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REVIEW PAPER / GYNECOLOGY

Prevalence and diagnosis of polycystic ovary syndrome (PCOS) in adolescents — what's new in 2023? Systematic review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting approximately 5 to 18% of women of reproductive age and 3 to 11% of teenagers. The diagnostic criteria used in adult patients are not suitable for the diagnosis of adolescent patients, because some of the features may be physiological for puberty, so research is still ongoing to improve the criteria for diagnosing PCOS in teenagers. Polycystic ovary syndrome is associated with hormonal and metabolic changes and may predispose to the occurrence of many other diseases, such as obesity, metabolic syndrome, hypertension, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Due to the high prevalence of PCOS and the various health problems it brings, it is necessary to select adolescent girls from the risk group, make an efficient diagnosis, start appropriate treatment, and lead the patient through a lifestyle change as soon as possible. Researchers' attention is increasingly focused on patients presenting with PCOS already in their teenage years. In our work, we want to look at the latest reports regarding the prevalence, pathophysiology and diagnosis of PCOS in adolescent girls.

Keywords: polycystic ovary syndrome; adolescent; oligomenorrhea; hirsutism; hyperandrogenism

INTRODUCTION AND BACKGROUND

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting approximately 5 to 18% of women of reproductive age, depending on the adopted criteria of diagnosis and ethnicity [1, 2]. Polycystic ovary syndrome is increasingly diagnosed in adolescence. It is estimated that this problem affects from 3 to 11% of teenagers [3]. Polycystic ovary syndrome in adult patients is diagnosed based on meeting two of the three Rotterdam criteria, such as oligoovulation or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian ultrasonography [4]. However, these criteria are not applicable in the diagnosis of adolescent girls, because some of the above features may be physiological for puberty [5]. Accordingly, in a publication by Ibanez et al. [6] new PCOS diagnostic guidelines were proposed, adapted to the age group of younger patients — irregular menstrual cycles and clinical and/or biochemical hyperandrogenism were indicated as diagnostic. In the criteria for the diagnosis of PCOS in adolescents proposed by Pena et al. [7] biochemical and/or clinical hyperandrogenism and irregular menstrual cycles were also assumed, while the evaluation of cycle irregularity was made dependent on the time elapsed since menarche. Polycystic ovary syndrome is associated with hormonal and metabolic changes in the patient's body, and therefore may predispose to the occurrence of many other diseases such as obesity, metabolic syndrome, hypertension, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD) [8–10]. Due to the high prevalence of PCOS and the various health problems it brings, it is necessary to select adolescent girls from the risk group, make an efficient diagnosis, start appropriate treatment, and lead the patient through a lifestyle change as soon as possible. Polycystic ovary syndrome research is increasingly focusing on the teenage population of patients. The frequency of occurrence of PCOS is still being studied and the diagnostic criteria refined to best meet the diagnostic needs of this age group. In our work, we want to focus and summarize the latest scientific reports on the prevalence and diagnosis of this particular group - adolescent patients with PCOS.

REVIEW

Methodology

A systematic review was conducted using the PubMed database using the terms (PCOS OR Polycystic Ovary Syndrome) AND (adolescence* OR girl*). The search was limited to papers published between 2022/07/01 and 2023/06/30. 139 publications were found. Two authors independently reviewed articles by title and abstract looking for studies on PCOS patients aged 9–23. Research that included only the adult population of patients (n = 82), case

reports (n = 1), systematic reviews and guidelines (n = 5), no full text (n = 2) were rejected. 49 papers on adolescent female patients were received. After reviewing the full text of the articles, 23 articles that met the inclusion criteria were selected. Differences in search results between authors were resolved through discussion. The search strategy is shown in Figure 1.

