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REVIEW PAPER

Endogenous and exogenous factors influencing anti-Müllerian hormone levels in women of reproductive age

Olga Jankowska [1], Wojciech Kraśnik [1], Jacek Kurzeja [1], Katarzyna Piotrowicz [2], Hubert Piotrowicz [2], Agnieszka Bajkacz [3], Anna Rogala [4], Joanna Osmólska [4]

[1] J. Strus City Multispecialty Hospital, Poznań, Poland
[2] University Clinical Hospital in Poznan, Poznań, Poland
[3] University Hospital in Wroclaw, Wrocław, Poland
[4] Poznan University of Medical Sciences, Poznań, Poland

ABSTRACT

Introduction and aim. Anti-Müllerian hormone (AMH) is a key marker of ovarian reserve (OR), which declines with advancing reproductive age. Certain pathological conditions can reduce OR or lower AMH levels independently of age, potentially impairing fertility. This study aims to review the scientific literature on factors influencing AMH levels and the causes of diminished OR, including lifestyle, diet, supplementation, pathogenic factors, environmental influences, and genetic predispositions.

Material and methods. This review was conducted using electronic databases, including PubMed and Google Scholar. A comprehensive search was carried out across these databases, covering the period from 2007 to 2024. The inclusion criteria encompass studies on AMH and factors influencing ovarian reserve, that present either quantitative or qualitative data.

Analysis of the literature. The most important factor determining the level of AMH is age. In addition, factors that may influence hormone levels include genetic background, autoimmune diseases, polycystic ovary syndrome (PCOS), environmental toxins, diet, supplementation, oral contraception, physical activity, and smoking.

Conclusion. The causes of reduced OR and abnormal AMH levels remain unclear in many cases. Recommendations for the prevention of pathologically reduced OR include lifestyle modifications, a diet rich in antioxidants, avoiding toxins, refraining from smoking, appropriate supplementation, genetic testing, and regular blood tests.

Keywords. anti-Müllerian hormone, fertility, ovarian reserve, reproduction

Introduction

Anti-Müllerian hormone

Anti-Müllerian hormone (AMH), also known as Müllerian-inhibiting substance, is produced by the gonads-Sertoli cells of the testes and granulosa cells of the ovaries.[1-3] Its name derives from its role during fetal development, where it induces the regression of Müllerian ducts in male fetuses.[2,3] Anti-Müllerian hormone is a glycoprotein belonging to the transforming growth factor β superfamily.[2,3] It is an important regulator of specific stages of folliculogenesis.[2] During reproductive maturity, AMH is produced by granulosa cells of primary, preantral, and small antral follicles. The highest concentration of AMH is observed in small antral follicles, while its expression is absent in atretic follicles.[2,3] Anti-Müllerian hormone production in female fetuses is detected in the granulosa cells of follicles starting around the 23rd week of fetal development.[4] The hor-

Corresponding author: Olga Jankowska, e-mail: jankowskaolga.jo@gmail.com

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mone level gradually rises until roughly the age of 25, after which it generally decreases with age due to the diminishing follicle pool until menopause, when it becomes undetectable.[1-4] The annual decline in AMH levels in healthy women aged 20 to 50 years is estimated to be approximately 5.7%.[1] However, AMH concentrations and the rate of decline are highly individual.[1] Research suggests that the rate of AMH decline could help predict the onset of menopause, regardless of baseline AMH levels or age.[5] The prediction of menopause timing could be improved by multiple AMH measurements. This approach may help identify women at risk of early menopause.[5] However, some studies suggest that using AMH measurements for this purpose is imprecise and, therefore, not recommended.[6] Most studies indicate that AMH levels remain relatively stable throughout the menstrual cycle and do not significantly vary between cycles.[2,3] Therefore, AMH measurements are recommended regardless of the menstrual cycle phase. Although some literature reports fluctuations, these are not considered clinically significant enough to justify AMH testing during specific menstrual phases.[3,4] Notably, there are pathological conditions in which AMH levels do not correlate with ovarian reserve (OR).[7] AMH concentrations may be falsely elevated or reduced due to follicular arrest at specific stages rather than the total pool of primordial follicles.[7] Clinically, AMH is useful in the diagnosis of polycystic ovary syndrome (PCOS) and primary ovarian insufficiency (POI). It is a key tool in assisted reproductive technologies (ART), aiding in the selection of the most appropriate procedure and predicting ovarian response to stimulation.[2,3,4,8]

