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New Findings on Anti-Mullerian Hormone in Polycystic Ovarian Syndrome Patients

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Abstract

Polycystic Ovarian Syndrome (PCOS) is the most complex and common endocrine disorders in women, associated with a wide range of symptoms such as, irregular menstrual cycle, acne, hirsutism and weight gain. Despite extensive research, the pathogenesis of the disease is not known yet. Genetic, endocrine and environmental factors have been discussed in the pathogenesis of PCOS. Compared with the general population, PCOS patients are at a greater risk of uterine cancer, cardiovascular problems and metabolic complications. Each of these issues may lead to death. However; Anti-Mullerian Hormone (AMH) is a unique biomarker of ovarian function in assessment of women's health. In addition, this can be used in treatment of infertility. It is argued that the amount of AMH in women with PCOS is more than normal but the cause of this increase has not been identified yet. Therefore, more research is needed to understand the role of this hormone in the pathophysiology of PCOS and its relationship with other factors. In this study findings regarding the anti-Mullerian hormone and polycystic ovary syndrome are reviewed.

Keywords: Anti-Mullerian Hormone; Infertility; Metabolic disorders; Polycystic ovary syndrome

Introduction

Polycystic Ovary Syndrome (PCOS) also known as chronic hyper androgenic syndrome or indolence ovary is associated with anovulation, and is said to be the most common endocrine, metabolic and multifactorial disorders, in women of childbearing age. This syndrome may have possible genetic origin and has the prevalence about 4-18%. According to the Stein and Leventhal in 1935, this syndrome known with menstrual problems, protests clinical and biochemical hyperandrogenism and polycystic ovaries [1]. PCOS have mentioned as 75% of infertility due to anovulation. In addition to infertility, this syndrome is associated with insulin resistance, hyperinsulinemia, hyperandrogenism, metabolic syndrome and increased risk of diabetes properties [2-4].

Although, the pathogenesis of PCOS is complex and not fully understood, but studies suggest that androgens and insulin are major causes of the disease [5]. Insulin has a major effect on the ovarian follicles, so hyperinsulinemia is associated with stunted growth of premature ovarian follicles [6]. Hyperandrogenism can increase the number of follicles in women with PCOS [7]. People with PCOS have higher levels of testosterone, insulin, triglycerides and cholesterol as well as lower levels of Sexual Hormone Binding Globulin (SHBG), and Follicle Stimulating Hormone (FSH) compared to healthy individuals [7, 8] (Figure 1).

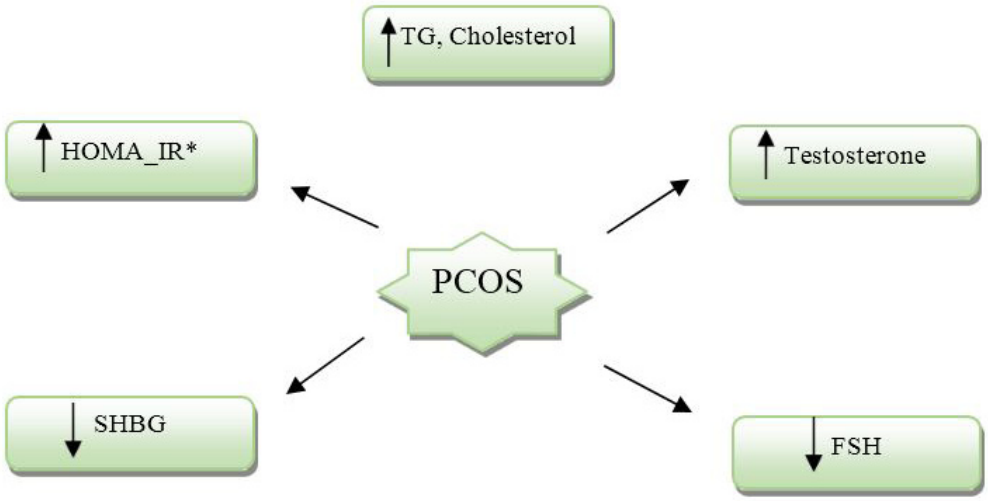

Figure 1: Characteristics of polycystic ovary syndrome.

