

REVIEW

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Role of anti-Mullerian hormone in polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common gynecological endocrine disorders affecting up to 10% of all females in their reproductive age, and its cause of onset is still elusive. A spectrum of recent research reflected diverse associations between increased plasma level of anti-Mullerian hormone (AMH) and different clinical features of PCOS. Since AMH levels reflect the pool of growing follicles that potentially can ovulate, it can be stated that serum AMH levels can be used to assess the “functional ovarian reserve,” rather mentioning it as the “ovarian reserve.” AMH also appears to be a premier endocrine parameter for the assessment of atrophied ovarian follicular pool in response to age of individuals. AMH hinders the follicular development as well as the follicular recruitment and ultimately resulting in follicular arrest which is the key pathophysiologic condition for the onset of PCOS. Furthermore, FSH-induced aromatase activity remains inhibited by AMH that aids emergence of other associated clinical signs of PCOS, such as excess androgen, followed by insulin resistance among the PCOS individuals. Given the versatile association of AMH with PCOS and scarcity in literature explaining the underlying mechanisms how AMH relates with PCOS, this review article will discuss the roles of AMH in the pathogenesis of PCOS which may introduce a new era in treatment approach of PCOS.

Keywords: Anti-Mullerian hormone, Folliculogenesis, Gonadotropins, Ovarian reserve, Polycystic ovary syndrome, Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is the most common gynecological endocrine disorders affecting up to 10% of all females in their reproductive age [1, 2]. In the year of 1935, Stein and Leventhal first pointed out the PCOS condition among seven patients suffering from amenorrhea, infertility, and hirsutism [3]. The disease is mainly characterized by an excess availability of androgen and ovarian dysfunctions [4]. Several research articles indicate that PCOS is the most common endocrine

and metabolic disorder in women of reproductive age [5–7]. The presence of any two of the conditions, i.e., the presence of oligo or anovulation, clinical or biochemical androgen excess or polycystic ovarian morphology detected by ultrasonography can be used as an identifying tool for the diagnosis of PCOS [8]. Insulin resistance, obesity and impaired gonadotropin release [3] is also correlated with PCOS. Apart from hormonal imbalance, genetic and environmental factors are also responsible for the disease [9]. Empirical studies carried out in pregnant rhesus monkeys treated with androgens showed morphological changes within ovary which are similar to PCOS and several PCOS associated symptoms in their female off-springs [10].

Anti-Müllerian hormone (AMH) known as Müllerian-inhibiting substance (MIS) is a homodimeric glycoprotein in nature belonging to the superfamily of

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transforming growth factor- β [11]. The “p” arm (small) of chromosome 19 contains the gene for AMH [12]. By considering its structure, AMH is also linked with other members of transforming growth β (TGF- β)-like inhibin and factor-bone morphogenetic proteins (BMP), etc., which are also regulator of ovarian folliculogenesis [13]. Besides that, they show wide range of functions due to their extensive expression as ligand, whereas the expression of AMH is limited to the primary sex organs only and thus probably exerting its action only on the reproductive organs [14]. Emerging evidences reveal that the serum level of AMH is 2–threefold increase in women suffering from PCOS compared to a normo-ovulatory control woman [15, 16]. AMH released from the granulosa cells of the ovarian follicles is a prime factor responsible for folliculogenesis in the ovaries [17]. In spite of substantial investigations and research work, the role of AMH remains elusive in PCOS, i.e., whether AMH is a significant marker of PCOS or a component accountable for PCOS. Henceforth, the aim of the present review article is to enumerate the physiological cross-talk between

AMH and PCOS besides discussing relevant studies highlighting the possible roles of AMH in the complex pathophysiology of PCOS (Fig. 1).

AMH and its receptors in ovary

AMH is synthesized as a pro-hormone. After its secretion, it participates in various biochemical pathways to produce a transforming growth factor- β -like functionally active C-terminal disintegrates which are noncovalently-attached [18, 19]. Ovarian granulosa cells are the only source of AMH [20], its concentration is inversely proportional with age, and it becomes faint after the menopause [21]. But its minute alteration in concentration can be seen during the menstrual cycle which is not so much significant [22–24]. Sertoli cells also express AMH in male reproductive system which inhibits the development of Müllerian ducts during the embryonic life and thus acts as a marker for the sexual differentiation besides differences in two different reproductive tracts [25–28]. When there is no influence of AMH, the Müllerian ducts give rise to the development of fallopian tube,

