REVIEW

Polycystic Ovary Syndrome (PCOS), Diagnostic Criteria, and AMH

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Abstract

The polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility and a notable proportion of women of reproductive age are affected. It may constitute a risk factor for cancer development. Different factors could result in different manifestations and many of these are related to predispositions. It is essential to establish criteria to achieve an exact diagnosis of PCOS, especially among adolescent patients because of the overlap between features of PCO syndrome and physiological findings in puberty. Day by day the technology of ultrasonography is improving and accuracy is increasing, but remains dependent on the specific equipment available. Some factors are inter-related in determining PCOS prognosis. Serum AMH is synthesized by small antral follicles, which are precisely those seen on ultrasound and could help us to diagnose PCOS but there are many aspects that still require elucidation. In this mini- review we have attempted to identify some of these correlations.

Keywords: Polycystic ovary syndrome- anti-Müllerian hormone- diagnosis- treatment

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Introduction

Polycystic Ovary Syndrome (PCOS) is the most common cause of chorionic anovulation and anovulatory infertility (Wood et al., 2007; Dumont et al., 2015). PCOS is mentioned as a common endocrinopathy in women who are at reproductive age and it is associated with metabolic disorder and reproductive dysfunction (Wood et al., 2007; Spritzer, 2014; Agapova et al., 2014; Azziz et al., 2004). Ovarian dysfunction continues to be the main feature which makes this syndrome the major cause of anovulatory associated with infertility (Baker et al., 2007; Hamilton-Fairley and Taylor, 2003). Most say 5%-10% of reproductive-age women are affected (Dumont et al., 2015; Azziz et al., 2004; Zawadski and Dunaif, 1992) but some say 6.6%-8% (March et al., 2010; Franks, 1995) and some others say PCOS is a disorder affecting up to 6%-10% of women in reproductive age (Rackow, 2012).

This syndrome can be defined by specific clinical and bio-chemical criteria, and also using ultrasonography (Lujan et al., 2008).

Clinical manifestations of PCO include menstrual irregularities, signs of androgen excess, obesity, and sometimes hirsutism. Hirsutism is defined as a score of 8 or more on the modified Ferriman-Gallway index (Ferriman and Gallwey, 1961). Oligomenorrhea is also one of the clinical manifestations of PCOS. Oligo/amenorrhea cycles are defined as 8 or less cycles per year and biochemical androgen measurements should be fulfilled in follicular phase in patients with preserved menstrual cycles (Spritzer, 2014). The clinical manifestations of PCOS are heterogeneous and it looks possible that patients may present some of various symptoms and signs. The heterogeneity seems to be adjusted by several factors, such as genetic factors, nutritional condition in the uterus, prenatal androgen exposure, insulin resistance, exaggerated adrenarche, and body weight changes (Abbott et al., 2009; Oberfield et al., 2011; Zhang et al., 2013).

Environmental status and factors, such as obesity, appear to exacerbate the underlying genetic predisposition. PCOS is characterized by increased levels of circulating androgen, polycystic ovarian morphology (PCOM), arrested follicle development, and anovulatory infertility.

PCOS is commonly associated with insulin resistance, hyperinsulinemia, components of the Metabolic Syndrome, and oligo anovulatory cycles (Wood et al., 2007; Baker et al., 2007; Hamilton-Fairley and Taylor, 2003; March et al., 2010; Franks, 1995, Ehrmann, 2005; Legro, 2001; Tsikouras et al., 2015). Although some of the clinical symptoms and presentations of PCOS is dependent on age, ovarian failure and hyper androgenism (HA) are common characteristics at any age (Tsikouras et al., 2015).

Although the pathogenesis of PCO syndrome is unknown, but it is believed that PCO is the result of different interactions between genetic and multiple environmental factors. This syndrome is a multi-factorial disease, and the different susceptibility of patients is probably determined by several genetic and environmental

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risk factors as told above (Spritzer, 2014; Tsikouras et al., 2015).

While during childhood first signs of the syndrome can be perceptible, the unique features of PCOS in puberty are not yet clear. Despite all of these difficulties, PCOS early diagnosis has great and undeniable importance, because its presence is related to a greater risk of future infertility, disease which is related to cardiovascular system, diabetes mellitus (type II), MetS (metabolic syndrome). The PCOS diagnosis in puberty can be difficult, because anovulation is common in young girls (in the first two years of menarche half of menstural cycles are anovulatory), and multiple follicles display on ultrasound is also a fairly common finding during puberty (Santoro and Neal-Perry, 2010). Thus, the main findings at present which indicate diagnosis of the syndrome at this age are biochemical hyperandrogenism or clinical hyperandrogenism with hair excess.

