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Review Article

Anti-Müllerian Hormone Gene Polymorphisms: Global Perspectives and Arab Population Insights

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Abstract

Introduction: *Anti-Müllerian Hormone* (*AMH*) gene polymorphisms significantly impact ovarian function, follicular development, and fertility outcomes. This review explores the global distribution of *AMH* gene polymorphisms, emphasizing unique genetic patterns in Arab populations due to high genetic diversity and consanguinity.

Methods: The review examines methodologies such as genetic analysis and hormone level measurement, along with their application in understanding *AMH* polymorphisms. It integrates findings from diverse populations to explore genetic, hormonal, and clinical correlations.

Results: Findings indicate a distinct distribution of *AMH* gene polymorphisms in Arab countries. These polymorphisms are associated with variations in hormonal profiles, ovarian reserve, and reproductive outcomes, particularly in assisted reproductive technologies (ART).

Conclusion: *AMH* gene polymorphisms have profound implications for reproductive health and fertility treatments. Tailored research addressing genetic, environmental, and socioeconomic factors is essential to understanding these polymorphisms and their interactions. This review underscores the importance of genetic screening and highlights potential advancements in personalized medicine and fertility care.

Keywords: anti-müllerian hormone, gene polymorphisms, reproduction, fertility, ART

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1. Introduction

Anti-Müllerian hormone (AMH), a glycoprotein produced by granulosa cells in ovarian follicles, plays a central role in the regulation of ovarian folliculogenesis [1, 2]. AMH is part of the transforming growth factor beta family, named for its role in male sex differentiation by causing the regression of Müllerian ducts. It is primarily recognized as a serum marker for ovarian function, reflecting both ovarian reserve and conditions like polycystic ovarian syndrome (PCOS) [3].

AMH functions by inhibiting the excessive recruitment of primordial follicles into the growing pool, ensuring the controlled progression of follicle maturation. AMH is produced by granulosa cells in growing follicles from the primary to small antral stages. Following a selection dependent on follicle-stimulating hormone (FSH), AMH expression decreases, although some remains in cumulus cells of preovulatory follicles. It is lost in atretic follicles and corpora lutea. This expression pattern is consistent across species and in the adult human ovary. AMH levels increase in follicles that are up to 8 mm and drop sharply in larger follicles, aligning with AMH concentrations in follicular fluid, which are highest in follicles up to 8 mm and decline thereafter [3, 4].

This regulation preserves the ovarian reserve and contributes to reproductive longevity [5]. AMH also modulates the sensitivity of follicles to FSH, maintaining a balance in ovarian function [1].

The *AMH* gene is located on the p arm of chromosome 19 and consists of 5 exons while the gene of *AMHR2* is located on chromosome 12 and is comprised of 11 exons [6, 7]. The pathway of AMH in human females begins with its production by granulosa cells in preantral and small antral ovarian follicles and its level strongly correlates with the size of primordial follicle pool and the number of antral follicles [3]. AMH binds to its receptor, *AMH receptor type II (AMHR2)*, which is expressed in the ovaries and the anterior pituitary [8]. This binding inhibits the expression of FSH receptors, thereby regulating follicular development and preventing premature activation of follicles. Polymorphisms of *AMH/AMHR2* could influence the ovarian stimulation outcomes [4, 7].

In parallel, gonadotropin-releasing hormone (GnRH) is released from the hypothalamus, stimulating the anterior pituitary to secrete FSH and luteinizing hormone (LH). AMH provides feedback to the hypothalamic-pituitary-gonadal (HPG) axis by modulating GnRH pulse frequency and amplitude, which influences the secretion of FSH and LH. Tanycytes in the hypothalamus facilitate communication between the cerebrospinal fluid and the neuronal environment, playing a role in the regulation of GnRH signaling [9]. This AMH-*AMHR2* signaling pathway plays a pivotal role in ovarian function by controlling the recruitment of primordial follicles and modulating their sensitivity to FSH [10, 11]. Figure **1** illustrates this critical pathway, emphasizing key points where genetic polymorphisms may disrupt its function and lead to reproductive health challenges. Genetic variations, particularly single nucleotide polymorphisms (SNPs) in the *AMH* and *AMHR2* genes, have been shown to impair this signaling cascade. For instance,

the *AMHR2* -482A>G polymorphism is associated with altered ovarian function, diminished ovarian reserve, and suboptimal outcomes in assisted reproductive technologies (ART) [8, 11].