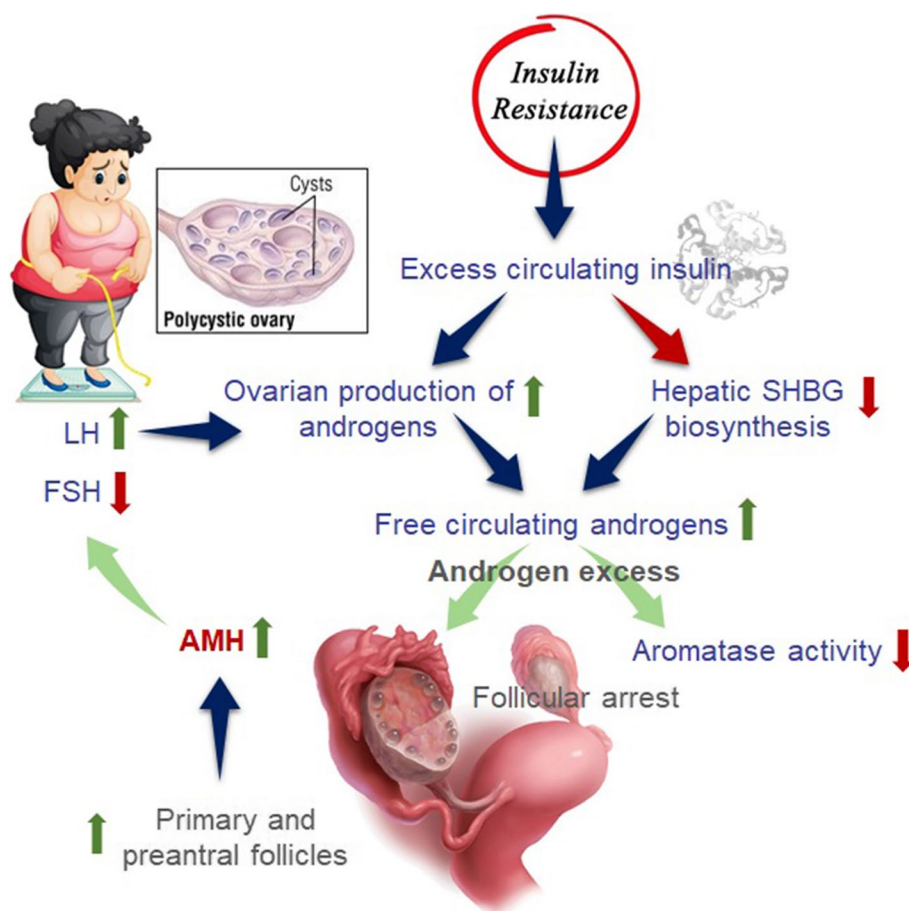


Fig. 1 Anti-Müllerian hormone (AMH) in the pathophysiology of polycystic ovary syndrome (PCOS)

uterus, cervix, and the upper one third of the vagina, and any alterations in AMH levels or its receptors may disrupt the development of female reproductive system [29]. The appearance of AMH usually be observed from the primary follicle stage during folliculogenesis; meanwhile, as this phase is FSH-dependent, the peak level of AMH expression is also observed from pre-antral and small antral follicles developed through the folliculogenesis and then gradually decreases along with the size of the follicle viz. the absolute absence of expression will be seen in the follicles' diameter with more than 8 mm [20, 30]. This pattern of AMH expression has been illustrated in several studies by comparing the expression of AMH-mRNA and AMH concentration respectively in the isolated human granulosa cells (GC) and in the follicular fluid [31, 32]. The expression of ovarian AMH and mRNA of anti-Müllerian hormone receptor type II (AMHR II) were explained by Baarends et al. [33] in in vivo adult rat model; also, it was observed that both the expressions were attenuated by the action of FSH and estrogen during the differentiation of antral follicles and which is thought to be a crucial event required for follicular selection [17, 34] as it is well-known that AMH hinders the follicular development. For the support of this last statement, an increased rate of folliculogenesis was observed with the involvement of multiple numbers of growing follicles in AMH knock-out animal [35, 36]. AMH-induced lack of FSH sensitivity was observed in granulosa cells, and it was also confirmed in vivo in AMH deficient mice [36]. In primates, declined follicular growth or development resulted by AMH due to depletion in FSH as well as cAMP-induced aromatase action indicating that AMH attenuated the mRNA expression of aromatase and mRNA expression of luteinizing hormone (LH) receptor-stimulated with cAMP and FSH, respectively [37]. In human granulosa cells, downregulation of aromatase mRNA expression and reduced synthesis of estradiol were obtained after the administration of AMH [34, 38]. Regarding the same, during the culture of the follicles, AMH was also responsible to lower the development of initially growing follicles [20]. Anti-Müllerian hormone receptor type I (AMHRI) and anti-Müllerian hormone receptor type II (AMHR II) are the two different types of transmembrane receptor proteins responsible for the AMH actions which are nothing, but the serine–threonine-specific kinase proteins and generally SMAD proteins [receptor-regulated Smads (R-Smad) and common Smad (Smad4)] [18] are the cytoplasmic effectors for these two receptors. These receptors are located on reproductive organs and on the Mullerian ducts [39]. Abundant expression of AMH and its receptor usually observed on the granulosa cells of follicles entered in preantral and small antral phases [40]. Establishment of

