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Review

New biomarkers for diagnosis and management of polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting young women. Even though the definition of PCOS has changed over the years, all diagnostic criteria include two or more of the following: oligomenorrhea/oligoovulation/anovulation, androgen excess and polycystic ovaries (PCO). Traditional method of assessing the ovarian morphology has been transvaginal pelvic ultrasound. Recent studies support that serum anti-Mullerian hormone (AMH) levels correlate with the number of ovarian follicles and cysts. Hence, measurement of AMH is adequate to make the diagnosis. Traditionally, hyperandrogenemia has been assessed by measuring total-testosterone. The literature stresses the importance of sex hormone binding globulin (SHBG) measurements and bioavailable-testosterone and free-testosterone calculations, because insulin resistance decreases SHBG, lowers total-testosterone, and leads to under-estimation of bioavailable- and free-testosterone. Since 50–60% of PCOS patients have metabolic syndrome, assessment of metabolic risk is also necessary. It is important to diagnose insulin resistance before development of glucose intolerance and diabetes. This requires measurements of not only plasma glucose but also insulin concentrations. Determination of HgBA1 can be informative as well. This review aims to present an accurate and cost-effective approach to diagnosis and management of PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a very common endocrine disorder affecting 6–10% of the women in reproductive age [1]. The syndrome was originally described by Stein and Leventhal in 1935 as combination of having multiple cysts in the ovaries, amenorrhea and androgen excess. Since then there have been three different definitions of PCOS (Table 1). Even though different definitions emphasize different aspects of the syndrome [2], all of the definitions include three main components: oligomenorrhea/oligoovulation/anovulation, androgen excess and polycystic ovaries (PCO) [3]. The 1990 definition by the National Institutes of Health requires presence of hyperandrogenism and oligomenorrhea, while having PCO by ultrasound is not mandatory. The 2003 definition by the Rotterdam workshop gives equal emphasis to all three, and having any two components fulfills the diagnosis [4]. The Rotterdam definition has been criticized because women without hyperandrogenism could be diagnosed with PCOS. The 2006 definition by the Androgen Excess PCOS Society emphasized androgen excess as the requirement and having either oligoovulation/anovulation or PCO fulfilled the diagnosis of PCOS [5]. (See Fig. 1.)

Definition of each criterion has also evolved. Currently hyperandrogenism is defined either clinically, as having hirsutism with Ferriman-Gallwey score ≥ 8, or biochemically, as having elevated total or free testosterone [6]. Oligomenorrhea is defined as < 9 menses per year. However, due to recent acceptance of oligoovulation as a criterion, women who have monthly menses can be diagnosed with PCOS if the cycles are not ovulatory. Finally, ultrasound criteria for PCO have been specified as ≥ 12 antral follicles, each smaller than 9 mm. Enlarged ovaries with volume of ≥ 10 ml are also accepted [7].

Definition of PCOS based on reproductive function and androgen excess ignores the metabolic aspects of the syndrome. In the USA, approximately 80% of the PCOS women are obese and 50% have metabolic syndrome [8–12]. Outside the USA, rate of obesity is 50%. Women with PCOS have 4-fold increase in prevalence of type 2 diabetes and 2.8-fold increase in gestational diabetes [13]. One out of 5 PCOS women develops diabetes before the age of 40 years [14]. Therefore, it

Abbreviations: ACTH, adrenocorticotropic hormone; AMH, anti-Mullerian hormone; FSH, follicle stimulating hormone; HgBA1, glycosylated hemoglobin; IRS1, insulin receptor substrate 1; LH, luteinizing hormone; NC-CAH, non-classical (adult onset) congenital adrenal hyperplasia; PCO, polycystic ovaries; PCOS, polycystic ovary syndrome; HBG, sex hormone binding globulin

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Table 1
Definitions of polycystic ovary syndrome.

	Hyperandrogenism	Oligomenorrhea/ oligoovulation	Polycystic ovaries
NIH	Yes	Yes	Optional
Rotterdam	Any 2 out of 3		
AE-PCOS Society	Yes	Any 1 out of 2	

was proposed that PCOS should be renamed as "Metabolic Reproductive Syndrome". Women who are diagnosed based on the NIH criteria are more likely to have metabolic abnormalities. When women are diagnosed based on the Rotterdam criteria, the women who have hyperandrogenemia are more likely to have insulin resistance as compared to the anovulatory women with normal androgen levels [11,15].

2. Morphologic evaluation

In PCOS, ovaries exhibit two types of dysfunction:

2.1. Ovarian follicles

During normal menstrual cycle, large numbers of follicles go through the maturation from primordial to pre-antral to antral follicles. One of the antral follicles is selected as the dominant follicle and ovulates, and the rest of the antral follicles regress. In PCOS, ovulation does not occur due to follicular arrest; the smaller follicles persist [16–20]. When examined by the ultrasound, these follicles appear as cysts. Hence, ultrasound findings of PCOS include > 12 cysts each smaller than 9 mm. A cyst larger than a centimeter is likely to represent a dominant follicle.

