The Innovation

Review

Clinical Applications of Serum Anti-Müllerian Hormone Measurements in Both Males and Females: An Update

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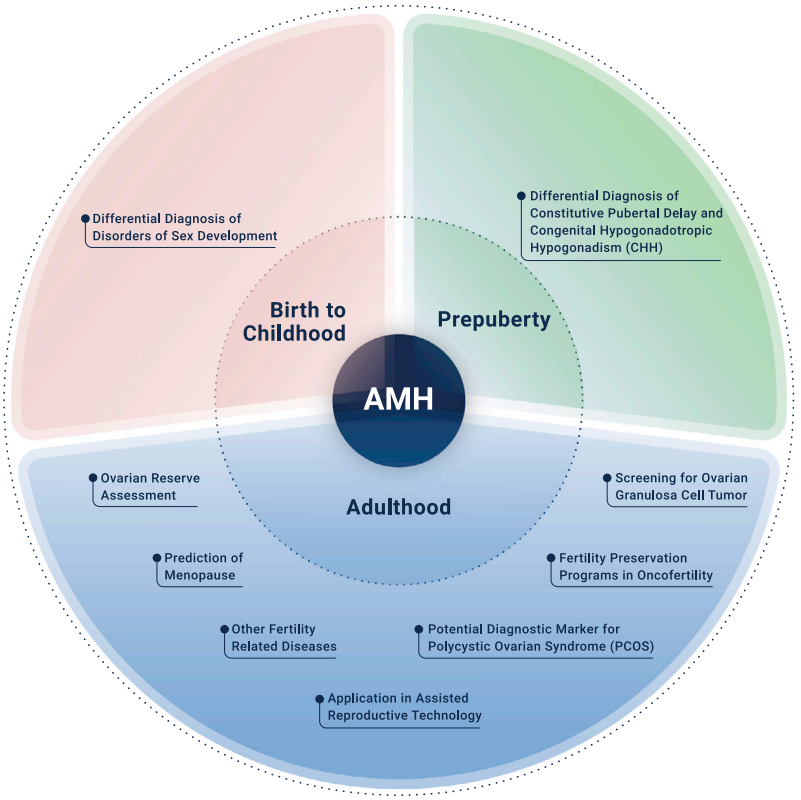
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Anti-Müllerian hormone (AMH) plays a key role in models assessing ovarian reserve
- AMH is used for the differential diagnosis of disorders of sex development
- AMH provides a molecular marker for related fertility and infertility disorders
- An international standard will aid in the development of various AMH assays

Review

Clinical Applications of Serum Anti-Müllerian Hormone Measurements in Both Males and Females: An Update

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Infertility is one of the most common non-communicable diseases, affecting both men and women equally. Ovarian reserve, the number of primordial follicles in the ovaries is believed to be the most important determinants for female fertility. Anti-Müllerian hormone (AMH) secreted from granulosa cells of growing follicles is recognized as the most important biomarker for ovarian reserve. Ovarian reserve models have been developed using AMH and other hormonal indicators, thus childbearing plans and reproductive choices could be arranged by women. In assisted reproductive technology cycles, measurement of AMH helps to predict ovarian response and guide recombinant follicle-stimulating hormone dosing in women. Serum AMH level is increasingly being recognized as a potential surrogate marker for polycystic ovarian morphology, one of the criteria for diagnosis of polycystic ovarian syndrome. AMH is also secreted by Sertoli cells of testes in men, and AMH measurements in the prediction of surgical sperm recovery rate in men have also been investigated. AMH levels are significantly higher in boys than in girls before puberty. Therefore, serum levels of AMH in combination with testosterone is used for the differential diagnosis of disorders of sex development, anorchia, non-obstructive azoospermia, and persistent Müllerian duct syndrome. Recently, serum AMH measurements have also been used in fertility preservation programs in oncofertility, screening for granulosa cell tumors, and prediction of menopause applications. In this review, we will focus on clinical application of AMH in fertility assessments for healthy men and women, as well as for cancer patients.

KEYWORDS: anti-Müllerian hormone assays; assisted reproductive technology; Sertoli cells; Granulosa cells; ovarian reserve; menopause; PCOS

INTRODUCTION

Infertility affected 48.5 million couples globally in 2012.[1] Recently, many women have tended to delay their childbearing plans in order to pursuit career goals, which may contribute to the high incidence of infertility worldwide. A major determinant of female reproductive potential is ovarian reserve, which is influenced by age, genetics, and environment. The ovarian reserve, the number of primordial follicles in ovarian cortex, is highly heterogeneous, ranging from tens to millions,[2] leads to the variation in the age of exhaustion of fertility (menopause) in women. Therefore, assessment of ovarian reserve is of great importance. Recently, ovarian reserve models have been developed, using anti-Müllerian hormone (AMH) and other indicators.[3,4] Due to the key role of AMH in ovarian reserve assessment, the physiology and clinical applications of AMH are reviewed here.

In 1947, Jost[5] discovered a substance that contributed to the regression of the Müllerian duct during the sexual differentiation of male embryos, denoted AMH. AMH is a member of the transforming growth factor β superfamily,[6,7] which has key roles in development and tissue homeostasis, including regulation of development of the male genital tract.[8]

In females, the secretion of AMH starts around the 36th week of gestation, then reaches a peak around 25 years of age, before declining to undetectable levels during the menopause.[9] AMH is secreted by ovarian granulosa cells (GCs) of preantral and small antral follicles.[9–11] One role of AMH in females is to inhibit primordial follicle recruitment[12] in a follicle-stimulating hormone (FSH)-independent manner.[13,14] In males, the secretion of AMH starts around the eighth week of gestation,[15] then declines in the first week after birth, rises rapidly during the first month, peaks at about 6 months of age, declines during childhood, falls to low levels in puberty, and decreases with age after sexual maturation.[16–18] AMH is secreted by immature Sertoli cells (SCs) and provides a valuable molecular marker for these unique cells.[19,20]

During embryonic development, AMH is associated with regression of the female (Müllerian) reproductive ducts as well as with the development of male reproductive ducts.[9] During adulthood, the role of AMH remains inconclusive. However, serum levels of AMH in adult men are similar to those in adult women, and decreasing serum AMH levels with age have been found in both sexes,[17,18,21] which indicates its potentially important role in adulthood. An increasing number of studies have shown that abnormal serum levels of AMH might indicate an abnormality of the reproductive system in both sexes.[19,22] In this paper, the clinical applications of serum AMH in fertility assessment and other reproductive-related disorders will be reviewed.