Prevalence and pathophysiology

Polycystic ovary syndrome is a disease that affects many women of childbearing age. The prevalence of PCOS varies depending on the age range of the population, ethnicity and the type of diagnostic criteria adopted. More and more studies show that this is not only a problem affecting young women, but it can have its beginnings in teenage years. In a population study of Korean women, the age-adjusted incidence of PCOS was found to be 2.8%, increasing in late teens, peaking at age 20 and beginning to decline at age 30 [11]. In a study of South Indian girls, the prevalence of PCOS was 6.8%. Most of the study participants diagnosed with PCOS had no prior knowledge of their disease (78.4%), while 6.8% had already been treated for PCOS. The source of knowledge about PCOS was most often teachers (37%), then doctors (31.5%), the Internet (11%) and friends (7.5%). Polycystic ovary syndrome awareness was higher among young women (84.9%) compared to adolescent girls (4.5%). Lack of information and publicity (63%) was considered the most important reason for the low level of awareness, which emphasizes the need for proper health education, as well as the implementation of programs to raise awareness and discuss the issues of PCOS among teenagers [12]. The study of patients aged 15–45 at Latifa Hospital, Dubai, UAE showed an increase in the annual point prevalence from 1.19% in 2020 to 2.72% in 2022, so the risk of being diagnosed with PCOS in the study population in 2022 increased 2.28 times compared to by 2020 [13]. A cross-sectional study of a population in India found a significant increase in irregular menstrual cycles in young girls during the second wave of COVID-19. In the study group, 11% of girls were diagnosed with PCOS. Insomnia, stress and depression were indicated as risk factors for irregular menstruation, and the importance of improving the lifestyle of young girls, which significantly affects their reproductive health, was emphasized [14]. In a study on the population of Iranian adolescents, it was noted that the prevalence of PCOS depends on the type of diagnostic criteria adopted and is 4.2% for Rotterdam, 3.6% for the National Institutes of Health (NIH), Androgen Excess–PCOS Society (AES) and Endocrine Society Clinical Practice (2013), 0.7% — European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) (2012) [15]. Among the tenth-grade schoolgirls in Guangzhou area, the prevalence

of PCOS was estimated at 3.86%. It was shown that among girls with obesity the frequency was much higher than among girls of normal weight. In addition, the incidence of PCOS in adolescents tends to increase slightly with age and gynecological age, but the difference was not statistically significant [16]. The prevalence depending on the research is presented in Figure 2.

The research also pays attention to groups of patients who should be given special care in the diagnostic process due to the increased risk of PCOS (Fig. 3). A cross-sectional study of a population of US children showed that patients with hidradenitis suppurativa (HS) were three times more likely to develop PCOS, therefore pediatric patients with HS and hyperandrogenism should be monitored for the presence of PCOS [17]. An important diagnostic clue for physicians providing pediatric care may also be the fact that daughters of mothers with PCOS have been shown to have higher levels of androgens during puberty. Therefore, it is necessary to observe those girls who, entering adulthood, may develop features that allow the diagnosis of PCOS [18]. A meta-analysis by Caiyi Long et al. [19] showed that the prevalence of PCOS among women < 25 years of age with type 2 diabetes was approximately 18% and was higher than among women without PCOS. The relationship between the occurrence of PCOS and Pilonidal Disease (PD) in teenage patients was also examined. It has been shown that adolescent women diagnosed with PD may have PCOS features, therefore, if PD and PCOS are suspected, the patient should be referred for further diagnostics to confirm the presence of PCOS. The prevalence rate among patients with PD and PCOS according to the original Rotterdam criteria was 26.1 [confidence interval (CI) 22.0–31.0] and 28.7 (CI 24.3–33.9) for patients with PCOS according to the modified Rotterdam criteria [20].

Despite the high prevalence of PCOS among women of reproductive age, we still do not know the exact etiology of this disease. Work is constantly underway to bring us closer to understanding the pathophysiology of PCOS, but it is certain that the formation of this syndrome has a multifactorial background. The Mendelian randomization (MR) study demonstrated the key role of obesity in children/adolescents on the pathophysiology of PCOS in adults. Moreover, overweight or obese adolescents were more likely to develop PCOS than overweight adults. In the group that included both adult and teenage patients, for each standard deviation increase in body mass index (BMI) (4.8 kg/m^2), the likelihood of PCOS increased by 2.76. Childhood weight had an independent effect on the likelihood of PCOS after accounting for adult body size [21]. Another study focused on the impact of childhood abuse on women's reproductive health, with particular emphasis on symptoms of polycystic

ovary syndrome. The study showed that across all subtypes of maltreatment, emotional abuse remained associated with PCOS, suggesting its unique impact on this endocrinopathy, although the reasons for this are still unknown and further research is needed in this area [22].

The causes of PCOS are also sought in genetic factors. The *miR-146a* (rs2910164) and *ADIPOQ* (rs182052) allelic variants have been shown to be associated with birthweight in SGA and may indicate an increased risk of health problems such as PCOS and obesity [23]. The protein encoded by the *YAP1* gene plays a key role in one of the main mechanisms regulating cell/organism metabolism and contributes to the pathogenesis of metabolic diseases, therefore, in a study by Lidak L et al. [24], it was decided to compare the frequency of single nucleotide variants (SNV) in the *YAP1* gene among adolescents with PCOS, adolescents at risk of developing PCOS and healthy adolescents. In this study, no significant associations were found between PCOS in adolescents and the five tested SNVs in the *YAP1* gene [24].