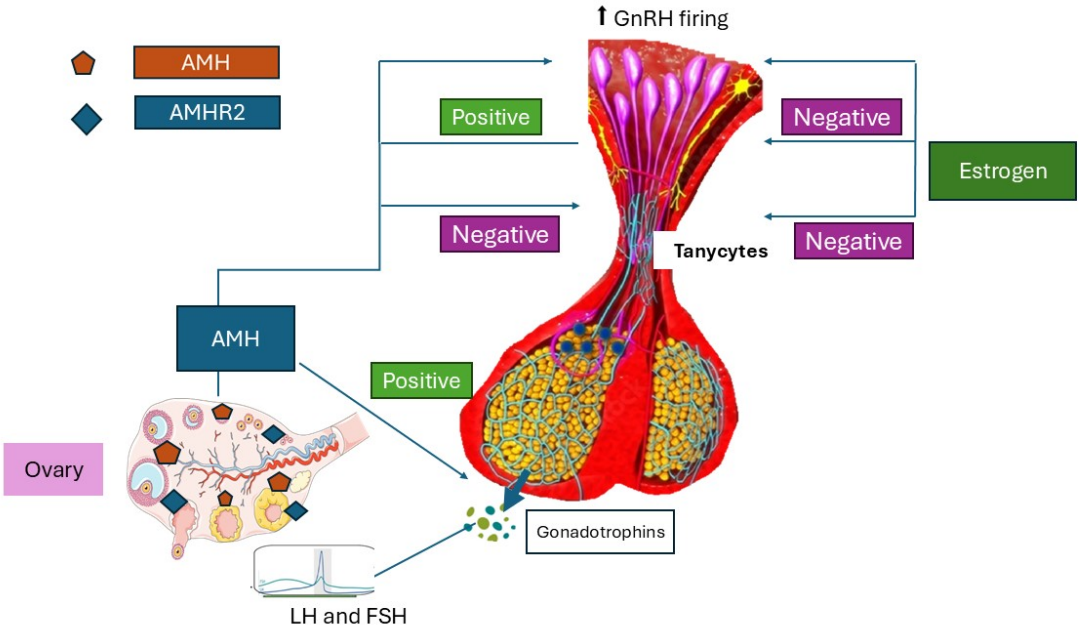

Figure 1: The AMH-*AMHR2* pathway: Regulation of ovarian function and hypothalamic-pituitary-gonadal axis. Anti-Müllerian Hormone (AMH) is the key ligand that binds to its receptor, *AMHR2*, to regulate ovarian follicle recruitment and sensitivity to follicle-stimulating hormone (FSH). Secreted by granulosa cells of growing ovarian follicles, AMH modulates the hypothalamic-pituitary-gonadal axis by influencing GnRH firing in the hypothalamus, which in turn regulates the secretion of gonadotropins, luteinizing hormone (LH), and FSH from the anterior pituitary.

AMH's role as a biomarker for ovarian reserve and its influence on ART outcomes underscores the need for in-depth exploration of its genetic underpinnings.

The global variation of *AMH* polymorphisms provides important insights into fertility genetics, which have significant clinical applications. By recognizing specific polymorphisms in various populations, healthcare professionals can customize fertility evaluations and treatments according to individual genetic profiles [12].

