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AMH and its Role in PCOS, a Mini Review

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PCOS is the one most common cause of infertility due to an ovulation and it is often diagnosed for the first time in the fertility clinics. The traits of the syndrome that female with an ovulatory or oligo-ovulatory PCOS exhibit include; hyperandrogenism, whether clinical and/or biochemical, and ultrasonic polycystic ovaries [1].

PCO affects about 10% of females. Increase in the burden of PCOS has led to a considerable amount of research into its risk factors, pathophysiology and the management [2]. There have been numerous theories that have been put forward for describing the etiology for an ovulation in PCO including; an excess of small antral follicles, hyperandrogenaemia, hyperinsulinaemia and dysfunctional feedback mechanisms [3].

Although PCOS is the most frequent endocrine disorder in women of reproductive age but its diagnosis remains one of the most challenging issues in endocrinology, gynecology, and reproductive medicine. It has been observed that for many years, different combinations of clinical (irregular menstrual cycles, hirsutism, and acne), biological (elevated serum testosterone or androstenedione levels or increased LH/FSH ratio), and Ultrasound (U/S) criteria have been proposed, with very little international consensus. In 2003 the Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine (ESHRE/ASRM)-sponsored PCOS consensus workshop group proposed that the diagnosis of PCOS should include two of the following three criteria: 1) oligo- and/or an ovulation, 2) clinical and/or biochemical hyperandrogenism and 3) polycystic ovaries on ultrasound [4]. It was proposed to include the Ultrasound (U/S) criteria in the definition of PCOS that is considered at the present time as the most specific, namely an increased ovarian volume (10 ml) and/or the presence of 12 or more follicles in each ovary measuring 2 - 9 mm [5]. But indeed, using a threshold of 12 for the Follicle Number Per Ovary (FNPO) showed that only 75% of PCOS patients were diagnosed whereas 99% of the normal women were under this cut off value [5]. Therefore this suggest that counting of the FNPO may not be easy to obtain with sufficient reliability by every group, moreover it is still debated whether a FNPO greater than 12 is specific of Polycystic Ovaries (PCO) [6].

Hence based on the recent research there are some new concepts which may help to coordinate past theories. Anti-Mullerian Hormone (AMH) is a member of the transforming growth factor ß family of growth and differentiation factors [7]. It has an integral role in the intrauterine development and sex differentiation of the male fetus. It is secreted from the Sertoli cells of the developing testes inhibiting ipsilateral mullerian duct development and thereby allowing the Wolffian duct system to prevail [8]. However, the role of AMH across the female reproductive life-span has only more recently come to light [2]. In the ovary, AMH has an inhibitory effect on primordial follicle recruitment as well as on the responsiveness of growing follicles to Follicle-Stimulating Hormone (FSH). The ovary-specific expression pattern in granulosa cells of growing non-selected follicles makes AMH an ideal marker for the size of the ovarian follicle pool and also a prognostic factor for fertility potential [7].

Women with PCOS have an increased number of small follicles in the pre-antral and antral stage, and therefore it is observed that their AMH serum concentrations are higher than their counterpart [2]. Since, Fallat., *et al*. first reported this in 1997, there have been several clinical studies that have confirmed the increased levels of serum AMH levels i.e. two to three times higher in PCOS compared with the lev-

els in women with normal ovaries [9-11]. Another study reported significantly elevated levels of AMH in normogonadotrophic, normoestrogenic, an-ovulatory patients compared with controls [12]. Moreover, female sufferings with PCO have higher levels of AMH whether obese or lean as compared to a female with no PCOS [13]. This has been reported in a study that recruited sample from a community that included both lean and overweight women. Elevated circulating AMH levels were found among PCOS females versus non-PCOS women, regardless of Insulin resistance and adiposity status [13]. Similarly another study suggested that non-obese adolescents with Polycystic Ovary Syndrome (PCOS) had higher levels of Anti-Mullerian Hormone (AMH) i.e. 1.49 times as compared to the controls [14].

Furthermore, AMH levels are positively correlated with individual features of PCOS, including LH concentrations, testosterone, mean ovarian volume and the number of ovarian follicles as reported by Laven., *et al* [10]. A recent study supports the finding that the level of AMH can help to demarcate between women with PCOS compared with women with polycystic ovarian morphology alone compared with controls [15]. Thus, not only is AMH elevated in women with PCOS but it also correlates with the severity of PCOS. It was reported in a recent study that the strongest group difference for AMH levels was found in the group with severe PCOS patients versus controls with age-adjusted odds ratio of 2.56 (95% Confidence Interval (CI) 2.00 - 3.27; $p < 0.0001$) [16]. Therefore, it is not just the mere increase in the number of these follicles that produce raised AMH levels but it is also the individual's follicles from a polycystic ovary that produces more AMH than their size-matched counterparts from a normal ovary. Findings from study by Pelatt., *et al*. suggests that the AMH production from the granulosa cells of a patient with ovulatory PCOS was three times higher compared with granulosa cells from normal ovaries and surprisingly, the AMH production from sized matched granulosa cells of a patient with an ovulatory PCOS was up to 75 times higher [17].

Hence as a diagnostic marker, AMH measurement has been found to offer a relatively high specificity and sensitivity (92 and 67%, respectively) for PCOS [11]. Thus in situations where accurate ultrasound data are not available or where there is lack of adequate quality of equipment used for sinology [18] AMH could be used instead of the follicle count as a diagnostic criterion for PCOS [11]. There was a study that suggested no association between AMH and PCOS but they believed that the study results may have been influenced by use of transabdominal U/S instead of trans-vaginal approach which usually tends to under estimate the prevalence of polycystic ovaries [19]. Hence in cases where vaginal scans are not feasible AMH may be used as a surrogate parameter in PCOS diagnosis [16].

In addition the use of AMH may also be useful in the therapeutic approach of PCOS patients. Indeed overweight women with PCOS who respond to weight loss with menstrual improvements have significantly reduced pre weight-loss AMH levels, indicating that baseline AMH may provide a potential clinical predictor of menstrual improvements with weight loss in PCOS [20]. Similarly, basal AMH level evaluation may be useful in the prediction of ovarian response to clomiphene citrate [21]. Finally it has been shown that metformin administration in women affected by PCOS is associated with a reduction in both AMH serum levels and antral follicles, suggesting that the measurement of AMH could be used to evaluate the treatment efficacy with insulin sensitizers [22].

Therefore through review we can propose the potential application of AMH as a diagnostic marker for PCOS. Moreover it will also be significant to clinicians for making their therapeutic decision.

Conflict of Interest

There is no conflict of interest.

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