Diagnostics

Diagnosis of PCOS in adolescent girls is still a controversial and widely researched topic. There are many doubts about which features can still be considered physiological for the maturation process, and which go beyond the norm. Diagnostic criteria for adults do not correspond to the diagnosis of this specific group of adolescent patients. There are still ongoing studies on the differences in the diagnosis of adults and adolescents, cut-off points for diagnostic parameters, new parameters that may facilitate diagnosis.

To investigate the differences between PCOS in adult and teenage patients, a study was conducted that compared clinical, hormonal, biochemical and ultrasound parameters. Interestingly, this study did not find a statistically significant difference in PCOS between adults and adolescents. Menstrual cycles of teenage and adult PCOS patients did not differ significantly. In laboratory studies, the mean serum LH/FSH, free testosterone, and insulin ratios were significantly higher in both adults and adolescents with PCOS compared to the control group [25].

It is essential for the correct diagnostic process to define the diagnostic boundaries of PCOS in adolescents. This problem was investigated in an article published in the European Journal of Endocrinology. In a large, well-characterized cohort of adolescents, the cut-off values for modified Ferriman–Gallwey (mFG) score, free testosterone (free T), free androgen index (FAI), and menstrual cycle length were shown to be at lower percentiles than previously accepted. The normative limits are for mFG score — 1.0 (65^{th} percentile of the population),

free T — 23.4 pmol/L (71st percentile of the population), FAI — 3.6 (70th percentile of the population) and length of the menstrual cycle — 29 days (59th percentile of the population). In connection with the above results, it is necessary to look again at the diagnostic norms in the case of adolescent female population [26].

Anti-Mullerian hormone (AMH) is a widely studied parameter. Studies have shown that AMH was significantly higher in adolescents with PCOS than in controls [27–29]. Based on the meta-analysis, AMH cut-off values for the diagnosis of PCOS in adolescents were established — depending on the study, they were 6.1, 6.26, 7.03, 7.11, 7.2 and 7.25 ng/mL (diagnostic accuracy is 81% for specificity and 66.3% for sensitivity). This study showed that the AMH level test with an estimated cut-off point of 6–7 ng/mL can be used as a diagnostic test for PCOS in adolescents [27]. Another study examined AMH in adolescent patients with irregular menstrual cycles and found that the highest AMH concentrations were found in girls with a combination of oligomenorrhoea, hirsutism, and polycystic ovarian morphology (PCOM). Anti-Mullerian hormone levels significantly increased with the increase in clinical symptoms of PCOS in adolescent girls with oligomenorrhoea [28]. In a long-term longitudinal study published in eClinicalMedicine, it was shown that in girls with high serum AMH concentrations [AMH > 30.0 pmol/L (13.35 ng/mL)] in mid-childhood (7.2 yrs.), significantly higher concentrations can be observed in adolescence LH, LH/FSH ratio, testosterone levels, higher total number of follicles and more frequent irregular cycles. It has been suggested that AMH in early life may be a useful clinical tool to predict future ovarian activity, but further research is needed to clarify whether AMH in childhood may be a predictor of PCOS in adulthood [30] (Fig. 4).

Currently, many studies are also focused on the study of androgens in PCOS patients. One of the studies showed that adolescent girls with PCOS had higher serum levels of 11-hydroxyandrostenedione (11-OHA4) and 11-hydroxytestosterone (11-OHT) than control groups without PCOS. Additionally, it was shown that 11-oxyandrogens correlate with the severity of hirsutism among untreated PCOS patients, but not with indicators of dysmetabolism. However, testosterone predicted PCOS status better than 11-oxyandrogens, which, as ROC curve showed, do not seem to have clinical utility when it comes to helping in the diagnosis of PCOS [31]. In another study of adolescent patients with oligomenorrhea, the concentration of androstenedione (A4) was found to be higher in adolescents with oligomenorrhea compared to regularly menstruating patients and was higher in the presence of hirsutism [28].

According to the current guidelines, ultrasonography is not relevant in the diagnosis of PCOS in adolescents, but the possibility of using it in this group of patients is still being studied. It has been shown that the presence of PCOM in a patient increases the probability of infrequent menstruation 10 times [28]. A comparative study of ultrasound parameters showed significantly higher mean ovarian volume and mean number of follicles with increased stromal echogenicity in both adult and adolescent PCOS patients. In both groups, ovarian morphology was positively correlated with serum LH and free testosterone [25]. The thickness of the endometrial strip (EMS) among teenage patients was also studied and showed that the EMS was thinner in the PCOS group than in the control group. There was no difference in EMS thickness in the PCOS group when stratified by intermenstrual intervals, insulin resistance, and other biochemical factors [32].

