Role of Anti-Müllerian Hormone in Male Reproduction and Sperm Motility

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Abstract

Anti-Müllerian hormone (AMH) is secreted by Sertoli cells and is responsible for the regression of Müllerian ducts in the male fetus as part of the sexual differentiation process. Serum AMH concentrations are at their lowest levels in the first days after birth but increase after the first week, likely reflecting active Sertoli cell proliferation. AMH rises rapidly in concentration in boys during the first month, reaching a peak level at ~6 months of age, and it remains high during childhood, then they will slowly decline during puberty, falling to low levels in adulthood. Serum AMH measurement is used by pediatric endocrinologist as a specific marker of immature Sertoli cell number and function during childhood. After puberty, AMH is released especially by the apical pole of the Sertoli cells toward the lumen of the seminiferous tubules, resulting in higher levels in the seminal plasma than in the serum. Recently, AMH has received increasing attention in research on male fertility–related disorders. This article reviews and summarizes the potential contribution of serum AMH measurement in different male fertility–related disorders.

Keywords
- anti-Müllerian hormone
- male infertility
- sperm motility

Anti-Müllerian hormone (AMH) is secreted by Sertoli cells in the testes of men. The recent establishment of reference range values for serum AMH in both boys and men could enhance understanding of its physiological implications in gonadal development and its variations during puberty.[1,2]

Interestingly, pediatric endocrinologists exploit blood AMH levels to assess the presence and functionality of testicular tissue in various pathological situations observed in infants and children. Meanwhile, in adult men, physicians specializing in male reproduction are investigating its potential use as a marker of male fertility. However, there is currently limited consideration given to the use of this marker in male infertility. This review aims to explore the utility of AMH as a biomarker of testicular function in different situations of male infertility related to gonadal disorders.

Role of AMH in Physiological Conditions

Biomolecular Characteristics

AMH is a dimeric glycoprotein that belongs to the transforming growth factor-β superfamily. The AMH gene was first sequenced and cloned in mammals in 1986.[3,4] The AMH gene shows remarkable conservation throughout evolution and has been identified in nearly all mammals, as well as in chickens, reptiles, marsupials, zebrafish, and amphibians.[5]

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The human AMH gene is 2.8 kb long and is located on chromosome 19p13.3. It contains five exons; the 3′ end of the fifth exon encodes the bioactive C-terminal domain.[4,6]

AMH binds to its exclusive AMH type II receptor (AMH-R2), which has been shown to interact with the type 1 receptor serine/threonine kinases ACVR1 (activin A receptor, type 1), BMPR1A (bone morphogenetic protein receptor, type 1A), and BMPR1B (bone morphogenetic protein receptor, type 1B).[3,7,8] Once AMH binds the complex formed by AMH-R2, ACVR1, BMPR1A, and BMPR1B, it leads to the phosphorylation of SMAD1/5/8 proteins, which are translocated to the nucleus and are involved in the regulation of gene expression.[9,10]

AMH and Gonadal Differentiation

At the 7th week of gestation, the undifferentiated gonad arising from the urogenital ridges differentiates into the testicular parenchyma. This differentiation into the testicle is determined by the 46,XY karyotype, the presence of SRY, and other genetic factors, such as SOX9 and SF1 (►**Fig. 1**).

Once the gonad is differentiated, Sertoli cells (cells supporting subsequent spermatogenesis) and Leydig cells (se-

