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Short Communication

# AMH, Folliculogenesis and PCOS

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Anti-Müllerian hormone (AMH) is a glycoprotein which relates in structure to inhibin and activin from the transforming growth factor. The role of this hormone is pivotal for the differentiation and development of Folliculogenesis [1]. AMH is secreted by the granulosa cells of the primordial follicles which are recruited. This expression continues to increase until primordial follicles have developed into small antral follicles approximately 4 - 6 mm in size. It is not produced by the ovary after menopause [2]. AMH expression was not observed in primordial follicles, whereas 74% of the primary follicles showed at least a weak signal in the granulosa cells.

Granulosa cells of secondary, pre-antral and small antral follicles ≤ 4 mm in diameter showed the highest level of AMH expression, whereas AMH expression gradually disappeared in larger (4 - 8 mm) antral follicles. In conclusion, in the human, AMH expression pattern is similar to the mouse and rat, indicating an important role of AMH in folliculogenesis [3].

AMH production regulates folliculogenesis via inhibition of follicle recruitment from the resting pool aiding in selection of the dominant follicle, after the follicle is about 8 mm, its production diminishes [4]. AMH serves as a molecular biomarker in estimating the ovarian reserve beside its function as a product of the granulosa cells, which envelop each egg and provide them with energy. In humans, it can help in predicting time of menopause using the number of cells in the follicular reserve [5]. During the early follicular phase, AMH levels are proportional to the antral follicle count [6]. Unlike other ovarian reserve markers as FSH and Inhibin, AMH does not vary much throughout the menstrual cycle, which makes it easier to use as an accurate estimate of ovarian reserve [7]. Female fertility starts to decline from the early twenties because of decreasing ovarian reserve; a term that refers to both the quality and the quantity of the ovarian follicle pool. Because of social changes which delay the first pregnancy among working women, many women will be faced with unexpected fertility. Ovarian reserve declines in different patterns among women which makes it difficult to estimate an individual woman's remaining reproductive ability. Hence, the increased need for the development of sensitive biomarkers of ovarian reserve in order to aid in providing accurate counselling, prognosis and treatment of infertile women problems [8]. Serum AMH concentrations have been correlated with the number of small follicles and hence ovarian reserve. As a marker of ovarian reserve, AMH may be useful both in reproductive lifespan expectancy of women and to predict ovarian response to stimulation cycles for *in vitro* fertilization (IVF), namely poor and hyper-responses. Besides assessment of ovarian reserve, AMH role is evolving in the diagnosis and management of various ovarian pathologies, including polycystic ovary syndrome (PCOS), granulosa cell tumours and early ovarian aging. Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age group [9], with a prevalence of 10 - 15% worldwide [10]. It is a heterogeneous, multisystem syndrome which presents with wide various clinical features and delayed sequel like type [11]. It is caused by imbalance of sex hormones FSH, LH, Testosterone, Estrogen which ultimately leads to menstrual irregularities, infertility, anovulation and other metabolic disturbances [12]. The Rotterdam consensus 2003 is the gold standard for diagnosing PCOS if 2 out of 3 criteria are present: (1) oligomenorrhea or amenorrhoea, (2) clinical and/or biochemical hyperandrogenism and (3) polycystic ovarian morphology on ultrasound with a cut- off of more than 12 follicles with a diameter of 2 - 9 mm or when ovarian volume is more than 10 $cm^3$.

Serum AMH has been used to quantify and qualify the response of ovarian follicles to ovulation induction as well as *in-vitro* fertilization (IVF) programmes. In women without PCOS, serum AMH has been found to be directly proportional with ovarian response to gonadotrophin stimulation [13].

In the past years, several studies have implicated anti-Müllerian hormone (AMH) in the pathophysiology of PCOS. It has been hypothesised that the high serum AMH levels lowers follicular sensitivity to circulating FSH thus preventing follicle selection resulting in follicle arrest at the small antral phase with failure to produce a dominant follicle. AMH also inhibits aromatase activity resulting in reducing follicular production of estragon (E2). This low level of E2 may add to the failure of ovum selection [14]. In the absence of AMH, more primordial follicles are recruited and FSH sensitivity was increased [15]. Several studies have shown that AMH reduces FSH- induced aromatase (Cyp19a1) expression and the secretion of oestrogen (E2) by human antral follicles, and that in follicular fluid, there is an inversion between AMH and E2. Hence, it is suggested that AMH in humans acts as a protector of follicle growth by preventing premature selection and E2 production of small antral follicles [16]. In PCOS, where AMH levels are increased, it displays an effect on follicular growth/survival and FSH sensitivity increasing exacerbation and leading to increased follicle numbers combined with follicular arrest. Several studies showed that the increased serum AMH level in PCOS is not only explained by the increased follicle number but also by increased production per follicle compared to normal ovaries [17]. It is noticed that the higher the AMH levels the higher the severity of PCOS symptoms, it is higher in PCOS patients with amenorrhea than in those with oligomenorrhea who had higher levels than those who have normal cycles [18]. AMH levels are higher in PCOS patients who do not ovulate than regularly ovulating patients who have polycystic ovaries [19]. AMH opposes the action of FSH [20]. FSH levels are lower in PCOS patients than in patients with normal ovaries although it is still within normal range [21]. PCOS patients are treated with FSH injection to promote ovulation or clomiphene citrate to promote FSH surge, hence it is suggested to have a role causing anovulation of those patients [22]. Amer., *et al*. (2013) postulated PCOS women with markedly raised circulating AMH seem to be resistant to hMG ovulation induction and may require a higher starting dose. They found circulating AMH levels to be negatively correlated with ovarian response to hMG. They have identified a cut-off level of serum AMH concentration (4.7 ng/ml), above which the chances of good ovarian response were markedly reduced from 100% (in women with lower AMH) to 35%. Furthermore, they have demonstrated that PCOS women with higher levels of AMH need increased doses and duration of HMG treatment. Furthermore, higher cancellation rates are seen in high AMH patients [23]. The same group studied the response of PCOS patients to induction of ovulation with clomiphene citrate, PCOS women with high circulating AMH (≥ 3.4 ng/mL) seem to be CC resistant and might prompt an increased dose [24].

Some authors hypothesised that that a higher AMH counteracts the effect of FSH which inhibits ovulation resulting in low progesterone. A positive feedback promotes LH and insulin release. This, in turn increases androgen production which accelerates the progress of primordial follicles to pre-antral and small antral follicles, which in turn, produce AMH, creating a vicious circle. They suggested, as a strengthening factor for their theory that surgical reduction (laparoscopic ovarian drilling) of these follicles restores normal ovulation by cutting this vicious circle. Amer., *et al*. (2017) revealed a statistically significant decline in serum AMH concentration after laparoscopic ovarian drilling [25]. Elting., *et al*. (2003) demonstrated that it is not infrequently women above 40 restore regular cycles probably because of accelerated loss of follicles at that age [26].

In conclusion, the greater the number of small antral follicles, the greater the ovulatory disturbance. The number of the pre-antral and small antral follicles reflect the level of AMH in serum which in turn cause the ovulation disturbance and infertility.

## Key Notes

1. AMH plays an important role in folliculogenesis.
2. It is secreted by the granulosa cells and the highest level of it is present in the granulosa cells of secondary, preantral and small antral follicles ≤ 4 mm in diameter.

3. Can be used to estimate ovarian reserve, to predict the onset of menopause, diagnose and mange PCOS, Granulosa cell tumour as well as early ovarian aging.

4. AMH is higher in PCOS patients with amenorrhea than in those with oligomenorrhea who had higher levels than those who have normal cycles.

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