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Review Article

Fundamentals to Diagnosing Polycystic Ovary Syndrome in Adolescents: A Critical Literature Review

Sebastião Freitas de Medeiros[1, 2, *], Ana Karine Lin Winck Yamamoto de Medeiros[3], Letícia Ferreira de Magalhães[2], Márcia Marly Winck Yamamoto[2], Matheus Antônio Souto de Medeiros[2]

[1]Department of Gynecology and Obstetrics, Medical School, Federal University of Mato Grosso, Cuiabá, Brazil

[2]Tropical Institute of Reproductive Medicine, Cuiabá, Brazil

[3]Departament of Medicine, University of Cuiabá, Cuiabá, Brazil

Abstract

Background: Because of this prevalence and frequent association with various comorbidites, the diagnosis of polycystic ovary syndrome (PCOS) must be performed as early as possible. Despite conflicting findings, many studies have been published on adolescents with a diagnosis of polycystic ovary syndrome. Methods: The Google Scholar and PubMed data bases were searched for publications in the English language reporting on PCOS diagnosis in adolescents. Results: A comprehensive analysis of data regarding the overlay of physiological ripening of menstrual cycle characteristics, androgen levels, and ovary aspects during puberty with the established criteria to diagnose PCOS in adults revealed that are liable diagnosis of PCOS in adolescence is possibleas soon as 2-3 years postmenarche. Persistant menstrual cycle intervals shorter than 21 days or longer than 45 days, total testosterone levels >1.9-2.0 nmol/l and ovary volume >10cm^3 after 15-16 years of age can be used to diagnose PCOS. Conclusion: When combined, any persistent deviation of physiological parameters in adolescents as a criterion to diagnose PCOS in adults allows a certain diagnosis of PCOS in adolescents.

Keywords

Polycystic Ovary Syndrome, Adolescents, Puberty, Menstrual Cycle, Androgens, Ultrasonic Diagnosis

1. Introduction

The diagnosis of polycystic ovary syndrome (PCOS) in adults is supported by three previous recommends. The National Institutes of Health (NIH) recommend identifying clinical and/or biochemical hyperandrogenism associated with menstrual cycle alterations after other conditions associated with hyperandrogenism have been excluded [1]. In a joint meeting in Rotterdam in 2003, the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) defined the need for two out of three criteria: clinical or biochemical hyperandrogenism, menstrual cycle alterations, and ovarian volume and/or morphology with a polycystic appearance [2]. In 2006, the Androgen Excess Society (AES) established that consideration should be given to hyperandrogenism menstrual

*Corresponding author: de.medeiros@terra.com.br (SebastiãoFreitas de Medeiros)

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cycle alterations and/or polycystic ovarian appearance in adolescents [3].The diagnosis of PCOS in adolescents is controversial. The Endocrine Society (ES) criterion does not consider acne a marker of clinical hyperandrogenism [4]. The Pediatric Endocrine Society (PES) defines biochemical hyperandrogenism as a T level of 50 ng/dl (1.7 nmol/l) and clinical hyperandrogenism only when moderate or severe hirsutism is present [5]. These definitions do not accurately discriminate the diagnosis between adolescents and adults [6]. Owing to the inconsistencies observed in ovarian morphology, menstrual patterns, and androgen levels in adolescence, the presence of all three criteria proposed by the Rotterdam consensus appears to be necessary for the diagnosis of PCOS in adolescents in the early years after menarche [7-9]. Therefore, when diagnosing PCOS in adolescents, physicians must ensure that patients are not just undergoing normal puberty changes. It has also been suggested that a diagnosis of PCOS not be established until 17 years of age (approximately 3-4 years after menarche) [8] or even to wait until 8 years after menarche to consider PCOM [10]. If these recommendations were accepted and considering that menarche occurs at 12-13 years, the PCOM criterion to diagnose PCOS could be used only in adulthood (from 20-21 years). However, this criterion of 8 years after menarche to assume that adolescents have PCOM is not supported by robust observational longitudinal studies but rather by expert opinions [10, 11]. The only available longitudinal study on ovarian appearance at all ages has considered ovarian volume alone, not morphology. A normative model, was subsequently used to stablish a normal ovarian maximum volume cutoff of 7.67 cm^3 at 18-20 years of age [12] (Figure 1). With respect to ovary appearance in PCOS diagnosis, the Rotterdam criteria clearly establish the presence of ovarian volume >10 cm^3 and/or PCOM [2]. Therefore, in accordance with the Rotterdam recommendations, the use of ovarian volume itself is a criterion to be validated.

