

EXCEPTIONAL DIAGNOSTICS FOR REPRODUCTIVE DISEASE STATE MANAGEMENT

Anti-Müllerian Hormone (AMH)



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AMH – Anti-Müllerian Hormone

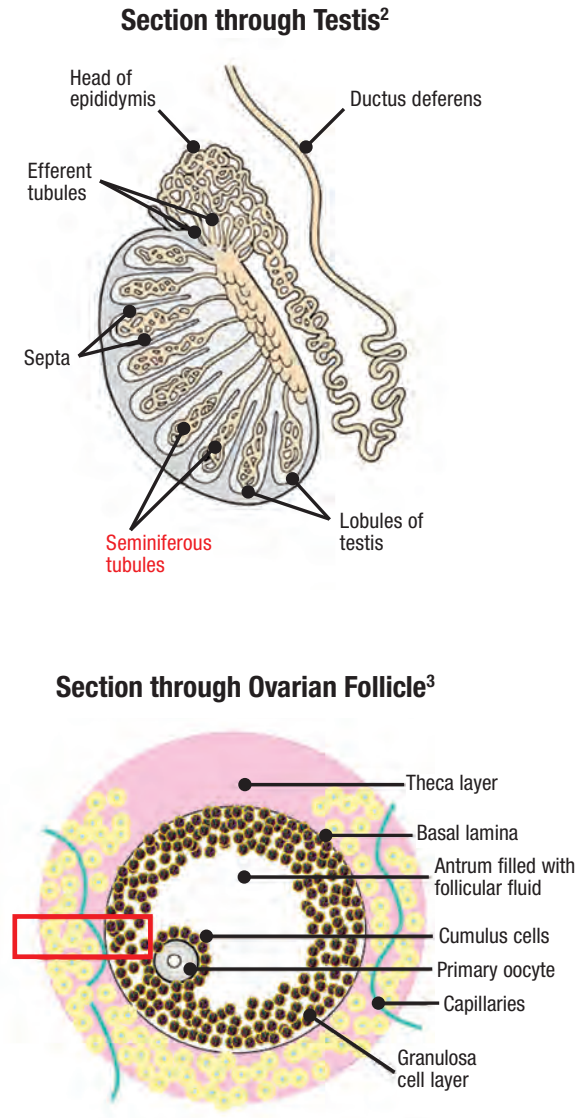
Introduction

Anti-Müllerian Hormone (AMH) is a glycoprotein dimer composed of two 72 kDa monomers¹. AMH belongs to the transforming growth factor- β (TGF- β) superfamily, which includes TGF- β as well as various inhibin and activin glycoproteins. All members of this family play a role in the growth and differentiation of tissues.

Anti-Müllerian Hormone can be found under the following names: Müllerian Inhibiting Substance (MIS), Müllerian Inhibiting Hormone (MIH), Müllerian Inhibiting Factor (MIF), Müllerian Inhibitor.

Biosynthesis

The expression of AMH is restricted to Sertoli cells of the fetal and postnatal testes in the male, and granulosa cells of the postnatal ovary in the female (Fig. 1).



90% of the testis consists of seminiferous tubules which are tightly coiled. The walls of the seminiferous tubules are made up of endothelial cells called Sertoli cells.

Structure of the Graafian follicle. The granulosa cell layer is avascular, the vessels being excluded by the basal lamina which is laid down early in follicle life. The basal lamina protects the oocyte.

Fig. 1: AMH production

Physiological Function

AMH is named for its first described function in fetal sex differentiation: regression of the Müllerian ducts during early male sexual differentiation. In addition to mediating this crucial aspect of fetal reproductive tract development, AMH plays critical regulatory roles in both the postnatal (developing) and mature gonad⁴

Let's follow the physiological function of AMH step-by-step in both males and females throughout the course of life.

Fetal Stage

The sex of a human being is determined at the very moment of fertilization. However, fetal sex differentiation starts around the 6th week of gestation. During early stages of mammalian development, fetuses of both sexes have two pairs of ducts: Wolffian and Müllerian (Fig. 2).

In the male fetus, Sertoli cells of the testes secrete AMH and androgens. Androgens cause the Wolffian ducts to develop into the male internal anatomy. AMH provokes irreversible Müllerian duct regression, which is completed by the end of the 9th week of gestation. The role of AMH is essential to this process. In fact, AMH is one of the first Sertoli-cell-specific proteins produced by the gonad.

In the absence of AMH, the Müllerian ducts of both sexes develop into the uterus, Fallopian tubes and upper part of vagina.

In the female fetus, the lack of AMH allows the Müllerian ducts to develop further, while the lack of androgens causes the Wolffian ducts to regress, producing the internal female anatomy.

