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Correlation of serum anti-mullerian hormone and age-related health problems with ovarian function

Jacky Zhuoxi Li [1, 2], Sea-Yuen Ho [1], Preston Corliss Loo [1], Chang King Cheung [1], Mary, Ngan Bing Cheung [1, *] and Wings Tjing Yung Loo [1]

[1] *Essence Medical Laboratory and P&P Dental and Medical Ltd, Hong Kong.*
[2] *Design Group International Pte Ltd, Singapore.*

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Abstract

The objectives of this paper were to analyse the correlation between serum Anti-Mullerian Hormone (AMH) and age-related health issues affecting ovarian function and explore the current opportunities for this novel technique. This article mainly focuses on reviewing the biological processes involved in the female reproductive system and the clinical basis of the development of technologies for female fertility. The Serum AntiMullerian Hormone (AMH) test is a valuable tool for the assessment of ovarian function. The AMH level of each individual sample is catalysed using a Roche Elecsys AMH analyzer and a chemiluminescence immunoassay (ECLA), which measures the light emission of the serum complex at 450 nm. The results demonstrated a strong association between serum AMH levels and age, establishing its reliability in the prediction of the ovarian reserve as well as reproductive lifespan. However, age is not the sole determinant for fertility. Genetic factors, oocyte quality, uterine thickness and other environmental factors showed a potential linkage with ovarian syndromes, which indicates poor ovarian function. Market expansion, raising awareness of reproductive health, policy support, and technological advancements provide multiple channels for the promotion of AMH test technology. These findings can be used for business planning or studying age-related changes on the AMH test.

Keywords: AMH; Ovarian function; Reproductive health assessment; Market analysis

1. Introduction

1.1. AMH formation

Anti-Mullerian Hormone (AMH), also known as Müllerian-inhibiting Substance (MIS), is a dimeric glycoprotein of the transforming growth factor beta (TGF-β) superfamily [1]. It is produced by granulosa cells (GCs) in the follicles of the ovaries from pre-antral to antral follicles [1]. After gradually reaching its size and state, AMH is secreted into the circulatory system by the ovaries in women [1]. AMH is coded by the AMH gene that resides on the short arm of chromosome 19 (sub-bands p13.2 to p13.3), with a molecular weight of approximately 140 kDa [2]. The bioactive segment of the AMH gene is located on the 3' end of the fifth exon which is rich in G-C. From testicular differentiation to puberty, the AMH gene is more highly expressed in the Sertoli cells in contrast to granulosa cells, which exhibit a lower expression from birth to menopause [3].

1.2. TGFβ/SMAD signalling pathway

Heterometric serine/threonine kinase transmembrane receptors are the two receptors that control the AMH signalling pathway, which include two types: type I and type II. Isolated AMHs (TGF-β superfamily ligands) bind to AMHRII receptors which induces the dimerization of type II molecules, which in turn recruits and phosphorylates AMHRI in

* Corresponding author: Mary, Ngan Bing Cheung

reverse [3]. Signals are transmitted through phosphorylation of regulated SMAD proteins by type I receptor kinases, and SMAD1 acts as the activated protein for signalling transmission in this pathway. Other ligands in the TGF-β superfamily such as bone morphogenetic proteins (BMPs) and certain growth and differentiation factors (GDFs) are also involved in this pathway [3].

1.3. Physiology role in the ovaries

AMH plays a key role in the early stages of follicular development by inhibiting primordial follicle recruitment and follicular atresia. The primordial follicles in the cortex of the ovary cannot be produced after birth and their physiological activity decreases with age. In other words, they are solely influenced by the genetic factors at birth [4]. However, the expression of AMH can be influenced by other sex hormones, such as Luteinizing hormone (LH), follicle-stimulating hormone (FSH) and oestradiol (E2), which act synergistically. AMH expression could be upregulated by BMPs and LH, and downregulated by FSH and E2 [4]. AMH levels quantitatively reflect the state of the follicles in the ovaries and the degree of follicular development, and luteinization regulates the expression of AMH [5].

