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Número especial 1E

Role of Genetic Polymorphisms in Polycystic Ovary Syndrome: Focus on *AMH* (rs10407022) and *AMHR2* (rs2272002)

Rol de los polimorfismos genéticos en el síndrome de ovario poliquístico: Enfoque en *AMH* (rs10407022) y *AMHR2* (rs2272002)

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Abstract

Polycystic ovary syndrome is a multifactorial endocrine disorder affecting a significant proportion of reproductive-aged women and is associated with various comorbidities. This review examines the influence of polymorphisms rs10407022 in the *AMH* gene and rs2272002 in the *AMHR2* gene on the pathogenesis of PCOS, focusing on their relationship with hormonal regulation and ovarian function. It explores how the rs10407022 polymorphism may affect *AMH* expression and levels in women with PCOS, while rs2272002, located in an intronic region, could influence the functionality of the *AMHR2* receptor. Despite advancements in identifying these variants, the heterogeneity of clinical results and genetic variability across different populations highlight the need to consider additional factors that may modulate the expression of these genes. A deeper understanding of these polymorphisms is essential for improving the diagnosis and treatment of PCOS, as well as addressing associated comorbidities. As research progresses, these polymorphisms are likely to facilitate the development of more personalized diagnostic and therapeutic approaches, thereby optimizing the management of PCOS and improving the quality of life for patients.

Keywords: Anti-Müllerian hormone, ovarian function, PCOS, hormonal regulation.

Resumen

El síndrome de ovario poliquístico es un trastorno endocrino multifactorial que afecta a una proporción significativa de mujeres en edad reproductiva y se asocia con diversas comorbilidades. Esta revisión examina la influencia de los polimorfismos rs10407022 en el gen *AMH* y rs2272002 en el gen *AMHR2* en la patogenia del SOP, centrándose en su relación con la regulación hormonal y la función ovárica. Se explora cómo el polimorfismo rs10407022 podría afectar la expresión de AMH y sus niveles en mujeres con SOP, mientras que el rs2272002, localizado en una región intrónica, podría influir en la funcionalidad del receptor AMHR2. A pesar de los avances en la identificación de estas variantes, la heterogeneidad de los resultados clínicos y la variabilidad genética entre diferentes poblaciones resaltan la necesidad de considerar factores adicionales que pueden modular la expresión de estos genes. Una comprensión más profunda de estos polimorfismos es esencial para mejorar los diagnósticos y tratamientos del SOP, así como para abordar las comorbilidades asociadas. A medida que la investigación avanza, es probable que estos polimorfismos permitan el desarrollo de enfoques diagnósticos y terapéuticos más personalizados, optimizando así el manejo del SOP y mejorando la calidad de vida de las pacientes.

Palabras Clave: Hormona antimülleriana, función ovárica, SOP, regulación hormonal.

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1 Introduction

Polycystic ovary syndrome (PCOS) is the most common multifactorial endocrine disorder in women of reproductive age, affecting up to 20% of this population worldwide [1]. The prevalence of diagnosis varies depending on the criteria used; generally, PCOS is defined by the presence of at least two of the following characteristics: (i) oligo- or anovulation, (ii) clinical and/or biochemical hyperandrogenism, and (iii) ultrasound evidence of polycystic ovarian morphology [2]. Under these conditions, PCOS is associated with a high risk of developing metabolic, cardiovascular, psychological, and even oncological comorbidities, generating significant impacts on patient health, as well as social and economic repercussions [3]. Moreover, it is estimated that around 50% of women with PCOS do not receive an adequate diagnosis, reducing the opportunity to manage the syndrome's associated consequences [4].

Despite decades of research, the etiology of PCOS remains difficult to pinpoint. This lack of clarity has limited the development of effective strategies for early intervention and prevention, hindering the ability to accurately predict the long-term health implications for patients [5]. Approximately 79% of the pathogenesis of PCOS is estimated to be attributable to genetic factors, positioning it as a polygenic disorder, while the remaining 21% corresponds to environmental and lifestyle factors [6]. Furthermore, studies in twins and families highlight the presence of a genetic component in PCOS, with a pattern of inheritance involving multiple genes [7, 8]. Over more than a decade, the function of over 70 candidate genes has been evaluated, with several single nucleotide polymorphisms (SNPs) identified in exonic and intronic regions, establishing associations between clinical and pathological features related to PCOS [9]. However, the results of these studies are inconclusive due to the genetic and phenotypic heterogeneity observed among patients [10]. Additionally, genetic variations may differ significantly between populations, underscoring the importance of conducting research in specific ethnic groups [11].