PHYSIOLOGY OF AMH

Prior to gonadal differentiation, both male and female mammalian embryos have two sets of paired reproductive ducts: the paramesonephric (Müllerian) and mesonephric (Wolffian) ducts.[23] In response to AMH and testosterone, which is secreted by immature SCs and Leydig cells respectively in male embryos,[24] the mesonephric ducts develop into the epididymides, vasa deferentes and seminal vesicles, while the paramesonephric ducts regress. In the absence of AMH and testosterone, the paramesonephric ducts of female embryos develop into the fallopian tubes, uterus, and proximal vagina, and the mesonephric ducts degenerate.[25]

Males

In males, AMH is secreted by immature SCs and its circulating concentration before puberty is extremely high compared with women.[26,27] As puberty progresses, immature SCs differentiate into mature SCs and AMH levels drop significantly.[17,18] In the absence of functional androgen signaling, FSH was reported to be responsible for transcriptional activation of *AMH* expression

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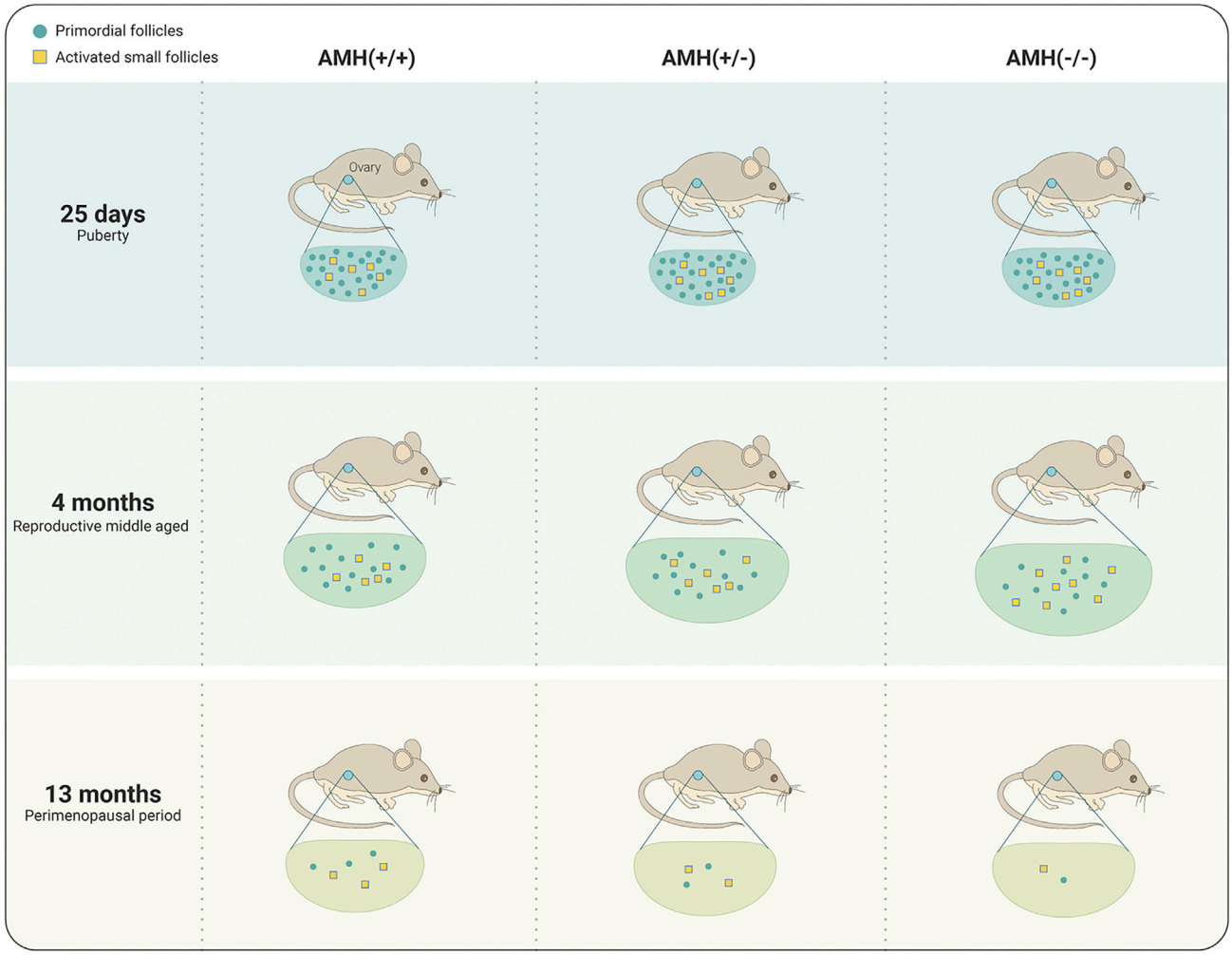

Figure 1. Summary of the Role of AMH in *AMH* Null Mice In *AMH*-null female mice 25 days after birth (equivalent to female puberty in humans), the number of primordial follicles was normal, but the numbers of activated follicle were elevated.[12] In 4 months old, AMH-null female mice (equivalent to reproductive middle age in humans), the number of primordial follicles was significantly reduced, while the number of activated follicles was significantly higher than normal, together with larger ovarian volume.[12] At 13 months old in AMH-null female mice (equivalent to the perimenopausal period in humans), the primordial and activated follicle numbers decreased significantly in *AMH*-null compared with control mice. The scheme is based on the data from Durlinger et al.[12] (https://doi.org/10.1210/endo.140.12.7204).