Ovarian reserve

Ovarian reserve refers to the reproductive potential of the ovaries, defined as the number of primordial ovarian follicles capable of maturing into viable oocytes.[9,10] It is genetically determined and declines with age. As the ovaries age, the follicular pool diminishes, oocyte quality decreases, and chromosomal abnormalities of the oocytes and miscarriage rates increase.[3,9] Clinicians consider several ovarian reserve tests, including follicle-stimulating hormone (FSH), estradiol (E2) and inhibin B levels on the third day of the menstrual cycle, AMH levels, antral follicle count (AFC) via ultrasound during the early follicular phase (days 2–5 of the cycle).[9] Among all the tests, serum AMH and AFC are the most reliable indicators of the ovarian pool.[11] Diminished ovarian reserve (DOR) refers to a reduced quantity and quality of oocytes in the ovaries. It affects nearly 10% of women seeking infertility treatment.[8] When DOR occurs at a young age, it often involves a reduced follicle count while maintaining normal oocyte quality. It remains unclear whether the reduced follicle pool results from an initially lower count or accelerated depletion due to excessive atresia. Anti-Müllerian hormone levels can help identify patients with DOR, even when menstrual cycles are regular and FSH levels are not yet elevated.[3] Signs of DOR include shorter menstrual cycles and lower estrogen levels, which may cause symptoms such as hot flashes, vaginal dryness, and night sweats.[10] However, many women with DOR are asymptomatic.[3] Diminished ovarian reserve increases the risk of early reproductive decline, infertility, poor ovarian response to stimulation, suboptimal ART outcomes, and recurrent miscarriage.[8,10] A severe form of DOR is premature ovarian insufficiency/failure (POI/POF), defined as ovarian failure before the age of 40.[10] According to the European Society of Human Reproduction and Embryology (ESHRE), the diagnostic criteria for POI include women under 40, menstrual disturbances lasting at least four months, and elevated FSH levels measured twice, at least one month apart.[2,10,12,13] Distinguishing between DOR and POI is crucial, as women with POI face additional health risks, requiring specialized care. Reduced estrogen levels increase the risk of osteoporosis, coronary artery disease, and psychological disorders such as anxiety and depression.[10,12]

The exact etiology of ovarian dysfunction often remains unknown, with idiopathic causes accounting for 50–90% of cases.[8,10,12] Proposed causes of DOR include genetic, autoimmune, iatrogenic, environmental factors, pharmacological and surgical treatments, infections, and lifestyle-related factors such as stress and nutrition (Fig. 1).[2,8,9,10,12,14] Modifiable factors, including lifestyle, diet, physical activity, and supplementation, are of growing interest. Identifying these modifiable factors to enhance OR and AMH levels is highly desirable and has been the subject of recent observational studies.[8] Raising awareness among women about the factors influencing fertility may facilitate timely diagnosis and help preserve reproductive potential. Currently, therapeutic alternatives for DOR include ovarian stimulation with gonadotropins, in vitro fertilization, and cryopreservation of oocytes, embryos or ovarian tissue[15] In certain cases, OR may be supported by medical treatments, such as ovarian platelet-rich plasma therapy.[16] Although this remains an experimental approach, it is a promising new treatment option.[16] For patients with the poorest prognoses for successful pregnancy, egg donation is often the only viable option, though it may be unacceptable to many patients. Therefore, the search for new therapeutic solutions is highly desirable.[16]

Aim

The aim of this study is to review the scientific literature on factors influencing AMH levels and the causes of DOR, including lifestyle, diet, supplementation, pathogenic factors, environmental influences, and genetic predispositions. This study seeks to raise aware-

ness among women about the factors affecting ovarian reserve, with a particular focus on high-risk groups at an increased risk of premature fertility decline. It also emphasizes the importance of lifestyle modifications, preventive measures, and the necessity of regular testing to monitor reproductive health.