Patients diagnosed with PCOS can be divided into groups depending on the PCOS phenotype. In the case of teenage patients, it was shown, that among the examined patients phenotype D (MI + PCOM-HA) was the most common phenotype and concerned 49.43% of patients, followed by phenotype A (MI + HA + PCOM; 22.72%), and phenotype B (MI + HA-PCOM; 14.20%) (Tab. 1). Analysis showed that hyperandrogenism in adolescents (A and B phenotypes) is associated with a more disturbed endocrine and metabolic profile than non-androgenic PCOS (D phenotype). Therefore, it is worth paying attention to this group of patients, providing them with early treatment, careful observation and recommending them to change their lifestyle to prevent the consequences of PCOS [33].

A research prepared by Kalra S et al. [34] emphasized the need for early diagnosis of PCOS, referral for appropriate care to improve reproductive, metabolic and general health in adolescents and young adults. For this purpose, a simple questionnaire was created that can be used as a screening tool for PCOS. The questionnaire is divided into three domains: Menstrual/Maternal, Metabolic, 'Misfit masculinity' (dermatological), and each domain consists of 3 possible symptoms that the patient may experience. According to the authors, an affirmative response to any two of the following three domains should prompt PCOS screening and referral to specialist health care. Such a form could be used in primary care to facilitate the identification of patients requiring further diagnosis for PCOS [34].

SUMMARY

Polycystic ovary syndrome is a disease affecting a growing number of adolescent girls and young women around the world, significantly affecting the mental health, reproductive health and quality of patient’s life. It is associated with many complications that significantly affect

the general health of the patient and require the involvement of multidisciplinary care. Due to the multimorbidity that affects a patient with PCOS, it is important to diagnose as early as possible, already in the teenage years, to start therapy and stop the metabolic sequence of PCOS consequences and to prevent distant complications in adult life. The etiology of PCOS remains unknown, but it is certainly complex and multifactorial. The influence of genetic, environmental and lifestyle factors is studied in order to understand the essence of this disease. We also know more and more about the causes of PCOS development, which may start long before birth. Further research is needed to identify the predisposing factors and causes of the development of polycystic ovary syndrome. There are ongoing discussions regarding the diagnosis of PCOS in adolescent girls and which criteria are appropriate to use in this age group. Studies examining the cut-off points of diagnostic parameters can provide us with a lot of new information regarding diagnostic procedures and clarify the adopted diagnostic limits. Detailed characterization of large groups of adolescent PCOS patients and careful analysis of data would be helpful in finding answers to many questions related to the occurrence of this syndrome among adolescents. The issue of the prevalence of PCOS in adolescent girls is undoubtedly a challenge both for doctors practicing direct care of patients and for researchers who face many unknowns to discover.

Article information and declarations

Author contributions

Karolina M. Jakubowska-Kowal — work design, article review, data collection, analysis and interpretation of results, manuscript preparation with input from all authors; Karolina J. Skrzynska — article review, data collection, analysis and interpretation of results; Aneta M. Gawlik-Starzyk — study conception and design, project supervision, substantive and language corrections.

All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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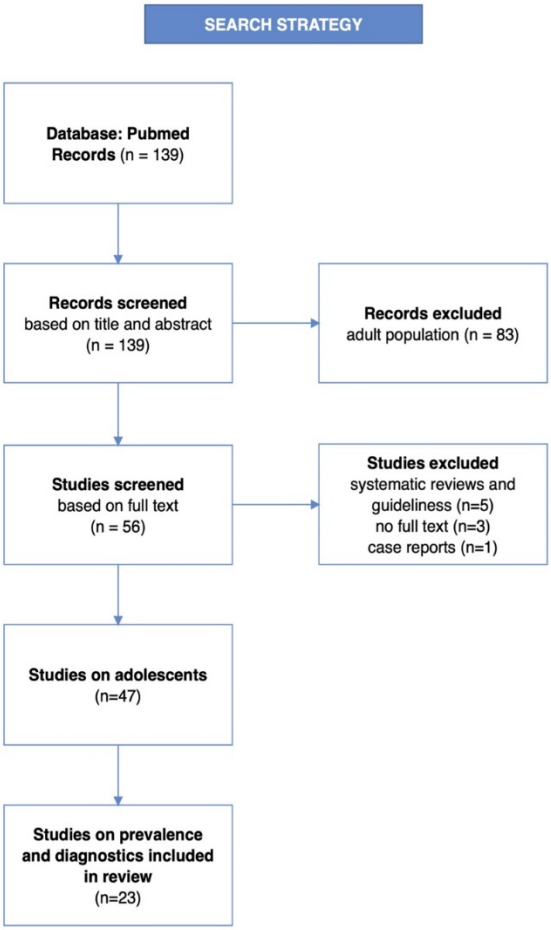

