Bangladesh J Obstet Gynaecol, 2022; Vol. 37(1): 47-62

Value of Assessing AMH in the Management of Polycystic Ovarian Syndrome (PCOS)

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Abstract:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age affecting 5 " 10% of women and is the leading cause of ovulatory dysfunction. Anti-mullerian hormone (AMH) is a dimeric glycoprotein releases from the granulosa cells of small preantral and antral follicles and these concentrations have shown to be proportional to the number of developing follicles in the ovaries. In women with PCOS serum levels are elevated 2- to 3- fold in comparison with normo-ovulatory women, consistent with the increased number of small antral follicles in these women. AMH production per granulosa cell is increased on average 75-fold in anovulatory PCOS compared with normal ovaries.

AMH is a marker for ovarian reserve of the women. It also can be used for diagnosis of PCOS. The high level of PCOS has negative effect on reproduction. It inhibits the function of FSH and causes follicular arrest and anovulation. In presence of high AMH there is poor response to oral ovulation inducing agent, gonadotropin and laparoscopic ovarian drilling. Quality of embryo, implantation rate and live birth rate are significantly reduced in presence of high AMH. High LH, hyperandrogenism, hyperinsulinemia have association with high AMH. Androgen is responsible for increasing the number of preantral follicles, hence AMH. Adjuvant therapy like metformin can correct hyperandrogenism, reduce the serum level of AMH and improve ovulation, pregnancy and live birth rate. Pre-treatment AMH level 7.77ng/ml is a cut-off level to predict the response to fertility treatment in PCOS. Ovulation, pregnancy and live birth rate are significantly lower when AMH level is >7.77ng/ml. So, to predict response to treatment and to fix the treatment plan value of assessment of AMH is important in case of PCOS.

Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age affecting 5 " 10% of women and is the leading cause of ovulatory dysfunction[1,2]. It is usually associated with insulin resistance, hyperandrogenemia, obesity and altered gonadotrophin release. Although ovarian hyperthichotic, hyperinsulinemia and hyper-androgenism are central to the endocrine disturbance in PCOS, many genetic and environmental factors have been identified to play a role in the underlying pathophysiology of this syndrome[3]. In spite of extensive research for many decades, the exact aetiology and pathogenesis of this complex disorder remain unexplored.

Anti-mullerian hormone (AMH) is a dimeric glycoprotein and a member of the transforming growth factor b (TGF-b) family of growth and differentiation factors[4].

AMH, is also called Mullerian-inhibiting substance (MIS), as it inhibits the development of mullerian system in male. In male fetal Sertoli cells produces AMH, which induces regression of the Mullerian duct and allows Wolffian ducts to develop into the male reproductive tract[5]. In the absence of AMH, the embryo develops into a female, allowing the Mullerian duct to differentiate into the upper vagina, uterus and oviduct.

In human AMH releases from the granulosa cells of antral follicles and there levels have shown to be proportional to the number of developing follicles in

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the ovaries. Therefore, AMH can be considered to be a marker for the process of ovarian ageing[6]. AMH has a wide variety of clinical applications, based on its ability to represent the number of antral and pre-antral follicles present in the ovaries7. It is an important regulator of folliculogenesis in the ovaries8. In women with PCOS serum levels are elevated 2- to 3- fold in comparison with normo-ovulatory women, consistent with the increased number of small antral follicles in these women[8,9].

As AMH is reflection of number of antral and preantral follicles so measuring the serum level of AMH can be considered as ovarian reserve. When AMH level is high it indicates vary good ovarian reserve and when value is low it indicates low ovarian reserve. Reduced number of follicles can be found in patients having pelvic irradiation, chemotherapy, uterine artery embolization or ovarian surgery due to endometriosis, neoplasia and PID. On the other hand, higher number of follicles are found in PCOS. These higher number of follicles lead to release high level of AMH. But is this good reserve or high value of AMH is good for reproduction? Not always. Low level of AMH is predictor of poor fertility outcome. Similarly extreme high level of AMH is also a predictor of poor fertility outcome. But it is still not very clear whether AMH is simply a marker which is increased in PCOS, or actually an important contributing factor to its pathophysiology.

In this review we are going to present the effect of AMH in PCOS patients where AMH level is usually high due to higher number of follicles and to find the way of solution if there is any.

What happens in PCOS?