Material and methods

This review was conducted using electronic databases, including PubMed and Google Scholar. Articles were selected based on their relevance to the topic. A comprehensive search was carried out across these databases, covering the period from 2007 to 2024. A thorough analysis of the literature was conducted, with a focus on the most recent articles published within the last five years. However, older studies were also considered if they presented significant findings. The articles were identified using a combination of keywords (in both Polish and English): ovarian reserve, fertility, anti-Müllerian hormone, AMH levels, premature ovarian failure/insufficiency, diet, supplementation, reproduction, environment. The inclusion criteria for this study encompass studies on AMH and factors influencing ovarian reserve, published in English or Polish, that present either quantitative or qualitative data. The exclusion criteria include irrelevant articles, studies with weak methodologies, and research published more than 17 years ago.

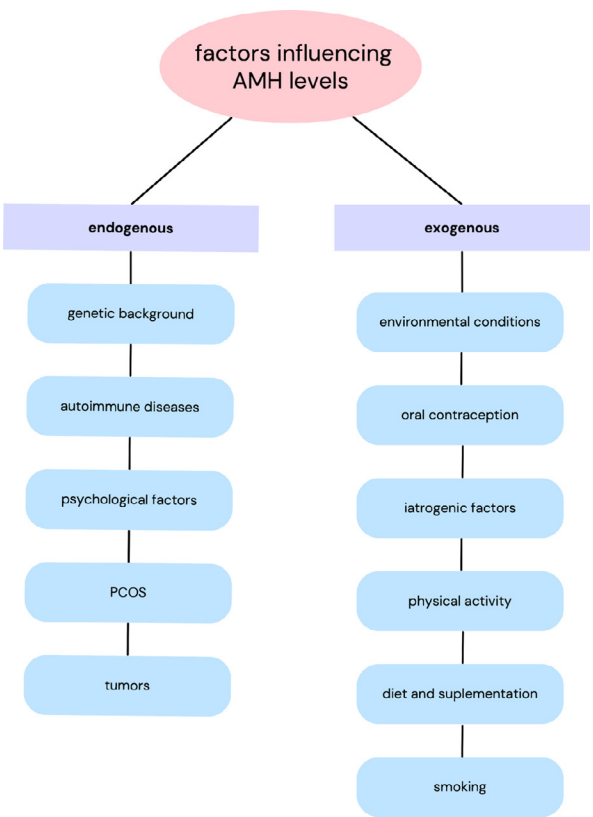

Fig. 1. Endogenous and exogenous factors influencing AMH levels

Analysis of the literature

Endogenous factors influencing AMH levels and OR

Genetic mutations and chromosomal aberrations

Multiple genetic mutations in both sex chromosomes and autosomes have been linked to POI.[10,15] X chromosome-related defects, including structural abnormalities or aneuploidy, account for the majority of genetic cases of POI.[10,15] The most common associated conditions include: Turner syndrome, fragile X syndrome, and trisomy X.[2,10,15] Women with Turner syndrome may experience follicular loss either prenatally or postnatally, depending on their karyotype. The loss of an X chromosome (45, X) leads to streak gonads with complete follicular depletion, whereas those with mosaicism, such as (45, X/46, XX), may undergo spontaneous puberty.[4,15] Fragile X syndrome is caused by a mutation in the *FMR1* gene (fragile X messenger ribonucleoprotein), one of the most common single-gene defects leading to POI in women with a (46, XX) karyotype.[10,15] The condition is characterized by a cytosine-guanine-guanine (CGG) trinucleotide repeat expansion, and the extent of its impact on OR is correlated with the length of the CGG sequence.[2,10,15]