PCOS is a disease that often presents during adolescent, but there is an overlap between features of PCO syndrome and physiological findings observed during the normal progression of puberty, and this matter makes the diagnosis more complicated in this age group (Roe and Dokras, 2011). Further, absence of universally accepted criteria for PCOS diagnosis for adolescents causes not to have a diagnosis with certainty and the variable diagnosis of PCOS poses a vast range of challenges. Different criteria that used for diagnosis of syndrome can result in different prevalence PCOS (Hart et al., 2011; Hickey et al., 2011).

Prevalence of the syndrome varies according to diagnostic consensus used, with estimates ranging from 9% according to National Institutes of Health consensus, up to 18% with the Rotterdam consensus (Azziz et al., 2004; March et al., 2010; Asuncion et al., 2000).

It is obvious that early diagnosis in adolescent age group would allow us for earlier treatment and even prevention of PCO-associated morbidity, but it should be noticed that premature diagnosis carries risks of psychological distress and unnecessary treatment (Agapova et al., 2014).

Numerous surveys have studied about appropriateness of applying adult criteria for adolescents because the sign of polycystic ovary syndrome during the post pubertal period overlap with normal physiologic changes in puberty. A high rate of menstural and anovulatory cycles could be observable in this age group, as well as difficulties that may occur in interpreting evidences of hyperandrogenism, either clinical or biochemical. A very common complaint is acne during adolescence but alopecia is one of the rare phenomena in girls, and sometimes hirsutism is border line and aggravates slowly (Spritzer, 2014; Carmina et al., 2010; Hardy and Norman, 2013). Thus, several criteria have been suggested specifically for adolescent. Carmina et al. 2010, and the 2012 ESHRE/ASRM criteria Workshop Group suggest PCOS definition for adolescents by the presence of all three of the Rotterdam 2003 (polycystic ovarian morphology, hyperandrogenism, and chronic anovulation) while Sultan and Paris proposes requiring four of five of: clinical hyperandrogenism, Oligomenorrhea or amenorrhea at least two years post menarche, biologic hyperandrogenism, insulin resistance, and polycystic ovary morphology (Carmina et al., 2010; Sultan and Paris, 2006; Fauser et al., 2012).

Criteria for diagnosis

Some sets of criteria for diagnosis have been proposed for PCOS: National Institutes of Health Criteria (NIH), defined in 1990 and include only presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhea anovulation (Zawadski and Dunaif, 1992). Later in 2003 the Rotterdam Criteria used polycystic ovarian morphology on ultrasound as a new criterion to be added to the two previous criteria of NIH. The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine Rotterdam consensus (ESHRE/ASRM) developed and enlarged the diagnosis of PCOS, requiring two of three features: anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) seen on ultrasound. Finally the Androgen Excess Society defined PCOS as hyperandrogenism with ovarian dysfunction or polycystic ovaries (Azziz et al., 2006). Thus the Androgen Excess Society (AES) considered that androgen excess is a central event in the development and pathogenesis of polycystic ovary syndrome, and established that androgen excess should be present and accompanied by oligomenorrhea or PCOM or both of them (Azziz et al., 2006).

Exclusion of other androgen excess disorders should be excluded such as non-classical congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess, as well as other causes of oligomenorrhea or anovulation (Spritzer, 2014).

PCOS and AMH

The Rotterdam Criteria considers the antral follicle count (AFC) on ultrasound as one of the diagnostic criteria. Day by day technology of ultra-sonography improves and accuracy of ultrasonography devices increases, so the number of follicles seen in ultrasonography increase too, but remain dependent on the specific equipment. Serum AMH is synthesized by small antral follicles, which are precisely the ones seen in ultrasound.

Even with the most advanced ultrasonography devices, evaluation of polycystic ovarian morphology (PCOM) for diagnosis of PCOS has high variability, and it can be difficult to count antral follicles trans-abdominally in virgins or obese. Thus, there is a need for objective parameters, and the serum AMH level could be useful for diagnosis of PCOS.

There is a problem to solve; the absence of a worldwide standard for serum AMH assay and inability to define thresholds make application of serum AMH level more difficult (Spritzer, 2014; Sahmay et al., 2014).