Increased number of follicles and high AMH

It is well known that PCOS ovaries comprise a higher number of pre-antral and small antral follicles indicating arrest of follicular development at the stage when AMH production is the greatest. AMH expression begins at the primary follicle stage and becomes peaks in FSH dependant preantral and small antral follicular stages of e”4mm size. With the development of follicles AMH expression gradually declines and is absent in follicles of larger than 8 mm[10,11]. Some authors reported that secretion of AMH declined when follicles reached to e”10 mm and this cessation is thought to be essential for dominant follicle selection[7,12]. In women with PCOS serum levels of AMH are elevated 2- to 3- fold in comparison with normal-ovulatory women[8,9] and the concentration of AMH in follicular fluid from women with anovulatory PCOS was found to be 5 times more compared with ovulatory women[13]. Pellatt et al. showed that AMH production per granulosa cell is increased on average 75-fold in anovulatory PCOS compared with normal ovaries[14]. It can be correlated with the findings of Catteau-Jonard et al that granulosa cells of polycystic ovaries have increased AMH mRNA expression[15]. So, it is not only the increased production of AMH from the increased number of follicles and increased granulosa cell population but also greater production of AMH by individual granulosa cell. Stubbs et al., suggested that AMH exhibits less inhibition on primordial follicles leading to normal folliculogenesis at early stage and increasing the number of pre-antral and small antral follicles, resulting in increased production of AMH[10].

The regulation of AMH production may depend on many intracellular and extracellular signals. One of these may be from oocytes, which stimulate AMH secretion by releasing growth differentiation factor 9 (GDF9) and bone morphogenetic factor 15 (BMP15). It is mentioned that AMH interferes with the concentration and action of FSH, but interestingly, FSH again prevents AMH overproduction by opposing the effects of GDF9 and BMP15[16]. As level of AMH is a reflection of a number of follicles as well as the extent of inhibition of FSH action, it should be emphasized that AMH is a recognized biomarker of female reproductive potential, reflecting the number of primary follicles and their response to exogenous gonadotrophins[17-19].

Several studies shown that increased level of AMH correlated with severity of the symptoms of PCOS[9, 12, 20-23] indicating that AMH is not only a biomarker of disease but actually contributes to PCOS pathogenesis.

AMH and ovulatory dysfunction in PCOS

High AMH and Follicular arrest

AMH plays a role in ovulatory dysfunction in PCOS as it inhibits folliculogenesis by interfering with the concentration and the actions of FSH in the ovaries[24-26]. Several investigators have reported that AMH concentrations are correlated with the degree of ovulatory dysfunction. Based on the level of AMH Pellatt et al.[25] divided the PCOS patient as anovulatory and ovulatory. Women with anovulatory PCOS were

found to have 18 times higher AMH concentrations than the women with ovulatory PCOS. Pigny et al.[9] suggested that the increased conc of AMH in PCOS inhibit the function of FSH during early folliculogenesis resulting in follicular atresia. They also reported that there is an association with high AMH production and larger number of 2 " 5 mm follicle but not the 6 " 9 mm follicular number[9]. According to their opinion, physiological negative influence from 2 " 5 mm follicle pool on the terminal follicle growth at the time of selection, causes anovulation and severe menstrual disorder, being highest in women with amenorrhoea[27]. Other researchers reported that adolescent girls with oligomenorrhoea have increased AMH concentrations compared with normo-ovulatory controls[28]. A high level of AMH (11.4ng/ml) also found in women with amenorrhoea[29]. Including all these observations it is predicted that anovulatory PCOS women have an increased number of AMH-producing small antral follicles (2 " 5 mm), which might create an extreme AMH-dominated micro-environment and impairs the action of FSH on the selectable follicles leading to anovulation.

AMH significantly decreases not only FSHR expression but also ovarian aromatase expression[30]. Due to inhibition of aromatase expression and long-lasting effect of excessive AMH resulting in defective selection of the dominant follicle, leads to "follicular arrest." As AMH inhibits the FSH-dependent factors necessary for follicle dominance, the high level of AMH in PCOS might be the central player in "follicular arrest."