1.4. Measurement

The most common tests for ovarian function include the transvaginal ultrasonography, FSH test, and AMH test. The AMH test measures the levels of AMH in serum collected from a blood sample, which serves as a reliable indicator of their egg count. A blood sample can be collected by inserting a small needle into a vein. Women have eggs in their ovaries that contain small sac-like structures known as follicles. Each follicle contains a single immature egg and secretes a certain amount of AMH, which contributes to the diagnosis of an ovarian mass and ovarian reserve. AMH levels correlate with egg count but do not predict egg quality, but age does. Even if serum AMH levels are low, high-quality eggs can still provide a chance of pregnancy, even with a decreased egg count [6]. Conversely, the chance of conceiving may be affected in elderly women with poor quality eggs regardless of their egg count. Thus, AMH levels can be used to assess the number of follicles in the ovaries and pre-evaluate ovarian reserve prior to infertility treatment, but this does not reflect oocyte health or chances of conception [6]. As a quantitative biomarker of ovarian reserve, AMH levels can help fertility specialists predict the number of eggs that are likely to develop during fertility treatment cycles, as well as determine whether the female is a suitable candidate for these treatments and the likelihood of treatment success [7]. AMH level measurement relies on advanced diagnostic technologies, including electrochemiluminescence and immunoassay methods. The Roche Elecsys AMH assay is a technique that quantifies AMH using automated immunoassay. The methodology mentioned was followed by a study by La Marca *et al* [8]. The separated serum collected from the blood samples of patients are loaded into the Roche Elecsys AMH analyzer, which automatically diluted the sample, and magnetic microparticles coated with antibodies specific for AMH are added. A reaction mixture forms by incubating the sample with a biotinylated detection antibody and a ruthenium-labelled streptavidin, which is then aspirated into the measuring cell of the analyzer. The resulting light emission is measured by a photomultiplier for quantifying the concentration of the AMH in the samples based on a direct proportion between the two. The analytical results are reported as AMH value in nanogram per millilitre (ng/ml) [8]. Other methods used for assessing ovarian function such as ultrasound and hormone tests, provide potential patients with more options. In 2010, Roche introduced the Roche AMH Plus assay [9], which was an improved version of the original Roche AMH assay. This updated its methodology from a two-site enzyme-linked immunosorbent assay (ELISA) to an automated electro chemiluminescence immunoassay (ECLA). The limitation of AMH testing could be the lack of standardization for accurately interpreting the AMH levels in clinical settings and its limited values in predicting ongoing pregnancy [10].

1.5. Fertility Disorders

Age is an independent predictor of ovarian reserve. Women in the late stage of childbearing tend to have a lower chance of spontaneous pregnancy and poorer pregnancy outcomes. Insufficient ovarian reserve capacity can lead to premature aging, prolonged menstrual cycles, aggravated cardiovascular problems, and even lead to symptoms such as menopause and infertility [11]. In this case, AMH levels are used as a predictive marker of ovarian function, indicating the number of antral follicles inside the ovaries. This helps with determining the reproductive capacity of women and the onset of menopause. Meanwhile, screening for AMH can also help assess a patient's response to ovarian stimulation, but it would not determine whether or not to proceed with a patient’s treatment. Premature ovarian insufficiency (POI) is a typical ovarian reserve deficiency disorder mainly caused by insufficient estrogen and the ovary's inability to release a sufficient number of eggs in a timely manner. POI shares similar symptoms with menopause, which leads to infertility [11]. Women with POI who are under the age of 40 often exhibit relatively high levels of circulating gonadotropins, an example would be serum FSH > 40 IU/L, resulting in the dysfunction such as irregular ovulation or primary amenorrhea. The serum AMH level can be used in Assisted Reproductive Technology (ART) for predicting POI, when it falls below 1.1 ng/ml [11]. However, there is no standardized cut off value or clear diagnostic time point for low AMH level detection, and the high cost excludes it from primary care. These factors lead to a failure in the use of AMH test in the

routine testing for POI diagnosis. Furthermore, AMH has not been substantiated by sufficient supporting data as a better predictor of spontaneous POI compared to antral follicle count (AFC), and therefore should only be used in cases of diagnostic uncertainty [11]. Less than 3% of women worldwide experience fertility disorders, which can be caused by Turner's syndrome, fragile X syndrome, and a mutation that inactivates the FSHR [12], etc. Moreover, POI may be a deleterious side effect of radiotherapy or chemotherapy on the ovaries.

2. Materials and methods

The research data and methods used for this paper overview came from an online database of PubMed and Oxford University Press (OUP) with minimal changes from personal interpretation.