Genome-wide association studies (GWAS) have identified multiple susceptibility loci; however, the exact functional mechanisms of many of these loci are still not fully understood [12, 13]. In particular, candidate genes related to the regulation of gonadotropin secretion, androgen production and action, follicular development, and insulin signaling control have been evaluated [14]. In this context, the anti-Müllerian hormone (*AMH*) gene and its receptor (*AMHR2*) have been studied for their potential contribution to the hormonal imbalances characteristic of the syndrome [15], as women with PCOS have been observed to exhibit *AMH* levels up to three times higher than those without the syndrome [16]. Moreover, it has been proposed that PCOS involves a dysregulation of *AMH* gene expression, with studies suggesting that elevated AMH levels are not only due to a higher number of follicles but also to increased *AMH* expression per follicle [17], alongside an overexpression of *AMHR2* in granulosa cells, in contrast to normoovulatory women, where *AMH* suppression occurs following follicular maturation [18].

Given the above, the objective of this review is to analyze and synthesize the available evidence on the role of a genetic polymorphism in the *AMH* (rs10407022) and *AMHR2* (rs2272002) genes in the pathogenesis of PCOS. The review will integrate recent research findings to provide a comprehensive view of the contribution of these polymorphisms in the context of PCOS and their potential clinical application.

2 Methodology

A comprehensive literature review was conducted using the Google Scholar, NCBI PubMed, and Scopus databases. Specific search terms were employed, such as 'genetic polymorphisms in *AMH*,' 'polymorphisms in AMHR2,' 'polycystic ovary syndrome and genetics,' 'rs10407022,' 'rs2272002,' and 'hormonal regulation in PCOS'. A total of 45 articles were selected, including both basic and clinical studies. Emphasis was placed on research published in the last five years to ensure the inclusion of recent and relevant work in the field, prioritizing studies related to genetic variability and its impact on hormonal regulation and ovarian function in women with PCOS.

3 Results

3.1 *AMH* and Follicular Development

AMH is a member of the transforming growth factor-beta (TGF-β) family, named after its role in male sexual differentiation, where it promotes the regression of the Müllerian ducts [19]. However, AMH is now widely recognized as a marker of ovarian function, being used to assess both ovarian reserve and its relationship with polycystic ovary syndrome [15]. This hormone plays a fundamental role in regulating follicular development within the ovary. Initially produced as a prohormone, AMH becomes active after the removal of the C-terminal fragment, and its active form specifically binds to the AMH type II receptor (AMHR2), which is the only known receptor for this hormone [20]. This specific binding activates AMH type I receptors (such as ALK2, ALK3, and ALK6) and triggers an intracellular signaling cascade that regulates gene expression in the cell nucleus [21].

Produced by granulosa cells of growing follicles, AMH's primary function is to inhibit the premature activation of primordial follicles, thus preserving the ovarian reserve in the long term [22]. It also controls the multiple recruitment of follicles and modulates their sensitivity to follicle-stimulating hormone (FSH), reducing FSH-dependent aromatase activity (Fig. 1) and preventing early follicular maturation [23].

During follicular development, at intrafollicular level, AMH is secreted in higher concentrations in preantral and small antral follicles (< 5 mm), until they reach a size of 8 mm, at which point its expression begins to decrease [18]. As the dominant follicle is selected, AMH levels decrease, becoming undetectable in follicles larger than 10 mm [21]. This process ensures precise control over follicular progression, preserving ovarian reserve and optimizing the selection of the most suitable follicles to continue maturation. Once the dominant follicle has been selected and exceeds 10 mm in size, luteinizing hormone (LH) levels increase, preparing it for ovulation. The LH surge is also essential to trigger follicular rupture and the release of the mature oocyte [24], thus completing the follicular selection cycle (Fig. 2).