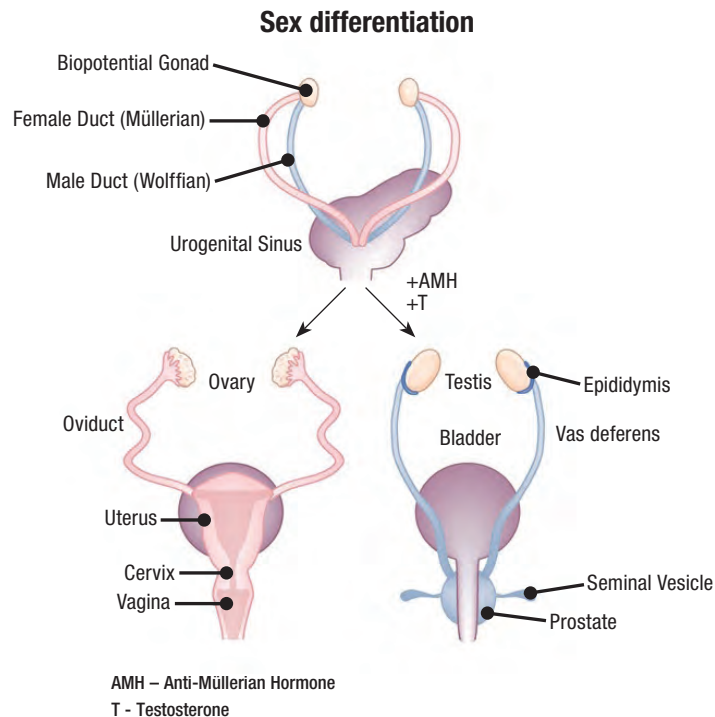


Fig. 2: Fetal sex differentiation in humans⁵

Postnatal Stage

Male

With the exception of a transient decline in the perinatal period, testicular AMH secretion is maintained at high levels until puberty, when Sertoli cell maturation is characterized by decreased AMH activity⁶. The decline of AMH production by Sertoli cells during puberty is related to pubertal development stage rather than to age. The most significant decrease in serum AMH occurs between Tanner stages II and III of pubertal development, simultaneous with an increase in intratesticular testosterone concentration – an event occurring earlier than the elevation of serum testosterone.

This poses the following question: given that AMH is down-regulated by testosterone, how is it possible that both AMH and testosterone levels are elevated during fetal life and in the first month after birth? It seems that testosterone does not inhibit AMH production in fetuses and newborns because of a lack of androgen receptor (AR) expression in Sertoli cells. The expression of AR increases progressively after birth⁶. In adults, AMH levels remain low (Fig.4 on page 6).

Female

In females, AMH is produced by ovarian granulosa cells. AMH production begins at the perinatal period, remains low throughout reproductive life (with a minor peak after puberty) and becomes extremely low after menopause⁷.

AMH expression is seen in follicles at several stages of folliculogenesis. Production occurs predominantly in preantral and early antral follicles (less than 4 mm in size) and declines during the final maturation process and luteinization.

AMH plays a role in the initial recruitment and selection of the dominant follicle. This process is shown in figure 3⁸. As stated above, AMH is produced by the growing follicles (primary and preantral) in the postnatal ovary and has two mechanisms of action:

- » Inhibition of initial follicle recruitment (pathway 1, Fig.3)
- » Inhibition of FSH-dependent growth and selection of preantral and small antral follicles (pathway 2, Fig.3)



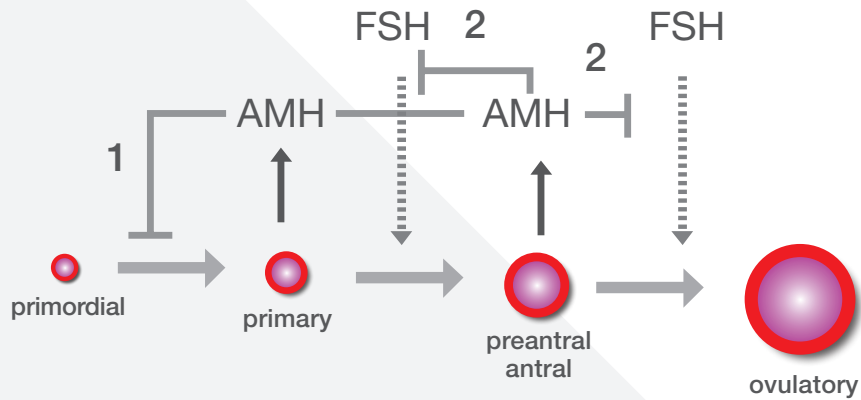


Fig.3: Model of AMH action in the ovary

This principle is consistent with changes in AMH levels as described above. From birth to puberty, ovarian size and antral follicle presence gradually increase (with a slight rise towards the onset of puberty), reaching their maximum levels after puberty. In this stage of a woman's life, both her ovarian reserve (reproductive capacity) and serum AMH levels are at their respective peaks. The decrease in female ovarian reserve with age is due to the decline in follicle count. AMH gradually decreases to very low levels after menopause, when the ovarian reserve is fully depleted.⁹

