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ROLE OF DECODING OF AMH IN THE DIAGNOSTIC ADVANCEMENTS IN PCOS

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Abstract

AMH has emerged as a pivotal biomarker for understanding the pathophysiology, diagnosis, and fertility implications of PCOS. This review delves into AMH's multidimensional involvement in PCOS, with an emphasis on pathogenic insights and diagnostic improvements. AMH levels in PCOS patients are significantly higher than in healthy controls, indicating the syndrome's etiology. According to studies, AMH is intricately linked to the hyperandrogenic and insulin-resistant milieu that characterizes PCOS, offering light on the underlying mechanisms that contribute to the disorder's development. Furthermore, AMH plays an important role in the diagnosis of PCOS. Its capacity to reflect ovarian follicular activity and reserve makes it useful for evaluating ovarian dysfunction and reproductive potential in PCOS patients. Diagnostic breakthroughs have used AMH measures to improve the accuracy of PCOS diagnosis, particularly in difficult instances where traditional approaches may fail. This review also looks at how AMH is progressing in therapy options for PCOS. It examines how AMH levels may influence treatment outcomes, such as ovulation induction and weight management, and provides insights into individualized therapy techniques.

Keywords: AMH, PCOS, Ovarian Reserve, Fertility, Diagnostic, Receptors.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an elaborate endocrine condition that affects a large proportion of women globally, with estimates indicating a frequency of up to 10% among reproductive-age women [1]. Its distinguishing characteristics include hyperandrogenism, ovulatory failure, and polycystic ovarian morphology [2]. Despite being a prevalent disorder, the actual etiology of PCOS remains unknown, and its care provides therapeutic hurdles due to its variability and diverse clinical symptoms [3]. Over the past several years, there appears to be an increasing interest in investigating potential treatment strategies for PCOS that go beyond traditional symptomatic care [4]. Anti-Müllerian hormone (AMH), a glycoprotein in the TGF-β family, could be a potential target [5]. AMH, which has previously been recognized for its significance in male sexual differentiation during embryogenesis, has recently received attention for its role in ovarian folliculogenesis and probable contribution to PCOS pathogenesis [6].

This introduction tries to explain the rationale for addressing AMH in PCOS therapies, beginning with a summary of current PCOS pathophysiology, and then moving on to examining AMH's involvement in ovarian function and its consequences in the setting of PCOS. Furthermore, it will discuss the limitations of existing treatment modalities

for PCOS and highlight the potential benefits of targeting AMH as a more targeted and effective approach to managing this complex syndrome.

The basics of AMH expression and action

AMH gene

Anti-Müllerian hormone (AMH) (Fig. 1) is a glycoprotein peptide weighing approximately 140 kDa. It is categorized within the subfamily of growth factors called transforming growth factor beta (TGF-β) [7]. AMH gene lies on the short arm of chromosome 19, between the regions p13.2 and p13.3. It is separated into five exons, comprising 275 base pairs (bp) [8].

The AMH gene is transcribed through a 180-bp region that is contiguous to the protein Sap62. It has three transcription binding sites: one is a 20-bp conserved motif that binds the orphan nuclear receptor SF-1, and the other is 50 bp upstream from the SF-1 binding site and stimulates the binding of SOX9, a high-mobility group protein. The final binding site, located downstream of the SF-1 binding site, binds to GATA-4 from the GATA transcription factor family. When SF-1 binds to the promoter, transcription upregulates. Furthermore, the interaction between SOX9, WT1, and GATA-4 modulates this process [9]. The product of the AMH gene is a precursor known as proAMH, consisting of 560 amino acids [10]. Following the removal of the 24 amino acid fragment, a molecule is glycosylated, resulting in the formation of two identical subunits having a molecular weight of 70 kDa connected by sulphide bridges. The N-terminal domain known as the "pro-region" (115 kDa AMHN) and the C-terminal domain, or "mature region" (25 kDa AMHC), are formed as a result of proAMH proteolysis [10]. The N-terminal segment is necessary for the protein to be active, which makes it unlikely that the other proteins in the TGF-β complex would be affected. The C-terminal segment is required for the biological functions of the protein and its binding. to receptors [11].

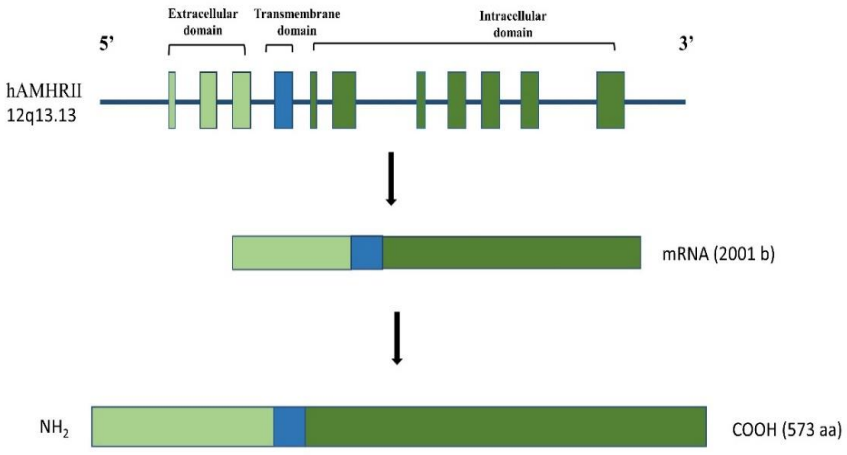

Fig 1: The human AMH receptor (AMHRII) gene, mRNA, and protein. The human AMHRII gene localized in chromosome 12, 12q13.13, is transcribed into 2001 base (b) mRNA, which is then translated into a 573 amino acid (aa) protein

AMH Receptors

The AMH signaling pathway is regulated by two heteromeric serine/threonine kinase transmembrane receptors, categorized into two types: type I and type II [12].

Anti-Müllerian hormone receptor I (AMHRI) is phosphorylated when free AMH binds to AMHRII. This phosphorylation activates cytoplasmic Smad proteins, which start downstream signaling. More specifically, AMH initiates Smad1 protein signal transduction but not Smad2 protein [12].

The Smad proteins translocate into the nucleus after becoming phosphorylated, where they can either stimulate or inhibit the transcription of particular genes [9].

The only receptor available for the AMH hormone is the AMH type II receptor. It expresses itself in the ovary soon after birth and lasts the entirety of an individual's life [13]. The ductal epithelium of the mammary gland, the prostate, the endometrial, the Sertoli and Leydig cells in the testes, and the theca and granulosa cells in the ovaries are all known to contain the AMHRII receptor [14–17].

Numerous cancer cell lines, including those from the ovarian, cervical, endometrial, and breast epithelium, have also been shown to express the receptor AMHRII [8,18].

In recent years, it has also been demonstrated that organs other than the gonads, including the motoneurons [19], neurons [20], hypothalamus [21], and gonadotropic cells of the pituitary gland [22], also express AMH, as shown in Table 1.

However, since serum AMH's expression profile corresponds to that of the gonads, this expression has little effect on circulating levels. The fact that AMHRII is more widely expressed emphasizes the importance of the effects of AMH shown in tissues that express AMHRII.

Table 1: AMH and AMHR2 distribution in both sexes

	Organs	Men	Women	Both	Reference
AMH Expression	Ovaries		****		23
	Testes	****			24
	Nervous system			*	25,26
	Pituitary gland			*	27
	Hypothalamus			*	28
AMHR2 Expression	Testes	****			24
	Ovaries		****		23
	Nervous system			*	25,26
	Pituitary gland			*	27
	Hypothalamus			*	28
	Uterus		**		23
	Placenta		*		23
	Breasts		*		29
	Pancreas			*	30
	Lungs			*	31
	Adrenals			**	30
	Prostate	*			32

The number of * represents the level of expression of AMH and AMHR2 in the different tissues.

Expression of AMH

AMH expression begins in primary follicles in the ovaries of every species that has been studied thus far. It peaks in pre-antral and small antral follicles, declines in large antral follicles, and eventually becomes almost undetectable—except in cumulus cells [23].

AMH secretion in the gonads corresponds to its detection in serum, even though AMH is expressed in endometrial and endometriotic cells [33].

For instance, there is an undetectable level of AMH in the serum of women who have had their ovaries removed. Beginning in the 36th week of pregnancy, the ovarian granulosa cells (GC) of the pre-antral and antral follicles release AMH in females [34].