Other single-gene defects associated with POI include mutations in growth factor genes, such as the *BMP-15* gene (bone morphogenetic protein 15), which plays a role in folliculogenesis and oocyte maturation.[2,10,15] Among autosomal single-gene mutations, the most notable are those affecting transcription factors, such as the *FOXL2* gene (forkhead box L2), which is associated with autosomal dominant blepharophimosis, ptosis, and epicanthus inversus syndrome; the *FIGLA* gene (folliculogenesis-specific basic helix-loop-helix); and the *NOBOX* gene (newborn ovary homeobox).[2,10,15] Another genetic condition linked to POI is classic galactosemia, where over 80% of affected girls develop POI, regardless of adherence to a strict galactose-restricted diet.[10] Although idiopathic POI, by definition, has no identifiable cause, it is believed to have an underlying genetic component.[10] If a standard genetic workup, including karyotyping and known gene mutation testing, is negative, Genome-Wide Association Studies (GWAS) may be employed to identify lesser-known genetic mutations.[10,15] For example, mutations in the *AMH* gene and its receptor gene *AMHR2* (anti-Müllerian hormone receptor type 2), along with defects in transcription factors regulating these genes, have been identified as causes of idiopathic POI.[2]

Autoimmune diseases

Autoimmune diseases are more prevalent in patients with POI than in the general population.[4,10,12,15] However, the pathogenesis of autoimmune POI remains poorly understood.[10] The most commonly associated autoimmune disorders include Addison's disease, Hashimoto's thyroiditis, systemic lupus erythemato-

sus, type 1 diabetes, celiac disease, Takayasu arteritis, Behçet's disease, myasthenia gravis, inflammatory bowel diseases, Sjögren's syndrome, and multiple sclerosis.[4,9,10,12,15] Among these, Addison's disease, myasthenia gravis, and autoimmune polyglandular syndrome type 1, which is caused by mutations in the *AIRE* gene, show the strongest correlations with POI.[15] There is a correlation between histologically diagnosed oophoritis and circulating adrenal or anti-ovarian antibodies.[10] However, the diagnostic validity and accuracy of antibody assays remain unestablished, leaving their specificity and pathogenic role uncertain.[10] Although endocrine abnormalities and impaired follicular growth due to autoimmunity have been hypothesized, the precise mechanisms underlying these processes remain unknown and require further investigation.[4,10]

Psychological factors

Several studies suggest that psychological well-being and mental stress can significantly impact OR.[3,9,17,18] Anxiety, depression, and other negative emotions have frequently been linked to reduced fertility. Hardy et al.[17] demonstrated that abnormal AMH levels, whether above or below the age-adjusted ranges, were linked to chronic abdominal pain and elevated urinary cortisol levels. Furthermore, serum AMH levels were significantly reduced in female rats exposed to chronic stress.[3,9] Research on occupational factors revealed that women engaged in physically demanding jobs, particularly those involving heavy lifting or night shifts, had lower ovarian reserves.[19] Psychological stress may impact the female reproductive system through the hypothalamus-pituitary-adrenal axis and the sympathetic-adrenomedullary pathway.[18] As a result, growing follicles may be lost due to oxidative damage to ovarian follicular cells, leading to a decrease in AMH levels.[18] It is also important to note that infertility itself represents a significant source of stress for patients, particularly women. Infertility-induced stress can negatively affect the outcomes of fertility treatments.[18]

PCOS

Anti-Müllerian hormone concentrations in both serum and follicular fluid are 2 to 4 times higher in women with PCOS compared to healthy counterparts.[2,4] In contrast to healthy women, a significant decline in AMH levels in PCOS patients is only observed after the age of 40.[3] Elevated serum AMH levels in PCOS may result from both an increased number of small antral follicles and AMH overexpression.[2] Studies suggest that this overexpression may be linked to hyperandrogenism.[2,4] Despite elevated AMH levels, histopathological examination of the ovaries in women with PCOS revealed a similar number of primordial follicles compared to the control group.[3]