High Androgen, LH, Insulin and AMH in PCOS

The cause of such high production of AMH in antral follicles from PCO 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 over production of androgens could be an intrinsic defect of thecal cells in PCOS[8,9,15,31,32] as androgens are produced in theca cells by the action of aromatase[33]. There is a strong correlation of high LH and androgen level with high AMH[9,15,20,21,23,29]. High LH is responsible for androgen synthesis from theca cells. These increased androgens stimulate FSH independent early-stage follicular growth, which contribute to increased production of AMH[34,35]. However, Carlsen et al did not find any changes of AMH concentration when androgen was suppressed by 6 months treatment with dexamethasone. It indicates that other mechanism might involve for production and maintenance of AMH in PCOS[36]. Though, a positive correlation between serum androgens and AMH concentration was found[37,38]. It is also due to intrinsic dysregulation of the granulosa cells, in which an increase in AMH receptor type II was described[39-41].

In insulin-resistant (IR) PCOS there is increased secretion of insulin, which is also responsible for the hypersecretion of androgen from ovaries and adrenals. This hyperandrogenemia causes increased production of AMH[42]. Many studies showed that there is a relationship between higher AMH concentration in PCOS patients with IR in comparison to PCOS patients without IR[43,44]. High LH increases AMH production 4-times in granulosa cells of PCOS ovaries[12] also causes increased AMH expression in granulosa cells of oligo/anovulatory PCOS women45 suggesting the role of high LH in overexpression of AMH and follicular atresia. So, there is a strong relationship between IR, hyperinsulinemia, hyperandrogenism, high LH and high AMH in PCOS lead to anovulation. However, other studies did not find any association between AMH and IR[15, 46-50].

Other factors influencing AMH level

Age: AMH level falls gradually with increment of age due to continuous atresia and apoptosis of follicular pool. In women, production starts from the 36th post-conception week. Then, after a transient neonatal peak, AMH levels remain low until puberty. Again, rises and remains as plateau in adolescent girls. AMH levels begin to fall after the mid-20s or at 30 and AMH serum levels eventually become undetectable several years before menopause[51-53]. Changes in AMH even precede modifications in FSH (follicle-stimulating hormone), inhibin B serum levels, and antral follicle count. AMH secretion drops dramatically before menopause due to the exhaustion of the follicle pool[54].

Intra-cycle and Inter-cycle variation: Variation in AMH levels could also be explained by biological variance. Contradictory results have been described regarding intra- and inter-cycle variability of AMH levels. Studies assessing the stability of AMH levels throughout the menstrual cycle have been conflicting and difficult to interpret due to different methods used to assay. Some studies showed that there is a slight fluctuation by chance, possibly due to gradual declining the number of follicles[55].

Melado et al described that woman regardless of their ovarian reserve, exhibited a statistically significant intra and inter-cycle variation and shown that AMH level varied 20.7% throughout the cycle from the first serum level at the beginning of the cycle to day 2/3 of the consecutive menses[56]. Other studies also have demonstrated substantial fluctuations in the menstrual cycle with AMH level highest in the mid-follicular phase, decreasing at the time of ovulation with a rise again in the luteal phase[57-60]. This finding would argue in favor of measuring AMH levels at the early follicular phase only. When using AMH serum concentration to evaluate functional ovarian reserve (FOR), which consists of cohorts of small growing follicles from 2 mm to 5 mm from which follicles are recruited to ovulate, the results of the latest studies should be taken into consideration. It has recently been shown that intracycle variation up to 20% of serum AMH level can be observed[56,61,62]. Furthermore, some studies also showed an inter-cycle variation of AMH serum level between 28 and 163% depending on the AMH assay used[61,63]. Therefore, it seems reasonable to make therapeutic decisions based on repeated assessments of AMH serum levels using the same assay.

Use of hormones: Hormonal contraception is a factor that influences AMH serum level. AMH serum level is lower and varies from 14 to 55% among women who use hormonal contraception[53]. This variation again depends on the method of contraceptive used[54].

For example, women using oral contraceptives or progesterone-only pills have 30 to 40% lower AMH serum levels. In comparison, women using intrauterine devices have 17% lower AMH serum levels. Oral contraceptives inhibit the formation of pre antral and antral follicles the source of AMH production. As a result, there is falling of AMH level after taking oral contraceptives.

Different studies shown that AMH levels decrease under current use of oral contraceptives[64-66] and lower level was not associated with previous use of oral contraception[67]. In PCOS, it has recently been shown[68] that in current users of hormonal contraception, SHBG was increased, leading to a diminished bioavailable androgen level, and that is why AMH and AFC levels were decreased.