Serum AMH levels are two to four times higher in PCOS-affected women and in their daughters. The higher number of small antral follicles, which express AMH the most, as well as the overexpression of AMH by these GCs are the two causes of the raised serum AMH levels in women with PCOS [35].

Modified GC receptivity to numerous hormones dysregulated in PCOS might lead to the overexpression of AMH and AMHR2. Indeed, androgens increase in vitro AMH mRNA levels exclusively in GCs from PCOS patients which overexpress the androgen receptor [23].

Estradiol (E2), on the other hand, mitigates AMH expression in the GCs of normal women while not regulating the expression of this gene in the GCs of PCOS women [36]. LH and E2 reduce AMHR2 mRNA levels in GCs from normal women, however, they are not modulated by these hormones in GCs from anovulatory women with PCOS.

Anti-Müllerian Hormone (AMH) regulates the number and selection of developing follicles for ovulation [37]. It functions as a negative regulator in the early stages of follicular development [38]. Essentially, AMH suppresses follicle recruitment and growth by lowering the influence of growth factors and gonadotropins, particularly follicle-stimulating hormone (FSH) [39]. To put it simply, AMH regulates the reproductive cycle by limiting the number of follicles that mature and preventing excessive proliferation.

Immature Sertoli cells in the testes generate AMH during embryonic development. AMH secretion begins in the ninth post-conception week and lasts until 2 years postnatally. It decreases during puberty and becomes undetectable in adults owing to high testosterone levels [40,41]. Whenever a male fetus has low or no AMH levels, both male and female genitalia develop simultaneously.

In the absence of AMH, the Müllerian ducts form the fallopian tube, uterus, cervix, and upper one-third of the vagina. Changes in AMH levels or receptors are capable of impacting the development of the female reproductive system.

In women, production begins in the 36th week after conception. After a brief neonatal rise, AMH levels remain low until puberty. Adolescent girls experience escalating AMH serum levels that eventually plateau. AMH serum levels start to decline in the mid-20s and become undetectable many years before menopause [42,43].

AMH also alters follicular growth and dynamics. It serves as an antagonist of follicle recruitment, effectively halting the process of primordial follicles developing into

expanding follicles. This mechanism contributes to follicular pool balance and regulates the follicle maturation rate. AMH also modulates follicular sensitivity to follicle-stimulating hormone (FSH), an important hormone in ovarian function [44].

At different phases of development, AMH affects the hypothalamic-pituitary-gonadal (HPG) axis and is implicated in the formation of ovarian follicles [45].

The number of antral follicles in the initial follicular stage of the menstrual cycle strongly influences the number of ovarian follicles, which is reflected in the serum AMH concentration [45,46,47].

Consequently, low serum AMH levels can be attributed to a decreased antral follicle count. Furthermore, neither the menstrual cycle phase nor exogenous sex steroids affect the blood level of AMH. Consequently, any day of the cycle can be used to collect blood samples [48].

The fact that AMH is a validated biomarker of female reproductive potential should be underlined. It represents the quantity of primary follicles and how they react to exogenous gonadotrophins [45,47,49].

Mechanism of action (MOA) of AMH (Fig. 2)

AMH in humans is activated by cleaving its 140-kDa precursor at a certain location, which results in a 110-kDa N-domain and a 25-kDa C-terminal domain which carries the bioactive site [50]. Although the half-lives of the precursor and its noncovalent forms in female serum are similar, methodological differences have made it difficult to determine the exact half-life [51]. The cleavage most likely takes place in the producing cells and is mediated by enzymes PC5 [52,53,54]. While serum and follicular fluid include both precursor and noncovalent forms, serum contains more of the latter, signifying further cleavage or degradation from outside cells. But without the N-terminal domain, the instability of the C-terminal segment makes it unlikely to circulate on its own. More research is necessary to fully understand the cleavage dynamics and functional consequences in the ovary [55].

AMH mostly interacts with AMHR2 via its C-terminal domain, most likely as a noncovalent complex. This notion is corroborated by the fact that AMH's N-terminal segment increases the C-terminal domain's activity and that, in lab settings, the noncovalent complex and the pure C-terminal fragment have similar affinities for AMHR2 [55].

While the noncovalent complex from follicular fluid efficiently binds to AMHR2 in vitro, the serum-derived complex fails to do so, implying that serum-related variables may impair AMH bioactivity. Laboratory investigations have demonstrated that when AMH and AMHR2 bind, the N-terminal domain of the noncovalent complex is cleaved, allowing for AMH signaling, with the C-terminal version being more potent than AMH noncovalent complex in stimulating the phosphorylation of SMAD 1, 5, or 8 [54,56].

The Q496 residue in the C-terminal domain is critical for promoting interactions with AMH type I receptors. Mutations at this location cause chronic Müllerian duct syndrome in men, making the AMH physiologically inactive. Further study on AMHR2 residues and their involvement in AMH signaling, together with experimental data indicating early monomer binding before dimerization, highlights the intricacy of AMH-mediated pathways [57].

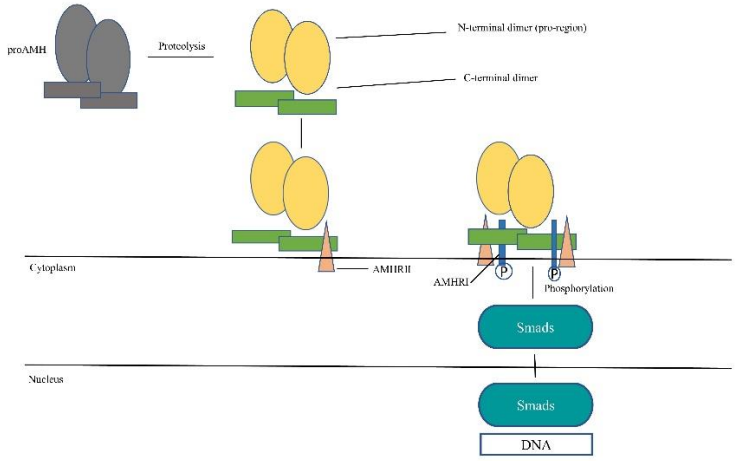

Fig 2: The mechanism of action of AMH action via receptor. Proteolysis of proAMH leads to a conformational change in the C-terminal domain that allows binding AMHR2. AMHR2 induces binding to the type I receptor, which is then phosphorylated by a kinase receptor type II.

AMH variability in PCOS

PCOS is a prevalent endocrine condition that impacts around 5 to 10 percent of women in their reproductive years worldwide [58]. According to the Rotterdam criteria, the diagnosis needs to include at least two of the following: polycystic ovarian morphology visible on ultrasound, evidence of elevated androgens either in biological tests or clinical signs like acne and hirsutism (excessive hair growth), and ovulation irregularities [59].

Four phenotypes can be defined by these criteria, the most severe of which combines all three features. Disruptions in the GnRH/LH pulsatility are also linked to PCOS, and these can result in high LH (luteinizing hormone) levels and frequently a raised LH/FSH (follicle-stimulating hormone) ratio [60]. PCOS-afflicted women frequently have metabolic difficulties such as weight gain, resistance to insulin, elevated levels of lipids, and type 2 diabetes.

Given that 20% to 40% of individuals exhibit familial clustering of PCOS symptoms, there is evidence of a genetic component [61]. Developmental variables may also be involved since, by the theory of the Developmental Origins of Health and Disease, abnormalities during the foetal and prepubertal stages might have long-term effects on reproduction and metabolism [62,63].

Levels of AMH are 2- to 4-fold greater in follicular fluid and serum of PCOS patients [64]. This rise is explained by the overexpression of AMH and its receptor (AMHR2) by granulosa cells (GCs), which may have been influenced by hormonal dysregulation, in addition to the number of tiny antral follicles releasing AMH [65,66].

According to research, hyperandrogenism, a defining symptom of PCOS, causes granulosa cells (GCs) to express more AMH in afflicted women. Although factors such as FSH, estradiol, and follicle proliferation under androgen influence can complicate this association, research consistently reveals a positive relationship between androgens and AMH levels for PCOS patients [67,68].

