PATHCHAT

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Anti-Müllerian hormone (AMH): Physiology and clinical utility

Physiology

Anti-Müllerian hormone (AMH), previously termed Müllerian-inhibiting substance, is a 140 kDa dimeric glycoprotein belonging to the TGF-β (transforming growth factor beta) superfamily.

AMH is expressed by the immature Sertoli cells from the time of sexual differentiation at approximately eight weeks' gestation, and is responsible for the involution of the Müllerian ducts in the male foetus through its interaction with the AMH type II receptor (AMHRII). Absence of AMH results in differentiation of the Müllerian ducts into the oviducts, uterus and upper third of the vagina in both genetic female and male embryos. Dysfunction of the AMH receptor has the same result.

In boys, AMH shows a significant increase from birth with a peak value at three months during transient activation of the hypothalamic-pituitary-gonadal axis (infantile minipuberty). AMH subsequently declines at one year and then remains relatively stable until puberty. With Sertoli cell maturation at the age of puberty, Sertoli cells become androgen receptor positive and respond to increased local testosterone by AMH-downregulation, with adults exhibiting only 3 to 4% of infant levels. From the time of puberty, AMH is negatively regulated by testosterone, and is therefore increased in patients with androgen insensitivity. Furthermore, high AMH levels relative to chronological age have been noted in boys with delayed puberty, whereas boys with precocious puberty had lower levels. No diurnal variation was found in AMH levels.

In contrast to boys, AMH levels are low in girls until puberty, although a relatively small increase is also seen from undetectable levels in cord blood to three months of age at the time of minipuberty (see above).

AMH is secreted by the granulosa cells of primary and pre-antral ovarian follicles, and is regarded as a predictor of the ovarian follicular reserve. Little is known about the physiological role in women, although it is postulated that it inhibits initial follicular recruitment (primordial to primary follicles) and follicle-stimulating hormone (FSH)-dependent follicle growth (pre-antral and antral follicles). Although there are slight fluctuations of AMH during the menstrual cycle, with peak values during the pre-antral and small antral stages, and decreases as the follicles grow larger, it is not considered significant enough to recommend sampling during a specific phase. After puberty, AMH concentration declines slowly over the reproductive life span as the size of the pool of follicles decreases and frequently reaches undetectable levels after natural or premature menopause.

Utility of AMH measurement

a. Children with ambiguous genitalia or bilateral cryptorchidism

AMH measurements are commonly used to evaluate testicular function/presence in infants with intersex conditions or ambiguous genitalia, as well as to distinguish between cryptorchidism (testicles present but not palpable and a measurable AMH) and anorchidism (absent testicles and undetectable value for AMH). Measurement of serum AMH does not require prior stimulation with gonadotropins (HCG).

b. Assessment of ovarian reserve

Since AMH is produced continuously in the granulosa cells of small follicles, the AMH level can be used as a surrogate marker of the ovarian follicle pool in terms of both quantity and quality. It is a superior marker of ovarian reserve compared to fluctuating levels of gonadotropins and ovarian steroid hormones.

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AMH is unaffected by pregnancy. Although oral or vaginal estrogen- or progestin-based contraceptives show minimal effect, it is preferable to determine AMH levels after discontinuation of the medication for at least 4 weeks. Changes in AMH levels are observed in early phases of ovarian failure in young women, even before FSH elevation is noted. It can therefore be utilised for confirmation of the diagnosis of premature ovarian failure, as well as in the prediction of the menopausal transition.

c. Use of AMH during in vitro fertilisation (IVF) treatment

Fertility studies have shown that females with higher AMH concentrations have a better response to ovarian stimulation and tend to produce more retrievable oocytes than those with low or undetectable levels. AMH shows a strong correlation with the antral follicular count (AFC), the number of oocytes retrieved, age, inhibin B and FSH levels. Significantly elevated AMH levels can be used to identify females at risk of ovarian hyperstimulation syndrome following gonadotropin administration. Serum AMH levels have greater value for predicting clinical pregnancy outcome in IVF cycles than age, serum FSH, inhibin B or oestradiol levels.

The following values can be used to predict the response following ovarian stimulation, but should be used in combination with clinical and ultrasound findings (AFC). These values have been adjusted for the new automated method (Beckman Coulter DXI) implemented by Ampath during March 2015.

SUGGESTED CUT-OFF VALUES		
ng/ml	pmol/l	Response to ovarian stimulation treatment
<0.17	<1.2	Negligible/non-responders
0.17–1.21	1.2–8.6	Reduced/poor response (≤ 2 eggs at oocyte retrieval)
1.22–2.30	8.7–16.4	Normal response (3–20 eggs at oocyte retrieval)
>2.30	>16.4	High/excessive response (> 20 eggs at oocyte retrieval)

AMH is seen to decline gradually during FSH administration as part of controlled ovarian hyperstimulation (COH). The negative role of FSH on AMH secretion is probably the result of follicular growth and a reduction in the number of small antral follicles.

d. AMH as a marker for polycystic ovarian syndrome (PCOS)

In patients with polycystic ovarian syndrome (PCOS), serum AMH levels are usually elevated due to large numbers of small follicles combined with increased production by each follicle. AMH measurement shows high specificity and sensitivity (92 and 67% respectively) when used as a marker for PCOS. It has therefore been proposed that AMH can be used instead of the follicle count as a diagnostic criterion for PCOS, where accurate ultrasonography is not available. AMH levels are higher in amenorrhoeic than oligomenorrhoeic women with PCOS, which could indicate a pathogenic role for AMH in PCOS-related anovulation. Metformin administration in PCOS-affected women is associated with a reduction in both AMH levels and antral follicles.

During assisted reproductive technology, the majority of women with ultrahigh AMH levels (> 10 ng/ml) have PCOS. These women should be recognised as a group at very high risk for ovarian hyperstimulation syndrome and their ovarian stimulation should be managed with extra caution. Women with less elevated AMH levels that respond to treatment also respond better to induction of ovulation.

e. AMH as tumour marker for granulosa cell tumours of the ovaries

Serum AMH concentrations may be increased in 76 to 93% of patients with ovarian granulosa cell tumours that comprise approximately 10% of all ovarian tumours. AMH combined with CA125 may be useful for monitoring response to treatment and follow-up of patients with these tumours, allowing earlier detection of recurrences.

Specimen collection requirements

Serum collected into a serum separator tube (SST) is the preferred sample and should be centrifuged within five hours of collection, after which it is stable at room temperature for one day. The cost of the test is approximately R600.

References:

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