expression of AMHR II mRNA in theca cells indicates a chance of intercellular AMH signaling control during the folliculogenesis [41]. Overall, AMH inhibits premature recruitment of the follicles and follicular maturation of the follicle during the folliculogenesis interestingly, and AMH will be suppressed if the follicles become large antral follicles followed by increased FSH (follicle-stimulating hormone) sensitivity leads to greater production of estrogen followed by two other physiological process, i.e., selection of follicle and successive release of ovum as seen in the normal ovary.

Role of AMH as a marker of ovarian reserve

The term “ovarian reserve” denotes the quantitative and qualitative measures of standing oocytes in both the ovaries, viz senile ovary can be defined as age related dwindle of ovarian reserve. Consequently, the remaining count of primordial follicles considered as a foremost marker to determine the ovarian reserve [42] which is burdensome to determine directly, although the width of the standing primordial follicular pool appears to be associated with the count of follicles that throw oneself into the pool of growing follicles [43–45] and these growing follicles are the only sources of AMH. Thus, circulating AMH level appears to indicate the size of the standing pool of primordial follicle as seen in different studies [46–49]. Nevertheless, there are no such clear evidences regarding the correlation between AMH level and oocyte quality, whereas the age-related declination of follicular pool was observed to be an explanation of diminished oocyte quality [50, 51]. Along with the number of primordial follicles, some endocrine parameters like FSH, estradiol, and inhibin B and ultrasonographic parameters like count of antral follicles and determination of ovarian volume are also considered as markers of ovarian reserve. Estimation of those parameters are directly or indirectly related with measurement of antral follicular pool. Quantitative assessment of antral follicle can be done directly by ultrasonographic estimation, whereas the estimation of inhibin B and estradiol levels during early follicular phase can be considered as indirect quantitative measurement of these antral follicles. On the other hand, both inhibin-B and estradiol are considered as strong predictive marker of antral follicular pool indirectly, as they usually control the FSH level by a negative feedback loop. Likewise, age-related declination of oocyte quantity leads to decreased levels of inhibin B and estradiol causes increase in FSH level [52]. But AMH is determined as a better marker forever for the quantitative assessment of oocyte/follicle pool than those three endocrine markers because of its stable plasma concentration even between the cycles. However, FSH, estradiol and inhibin B show fluctuations [53, 54] between the

cycles. Henceforth, AMH demonstrates the sustained non-cyclic development of the follicles. Thus, comparatively less influence of AMH levels can be observed by such circumstances that deaden the later FSH-dependent phases of follicular growth as seen during pregnancy [55] or hormonal contraception [56, 57] or hormonal therapy with gonadotropin-releasing hormone (GnRH) agonist [58]. Moreover, regarding the ovarian reserve, the exact cutoff value of AMH is lacking till date; but multiple longitudinal evidences has described that AMH appeared to be as best hormonal parameter to determine the ovarian aging [59, 60] and can be used as a predictive marker for the onset of menopause [61–63]. Interestingly, in case of fertile or infertile women, stress or any other psychological conditions are not related to AMH level. However, the link in between obesity and AMH remains controversial [64–68] and probably that same arguments were also observed in the relationships between the AMH and body mass index (BMI) [69, 70]. On the other hand, as PCOS or IR (insulin resistance) is now a day being predicted by several anthropometric parameters like waist to height ratio (WHtR), waist to hip ratio (WHR), and waist circumference (WC) [71]; thus, in near future, it is a loop that increased AMH level might be predicted through these anthropometric parameters in near future.