through the activation of nuclear factor kappa-B (NF-κB) in mice.[19,28] In the presence of functional androgen signaling, testosterone was negatively correlated with *AMH* expression in both humans and mice,[19] possibly via the negative regulation of NF-κB by androgen receptors.[29] The sex-determining region Y box 9 (Sox9),[30,31] steroidogenic factor-1 (SF1),[32,33] and GATA factors[34–36] were also implicated in the transcriptional regulation of *AMH*; however, their transcriptional activity was less than that of NF-κB in SMAT1 cells, a mouse immortalized immature Sertoli cell line.[28] The number of immature SCs produced during the perinatal period ultimately determines the number of germ cells in adult men.[37,38] Because AMH is a functional marker of immature SCs, it is possible that higher AMH levels in early life will lead to increased support (by mature SCs) of germ cells in adulthood; thus, AMH levels might be linked to male fertility and infertility.

Females

In females, AMH is secreted by preantral and small antral follicles in the ovary.[12,14] It is first secreted by fetal GCs at 36 gestational weeks,[9] and the serum AMH level at birth is 1.66 ng/mL. A continuous rise was found to persist to about 10 years of age, peaking in adolescence, and then declining with age after the age of 18 years until menopause in a Chinese cohort.[39]

AMH acts to provide feedback inhibition of follicle development at two levels. Firstly, it inhibits recruitment of primordial follicles into the growing pool; and secondly, it reduces the sensitivity of antral follicles to FSH,[40] which is a feedback mechanism of AMH and FSH after menarche. AMH controls the recruitment mechanism of primordial follicle into primary follicles, to regulate the reproductive life span. A high level of serum AMH during adolescence may serve as the first predictor for natural fertility and reproductive life span.[41]

The most accepted role of AMH verified by mouse models is to inhibit the recruitment of primordial (resting) follicles.[12,42,43] There is evidence showing that AMH null mice display an increased recruitment of primordial follicles. Nevertheless, these mice do not have proportionally more preovulatory follicles.[44] Studies have demonstrated that AMH produced by GCs of the growing follicle suppresses development of the primordial follicles.[45,46] In AMH knockout mice, increased FSH-dependent recruitment of small antral follicles and premature exhaustion of the primordial follicle reserve were observed.[47] Furthermore, *in vitro* studies shown the inhibitory effect of recombinant AMH on early human ovarian follicular development *in vitro* by suppressing the initiation of primordial follicle growth.[48] Dynamic changes in murine ovarian follicle numbers and volumes at different reproductive ages in *AMH* gene null mice and controls are shown in Figure 1, based on data from Durlinger et al.[12] The secretion of AMH is independent of gonadotropins,[13,49] so the expression of *AMH* is barely affected by the cyclical fluctuations of gonadotropins (Gn), and its circulating protein level remains relatively stable during the menstrual cycle.[50,51]

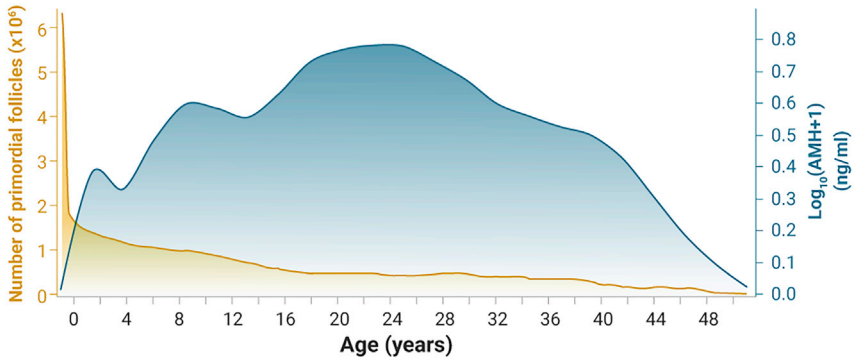

Figure 2. Dynamic Changes in AMH Levels and Changes in the Numbers of Atretic Follicles with Age The figure is based on the studies by Faddy et al.[75] reporting that the number of primordial follicles was 6–7 million during fetal life (around midgestation), approximately 1–2 million at birth, 300,000–500,000 at the start of puberty, and 1,000 at 51 years of age.[75,76] AMH levels are based on the model proposed by Kelsey et al.[77] to predict menopause. Yellow represents number of primordial follicles ($\times 10^6$), while blue represents $\log_{10}$(AMH + 1) (ng/mL).

Although the transcriptional regulation of *AMH* in women remains mostly unclear, there could be common regulatory mechanisms in both sexes. Because *AMH* is regulated by NF-κB in males, is it possible that this factor also regulates *AMH* transcription in females? It is known that NF-κB regulates expression of the androgen, estrogen, glucocorticoid, and progesterone receptors.[29] The possible role of NF-κB in the aforementioned recombinant *AMH*-induced changes to circulating estradiol (E2), progesterone, and testosterone levels needs further investigation. Recent studies using animal models have revealed key underlying mechanisms of AMH actions in females.[43,52] Receptors for AMH are found in the hypothalamus, which suggests that AMH might regulate follicular development through the hypothalamic-pituitary-gonadal (HPG) axis, and that an excess of AMH can induce ovulatory disorders. In addition, AMH was found to inhibit the production of E2 by inhibiting the expression of aromatase.[42,43,53] Conversely, E2 inhibited *AMH* transcriptional activation through estrogen receptor-beta (ERβ) in growing follicles.[54] Normal oocyte development needs an increase in E2 levels, which could explain the dynamic decrease in AMH levels during ovarian stimulation.[55]