In Arab countries, unique genetic profiles driven by high consanguinity and genetic diversity create a distinct landscape for *AMH* polymorphism studies. The prevalence of consanguineous marriages and associated genetic disorders highlight the importance of targeted research to characterize these polymorphisms and their clinical implications [13]. Research findings from Arab populations on *AMH* gene polymorphisms can enhance global fertility treatments by enabling personalized medicine tailored to individual genetic profiles, improving screening practices for early detection of fertility issues, and fostering culturally sensitive treatment approaches. This review aims to provide a comprehensive overview of *AMH* gene polymorphisms globally, with a particular focus on their types, distribution,

and clinical effects in Arab populations, alongside insights into relevant genetic and environmental interactions.

2. Methods

To conduct a comprehensive literature review on *AMH* gene polymorphisms with a focus on Arab populations, the author implemented a systematic search strategy across multiple databases and search engines. the search used the formula: ("Anti-Müllerian hormone" OR "AMH" OR "AMHR2" OR "gene polymorphisms" OR "Arab populations") AND ("fertility" OR "ovarian reserve" OR "polycystic ovary syndrome"). The databases searched included PubMed, Google Scholar, Web of Science, and Scopus. Inclusion criteria encompassed peer-reviewed articles published in English that focused on *AMH* gene polymorphisms in Arab populations, particularly studies exploring the relationship between these polymorphisms and fertility or ovarian reserve. Exclusion criteria included articles not published in English, papers lacking empirical data or methodological rigor, and duplicate publications. The initial search retrieved a total of 4488 articles, combining specific and broader queries. After screening titles and abstracts, the full text of potentially relevant studies were reviewed to assess their eligibility based on the defined criteria. Data extraction focused on key findings related to *AMH* gene polymorphisms and their implications for reproductive health within Arab populations.

3. Results

The systematic search identified a total of 4488 articles. After the removal of 2500 duplicates, 1988 articles remained for screening based on titles and abstracts. At this stage, 1800 articles were excluded due to irrelevance or failure to meet the inclusion criteria.

A total of 188 full-text articles were reviewed for eligibility, leading to the inclusion of 28 studies that met every criterion. These selected studies examined diverse reproductive health conditions and their associations with *AMH* gene polymorphisms, emphasizing their impact on ovarian reserve, fertility, and specific conditions such as PCOS (Figure **2**).

3.1. Global Patterns of *AMH* Gene Polymorphisms

3.1.1. Types of Polymorphisms

Key *AMH* polymorphisms include rs10407022, rs2002555, and *AMHR2* variants such as rs11170555 and rs3741664, which influence hormone levels (e.g., AMH, estradiol, FSH) [14]. Variants like c.146T>G, studied in ART outcomes, demonstrate varying impacts on serum AMH levels [15]. Polymorphisms in

the *AMH* gene and *AMHR2* occur at the Ile49Ser (rs10407022) and -482A>G (rs2002555) restriction sites, respectively were reported and linked to women's reproductive status, including infertility [4]. Polymorphisms in women with PCOS, such as *AMHR2* -482A>G, correlate with altered luteinizing hormone levels and metabolic markers, indicating their role in follicular development and ovarian response [16]. A summary of key studies on *AMH* gene polymorphisms and their implications for reproductive health is presented in Table **1**.