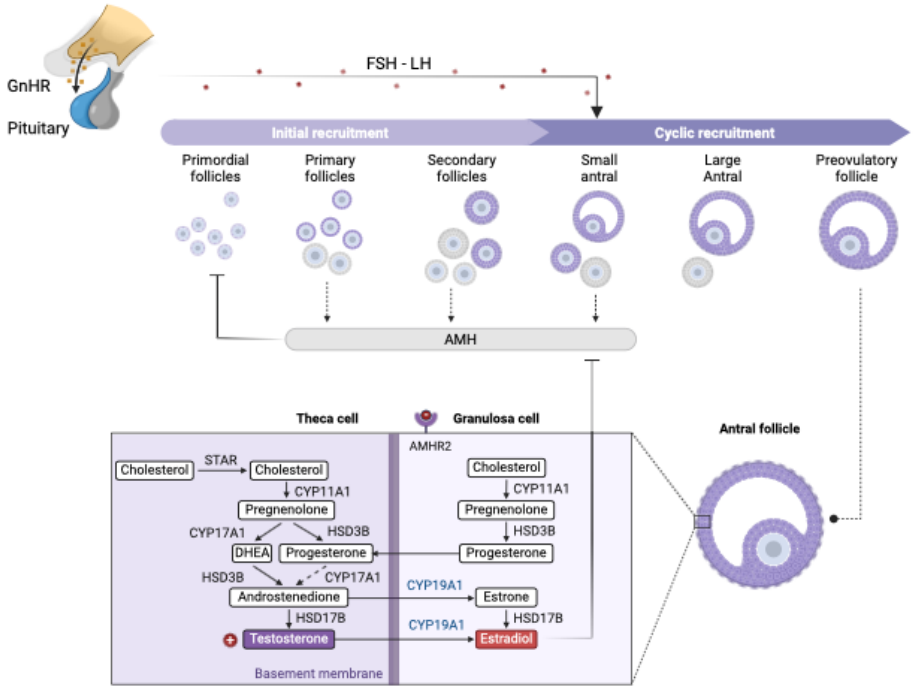

Figure 1: **Production and Action of AMH in Folliculogenesis.** Gonadotropin-releasing hormone (GnRH) stimulates the pituitary gland to release FSH and LH, which travel through the bloodstream to the ovary. FSH participates in the selection of the dominant follicle. During follicular development, AMH is primarily secreted by preantral and small antral follicles, inhibiting both the initial recruitment of primordial follicles and FSH-dependent maturation by reducing the follicles' sensitivity to this hormone. LH stimulates the production of testosterone in the theca cells and reduces the expression of the AMHRII receptor in granulosa cells. As estradiol (E_2) levels increase, AMH production is inhibited, facilitating the maturation of follicles selected for ovulation.