5α-dihydrotestosterone (5α-DHT), a non-aromatizable androgen, specifically enhances AMH mRNA levels in GCs from PCOS patients with elevated androgen

receptors (AR) [69]. This proposes a direct androgen-induced mechanism responsible for AMH overexpression in PCOS.

These findings emphasize the importance of hyperandrogenism in the dysregulation of AMH in PCOS, as well as the intricate interplay between androgens, follicular growth, and AMH production. Understanding these molecular processes is critical for deciphering PCOS pathogenesis and creating targeted treatments.

Although research on the AMH-insulin resistance link in PCOS is inconsistent, studies such as Liu et al. show that insulin can dose-dependently boost AMH mRNA expression in GCs from both PCOS and normal women [36]. Furthermore, enhanced AMH cleavage in association with metabolic parameters shows that metabolic variables may worsen AMH dysregulation in PCOS, especially given these women's heightened vulnerability to metabolic diseases.

The modulation of AMHR2 expression in PCOS has received little attention, although it is emerging as an important factor. In vitro studies indicate that the increased AMHR2 expression in PCOS granulosa cells (GCs) may be related to the lack of the inhibitory effects of estrogen (E2) and luteinizing hormone (LH) seen in normal women [23].

Recent suspicions have emerged about the role of AMH overexpression in PCOS pathogenesis. Certain single nucleotide polymorphisms (SNPs) in the AMH and AMHR2 genes, such as AMH Ile49Ser and AMHR2-482A>G, have been associated with PCOS and demonstrate decreased bioactivity. Furthermore, heterozygous mutations near AMH and AMHR2, which are seen in certain PCOS-affected individuals with low serum AMH levels, reinforce this association [70-73].

While these findings may explain enhanced theca cell testosterone synthesis and primordial follicle recruitment, such effects could also be caused by increased androgen and LH expression, respectively. However, a reduction in AMH/AMHR2 system activity alone does not fully account for the range of reproductive problems reported in PCOS [74].

These findings emphasize the intricate interplay of genetic, hormonal, and regulatory variables that contribute to PCOS pathogenesis. To precisely determine how AMHR2 dysregulation contributes to the variety of symptoms associated with this condition, further research is required.

AMH Measurement

AMH has been measured using a variety of commercial enzyme-linked immunosorbent test (ELISA) kits, each with its differences in antibody pairings, standard curve ranges, and limits of detection [75] (Table 2). The development of AMH tests is an important step forward in clinical epidemiology Nevertheless, despite these advancements, there are still no well-recognized, standardized assay techniques or materials for determining serum AMH concentrations. Furthermore, the lack of conversion techniques to evaluate the comparability of AMH assays makes it difficult to interpret results from various research studies. For any clinical application of AMH, these exact definitions are necessary. With a lower detection threshold, the Ansh Laboratories picoAMH test is particularly notable for being the most sensitive assay for identifying low amounts of AMH [76].

Table 2: Measurements of different AMH assays

AMH Assay Year	Manufacture Company	Limit	Standard Curve Range	Description
IOT, 1999	Immunotech	0.05 ng/mL	0.1-24.5 ng/mL	A monoclonal antibody pair was directed, one directed at the pro region and the other at the mature region.
DSL, 2003	Diagnostic systems laboratories	0.006 ng/mL	0.05-15 ng/mL	Both monoclonal antibodies were directed at the mature region
GEN II Generation, 2010	Beckman coulter	0.16-22.5 ng/mL	0.08 ng/mL	The DSL antibodies were used in the assay, which was standardized to the IOT assay
Ultrasensitive, 2012	Ansh labs	0.083-14.2 ng/mL	0.023 ng/mL	Monoclonal antibody pair directed against specific linear epitopes in the stable pro region and mature region of the associated form of human recombinant AMH
PicoAMH, 2013	Ansh labs	0.001-0.746 ng/mL	0.001 ng/mL	

The following are the limitations of AMH:

- Women's AMH levels fall at different rates with age. It is still necessary to develop an international standard for age-specific AMH diagnostic thresholds for assessing functional ovarian reserves or estimating menopausal age [77].
- There are a few endogenous and exogenous factors that may affect serum AMH levels, making it more difficult to accurately interpret AMH results in a clinical environment [78].
- AMH levels shouldn't be used as a fertility test because the predictive value of AMH for a successful clinical pregnancy (in both natural and assisted reproduction) is not very high [79].
- Due to intra-assay/interassay variations, the manual enzyme-linked immunosorbent assay (ELISA) for AMH evaluation has limitations and requires careful sample preparation and preservation. On the other hand, automated AMH assay technologies provide increased sensitivity, improved precision, quicker turnaround times, and national accessibility. Because of their better performance and useful benefits, automated platforms ought to be used as the industry standard for calculating AMH [77].

Role of AMH as a marker of ovarian reserve

The quantity and quality of eggs, or oocytes, in the ovaries are referred to as ovarian reserve. An ovary that has lost ovarian reserve as a result of age-related factors is considered senile. One important indicator for determining ovarian reserve is the quantity of primordial follicles, or early-stage eggs [80]. It can be difficult to quantify this count precisely, though Research indicates that there may be a relationship between the number of follicles that enter the pool of growing follicles and the length of the primordial follicular pool [81-83]. The only source of AMH is these developing follicles. Consequently, the amount of AMH in the blood can serve as a proxy for the primordial follicle pool's size, which in turn represents ovarian reserve. Numerous research investigations have noted this association [84-87]. An initial quantity of

oocytes, typically ranging from one to two million, is present in females at birth [88]. AMH inhibits Leydig cell differentiation and promotes follicular maturation, but it is not crucial to ovarian differentiation [89]. By attracting primordial follicles during folliculogenesis (Fig. 3), it plays a crucial role in controlling follicular maturation. The amount of ovarian reserve and a woman's potential for ovulation are directly correlated with the levels of AMH found in serum [90].

An additional differentiation can be pointed out between a functional ovarian reserve (FOR) and an ovarian reserve. There is no correlation between the blood concentration of AMH and the number of primordial follicles in young women since AMH is expressed by a certain population of developing follicles [91]. The pool of follicles, with a diameter of 2 to 5 mm, among which one follicle is chosen by FSH and will ovulate, is known as the FOR [90]. FOR release AMH during the follicular phase. The quantity of developing follicles drawn from the primordial pool is indicated by the blood's level of AMH. Since there isn't a direct blood marker for ovarian reserve, this functions as an indirect indicator. Serum AMH levels essentially indicate the activity of developing follicles and offer important insights into ovarian reserve [90]. Serum levels of AMH gradually rise to a peak and plateau at age 25; the serum level begins to decline then. Individuals with elevated AMH levels who do not have PCOS are typically quite fertile [92]. It is crucial to remember that serum levels of AMH are influenced by various factors, including vitamin D and hormonal contraception. Women using hormonal contraception had reduced AMH serum levels, which range from 14 to 55% [91]. levels of AMH are affected during pregnancy. The second and third trimesters are marked by a significant fall in AMH levels, which suggests that ovarian activity is lower during this time. On the other hand, compared to preconception levels, the AMH concentration is rather steady during the first trimester and recovers to normal following delivery [93]. Recent research suggests a link between higher serum levels of vitamin D and higher amounts of AMH in the bloodstream. Vitamin D and AMH levels might change periodically throughout the year [92]. This link is due to the occurrence of a vitamin D-responsive element inside the AMH gene promoter, which allows vitamin D levels to impact AMH concentrations [94].

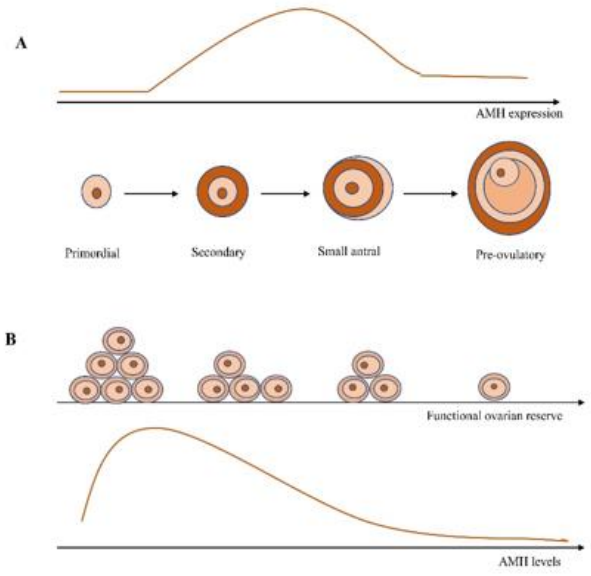

Fig 3: Anti-müllerian hormone (AMH) expression and concentration about folliculogenesis and ovarian reserve

AMH and cancer gynecological tumors and cancer

One common type of gynecological cancer is ovarian cancer, which comes in three primary categories: germ cell tumors, stromal tumors, and epithelial tumors. Of these, 82% of all ovarian malignancies are epithelial ovarian tumors, which are the most common type. In contrast, germ cell tumors account for 3% of ovarian cancers and are further divided into juvenile and adult types [95]. It is interesting to note that AMH can affect the development of breast, endometrial, and prostate cancers in addition to its main association with germ cell malignancies [15,32,96]. Considering its stability throughout the menstrual cycle, AMH is a reliable tumor marker for both primary and recurrent GCT incidence, in addition to inhibin B [97].

