Gineco.eu[11] 196-198 [2015]
DOI: 10.18643/gieu.2015.196

New trends in diagnose of polycystic ovarian syndrome

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Abstract

Polycystic ovarian syndrome (PCOS) is a heterogeneous condition, is present in 12–21% of women of reproductive age. The Rotterdam Criteria for PCOS require the presence of two of the following criteria: oligo/anovulation, hyperandrogenism antral follicle count (AFC) on ultrasound. The purpose of this paper is to bring new information from recent studies regarding the diagnosis of this disease using anti-Mullerian hormone (AMH) vs. AFC. AMH levels accurately reflect the ovarian follicular reserve and could be considered as an extremely sensitive marker of ovarian aging. Special reference is made to the possible implications of AMH in the pathogenesis of PCOS. The measurement of AMH was made by some clinicians the gold standard for diagnosis of PCOS. Because the serum concentrations of AMH is increased in most patients with PCOS and it is an association between the performance of serum AMH and AFC, has led to compare the performance of AMH levels and AFC in diagnosis of PCOS. With evolving progress in ultrasound device, recent studies have suggested increasing the threshold of AFC to 19 or even 26. The real-time interpretation of two-dimensional ultrasonography may underestimate the absolute number of follicles compared with three-dimensional ultrasound.
Keywords: *polycystic ovarian syndrome, anti-Müllerian hormone, antral follicle count*

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous condition, being present in 12-21% of women of reproductive age. Up to 70% of women with PCOS remain undiagnosed, this depending on the criteria used and the population assessed[1]. Estimates vary, which includes a wide range of clinical, biochemical and ultrasound features, all of this are important and relevant both clinically and from a pathophysiological point of view.

The Rotterdam Criteria (ROT) for PCOS require the presence of two of the following: oligo/anovulation, hyperandrogenism and antral follicle count (AFC) on ultrasound, excluding other aetiologies such as congenital adrenal hyperplasia, androgen secreting tumours, Cushing syndrome, thyroid dysfunction and hyperprolactinaemia. Recent studies have shown that 50% of women with PCOS fulfil the criteria of metabolic syndrome and that PCOS have an increased risk for the development of cardiovascular disease and type 2 diabetes mellitus[2,3]. Although PCOS commonly occurs in adolescence, its diagnosis is not straightforward because menstrual irregularities, hirsutism and acnee are frequently transient and non-progressive in this age group[4].

Management of PCOS involves attention to current symptoms, fertility and psychosocial issues, as well as prevention of related future health problems. The purpose of this paper is to bring new information from recent studies regarding the diagnosis of this disease using anti-Mullerian hormone (AMH) vs. AFC[4].

Received: *October 17, 2015*
Revised: *November 21, 2015*
Accepted: *November 29, 2015*

Management of PCOS

In the current studies the results are not identical, even with wide variations. This heterogenity is due to the absence of well-defined populations included in different studies. Also, the variability of results can be explained by the problem of different serum AMH assays. Recent data have shown that there are fluctuations of the AMH level throughout the cycle (i.e. with lower levels during the early secretory phase) or even between consecutive cycles. Those fluctuations are not considered clinically significant to recommend the measurement of AMH concentrations at a specific phase of the menstrual cycle[5]. Because AMH dosage with different methods reviled different results, it is a definite need for standardization in this field. AMH is a member of the transforming growth factor-β superfamily. AMH levels accurately reflect the ovarian follicular reserve and could be considered as an extremely sensitive marker of ovarian aging. AMH is produced by ovarian granulosa cells, predominantly from growing preantral and early antral follicles, and is elevate in adolescents with PCOS[6,7]. Production of AMH begins in the fetus. Levels are low until age 8 years, rise until puberty and, at age 25, begin to decline steadily until menopause[8]. The close relationship with follicle number suggests that AMH may serve as a marker for the presence of PCOS[9]. Indeed, adolescents with PCOS have a higher AFC and a larger ovarian size than adolescents without PCOS[10], which is supportive of this premise. Special reference is made to the possible implications of AMH in the pathogenesis of PCOS and obesity. Also, AMH

concentrations in women with PCOS were independently and positively correlated with testosterone, androstendione and free androgen index values. Some studies sugest it is a linear relation between AMH and hirsutism and oligomenorrhea[11]. In clinical practice, it is useful for prediction of poor responders and ovarian hyperstimulation syndrome. Moreover, it is positively correlated with pregnancy rates. The measurement of AMH was made by some clinicians the gold standard for diagnosis of PCOS.

A cut-off value accepted was 3.8 ng/mL, ROT analysis showed that AMH alone had 80% sensitivity and 80.2% specificity for the diagnosis of PCOS. After reassessing the patients with new method using the 3.8 ng/mL AMH cut-off with, the diagnostic criteria was established (presence of two of the three parameters): oligoamenorea (OA), hyperandrogenia (HA) and AMH. This combination was found to have 100% specificity and 96% sensitivity for the diagnosis of PCOS[12]. In other analysis, an AMH value of 3.4 ng/mL best distinguished between PCOS and controls. This value had a sensitivity of 40% and a specificity of 93.8% for PCOS[13].

The number of follicles considered necessary to establish the diagnosis of polycystic ovaries by ultrasonography has changed over the years. Several authors have suggested that the increase in the size of the stroma and its blood flow are more specific markers because they relate to the endocrine dysfunction seen in women with PCOS[14].