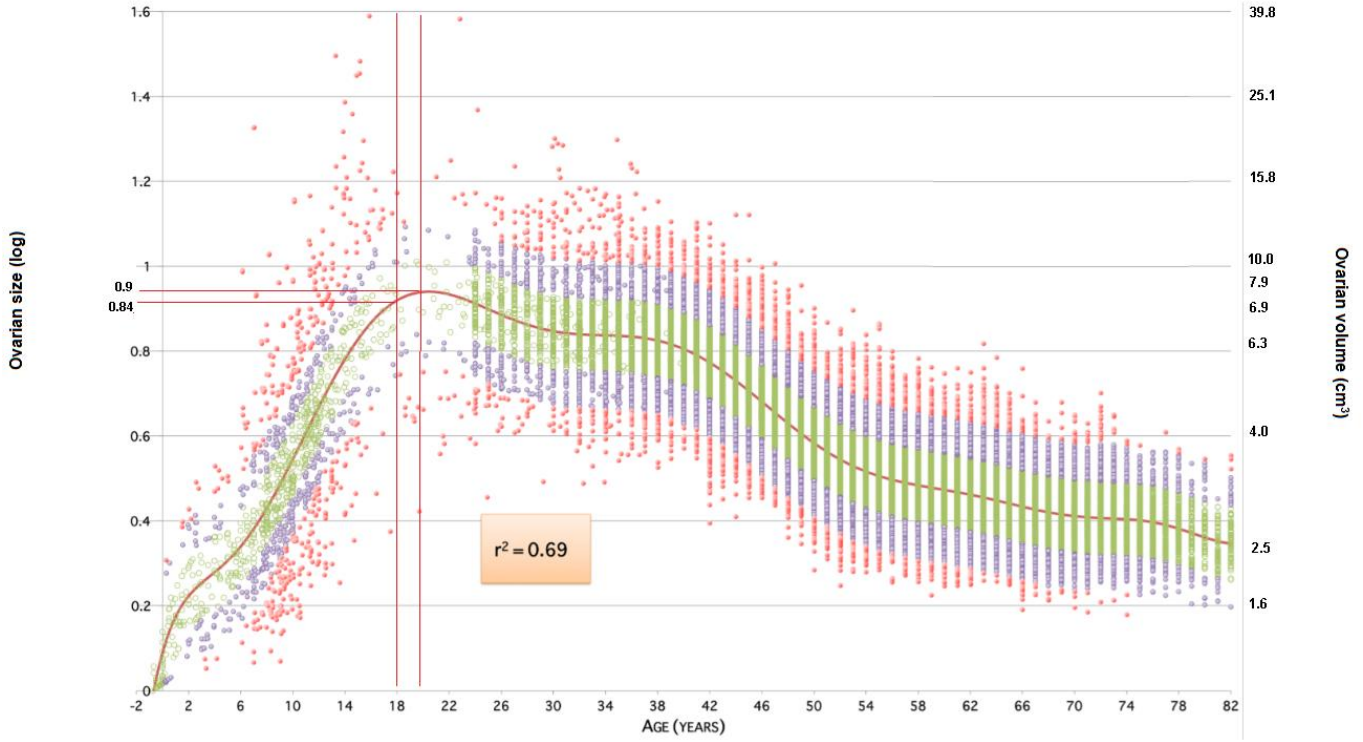

Figure 1. *The ultrasonographic evaluation of ovarian volume validated model of a log-adjusted ovarian volume throughout life.*

Adapted from T W Kelsey et al, Plos One, 8(9), 2013, https://doi.org/10.1371/journalpone.0071465