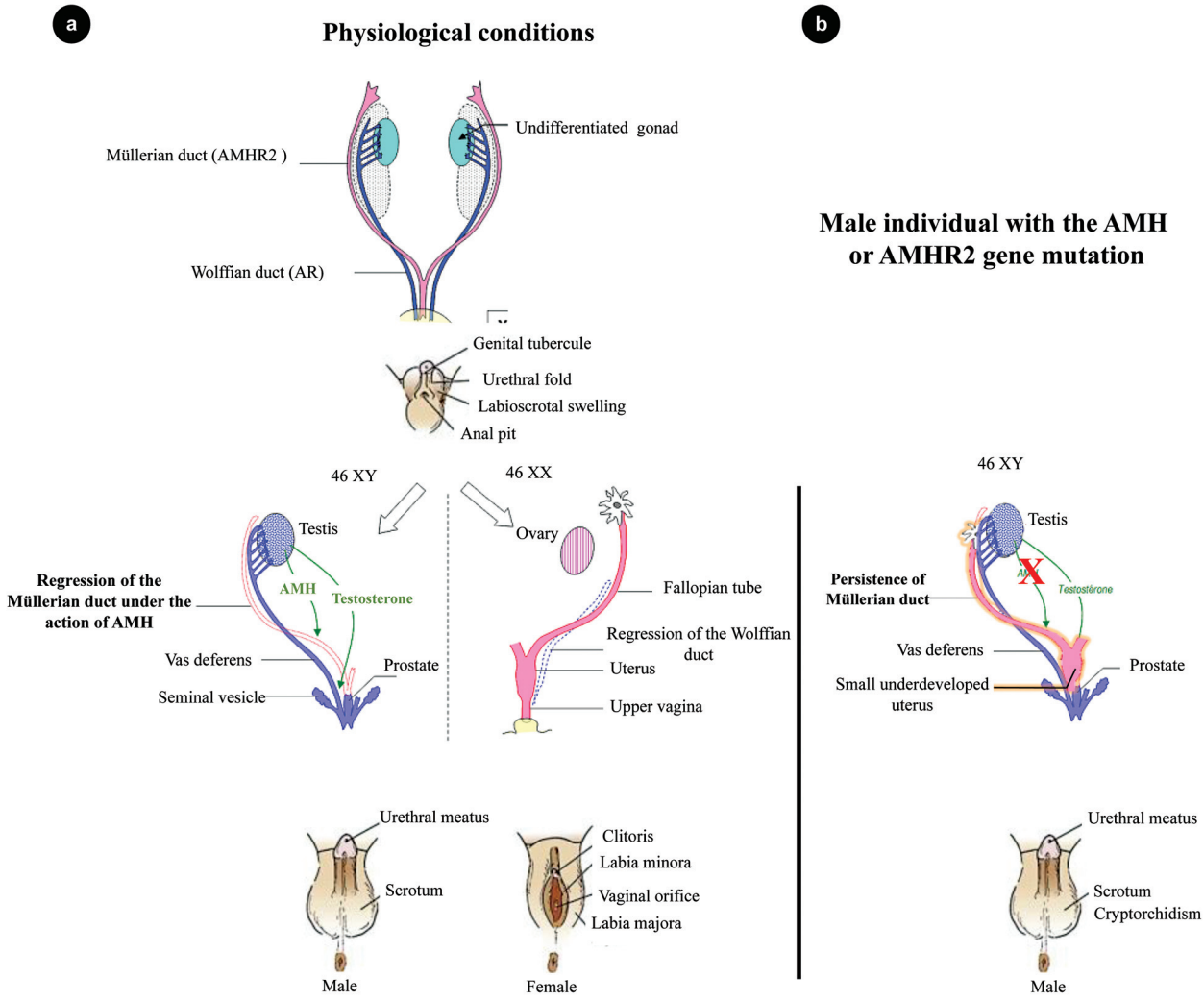

Fig. 1 Development of internal and external genitalia in male and female fetuses. The reproductive tracts of both females and males originate from the same embryonic tissues. The gonads and internal and external genitalia begin as bipotential tissue. (**a**) In male fetuses, under the action of testosterone (produced by Leydig cells), the mesonephric ducts (Wolffian ducts) develop to form the primary male genital ducts. They give rise to efferent ductules, the epididymis, vas deferens, and seminal vesicles. However, paramesonephric ducts (Müllerian ducts) degenerate in the presence of AMH (produced by Sertoli cells in the testes). There are no Leydig cells in the female fetus that produce testosterone. In the absence of testosterone, the Wolffian ducts degenerate. The absence of AMH permits the development of Müllerian ducts. The cranial part becomes the fallopian tubes, the horizontal part becomes the fallopian tubes, and the caudal part fuses to form the uterus, cervix, and upper one-third of the vagina. The lower two-thirds of the vagina are formed by the sinovaginal bulbs (derived from the pelvic part of the urogenital sinus). (**b**) Mutations in AMH or its receptor AMHR2 gene lead to the absence or dysfunction of the AMH signaling pathway, which is responsible for persistent Müllerian duct syndrome. Male patients with persistent Müllerian duct syndrome are born with a persistent Müllerian duct derivative, revealed as undescended testes (cryptorchidism), and the presence of a small underdeveloped uterus. AR, androgen receptor; AMHR2, AMH receptor.

creting testosterone) appear. At the 8th week of gestation, AMH is secreted by immature Sertoli cells and is responsible for the regression of the Müllerian ducts in the male fetus during the sexual differentiation process (►**Fig. 1**).[5]

Experimental studies in mice that induced overexpression or disruption of the AMH pathway have contributed to the understanding of the mechanisms underlying the regression of the Müllerian ducts.