DEVELOPMENT OF AMH ASSAYS

Measurements of serum concentrations of AMH have been used along with other measurements, such as for FSH, luteinizing hormone (LH), and E2, for a wide variety of clinical applications.[11,22,56–58] The clinical use of AMH has advantage over other assays because of its relatively stable level across the menstrual cycle.[50,59,60] Nevertheless, recent studies have suggested that there is a considerable amount of variation in the level of AMH across cycles in certain women, which implies a risk of misclassification if the variation is beyond 20%.[61] In addition to biological variability, there have been concerns regarding differences between assays. The major differences arise from calibrators/standards, antibodies, and assay methodology.[62]

The first-generation AMH assays came from Diagnostic Systems Laboratory (Webster, United States) and Immunotech (Oxford, UK) as sandwich ELISAs (both assays are out of market now). The Gen II ELISA by Beckman Coulter (Brea, CA) replaced both of these. In 2013, Ansh Labs LLC (Webster, TX) introduced an ultrasensitive AMH assay using a new pair of antibodies. In 2016, two additional immunoassays were introduced by Beckman Coulter (Access) and Roche (Elecsys, Mannheim, Germany) using automated chemiluminescence platforms. These two automated assays use the same antibody pair as the Beckman Coulter Gen II.

In 2016, Li et al.[63] compared the four AMH assays from Beckman Coulter (Access), Roche, Ansh Labs, and Beckman Coulter (Gen II ELISA) and showed good correlations between these assays, but significantly different AMH values when the four assays were compared on the same serum samples. Nevertheless, all methods demonstrated excellent discrimination of women with polycystic ovarian syndrome (PCOS) from normal ovulatory controls, with areas under the receiver operating characteristic curve being over 0.9.[63] These assays have different analytical performances, such as dynamic range, limit of detection, limit of quantification.

Recently, Ansh Labs introduced a third-generation assay, picoAMH, with more than 10-fold better sensitivity than the previous ultrasensitive AMH assays. This assay was developed to lower the limit of detection to suit the needs for detecting very-low-level AMH in women reaching menopause, in oncofertility studies, and in women with premature ovarian failure. In the United States, the Beckman Coulter Access AMH assay and Roche Elecsys AMH assay were cleared by the Food and Drug Administration (FDA) for use in the assessment of ovarian reserve in women presenting to assisted reproductive technology (ART) clinics. In 2018, the Ansh Labs Menocheck picoAMH assay was cleared by the FDA for use in the determination of menopausal status. Over the past decade, the applications of AMH in clinical practice have been maturing, but standardized AMH tests are still lacking. Internationally standardized assays would provide confidence in cited reference ranges and clinically validated cutoff values. An international standard will support the development of AMH immunoassays that are calibrated to recombinant human AMH.[64]

CLINICAL APPLICATIONS OF AMH

Associations between AMH and Fertility in Females

Fertility is defined as the natural capability of a couple to establish a clinical pregnancy.[65] Any factor affecting the quantity and quality of oocytes or spermatozoa, as well as factors affecting the process of fertilization and embryo implantation, affect human fertility. Ovarian aging is the most important determinant of female fertility.[66] It is established that the age-related decrease in ovarian function is related to the gradual loss of primordial follicles[67,68], when follicular atresia takes place.[69,70] Follicular atresia is a Gn-independent process[71] that starts before birth.

Several lines of evidence derived from clinical and basic science studies collectively support the role of AMH in follicular atresia. By the onset of puberty, 95% (or 1.9 million out of 2 million) of all follicles are lost. AMH is the key regulator that inhibits the default mode of atresia from occurring.[71] Studies reported that AMH levels are not stable during childhood, but rise during infancy and continue during the years leading up to puberty, roughly doubling between ages 4 and 8 years and then reaching a plateau during adolescence. Young girls have more primordial follicles activated before puberty, but, because a Gn releasing hormone-dependent feedback loop is not established, the follicles go to atresia.[72] The highest rate of recruitment of non-growing follicles takes place between birth and 14 years of age.[73] Before entering puberty, around 95% of all primordial follicles undergo atresia,[71] which is induced by considerable granulosa cell apoptosis within the follicle.[74] One function of AMH is to slow the recruitment of primordial follicles,[12,53] so the high level of AMH after puberty might be responsible for the subsequent decreased rate of follicular atresia. The dynamic changes in AMH levels and the numbers of primordial follicles with age are indicated in Figure 2. As we can see, both AMH and primordial follicles decrease with age after sexual maturation, which indicates that AMH is a marker in ovarian aging.

The most accepted predictor for female fertility is ovarian reserve (OR). We have previously established two models, termed AAFA and AFA, for estimating OR. The AAFA model uses four predictors (circulating AMH, the antral follicle count [AFC]; circulating basal FSH, and female age),[4] while the AFA model uses just three predictors (circulating AMH, circulating basal FSH, and age).[3] The main effects of each variable on the AAFA model were

AMH 62.0%, AFC 17.5%, FSH 12.4%, and age 8.1%,[4] while the main effects on the AFA model were AMH 85.2%, FSH 6.8%, and age 2.8%.[3] Ovarian reserve is ranked according to the predicted probability of a poor ovarian response and is further classified into groups A–D according to OR, from adequate to poor, respectively. We further discovered that the clinical pregnancy and live birth rates for women in group D (with diminished OR) were significantly lower than in groups A and B, which indicates decreased female fertility in the population with a diminished ovarian reserve. The use of serum AMH as a potential marker for female fertility might offer several advantages over traditional markers of OR.[4,56,78–84]

Menopause refers to the cessation of menses and the termination of ovarian follicular maturation caused by the reduced production of estrogen and progesterone in the ovary,[85] which leads to complete loss of fertility and many other symptoms. Recently, with recognition of the role of AMH and the development of AMH assays, many studies about predicting the time to the final menstrual period (FMP) have been conducted.[77,86–91] Finkelstein et al.[86] published an excellent study about the importance of AMH over FSH levels in predicting FMP; however, they included only women in their late reproductive periods. Another study, by Bertone-Johnson et al.,[87] included younger women. The blood samples of the participants were collected in 1996–1999, and follow-up was conducted until 2011 to get information about the time to the FMP. Cases of early menopause were women aged less than 45 years and the matched control cases were women who underwent menopause after the age of 45 years, matched 1:1. Matching criteria were based mainly on the women's age at blood sampling (±4 months) and other factors. They discovered significant associations between AMH and the time of menopause, irrespective of smoking habit, adiposity, history of infertility, and menstrual cycle characteristics. However, case control studies are often used to screen risk factors for a certain disease, and such a design means that the time to FMP could not be predicted. In the future, to predict the specific time to FMP in younger women, a cohort study with a large number of women of reproductive age is needed. With the increasing recognition of the role of AMH in ovarian aging and the increasing standardization of AMH kits, the specific time to FMP in younger women should be predictable, which would be beneficial to young women in terms of their plans for childbearing.