Levels

Physiological variations in AMH level are a function of both sex and age (Fig.4 and Fig.5). AMH levels do not exhibit circadian fluctuation and remain stable throughout the menstrual cycle (Fig.6).¹⁰

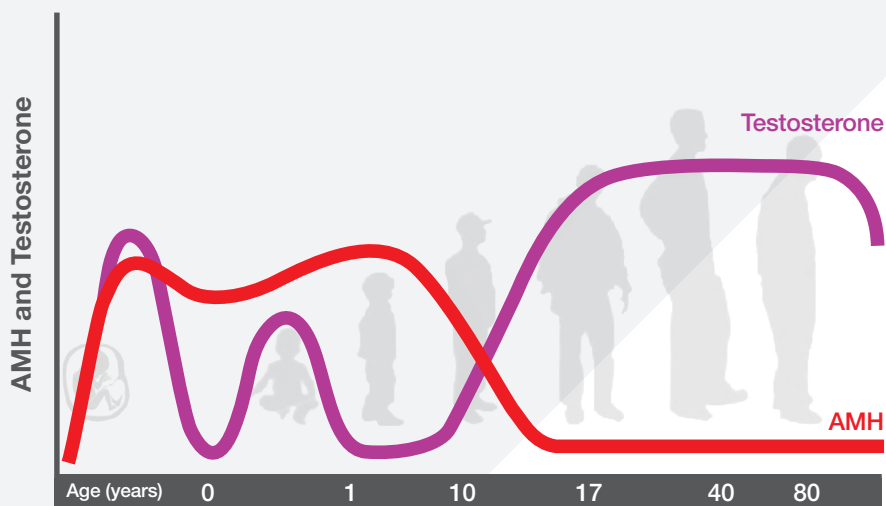


Fig.4: AMH and testosterone levels in males¹¹

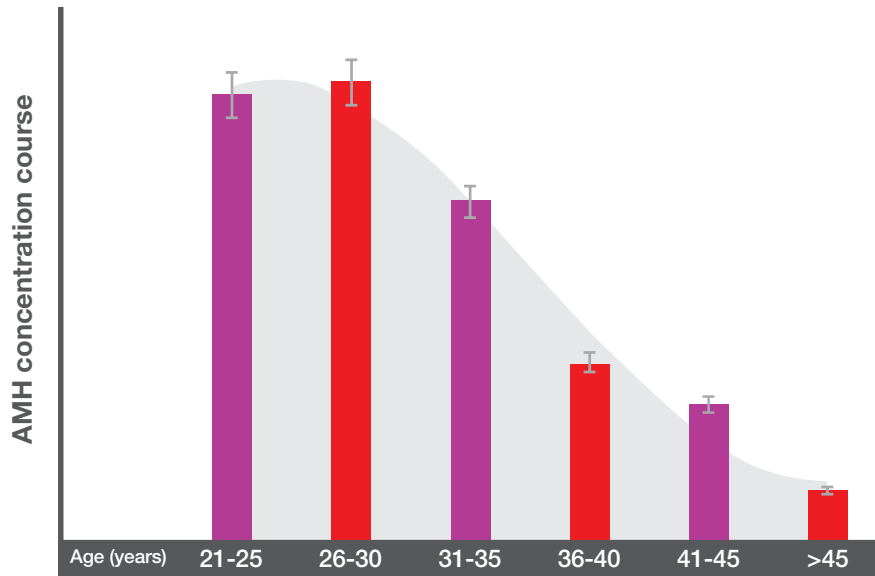


Fig.5: AMH levels in females throughout childbearing age¹²

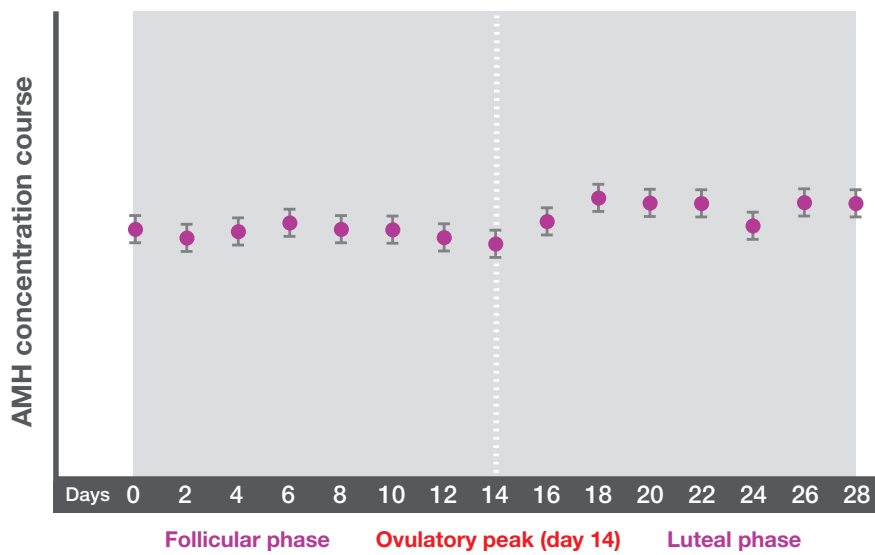


Fig.6: AMH levels throughout the menstrual cycle¹²

Diagnostic Utility – Prospects and Possibilities

Measurement of serum AMH levels provides a useful marker of reproductive status both in males and females. Abnormal AMH levels can be found in a broad spectrum of disorders, including:

Elevated AMH Levels

- » delayed puberty in boys
- » gonadotropin-independent precocious puberty in boys
- » testotoxicosis in boys
- » some cases of androgen insensitivity syndrome
- » some cases of testosterone biosynthetic defects
- » disgenetic testes or ovotestes in children with intersex conditions
- » Sertoli-Leydig cell ovarian tumors
- » polycystic ovary syndrome (PCOS)
- » granulosa cell tumors

Decreased AMH Levels

- » cryptorchidism and anorchia in boys
- » some cases of precocious puberty
- » testicular dysgenesis
- » premature menopause



Diagnostic Utility – Practical Applications

AMH is essential for correct male sexual differentiation as well as regulation of follicle maturation in females.

Determination of serum AMH levels is important in the evaluation of the functional state of gonads and related disorders.

In particular, AMH determination is used for:

Determination of Ovarian Status in Women

AMH levels reflect the continuous decline of the oocyte/follicle pool with age and thus ovarian aging and menopausal transition. It is measured in conjunction with FSH and inhibin B.¹³

AMH determination is also used (again with FSH and inhibin B) as a good marker of ovarian responsiveness in patients undergoing assisted reproductive technology.

Diagnosis and Follow Up of Polycystic Ovary Syndrome (PCOS)

Serum AMH levels are elevated in normogonadotropic anovulatory infertile women with PCOS.

Diagnosis and Management of Granulosa Cell Tumors