Although serum AMH levels are higher in these individuals than in those without tumours, it can only be used effectively in patients under the age of 65 [98]. Regardless of their illness, elderly women's serum AMH levels are too low to assess. The higher level of AMH in tumors is attributed to bigger granulosa cells that release more AMH into the circulation [97]. The same positive connection between high circulating AMH levels and an increased risk of breast cancer has been discovered in breast cancer patients [99].

While most ovarian cancers emerging from the Müllerian tract are thought to grow via the fimbriated end of the fallopian tube, there are distinct tumor types that arise from the secondary Müllerian system [100]. The involvement of AMH in the regression of Müllerian ducts during male gender development in embryos has prompted scientists to investigate its potential as a therapy for epithelial ovarian cancer [101]. Recombinant AMH has been shown in studies to successfully limit the growth of several ovarian cancer cell lines, including OVCAR 8 and IGROV 1. These findings point to a possible option for using AMH in targeted therapy for epithelial ovarian cancer [102]. The levels of AMH differ between healthy individuals and cancer patients, which has consequences for ovarian reserve. For example, young breast cancer patients (28–44 years old) had AMH levels comparable to healthy women of a comparable age (30–44 years old), implying that breast cancer has no substantial impact on ovarian reserve [103].

However, those suffering from Hodgkin lymphoma had lower AMH levels and a reduced ovarian reserve when compared to healthy women [104]. Notably, serum AMH levels can indicate post-cancer treatment ovarian function and prospective recovery; greater AMH levels correspond to faster restoration of ovarian function and fertility. As a result, testing AMH in patients' serum is regarded as a more robust and reliable approach to determining ovarian reserve than measuring FSH or inhibin B levels [105].

Artificial Reproductive Technology

Exogenous FSH treatment affects the hormonal modulation of ovarian function in women with reproductive challenges. Predicting an ovarian response before stimulation allows for personalized counseling and optimal gonadotrophin dosage for each patient [106]. Assisted reproductive technology (ART) results are strongly reliant on the ovarian response to stimulation, which reflects ovarian reserve in terms of egg number and quality. Because of its higher sensitivity than procedures such as day-three FSH, AMH measurement has become routine practice in ART centres [107]. A low response to controlled ovarian hyperstimulation (COH) is commonly characterized as extracting five or fewer oocytes or canceling the cycle, although the optimal range

for oocyte retrieval is between 10 and 12 [108]. To optimize stimulation, national recommendations advocate adjusting gonadotropin doses depending on individual ovarian reserve markers, such as specific AMH levels [12].

Endometriosis is prevalent amongst infertile women, with studies indicating that 20-50% of those facing infertility have endometriosis [109]. Endometriosis and infertility are associated via complicated pathways, with reduced ovarian reserve being indicated as a contributing factor. Chronic inflammation, increased oxidative stress, dysregulated cell cycles, and endometriosis-related poor angiogenesis all contribute to this impairment [110]. Kitajima et al. found reduced AMH levels in peritoneal fluid among women with endometriosis compared to a control group without the disorder. This study emphasizes the impact of endometriosis on ovarian function and the potential role of AMH as a diagnostic marker in measuring ovarian reserve in women with endometriosis-related infertility [111]. Endometriosis is usually treated with an amalgam of surgery and medications, such as pain relievers and hormone therapy [112]. However, these treatments frequently fail to cure the disease and are linked with high rates of clinical recurrence. While surgical intervention is successful at lowering symptoms, it can also reduce ovarian reserve and AMH levels.

Laparoscopic surgery has been regarded as the primary treatment for endometriosis-related infertility, with assisted reproductive technology (ART) as a backup option [109]. A combination of laparoscopic surgery and ART has resulted in higher pregnancy rates in endometriosis-related infertility cases. However, such procedures have the potential to produce iatrogenic damage, including ovarian reserve loss and scar formation [109], particularly following ovarian surgery, which specifically lowers AMH levels and antral follicle count (AFC), contributing to diminished fertility [113]. To address the reduction in fertility associated with endometriosis treatment, women with endometriosis can get oocyte cryopreservation as a preoperative fertility preservation therapy. This method seeks to reduce the effect of surgical operations on ovarian function and fertility [109].

Menopause

AMH has emerged as a useful marker for predicting menopause age, providing important information about women's reproductive health and possible fertility loss [114]. As women age, their ovarian reserve steadily declines, resulting in menopause—a natural physiological shift that signals the end of reproductive potential [115]. Given that genetic variables have been demonstrated to influence menopause, a woman's mother's age at the onset of menopause may be a good indicator of her own. It is known that genetic variations account for up to 50% of the variation in menopausal age [116]. Ovarian follicles produce AMH, which indicates the number of remaining primordial follicles in the ovaries and so serves as an indirect indicator of ovarian reserve [117]. Lower levels of AMH are often associated with decreasing ovarian function and imminent menopause. Dolleman et al. found from population-based cohort studies that the AMH predicts menopause onset age more accurately than the mother's age hereditary factor [118]. The accuracy of the AMH in predicting the onset of menopause over estradiol, FSH, or inhibin B has also been demonstrated by another research. From the moment of a female's birth, the AMH progressively rises and peaks at approximately 25 years of age. After that, AMH levels in post-menopausal women start to progressively decline until they are almost undetectable [119]. On the other hand, some argue that AMH may not be a reliable indicator of total

ovarian age. This opinion is supported by De Kat et al., who note that although AMH and other ovarian reserve indicators are connected to menopause age, they might not accurately depict the precise course of an individual's ovarian aging cycle [120].

While AMH was a strong predictor of time till menopause (TTM) and time until early menopause, it was discovered in a prospective cohort research by Depmann et al. that AMH had low predictive power for the age at which menopause begins. This suggests that although AMH can be a helpful predictive model for younger women who want to know if they might go through menopause early, its accuracy in identifying the precise age at which menopause begins may have some mistakes [121]. Another important factor to note is that as women age, AMH's predictive capacity declines. This suggests that, while AMH may be more trustworthy in predicting menopause timing in younger women, its accuracy declines as women approach menopause. These findings underscore the complexities of utilizing AMH alone to predict menopausal age, implying that other factors, such as genetic predispositions and lifestyle effects, also play important roles in determining the time of menopause onset. Thus, while AMH is still a useful tool for monitoring ovarian reserve and possible fertility reduction, its capacity to predict the exact age of menopause onset should be regarded with caution, particularly in older women or those with unique health profiles.

CONCLUSION

Serum anti-Müllerian hormone (AMH) levels are significantly higher among individuals with polycystic ovary syndrome (PCOS) than in their healthy counterparts, underscoring the significance of AMH as a PCOS diagnostic tool. It is especially beneficial in situations where evaluating the ovaries is difficult, including in obese, nulliparous, and individuals with limited echogenicity during ultrasound examinations, where reliable determination of the antral follicle count (AFC) is challenging.

Although AMH helps identify PCOS and provides insight into its pathophysiology and phenotypic variations, determining an exact AMH concentration threshold is a difficult task. Nevertheless, AMH has the potential to develop into a reliable diagnostic tool for PCOS with improved assay standardization. AMH is linked to the suppression of follicular growth and ovulation in the context of PCOS pathophysiology, which may add to treatment complications. Further in-depth investigations are imperative to elucidate AMH's intricate role in PCOS etiology, paving the way for targeted therapeutic interventions.