Associations between AMH and Fertility in Males

In males, AMH is secreted by SCs[19], which share the same origin as GCs before the initiation of sexual differentiation in early gestation.[92,93] AMH is a well-known proxy for the number of immature SCs.[93] Germ cell numbers in adult testes are closely linked to the numbers of immature SCs produced during perinatal development,[37,38] suggesting an important role for AMH in establishing male fertility. Men exhibit declining serum AMH levels with age after sexual maturity,[17,18,21] which indicates an age-related reduction in SC function. In addition, the function of SCs declines earlier than that for Leydig cells in aging men,[94] which suggests that decreased SC numbers might be an early event of male infertility. Therefore, decreased serum AMH levels could be an early sign of infertility in men.

Although early SC injury can cause a transient increase in AMH, such as in prepubertal patients with Klinefelter syndrome (KS)[95] and in patients with early-onset varicocele[96], over time, severe damage to SCs leads to a decreased serum AMH concentration and impaired fertility. A study of adult men showed that the circulating AMH levels of infertile men were 60% lower than the corresponding control group.[97] Non-obstructive azoospermia (NOA), characterized by the absence of spermatozoa in semen samples resulting from impaired spermatogenesis,[98] directly causes male infertility, and the concentration of serum AMH in such men decreases more significantly than among those with varicocele.[96] An extreme example is in patients with anorchia (loss of fertility), where the AMH concentration is so low that it is undetectable. The above results suggest that, within a certain low concentration range, the lower the serum AMH concentration, the worse the man's fertility.

Fertility problems are frequently encountered in patients affected by disorders of sex development (DSD). AMH, produced by fetal SCs, and testosterone, produced by fetal Leydig cells, are responsible for male genital differentiation.[19,24,99] Dysfunction of either one or both of them may result in DSD. Persistent Müllerian duct syndrome (PMDS) is one kind of DSD; the function of SCs in these patients is severely impaired and these patients are always infertile.[19] The Leydig cell function of patients with PMDS is generally normal,[100] manifested by normal levels of serum testosterone and LH.[100,101] Mutations in the *AMH* gene or its receptor gene (*AMRHII*) account for 88% of the overall PMDS patients[100]; moreover, we cannot rule out the possibility of *AMH* or *AMHRII* mutations in the remaining 12% of patients with idiopathic PMDS because *AMH* or *AMHRII* mutations might be under-detected and the sensitivity and specificity of sequencing can be limited.[100] In patients with *AMH* mutations, very low or undetectable serum AMH levels are detected combined with normal serum inhibin B levels, while, in patients with *AMHRII* mutations, the serum AMH level is normal but serum inhibin B is undetectable.[100,101] To distinguish PMDS from mixed DSD, which is a disorder of both Leydig cells and SCs,[102] no external genital ambiguities, especially the lack of hypospadias, are the main clinical features. In individuals with mixed DSD, subnormal levels of both serum AMH and testosterone and external genital malformations were discovered. If a 46 XY karyotype infant has bilateral nonpalpable testes, a serum AMH test is needed to distinguish anorchia from the situation of bilateral abdominal testes to avoid surgical exploration,[103] and the use of other hormone tests, including those for FSH, LH, inhibin B, and testosterone.[103]

Studies on unilateral undescended testes (UDT) revealed that the undescended testes were smaller than the normally descended testes.[104,105] Given that the SCs account for 75% of testis mass in boys,[106,107] there might be a decline in the number of SCs in cases of UDT. The degree of AMH decrease in boys with UDT (unilateral cryptorchidism) is related to the severity of dysfunction,[108–110] which suggests that impaired function of SCs might be an early event of UDT. Infertility is a long-term concern for such patients,[103] with risks of 30% and 54% in UDT and bilateral cryptorchidism, respectively,[111–115] linked to the duration of testicular exposure to abdominal temperature. Risks of future infertility of 75%–100% were found in boys with bilateral undescended testes in whom no germ cells were found on biopsy.[116] In conclusion, the degree of male infertility caused by UDT is related to the severity of injury to SCs, manifested by the degree of abnormal declines in AMH levels.

AMH IN ART FOR BOTH SEXES

In Females

For women, the most established use of AMH analysis is predicting ovarian response (the number of mature oocytes) during ovarian stimulation.[11,22] AMH cutoff values are recommended by the European Society of Human Reproduction and Embryology (ESHRE)[117] and the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group,[118] to individualize strategies for ovarian stimulation. Recent data have suggested that individualized treatment considering AMH levels contributed to a reduced cost during ART treatment.[119] AMH provides one of the key indicators for individualized counseling and ovarian stimulation. However, there is debate concerning the suitability of the ESHRE and POSEIDON recommendations, and a better model for directing individualized ovarian stimulation is needed in the future.