Figure 1. Search strategy presented on the flow diagram

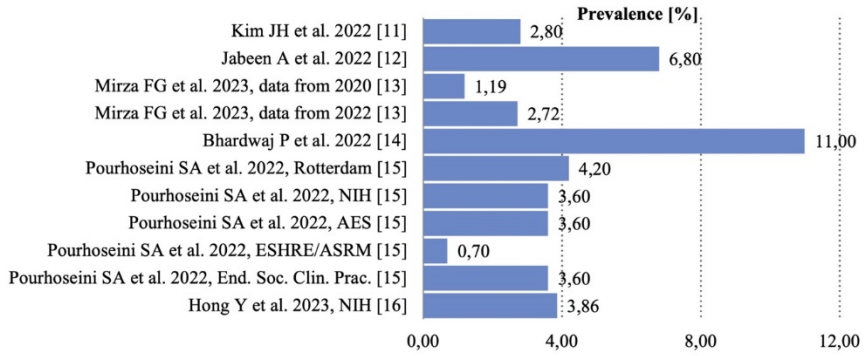

Figure 2. The prevalence of polycystic ovary syndrome (PCOS) among adolescent patients depending on the research

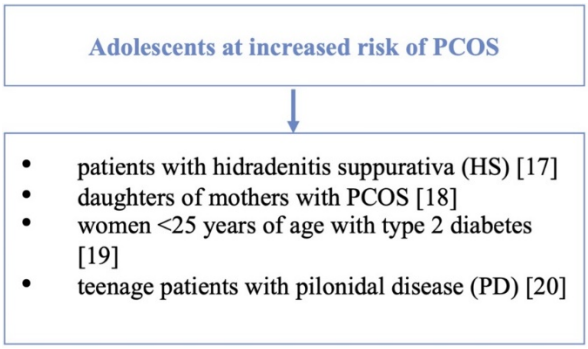

Figure 3. Adolescent at increased risk of polycystic ovary syndrome (PCOS) based on the latest research

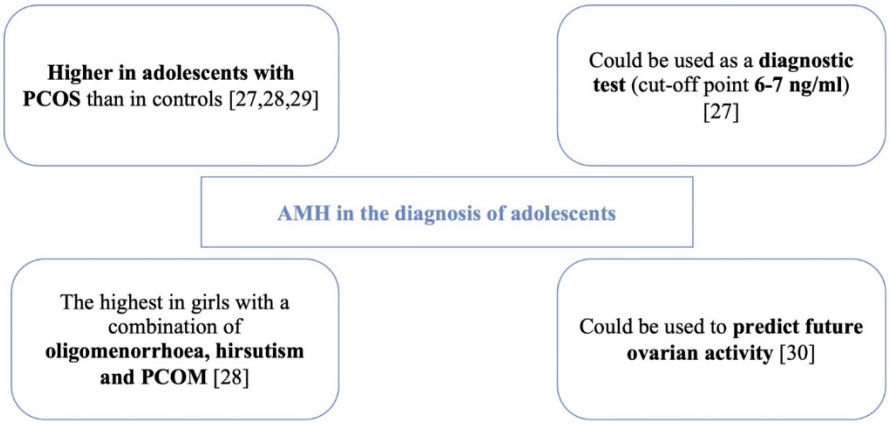

Figure 4. Summary of the latest reports on anti-Mullerian hormone (AMH) in the diagnosis of adolescents; PCOS — polycystic ovary syndrome; PCOM — polycystic ovarian morphology

Table 1. Prevalence of polycystic ovary syndrome (PCOS) depending on the phenotype among adolescent patients

	Rotterdam's classification	**Diagnostic criteria**	**Prevalence**
Group 1	Phenotype A	Menstrual irregularities (MI) + hyperandrogenemia clinical and/or biochemical [HA(C/B)] + polycystic ovarian morphology (PCOM)	22.72%
Group 2	Phenotype B	MI + HA(C/B) + PCOM	14.20%
Group 3	Phenotype D	MI + PCOM — HA (C/B)	49.53%