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Invited critical review

AMH: An ovarian reserve biomarker in assisted reproduction ☆

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ABSTRACT

Ovarian reserve tests provide knowledge of a possible response to controlled ovarian hyperstimulation in patients undergoing assisted reproduction treatment, allowing management and alteration of treatment protocol with the appropriate dose of gonadotrophin. Several parameters have been used as predictors of ovarian response. The basal FSH serum level on the third day of the menstrual cycle seemed to be the best predictor, but with significant intraindividual variability from one cycle to another. Thus, the anti-Müllerian hormone (AMH) emerges as a new ovarian test marker. AMH is produced exclusively in the gonads, by the granulosa cells, and plays an important role in folliculogenesis, acting on the modulation of follicular recruitment in the granulosa cells in order to limit the number of recruited oocytes and to regulate the number of growing follicles and their selection for ovulation. It has been suggested that AMH is strongly associated with oocyte yield after ovarian stimulation and could therefore be capable of predicting the ovarian response and the quality of oocytes and embryos. In this review, we discuss the role of AMH in assisted reproduction outcomes.

Contents

Abbreviations: AMH, anti-Müllerian hormone; IVF, in vitro fertilization; COH, controlled ovarian hyperstimulation; FSH, follicle-stimulating hormone; OHSS, ovarian hyperstimulation syndrome; MIS, Müllerian-inhibiting substance; bp, base pairs; mRNA, messenger RNA; mm, millimeter; AMHR, anti-Müllerian hormone receptor; PCOS, polycystic ovary syndrome; PCO, polycystic ovary; AFC, antral follicle counting; Ser, serine; pmol/l, picomoles per liter; ng/ml, nanograms per milliliter; BMI, body mass index; LH, luteinizing hormone; SNP, single nucleotide polymorphism; ART, assisted reproduction technique; ELISA, enzyme-linked immunosorbent assay; DSL, Diagnostic Systems Laboratories; ICSI, intracytoplasmic sperm injection; AUC, area under the curve; LoD, limit of detection; LoQ, limit of quantitation.

☆ The authors have nothing to disclose.

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1. Introduction

1.1. Objective

To review the role of the anti-Müllerian hormone in assisted reproduction outcomes.

2. Background

Conjugal infertility is characterized by the absence of spontaneous pregnancy after the minimum period of twelve months, with the practice of regular and unprotected intercourse [1].

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In vitro fertilization (IVF) is a complex multistep process that comprises the collection of oocyte-containing follicles after controlled ovarian hyperstimulation (COH) with FSH (follicle-stimulation hormone), oocyte fertilization, embryo development, embryo transfer to the uterus, and implantation. All these steps are critical for successful IVF. However, the initial critical step of this complex procedure is the COH whose aim is to safely obtain a high number of mature oocytes, so as to allow the selection of the most viable embryo for transfer. Both quantitative and qualitative factors in oocyte production have a high influence on the IVF outcome [2,3].

In human assisted reproduction, the ovulation response to exogenous FSH therapy is variable, and the ovarian response to gonadotropin stimulation is difficult to predict. In young ovulating women undergoing the in vitro fertilization (IVF) protocol, standard stimulation can result in both a satisfactory answer or an inadequate response requiring FSH dose adjustment, or ovarian hyperstimulation syndrome (OHSS). The latter is a serious and potentially fatal complication of IVF, characterized by enlarged ovaries and fluid leakage into the abdominal cavity, resulting in ascites, hypovolemia and hemoconcentration [4,5]. Identifying patients with potential to develop hyper-response or inadequate response to the standard treatment would be of great clinical value.

Several parameters have been postulated as predictors of ovarian response. Since the ovarian function cannot be measured directly, the use of serum markers [FSH, inhibin B, 17-β-estradiol and anti-Müllerian hormone (AMH)] and/or ultrasound variables [ovarian volume, measurement of antral follicles, ovarian stromal blood flow] has been proven useful although limited [6]. For some authors these markers do not reflect the complex follicular dynamics, and none of them shows strong correlation with the population of primordial follicles that remain in the gonad [7]. Although Hansen et al. [8] concluded in their study that antral follicle count (AFC) and serum AMH correlate with ovarian primordial follicle number even after adjustment for chronological age.

However, among the parameters used as predictors of ovarian response nowadays, the level of basal FSH on the third day of the menstrual cycle seemed to have the best predictive ability, but a significant intraindividual variability from one cycle to another has been observed [9]. In this context, the anti-Müllerian hormone (AMH) emerges as a new marker of ovarian reserve.