Practical limitations in defining PCOS in adolescents are based on the physiological changes in reproductive axis maturation present in this age group, normally elevated androgen levels (mainly adrenal) in adolescence, physiologically irregular cycles at least in the first year postmenarche, and the presence of multicystic ovaries that are common in puberty and overlap the three main parameters used in the diagnosis of PCOS [13, 14]. Because it is possible to have either a delayed or accelerated appearance of PCOM in the ovaries during puberty, the current literature is inconsistent, and a universal agreement is lacking. Considering the uncertainties related to ovarian morphology, the diagnosis of PCOS

during puberty could be confirmed via the criteria proposed by the NIH instead of the Rotterdam proposal. However, if we use the NIH criteria, approximately 15% of women with the syndrome but with normoandrogenaemia would not be included even if they may have ovaries with polycystic aspects. The use of an ovarian volume >10cm^3 should be considered when the Rotterdam criteria are used. In this conflicting scenario, this extensive narrative review aims to individually examine the presence and modifications of each criterion used for diagnosing PCOS in adolescents. Additionally, this study aims to provide a rationale for diagnosing PCOS in adolescents in a timely and reliable manner as early as possible, while minimizing overdiagnosis.

2. Characteristics and Dynamics of Androgen Levels in Adolescence

Longitudinal studies on the dynamics of androgens before and after menarche are scarce [15-19]. However, the levels of androgens in adolescents are well established compared with those in adults [20-23]. Initially, the physiological aspects of adrenal and ovarian androgen production should be considered from 10 to 19 years of age. Importantly, the quantification of androgens, particularly testosterone, in women may not be accurate because levels are located at the lower end of the concentration range of immunoassay sensitivity or at their detection limits. Owing to the variation in androgens according to the menstrual cycle phase, in adolescent girls who have already started menstruating, blood samples for hormonal assays should be collected in the early follicular phase. Since irregular cycles are common in this phase of life or with infrequent menstruation or amenorrhea, progesterone measurements ensure that the sample is collected in the follicular phase [23]. Because of the diurnal variation in some androgens (androstenedione, 17-hydroxyprogesterone), blood collection should be performed in the morning [24]. With the maturation of the reticular zone of the adrenal cortex at 7-8 years of age, the serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase. Shortly thereafter, the elevation of androstenedione (A4) begins at 8-10 years and gradually increases throughout puberty [18, 19], with a normal maximum level<8.4 nmol/l [21]. The adrenal androgens undergo a new elevation between 12 and 13 years of age, coinciding with the age of menarche. In very old assays, DHEA levels increase from 48 ng/100 ml (4 nmol/l) to 561 ng/100 ml (16 nmol/l) between 7 and 13 years of age and tend to stabilize after this age [18, 19]. Currently, using new assays, it appears that DHEAS levels can oscillate between 2.1-7.1 μmol/l in adolescents between 12 and 19 years of age and with regular cycles [20, 25-28]. In summary, in adolescents, DHEAS levels increase from adrenarche to 1-3 years postmenarche [20, 21, 29]. If menstrual irregularity persists after 2 years of menarche, DHEAS levels may reach 8.1 μmol/l [28]. With respect to androstenedione (A4) it was shown that between 6 and 16 years of age, it increased from 0.34 nmol/l to 2.8 nmol/l [20]. However, its level may reach 7.9 nmol/l and this concentration should be considered the maximum limit in adolescence [23, 27]. Using liquid chromatography-mass spectrometry, the levels of A4 were shown to increase from 9 ng/dl (0.6 nmol) to 94 ng/dl (3.3 nmol/l) between 7 and 18 years of age [30] (Table 1). In general, adolescents with a mean age of 16-17 years present average levels of A4 between 2 nmol/l and 8 nmol/l [15, 21, 23, 25-28, 31-35]. Furthermore, in a study with adolescents, considering the 90th percentile, maximum levels of A4 of 6.3 nmol/l, DHEA of 19.9 nmol/l, and DHEAS of 8.1 pmol/L were observed in normal adolescents [28].

Table 1. *Androgen levels in young girls using liquid chromatographymass spectrometry.*

Agerange	Androgen (nmol/l)	Result*
4-6	A4	0.50 (0.1-1.5)
	T	0.20 (<0.1-0.7)
7-9	A4	0.66 (0.2-2)
	T	0.19 (0.1-2)
10-12	A4	1.43 (0.1-5.6)
	T	0.54 (0.1-1.5)
13-15	A4	3.3 (0.1-1.5)
	T	0.76 (0.1-2.0)
15-18	A4	3.3 (1-5.5)
	T	0.91 (0.1-1.7)

*Are given in median and range.
Data retrieved from AE Kulleetal, J Clin Endocrinol Metab. 95(5): 2399-2408, 2010.