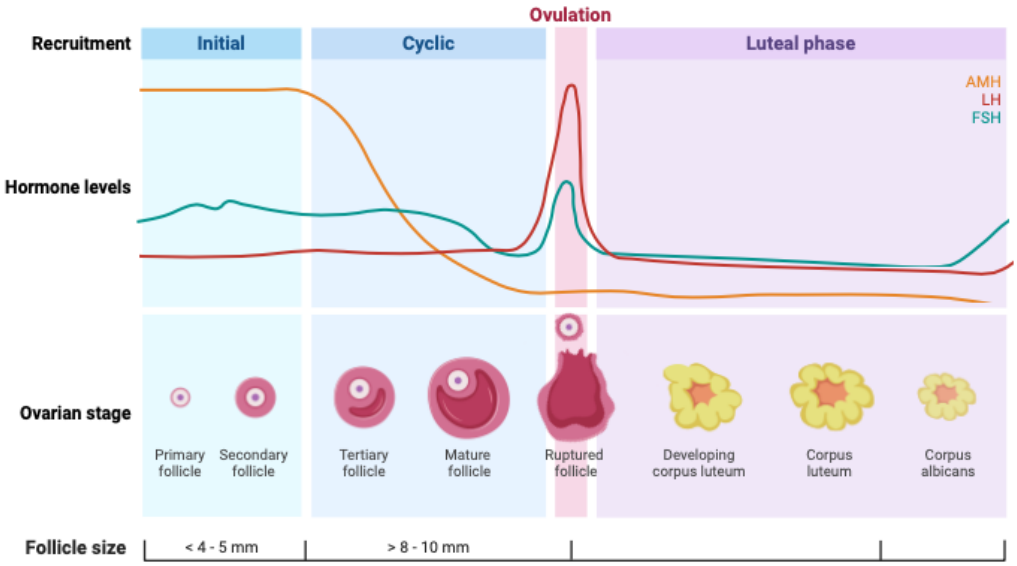

Figure 2: **Comparison of Intrafollicular Hormonal Levels During Follicular Development.** During the initial recruitment phase, intrafollicular AMH levels are elevated and associated with the development of small follicles (< 5 mm). As FSH promotes follicular growth, follicles can reach sizes of up to 8 mm, at which point intrafollicular AMH levels begin to decline. However, it is important to emphasize that serum AMH concentrations remain relatively stable throughout the menstrual cycle, being proportional to ovarian reserve [21]. During ovulation, LH peaks, triggering the rupture of the mature follicle (> 10 mm) and the release of the oocyte. At this stage, intrafollicular AMH levels may drop to nearly undetectable levels, while serum concentrations of LH and FSH stabilize.

The balance between AMH, FSH, and LH ensures controlled follicular development, which is key to a healthy ovulatory cycle. In PCOS, altered AMH production and action play a key role in its pathogenesis. Women with PCOS often have elevated serum AMH levels due to the increased number of small antral follicles [25]. This excessive AMH impairs follicular recruitment, reduces FSH sensitivity, and inhibits proper follicular maturation, contributing to the anovulation characteristic of the syndrome [26]. Additionally, altered AMH levels can affect ovarian responsiveness to FSH and LH, leading to hormonal imbalances that exacerbate PCOS symptoms [27], such as menstrual irregularity and hyperandrogenism.

3.2 Genetic Polymorphisms in *AMH* and *AMHR2*

The AMH gene is located on chromosome 19p13.3 and is composed of five exons that encode a protein of approximately 560 amino acids [28]. Genetic variability in this gene has been studied due to its potential association with the pathogenesis of PCOS, particularly in relation to the elevated AMH levels observed in women with the syndrome. It has even been suggested that serum AMH levels could function as a predictor for confirming a diagnosis of PCOS in reproductive-aged women when analyzed alongside the other Rotterdam criteria [29, 30].

One of the most studied SNPs in the AMH gene is rs10407022, located in the coding region of the gene. This SNP causes a missense mutation or missense variant, described as S (Ser) > I (Ile) [31]. In this variant, serine, a polar amino acid, is replaced by isoleucine, a non-polar amino acid, which can alter the structure and function of the protein due to the differences in the chemical properties of these amino acids [32]. This polymorphism has been linked to E_2 levels in normo-ovulatory women, suggesting that it influences intra-ovarian FSH sensitivity and, therefore, the regulation of aromatase activity [33]. However, the results have been inconsistent across different populations. A study in 331 Dutch Caucasian women with PCOS found an association between this polymorphism and follicle count, androgen levels, and the percentage of women with polycystic ovaries [34]. In contrast, a study conducted in 335 Euro-American women found no genotype-phenotype association with PCOS [35].

Although some studies have reported significant associations between the rs10407022 polymorphism and PCOS characteristics, such as E_2 levels and follicle number, the lack of consistent replication in different ethnic groups suggests the possible influence of additional factors. For example, studies conducted in Han ethnicity women [36] and subsequent meta-analyses [37] have produced mixed results, highlighting the need to consider other elements, such as interactions between genetic variations and environmental factors.

Since PCOS is a multifactorial disorder, the difficulty in identifying consistent associations between genetic polymorphisms and the syndrome could be partly due to inadequate sample sizes and the focus on monogenic traits [8]. Larger, prospective studies using multifactorial approaches could provide a more comprehensive view of the genetic basis of PCOS [38].

