PCOS and Hyperprolactinemia: Conflicting Conditions or Comorbidities?

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Abstract

Currently, hyperprolactinemia is considered as a condition to be excluded during the diagnosis of polycystic ovarian syndrome (PCOS), because it often demonstrates clinical signs similar to PCOS. However, some publications have reported “the prevalence of hyperprolactinemia in PCOS,” which does not agree with the statement above statement. The publications presented in this review demonstrate conflicting approaches to considering the association of hyperprolactinemia and PCOS. On the one hand, the current consensus on the diagnosis of PCOS assumes the exclusion of patients with hyperprolactinemia, and on the other hand, some authors consider hyperprolactinemia as an acceptable condition and estimate its prevalence in PCOS. Based on the analysis of the literature, we have demonstrated a contradictory attitude towards the association between hyperprolactinemia and PCOS. To overcome the contradiction, we consider it appropriate to use the term “potential PCOS” before the final assessment of the contribution of hyperprolactinemia to the development of symptoms similar to PCOS. The final diagnosis of PCOS in the presence of hyperprolactinemia is possible only after its correction and reassessment of all symptoms. (**International Journal of Biomedicine. 2021;11(4):480-483.**)

Key Words: obstetricians-gynecologists • stress • professional burnout • biomarkers

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Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in the female population.⁽¹⁾ Currently, hyperprolactinemia is considered as a condition to be excluded during the diagnosis of PCOS, because it often demonstrates clinical signs similar to PCOS. However, some publications have reported “the prevalence of hyperprolactinemia in PCOS,” which does not agree with the statement above statement.

The purpose of this brief review was to systematize the available conflicting data on the associations between hyperprolactinemia and PCOS.

The information search was conducted using Internet resources (PubMed, EMBASE) and literature sources for the years 2000-2021.

The epidemiology of PCOS is well studied, but the prevalence of the syndrome varies from 2.2% to 15%,⁽²⁻⁶⁾ depending on the diagnostic criteria used and the characteristics of the population sample. In women with an irregular menstrual cycle, the incidence of PCOS ranges from 16.5% to 46%,^(7,8) and with anovulatory infertility - from 55% to 91%.^(9,10) Diagnosis of PCOS is based on the registration of clinical and laboratory manifestations of hyperandrogenism, assessment of menstrual and ovulatory function, as well as ovarian morphology using ultrasound. The Harmonized Criteria of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ASRM/ESHRE), adopted in Rotterdam (2003),⁽¹¹⁾ are currently used to diagnose PCOS. According to this consensus, the diagnosis of PCOS can be confirmed by the presence of at least two of the following three criteria: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, polycystic ovarian morphology on ultrasound. This approach to the diagnosis of PCOS is confirmed in the international recommendations for

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the assessment and treatment of PCOS, presented in 2018.⁽¹²⁾ Clinical signs of hyperandrogenism include hirsutism, acne, and androgenetic alopecia. According to various sources, hirsutism occurs in the majority of women with PCOS^(13–16) and acne in 15%–25% of them;^(17,18) however, their diagnostic significance as a marker of hyperandrogenism is debatable.^(19,20) Although androgenic alopecia is considered a sign of PCOS, the relationship between these states has not been definitively determined.⁽²¹⁾ Among the reproductive disorders associated with PCOS, the most important are infertility^(22,23) and miscarriage, as well as failures with IVF.^(24,25) At the same time, several scientists consider PCOS as a factor that does not affect the frequency of miscarriages.⁽²⁶⁾ In patients with PCOS, the risk of developing preeclampsia and hypertension during pregnancy is up to four times higher, and the risk of premature birth is almost twice as high.⁽²⁷⁾ Along with reproductive disorders, PCOS is associated with insulin resistance, impaired glucose tolerance, and diabetes mellitus, as well as cardiovascular diseases, all of which determine the long-term consequences of this disease.⁽²⁸⁾