AMH is highly correlated with AFC, and it is considered to be the best predictive marker for ovarian hyper- or hypo-responses.[10,56,120,121] However, although AMH and AFC are strongly linked, with a correlation coefficient of 0.73 reported by Fanchin et al.,[122] they are not always in a linear relationship. For example, we have established an AAFA model for assessing OR using a poor response of fewer than five oocytes retrieved as the outcome variable, and then ranking the OR according to the predicted probability of a poor ovarian response.[4] We divided the population into 16 subgroups in the order of OR from good to bad. Subgroups 1–3 and 14–16 accounted for the majority, with AMH and AFC levels high or low at the same time, but there were a few groups with an intermediate OR, with high AMH and low AFC (accounting for 14.8%), or low AMH and high AFC (accounting for 4.9%). Another example is that, in patients with hypogonadotropic hypogonadism, the AFC is extremely low because of the extremely low level of FSH, but such young

patients still have sufficient OR, normal AMH levels, and good pregnancy outcomes when receiving ovarian stimulation. The explanation might be that AMH and AFC respond to different stages of follicular development. AMH is mostly secreted by preantral and small antral follicles, which reflects the Gn-independent phase of follicular development,[13] while the AFC is based on follicles of more than 2 mm in diameter, which reflects the early phase of Gn-dependent follicular development. However, when the OR is depleted to a certain threshold, both AMH and AFC will be affected and decrease to near zero.

AMH cutoff points have been used frequently to estimate the OR and predict ovarian responses. However, its sensitivity and specificity are suboptimal.[123,124] Recently, dynamic AMH changes during ovarian stimulation were found to be associated with oocyte yield and pregnancy outcomes,[55] which suggests that the dynamic changes in AMH levels combined with other indicators might provide another choice for predicting ART response, oocyte quality, and pregnancy outcomes. The exact mechanism for the reduced AMH levels during ovarian stimulation remains unclear. A reasonable explanation for the dynamic decrease in AMH levels during ovarian stimulation is that AMH is produced by secondary, preantral, and small antral follicles in the early phase of stimulation and declines as these follicles are recruited into dominant growing follicle cohorts.[125] However, it is unclear whether this decreased AMH level during ovarian stimulation is caused by a decrease in the total number of activated small follicles in response to stimulation or by a decrease in AMH secretion at the single-follicle level. Furthermore, FSH controls the expression of AMH via oocyte-derived factors, such as GDF9 and BMP15, by negative feedback loop.[126] In addition, why is the dynamic decrease in AMH level during ovarian stimulation related to good pregnancy outcome? It has been well documented that AMH contributes to the inhibition of E2 production by suppression of aromatase expression,[42,43,53] and, in return, E2 inhibits the transcriptional activation of *AMH* via ERβ in growing follicles.[54] Thus, it is possible that a sufficient rise in E2 levels during ovarian stimulation needs a decrease in the AMH level. Likewise, a sufficient increase in E2 during pregnancy may be required for a dynamic decrease in AMH levels. One study reported that pregnancies lacking a decline in AMH levels had a higher risk of preterm birth and might require interventional therapies, such as supplemental E2 and progesterone.[127]

In Males

Although AMH analysis has been applied widely in ART-related clinical practice for women, AMH has not been routinely used in the diagnosis and treatment of male infertility. In men, the most promising application appears to be the differential diagnosis of NOA from obstructive azoospermia (OA).[19] Furthermore, serum AMH tests might also contribute to a differential diagnosis between anorchidism and cryptorchidism.[101,128,129] The rationale is similar to that for the differential diagnosis of NOA and OA; that is, AMH is secreted by SCs. If AMH is particularly low and unable to support the steroidogenic function of Leydig cells, the diagnosis is NOA or anorchia; otherwise, OA or cryptorchidism is to be suspected.[19,130]

Because AMH is secreted by immature SCs,[19] and spermatogenesis requires functional SCs, some studies have explored using AMH levels to predict the sperm recovery rate (SRR) of testicular sperm extraction (TESE) or microdissection TESE (MD-TESE) for patients with NOA.[131–134] However, the utility of AMH analysis has been inconclusive in this regard. One core issue might be that it remains unknown to what extent a decline in AMH reflects the complete loss of SC support for spermatogenesis. A multivariate mathematic model combining AMH, inhibin B, testosterone, and other clinical characteristics could be promising for predicting the SRR during TESE/MD-TESE procedures.

AMH AND PCOS-LIKE PHENOTYPES

In Females

PCOS is a common endocrine disorder affecting approximately 6%–20% of women of reproductive age.[135] However, the etiology of PCOS remains complicated because of its heterogeneous characteristics, which include disruption to endocrine, metabolic, psychological, or reproductive functions. Hyperandrogenism can contribute to the pathophysiology of PCOS, supported by the appearance of PCOS-like phenotypes induced by different androgens in animal models,[136,137] but how excessive androgens are produced remains largely unknown. It has been proposed that excessive androgen levels can be induced by insulin resistance and hyperinsulinemia,[138,139] or by the disturbed regulation of kisspeptin.[140–144] However, this hypothesis was not supported by animal models, because no PCOS-like phenotype was induced by manipulating insulin or kisspeptin levels in animal models.[43,145] In 2016, Giacobini and coworkers found that the AMH receptor was expressed in hypothalamic Gn-releasing hormone-producing neurons and AMH was involved in regulating the HPG axis.[52] They proposed that AMH might be responsible for the excessive androgens in patients with PCOS.[52] A model of AMH-induced activation of the HPG axis in PCOS patients is shown in Figure 3. We believe that this research was a breakthrough for the diagnosis and treatment of PCOS.[43,52]

Women with PCOS have elevated serum AMH levels and later age at menopause compared to women without PCOS.[146] In the PCOS women, the high AMH level inhibits the recruitment of primary follicles from the primordial pool and fewer growing follicles but more 2–6-mm non-growing follicles.[147] These 2–6-mm follicles produce highest amount of AMH per follicles. The AMH produced by the pool of non-growing follicles acts as a negative paracrine feedback signal on neighboring primordial follicle initiation.[71]

If AMH represents a significant driving force for PCOS, AMH could provide a potential indicator for its diagnosis, although AMH as a single-index diagnosis for PCOS remains to be established. We believe that a single indicator alone has its drawbacks. For example, AMH levels decrease with age, so older women with PCOS will have lower AMH levels despite exhibiting PCOS symptoms. Thus, we believe that a mathematical model combining AMH and age and other predictors, such as body mass index, might be required for the future diagnosis of PCOS. Age-stratified thresholds for AMH have been reported for the diagnosis of PCOS,[148] and AMH is predicted to replace AFC as a diagnostic indicator for this syndrome.[149]

