, they increase the risk of cardiovascular disease and mortality. PCOS may precede and contribute to the development of OSA, while OSA may worsen the clinical symptoms of PCOS.<sup>42</sup>

### 3.7. Depression and symptoms of anxiety

In women with PCOS, symptoms of depression occur more frequently than in the control group, including severe episodes of depression and recurrent depression, as well as symptoms of anxiety and generalized anxiety disorder. Some studies suggest that the occurrence of these abnormalities may be related to obesity, insulin resistance, hyperandrogenisation and infertility. Disorders of the hypothalamic-pituitary-adrenal axis may also cause depression in the PCOS group, in which a higher concentration of cortisol after stress exposure was demonstrated compared to the control group. Screening for anxiety and depression in women with PCOS is recommended at the time of diagnosis.<sup>45,46</sup>

### 3.8. Eating disorders

Eating disorders (ED) include anorexia nervosa, bulimia (bulimia nervosa – BN), binge eating disorder (BED) and night eating syndrome. BED occurs at a frequency of around 2% in the general population. BED is a disorder occurring in patients with metabolic disorders which makes it particularly important for women with PCOS.<sup>47</sup> Studies have shown that patients with PCOS have an increased appetite, impaired impulse control and are dissatisfied with the appearance of their body. It has been shown that BED can cause weight gain, impaired insulin secretion and androgen overproduction. Literature review shows that among PCOS women there is an increased incidence of BN and binge

bouts compared to healthy women, and that among women with BN and BED detection polycystic ovaries in ultrasound is more likely. ED may have a negative effect on the outcome of PCOS treatment.<sup>48,49</sup> Studies have shown that dissatisfaction with the appearance of your body in adolescents is associated with the subsequent onset of depression, which explains the higher rates of depression symptoms among women with PCOS. For this reason, ED screening is recommended among women with symptoms of depression and anxiety and early psychotherapy is recommended in women with PCOS.

### 3.8. Reduced quality of life

Health related quality of life (HRQoL) is a subjective, multidimensional and time-dependent perception of well-being by the patient, regarding the space between the given person, their illness and the environment in which they live. The polycystic ovary syndrome questionnaire (PCOSQ) and its modified version (modified PCOSQ – MPCOSQ) are a measure of HRQoL developed specifically for use in women with PCOS. Symptoms of PCOS, including menstrual disorders and hyperandrogenemia, can lead to a significant reduction in the QoL, mood disorders, problems in marriage and social life and impairment of sexual functions.<sup>50</sup> The main factors lowering QoL in women with PCOS is low sexual satisfaction caused mainly by weight gain and hirsutism, acne, hair loss, mood disorders, irregular menstruation and infertility. There are reports that lifestyle changes, followed by weight loss and improved appearance, may improve the QoL of women with PCOS.<sup>51,52</sup>

Historically, the National Institutes of Health criteria were used to diagnose PCOS; the Rotterdam 2003 criteria are the most widely used today. PCOS is also diagnosed on the basis of the 2006 criteria of The Androgen Excess and PCOS Society (Table).<sup>10</sup>

Diagnosis of PCOS is problematic, among others because, patients with the syndrome have not only hormonal disorder not but also suffer from metabolic disorders. Despite numerous expert discussions metabolic disorders are

not in any of the criteria, despite the unmistakable relationship with PCOS.<sup>25</sup> The syndrome is distinguished by different phenotypes with high gonadotrophin concentration and normal insulinemia, as well as the lack of gonadotrophin secretion disturbances and hyperinsulinaemia.<sup>53,54</sup> The common cause of the development of the PCOS and MS are insulin resistance and hyperinsulinemia, so some scientists suggest that the MS should be included in the PCOS diagnosis criteria.<sup>55</sup>

## 5. CONCLUSIONS

PCOS is a clinical heterogeneous disease entity with unknown etiology being the subject of scientists' discussion. PCOS is the most common endocrine disorder among women of reproductive age, characterized by hyperandrogenism and infertility and affecting distant complications. Women with PCOS more often develop MS, and insulin resistance has crucial role in the pathogenesis of the syndrome. Women with PCOS have more frequent cardiovascular diseases, although it has not been clearly established whether their mortality increases. Diagnosis, prophylaxis and treatment of PCOS should be the primary task of endocrinologists, gynecologists and psychologists.

### Conflict of interest

The authors have no potential conflicts of interest.