References

1) Yasmin A, Roychoudhury S, Paul Choudhury A, Ahmed AF, Dutta S, Mottola F, Verma V, Kalita JC, Kumar D, Sengupta P, Kolesarova A. Polycystic ovary syndrome: An updated overview foregrounding impacts of ethnicities and geographic variations. Life. 2022 Nov 25;12(12):1974.

2) Kanbour SA, Dobs AS. Hyperandrogenism in women with polycystic ovarian syndrome: Pathophysiology and controversies. Androgens: Clinical Research and Therapeutics. 2022 Mar 1;3(1):22-30.

3) Jensterle M, Herman R, Janež A. Therapeutic potential of glucagon-like peptide-1 agonists in polycystic ovary syndrome: from current clinical evidence to future perspectives. Biomedicines. 2022 Aug 16;10(8):1989.

4) Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2013 Dec 1;98(12):4565-92.

5) Josso N, di Clemente N. Transduction pathway of anti-Müllerian hormone, a sex-specific member of the TGF-β family. Trends in Endocrinology & Metabolism. 2003 Mar 1;14(2):91-7.

6) Zhang Z, Zhu B, Chen W, Ge W. Anti-Müllerian hormone (Amh/amh) plays dual roles in maintaining gonadal homeostasis and gametogenesis in zebrafish. Molecular and Cellular Endocrinology. 2020 Nov 1; 517:110963.

7) Hart KN. *Structural and Functional Studies of Anti-Müllerian Hormone (AMH) and its Receptor* (Doctoral dissertation, University of Cincinnati).

8) Peluso C, Fonseca FL, Rodart IF, Cavalcanti V, Gastaldo G, Christofolini DM, Barbosa CP, Bianco B. AMH: An ovarian reserve biomarker in assisted reproduction. Clinica Chimica Acta. 2014 Nov 1;437:175-82.

9) Josso N, di Clemente N, Gouédard L. Anti-Müllerian hormone and its receptors. Molecular and cellular endocrinology. 2001 Jun 20;179(1-2):25-32.

10) Rzeszowska M, Leszcz A, Putowski L, Hałabiś M, Tkaczuk-Włach J, Kotarski J, Polak G. Anti-Müllerian hormone: a critical factor for female fertility and reproductive health. Ginekologia polska. 2016;87(7):532-7.

11) Rzeszowska M, Leszcz A, Putowski L, Hałabiś M, Tkaczuk-Włach J, Kotarski J, Polak G. Anti-Müllerian hormone: structure, properties and appliance. Ginekologia polska. 2016;87(9).

12) Bedenk J, Vrtačnik-Bokal E, Virant-Klun I. The role of anti-Müllerian hormone (AMH) in ovarian disease and infertility. Journal of assisted reproduction and genetics. 2020 Jan;37(1):89-100.

13) Visser JA, Themmen AP. Anti-Müllerian hormone and folliculogenesis. Molecular and cellular endocrinology. 2005 Apr 29;234(1-2):81-6.

14) Pfennig F, Standke A, Gutzeit HO. The role of Amh signaling in teleost fish–multiple functions not restricted to the gonads. General and Comparative Endocrinology. 2015 Nov 1;223:87-107.

15) Segev DL, Hoshiya Y, Hoshiya M, Tran TT, Carey JL, Stephen AE, MacLaughlin DT, Donahoe PK, Maheswaran S. Mullerian-inhibiting substance regulates NF–κB signaling in the prostate in vitro and in vivo. Proceedings of the National Academy of Sciences. 2002 Jan 8;99(1):239-44.

16) Wang J, Dicken C, Lustbader JW, Tortoriello DV. Evidence for a Müllerian-inhibiting substance autocrine/paracrine system in adult human endometrium. Fertility and sterility. 2009 Apr 1;91(4):1195-203.

17) Segev DL, Hoshiya Y, Stephen AE, Hoshiya M, Tran TT, MacLaughlin DT, Donahoe PK, Maheswaran S. Müllerian inhibiting substance regulates NFκB signaling and growth of mammary epithelial cells in vivo. Journal of Biological Chemistry. 2001 Jul 20;276(29):26799-806.

18) La Marca A, Volpe A. Anti-Müllerian hormone (AMH) in female reproduction: is measurement of circulating AMH a useful tool?. Clinical endocrinology. 2006 Jun;64(6):603-10.

19) Wang PY, Koishi K, McGeachie AB, Kimber M, MacLaughlin DT, Donahoe PK, McLennan IS. Mullerian inhibiting substance acts as a motor neuron survival factor in vitro. Proceedings of the National Academy of Sciences. 2005 Nov 8;102(45):16421-5.

20) Lebeurrier N, Launay S, Macrez R, Maubert E, Legros H, Leclerc A, Jamin SP, Picard JY, Marret S, Laudenbach V, Berger P. Anti-Mullerian-hormone-dependent regulation of the brain serine-protease inhibitor neuroserpin. Journal of Cell Science. 2008 Oct 15;121(20):3357-65.

21) Cimino I, Casoni F, Liu X, Messina A, Parkash J, Jamin SP, Catteau-Jonard S, Collier F, Baroncini M, Dewailly D, Pigny P. Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion. Nature communications. 2016 Jan 12;7(1):1-2.

22) Bédécarrats GY, O'Neill FH, Norwitz ER, Kaiser UB, Teixeira J. Regulation of gonadotropin gene expression by Müllerian inhibiting substance. Proceedings of the National Academy of Sciences. 2003 Aug 5;100(16):9348-53.

23) Di Clemente N, Racine C, Pierre A, Taieb J. Anti-Müllerian hormone in female reproduction. Endocrine reviews. 2021 Dec 1;42(6):753-82.

24) Josso N, Picard JY. Genetics of anti-Müllerian hormone and its signaling pathway. Best Practice & Research Clinical Endocrinology & Metabolism. 2022 Jan 1;36(1):101634.

25) Wang PY, Koishi K, McGeachie AB, Kimber M, MacLaughlin DT, Donahoe PK, McLennan IS. Mullerian inhibiting substance acts as a motor neuron survival factor in vitro. Proceedings of the National Academy of Sciences. 2005 Nov 8;102(45):16421-5.

26) Lebeurrier N, Launay S, Macrez R, Maubert E, Legros H, Leclerc A, Jamin SP, Picard JY, Marret S, Laudenbach V, Berger P. Anti-Mullerian-hormone-dependent regulation of the brain serine-protease inhibitor neuroserpin. Journal of Cell Science. 2008 Oct 15;121(20):3357-65.

27) Bédécarrats GY, O'Neill FH, Norwitz ER, Kaiser UB, Teixeira J. Regulation of gonadotropin gene expression by Müllerian inhibiting substance. Proceedings of the National Academy of Sciences. 2003 Aug 5;100(16):9348-53.

28) Cimino I, Casoni F, Liu X, Messina A, Parkash J, Jamin SP, Catteau-Jonard S, Collier F, Baroncini M, Dewailly D, Pigny P. Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion. Nature communications. 2016 Jan 12;7(1):1-2.

29) Segev DL, Ha TU, Tran TT, Kenneally M, Harkin P, Jung M, MacLaughlin DT, Donahoe PK, Maheswaran S. Müllerian inhibiting substance inhibits breast cancer cell growth through an NFκB-mediated pathway. Journal of Biological Chemistry. 2000 Sep 15;275(37):28371-9.

30) Barret JM, Nicolas A, Jarry A, Dubreuil O, Meseure D, Passat T, Perrial E, Deleine C, Champenois G, Gaillard S, Duchalais E. The expression of anti-Müllerian hormone Type II receptor (AMHRII) in non-gynecological solid tumors offers potential for broad therapeutic intervention in cancer. Biology. 2021 Apr 7;10(4):305.

31) Beck TN, Korobeynikov VA, Kudinov AE, Georgopoulos R, Solanki NR, Andrews-Hoke M, Kistner TM, Pépin D, Donahoe PK, Nicolas E, Einarson MB. Anti-Müllerian hormone signaling regulates epithelial plasticity and chemoresistance in lung cancer. Cell reports. 2016 Jul 19;16(3):657-71.

32) Segev DL, Hoshiya Y, Hoshiya M, Tran TT, Carey JL, Stephen AE, MacLaughlin DT, Donahoe PK, Maheswaran S. Mullerian-inhibiting substance regulates NF–κB signaling in the prostate in vitro and in vivo. Proceedings of the National Academy of Sciences. 2002 Jan 8;99(1):239-44.