Total testosterone (T) levels stabilize in the middle of puberty years, reaching levels compatible with those of adultwomen already in middle-pubertal years, with normal levels ranging from 0.60-0.80nmol/l at the beginning of puberty and 0.82-0.90nmol/l at the end of adolescence [20, 34, 36-38]. In cross-sectional study design, serum levels of T begin to stabilize at 14 years of age, and its levels in adolescents do not exceed 29-37ng/dl (1.0-1.3nmol/l), a result that is consistent with the findings of various studies [17, 36, 37, 39]. However, when LC-MS/MS was used in adolescents 16-19 years old, a T level of 0.87nmol/l was found, with a lower limit of 0.8nmol/l and an upper limit of 1.7nmol/l [40]. Other researchers accept a normal upper limit of 40/50ng/dl (1.4nmol/l-1.70nmol/l) [18, 26, 32, 35, 41, 42]. In longitudinal studies, T levels were shown to increase from 10ng/dl (0.35nmol/l) to 40ng/dl (1.39nmol/l) in adolescents between 8 and 14 years of age [43]. Together, the available studies in-

dicate that normal adolescents have T levels under 1.0nmol/l. Reports on free T levels in normal adolescents are scarce, ranging from 0.005pmol/l at the beginning of puberty to 0.014pmol/l at the end of puberty [23, 35, 44].

Considerations Regarding Androgen Levels in Adolescents

1. Despite the type of assay used, the quantification of androgen levels, particularly testosterone levels, may not be accurate in women, even in adults.
2. Androgen levels begin to increase at 7-10 years of age throughout puberty and tend to stabilize with menarche.
3. Two years after menarche, the maximum normal DHEAS level is 8.1pmol/l.
4. The normal maximum level of androstenedione in adolescence is7nmol/l.
5. The total testosterone level in normal adolescents is usually ≤1.0nmol/l, with a maximum normal cut off level of <1.9-2.0nmol/l.

3. Characteristics of Menstrual Cycles in Adolescents

The parameters of normality for menstrual cycles in adolescence include onset, frequency, regularity, duration, and volume [45]. In different countries, the first menstruation, the final event of puberty, occurs approximately 2-3 years after thelarche, approximately 12-13 years of age [46-48], with 95%-98% of adolescents menstruating by age 15 [47, 49]. In the standard adult menstrual cycle, the interval between menstruations is 23-35 days, with an average of 28 days [50]. In the first 1-2 year postmenarche, cycles may continue to be irregular, ranging from 21 to 45 days in 90% of adolescents [51, 52]. Some studies have reported regular cycles with intervals between 21-45 days in the first year postmenarche [50, 51, 53] and between 21-34 days in the second and third years post-menarche [51, 54-57].

Around the third year postmenarche, between 15 and 16 years of age, approximately 60% - 80% of cycles assume a typical pattern of adult women [50, 53, 58-60]. At the age of 17 (4-5 years postmenarche), only 3%-4% of adolescents have menstrual cycles with intervals shorter than 22 days, and 3.4% of them have cycles longer than 35 days [61]. Notably, in different populations, the time between menarche and the establishment of regular cycles varies from months to years [56, 57, 62-64]. With respect to the establishment of ovulation, the proportion of ovulating adolescents with regular cycles increases from 45% in the second year postmenarche to 70% between 2 and 3 years postmenarche and between 80% and 90% at 5 years of gynecological age [53, 56, 57, 65].

Considerations Regarding Menstrual Cycle Intervals in Adolescents

1. Most adolescents establish menstrual cycles with intervals of 21-45 days with in the first two years after menarche (Level B).
2. A persistent menstrual interval equal to or greater than 90 days in the first year post menarche is uncommonand requires further investigation (Level B).
3. The absence of menstruation at the age of 15 years or 2 to 3 years after thelarche requires further investigation (Level B).