AMH levels may even be increased after discontinuation of oral contraceptives69. Both findings suggest that there is a reversible suppressive effect of oral contraceptives on AMH. Panidis et al.[70] have shown a significant decrease in serum AMH levels in women with PCOS with ethinylestradiol + CPA but not with use of ethinylestradiol + drospirenone.

GnRH agonist also has some effect on AMH. It was observed that under mid-luteal GnRH agonist administration AMH levels changed significantly across the initial 4 weeks[71,72]. Such observations suggest that if a patient is receiving GnRH agonist medication, AMH may not be a reliable marker of ovarian reserve.

Use of Vitamin D: Recent studies also showed an impact of vitamin D serum concentration on AMH serum levels. Both vitamin D and AMH present seasonal serum variability during the year, with higher concentration during the summer and lower concentration during the winter. It was indicated that higher vitamin D serum concentration results in higher AMH serum levels[73-75]. Other researchers reported that supplementation of vit. D3 in D3 deficient PCOS women has been shown to improve elevated androgen levels, insulin resistance and menstrual cyclicity[76,77] and reduce AMH level[78,79].

Use of Metformin: Long term use of metformin is associated with reduction of AMH. There was signiûcant reduction in AMH concentrations after 6-month80 and 8 months metformin therapy81. It is postulated that increased follicle recruitment in a better endocrine environment of less insulin is responsible for less AMH secretion.

Genetic factors: Genetic factors might have some role in AMH overexpression in PCOS. Investigations shows that ALK2, its receptor and their encoding gene ACVR1 are involved in AMH/BMP signaling, and in the aberrant follicle development in PCOS. The association between a genetic variant of ACVR1 with AMH concentrations and folliculogenesis in PCOS suggests the role of ALK2 signaling in ovulatory disturbances in PCOS[82]. Serine polymorphisms of AMH and its receptor83 and genetic variants across the genome[84] are associated with high AMH.

BMI and smoking: BMI also has an influence on AMH level. Study shows that there is a negative correlation between BMI and AMH serum levels[85]. In obese patients, adipose tissue can be a site of androgen production. The androgenic enzyme Aldo-keto reductase type 3 (AKR1 C3) is expressed in adipose tissue and is stimulated by insulin in obese women[86]. Current smoking has also been associated with lower

AMH levels[64]. The clinical relevance of these observations remains to be determined.

Role of AMH in the diagnosis of PCOS

Diagnosis of PCOS is not difficult. According to Rotterdam criteria, if any 2 features out of 3 a) oligoovulation and/or anovulation, b) excess androgen activity and c) polycystic ovaries - are present, diagnosis of PCOS can be confirmed. However, AMH can be used as a diagnostic tool for diagnosis of PCOS. As there is a strong correlation between circulating AMH levels and antral follicle count on ultrasound, AMH has been proposed as an alternative diagnostic tool for the diagnosis of PCOS[16,87,88].

Even though serum AMH would be theoretically more accurate than AFC, as many small follicles may be non-visible on ultrasound[87-89]. According to Rotterdam consensus using 12 follicles of 2–9 mm diameter per ovary is diagnostic for PCOM[90]. This cut off is highly dependent on ultrasound machine and operator skill. Therefore, with the latest ultrasound generation, diagnostic number of follicles are now up to 19 or 25[89, 91, 92]. Assay of serum AMH is not homogenous[93]. Part of this heterogeneity is due to the lack of a well-defined population. Additionally, there are technical issues in AMH assays leading to the heterogeneity of the results. For these reasons, it may not be possible to propose a consensual and universal diagnostic tool and it should not be used as an alternative or a single test for PCOS diagnosis. To date a cut-off at 35 pmol/L (4.9 ng/mL) with the enzyme immunoassay AMH-EIA (EIA AMH/MIS kit) ("Immunotech", ref A16507) provided by Beckman Coulter (France) had a good specificity (97 %) and a better sensitivity than the AFC (92 %) to distinguish women with PCOS from normal women[88]. This result was obtained after the exclusion of women with asymptomatic PCO from the control group.