Given that AMH signaling depends on its specific receptor AMHR2, it is reasonable to postulate that genetic variations in *AMHR2* could also significantly affect follicular development and PCOS pathogenesis. The *AMHR2* gene is located on chromosome 12q13.13 and is composed of 11 exons that encode a receptor protein of approximately 573 amino acids [28], crucial for mediating AMH signaling. Among the SNPs identified in this gene is rs2272002, located in an intronic region [39], which has been suggested as a possible contributor to PCOS risk and poor ovarian response [40, 41].

Although variation in intronic regions might seem less critical than mutations in coding regions, recent studies have highlighted the role of these sequences in RNA transcription and processing regulation [42]. In this sense, rs2272002 could indirectly affect AMHR2 receptor functionality and its ability to mediate AMH response in the ovary. Like polymorphisms in promoter regions that have been shown to alter serum AMH levels independently of the total number of follicles [9], it is plausible that intronic variants like rs2272002 may also modulate gene expression and thus ovarian sensitivity to AMH.

Despite advances in identifying genetic variants associated with PCOS, the contribution of polymorphisms in *AMH* and *AMHR2* to the syndrome's pathogenesis remains a challenging area of study. The heterogeneity of the results suggests that while these variations may influence PCOS development, they likely interact with other genetic and environmental factors, adding complexity to the understanding of this multifactorial disorder.

3.3 Clinical Implications and Future Perspectives

Both the rs10407022 polymorphism in the *AMH* gene and the rs2272002 polymorphism in the *AMHR2* gene are examples of how genetic variability can influence susceptibility to PCOS and affect reproductive function in women. As larger studies in more diverse populations are conducted, it is likely that a better understanding of how these genetic variants influence PCOS pathogenesis will be achieved. Ultimately, the identification of specific polymorphisms could guide more precise diagnostic strategies and enable personalized treatments based on the patient's genetic profile [43].

However, the variability in results obtained to date highlights the importance of considering additional factors, such as epigenetics, gene interactions, and environmental factors (e.g., lifestyle, exposure to endocrine disruptors). These factors could modulate the expression of *AMH* and *AMHR2* genes, influencing the clinical manifestation of the syndrome [44]. Furthermore, it is essential to deepen our understanding of the molecular mechanisms linking these genetic variants to ovarian dysfunction, which could open new therapeutic opportunities, such as specific modulators of *AMH* or *AMHR2*, to regulate hormone levels in women with PCOS.

A promising future perspective is the integration of genomics and pharmacogenomics into the management of PCOS. This will allow for the identification of patients at higher risk of developing associated complications, such as insulin resistance, infertility, or cardiovascular diseases. Additionally, personalizing therapeutic interventions based on an individual's

genetic profile could optimize treatment effectiveness and minimize side effects [45], providing a more precise approach tailored to each patient's specific needs. This evolution in clinical practice would not only improve the quality of life for women affected by PCOS but could also reduce the economic burden associated with the syndrome's comorbidities.

4 Conclusion

PCOS represents a complex disorder with multiple etiological factors. This review of the rs10407022 polymorphism in the *AMH* gene and the rs2272002 polymorphism in the *AMHR2* gene highlights their potential influence on the syndrome's pathogenesis, as well as their relationship with hormonal regulation and ovarian function. Despite advances in identifying these variants, the heterogeneity in clinical outcomes underscores the need to consider additional factors that may modulate the expression of these genes and their impact on reproductive health.

A comprehensive understanding of how these polymorphisms contribute to PCOS is crucial not only for improving diagnosis and treatment but also for enhancing fertility outcomes. Identifying these genetic variations may guide reproductive strategies and help reduce the risk of infertility in affected patients. As research progresses, opportunities will arise to develop more personalized therapeutic approaches tailored to the specific needs of patients. The integration of genetics, endocrinology, and environmental considerations offers a promising avenue to optimize treatment and improve the quality of life for women dealing with this multifactorial disorder.

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Ethical Considerations

Since this article is a narrative review that does not entail the collection, analysis, or reporting of data from human participants or animals, ethical approval or specific ethical considerations are not applicable. All referenced sources have been duly cited to uphold academic integrity.

Author Contributions

All authors contributed equally to the conceptualization, writing, review, and approval of the final manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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