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**Table. Diagnosis criteria of PCOS.**

| Definition, Year                       | PCOS recognition criteria <sup>a</sup>  |
|--|---|
| National Institutes of Health, 1990    | 1. Hyperandrogenism (clinical and/or biochemical)<br>2. Ovarian dysfunction (oligoovulation or lack of ovulation)   |
| Rotterdam (ESHRE/ASRM), 2003           | Presence of two of the following three criteria:<br>1. Hyperandrogenism (clinical and/or biochemical)<br>2. Ovarian dysfunction (oligoovulation or lack of ovulation)<br>3. Presence of polycystic ovaries in ultrasound examination <sup>b</sup> |
| Androgen Excess Society, 2006          | Presence of all of the below listed criteria:<br>1. Hyperandrogenism (clinical and/or biochemical)<br>2. Ovarian dysfunction (oligoovulation or lack of ovulation and/or presence of polycystic ovaries in ultrasound examination <sup>b</sup> )  |
| Androgen Excess and PCOS Society, 2009 | Presence of all of the below listed criteria:<br>1. Hyperandrogenism (clinical and/or biochemical)<br>2. Ovarian dysfunction (ovarian dysfunction and/or presence of polycystic ovaries in ultrasound examination <sup>b</sup> )                  |

Comments: <sup>a</sup> .....; <sup>b</sup> .....

## References

- 1 Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol*. 2014;6:1–13.
- 2 Wallace AM, Sattar N. The changing role of the clinical laboratory in the investigation of polycystic ovarian syndrome. *Clin Biochem Rev*. 2007;28(3):79–92.
- 3 Azziz R, Carmina E, Dewailly D, et al.; Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab*. 2006;91(11):4237–4245. <https://doi.org/10.1210/jc.2006-0178>.
- 4 Randeve HS, Tan BK, Weickert MO, et al. Cardiometabolic aspects of the polycystic ovary syndrome. *Endocr Rev*. 2012;33(5):812–841. <https://doi.org/10.1210/er.2012-1003>.
- 5 Spritzer PM, Barone CR, Oliveira FB. Hirsutism in polycystic ovary syndrome: Pathophysiology and management. *Curr Pharm Des*. 2016;22(36):5603–5613. <https://doi.org/10.2174/1381612822666160720151243>.
- 6 Sachdeva S. Hirsutism: Evaluation and treatment. *Indian J Dermatol*. 2010;55(1):3–7. <https://doi.org/10.4103/0019-5154.60342>.
- 7 Martin KA, Anderson RR, Chang RJ, et al. Evaluation and treatment of hirsutism in premenopausal women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2018;103(4):1233–1257. <https://doi.org/10.1210/jc.2018-00241>.
- 8 Ozdemir S, Ozdemir M, Gökemli H, Kiyici A, Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. *Acta Obstet Gynecol Scand*. 2010;89(2):199–204. <https://doi.org/10.3109/00016340903353284>.
- 9 Rausch ME, Legro RS, Barnhart HX, et al; for the Cooperative Multicenter Reproductive Medicine Network. Predictors of pregnancy in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2009;94(9):3458–3466. <https://doi.org/10.1210/jc.2009-0545>.
- 10 Azziz R, Carmina E, Dewailly D, et al; Task Force on the Phenotype of the Polycystic Ovary Syndrome of the Androgen Excess and PCOS Society. The androgen excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril*. 2009;91(2):456–488. <https://doi.org/10.1016/j.fertnstert.2008.06.035>.
- 11 Yuan C, Liu X, Mao Y, Diao F, Cui Y, Liu J. Polycystic ovary syndrome patients with high BMI tend to have functional disorders of androgen excess: a prospective study. *J Biomed Res*. 2016;30(3):197–202.
- 12 Lowenstein EJ. Diagnosis and management of the dermatologic manifestations of the polycystic ovary syndrome. *Dermatol Ther*. 2006;19(4):210–223. <https://doi.org/10.1111/j.1529-8019.2006.00077.x>.