4. Characteristics of Ovarian Morphology and Volume in Adolescence

The recommended tool for assessing ovarian volume and morphology in adolescents is vaginal ultrasonography when the adolescent has already initiated sexual activity. When the abdominal route is used, precision in defining the images is lost, especially in obese adolescents [66, 67]. Two aspects should be considered in ovarian ultrasonographic evaluation in adolescence: volume and morphology. However, knowledge about the changes in these two parameters throughout adolescence is limited, with few longitudinal studies.

4.1. Ovarian Volume

The ovarian volume, clearly increases from 10 years to 20 years of age, reaching the adult ovarian volume by age 20 [12, 27, 68]. There is disagreement in the literature about the age at which the ovary will reach its maximum volume, but there is agreement regarding this maximum volume in adolescence [12]. After reaching its maximum volume in adolescence, the ovarian volume remains stable until the fourth decade of life [31, 69]. It has been reported that a maximum ovarian volume of 7.8 cm^3 is reached between 1 and 4 years postmenarche (approximately 14-17 years of age) [70, 71]. The ovarian volume between birth and puberty varies between 0.7 $cm^3$and 8.0 cm^3, with a maximum of up to 7.8 years postmenarche [27, 67]. Using a normative model, the ovarian volume from birth to age 82 was estimated [12] and this study also revealed that 69% of the changes in ovarian volume are due to age, with the volume being reduced to 0.7 cm^3 at menopause. Thus, various studies have proposed a cutoff of 7.8-8.0 cm^3 for maximum ovarian volume in adolescents. Additionally, studies correlating age and LH levels in adolescents have reported that ovarian growth ranges from 4.0 cm^3 at 13 years to 7.8 cm^3 at 20 years [72, 73].

4.2. Ovarian Morphology

High ovarian follicular turnover in adolescence is associated with a progressive increase in both the number and size of follicles [74, 75]. These follicular dynamics can result in ovaries with a multicystic, multifollicular, or polycystic morphology [76, 77]. Multicystic or multifollicular features, which are common in the first year postmenarche due to an imbalance in follicle stimulating hormone (FSH), androgens

and anti-Mülleriame hormone (AMH) [78], may be diagnosed when more than 4 follicles are randomly distributed in the ovaries [79-82]. During the normal adolescence the ovaries may then present multicystic and polycystic morphology [83-86]. Owing to the presence or absence of a cystic structure, the ovary is usually described as a) being homogeneous if no cystic structure is detected in the ovary, b) being microcystic if a clearly outlined cyst smaller than 9 mm in size is present, c) being macrocystic if one or more cysts exceeding 9 mm in size is present, and d) being polycystic if more than 10 cysts smaller than 9 mm and/or hyperechogenic stroma are present [68, 87]. These aspects may be modified with age [27, 32], and may disappear after two years postmenarche when the ovary assumes normal adult morphology in most cases [84, 88-92]. Around the time of menarche, the number of large antral follicles reaches its maximum [93], but these follicles can later undergo remission [91]. Clearly, more longitudinal data are needed to define the limits of physiological changes in ovarian morphology in adolescence [91, 94, 95]. PCOM can be found in approximately 13%-34% of normal adolescents [2, 3, 52]. Notably, ovarian morphology is a useful biomarker for early reproductive dysfunction beginning in the first years after menarche [94]. However, despite some disagreement regarding whether PCOM is normally present in adolescents and if it must be valorized as an abnormal finding, but when it is persistent additional investigations should be performed.

4.3. Considerations Regarding Ovarian Volume and Morphology in Adolescence

1. Between 15 and 19 years of age, the ovarian volume increases from 4.0cm^3 to a maximum of 8.0cm^3.
2. The maximum ovarian volume in normal adolescents does not exceed 7.8cm^3-8.0cm^3 and this volume is reached between 4.0 and 7.8 years after menarche.
3. The persistence of PCOM requires further investigation.
4. In obese adolescents, abdominal ultrasound is not sufficiently accurate, and magnetic resonance imaging may be exceptionally useful for ovary examination in doubtful cases.