Anti-Müllerian hormone (AMH) was isolated and purified in 1984 (Rajpert-De Meyts et al., 1999). AMH is a member of transforming growth factor-beta (TGF-β) superfamily. It is secreted by the granulosa cells of small antral and pre-antral follicles to regulate early follicular development (Sahmay et al., 2014). AMH expression

starts around the 25th week of gestation and continues until menopause (Rajpert-De Meyts et al., 1999; Kuiri-Hanninen et al., 2011). AMH has an inhibitory effect on early follicular recruitment and causes a prevention of the entry of primordial follicles/oocytes (Iliodromiti et al., 2013). AMH also has minimal inter- and intracycle variability (Fanchin et al., 2005; Hehenkamp et al., 2006). AMH serum levels are closely correlated with the number of early antral follicles in both healthy women and women with PCOS (Franks et al., 2008; Pigny et al., 2003; Weenen et al., 2004) and it is mostly produced by granulosa cells of follicles from 2 to 9 mm in diameter (60%) precisely the ones seen in ultrasonography (Jeppesen et al., 2013). Serum AMH level has more sensitivity than the AFC because it also reflects pre-antral and small antral follicles (< 2 mm) which are hardly seen in ultrasound, therefore it is a deeper vision for growing follicular pool than the AFC (Dewailly et al., 2014). So AMH could be noticed as a suitable hormonal marker of the ovarian follicular count (Pigny et al., 2006) and we can assume that serum AMH level is an indirect reflection of ovarian reserve. So serum AMH level could be replaced by AFC and PCOM (van Rooji et al., 2002; Fanchin et al., 2003).

Using serum AMH assay has some benefits in comparison with other markers of ovarian reserve, for example its plasmatic level is quite stable from one cycle to another (Fanchin et al., 2005; van Disseldorp et al., 2010) but the AFC and the FSH E2 pair have to be measured on the first 5 days of the cycle (Hehenkamp et al., 2006; La Marca et al., 2006; Tsepelidis et al., 2007). It can be noticed that AMH level is independent from the hypothalamus-pituitary axis (Tran et al., 2011). A matter about AMH must be noticed, like other hormones; AMH can be influenced by some factors. Obesity is sometimes associated with a significantly lower level of serum AMH (Iliodromiti et al., 2013; Freeman et al., 2007; Steiner et al., 2010).

The cause of high production of AMH in antral follicles of PCOS is currently unknown but there is evidence to support a role played by androgens. Indeed a positive correlation between serum androgen and AMH levels has been reported and the production of androgens could be on intrinsic defect of thecal cells in PCOS (Pigny et al., 2003; Laven et al., 2004; Gilling-Smith et al., 1994; Carlsen et al., 2009; Eldar-Geva et al., 2005). Some investigators have suggested that increased AMH levels result from the stimulatory effect of androgens in early follicular grow (Jonard and Dewailly, 2004), and others have concluded that AMH can be utilized as a diagnostic marker for ovarian hyperandrogenism (Dewailly et al., 2010). Most researchers agree that AMH should be considered as a marker for increased ovarian reserve (Rosenfield et al., 2012). Impaired folliculogenesis may cause excess accumulation of pre-antral and small antral follicles, which may ultimately cause the increased AMH levels associated with PCOS (Wang et al., 2007).

In a study the utility of AMH in combination with PCOS features for diagnosis of PCO was assessed (Sahmay et al., 2014). When they evaluated AMH among the patients diagnosed with PCOS according to all three diagnostic criteria (the Rotterdam, Androgen Excess Society and National Institute of Health) as a single screening tool, it had relatively low sensitivity and specificity for diagnosis of PCOS. They suggested that satisfactory diagnostic potential can be achieved by combining the AMH level with other clinical symptoms. The combination of AMH levels (cutoff value = 3.8 ng/mL) with the presence of hyperandrogenism (HA) was found to have 73% sensitivity and 99% specificity for diagnosing PCOS among patients previously diagnosed with PCOS according to the Rotterdam criteria. Combined with oligo/amenorrhea (OA), the system showed 69% sensitivity and 99% specificity, and combined with either OA or HA resulted in 83% sensitivity and 100% specificity. They also found that increased AMH level was not correlated with BMI.

They found that AMH levels were significantly higher in PCOS patients with HA than without HA; indicating that HA is associated with an extra increase in AMH. This may reflect the severity of disruption of folliculogenesis in patients with HA. Serum AMH levels maybe related to the severity of the syndrome because they have been observed to be higher in women with insulin-resistant PCOS that in patients with normal insulin sensitivity (Fleming et al., 2005).

It is now undeniable that serum AMH is a valuable tool for the diagnosis of PCOS. However, it must be noticed that the thresholds for high serum AMH level, have to be reviewed and validated worldwide. There is a lack of well-defined population and some other matters like stability and heterogeneity of circulating AMH, wide range of values, inter-laboratory variability and different immunoassay used worldwide, but AMH can be introduced as a criteria for PCOS diagnosis.

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