Role of AMH in PCOS pathogenesis

Nowadays, PCOS has become the most frequent and concerning worldwide health issue among the women of reproductive age [72]. PCOS ovaries account for a huge presence of follicles with the diameter of up to 7 mm [73, 74], signifying the limited follicular growth at the moment when synthesis of AMH is highest. However, numerous observations explained that serum AMH level must be increased among the PCOS individuals as compared to control ovaries [59, 75, 76]. Moreover, the follicular fluid concentration of AMH was observed as five-folds greater among the anovulatory PCOS individuals when compared with ovulatory individuals [76]; it is because of sharp increased synthesis of AMH from each granulosa cells (approximately seventy-five-folds) in polycystic ovary (PCO) as compared with normal ovarian granulosa cells [34] as the granulosa cells of PCO may express increased AMH mRNA [77, 78]. These evidences conclude that increased AMH is not only due to the greater follicular count followed by greater granulosa cell density, but also due to increased synthesis in each granulosa cell causes excess AMH availability among the PCOS individuals. Thus, AMH was found to be associated to predict the harshness of PCO state including its diagnostic criteria like oligo/amenorrhea, hyperandrogenism, and polycystic ovarian morphology [79–82] conferring brace to the concept that, beside a biomarker,

AMH has important contributions for the pathogenesis of PCOS too.

Role of AMH in alteration of gonadotropin functions

Several studies reported, about 50% of women suffering from PCOS has an elevated level of luteinizing hormone (LH) without any metabolic impairment [83, 84]. Few studies have reported as well in this regard and augmented GnRH secretion might result from failure of negative feedback following exposure of the prenatal hypothalamus to androgens [85]. On the other hand, the mean FSH level was found to be lower in comparison to the controls. Until now, the particular reason for such incidence remains elusive. Literature review revealed that in the past, a higher ratio of LH/FSH was used as a diagnostic criterion. Later on, it was found to be very much insensitive and was rejected. Moreover, it was found that AMH is responsible for the impairment of gonadotropin function.

Converging evidences propose that AMH and luteinizing hormone (LH) concentrations among the patients suffering from PCOS are positively correlated [86] irrespective of androgen and FSH concentrations [87–89]. However, there lies a controversy regarding this relationship/association. Several *in vitro* (from luteinized GCs) studies [90, 91] opined that LH can stimulate both release and expression of AMH, whereas according to *in vivo* studies, AMH synthesis starts in the primary follicles and increases before the release of LHR though expression of GC delays luteinizing hormone receptor (LHR) [20]. Conversely, empirical studies have also shown that AMH has extra gonadal effects as well as aids in the stimulation of GnRH neurons. Several research articles denoted that in murine and adult humans, 50% of GnRH neurons have AMH type 2 receptor [92]. Moreover, *in vivo* and *in vitro* studies proposed AMH stimulates the pulsatile release of GnRH-dependent LH via central action. The electrophysiological trials indicated exogenous AMH amplifies/augments GnRH neurons' neuronal activity. Besides those, the AMHR2 is also distributed in the hypothalamic region and which is supposed to synergistically steers the synthesis and secretion of GnRH from the hypothalamic neuronal cells [93]. As the release of GnRH is steered by the hypothalamic neurons, the yield and pulsatility of LH in the anterior pituitary is elevated. Furthermore, AMH shows its effects on the pituitary level [94, 95] as well as control the functions of gonadotropic cells. The expression of AMHR2 gene in gonadotropic cells in both human and mouse were observed to be activated by GnRH. Converging evidences demonstrated that the release of GnRH at an elevated frequency (one pulse per 30 min) raised the expression of AMHR2 by the gonadotropic cells, whereas poor frequency (one