Overexpression of AMH in transgenic female mice was associated with a lack of uterus and oviducts. Homozygous knockout of the AMH gene, SOX9, or SF1-response elements on the AMH promoter in male mice was associated with persistent Müllerian derivatives, but with normal male Wolffian duct derivatives and external genitalia and sperm production.

A preclinical study showed that Müllerian duct regression requires activation of the β-catenin pathway in Müllerian duct mesenchymal cells. The AMH signaling pathway activates the expression of multiple Wnt genes, which are implicated in the regulation of β-catenin degradation. When Wnt binds to its receptors, it inhibits the serine/threonine kinase GSK-3, leading to the accumulation of β-catenin and its translocation to the nucleus. In the nucleus, β-catenin activates the expression of Osterix genes, which are involved in apoptosis and Müllerian duct regression.[11]

During the initial stages of fetal development, AMH expression is triggered by the SOX9 gene and enhanced by SF1 and WT1, without being influenced by gonadotropic regulation.[12,13] The testosterone secreted by Leydig cells and not AMH is involved in the development of both external (masculinization of the genital ridges and urogenital sinuses) and internal (Wolffian duct structures) genital organs (►**Fig. 1**).

AMH and Gonadal Maturation

Serum AMH Variations from Neonatal Period to the Puberty

At birth, gonadotropin, testosterone, and AMH levels are transiently low. Minipuberty consists of the neonatal activation of the hypothalamic–pituitary–gonadal (HPG) axis, mainly in the first 6 months in boys (►**Fig. 2a**). An increase in gonadotropins induces gonadal activation. Consequently, testosterone levels rise in boys with peak levels at 1 to 3 months of age, resulting in penile and testicular growth.[14] After the third month of age, serum testosterone concentrations declined following LH levels toward the age of 6 months. Subsequently, the HPG axis remains quiescent until puberty by mechanisms that remain elusive.

The Sertoli cell–specific peptides inhibin B and AMH increase from the first week of birth, likely reflecting active Sertoli cell proliferation.[15] The increase in serum AMH levels is related to follicle-stimulating hormone (FSH)-induced Sertoli cell proliferation and the activation of AMH gene transcription through a pathway mediated by cAMP.[16] Serum AMH concentration rises rapidly in boys during the first