Serum AMH levels are increased in granulosa cell tumors, and this serves as an extremely sensitive and specific marker in the follow-up of ovariectomized patients. Early detection of recurrences is of great importance, as granulosa cell tumors are characterized by a high incidence of recurrence — even more than 10-20 years after the resection of the primary tumor.¹³

Diagnosis and Differential Diagnosis of Precocious and Delayed Puberty in Boys

AMH determination is often used in conjunction with measurement of LH and testosterone levels. In normal and precocious puberty, there is a negative correlation between serum testosterone and AMH levels.

Central precocious puberty is characterized by an elevation of pituitary gonadotropins and testicular androgens, and normal or declining AMH.

Gonadotropin-independent precocious puberty, or testotoxicosis, is characterized by high androgen levels, extremely low or undetectable gonadotropin levels and abnormally high AMH production.⁹

Diagnosis of Cryptorchidism and Anorchia in Boys

In newborn boys, there is 3-6% incidence of cryptorchidism or undescended testes (up to 30% of premature infants). This declines to 1-2 % by 3 months of age due to spontaneous testicular descent. Treatment (hormonal and surgical) begins in the 6th month. AMH levels may be used to distinguish undescended testes (normal values) from anorchia (extremely low or undetectable values)⁴

Differential Diagnosis of Intersex Conditions in Children

AMH levels reflect the functioning of Sertoli cells. Thus AMH levels are often determined in conjunction with those of testosterone, which reflects the functioning of Leydig cells.

Conditions associated with normal parenchymal tissue and an absence of androgen action, such as androgen insensitivity syndrome or testosterone biosynthetic defects, are characterized by normal or elevated AMH levels.

Testicular dysgenesis is characterized by low values of both AMH and testosterone.

AMH determination helps to differentiate between gonadal and non-gonadal causes of mild virilization in phenotypic prepubertal girls. Undetectable levels are found in 46,XX prepubertal virilized girls with ovaries. Increased levels are found in children with disorders of testosterone secretion, androgen insensitivity, disgenetic testes and ovotestes. Extremely high levels are found in girls with virilizing Sertoli-Leydig cell ovarian tumors⁴

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