For the first time, anti-Mullerian hormone became known because of its role in the differentiation of male reproductive system. AMH is secreted by sertoli cells and causes regression of müller duct in men. In 1980, for the first time AMH was detected in ovarian granulosa cells and later it was reported that the hormone had been produced from ovarian granulosa cells in 36th week of pregnancy and this process containing until menopause [9]. In women, the hormonal effects also exist after birth, so it is clear that serum levels of anti- Mullerian hormone is one of the ovarian reserve markers. In 1997, Fallat et al. argued higher levels of AMH in women with PCOS compared with normal population, yet the exact cause of this rise has remained unknown. It is likely that ovarian androgen levels are the decisive factor, because studies have shown a correlation between the levels of AMH and androgens. Therefore, the increased number of follicles following by hyperandrogenism leads to increased production of anti-Mullerian hormone. There is also a link between insulin resistance and AMH [10].

Anti-Mullerian Hormone positively is associated with issues such as concentrations of Luteinizing Hormone (LH), testosterone, mean ovarian volume and the number of ovarian follicles [11]. Number of studies have shown that AMH is also associated with an increase in severity of PCOS [12]. Also, there is an inverse relationship between age and Anti-Mullerian hormone levels, gradually increasing with age contributing to diminished levels of AMH. This represents a gradual decrease in the number of follicles and leads to the stage of menopause [9]. (Figure 2).

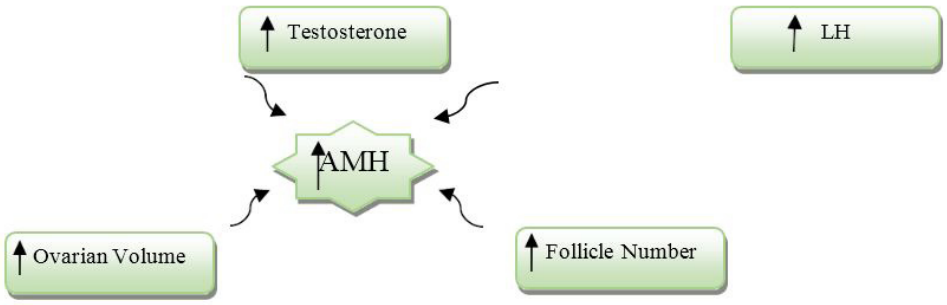

Figure 2: Factors influencing the increase in anti-Mullerian hormone.

Anti-Mullerian Hormone: Physiology and Function

AMH is a 140-kDa homodimer glycoprotein with disulfide connections and a member of transforming growth factor-β family, its gene is located on chromosome 19 (19p13.3). It is not clear exactly in what stage of folliculogenesis this hormone is secreted, but in

general we can say that this hormone is produced by granulosa cells of primary, pre-antral and small antral follicles (4-6 mm) and its secretion gradually declines during the later stages of follicular growth. In specific, it is undetected in follicles greater than 8 mm [9]. This stop in AMH production is essential for the process of selecting the dominant follicle [8]. Serum levels of AMH are associated with the number of small follicles and with the ovarian reserve. The Size of the small follicles are relatively stable during the menstrual cycle and it would appear that AMH concentration has some fluctuations during the menstrual cycle, thus, measure it in each day of the menstrual cycle is reliable, however a specific threshold of AMH levels has not yet been defined in normal subjects and in patients with PCOS [9].