33) Carrarelli P, Rocha AL, Belmonte G, Zupi E, Abrão MS, Arcuri F, Piomboni P, Petraglia F. Increased expression of antimüllerian hormone and its receptor in endometriosis. Fertility and sterility. 2014 May 1;101(5):1353-8.

34) Rajpert-De Meyts E, Jørgensen N, Græm N, Müller J, Cate RL, Skakkebæk NE. Expression of anti-Mullerian hormone during normal and pathological gonadal development: association with differentiation of Sertoli and granulosa cells. The Journal of Clinical Endocrinology & Metabolism. 1999 Oct 1;84(10):3836-44.

35) Qi X, Pang Y, Qiao J. The role of anti-Müllerian hormone in the pathogenesis and pathophysiological characteristics of polycystic ovary syndrome. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016 Apr 1;199:82-7.

36) Pierre A, Taieb J, Giton F, Grynberg M, Touleimat S, El Hachem H, Fanchin R, Monniaux D, Cohen-Tannoudji J, Di Clemente N, Racine C. Dysregulation of the anti-Müllerian hormone system by steroids in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2017 Nov 1;102(11):3970-8.

37) Peluso C, Fonseca FL, Rodart IF, Cavalcanti V, Gastaldo G, Christofolini DM, Barbosa CP, Bianco B. AMH: An ovarian reserve biomarker in assisted reproduction. Clinica Chimica Acta. 2014 Nov 1; 437:175-82.

38) La Marca A, Volpe A. Anti-Müllerian hormone (AMH) in female reproduction: is measurement of circulating AMH a useful tool? Clinical endocrinology. 2006 Jun;64(6):603-10.

39) Durlinger AL, Gruijters MJ, Kramer P, Karels B, Kumar TR, Matzuk MM, Rose UM, de Jong FH, Uilenbroek JT, Grootegoed JA, Themmen AP. Anti-Mullerian hormone attenuates the effects of FSH on follicle development in the mouse ovary. Endocrinology. 2001 Nov 1;142(11):4891-9.

40) Silva MS, Giacobini P. New insights into anti-Müllerian hormone role in the hypothalamic–pituitary–gonadal axis and neuroendocrine development. Cellular and molecular life sciences. 2021 Jan;78(1):1-6.

41) Dąbkowska-Huc A, Cygal A, Skałba P. The influence of anti-Mullerian hormone on folliculogenesis. Ginekologia polska. 2008;79(2).

42) Lv PP, Jin M, Rao JP, Chen J, Wang LQ, Huang CC, Yang SQ, Yao QP, Feng L, Shen JM, Feng C. Role of anti-Müllerian hormone and testosterone in follicular growth: a cross-sectional study. BMC Endocrine Disorders. 2020 Dec; 20:1-0.

43) Anderson RA, Su HI. The clinical value and interpretation of anti-Müllerian hormone in women with cancer. Frontiers in endocrinology. 2020 Oct 7; 11:574263.

44) Juengel JL, Cushman RA, Dupont J, Fabre S, Lea RG, Martin GB, Mossa F, Pitman JL, Price CA, Smith P. The ovarian follicle of ruminants: the path from conceptus to adult. Reproduction, Fertility and Development. 2021 Jul 2;33(10):621-42.

45) Moolhuijsen LM, Visser JA. AMH in PCOS: Controlling the ovary, placenta, or brain? Current opinion in endocrine and metabolic research. 2020 Jun 1; 12:91-7.

46) Kostrzewa M, Głowacka E, Stetkiewicz T, Grzesiak M, Szyłło K, Wilczyński J. Is serum anti-Müllerian hormone (AMH) assay a satisfactory measure for ovarian reserve estimation? A comparison of serum and peritoneal fluid AMH levels. Advances in Clinical and Experimental Medicine. 2020;29(7).

47) Dumont A, Robin G, Dewailly D. Anti-müllerian hormone in the pathophysiology and diagnosis of polycystic ovarian syndrome. Current Opinion in Endocrinology, Diabetes and Obesity. 2018 Dec 1;25(6):377-84.

48) Lv PP, Jin M, Rao JP, Chen J, Wang LQ, Huang CC, Yang SQ, Yao QP, Feng L, Shen JM, Feng C. Role of anti-Müllerian hormone and testosterone in follicular growth: a cross-sectional study. BMC Endocrine Disorders. 2020 Dec; 20:1-0.

49) Neven AC, Laven J, Teede HJ, Boyle JA. A summary on polycystic ovary syndrome: diagnostic criteria, prevalence, clinical manifestations, and management according to the latest international guidelines. InSeminars in reproductive medicine 2018 Jan (Vol. 36, No. 01, pp. 005-012). Thieme Medical Publishers.

50) Pepinsky RB, Sinclair LK, Chow EP, Mattaliano RJ, Manganaro TF, Donahoe PK, Cate RL. Proteolytic processing of mullerian inhibiting substance produces a transforming growth factor-beta-like fragment. Journal of Biological Chemistry. 1988 Dec 15;263(35):18961-4.

51) Griesinger G, Dafopoulos K, Buendgen N, Cascorbi I, Georgoulias P, Zavos A, Messini CI, Messinis IE. Elimination half-life of anti-Müllerian hormone. The Journal of Clinical Endocrinology & Metabolism. 2012 Jun 1;97(6):2160-3.

52) Nachtigal MW, Ingraham HA. Bioactivation of Müllerian inhibiting substance during gonadal development by a kex2/subtilisin-like endoprotease. Proceedings of the National Academy of Sciences. 1996 Jul 23;93(15):7711-6.

53) Pankhurst MW, McLennan IS. A specific immunoassay for proAMH, the uncleaved proprotein precursor of anti-Müllerian hormone. Molecular and Cellular Endocrinology. 2016 Jan 5;419:165-71.

54) Pierre A, Racine C, Rey RA, Fanchin R, Taieb J, Cohen-Tannoudji J, Carmillo P, Pepinsky RB, Cate RL, Di Clemente N. Most cleaved anti-Müllerian hormone binds its receptor in human follicular fluid but little is competent in serum. The Journal of Clinical Endocrinology & Metabolism. 2016 Dec 1;101(12):4618-27.

55) Wilson CA, di Clemente N, Ehrenfels C, Pepinsky RB, Josso N, Vigier B, Cate RL. Mullerian inhibiting substance requires its N-terminal domain for maintenance of biological activity, a novel finding within the transforming growth factor-beta superfamily. Molecular Endocrinology. 1993 Feb 1;7(2):247-57.

56) Di Clemente N, Jamin SP, Lugovskoy A, Carmillo P, Ehrenfels C, Picard JY, Whitty A, Josso N, Pepinsky RB, Cate RL. Processing of anti-mullerian hormone regulates receptor activation by a mechanism distinct from TGF-β. Molecular endocrinology. 2010 Nov 1;24(11):2193-206.

57) Belville C, Van Vlijmen H, Ehrenfels C, Pepinsky B, Rezaie AR, Picard JY, Josso N, Clemente ND, Cate RL. Mutations of the anti-mullerian hormone gene in patients with persistent mullerian duct syndrome: biosynthesis, secretion, and processing of the abnormal proteins and analysis using a three-dimensional model. Molecular Endocrinology. 2004 Mar 1;18(3):708-21.

58) Khan MJ, Ullah A, Basit S. Genetic basis of polycystic ovary syndrome (PCOS): current perspectives. The application of clinical genetics. 2019 Dec 24:249-60.

59) Kiran Z. Diagnostic criteria for polycystic ovary syndrome. InPolycystic Ovary Syndrome 2024 Jan 1 (pp. 61-74). Elsevier.

60) Maheshwari N, Hassan T, Rashid G. PCOS and the Rhythmicity of GnRH: The Impact of FSH and LH on Menstrual Health. Obstetrics and Gynecology Advances. 2023:27.

61) Dumesic DA, Hoyos LR, Chazenbalk GD, Naik R, Padmanabhan V, Abbott DH. Mechanisms of intergenerational transmission of polycystic ovary syndrome. Reproduction. 2020 Jan 1;159(1):R1-3.