Neoplasms

Anti-Müllerian hormone levels are elevated in 76–93% of women diagnosed with granulosa cell tumors.[3,20] This marker can be detected at an early stage of the disease, even before clinical symptoms appear. Additionally, AMH is a highly sensitive and specific marker for detecting recurrence in patients with folliculomas who have undergone oophorectomy.[3,4,20]

On the other hand, the determination of AMH concentrations in the serum of patients with epithelial ovarian cancer is not considered useful. Studies have examined AMH concentrations in ovarian cancer patients in relation to clinicopathological features, such as the pathological subtype of the tumor, FIGO (The International Federation of Gynecology and Obstetrics) stage, and tumor grading.[20] However, no significant correlations were observed between serum AMH levels and these factors.[20] Additionally, no association was found between serum AMH concentrations and the five-year survival rate.[20]

Exogenous factors influencing AMH levels and OR

Environment

Organic compounds that are ubiquitous in drinking water, food, food packaging, cosmetics, paints, or on frying pans, as well as other substances, may contribute to a decrease in OR.[9,10,21] Exposure to poly- and perfluoroalkyl substances, known as perfluoroalkyl and polyfluoroalkyl substances (PFAS), leads to a reduction in the number of follicular cells and may contribute to the development of infertility.[9] The effect of PFAS is dose-dependent and results in a decrease in E2 and progesterone levels in serum.[9] The toxicity of 3-monochloropropanediol esters also affects ovarian function by regulating follicular development and increasing the expression of inflammatory factors.[9] Chronic exposure to propylparaben or bisphenol A indicates potential toxicity to the ovaries.[9] Fenvalerate, a pesticide widely used in modern agriculture, inhibits follicle expansion by disrupting steroidogenesis.[9] Recent research has also shown that perfluorooctanoic acid, a substance commonly found in Teflon pans, is elevated in follicular fluid in patients with DOR and affects the composition of follicular fluid.[9] Phthalates, used in cosmetics (cosmetics, toiletries, food packaging), medical products, containers, toys, or building materials, have been identified as endocrine-disrupting chemicals and are considered potential risk factors for POI.[9,10,21] Numerous studies have shown a reduction in the ovarian follicle count after exposure to phthalates in mice of different ages.[10,22]

Diet

Some studies suggest that proper nutrition can influence AMH levels, OR, and the timing of menopause. However, these factors remain unclear due to inconsistencies in

findings, and the relationship between diet and OR has not been definitively proven.[1]

The greatest potential is attributed to a diet rich in antioxidants. Increased accumulation of reactive oxygen species (ROS) is one of the better-known causes of ovarian failure and decreased OR.[12,23] It is suggested that unexplained infertility may be caused by an imbalance between the levels of ROS and antioxidants.[24] The increase in free radical production, coupled with a reduced amount of antioxidants leads to oxidative stress.[12,23,24] Therefore, there is growing attention to mitochondrial function in the context of fertility. Mitochondrial dysfunction leads to increased accumulation of free radicals, which amplifies defense mechanisms and may cause apoptosis in granulosa cells and tissue damage, resulting in infertility and even POI.[12,23] The intake of antioxidant compounds, both through nutrition and supplements (described in more detail below), aims to protect against ROS accumulation, inhibit apoptosis, and reduce oxidative stress.[12,23]

In one study by Hu et al.[25] using animal models, protective effects of natural compounds with antioxidant activity, such as phenols, flavonoids, polyphenols, and alkaloids, in POI were demonstrated. Among flavonoids, quercetin received particular attention. It improved the quality of oocytes and embryos by affecting proliferation and apoptosis and reducing oxidative stress in granulosa cells.[25] Treatment with other natural products like icariin, resveratrol, and curcumin significantly increased AMH levels in animal models of POI.[25] Another important antioxidant is vitamin C, which plays a key role in collagen synthesis in the extracellular matrix of the corpus luteum.[24] These results suggest that the intake of antioxidants contributes to the improvement of ovarian function, the restoration of follicle count, and consequently an increase in AMH levels.[24,25]