5. Critical Analysis of the Criteria Used to Diagnose PCOS in Adolescents

First, it is essential, as it is in adults, to exclude other disorders with persistent hyperandrogenism such as thyroid disorders, hyperprolactinemia, late-onset congenital adrenal hyperplasia, Cushing's syndrome, adrenal tumors, and functional ovarian tumors, in adolescents. Persistent menstrual irregularities or amenorrhea, hyperandrogenism, and polycystic ovarian morphology (PCOM) and ovarian volume are crucial in the diagnosis of PCOS in adolescents. After the Rotterdam meeting, two out of three criteria were sufficient to confirm PCOS in adults. This means that adult women with ovulatory and regular cycles (phenotype C) or with normal androgens (phenotype D) can receive a definitive diagnosis of PCOS [27, 96-98]. Therefore, PCOM is not absolutely necessary for a PCOS diagnosis even in adults. When the Rotterdam criteria are used for the diagnosis of PCOS in adolescents, many patients can be classified as phenotype C or D. Diagnosing PCOS in adolescents remains controversial because of the overlap between physiological puberty events and the cardinal criteria used for its diagnosis. Some authors prefer to use frequent/infrequent menstrual cycles or amenorrhea combined with hyperandrogenism to diagnose PCOS in adolescents (NIH criteria) [1, 91, 99]. Others have recommended the use of three Rotterdam criteria: menstrual irregularities/amenorrhea, hyperandrogenism, and PCOM or ovary volume >10 cm^3 [6, 8, 9]. Some others reject diagnosing PCOS in adolescents via the PCOM and recommend classifying these adolescents only ‘’as being at risk’’ for PCOS [10]. If the ovary volume is <10 cm^3, it appears to be better to use the NIH criteria and close the diagnosis of PCOS as early as possible. Otherwise, because PCOM is not necessary for a definitive diagnosis, an ovarian volume>10 cm^3 may be used. Unfortunately, delayed diagnoses of true PCOS still occur in adolescents [99, 100]. The reliance on relatively old publications and the need to reconcile conflicting aspects of PCOS diagnosis in adolescence with new publications stresses the need for further research in this area. Despite these challenges, it is crucial to highlight the most relevant points to guide clinical care and research in diagnosis of PCOS in adolescents.

5.1. Rationale of Frequent/Infrequent Menstruations/Amenorrhea to Diagnose PCOS in Adolescence

This biomarker of PCOS primarily manifests in the peripubertal period [101]. As reviewed in this article, irregular menstrual cycles are common in adolescents, especially at 1 to 3 years after menarche [102, 103]. As shown previously, in the third year postmenarche, 95% of adolescents present regular menstrual cycles ranging from 21-45 years [57, 59]. Therefore, the persistence of cycles with intervals exceeding 45 days at 2-3 gynecological years (approximately 15 to 16 years of age), associated with any other criterion used for PCOS diagnosis is linked to persistent abnormalities and allows a reliable diagnosis of PCOS at these ages [104, 105]. The persistence of cycles lasting less than 20 days after 2-3 years postmenarche can also be used as a criterion for diagnosing PCOS with certainty [6, 45, 61, 103, 106]. These aspects can be assumed in clinical practice to diagnose PCOS because, among normal adolescents, only 3%-10% maintain cycles lasting 21 days, and only 3%-4% have cycles lasting more than 35 days after 2-3 years of menarche [34, 55, 61, 66]. Furthermore, the diagnosis of PCOS in adolescents is robust in cases of persistent cycles of over 45 days or amenorrhea from the first year after menarche [33, 106,

107]. In summary, when menstruation occurs more frequently than every 21 days or less frequently than every 45 days or every 90 days, these parameters should be used as reliable criteria to diagnose PCOS in adolescents aged 13 to 16 years. By considering only infrequent/amenorrheic menstrual cycles combined with hyperandrogenism, an early diagnosis of PCOS is correct in at least approximately 80% of adolescents [28, 33, 44, 66, 108]. In conclusion, waiting for 2-3 years after menarche to diagnose PCOS in adolescents presenting long cycles or amenorrhea since menarche when it is combined with hyperandrogenism or an ovarian volume ≥10 cm^3 is inappropriate [6, 44, 109].