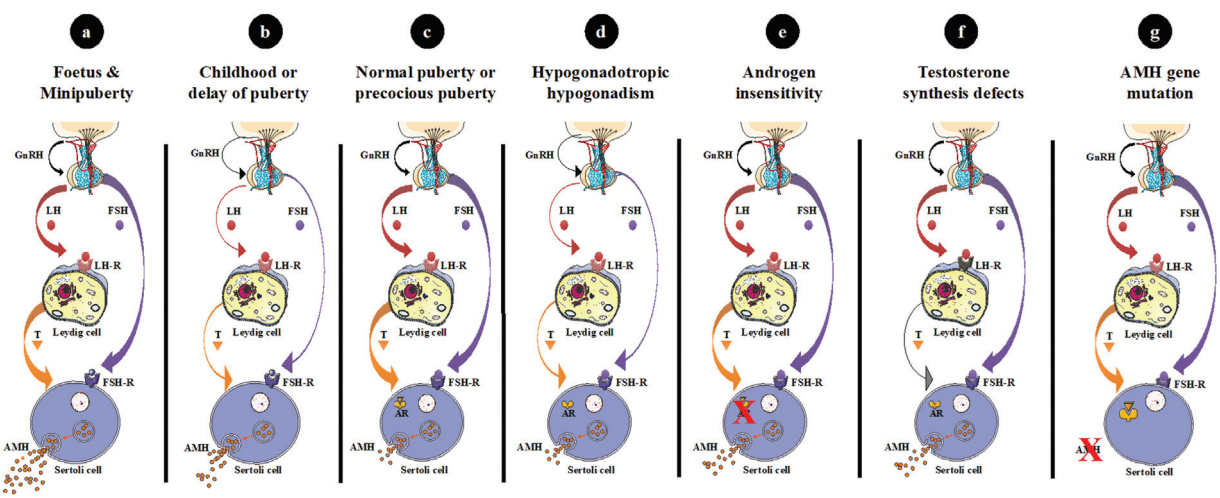

Fig. 2 Regulation of testicular AMH production by follicle-stimulating hormone (FSH) and testosterone under physiological and pathological conditions. FSH stimulates and testosterone inhibits AMH expression in Sertoli cells; however, basal AMH production is independent of the action of gonadotropins or androgens. (**a**) In the fetal period and during minipuberty, the hypothalamic–gonadotrope axis is active. FSH stimulates AMH expression, whereas testosterone cannot inhibit it, because Sertoli cells do not express the androgen receptor. (**b**) During childhood, and in boys over 14 years of age with constitutional delay of puberty, the hypothalamic–gonadotrope is "quiescent," resulting in stable blood levels and basal AMH production. (**c**) In boys with normal or precocious puberty, the increase in intratesticular androgen concentration inhibits AMH expression, which overrides FSH stimulation, resulting in a decrease in blood AMH levels. (**d**) Basal AMH production was observed in individuals with hypogonadotropic hypogonadism, with no further FSH stimulation or testosterone inhibition. (**e** and **f**) In patients with androgen insensitivity syndrome or with testosterone synthesis defects, we observed only the effect of FSH stimulation on AMH expression, which cannot be antagonized by testosterone, resulting in high AMH production in infancy, pubertal age, and in adults. (**g**) In individuals with a mutation in the AMH gene, there was no basal production of AMH, and there was no effect of FSH stimulation. AR, androgen receptor; FSH-R, FSH receptor; LH-R, LH receptor; T, testosterone.

month, reaching a peak level at ~3 to 6 months of age (►**Fig. 2a**).[17] Notably, the increased levels of androgens in the testes during the fetal period and early postnatal life were unable to downregulate the expression of AMH because Sertoli cells do not express the AR during that timeframe (►**Fig. 2a**).

Subsequently, serum gonadotropin concentration decreases again, resulting in a decrease in testicular testosterone secretion. Conversely, Sertoli cells remain intensely active; they proliferate, resulting in an increase in testis size from ~0.5 cm^3, in the first year of life, to 1.5 cm^3 at 10 years of age.[18,19] Therefore, the circulating AMH levels remain high during childhood. Interestingly, because AMH is exclusively secreted into circulation by Sertoli cells, it is considered one of the most useful markers for studying testicular function during the prepubertal period in male children (►**Fig. 2b**).[20]

The onset of puberty triggers the progressive activation of the HPG axis, leading to a rise in intratesticular testosterone and a subsequent decrease in serum AMH levels.[2] This decrease was mediated by the expression of a functional androgen receptor (AR) in human Sertoli cells (►**Fig. 2c**).[21] The downregulation of AMH expression mediated by androgens occurs concomitantly with the appearance of meiotic germ cells in the seminiferous tubules, indicating Sertoli cell maturation.[22–24] Accordingly, serum AMH level is a good marker of androgen action in the testis upon the onset of puberty.

Interestingly, in patients with central precocious puberty and in gonadotropin-independent precocious puberty, as observed in boys with McCune-Albright syndrome, the increase in androgen levels is clearly responsible for AMH downregulation independent of gonadotropin levels (►**Fig. 2c**).[25] In fact, the decrease in blood AMH concentration reflects an increase in intratesticular and not necessarily circulating serum testosterone levels, as observed in the earliest stages of puberty.

On the contrary, in patients with untreated congenital hypogonadotropic hypogonadism (HH), serum AMH levels increased upon administration of recombinant FSH due to the FSH-induced proliferation of Sertoli cells.[26] However, additional treatment with human chorionic gonadotropin (hCG) results in a decline in AMH levels related to the hCG-induced increase in testosterone levels, which inhibits AMH that overrides FSH-initiated AMH transcription.[26] Conversely, the administration of exogenous testosterone did not result in a decrease in AMH concentrations. This finding suggests that intratesticular testosterone levels remain low.[26]

In Adults

In adult males, spermatogenesis is under the control of FSH and LH. FSH acts directly on Sertoli cells, and LH induces testosterone production after Leydig cell stimulation. Intratesticular testosterone acts through a paracrine mechanism on AR expressed by target cells located in the seminiferous tubules.[12,13,15] In adults, Sertoli cells express AR and also AMH-R 2, suggesting an autocrine effect of AMH. In cases of infertility, in the absence of an androgen-inhibitory effect, FSH can increase testicular AMH secretion in adult men.[26] Additionally, paracrine effects of AMH on Leydig cells and adult germ cells have been reported, as AMH directly inhibits Leydig cell differentiation and steroidogenesis, and might be involved in sperm motility.[27] AMH-R2 has also been detected in the prostate, lungs,[28,29] and several other organs, including the brain and the pituitary.[1,30,31] Recently, we reported that AMH-R2 is expressed in human gonadotroph cells and spermatozoa.[1] This finding suggests that the biological effects of AMH are much broader than previously thought.