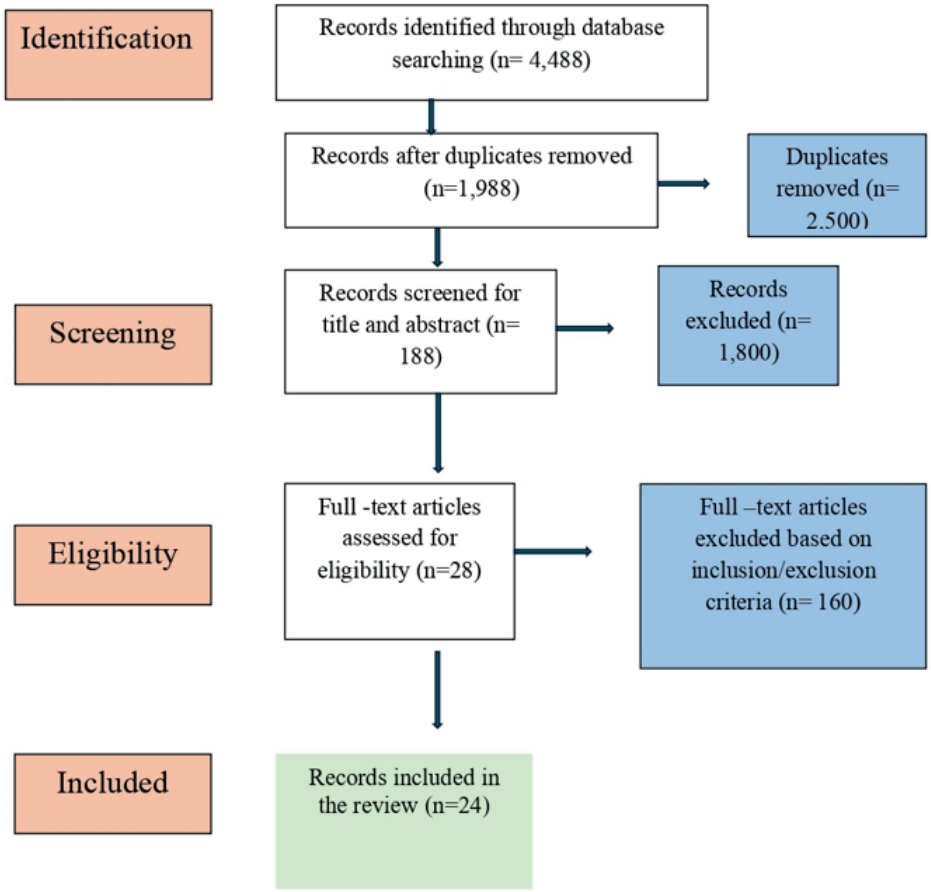

Figure 2: Search algorithm of studies included in the review.

Table 1: Key published studies on *AMH* gene polymorphisms and reproductive health.

Author(s)	Year	Study title	Key findings	Methodology/focus
Colaco et al. [30]	2022	Association of *AMH* and *AMHR2* gene polymorphisms with ovarian response and pregnancy outcomes in Indian women	SNPs in *AMH* genes were linked to ovarian stimulation outcomes and variability in ART success rates	Genotyping and ovarian stimulation data
Cheng et al. [31]	2019	Association of gene polymorphisms in the anti-müllerian hormone signaling pathway with ovarian function: a systematic review and meta-analysis	*AMH* polymorphisms were shown to influence ovarian reserve and ART outcomes	SNP analysis and ovarian reserve study

Table 1: Continued.

Author(s)	Year	Study title	Key findings	Methodology/focus
Peluso et al. [32]	2014	AMH: An ovarian reserve biomarker in assisted reproduction	Reviewed studies linking *AMH* gene polymorphisms to hormone levels, ovarian function, and ART outcomes	Systematic review of *AMH* polymorphisms
Zheng et al. [19]	2016	*Anti-Müllerian hormone* gene polymorphism is associated with androgen levels in Chinese polycystic ovary syndrome patients with insulin resistance	*AMHR2* polymorphisms were associated with PCOS, altered hormone levels, and ovarian reserve	Genetic correlation with PCOS and hormones
Kevenaar et al. [33]	2007	Anti-Müllerian hormone and anti-Müllerian hormone type II receptor polymorphisms are associated with follicular phase estradiol levels in normo-ovulatory women	Identified *AMHR2* polymorphisms influencing ovarian function in normo-ovulatory women	Genetic study in normo-ovulatory women
Leonte et al. [34]	2007	Anti-Mullerian hormone (AMH) as a useful marker in diagnosis of polycystic ovary syndrome	Found AMH levels were nearly three times higher in women with polycystic ovary syndrome (PCOS) compared to controls	Genetic and hormonal study on PCOS
Chen et al. [18]	2020	Can polymorphisms of AMH/AMHR2 affect ovarian stimulation outcomes? A systematic review and meta-analysis	Correlated genetic variations with ART success, emphasizing polymorphisms' predictive value	Meta-analysis of ovarian stimulation data
Khan et al. [35]	2019	Genetic basis of polycystic ovary syndrome (PCOS): Current perspectives	Explored *AMH* polymorphisms' role in PCOS pathophysiology and ovarian response	Genetic and hormonal study on PCOS
Anttonen et al. [36]	2011	Anti-Müllerian hormone inhibits growth of AMH type II receptor-positive human ovarian granulosa cell tumor cells by activating apoptosis	Suggested therapeutic potential of targeting AMH pathways in ovarian cancer treatment	Gene expression analysis in ovarian cancer