2.2. Ovarian size and stroma

The stroma of the ovary contains the theca cells which produce testosterone [21,22]. In PCOS, the stroma is enlarged, causing larger ovarian volume. When examined by ultrasound, the ovaries are larger than 10 ml [23,24].

3. Biochemical evaluation

3.1. Evaluation of the follicles/cysts

Anti-Mullerian hormone (AMH) secreted by the granulosa cells are now used as a biomarker to assess the number of follicles in the ovaries [25]. Follicles at all stages of development produce AMH; starting in the primordial follicles and reaching its peak in the preantral and small antral follicles [26]. As the follicles get larger and become FSH-dependent, AMH production decreases [27]. Anti-Mullerian hormone found in circulation is produced mostly by the follicles ranging 2–9 mm. Serum AMH levels correlate strongly with the antral follicle count determined by ultrasound [28].

Total number of ovarian follicles is increased in PCOS. This is especially true for the pre-antral and antral follicles which produce large amounts of AMH [29,30]. Several studies demonstrated that serum levels of AMH above 5 ng/ml (35.7 pmol/L) can be used for diagnosing PCOS [31,32]. Use of AMH in adolescent patients has been questions because adolescents can have PCO morphology without having the syndrome [33]. However, it was shown that in adolescent girls the average AMH concentration is around 3 ng/ml, regardless of ethnicity [34]. Hence, serum AMH is still a valuable tool for diagnosing PCOS during adolescence. Advantages of AMH measurement are that it can be done when transvaginal ultrasound is not feasible. It provides quantitation to the cysts and higher AMH concentrations may point to more severe disease [35]. It correlates with the phenotype: The highest levels of AMH are seen when all three components of PCOS (hyperandrogenemia, anovulation and PCO) are present. Hyperandrogenism has the weakest relationship to AMH [36]. Obesity can cause relative decrease in AMH in PCOS patients [37]. During ovulatory menstrual cycles, AMH levels are approximately 8% lower during the luteal phase as compared to the follicular phase [38]. However, this is not a significant factor for diagnosis of PCOS because the majority of the patients are anovulatory. Combined contraceptives suppress AMH levels regardless of the route of administration, in a time dependent manner, approximately by 30% to 50% [39,40]. Administration of GnRH agonist leupride also suppresses AMH [41].

Potential value of AMH in predicting the response to infertility treatment with clomiphene or gonadotropins has been investigated in PCOS. It appears that relatively lower AMH values are consistent better success rate in PCOS, and AMH concentration over 10 ng/ml may signal poor response to treatment [42,43].

Even though AMH is a very valuable biomarker, the assay can be challenging for various reasons: There are more than one form of AMH in the circulation. Anti-Mullerian hormone is secreted as an inactive pro-hormone, and becomes bioactive after cleavage and glycosylation [44,45]. In addition, AMH may not be stable during storage, and complements can interfere with the immunoassay. The normal range for AMH shows great variability depending age and sex; assays with different sensitivities are needed. Therefore, when using AMH as a diagnostic tool, it is extremely important to know the specifics of the assay employed.

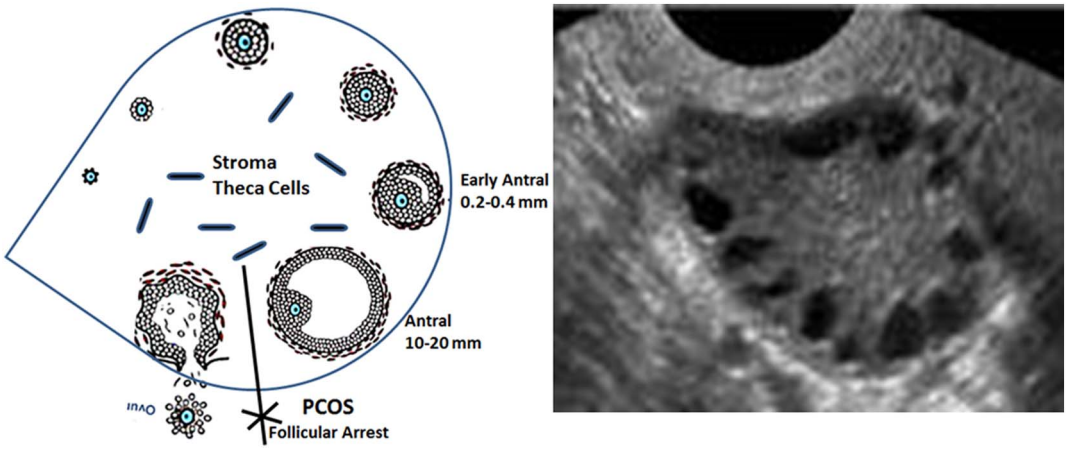

Fig. 1. Ovarian structure and follicle development in polycystic ovary syndrome and characteristic appearance of the ovarian cysts by ultrasound.