Animal studies indicate that AMH has an inhibitory effect on the primordial follicles maturation, thereby in this way preventing the fast completion of these follicles. AMH also makes follicles less sensitive to FSH and plays an important role in normal folliculogenesis [10-11]. With the arrival of a follicle to a certain size (8 mm) during follicular growth, AMH expression is reduced, resulting in an increased sensitivity of the follicles to FSH in circulation, thus lower levels of AMH provides an opportunity for follicular growth and ovulation time. Previous studies have shown that serum concentration of AMH increased 2-3 times in PCOS women than normal individuals. Followed by that, an increase of 2 to 3 times of the number of small follicles (2-5 mm) was also seen [12-13]. So we can say that increasing concentrations of AMH could be involved in the pathogenesis of PCOS. It seems that AMH can cause anovulation in patients with PCOS in three ways: Increased serum concentrations of AMH reduces the sensitivity of antral follicles to circulating FSH, and after that it prevents the selection of the dominant follicle; Leading to an end in antral follicle growth phase, and causing anovulation in patients [14-15]. Moreover, results of some studies have shown that AMH reduce the number of LH receptors in granulosa cells and prevents ovulation in PCOS [16]. Studies suggest that AMH inhibits the activity of the aromatase enzyme, leading to reduction in follicular estradiol production and as a result, the estrogen level is decreases, associating with a defect on dominant follicle selection [15]. [Figure 3].

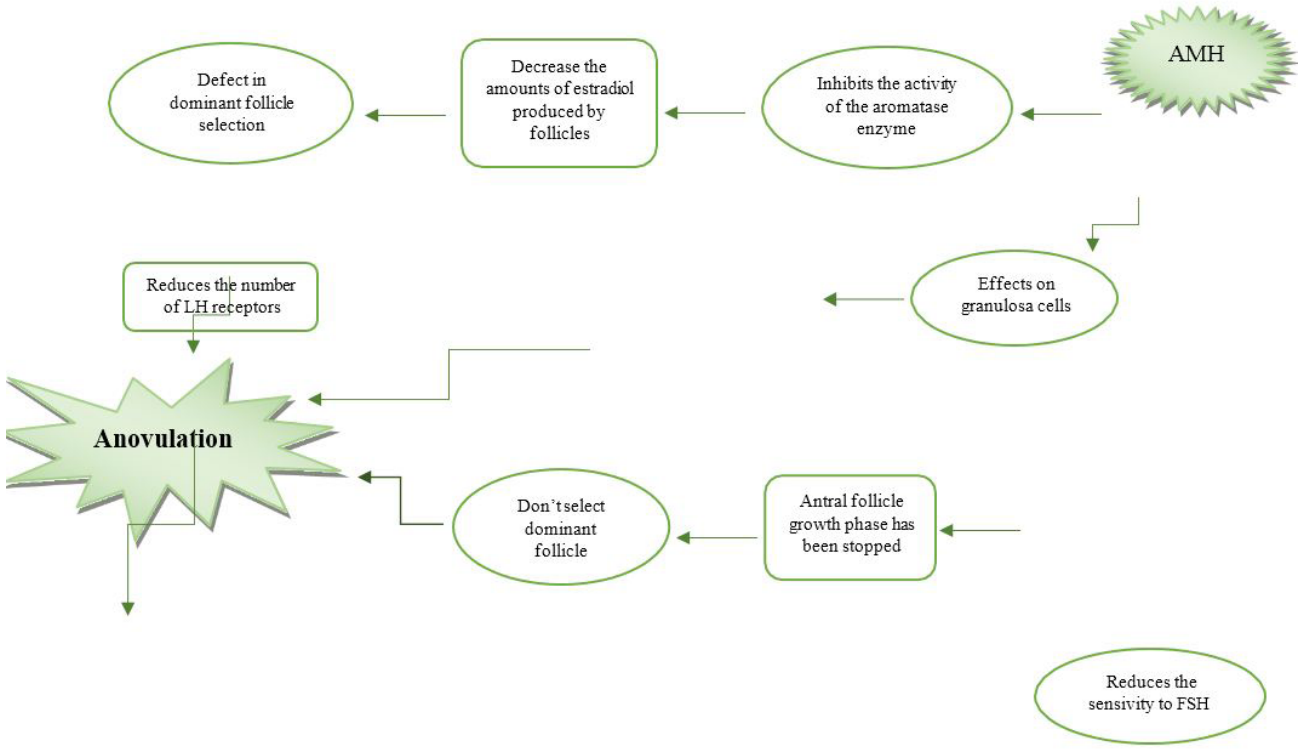

Figure 3: Performance of Anti-Mullerian Hormone in the absence of ovulation in patients with PCOS AMH relation to fatty tissue in PCOS.