In a prospective study conducted on women aged 20–50 years, dairy consumption was inversely correlated with the annual decline in AMH levels and a lower risk of rapid AMH decline, regardless of baseline age, body mass index (BMI), and total caloric intake.[1] Additionally, the consumption of berries and the total calcium intake level were inversely correlated with the annual decline in AMH. In this study, other dietary factors were not associated with the rate of AMH decline.[1]

A review by Prieto-Huecas et al.[14] analyzed the impact of nutritional status on OR. A high BMI was correlated with a decrease in OR.[14] Overweight and obesity negatively impact ovarian function. According to the literature review, women with a high BMI exhibit lower AMH and AFC levels compared to those with a normal BMI. Additionally, obesity and overweight may negatively impact oocyte quality, contributing to an increased rate of infertility.[14]

In a cohort study involving 296 premenopausal women (aged 35–45 years), AMH levels were positively correlated with total carbohydrate intake and inversely proportional to total fat intake.[26]

One cross-sectional study involving 234 adult women from an infertility clinic in Iran showed that serum AMH levels were negatively correlated with the consumption of fast food and saturated fats. Additional adjustments for BMI and physical activity did not change the results. This study, however, did not show a significant association between the consumption of fruits, vegetables, dairy products, and salt with AMH levels among adult women without PCOS.[27]

In an animal study, Hohos et al.[28] demonstrated that higher levels of n-3 docosahexaenoic acid, docosapentaenoic acid, and eicosapentaenoic acid in serum were positively associated with the number of primary follicles. It was found that omega-3 fatty acids may contribute to improving OR by reducing inflammation and oxidative stress.[27,28]

Supplementation

Supplements that may affect the level of the AMH hormone include coenzyme Q10, vitamin D, hehydroepiandrosterone (DHEA), selenium, and vitamin E. The mechanism of action of these supplements primarily relies on their antioxidant effects.[12,23,24,25,29]

Coenzyme Q10

Coenzyme Q10 (CoQ10) is an essential component of the mitochondrial electron transport chain, playing an important antioxidant role.[29] One study conducted on rat models assessed the protective effect of CoQ10 on ovaries and OR.[23] Cisplatin was used as a source of oxidative stress in ovarian tissue, while CoQ10 acted as an antioxidant.[23] The AFC significantly increased during the use of CoQ10 in combination with cisplatin, while the number of atretic follicles decreased significantly. These findings suggest that CoQ10 may be effective in protecting OR and preventing ovarian damage related to oxidative stress. AMH levels in the group receiving the combination of Cisplatin + CoQ10 were higher than in the group receiving cisplatin alone, but this difference was not statistically significant.[23] It is believed that CoQ10 supplementation may protect the ovaries by improving mitochondrial function, counteracting both mitochondrial and physiological ovarian aging.[23] Another study conducted on women confirmed the positive impact of CoQ10 supplementation among those with reduced OR undergoing gonadotropin stimulation during ART.[29] The intervention in the study group included oral administration of 200 mg CoQ10 three times a day for 60 days. The results showed that CoQ10 improved ovarian response to stimulation, as well as improved oocyte and embryo quality in young patients with poor prognosis and reduced OR.[29]