- 13 Gupta M, Mysore V. Classifications of patterned hair loss: A Review. *J Cutan Aesthet Surg*. 2016;9(1):3–12. <https://doi.org/10.4103/0974-2077.178536>.
- 14 Ozdemir S, Ozdemir M, Gökemli H, Kiyici A, Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. *Acta Obstet Gynecol Scand*. 2010;89(2):199–204. <https://doi.org/10.3109/00016340903353284>.
- 15 Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol*. 1935;29(2):181–191. [https://doi.org/10.1016/S0002-9378\(15\)30642-6](https://doi.org/10.1016/S0002-9378(15)30642-6).
- 16 Bhattacharya S, Porter M, Amalraj E, et al. The epidemiology of infertility in the North East of Scotland. *Hum Reprod*. 2009;24(12):3096–3107. <https://doi.org/10.1093/humrep/dep287>.
- 17 Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. *Int J Womens Health*. 2015;7:745–763. <https://doi.org/10.2147/IJWH.S70314>.
- 18 Wood JR, Dumesic DA, Abbott DH, Strauss JF 3rd. Molecular abnormalities in oocytes from women with polycystic ovary syndrome revealed by microarray analysis. *J Clin Endocrinol Metab*. 2007;92(2):705–713. <https://doi.org/10.1210/jc.2006-2123>.
- 19 Bolúmar F, Olsen J, Rebagliato M, Sáez-Lloret I, Bisanti L. Body mass index and delayed conception: a European multicenter study on infertility and subfertility. *Am J Epidemiol*. 2000;151(11):1072–1079. <https://doi.org/10.1093/oxfordjournals.aje.a010150>.
- 20 Rajashekar L, Krishna D, Patil M. Polycystic ovaries and infertility: Our experience. *J Hum Reprod Sci*. 2008;1(2):65–72. <https://doi.org/10.4103/0974-1208.44113>.
- 21 Bednarska S, Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: What's new? *Adv Clin Exp Med*. 2017;26(2):359–367. <https://doi.org/10.17219/acem/59380>.
- 22 Woźny Ł, Danikiewicz M, Stefanowicz M, et al. The importance of platelet phosphofructokinase (PFKP) rs6602024 polymorphism in pathogenesis of obesity. *Ann Acad Med Siles*. 2017;71:173–182. <https://doi.org/10.18794/aams/64163>.
- 23 Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93(1):162–168. <https://doi.org/10.1210/jc.2007-1834>.
- 24 Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. *BjOG*. 2006;113(10):1148–1159. <https://doi.org/10.1111/j.1471-0528.2006.00990.x>.
- 25 Kruszyńska A, Słowińska-Strzednicka J. Progress in diagnosis and treatment of polycystic ovary syndrome. *Post N Med*. 2008;3:148–153 [in Polish].
- 26 Pasquali R. Obesity and androgens: facts and perspectives. *Fertil Steril*. 2006;85(5):1319–1340. <https://doi.org/10.1016/j.fertnstert.2005.10.054>.
- 27 Savage DB, Petersen KF, Shulman GI. Disordered lipid metabolism and the pathogenesis of insulin resistance. *Physiol Rev*. 2007;87(2):507–520. <https://doi.org/10.1152/physrev.00024.2006>.
- 28 Turner N, Cooney GJ, Kraegen EW, Bruce CR. Fatty acid metabolism, energy expenditure and insulin resistance in muscle. *J Endocrinol*. 2014;220(2):T61–79. <https://doi.org/10.1530/JOE-13-0397>.
- 29 Carmina E. Metabolic syndrome in polycystic ovary syndrome. *Minerva Ginecol*. 2006;58(2):109–114.
- 30 Baldani DP, Skrgatic L, Ougouag R. Polycystic ovary syndrome: Important underrecognised cardiometabolic risk factor in reproductive-age women. *Int J Endocrinol*. 2015;2015:786362. <https://doi.org/10.1155/2015/786362>.
- 31 Stovall DW, Bailey AP, Pastore LM. Assessment of insulin resistance and impaired glucose tolerance in lean women with polycystic ovary syndrome. *J Womens Health*. 2011;20(1):37–43. <https://doi.org/10.1089/jwh.2010.2053>.