5.2. The Use of Clinical and Biochemical Hyperandrogenism for the Diagnosis of PCOS in Adolescents

Owing to relative hyperandrogenism during early puberty compared with that during mid and late puberty, this physiological characteristic should be considered before establishing a definitive diagnosis of hyperandrogenism or PCOS [37]. Clinical/biochemical hyperandrogenism is a crucial biomedical marker for diagnosing PCOS at all ages, considering the current recommendations. With respect to clinical hyperandrogenism in adolescents, the presence of thick, dark hair after menarche indicates a high likelihood of PCOS [35, 110, 111]. The presence of acne should not be considered. The persistence of clinical hyperandrogenism at 16 years of age is strongly associated with the development of PCOS [112, 113]. As previously described, considering biochemical hyperandrogenism, after adrenarche, DHEAS levels gradually increase from 50 µg/dl (1.35 µmol/l) to 200-250 µg/dl (5.4-6.8 pmol/l) by the end of adolescence [25, 26, 113]. In a Brazilian study, as already described, adolescents with PCOS had mean DHEAS levels of 5.8 pmol/l with a 90th percentile cutoff 8.1 µmol/l [28]. Others consider a cutoff of 7.1 µmol/l as the superior limit for this steroid [27]. A4, 25% of which is produced by the adrenals and 25% by the ovaries, also increases in late puberty, with levels ranging from a minimum of 4ng/dl (1.4nmol/l) to a maximum of 240 ng/dl (8.3nmol/l) between the ages of 10 and 19 years [26, 114, 115]. A cutoff point >8.7 nmol/l for A4 can be used to diagnose biochemical hyperandrogenism in adolescents [28, 116, 117]. The biochemical definition of hyperandrogenism in adolescents on the basis of T levels is not universally accepted, but persistent total testosterone concentrations above 55ng/dl (or 1.9 nmol/l) after 14 years of age are accepted as the cutoff point [28, 35, 118-120]. Additionally, testosterone levels >1.3nmol/l (37 ng/dl) are found in only 7% of normal adolescents [119]. In contrast, testosterone levels between 40 ng/dl and 79 ng/dl (1.4 nmol/l - 2.0 nmol/l) have been found in adolescents already diagnosed with PCOS [23, 28, 66, 121-123]. In conclusion, a persistent level of T >1.9 nmol/l certainty allows the diagnosis of biochemical hyperandrogenism in adolescents without considering PCOM morphology. High androgen levels must be combined with persistent menstrual cycle abnormalities < 21 days or > 45 days or amenorrhea to close the PCOS diagnosis in adolescents 2-3 years after menarche.

6. Rationale of the Use of Ovary Volume and Morphology to Diagnose PCOS in Adolescents

The first study which ultrasonographic examinations to diagnose PCOS, conducted via the abdominal route suggested the presence of ≥10 follicles measuring 2-8 mm [124]. Furthermore, in 2003, 12 follicles measuring 2-9 mm in length in both ovaries were proposed [125]. In the same year, the Rotterdam Consensus proposed the finding of 12 follicles measuring 2-9 mm or having an ovarian volume >10 cm^3 [2, 66]. Following the introduction of new machines with transducers ≥8 MHz, the number of follicles was increased to 20-25 follicles of 2-9 mm, but an ovarian volume >10 cm^3 was maintained [126-128]. However, the use of these ultrasound criteria in adolescents for the diagnosis of PCOS is controversial because: a) the finding of a multicystic appearance, or even classical PCOM, in normal adolescents is common (11% to 40%) [9, 14, 33, 67, 84, 129, 130], b) the evolution of normal ovarian aspects to achieve abnormal persistent PCOM in adolescents between 10 and 19 years of age has not yet been established, and c) the low quality of ultrasonographic findings must e considered when a transabdominal approach is used. The multifollicular appearance may revert to normal when regular and ovulatory cycles are achieved [131]. Otherwise, the polycystic ovary morphology may not revert [132]. In a recent community-based study polycystic ovary morphology in adolescents was used as part of the PCOS diagnosis and was associated with infrequent menstrual cycles (67%) and/or hyperandrogenism (66%) [133]. Moreover, ovarian volume is also accepted as a useful parameter for diagnosing PCOS in adolescents, with a cutoff point of 10cm^3. This volume is correlated with testosterone levels in some studies [27, 70, 109, 134]. Notably, when the cutoff point of the ovary is >10 cm^3, the diagnosis of PCOS presents specificity and sensitivity higher than 80% [135], even when older machines are used [109]. Therefore, an ovarian volume >10 cm^3 has proven to be a reliable parameter for diagnosing PCOS even before 8 years postmenarche [11, 44, 109, 136]. This ovarian characteristic becomes permanent in most adolescents, especially when associated with irregular cycles or hyperandrogenism [27, 79, 81, 137]. Furtermore it should be noted that PCOM is a sign, not a diagnosis [136]. Currently, to diagnose PCOS in adolescents PCOM morphology is recommended for use only 8 years postmenarche [9, 10]. However, making a reliable diagnosis of PCOS in adolescents before the age of 19, or before 8 years post-menarche, has been performed by several researchers [6, 23, 44, 77, 110, 138, 139]. Furthermore, some of these studies used all three criteria of Rotterdam. In this case, because an early diagnosis of