Vitamin D

Both animal and human studies provide evidence highlighting the significant role of vitamin D in female reproductive physiology.[7] It has been shown that elements in the promoter of the *AMH* gene respond to vitamin D, which explains its effect on *AMH* gene expression.[7,30] Nonetheless, the results of studies investigating the relationship between serum vitamin D and AMH levels are inconclusive.[7,30] It is also possible that vitamin D increases AMH levels without affecting the number of ovarian follicles.[30] However, vitamin D is a relatively safe and affordable supplement, with growing evidence suggesting its potential benefits for multiple aspects of human reproduction including increased pregnancy and live birth rates following ART, as well as a reduced risk of miscarriage and related complications.[7] Vitamin D deficiency causes a 75% decrease in fertility in rats and increases the risk of fetal growth disorders.[7] One study found that AMH levels significantly decreased after vitamin D supplementation in women with PCOS, whereas it significantly increased in women without PCOS.[7] Other studies have demonstrated that, in patients with vitamin D deficiency, supplementation led to a significant increase in AMH serum levels.[30] Dennis et al.[31] examined the effects of high-dose vitamin D supplementation, finding that AMH levels in women receiving vitamin D3 gradually increased over the course of a week. The results confirmed a positive relationship between vitamin D and AMH in healthy young women.[27,31]

Selenium and vitamin E

Selenium and vitamin E are cofactors of antioxidant enzymes, including glutathione peroxidase, and play an important role in removing ROS from the ovaries.[12] Glutathione peroxidase is one of the most important antioxidants preventing ROS production in the ovaries.[12] It has been demonstrated that selenium accumulates in granulosa cells of healthy and large follicles, but is not present in small and atretic follicles.[12] In a study by Delkhorramy et al.[32], plasma selenium levels were found to be lower in patients with idiopathic POI compared to healthy, fertile women.[32] Vitamin E is another vital component of the cellular antioxidant system. Its deficiency accelerates the peroxidation of membrane lipids, leading to faster cell destruction. The antioxidant effects of selenium and vitamin E enhances each other.[12] Vitamin E functions as a cofactor for glutathione peroxidase, and the enzyme's activity is dependent on adequate selenium levels. Therefore, a deficiency in either vitamin E or selenium leads to dysfunction of this enzyme.[12] In a study involving 70 participants, 35 women in the treatment group received 200 mcg of selenium and 400 IU of vitamin E, while 35 women in the control group received a placebo. AMH and AFC levels were measured in both groups after 12 months. Before the intervention, AMH levels did not differ significantly between the groups.. After the intervention, there was a significant increase in AMH levels and the number of antral follicles in the selenium + vitamin E supplementation group compared to the placebo group.[12]

Dehydroepiandrosterone (DHEA)

Studies suggest that women with POI have lower androgen levels compared to healthy women.[33] Conversely, women with higher levels of androgens in the blood tend to have a higher small AFC, suggesting that androgens contribute to their development.[33,34] Research indicates that DHEA supplementation increases AMH in women with DOR. Beneficial effects of supplementation are also observed in terms of AFC, E2, inhibin B, and FSH levels.[33,35] In a rat model of DOR, DHEA administration partially reduced the atresia rate of follicles.[36] Following supplementation, the treated animals showed a markedly increased number of primary and growing follicles compared to the untreated group. Despite androgen supplementation, the follicle count remained lower than in control rats without DOR.[36] Another study demonstrated that four months of DHEA therapy significantly improved OR parameters, such as AMH and FSH levels on day 2 of the cycle.[37] However, no significant improvement in AFC was observed. DHEA therapy in this study improved the hormonal profile of all patients with poor OR, but improvement in fertilization was only observed in patients under 38 years of age.[37] It is suggested that DHEA supplementation may impact OR by stimulating the maturation of primary follicles to pre-antral ones, increasing the expression of androgen and FSH receptors in the ovaries.[33] Supplementation may also improve the number of in vitro embryos in some patients.[33] It is important to note that DHEA supplementation is particularly effective in women with low endogenous DHEA levels. Supplementation of DHEA is probably ineffective if endogenous DHEA levels are normal.[33]

Despite the substantial body of literature on DHEA use in patients with DOR, much of the evidence is still insufficient to draw definitive conclusions.[34] The ESHRE guidelines do not recommend any treatment for premature ovarian insufficiency, aside from oocyte donation, and emphasize the limited scientific evidence supporting the effectiveness of androgen supplementation[13,33] Nonetheless, infertility centers have already started androgen treatment for patients with reduced OR in an attempt to improve reproductive outcomes.[34]