The previous and current consensuses on the diagnosis of PCOS require the exclusion of other diseases with similar symptoms, including hyperprolactinemia. Hyperprolactinemia is found in almost 30% of women with secondary amenorrhea and is a common cause of amenorrhea and infertility. There are many reasons for the development of this condition: physiological (pregnancy, lactation, exercise), taking medications that disrupt the production of dopamine (for example, antipsychotics, antidepressants, sequential contraceptives, antihypertensives, and others), primary hypothyroidism, and chronic renal failure.⁽⁷⁾ Like PCOS, hyperprolactinemia is often the cause of reproductive loss.⁽²⁹⁾ Hyperprolactinemia often demonstrates clinical signs similar to PCOS, and it is associated with excess androgen production by the adrenal glands in vivo and in vitro,^(30,31) suggesting a potential mechanism by which it may contribute to hyperandrogenism. Elevated prolactin levels are found in 6% of women with hirsutism.⁽³²⁾ Therefore, when diagnosing PCOS, it is necessary to exclude hyperprolactinemia as a disease with similar symptoms.

However, some authors evaluated “the prevalence of hyperprolactinemia in PCOS,” which contradicts the approved approaches to the diagnosis of PCOS. Thus, Filho et al.⁽³³⁾ detected hyperprolactinemia in 16% of patients with PCOS. The authors showed that hyperprolactinemia is not a clinical manifestation of PCOS but is caused by other etiological factors, which logically requires further examination for other causes of hyperprolactinemia. Hayashida et al.⁽³⁴⁾ found macroprolactinemia in 6% of cases in a group of 227 women with PCOS. In 2018, a study by Kyritsi et al.⁽³⁵⁾ reported that the prevalence of idiopathic hyperprolactinemia in a group of 76 PCOS patients reached 26%. A clinical case with twin sisters with signs of PCOS associated with idiopathic hyperprolactinemia was described by Goyal et al.⁽³⁶⁾ Several authors have suggested that PCOS causes hyperprolactinemia due to a relative hyperestrogenemia in anovulatory women.^(37,38) This hypothesis is supported by various experimental studies that have shown an increase in the secretion of prolactin

under the influence of estrogens.⁽³⁹⁾ Nevertheless, there are few studies on this topic, and none of them has convincingly demonstrated a clear pathogenetic link between PCOS and hyperprolactinemia.

Thus, the publications presented in this review demonstrate conflicting approaches to considering the association of hyperprolactinemia and PCOS. On the one hand, the current consensus on the diagnosis of PCOS assumes the exclusion of patients with hyperprolactinemia, and on the other hand, some authors consider hyperprolactinemia as an acceptable condition and estimate its prevalence in PCOS.

Conclusion

Hyperprolactinemia and PCOS are known as conditions with similar clinical manifestations, and current guidelines on PCOS diagnosis consider hyperprolactinemia as exclusion criteria. However, some authors indicate a proportion of patients with hyperprolactinemia and PCOS that does not correspond with the previously mentioned consensuses.

In our opinion, the data on the prevalence of hyperprolactinemia in women with signs of PCOS are of interest. However, it is better to use the term “potential PCOS” in such cases, and diagnose PCOS only when clinical signs of this syndrome occur after correction of hyperprolactinemia. According to this point of view, our brief review summarizes current research data assessing the frequency of hyperprolactinemia in “potential PCOS.” Nowadays, the literature regarding the prevalence of hyperprolactinemia in women with symptoms of PCOS is still unclear, and more studies are needed, including those designed to estimate asymptomatic hyperprolactinemia with the evaluation of macroprolactin.^(40,41) Several studies have shown that approximately 40% of patients with hyperprolactinemia have macroprolactinemia.^(42,43) Because macroprolactinemia is a common cause of hyperprolactinemia, routine screening for macroprolactin could eliminate unnecessary diagnostic testing and treatment.^(44,45)

Based on the analysis of the literature, we have demonstrated a contradictory attitude towards the association between hyperprolactinemia and PCOS. To overcome the contradiction, we consider it appropriate to use the term “potential PCOS” before the final assessment of the contribution of hyperprolactinemia to the development of symptoms similar to PCOS. The final diagnosis of PCOS in the presence of hyperprolactinemia is possible only after its correction and reassessment of all symptoms.

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Competing Interests

The authors declare that they have no competing interests.

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