pulse in every 2 h) has no consequence in primates [95, 96]. The relationship between GnRH pulsatility and activation of pituitary AMHR2 in humans, particularly individuals suffering from PCOS till date remain vague. Thus, still it is difficult to make any possible interlink between extra gonadal action of AMH and pathophysiological onset of PCOS in this regard. Apart from the high LH, low circulating FSH is found to be associated with PCOS and it is well known to all and subsequently alterations of physical morphology (e.g., high BMI, low WHtR), high WC or WHR, besides the intra-ovarian morphology like the presence of small diameter follicles usually found in PCOS individuals. AMH is associated with PCOS; however, the relationship between AMH and FSH levels is yet to be established; still, several works have been done in this perspective [97]. Again, congenital gonadotropic impairments lead to a decline in the AMH level, whereas it rises under the influence of exogenous FSH [98]. Henceforward, we can conclude that the relationship between AMH and FSH is obscure and it varies depending upon the disease condition. Additionally, activation of pulse frequency of GnRH and an increased AMH level raises the release of LH and decline in the FSH [99]. In other words, AMH is responsible for neuronal and hormonal dysregulation of PCOS; however, no human experiments have been found so far to prove the fact.

Role of AMH in irregular ovulation

It is now clear that, AMH restricts the folliculogenesis in the ovaries by fading the circulating levels and functions of FSH [100, 101]. But several studies reported that the grade of irregular ovulation is also associated with circulating AMH levels. Regarding the same, a group of researchers recommended that PCOS can be classified into individuals with ovulation and the individuals with anovulation, and the second one classification was made on the basis of circulating AMH as they were observed with eighteen times greater AMH levels than the PCOS individuals with ovulation (normo-ovulatory) [100]. Moreover, irrespective to polycystic ovarian condition, patients with anovulation were found with increased AMH levels (which was also found to be associated with the duration of menstrual cycle) as compared with normo-ovulatory individuals [102]. Probably, the two different reasons can be marked for the same, the increased number of antral follicles with small diameter (2 mm to 5 mm approximately) and increased level of AMH are positively correlated; parallelly, the follicular arrest usually seen among PCOS patients due to the inhibition of FSH action by the increased AMH levels and signifies the negative correlation between these two hormones [16, 103]. The count of the same size follicles was found to be positively associated with seriousness of menstrual

irregularity among the PCOS women, and their association was found strongly among the individuals with amenorrhea [88, 104]. Eventually, increased level of AMH was also observed the adolescent individuals with oligomenorrhoea as compared to control subjects [105–108]. Besides those, AMH concentration was observed as a predictor for amenorrhea among the patients suffering from high circulating AMH [109–111]. These observations recommend that increased small antral follicles with diameters of 2–5 mm are common in the patients of PCOS suffering from anovulation too, probably responsible to build an intra-ovarian AMH reach condition which diminishes the FSH action during the follicular section and thus resulting as anovulation among the PCOS individuals. Some invitro studies as well as some studies on animal models have also confirmed the role of AMH on follicular development and expressions of PCOS characteristics. Although it is believed that the prognosis of anovulation is related to increased AMH level in PCOS, but the exact reason of the elevation of AMH is still in dark. However, the features which are firmly correlated to the pathogenesis of PCOS includes elevated LH level, hyperandrogenism, metabolic syndrome, and/or insulin resistance may be involved. In this regard, it has been seen that LH level and androgen concentration is correlated with AMH levels according to several research works [79–81, 112]. LH is believed to be in behind the elevated production of AMH from granulosa cells of polycystic ovaries only but not from normo-physiologic ovaries [91]. Furthermore, increased AMH expression was observed without any change of AMHR2 appearance in the GCs of PCOS individuals with oligo/anovulation in response to LH, but this observation was not found among the ovulatory PCOS individuals or among control groups possess less AMHR2 appearance in their granulosa cells [113, 114] which indicate the effect of LH on increased AMH level followed by AMH dominated restrictions in follicular growth. In addition to this, androgens regulate the FSH-dependent initial growth stages of follicles [115, 116] which might amplify an excess production of AMH. However, the fact remains controversial. Studies done by Carlsen et al. did not show any remarkable change in AMH concentration in PCOS while suppressing androgens for six months with administration of dexamethasone. He carried out a 6-month study through androgen suppression, and it did not show any alterations in the AMH level [117, 118]. Contrariwise, insulin resistance (IR), hyperinsulinemia, and homeostatic model assessment (HOMA-IR) were found to be associated with AMH concentration with positive correlation among the individuals suffering from PCOS [119–121]. Again, another study showed a positive relationship in between serum fasting insulin and AMH level