In Males

It remains unknown whether a PCOS equivalent is present in males. It has been reported that male relatives of women with PCOS exhibit hormonal and metabolic abnormalities, with an increased incidence of early-onset (<35 years old) androgenetic alopecia and an increased prevalence of type II diabetes mellitus and cardiovascular disease,[150,151] which collectively suggest the existence of a male equivalent for PCOS via the inheritance of susceptibility genes. Although similar clinical features of PCOS observed in women have been found in male subjects with male PCOS equivalence syndrome, the exact mechanism of the hormone and metabolic background of these patients has not been clarified.[152] As AMH has been identified to be the driving force for elevated LH, hyperandrogenemia, and ovulatory disorders of PCOS,[153] whether AMH could also be used for predicting or diagnosing the PCOS equivalent in men, to apply early lifestyle interventions to manage the progression of this condition, is worth investigating in the future.

AMH IN CHEMOTHERAPY

In Females

Because of chemotherapeutic damage to follicles, chemotherapy often impairs future reproductive potential, especially OR.[154,155] As mentioned above, AMH is produced by preantral and small antral follicles in the human ovary[12,14] and acts in an FSH-independent manner.[13,14] Patients whose AMH levels were higher before chemotherapy maintained better menstrual cycles after treatment, and they had a higher probability to achieve pregnancy.[156,157] Therefore, for patients receiving chemotherapy, it is important to assess their OR function regularly. We have established two OR models termed AAFA[4] and AFA;[3] and these could be of great importance for the survivors of chemotherapy to assess their OR, predict reproductive life span, and arrange their childbearing planning, and might be useful clinically.

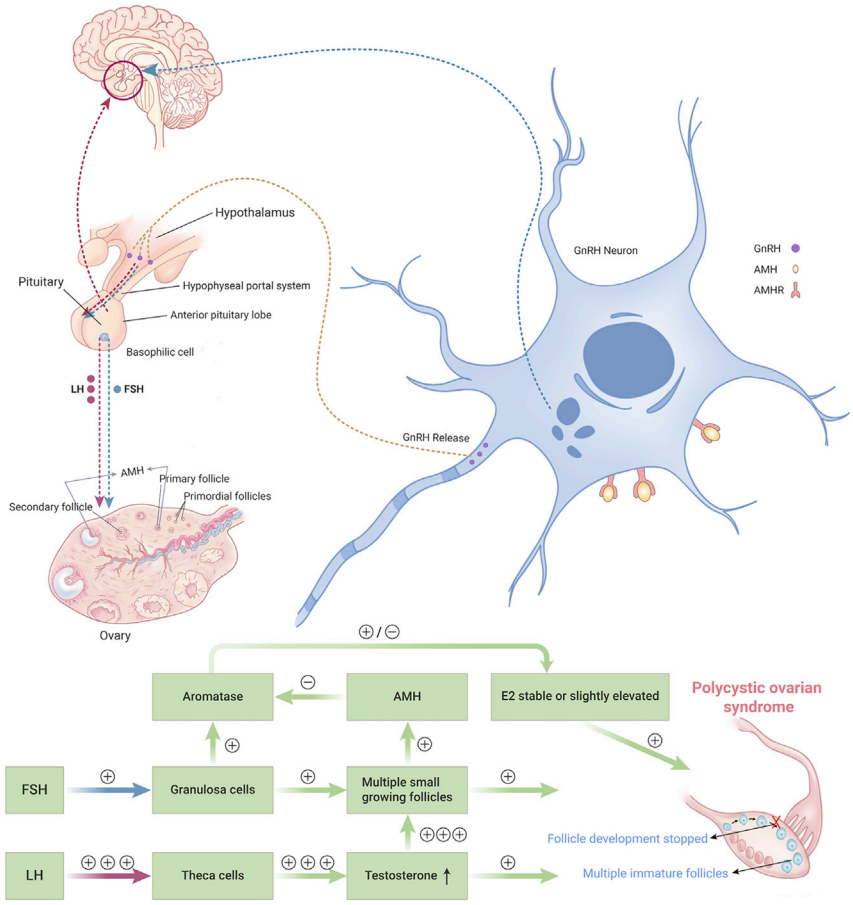

Figure 3. AMH Stimulates the HPG Axis in Females with Polycystic Ovarian Syndrome Here, plus (+) means stimulation, while minus (−) means inhibition.

In Males

Can an AMH-related assessment of fertility before or after chemotherapy be applied to men? For example, could we use dynamic changes to serum AMH levels pre and post chemotherapy to evaluate testicular damage? AMH levels were reported to rise shortly after chemotherapy.[158] Other studies have reported a transient increase in AMH levels after testicular injury. For example, AMH levels were elevated in prepubertal and pubertal boys with varicocele[96] and were significantly decreased in subfertile men with severe varicoceles.[97] In addition, boys with KS (characterized by accelerated germ cell depletion from puberty)[19] exhibit a delay in the puberty-related decline of AMH, followed by a quick reduction of AMH, inhibin B, and testosterone levels in adulthood.[19,95] These examples indicate a compensatory increase in SC function in the early onset of testicular injury and the long-term decrease in SC function caused by severe testicular damage. Thus, it is possible that AMH might not be a good marker for evaluating testicular injury shortly after chemotherapy but could provide a suitable marker for evaluating long-term damage.