Due to new automatized serum AMH assays or the ultrasensitive assay, a high serum AMH level could then become a reliable and accurate marker for PCOM, and eventually replace the AFC, which also suffers from great controversy in the literature. Serum AMH level is also correlated to the severity of PCOS symptoms[25] and is higher when hyperandrogenism[15, 25] or oligo-anovulation is present[8,12,94]. By a principal component analysis, it has been shown a high serum AMH level can be considered as a marker of hyperandrogenism and could also be used as a substitute for this item in the Rotterdam classification[83]. A number of studies have evaluated the serum level of AMH in PCOS and normal women to identify the PCOS by AMH level. Laven et al demonstrated that AMH level was higher in PCOS and PCOM (9.3 ng/ml) than those without PCO morphology alone (6.4ng/ml) and healthy controls (2.1 ng/ml)[8].

Lie et al reported AMH 9.1 $\mu gm/L$ in PCOS and 2.1 in control women95. Similarly, Yue et al reported that AMH was 5.7 ng/ml in healthy controls, 9.3 ng/ml in women with PCOS and 9.9 ng/ml in women with three main features of PCOS[96]. A meta-analysis mentioned that an AMH of 4.7ng/ml had a sensitivity 79.4% and specificity 82.8% to identify PCOS[93]. In summery a number of studies suggest that AMH be used as a diagnostic tool of PCOS, but challenges are there due to variation of result by manual and automated assay. Pigny et al examined five commercial assays and found similar result in manual assay and 23-30% lower values in automated assay[97].

In adolescent and young women with PCOS, it is sometimes difficult to evaluate the ovaries on ultrasonography. Adolescents with PCOS have higher serum AMH levels98,99. Although serum AMH levels cannot be used independently, they may be helpful as a part of an algorithm, along with clinical signs, androgen levels, and ultrasound[99]. They also have a higher antral follicle count and a larger ovarian size than adolescents without PCOS. Therefore, it is sometimes difficult to estimate the number of small follicles of ovaries on ultrasonography in this group. Considering this difficulty serum AMH assay is therefore a true alternative, as it is recommended by the American association of clinical endocrinologists[100].

Role of AMH in ovarian reserve testing in PCOS

Both antral follicles counting (AFC) and AMH are regarded as indicators of ovarian reserve. AMH is an indirect marker of ovarian reserve in women as it is released from small antral and preantral follicles. Due to its origin, its serum concentration does not correlate with the number of primordial follicles. That is why it can be said that AMH serum level reflects functional ovarian reserve (FOR), which consists of cohorts of small growing follicles from 2 mm to 5 mm from which follicles are recruited to ovulate[101, 102]. On the other hand, several evidence-based studies have suggested counting the follicles of the size of 2 to 10 mm for AFC[103,104]. Thus, AFC are the number of follicles

smaller than 10 mm in diameter detected by Transvaginal Ultrasound (TVUS) in the early follicular phase. Secretion of AMH diminished when follicle size reached to 8 mm[10,11]. That is why counting antral follicle is more predictable for any particular cycle.

In PCOS numerous follicles of 2-10 mm size are visible by USG which can be counted as antral follicle. As both AFC and AMH levels are the best candidates as biomarkers to predict the ovarian reserve, the large number of antral follicles in PCOS is enough to predict that. So, for only ovarian reserve testing AMH assay is not necessary so long transvaginal USG is present. But to assess ovarian response to the stimulation it is necessary to do the test.

AMH and response to stimulation

Response to oral ovulation inducing drug: Serum level of AMH is strongly associated with number of follicles in PCOS. The more the number of follicles the more the AMH secretion. As AMH has an inhibitory effect on follicular recruitment in PCOS, it can be hypothesised that women with a high level of AMH has a poor response to ovulation induction or ovarian stimulation. In other words, it can be said that serum AMH levels reflect the ovarian response to stimulation.

Xi Wenyan et al proved in a study that in response to clomiphene citrate, patients who ovulated had a significantly lower serum AMH concentration in comparison to non-responder (5.34 ±1.97vs 7.81±3.49 ng/ml, p=<0.001)105. Antral follicle count and ovarian volume were significantly lower in the group of low AMH. In addition, the pregnancy rate was higher in patients having lower level of AMH compared to patients who had no pregnancy (4.81±2.06 vs. 6.89 ± 2.95 ng/ml, p<0.01). According to the result of this study, patients with AMH <7.77 ng/ml had significantly higher ovulation and pregnancy rates than those with AMH of >7.77ng/ml. Considering the facts, the authors fixed a cut-off value of AMH 7.7 ng/ml above which chances of ovulation and pregnancy are significantly reduced. From the result of this study, it can be said that high AMH impaired folliculogenesis and granulosa cell function. Though in general it is said that the response of COH is more when the AMH level is more, Amer et al explained that the contradiction may be due to the different spectrum of circulating AMH in women with or without PCOS[106].