Since early 1980s, it has been suggested that PCOS may have links to obesity, glucose intolerance and biochemical signals of insulin increased levels. The actual prevalence of obesity in patients with PCOS is still by unknown, and findings suggest that it is affected by racial diversity. It is estimated that about 50% of women with PCOS are obese. Obesity has a negative effect on

body's hormone metabolism; and it seems that hormones secreted from adipose tissue can be associated with AMH levels in PCOS. Further studies are necessary to explain this relationship [13-16].

Some Studies suggest that in obese patients, serum level of AMH is reduced and obesity is associated with an increase in levels of leptin and reduction of adiponectin. Correlation between AMH level and related factors from adipose tissue have not been reported clearly [17-21].

Results have shown that nutritional status and obesity can affect AMH synthesis [13-16]. Some researchers have reported lower levels of AMH in obese women and an inverse relationship has been achieved between AMH and BMI [17, 18], while others could not identify a link between nutritional factors, BMI and AMH [19, 20]. A recent study has shown that leptin and not adiponectin may affect the synthesis of AMH in women. Based on the above, we can conclude that there is an inverse relationship between the level of insulin, HOMA-IR (insulin resistance) and AMH. Furthermore, there is a positive correlation between AMH and adiponectin [21]. Other findings suggest that hormone deficiency is linked to obesity and fat tissue is associated with decreased ovarian reserve in obese women with PCOS and non-obese women with PCOS [22]. [Table 1].

Authors	AMH	Results
Olszanecka-Glinianowicz et al. 2015 [21]	Leptin, Adiponectin	An inverse relationship between Insulin, Insulin resistance and AMH, also there is a positive correlation between adiponectin and AMH
Montazerifar et al. 2016 [22]	Omentin-1	Inverse relationship between Omentin-1 and AMH
Wafaa et al. 2016 [23]	Adiponectin	Adiponectin levels decreased and AMH increased significantly in PCOS
Hamza et al. 2016 [24]	Leptin	No relationship between Leptin and AMH
Merhi et al. 2013 [25]	Leptin	Leptin suppresses AMH gene expression through the JAK2/STAT3 pathway in luteinized granulosa cells of women undergoing IVF
Sahmay et al. 2013 [26]	BMI	No relationship between BMI and AMH
Buyuk et al. 2011 [27]	BMI	Decrease AMH in obese women

Table 1: Summary results of some studies related to obesity, hormone secreted by adipose tissue and its relationship with AMH in PCOS.

Relationship Between Anti-Mullerian Hormone and Oxidative Stress and Anti-Oxidants

PCOS with abnormal levels of oxidative stress and inflammatory markers have been linked and oxidative stress may have a role in the pathophysiology of PCOS. According to recent studies have proved to show a negative association for the iron and obesity with ovarian volume and levels of AMH in PCOS. Ferritin and Transferrin binds to iron are significantly higher in PCOS group and this difference in obese patients is higher. The study showed that obesity and increased levels of ferritin as an antioxidant is negatively associated with ovarian volume and the level of AMH in women with PCOS [28].

Oxidative stress is an imbalance between free radical production and antioxidant defenses of the body [29] and may increase insulin production and androgen production in the ovaries and distribute in folliculogenesis. Many studies have shown high levels of oxidative stress markers such as serum malondialdehyde (MDA) and decreased serum total antioxidant capacity (TAC) with disturbances in lipid profile in patients with polycystic ovary syndrome [30] [Table 2].

Other studies have shown that oxidative stress involved in pathogenesis of insulin resistance and hyperandrogenism and anovulation in women with PCOS [Table 2].