in women irrespective of PCOS condition [122, 123]. According to few studies' opinion, such alterations may be due to two different causes: either insulin typically affects granulosa cells which probably alters the synthesis and release of AMH or an augmented yield of androgen in hyperinsulinemia condition in PCOS might be responsible [123–125]. However, more research needs to be carried out to find out the correlation between insulin and AMH level as well as the rise in insulin-dependent AMH in PCOS individuals. Genetic factors might be another reason which can be responsible for the over-expression of AMH among the individuals with PCOS. The involvement of activin receptor-like kinase-2 (ALK2) and its receptor in follicle development during PCO morphology was investigated by Kevenaar et al., and they found a significant association between activin A receptor type 1 (ACVR1), serum AMH, and folliculogenesis among PCOS individuals suggesting the probable involvement of ALK2 pathway responsible for irregular ovulation in patients with PCOS [126]. A growing body of evidences denoted the dramatic as well as vital role of AMH for the conversion of primary follicles from primordial follicles in both control and PCOS individuals. AMH immunostaining is found to be lesser in the in primordial follicles of the anovulatory PCOS women in contrast to normo-ovulatory PCOS patients [30]. Remarkably, in anovulatory and normo-ovulatory PCOS women, the appearing strength of AMH on immunohistochemical method remained the same in both the follicles, i.e., pre-antral and antral follicles [30]. Thus, anovulatory PCOS women are consisting of low-grade hindrance of AMH on primordial follicles followed by early folliculogenesis resulting as aggregation of multiple pre-antral and/or small follicles subsequently causes excess synthesis and secretion of AMH correlating a loop of vicious cycle in positive feedback mechanism.

AMH and hyperandrogenism

Mounting evidences revealed that theca interna cells produce androgens and aromatase enzyme converts it to estrogen in the granulosa cells [127, 128]. Again, LH activates steroidogenesis and thereby yields androgens from the theca interna cells. Emerging studies denoted that in PCOS women, an increased serum level of AMH is positively correlated with serum androgens such as testosterone and androstenedione levels [122, 129, 130], which might be responsible for hyperandrogenism in women with PCOS. Literature review depicted that a decline in the aromatase activity in granulosa cells in polycystic ovaries might be a cause for AMH induced hyperandrogenism [96, 131]. Various researches tried to highlight the accurate role of AMH on CYP19 in granulosa cells and emerged a crucial fall in FSH induced estradiol

synthesis through AMH-induced aromatase (CYP19) inhibition in granulosa cells [132–134]. Such relationship might be a cause for the interrelationship of an increased AMH level and poor level of estradiol in PCOS [134]. Chang et al. reported a similar decline in aromatase mRNA expression followed by estrogen production due to reduced FSH in response to AMH which in turn causes an elevated level of androgens consecutively and such incident indicates the paracrine action of AMH on theca interna cells resulting in alteration of normal ovarian physiology and proceedings of PCO condition [135]. Moreover, AMH-mediated hindrance of FSH-dependent aromatase activity might be responsible for the irregular development of follicles in PCOS. Thus, AMH may be responsible for hyperandrogenism in women suffering from PCOS although, associated other factors may also be directed for the hormonal alteration in PCOS.

Conclusions

This review has concisely explained the association of AMH with the pathophysiology and clinical observations of PCOS. To summarize, AMH represses follicular developments, recruitments, and cause anovulation. The key underlying mechanisms may include AMH-mediated hyperandrogenism and IR in women with PCOS. Increased level of AMH may even attribute to failure in basic treatment outcomes for PCOS through weight reduction, ovulation induction, etc. However, several studies have reported that AMH levels can be managed by drugs like clomiphene citrate or metformin, along with receptor level modifications. Extensive studies are still required to fully understand the detailed role of AMH in the etiopathology of PCOS which will also show future path to treat the disease clinically.

Abbreviations

AMH: Anti-Müllerian hormone; MIS: Müllerian-inhibiting substance; TGF- β : Transforming growth β ; BMP: Bone morphogenetic proteins; AMHRI: Anti-Müllerian hormone receptor type II; AMHRI: Anti-Müllerian hormone receptor type I; SMAD: Suppressor of mothers against decapentaplegic; FSH: Follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; IR: Insulin resistance; WHtR: Waist to height ratio; WHR: Waist to hip ratio; WC: Waist circumference; PCO: Polycystic ovary; LH: Luteinizing hormone; LHR: Luteinizing hormone receptor; GC: Granulosa cells; HOMA-IR: Homeostatic model assessment for insulin resistance; ALK2: Activin receptor-like kinase-2; CYP19: Aromatase enzyme complex.

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