Contraception

The scientific literature suggests that contraception may affect AMH levels, although the data remain conflicting. Studies suggest that women using oral contraceptives

(OC) tend to have a lower average AMH level compared to those not using them.[3,4,9] For instance, in a cohort study involving 863 women (228 women using OC and 504 women not using OC, serum AMH levels were 29.8% lower in those using OC compared to those not using them.[38] Nevertheless, the total follicle count, including primary follicles, remained unaffected.[38] AMH levels can still be measured while using hormonal contraception to asses OR, but the findings from this study should be taken into consideration when analyzing results. Measuring AMH during the use of OC may not serve as a fully reliable marker of OR.[3]

Iatrogenic factors – radiotherapy, chemotherapy, surgical treatment

Exposure to radiotherapy, chemotherapy, or surgical treatment can lead to a reduction in OR. Cancer treatment, often with gonadotoxic effects, are a known cause of POI.[2,3,12] The majority of studies have demonstrated that AMH levels are not detectable in women who have undergone cancer treatment and received pelvic radiotherapy or chemotherapy with alkylating agents.[2] AMH is considered an invaluable marker of OR in women at risk of ovarian damage from these treatments, enabling preventive measures like cryopreservation.[3] AMH concentration measurements, both before and after chemotherapy, can also help assess the toxic effects of specific chemotherapeutic agents on the ovaries.[3] Cyclophosphamide, a commonly used chemotherapy drug, is particularly well-studied for its negative impact on reproductive health, influencing both the risk of POI and the age of menopause onset.[15,41] Another clinical-control study confirms the hypothesis that exposure to alkylating agents and pelvic radiation is linked to a decrease in OR, as indicated by higher FSH levels and lower AMH and AFC levels compared to the control group.[15,40]

Physical activity

While a sedentary lifestyle generally negatively impacts reproductive function, excessive physical activity can also have adverse effects on reproductive health. Studies have shown that women who engage in intense training regularly tend to have lower AMH levels compared to those leading a sedentary lifestyle. The negative impact on AMH levels is more pronounced with longer durations of intense sports activity and more frequent weekly training sessions. In contrast, moderate physical activity, such as brisk walking or cycling, is considered optimal for maintaining reproductive health and supporting healthy AMH levels.[26]

Smoking

Smoking is widely recognized as one of the most significant risk factors for reduced OR and premature menopause.[3,12,15,21,26] However, not all studies confirm this relationship.[26] For instance, a cross-sectional study by Dölleman et al.[42] suggested that smoking is associated with lower AMH levels, regardless of the dose, though this effect appears to be reversible.[26,42] In a retrospective study, Barrier et al.[43] found that AMH levels were significantly lower in smokers compared to non-smokers, with the impact being more pronounced in those who smoked daily. The degree of AMH reduction was also found to depend on the total smoking dose, measured in pack-years. Further research is needed to clarify the precise relationship between smoking and OR indicators.[3,26]

Conclusion

Anti-Müllerian hormone is a crucial marker of OR, widely used in infertility clinics to assess eligibility for ART. For many women struggling with conception, an abnormal AMH result can lead to significant stress and anxiety. Unfortunately, the causes of reduced OR and abnormal AMH levels relative to age remain unclear in many cases. Primary prevention strategies emphasize lifestyle modifications, such as following a diet rich in antioxidants, avoiding smoking, and minimizing exposure to toxins. Additionally, genetic predisposition screening is recommended. Studies suggest that appropriate supplementation may be effective in many cases. It is essential to raise awareness among women regarding the factors influencing OR, as early diagnosis can facilitate timely interventions, including preservation of fertility. It is important to note that AMH serum levels should not be considered in isolation, and reliance on a single measurement is not recommended. Given the significance of AMH, the various factors influencing its levels, and the impact of AMH decline on both reproductive and non-reproductive health, further research is essential.

Declarations

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Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

Data availability

No datasets were generated or analyzed during the current study.

Ethics approval
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