Authors	Factors	Results
Hamza et al. 2016 [24]	And Antioxidant AMH	Anti-oxidants have positive effects on AMH and Inhibin B
Yong et al 2015 [28]	AMH and Ferritin ,teransferin bound iron	Obesity and increased levels of Ferritin as an anti-oxidant have a negative effect on ovary volume and AMH levels in PCOS
Koninger et al. 2014 [31]	AMH and Afamin	There isn't a significant relationship between Afamin (A binding protein to the vitamin E anti-oxidant) and AMH
Diamanti-Kandarakis et al. 2009 [32]	AMH And AGEs Advanced glycosylated end products	There is an increased levels of AGEs and AMH in PCOS and a positive correlation between these factors and anovulation detected which means that a relationship between this stress oxidative marker and AMH may exist in anovulation mechanism

Table 2: Results of some studies on antioxidants and oxidative stress in patients with PCOS and their relation to AMH.

Anti-Mullerian Hormone in The Diagnosis of PCOS

A diagnostic criterion for PCOS has been the subject of various studies in recent years. Rotterdam criteria (2003) is the main methods used by researchers and clinicians to recognize PCOS. And its use in thought to be associated with problems in diagnosis such as, the unavailability of reliable ultrasound, Inability to recognize oligo menorrhea and amenorrhea due to the defected history taken from patients, and the lack of specificity for PCOS. As a result, efforts to achieve an accurate and simple method for the diagnosis of PCOS continue yet [33-38]. Since serum anti-Müllerian hormone is associated with ovarian follicles growing, recently it is considered as a measurement of AMH as a diagnostic marker of ovarian function [39].

Numerous studies have shown that serum levels of AMH in PCOS women increase around 2 to 3 folds compared to normal individuals [39-42]. In fact, AMH levels related with the number of follicles in the ovaries seen by ultrasound and levels of testosterone, LH and other factors which are identified in PCOS. So the level of AMH can be indicative of PCOS in women with hyperandrogenism and oligo menorrhea or amenorrhea, in cases where reliable ultrasound is not available [43-47].

Anti-Mullerian Hormone - Drug Treatment

The effects of treatment on AMH levels in patients with PCOS is different, because certain studies have shown that following the treatment of patients with drugs such as metformin and dexamethasone, AMH levels do not change, and at some metformin therapy in PCOS women, AMH significantly reduces and improves reproductive function and insulin resistance and hyperandrogenism [48-50]. Improvement in insulin resistance and hyperandrogenism with follicle growth stimulation and decrease in their number reduces the amount of AMH. However, the decrease in AMH happened after 6 months' treatment and improvement in the process of ovulation was evident after 4 months. Thus, changes in AMH are delayed until time to call a new group of antral follicles with normal androgens and insulin under new conditions [49].

Anti-Mullerian Hormone and Response to Infertility Treatment

It is argued that the amount of AMH may be an indicator of antral follicles, and as a result, this can predict poor ovarian response and the lack of pregnancy in women with PCOS undergoing infertility treatment. The results of some studies are summarized in Table 3:

Authors	Results
Mehrabian et al 2016 [51]	AMH is not an appropriate predictor of responding to treatment with clomiphene + gonadotropin in women with PCOS
Kim et al. 2013 [52]	AMH is not an appropriate predictor of responding to treatment with clomiphene + gonadotropin in women with PCOS
Amer et al. 2013 [53]	AMH is an appropriate predictor of responding to treatment with gonadotropin in women with PCOS. There is an resistance to gonadotropins in women with a high levels of AMH
Aleyasin et al. 2011 [54]	There is not a specific relationship between AMH and pregnancy rate in PCOS but there is a significant relationship between AMH and the number of oocytes, mature oocytes and implanted fetus

Table 3: Results of some studies related to infertility in women with PCOS AMH and response to treatment.

Conclusion

In conclusion, it is argued that further studies are essential in this field in order to understand the associated issues raised above. The Study of AMH can increase our knowledge about ovarian physiology and its associated pathophysiology. The relationship between different factors such as androgens, FSH, LH, ovarian steroids and other internal and external factors has been the subject of studies in recent years, but the role of AMH in ovarian and folliculogenesis defects is not yet clear.

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