3. Results and discussions

3.1. Genetics effect on ovarian aging

Menopause before 40 indicates the failure of ovarian function (POF). There has been extensive research exploring the relationship between AMH and ovarian aging in recent years [13]. Ovarian aging refers to the physiological process by which a woman's natural fertility declines and culminates in menopause when they age [13]. The onset of menopause is determined by both genetic factors and non-genetic factors, which have complicated interactions with each other, contributing to a 50% of the total difference. A research study published in Nature reveals the genetic mechanisms for controlling ovarian aging, identifying 290 genes related to human reproductive age, many of which are involved in the DNA repair [13]. Two cell cycle checkpoint pathway genes, checkpoint kinase 1 and 2 (CHEK1 and CHEK2), contribute to various DNA repairs in the ovaries. The CHEK1 gene regulates DNA repair of the egg cells, while CHEK2 gene directly eliminates the damaged egg cells that are intended for repair [13]. Overexpression of CHEK1 or the knockout of CHEK2 in mice has been shown to be able to extend reproductive life expectancy by up to 25%, equivalent to a 10 year extension in humans. Higher CHEK1 gene activity and lower CHEK2 gene activity in women could give rise to a greater number of eggs, prolonged egg lifespan, and a later onset of menopause, extending their reproductive life [13]. Conversely, women with naturally decreased CHEK2 experience a delay in menopause by an average of 3.5 years compared to those with normal CHEK2 activity. In addition, women who enter menopause earlier are at an increased risk of developing a number of conditions such as type 2 diabetes, poor bone health, and fractures. However, by eliminating the CHEK2 gene, which acts as a tumor suppressor gene (TSG), may increase the risk of hormone sensitive cancers such as breast and ovarian cancer [13]. The results have shown the importance of genetics in controlling the natural age of menopause, greatly aiding women in pre-planning their family life. Last but not least, it is preferable to overexpress CHEK1 gene instead of eliminating the CHEK2 gene for prolonging reproductive life due to its potential to regulate the risk of cancer [13].

3.2. Correlation with age

The result of serum AMH levels in healthy pre-menopausal females of different ages can be found in Kelsey results [14]. From the result of modelized data, females at the age of 24.5 years showed the highest AMH level across all age groups. It is also worth considering that the variation in serum AMH levels in any age group collected is the result of a total of 3260 data points presented in the model, yielding a coefficient of determination of 0.34, indicating that 34% of this in serum AMH concentrations was attributable to age alone[14]. AMH typically exhibits a negative correlation with age due to the decrease in the number of primordial follicles in the ovaries. However, the change of AMH level varies among different age groups is conditional [14]. A study conducted by Lie Fong on assessing serum AMH level in healthy females from infancy to the reproductive periods, statistically summarized that, AMH levels trended upwards and reached a stable plateau at approximately 25 years of age [15]. This combined with the result of the AMH model, showed that before reaching peak AMH levels, the serum AMH levels showed an overall increase with age growth whereas from approximately 25 years old and onward, an evident decline was observed and AMH levels eventually decrease to an undetectable level, which is the indication of menopause [15]. Therefore, AMH levels showed a positive correlation with age before peaking, followed by a negative correlation afterwards. This trend could be caused by the increased rate of primordial follicle recruitment before conception and a progressive decrease in the number of remaining unactuated follicles in later phases. The main individual differences are in the rate of depletion and the original size of the follicle pool [15].

3.3. Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder affecting approximately 10% of adolescents and women of childbearing age worldwide [16]. Irregular periods, excess androgen, or polycystic ovaries are the most common

symptoms of this abnormal condition. For women with PCOS, numerous small fluid-filled sacs (ovarian cysts) grow outside on the edge of the ovaries, containing immature eggs and leading to abnormal ovulation [16]. Women with PCOS are at a higher risk for type 2 diabetes, cardiovascular disease, and other long term health implications. Meanwhile, it has been reported that women with PCOS may have AMH levels two to four times higher than healthy women due to the increased number of follicles that are produced, leading to higher AMH levels being secreted and resulting in hormonal imbalance [16]. For women with PCOS, it is not meaningful to evaluate their ovarian reserves based on their AMH levels as their AMH levels are significantly higher than that of normal controls and does not correlate with age [17]. Despite the low chance of pregnancy with polycystic ovaries, early treatment is still recommended. The primary cause of polycystic anovulation is the increase in the number of preantral follicles, the weakening of follicular selection, and the formation of non-dominant follicles, suggesting that there is a growth disorder of the early follicles in the ovaries [17]. Secondly, AMH is mainly expressed in the granulosa cells of primary ovarian follicles, secondary follicles, and small antral follicles, with its expression decreasing in large antral follicles and absent in atretic follicles and FSH-dependent follicles. In this way, AMH levels are greatly increased in PCOS patients [17].

3.4. Challenges in assays

Moolhuijsen & Visser compared various serum AMH assays [18]. Among these assays used to determine serum AMH levels, the picoAMH test had the highest limit of detection (LoD) at 0.0013 ng/ml. The LoD of different manual assays ranked from low to high are as follows: pico AMH test (Ansh Labs), ultrasensitive AMH ELISA (Ansh Labs), Gen II test (Beckman Coulter). Two automated assays from Roche utilize the same antibody pairs as Gen II assay, suggesting no obvious boundary between different assay types. In addition, when comparing efficiency of manual assays and the automated assays, automated assays offer advantages over manual assays, including higher precision, better reproducibility, faster measurement speed, and lower labour requirements [18]. However, direct comparison of AMH results obtained from these essays are not reliable due to multiple factors. Variations in assay results could be caused by factors such as the differences in assay sensitivity determined by LoD, differences in antibody pairs used to detect AMH isoforms, sample instability, or a matrix effect that affects interlaboratory reproducibility [18]. Further research is needed to allow proper comparison of different assays using larger, clearly defined cohorts stratified by age.