3.1.2. Distribution and Frequency

AMH polymorphisms, particularly rs10407022 and rs2002555, exhibit varying prevalence and hormonal associations across different populations, with some studies indicating minimal hormonal effects in certain groups [17, 18]. In contrast, the *AMHR2* polymorphism rs11170555 has been positively correlated with ovarian hormone levels, suggesting its role in ovarian function [19]. Furthermore, in insulin-resistant cases of PCOS, significant differences in *AMH* genotypes highlight the intricate relationship between metabolic and reproductive health, as specific *AMH* genotypes are linked to variations in serum levels of luteinizing hormone, testosterone, and insulin resistance [19]. This underscores the importance of genetic factors in understanding and managing conditions like PCOS.

3.2. Clinical Implications of AMH Polymorphisms

3.2.1. Reproductive Health Outcomes

Variants such as *AMHR2* 482 A>G play a significant role in influencing reproductive health [18, 20]. These polymorphisms disrupt the AMH-*AMHR2* signaling pathway, which is critical for follicular development and ovarian function. As a result, women carrying these variants often exhibit poor ovarian reserve, leading to diminished responses during controlled ovarian stimulation [18]. This is particularly evident in unexplained infertility cases where the genetic variations interfere with follicular recruitment and maturation. In addition, certain single nucleotide polymorphisms (SNPs) within the *AMH* and *AMHR2* genes have been associated with earlier onset of menopause, especially when compounded by lifestyle factors and genetic predispositions such as high parity [8, 17]. These findings underscore the multifactorial nature of reproductive outcomes where genetic and hormonal pathways converge.

3.2.2. Applications in ART

AMH polymorphisms significantly enhance the precision of ART. Genetic variants such as *AMHR2* -482 A>G are crucial in determining ovarian responsiveness to gonadotropin stimulation [20]. Women with these polymorphisms often require higher gonadotropin doses due to reduced follicular sensitivity, which impacts the total number of mature oocytes retrieved during stimulation cycles. Furthermore, these polymorphisms are instrumental in guiding patient-specific ART protocols. For instance, *AMHR2* variants are linked to suboptimal follicular development, necessitating adjustments in medication regimens to optimize outcomes [21]. Clinicians can use *AMH* genotyping as a biomarker to predict ovarian stimulation success and avoid unnecessary treatment cycles, thereby improving overall ART success rates.

3.3. AMH Polymorphisms in Arab Populations

Arab populations exhibit significant genetic diversity and a high prevalence of consanguinity, leading to unique profiles of *AMH* polymorphisms. These genetic variations have critical implications for reproductive health and fertility outcomes. For instance, a study conducted among Bahraini women indicated that genotyping *AMH* polymorphisms could enhance the success of fertility treatments [22]. However, comprehensive research is essential to mapping these genetic variants across the Arab region.

The cultural practice of consanguineous marriages in Arab countries increases the frequency of rare and region-specific *AMH*-related genetic variants. In Egypt, research by Motawi et al. explored *ESR2* and the *FSHR* gene polymorphisms and their role in ovarian response to controlled ovarian hyperstimulation,

highlighting significant correlations between specific genetic variants and low *AMH* level combined with suboptimal ovarian response in women undergoing IVF treatment [23]. Another Egyptian study investigated the relationship between AMH receptor polymorphisms and PCOS, concluding that certain *AMHR2* gene variants (rs17854573) were more prevalent among Egyptian women with PCOS, further emphasizing the genetic influence on reproductive disorders [24]. Expanding such studies across other Arab populations will be instrumental in identifying unique patterns of genetic variation and advancing fertility care tailored to population-specific needs.