The classical image of an polycystic ovary is: an enlarged ovary containing an increased number of small follicles arranged peripherally around an enlarged and hyperechogenic ovarian stroma that demonstrates increased blood flow on Doppler examination[15]. Two distinct types of polycystic ovary are seen on ultrasound. The follicles may be located peripherally, in the classical type, or they may be found scattered randomly or uniformly throughout the ovarian parenchyma. These patterns are histological different have true pathological differences and are specific endocrine patterns. The new ROT classification supports the objective role of ultrasound in the diagnosis of PCOS which should include either 12 or more follicles measuring 2-9 mm in diameter or an increased ovarian volume, 10 cm^3 in either ovary. Until now, ultrasound alone is not reliable in the diagnosis of polycystic ovaries in adolescent and young women. Up to 70% of young women may have polycystic ovaries on ultrasound[16]. A decade-old diagnostic threshold for PCOS should be revised. The technique for two dimensional ultrasound is very important. After the longest medial axis of the ovary is been determined, the length and thickness are measured and the area is calculated using a manual or automatic ellipse to outline the ovary. Ovarian area is used as a variable because its specificity and sensitivity are higher than those of ovarian volume. All follicles 2 to 9 mm in diameter are counted. The diameter of several follicles are calculated by taking the mean of the longitudinal and anteroposterior diameters. The clinical significance of 3-dimensional (D) ultrasound remains to be determined, but the automated technique is significantly quicker than is making measurements using 2D ultrasound imaging. Most studies have been performed using 2D ultrasound, which has the intrinsic limitation that it can only assess the ovary in a single plane instead of the whole tissue. The 3D ultrasound provides a more global assessment of an organ and improves spatial orientation, which facilitate correct structural classification and more reliable, valid measures of volume and blood flow[17]. A task force from the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) reviewed results from recently published studies[18,19] and reported an urgent need to update the diagnostic criteria, recommending that the threshold be increased to ≥25 follicles when using new ultrasound devices.

In a study comparing ovarian characteristics of women diagnosed with PCOS versus healthy volunteers, the most accurate diagnosis of PCOS is associated with a follicle number per ovary (FNPO) of 26, rather than the FNPO of 12 proposed as the diagnostic criteria at a 2003 workshop in Rotterdam. The FNPO analysis showed that a threshold of 26 follicles match the best compromise between sensitivity (85%) and specificity (94%) when discriminating between women with PCOS and control participants. With FNPO, the best compromise was 9 follicles, with a sensitivity of 69% and a specificity of 90%. An OA threshold of 10 cm^3 had a sensitivity of 81% and a specificity of 84%[20].

Other opinions suggest the using only of ovarian volume ≥10 mL in the detection of PCOS (in the absence of a dominant follicle or a *corpus luteum*) when a new ultrasound device is not available[20].

The implication of PCOS in endocrinology

PCOS is a complex heterogeneous endocrine disorder. Because of long term sequel of PCOS including infertility, endometrial hyperplasia, metabolic syndrome, and cardiovascular risk factor, early identification of at risk women would be very useful. The described relationship between AMH and androgens was supported by the correlation of AMH with both free testosterone and androstenedione. It has been suggested that androgens may stimulate AMH production by increasing follicle number; however, it is still unclear whether the relationship is causative or simply incidental in which both androgens and AMH are products of the large number of follicles in PCOS[19]. The 2003 Rotterdam consensus represents an important first step in defining uniform diagnostic criteria for PCOS and specific ultrasound features of a polycystic ovary. From the antral follicle count and size of antral follicles can derive a lot of information about the biochemical status of the patient. Although a number of groups have tried to define the 3D ultrasound features of a polycystic ovary, with mixed results. Even with the most technically advanced ultrasonography devices, it can be difficult to count antral follicles transabdominally in virgin or the obese

patients. Thus, the need for objective parameters, and the serum AMH level could serve for the diagnosis of PCOS[20].

Satisfactory diagnostic potential can be achieved by combining the AMH level with other clinical symptoms. When the AMH cut-off value was set as 3.8 ng/mL, ROT criteria provided maximum sensitivity and specificity for the diagnosis of PCOS.

For patients with an uncertain history of menstruation, a combination of AMH levels only with HA may be useful for diagnosis. This combination had higher sensitivity when ROT weas considered to be gold standards. The combination of AMH only with OA, on the other hand, had relatively lower sensitivity and specificity in all three classical systems than did the combination of AMH and HA[20].

Otherwise, referring to the ovaries as being polycystic can be misleading; the term has negative connotations and its use distracts from the real problems of subfertility, menstrual disorders and hyperandrogenism. In the opinion of some authors, the sonographic ovarian appearance would be better described simply as being one of an increased number of follicles, or 'multifollicular'. Therefore, the term PCOS can be replaced by anovulatory hyperandrogenism[21].

Hystological analysis has to represent the gold standard, therefore, and the performance of ultrasound must be considered against this.

These are important considerations because they show that the disease goes beyond the capabilities of ultrasound, which can only offer a superficial, macroscopic assessment of a complicated pathophysiological process[22].

Conclusions and future overview

In conclusion, the serum AMH level alone, with a cut-off value as 3.8 ng/mL is a useful marker for diagnosing PCOS and is correlated with conventional diagnostic criteria. The combination of the serum AMH level with HA and/or OA markedly increases the diagnostic capability for PCOS and can be introduced as an objective and well structured criteria. With evolving progress in ultrasound device, the recent studies have suggested increasing the threshold of AFC to 19 or even 26 follicles.

The real-time interpretation of 2D ultrasonography may underestimate the absolute number of follicles compared with 3D ultrasound. The 3D ultrasound requires further randomized studies to define the diagnostic criteria for PCOS. ■

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