3.5. Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis

From the results collected, AMH, produced by the small follicles in the ovaries, was found to be a more reliable marker of ovarian function over other hormones such as FSH. FSH is produced by the pituitary gland and could act as an indirect marker for assessing ovarian function, with levels that fluctuate during or between menstrual cycles and peaking before ovulation [19]. In contrast, AMH is produced by the granulosa cells in the ovaries, meaning it directly reflects the ovarian reserve and minimizes the influence of other hormones. This inference is well-founded, as the standardized AMH levels (ng/ml) remain relatively stable throughout the whole menstrual cycle in young healthy women [19]. Low AMH levels may indicate a shortening of the reproductive window, while high AMH levels suggest a potential risk of developing PCOS. Researchers have also observed that AMH levels decline several years before FSH level rise, therefore the AMH can be a much earlier and more sensitive indicator of ovarian aging in the specific age groups compared to FSH [20]. In addition, AMH levels may indicate the potential response to ovarian stimulation during assisted reproductive technologies (ART) such as in vitro fertilization (IVF) [8], with lower serum AMH levels associated to poor ovarian response to IVF treatment [21]. For example, when predicting ovarian hyperstimulation syndrome (OHSS), high AMH levels may indicate an over-response to IVF drugs. Therefore, the AMH test has been used clinically to help predict ovarian mass and response to gonadotropins in recent studies.

3.6. Effects in the global market

The target group for the AMH test is widely used and can be utilized by all women with reproductive health concerns. This includes women considering IVF or other fertility drug treatment, planning a current or future pregnancy, considering delaying childbirth, wanting to predict the onset of menopause, assessing the risk of premature decline in fertility, and women considering fertility preservation (or egg freezing) [22]. In Hong Kong, research of blood samples can be carried out at local fertility clinics and healthcare centres such as the Essence Medical Laboratory. The global market size for AMH testing was approximately two hundred and twenty million US dollars in 2021 and is expected to reach two hundred and fifty million US dollars in 2022, with a Compound Annual Growth Rate (CAGR) percentage of 11.35%, and is projected to exceed four hundred million US dollars by 2027 [23]. According to a market report from Polaris Market Research (2021), North America and Europe hold the highest market shares in the fertility test market. This could be due to high demand for fertility testing and treatment in these regions as well as the availability of state-of-the-art diagnostic tools and well-established treatment systems [23]. Meanwhile, the Asia-Pacific region had the fastest growth rate in AMH testing, including China and India, which could help to drive technological innovation and the awareness of fertility testing in the following years. The rapid development of the market in these regions could

have been due to the large population of women of reproductive age, increased awareness of reproductive health, or the rising prevalence of reproductive disorders.

AMH testing has been approved by the National Medical Products Administration (NMPA) in China since 2015, coinciding with the implementation of the two-child policy which has increased the demand for fertility testing and treatment. The promotion of fully automated electrochemiluminescence AMH testing, represented by Roche's Elecsys test kit, has been widely used in clinical settings. Across all patients coming for sex hormone or AMH test in hospitals specifically, the elderly, infertile patients, and couples experiencing difficulty conceiving show the most interest in fertility tests, whereas all women over the age of 35 are recommended by the American College of Obstetricians and Gynecologists (ACOG) to take an AMH test in order to assess their fertility rate. In China, AMH testing and treatment are not widely covered by medical insurance, except for citizens in Beijing. For all regions in need of fertility testing, the AMH test overall has seen an increase in market demand, making it a crucial auxiliary diagnostic tool for women with reproductive concerns. These findings can be used for market investigation or for developing potential customers bases in the fertility testing market.

4. Conclusion

This case study concludes that AMH levels are a reliable marker for ovarian reserve although there is no unified standard to refer to in the clinical research. There is a direct correlation between AMH levels and increasing age, peaking at a certain age before declining. Factors such as genetics, the development of PCOS, and the specific assays used for testing can also affect the detection of AMH levels. AMH levels can also be used in assisted reproductive technology to support the prediction and treatment of fertility-related disorders. The market for AMH testing is currently dominated by Europe and the US, with significant potential for development in the Asia-Pacific region. This is due to factors such as delayed fertility age, increased awareness of women's reproductive health and supportive population policies. There are both opportunities and challenges in the marketing of AMH testing.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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