2.1. Anti-Müllerian hormone — AMH

The anti-Müllerian hormone, also called Müllerian-inhibiting substance (MIS), is a dimeric glycoprotein [10] and a member of the transforming growth factor β family [10–12]. It is a homodimeric disulfide-linked glycoprotein with a molecular weight of 140 kDa. The gene (MIM: 600957 and gene ID: 268) is located on the short arm of chromosome 19, at 19p13.3 [Cohen-Haguenauer et al.], and is divided into five exons, with 2750 bp [13,14].

The existence of AMH was first suggested by the French scientist Alfred Jost in the 1940s. He showed that a testicular product different from testosterone was responsible for the progression of Müllerian ducts in male fetuses, which he named "hormone inhibitrice" or Müllerian inhibitor [15].

During male sex differentiation, AMH is produced and synthesized by the Sertoli cells and induces degeneration of the Müllerian duct system, while Leydig cells produce testosterone, which stimulates the differentiation of the Wolffian duct into the epididymis, vas deferens and seminal vesicles [16,17]. In females, the absence of this hormone is responsible for the development of the female reproductive tract, where the Müllerian ducts differentiate into the oviducts, uterus and upper part of the vagina [18,19].

AMH is produced exclusively in the gonads, in females by the granulosa cells of pre-antral and antral follicles [10–12,16], starting in the human fetus after 36 weeks of gestation [20]. It seems to be derived only from the ovary, since premenopausal women who underwent bilateral oophorectomy and menopausal women are associated with undetectable AMH concentrations [21]. The antral follicle granulosa cells secrete AMH into the follicular fluid and into the blood circulation [22].

AMH continues to be expressed in the growing follicles [23] until they reach a size of 4–6 mm and a differentiation state at which they become receptive to exogenous FSH [16], and may be selected for dominance [23].

AMH also inhibits the sensitivity of antral follicles to FSH in cycle recruitment and the activity of the enzyme aromatase, reducing estrogen biosynthesis [24].

Moreover, according to some authors, AMH is expressed in the follicles that have undergone recruitment from the primordial follicle pool and have not been selected for dominance [18,25,26] (Fig. 1). Before these important events, AMH is not expressed [17] and it is not expressed in the theca or atresia cells either [18,25,26].

Granulosa cells of primary follicles show homogeneous AMH expression, but maximal expression occurs in late pre-antral and small antral follicles. The expression declines as the pre-ovulatory follicles mature [16,27]. In large follicles, AMH is mainly produced in the cells near the oocyte and in a few cells surrounding the antrum [18]. Antral follicles are considered the first source of circulating AMH, as they contain a large number of granulosa cells [28].

The effect of AMH on ovarian activity is complex, and the role of this hormone is so far not completely understood [29], however AMH seems to regulate the number of growing follicles and their selection for ovulation [20].

The transition from primordial into growing follicles is enhanced in the absence of AMH, resulting in the early exhaustion of the primordial follicle pool [30]. Granulosa cells secrete AMH into the bloodstream and follicular fluid, however the role of AMH in this compartment is not clear [28].

The serum AMH allows estimating indirectly whether the number of available oocytes is above, at or below the expected value for age, thus allowing an attempt to predict the reproductive longevity. Besides acting on the modulation of follicular recruitment [20,31], AMH also acts in the pre-granulosa cells, in order to limit the number of recruited oocytes [17]. Once AMH is not secreted by the dominant follicle, the serum AMH might not show fluctuation during the menstrual cycle, although some authors suggested that AMH is subject to inter-cycle variations [32].

This hormone may serve in clinical practice as a useful diagnostic tool in differentiating the various causes of secondary oligo-amenorrhea [28,33,34]. Evidence indicates that AMH evaluation allows distinguishing who falls into class II and class III amenorrhea [27,35,36]. Moreover, AMH has another important function: assessing the severity of ovarian damage after ovarian surgery or chemotherapy [37–40] and also for a specific follow-up of granulosa cell tumors [41]. Some authors classified AMH as a new endocrine parameter for the investigation of ovarian function, emerging as a new marker of ovarian reserve and being useful in reproductive treatment [27,33,36,42].

Durlinger et al. [20] study the ovaries from AMH-null and wild-type mice and showed that in the AMH-null mice the recruitment from the primordial follicle pool is increased, because their size was significantly decreased compared to the wild-type mice. This increased recruitment may start even before the estrous cycles start.

Another study of the same group, with "in vitro" and "in vivo" follicle cultures, showed that the follicles are more sensitive to FSH in the absence of AMH, inhibiting the growth of pre-antral follicles [30]. Moreover, in an "in vivo" model where follicle dynamics were compared in wild-type and AMH-null mice in the presence of low and high FSH serum concentrations, the results showed that independently of the level of FSH (low or high), the AMH-null mice showed a better response regarding follicle number and development stage than the wild-type mice [30]. Based on this information, some authors hypothesized that AMH may be one of the factors involved in determining the responsiveness of ovarian follicles to FSH during cyclic recruitment [36].