62) Risal S, Pei Y, Lu H, Manti M, Fornes R, Pui HP, Zhao Z, Massart J, Ohlsson C, Lindgren E, Crisosto N. Prenatal androgen exposure and transgenerational susceptibility to polycystic ovary syndrome. Nature Medicine. 2019 Dec;25(12):1894-904.

63) Stener-Victorin E, Padmanabhan V, Walters KA, Campbell RE, Benrick A, Giacobini P, Dumesic DA, Abbott DH. Animal models to understand the etiology and pathophysiology of polycystic ovary syndrome. Endocrine reviews. 2020 Aug;41(4): bnaa010.

64) Rudnicka E, Kunicki M, Calik-Ksepka A, Suchta K, Duszewska A, Smolarczyk K, Smolarczyk R. Anti-müllerian hormone in pathogenesis, diagnostic and treatment of PCOS. International journal of molecular sciences. 2021 Nov 19;22(22):12507.

65) Pellatt L, Hanna L, Brincat M, Galea R, Brain H, Whitehead S, Mason H. Granulosa cell production of anti-Mullerian hormone is increased in polycystic ovaries. The Journal of Clinical Endocrinology & Metabolism. 2007 Jan 1;92(1):240-5.

66) Catteau-Jonard S, Jamin SP, Leclerc A, Gonzalès J, Dewailly D, Di Clemente N. Anti-Mullerian hormone, its receptor, FSH receptor, and androgen receptor genes are overexpressed by granulosa cells from stimulated follicles in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2008 Nov 1;93(11):4456-61.

67) Wongwananuruk T, Panichyawat N, Indhavivadhana S, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Pratumvinit B. Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women. Taiwanese Journal of Obstetrics and Gynecology. 2018 Aug 1;57(4):499-506.

68) Matsuzaki T, Munkhzaya M, Iwasa T, Tungalagsuvd A, Yano K, Mayila Y, Yanagihara R, Tokui T, Kato T, Kuwahara A, Matsui S. Relationship between serum anti-Mullerian hormone and clinical parameters in polycystic ovary syndrome. Endocrine Journal. 2017;64(5):531-41.

69) Mori T. Regulatory principles of follicular development. Ovarian stimulation protocols. 2016:1-6.

70) Kevenaar ME, Laven JS, Fong SL, Uitterlinden AG, de Jong FH, Themmen AP, Visser JA. A functional anti-mullerian hormone gene polymorphism is associated with follicle number and androgen levels in polycystic ovary syndrome patients. The Journal of Clinical Endocrinology & Metabolism. 2008 Apr 1;93(4):1310-6.

71) Wang F, Niu WB, Kong HJ, Guo YH, Sun YP. The role of AMH and its receptor SNP in the pathogenesis of PCOS. Molecular and cellular endocrinology. 2017 Jan 5; 439:363-8.

72) Pabalan N, Montagna E, Singian E, Tabangay L, Jarjanazi H, Barbosa CP, Bianco B. Associations of polymorphisms in anti-Müllerian hormone (AMH Ile49Ser) and its type II receptor (AMHRII-482 A> G) on reproductive outcomes and polycystic ovary syndrome: a systematic review and meta-analysis. Cellular Physiology and Biochemistry. 2016 Nov 17;39(6):2249-61.

73) Georgopoulos NA, Karagiannidou E, Koika V, Roupas ND, Armeni A, Marioli D, Papadakis E, Welt CK, Panidis D. Increased frequency of the anti-Müllerian-inhibiting hormone receptor 2 (AMHR2) 482 A> G polymorphism in women with polycystic ovary syndrome: relationship to luteinizing hormone levels. The Journal of Clinical Endocrinology & Metabolism. 2013 Nov 1;98(11): E1866-70.

74) Pierre A, Peigné M, Grynberg M, Arouche N, Taieb J, Hesters L, Gonzalès J, Picard JY, Dewailly D, Fanchin R, Catteau-Jonard S. Loss of LH-induced down-regulation of anti-Müllerian hormone receptor expression may contribute to anovulation in women with polycystic ovary syndrome. Human reproduction. 2013 Mar 1;28(3):762-9.

75) Su HI, Sammel MD, Homer MV, Bui K, Haunschild C, Stanczyk FZ. Comparability of antimüllerian hormone levels among commercially available immunoassays. Fertility and sterility. 2014 Jun 1;101(6):1766-72.

76) de Kat AC, Broekmans FJ, van Westing AC, Lentjes E, Verschuren WM, van der Schouw YT. A quantitative comparison of anti-Müllerian hormone measurement and its shifting boundaries between two assays. Maturitas. 2017 Jul 1; 101:12-6.

77) Tehrani FR, Firouzi F, Behboudi-Gandevani S. Investigating the clinical utility of the anti-mullerian hormone testing for the prediction of age at menopause and assessment of functional ovarian reserve: a practical approach and recent updates. Aging and Disease. 2022 Apr;13(2):458.

78) Moolhuijsen LM, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. The Journal of Clinical Endocrinology & Metabolism. 2020 Nov;105(11):3361-73.

79) Mafruchati M. Infertility Management as A Basis for Embryo Research. Zifatama Jawara; 2023 May 1.

80) Nakamura S, Tanaka III IB, Komura J, Tanaka S. Premature menopause and obesity due to oocyte loss in female mice chronically exposed to low dose-rate γ-rays. Radiation Protection Dosimetry. 2022 Sep;198(13-15):926-33.

81) Schuh SM, Kadie J, Rosen MP, Sternfeld B, Pera RA, Cedars MI. Links between age at menarche, antral follicle count, and body mass index in African American and European American women. Fertility and Sterility. 2019 Jan 1;111(1):122-31.

82) Grynberg M, Labrosse J, Bennani Smires B, Sifer C, Peigne M, Sonigo C. Could hormonal and follicular rearrangements explain timely menopause in unilaterally oophorectomized women? Human Reproduction. 2021 Jul 1;36(7):1941-7.

83) Iwase A, Sugita A, Hirokawa W, Goto M, Yamamoto E, Takikawa S, Nakahara T, Nakamura T, Kondo M, Kikkawa F. Anti-Müllerian hormone as a marker of ovarian reserve following chemotherapy in patients with gestational trophoblastic neoplasia. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013 Apr 1;167(2):194-8.

84) Kevenaar ME, Meerasahib MF, Kramer P, van de Lang-Born BM, de Jong FH, Groome NP, Themmen AP, Visser JA. Serum anti-mullerian hormone levels reflect the size of the primordial follicle pool in mice. Endocrinology. 2006 Jul 1;147(7):3228-34.

85) Appt SE, Clarkson TB, Chen H, Adams MR, Christian PJ, Hoyer PB, Wilson ME, Kaplan JR. Serum antimüllerian hormone predicts ovarian reserve in a monkey model. Menopause. 2009 May 1;16(3):597-601.

86) Vignali M, Mabrouk M, Ciocca E, Alabiso G, Barbasetti di Prun A, Gentilini D, Busacca M. Surgical excision of ovarian endometriomas: Does it truly impair ovarian reserve? Long term anti-Müllerian hormone (AMH) changes after surgery. Journal of Obstetrics and Gynaecology Research. 2015 Nov;41(11):1773-8.

87) Iwase A, Osuka S, Goto M, Murase T, Nakamura T, Takikawa S, Kikkawa F. Clinical application of serum anti-Müllerian hormone as an ovarian reserve marker: a review of recent studies. Journal of Obstetrics and Gynaecology Research. 2018 Jun;44(6):998-1006.

88) Carlson BM. Human embryology and developmental biology. Elsevier Health Sciences; 2018 Nov 30.

89) Racine C, Rey R, Forest MG, Louis F, Ferré A, Huhtaniemi I, Josso N, Di Clemente N. Receptors for anti-Müllerian hormone on Leydig cells are responsible for its effects on steroidogenesis and cell differentiation. Proceedings of the National Academy of Sciences. 1998 Jan 20;95(2):594-9.

90) Moolhuijsen LM, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. The Journal of Clinical Endocrinology & Metabolism. 2020 Nov;105(11):3361-73.

91) Rudnicka E, Kunicki M, Calik-Ksepka A, Suchta K, Duszewska A, Smolarczyk K, Smolarczyk R. Anti-müllerian hormone in pathogenesis, diagnostic and treatment of PCOS. International journal of molecular sciences. 2021 Nov 19;22(22):12507.