Mahran et al also evaluated the impact of AMH in 187 cycles of 60 anovulatory PCOS women and found circulating AMH levels to be negatively correlated with the chance of ovulation. They found excessive circulating AMH was associated with poor ovarian response to clomiphene citrate ovulation induction, though they set 3.4ng/ml as optimum cut-off level for prediction of ovarian response to CC in PCOS[107]. Alizzi et al developed a predictive pregnancy score from different parameters like basic, clinical, laboratory, and ultrasound with induction by 5 mg letrozole to individualize ovulation induction protocol in PCOS women[108]. In that study it was found that AMH level was higher in the group who did not ovulate with 5 mg letrozole (7.3 ±0.6 vs 6.2±0.5, p=<0.001). So, by assessing AMH, response to oral ovulation-inducing agents can be predicted in PCOS patients. There is a strong correlation with high AMH and high androgen level. So, it is likely to get a poor response by oral ovulation-inducing agents in presence of high AMH.

Other study also demonstrated that AMH levels were significantly lower among women who achieved ovulation compared with women who did not achieve it[109].

Response to gonadotropin:

The severity of PCOS is associated with an increasing number of small follicles which produce AMH, and in turn, AMH has an impact on CC/gonadotropins response. The high AMH concentration could influence the sensitivity of follicles to gonadotropin stimulation. Amer et al found in their study that circulating AMH level was negatively correlated with ovarian response to HMG in PCOS women[106]. They mentioned the cut-off level of serum AMH concentration 4.7ng/ml, above which the chances of good ovarian response were markedly reduced from 100% to 35%. They concluded that high circulating AMH is associated with ovarian resistance to gonadotropin stimulation. Women with higher level of AMH required higher doses of Gonadotropin and longer duration of treatment. In addition, there was significantly higher cancellation rate (39% vs 0%) in patients with higher AMH (>4.7ng/ml vs <4.7ng/ml). As the pre-treatment serum concentration of high AMH diminishes the chances of a response to the drug, in case of a higher concentration of serum AMH, higher doses of gonadotropins and extended treatment are recommended[110]. In spite of resistance to stimulation in presence of markedly raised AMH, ovarian hyperstimulation could still occur in PCOS patients with moderately raised circulating AMH (4.7-10.2ng/ml)[106].

A number of researchers have been used AMH levels as markers of COH outcomes such as the total dose of gonadotrophins used, estradiol level on the day of hCG, number of mature follicles on the day of hCG and number of oocytes retrieved[111-113]. Penarrubia et al. showed that the serum AMH level on stimulation Day 5 is a better predictor of cycle cancellation than the basal AMH level[114]. Silberstein et al demonstrated that the AMH level on the day of hCG correlated with COH outcomes, including the number of mature follicles, number of oocytes retrieved, estradiol levels and embryo morphology score[115]. In that study baseline AMH was measured before gonadotrophin administration, to adjust the gonadotrophin starting dose-depending on the basal AMH level. If serum AMH levels on D5 or on the day of hCG are used as predictive markers, they are significantly correlated with COH outcomes, but gonadotrophin dose adjustment is less effective for control of ovarian response

AMH and ovarian Drilling.

Laparoscopic ovarian drilling (LOD) is one of the strategies applied in some groups of PCOS infertility patients. It is established that LOD could be an alternative to ovulation induction with gonadotropins for those who do not respond to clomiphene. This technique avoids multiple pregnancies related to gonadotropin treatments and provides a comparable pregnancy rate116. Preoperative high AMH concentrations could indicate the failure of induction of ovulation after LOD.