- <sup>32</sup> Ramos RB, Spritzer PM. FTO gene variants are not associated with polycystic ovary syndrome in women from Southern Brazil. *Gene*. 2015;560 (1):25–29. <https://doi.org/10.1016/j.gene.2015.01.012>.
- <sup>33</sup> Flannery CA, Rackow B, Cong X, Duran E, Selen DJ, Burgert TS. Polycystic ovary syndrome in adolescence: impaired glucose tolerance occurs across the spectrum of BMI. *Pediatr Diabetes*. 2013;14(1):42–49. <https://doi.org/10.1111/j.1399-5448.2012.00902.x>.
- <sup>34</sup> Rachoń D, Teede H. Ovarian function and obesity – inter-relationship, impact on women’s reproductive lifespan and treatment options. *Mol Cell Endocrinol*. 2010;316(2):172–179. <https://doi.org/10.1016/j.mce.2009.09.026>.
- <sup>35</sup> Wild RA, Carmina E, Diamanti-Kandarakis E, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AEPCOS) Society. *J Clin Endocrinol Metab*. 2010;95(5):2038–2049. <https://doi.org/10.1210/jc.2009-2724>.
- <sup>36</sup> Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol*. 2010;53(2):372–384. <https://doi.org/10.1016/j.jhep.2010.04.008>.
- <sup>37</sup> Baumeister SE, Völzke H, Marschall P, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. *Gastroenterology*. 2008;134(1): 85–94. <https://doi.org/10.1053/j.gastro.2007.10.024>.
- <sup>38</sup> Cerda C, Pérez-Ayuso RM, Riquelme A, et al. Nonalcoholic fatty liver disease in women with polycystic ovary syndrome. *J Hepatol*. 2007;47(3):412–417. <https://doi.org/10.1016/j.jhep.2007.04.012>.
- <sup>39</sup> Setji TL, Holland ND, Sanders LL, Pereira KC, Mae Diehl A, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2006;91(5):1741–1747. <https://doi.org/10.1210/jc.2005-2774>.
- <sup>40</sup> Rocha ALL, Faria LC, Guimarães TCM. Non-alcoholic fatty liver disease in women with polycystic ovary syndrome: systematic review and meta-analysis. *J Endocrinol Invest*. 2017;40(12):1279–1288. <https://doi.org/10.1007/s40618-017-0708-9>.
- <sup>41</sup> Tasali E, Van Cauter E, Ehrmann DA. Polycystic ovary syndrome and obstructive sleep apnea. *Sleep Med Clin*. 2008;3(1):37–46. <https://doi.org/10.1016/j.jsmc.2007.11.001>.
- <sup>42</sup> Kahal H, Kyrou I, Tahrani AA, Randeve HS. Obstructive sleep apnoea and polycystic ovary syndrome: A comprehensive review of clinical interactions and underlying pathophysiology. *Clin Endocrinol (Oxf)*. 2017;87(4):313–319. <https://doi.org/10.1111/cen.13392>.
- <sup>43</sup> Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab*. 2001;86(2):517–520.
- <sup>44</sup> Gopal M, Duntley S, Uhles M, Attarian H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. *Sleep Med*. 2002;3(5):401–404. [https://doi.org/10.1016/S1389-9457\(02\)00033-3](https://doi.org/10.1016/S1389-9457(02)00033-3).
- <sup>45</sup> Cooney LG, Dokras A. Depression and anxiety in polycystic ovary syndrome: Etiology and treatment. *Curr Psychiatry Rep*. 2017;19(11):83. <https://doi.org/10.1007/s11920-017-0834-2>.
- <sup>46</sup> Dokras A. Mood and anxiety disorders in women with PCOS. *Steroids*. 2012;77(4):338–341. <https://doi.org/10.1016/j.steroi.2011.12.008>.
- <sup>47</sup> Lee I, Cooney LG, Saini S, et al. Increased risk of disordered eating in polycystic ovary syndrome. *Fertil Steril*. 2017;107(3):796–802. <https://doi.org/10.1016/j.fertnstert.2016.12.014>.
- <sup>48</sup> Paganini C, Peterson G, Stavropoulos V, Krug I. The overlap between binge eating behaviors and polycystic ovarian syndrome: an etiological integrative model. *Curr Pharm Des*. 2018;24(9):999–1006. <https://doi.org/10.2174/138161282466171204151209>.
- <sup>49</sup> Bernadett M, Szemán-NA. Prevalence of eating disorders among women with polycystic ovary syndrome. *Psychiatr Hung*. 2016;31(2):136–145.
- <sup>50</sup> Bazarganipour F, Taghavi SA, Montazeri A, Ahmadi F, Chaman R, Khosravi A. The impact of polycystic ovary syndrome on the health-related quality of life: A systematic review and meta-analysis. *Iran J Reprod Med*. 2015;13(2):61–70.
- <sup>51</sup> Khomami MB, Tehrani FR, Hashemi S, Farahmand M, Azizi F. Of PCOS symptoms, hirsutism has the most significant impact on the quality of life of Iranian women. *PLoS ONE*. 2015;10(4):e0123608. <https://doi.org/10.1371/journal.pone.0123608>.
- <sup>52</sup> Hahn S, Janssen OE, Tan S, et al. Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *Eur J Endocrinol*. 2005;153(6):853–860. <https://doi.org/10.1530/eje.1.02024>.
- <sup>53</sup> Lashen H. Role of metformin in the management of polycystic ovary syndrome. *Ther Adv Endocrinol Metab*. 2010;1(3):117–128. <https://doi.org/10.1177/2042018810380215>.
- <sup>54</sup> Park CH, Chun S. Association between serum gonadotropin level and insulin resistance-related parameters in Korean women with polycystic ovary syndrome. *Obstet Gynecol Sci*. 2016;59(6):498–505. <https://doi.org/10.5468/ogs.2016.59.6.498>.
- <sup>55</sup> McCartney CR, Marshall JC. Polycystic ovary syndrome. *N Engl J Med*. 2016;375(1):54–64. <https://doi.org/10.1056/NEJMcpl514916>.