92) Yue CY, Lu LK, Li M, Zhang QL, Ying CM. Threshold value of anti-Mullerian hormone for the diagnosis of polycystic ovary syndrome in Chinese women. PLoS One. 2018 Aug 28;13(8):e0203129.

93) Köninger A, Kauth A, Schmidt B, Schmidt M, Yerlikaya G, Kasimir-Bauer S, Kimmig R, Birdir C. Anti-Mullerian-hormone levels during pregnancy and postpartum. Reproductive biology and endocrinology. 2013 Dec;11:1-9.

94) Dennis NA, Houghton LA, Jones GT, Van Rij AM, Morgan K, McLennan IS. The level of serum anti-Müllerian hormone correlates with vitamin D status in men and women but not in boys. The Journal of Clinical Endocrinology & Metabolism. 2012 Jul 1;97(7):2450-5.

95) Cannistra SA. Cancer of the ovary. New England Journal of Medicine. 1993 Nov 18;329(21):1550-9.

96) Renaud EJ, MacLaughlin DT, Oliva E, Rueda BR, Donahoe PK. Endometrial cancer is a receptor-mediated target for Mullerian Inhibiting Substance. Proceedings of the National Academy of Sciences. 2005 Jan 4;102(1):111-6.

97) Färkkilä A, Koskela S, Bryk S, Alfthan H, Bützow R, Leminen A, Puistola U, Tapanainen JS, Heikinheimo M, Anttonen M, Unkila-Kallio L. The clinical utility of serum anti-M üllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors—A comparative study with inhibin B. International Journal of Cancer. 2015 Oct 1;137(7):1661-71.

98) Chong YH, Campbell AJ, Farrand S, McLennan IS. Anti-Müllerian hormone level in older women: detection of granulosa cell tumor recurrence. International Journal of Gynecologic Cancer. 2012 Nov 1;22(9).

99) Ge W, Clendenen TV, Afanasyeva Y, Koenig KL, Agnoli C, Brinton LA, Dorgan JF, Eliassen AH, Falk RT, Hallmans G, Hankinson SE. Circulating anti-Müllerian hormone and breast cancer risk: A study in ten prospective cohorts. International journal of cancer. 2018 Jun 1;142(11):2215-26.

100) Dubeau L. The cell of origin of ovarian epithelial tumours. The lancet oncology. 2008 Dec 1;9(12):1191-7.

101) Basal E, Ayeni T, Zhang Q, Langstraat C, Donahoe PK, Pepin D, Yin X, Leof E, Cliby W. Patterns of Müllerian inhibiting substance type II and candidate type I receptors in epithelial ovarian cancer. Current molecular medicine. 2016 Mar 1;16(3):222-31.

102) Stephen AE, Pearsall LA, Christian BP, Donahoe PK, Vacanti JP, MacLaughlin DT. Highly purified mullerian inhibiting substance inhibits human ovarian cancer in vivo. Clinical Cancer Research. 2002 Aug 1;8(8):2640-6.

103) Su HI, Flatt SW, Natarajan L, DeMichele A, Steiner AZ. Impact of breast cancer on anti-mullerian hormone levels in young women. Breast cancer research and treatment. 2013 Jan;137:571-7.

104) Lawrenz B, Fehm T, von Wolff M, Soekler M, Huebner S, Henes J, Henes M. Reduced pretreatment ovarian reserve in premenopausal female patients with Hodgkin lymphoma or non-Hodgkin-lymphoma—evaluation by using antimüllerian hormone and retrieved oocytes. Fertility and sterility. 2012 Jul 1;98(1):141-4.

105) Goldman KN, Chenette D, Arju R, Duncan FE, Keefe DL, Grifo JA, Schneider RJ. mTORC1/2 inhibition preserves ovarian function and fertility during genotoxic chemotherapy. Proceedings of the National Academy of Sciences. 2017 Mar 21;114(12):3186-91.

106) Umarsingh S, Adam JK, Krishna SB. The relationship between anti-Müllerian hormone (AMH) levels and pregnancy outcomes in patients undergoing assisted reproductive techniques (ART). PeerJ. 2020 Dec 22;8:e10390.

107) Shruthi A. A Study to Correlate Serum Anti Mullerian Hormone, Basal Follicle Stimulating Hormone and Antral Follicle Count in Primary Infertility, as a Measure of Ovarian Reserve (Doctoral dissertation, Rajiv Gandhi University of Health Sciences (India)).

108) Chen YH, Xu XH, Wang Q, Zhang SD, Jiang LL, Zhang CL, Ge ZJ. Optimum oocyte retrieved and transfer strategy in young women with normal ovarian reserve undergoing a long treatment protocol: a retrospective cohort study. Journal of assisted reproduction and genetics. 2015 Oct; 32:1459-67.

109) Coccia ME, Nardone L, Rizzello F. Endometriosis and infertility: a long-life approach to preserve reproductive integrity. International journal of environmental research and public health. 2022 May 19;19(10):6162.

110) Henry L, Vervier J, Boucher A, Brichant G, Gaspard O, Labied S, Munaut C, Ravet S, Nisolle M. Oocyte cryopreservation in patients with endometriosis: current knowledge and number needed to treat. Journal of Clinical Medicine. 2022 Aug 4;11(15):4559.

111) Kitajima M, Matsumoto K, Murakami N, Kajimura I, Harada A, Kitajima Y, Masuzaki H, Miura K. AMH Concentrations in Peritoneal Fluids of Women with and without Endometriosis. Frontiers in Surgery. 2020 Nov 11; 7:600202.

112) Zhang H, Luo Q, Lu X, Yin N, Zhou D, Zhang L, Zhao W, Wang D, Du P, Hou Y, Zhang Y. Effects of hPMSCs on granulosa cell apoptosis and AMH expression and their role in the restoration of ovary function in premature ovarian failure mice. Stem cell research & therapy. 2018 Dec; 9:1-2.

113) Hong YH, Lee HK, Kim SK, Lee JR, Suh CS. The significance of planned fertility preservation for women with endometrioma before an expected ovarian cystectomy. Frontiers in Endocrinology. 2021 Dec 15; 12:794117.

114) Nelson SM, Davis SR, Kalantaridou S, Lumsden MA, Panay N, Anderson RA. Anti-Müllerian hormone for the diagnosis and prediction of menopause: a systematic review. Human Reproduction Update. 2023 May 1;29(3):327-46.

115) Laisk T, Tšuiko O, Jatsenko T, Hõrak P, Otala M, Lahdenperä M, Lummaa V, Tuuri T, Salumets A, Tapanainen JS. Demographic and evolutionary trends in ovarian function and aging. Human reproduction update. 2019 Jan 1;25(1):34-50.

116) Laven JS. Genetics of early and normal menopause. InSeminars in reproductive medicine 2015 Nov (Vol. 33, No. 06, pp. 377-383). Thieme Medical Publishers.

117) Iwase A, Hasegawa Y, Tsukui Y, Kobayashi M, Hiraishi H, Nakazato T, Kitahara Y. Anti-Müllerian hormone beyond an ovarian reserve marker: the relationship with the physiology and pathology in the life-long follicle development. Frontiers in Endocrinology. 2023 Nov 3;14:1273966.

118) Dolleman M, Depmann M, Eijkemans MJ, Heimensem J, Broer SL, Van Der Stroom EM, Laven JS, Van Rooij IA, Scheffer GJ, Peeters PH, Van Der Schouw YT. Anti-Müllerian hormone is a more accurate predictor of individual time to menopause than mother's age at menopause. Human reproduction. 2014 Mar 1;29(3):584-91.

119) Kruszyńska A, Słowińska-Srzednicka J. Anti-Müllerian hormone (AMH) as a good predictor of time of menopause. Menopause Review/Przegląd Menopauzalny. 2017 Jun 30;16(2):47-50.

120) De Kat AC, Broekmans FJ, Lambalk CB. Role of AMH in prediction of menopause. Frontiers in Endocrinology. 2021 Sep 14;12:733731.

121) Depmann M, Eijkemans MJ, Broer SL, Tehrani FR, Solaymani-Dodaran M, Azizi F, Lambalk CB, Randolph Jr JF, Harlow SD, Freeman EW, Sammel MD. Does AMH relate to timing of menopause? Results of an individual patient data meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2018 Oct;103(10):3593-600.