Reduction of AMH following laparoscopic ovarian drilling (LOD) is associated with treatment response in PCOS. Several studies on PCOS women reported that serum AMH concentrations were decreased following LOD117-120. Another study has shown that there was a significant reduction of AMH, which was correlated with reduced ovarian power Doppler blood flow indices in PCOS women following LOD118. Amer *et al.* reported that pre-operative serum AMH concentration was predictive of treatment response to LOD as reflected by signiûcantly greater ovulation rate in women with lower pre-treatment AMH concentration. This study found excessive pre-treatment circulating AMH was associated with poor ovarian response to LOD. They observed cut-off level of AMH 7.7 ng/ml was predictive of ovulation following LOD. LOD was carried out using a monopolar electrocautery needle. Four punctures were made per ovary at a power setting of 30 W applied for 5 s per puncture[117]. Although the mechanism of LOD is not clear, it is thought that the destruction of ovarian theca cell mass causes a rapid decrease in androgen levels.

Moreover, destruction of AMH-producing granulosa cells causes reduced synthesis of AMH. Therefore, decreased local ovarian production of AMH following LOD may lead to increased follicular responsiveness to FSH and release from the follicular arrest. Women who ovulated in response to LOD had a significantly lower pre-operative AMH compared with the non-responders. AMH was found to be a useful predictor of ovulation after LOD.

AMH and Assisted Reproductive Technology:

Reshef et al shown that women with PCOS undergoing assisted reproduction, had significantly higher live birth rate (LBR) when AMH was lower (< 3.32 ng/ml, 65.2%) than those with average (3.32–8.27 ng/ml, 46.7%) or high serum AMH levels (> 8.27 ng/ml, 43.5%). There was also an inverse relationship of implantation, CPR, and multiple pregnancy rate, with serum AMH121. In this study, there was a significant increase in live birth rate per embryo transfer (LBR) in PCOS women in the low AMH group (65.2%) compared to the average AMH (46.7%) and high AMH (43.5%) groups.

Numerous studies indicate the role of both low and high AMH in predicting IVF results[115,122-124]. The data regarding the prediction of serum AMH levels in women with diagnosed PCOS undergoing IVF procedures are not always consistent[125-130]. Silbersteinet[115] showed a correlation between AMH and embryo quality and mentioned that implantation rate (IR) and clinical pregnancy rate (CPR) were higher when AMH was higher than 2.7 ng/ml. Another study found a strong association between serum AMH on day 3 of the stimulation cycle and the IR and CPR[127]. A cut-off value of AMH was set as 3.2 ng/mL for predicting CPR, with a sensitivity of 72.7% and specificity of 77.3%.

PCOS has been shown to have a detrimental effect on endometrial homeostasis and receptivity[131]. Moreover, women with high serum AMH are at increased risk for developing ovarian hyperstimulation syndrome, which can abnormally affect endometrial receptivity, thereby affecting IR and LBR. Endometrial receptivity is also lowered by certain angiogenic factors, like VEGF and TGF-â, which are dysregulated in PCOS[132]. Moreover, elevated levels of AMH in

PCOS lead to aberrant folliculogenesis, altered endometrial receptivity and abnormal placentation. A recent study in PCOS women showed that higher AMH level was associated with decreased endometrial thickness in ovulation induction cycles[133]. Thus, the negative impact of elevated serum AMH levels on endometrial receptivity could explain the associated low implantation and live birth rates.

Conclusion

Assessing serum AMH is needed for two purposes. One is to assess ovarian reserve and the other is to predict ovarian response to stimulation. In PCOS, assessing AMH has multiple roles to play. AMH can be used to diagnose PCOS, assess ovarian reserve, and predict response to treatment. It can predict the response to oral drugs, gonadotropin, laparoscopic ovarian drilling and finally, the outcome of in vitro fertilization. As there is an association with high AMH and hyperinsulinemia and hyperandrogenism pre-induction adjuvant therapy can be given to improve the response. Moreover, the starting dose of an oral drug can be fixed according to the level of AMH. Pre-treatment measurement of AMH could help in counselling the patient regarding hyper response or poor response to gonadotropin therapy. It is also important to fix the starting dose of gonadotropin in ART cycles. Patients with markedly raised AMH can be given a high starting dose of gonadotropin. Excessive pre-treatment AMH was associated with poor response to stimulation after LOD following the rule of four for drilling. So, by omitting the rule of four for ovarian drilling both the number of punctures and power setting can be increased according to the level of AMH and volume of the ovary. Further research is needed in this area.

Though assessing AMH in PCOS has a valuable impact on predicting the response to treatment and fixing the starting dose of drugs, it is not mandatory to measure it for diagnosis of PCOS and to assess ovarian reserve.

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