3.4. Factors Shaping *AMH* Gene Polymorphisms

3.4.1. Environmental and Lifestyle Influences

Diet, exposure to endocrine disruptors, and lifestyle factors like smoking modulate AMH expression and ovarian health. These factors amplify the variability in AMH-related outcomes, particularly in environmentally stressed regions [25, 26]

Cultural practices such as consanguinity shape the prevalence of *AMH* polymorphisms. Limited healthcare access and fertility treatment awareness further influence reproductive outcomes, necessitating community-specific interventions [25, 27].

3.4.2. Genetic and Epigenetic Modifications

Epigenetic mechanisms, including DNA methylation, play a pivotal role in regulating *AMH* gene activity. These processes interact with genetic polymorphisms, modulating ovarian reserve and affecting overall reproductive outcomes [17, 21]. DNA methylation, specifically in the promoter regions of the *AMH* gene, can influence gene expression, altering the bioavailability and functionality of AMH.

Moreover, single nucleotide polymorphisms (SNPs) within the *AMH* and *AMHR2* genes may amplify or suppress the effects of epigenetic modifications, creating a complex network of genetic and environmental interactions [14]. For instance, polymorphisms such as *AMHR2* -482A>G have been shown to impact AMH signaling pathways, which are further modulated by epigenetic changes [28]. These interactions underscore the importance of studying both genetic and epigenetic factors in fertility research.

Incorporating epigenetic studies into genetic analyses provides a more comprehensive understanding of *AMH* polymorphisms, highlighting their multifaceted influence on ovarian function and reproductive health. This integrated approach is critical for advancing personalized medicine, particularly in the context of fertility treatments and ART [29].

3.5. Methodological Approaches

Research on *AMH* polymorphisms employs a variety of methodological approaches to explore their implications in reproductive health. Key techniques include polymerase chain reaction (PCR) for amplifying specific regions of the *AMH* gene, enabling the identification of single-nucleotide polymorphisms (SNPs) that may influence hormone levels and reproductive outcomes. Advanced SNP genotyping technologies, such as high-throughput sequencing, are utilized to detect genetic variants in the *AMH* and *AMHR2* genes, establishing correlations with clinical traits. Hormone level assays, particularly enzyme-linked immunosorbent assays (ELISA), measure serum AMH concentrations to provide insights into ovarian reserve and follicular development. Additionally, emerging pharmacogenomic tools predict responses to ART, allowing for personalized treatment protocols that enhance ovarian stimulation effectiveness. Systematic reviews and meta-analyses synthesize findings from multiple studies, establishing robust clinical guidelines that clarify the role of *AMH* polymorphisms in reproductive health. Collectively, these approaches advance personalized medicine in reproductive health, aiming to improve management strategies for conditions such as PCOS and enhance the success rates of ART.

4. Conclusion

AMH gene polymorphisms offer critical insights into reproductive health, with specific variants influencing hormone levels, ovarian function, and ART outcomes. Unique patterns observed in Arab populations, driven by genetic diversity and consanguinity, highlight the need for targeted research. Future studies should prioritize large-scale genomic analyses, integrate environmental and lifestyle factors, and develop accessible diagnostic tools. These efforts will enhance personalized fertility care and address regional disparities in reproductive health.

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Ethical Approval

The research is exclusively based on published literature; Ethical Approval is not required.

Conflict of Interest

The author declares that there are no conflicts of interest.

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Author Contribution

Huda Omran is responsible for all aspects of this work, including the conception and design of the study, data collection and analysis, manuscript writing, and final approval of the version to be published.

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During the preparation of this review the author used ChatGPT in data collection. After using this AI tool/service, the author revised and edited the content and takes full responsibility for the publication.

Data Sharing Statement

All data collected or analyzed are included in this published article. Further inquiries can be directed to the corresponding author.

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