AMH IN OVARIAN GC AND TESTICULAR SC TUMORS

SCs and GCs have the same developmental origin during embryogenesis,[93] so SC tumors (SCTs) and GC tumors (GCTs) share common gene expression patterns. As described above, AMH is a marker for ovarian GCs of immature follicles[22] and for immature testicular SCs.[19] Tumor cells are typically undifferentiated, so AMH would be predicted to be highly expressed in both GCTs and SCTs. Indeed, AMH was overexpressed in GCTs,[159] and was not found in other types of gonadal or nongonadal tumors.[160] A combination of AMH and inhibin B treatment was shown to increase the accuracy of differentially diagnosing GCTs from epithelial ovarian carcinomas and endometriomas.[161]

AMH could be used as a potential marker for male SCTs; however, human testicular SCTs are very rare and account for only 0.4%–1.5% of testicular tumors.[162] Therefore, current research on SCTs is mostly in the stage of animal experimentation. Thus, canine AMH levels were higher in an SCT group (22 ng/mL) compared with a normal control group (10 ng/mL), while AMH levels with other types of testicular tumor ranged between these two groups.[163,164] More investigations are needed to determine the diagnostic threshold of AMH for SCTs in humans.

AMH IN THE DIFFERENTIAL DIAGNOSIS OF CONSTITUTIVE PUBERTAL DELAY AND CONGENITAL HYPOGONADOTROPIC HYPOGONADISM IN PREPUBERTAL BOYS

Delayed sexual maturation in prepubertal boys is the common clinical characteristics of boys with constitutive pubertal delay or congenital hypogonadotropic hypogonadism (HH). As is known, the clinical value of serum Gn and testosterone is limited, because of their low serum levels in both conditions. Thus, AMH as a marker of immature SCs is of great potential importance in the differential diagnosis between constitutive pubertal delay and congenital HH.[16,165] Decreased numbers of SCs were reported in patients with congenital HH, accompanied by low levels of serum AMH.[166–168] However, in boys with constitutive pubertal delay, SC function is normal, so the serum AMH levels are also normal.[169]

SUMMARY AND PROSPECTS

AMH is secreted by immature SCs in men[19,20] and GCs of small growing follicles in women,[9–11] where it has important roles in regulating genital tract development and function.[6,7] In male embryos, the production of AMH starts in the eighth gestational week and is responsible for regression of the Müllerian ducts.[15] In female embryos, AMH is not expressed until the 36th week of gestation, when the primordial follicle pool is fully differentiated.[9] The production of AMH in both men and women is shown in Figure 4, which is based on data from several studies.[9,15,17,39]

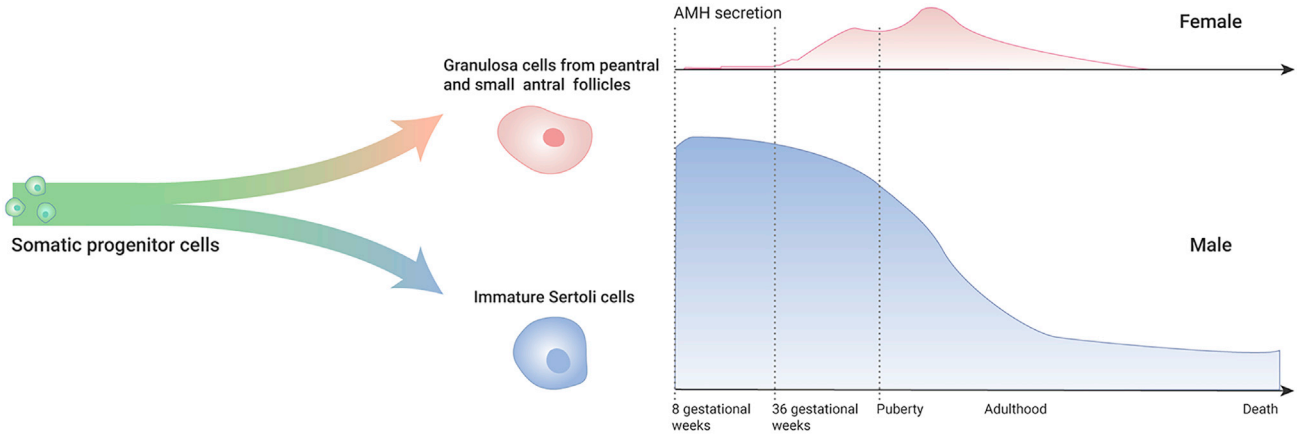

Figure 4. Production of AMH in Both Sexes The production and serum level of AMH throughout the life span in both male and female humans.

AMH levels vary considerably between boys and girls, and this marked sex difference in AMH levels lasts until puberty. Therefore, serum levels of AMH are often used for the diagnosis of DSDs.[19] After sexual maturity, AMH levels become similar in men and women, and an age-related decline in AMH levels is found in both sexes.[17,18,21] As shown in Figure 2, when the primordial follicle pool is depleted at menopause, circulating AMH becomes undetectable. Therefore, AMH is often used to assess fertility and predict ovarian aging. As an indicator of OR, AMH is also often used to predict the ovarian response and to guide recombinant FSH dose during ovarian stimulation in ART.[10,170] AMH levels are positively correlated with the number of small growing follicles in women and immature SCs in men, so AMH might serve as a diagnostic marker for GCTs and SCTs. Serum AMH levels have also been used for predicting and evaluating ovarian damage before and after chemotherapy.

Women with PCOS have elevated serum AMH levels and later age at menopause compared with women without PCOS.[146] In a mice model, excess AMH was reported to be involved in regulating the HPG axis,[52] and excess AMH leads to hyperandrogenemia and anovulation,[43] which may contribute to the onset of PCOS. Thus, AMH is being increasingly recognized as a marker for the diagnosis of this disorder, although a specific cutoff value needs further improvement. The potential application of AMH in cases of male androgenetic alopecia could be another future direction for AMH-related studies in men, because androgenetic alopecia is potentially the equivalent of PCOS.

Studies on the clinical application of AMH in adult men are limited. However, based on the homology between SCs in men and GCs in women, it has been suggested that AMH might provide a valuable indicator for several male infertility-related disorders. For example, the absence of AMH in adult men indicates the absence of functional testicular tissue and could provide a differential diagnosis between NOA and OA in men or for the differential diagnosis between anorchia and cryptorchidism in boys.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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