PCOS is important and relevant, the use of 3D ultrasound or magnetic resonance imaging can be use in doubtful cases [34, 140, 141]. Alternatively, the PCOM criterion may be replaced by increased anti-Mullerian hormone levels associated with hyperandrogenism to confirm the PCOS diagnosis [142]. In conclusion, with respect to the ovarian aspect, a parameter of an ovarian volume >10 cm^3 alone in adolescence should be a recommended criterion for the diagnosis of PCOS during this period if combined with other parameters.

7. Concluding Remarks and Final Considerations for Diagnosing PCOS in Adolescents

The present review is supported by many studies recommending a reliable diagnosis of PCOS as early as possible in adolescents. The extensive literature analyzed, allows us to conclude the following:

1. To wait for 8 years postmenarche to perform definitive PCOS diagnosis, based on the classic ovarian PCOM is not supported by any observational study, instead it is based on expert opinions (level D).
2. PCOM, as currently described, is not a necessary criterion to confirm the diagnosis of PCOS in adolescents (level A).
3. An ovarian volume ≥10$cm^{3,}$ found 2-3 years after menarche, even when identified by abdominal ultrasound, is by itself a reliable ovarian criterion for diagnosing PCOS in adolescents (level B).
4. In steady use of terminology ‘’at risk’’ for PCOS’’in the absence of PCOM, it is adequate to use the NIH criteria or, if wanted, to use simply ovarian volume as the third criterion (level A).
5. To avoid over diagnosis and to harmonize with the aspect of ovarian morphology, the combined use of additional clinical and laboratory data may be necessary (level B).
6. Persistent menstrual cycles with intervals <21 days or >45 days or amenorrhea support the diagnosis of PCOS in adolescents as early as two years postmenarche (level B).
7. Persistent mild or severe hirsutism is a reliable sign of clinical hyperandrogenism in adolescents, but acne should not be considered (level C).
8. Persistent testosterone levels ≥1.9nmol/l in adolescents characterize biochemical hyperandrogenism (level B).
9. Overall, as in adults, combining at least two of the proposed criteria to confirm PCOS in adolescent girls is recommended.

Abbreviations

A4	Androstenedione
AES	Androgen Excess Society
AMH	Anti-Mullerian Hormone
ASMR	American Society for Reproductive Medicine
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone Sulfate
ES	Endocrinology Society
ESHRE	European Society of Human Reproduction and Embriology
FSH	Follicle Stimulating Hormone
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LH	Luteinizing Hormone
NIH	The National Institute of Health
PCOM	Polycystic Ovary Morphology
PCOS	Polycystic Ovary Syndrome
PES	Pediatric Endocrine Society
T	Total Testosterone

Statement of Ethics

The study was approved by the Federal University of Mato-Grosso Committee for Ethics in Research (decision No.093/FCM/03).

Author Contributions

Sebastião Freitas de Medeiros: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing

Leticia Ferreira de Magalhães: Writing – review & editing

Ana Karine Lin Winck Yamamoto: Writing – review & editing

Matheus Antonio Souto de Medeiros: Writing – review & editing

Márcia Marly Winck Yamamoto: Writing – review & editing

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Data Availability Statement

The research data are not publicly available on legal or ethical grounds. In addition, all the data produced and analyzed during this study were included in these articles. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare that there are either no financial or other conflicts of interest that could be perceived as prejudicing the impartiality of this study.

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