AMH in Pathological Conditions

Clinical Phenotype of Male Individuals with Sex Development Disorders Related to a Mutation in AMH or Its Receptor AMH-R2 Gene

In males, genital differentiation is driven by two hormones, testosterone and AMH, which are produced by fetal Leydig and Sertoli cells, respectively. The expression of AMH is responsible for the regression of fetal Müllerian ducts (►**Fig. 1**). However, testosterone secretion maintains Wolffian ducts and contributes to the virilization of the external genitalia.[32]

Disorders of sex development in males may result from defects in the signaling of AMH, testosterone, or both hormones.

Mutations in AMH or its AMH-R2 gene lead to the absence or dysfunction of the AMH signaling pathway, which is responsible for persistent Müllerian duct syndrome (►**Figs. 1b** and **2g**). Male patients with persistent Müllerian duct syndrome are born with a persistent Müllerian duct derivative, revealed as undescended testes (cryptorchidism), and the presence of a small underdeveloped uterus.[33] Various mutations in AMH and its receptor AMH-R2 have been reported in ~88% of male individuals with cryptorchidism and persistent Müllerian duct syndrome.[33]

The absence of external genital ambiguity is the main feature of male individuals with persistent Müllerian duct syndrome that distinguishes it from mixed gonadal dysgenesis, which is an early-onset complete type of sex development disorder with fetal hypogonadism resulting from dysfunction of both Leydig and Sertoli cells.[13]

Infertility Related to Congenital Gonadal Disorders

AMH is a reliable biomarker that can be used from neonatal age. Unlike serum inhibin B, which cannot discriminate between ovarian and testicular tissues, serum AMH could be very helpful for pediatric endocrinologists.

Serum AMH is useful for the following purposes:

- Detect the existence of testicular tissue in the event of a rather high value.
- Distinguish between congenital disorders affecting whole testicular differentiation (gonadal dysgenesis) and ovarian gonadal tissue differentiation in the event of a rather low serum AMH value.

However, serum AMH cannot be used as the only biological marker to assign a child with disorders of sex development, but is used concomitantly with other markers, such as

SRY research, karyotype, and blood testosterone concentrations.[34] In early childhood, the secretion of AMH by Sertoli cells remains high and independent of gonadotropin stimulation. Therefore, measuring gonadotropins may not provide useful information. For boys with gonadal dysgenesis or disorders of sex development, measuring serum AMH can help assess the state of the testicular parenchyma, particularly Sertoli cell function, during childhood, puberty, and adulthood.

Reproduction of Adult Men with a History of Cryptorchidism

The descent of the testis from a temporary intra-abdominal site during fetal life to the permanent scrotal location after birth is crucial for spermatogenesis in mature testes. The etiology of undescended testis or cryptorchidism is still surrounded by much controversy.[35]

Cryptorchidism is one of the most common congenital malformations in males, with a prevalence of 1.6 to 5.7%.[36] In patients with a history of cryptorchidism, the risk for infertility and testicular cancer is highly increased.[35,37,38] A measurable value of AMH in a boy with bilateral cryptorchidism is predictive of undescended testes, whereas an undetectable value is strongly suggestive of anorchia.

Unilateral cryptorchidism is associated with increased risk of infertility in adulthood. Up to 30% of men with a medical history of surgery in childhood for unilateral cryptorchidism are likely to be subfertile later in life. Furthermore, the prevalence of infertility is more important and close to 54% in cases of surgery's history for bilateral cryptorchidism.[20,39,40] Several studies have reported that serum AMH concentrations are lower in healthy boys with cryptorchidism than in their age-matched counterparts with palpable testes.[41–43] In men with a history of operated or persistent cryptorchidism, serum AMH values were positively correlated with testicular volume and sperm parameters and negatively correlated with serum FSH levels. Accordingly, this biological marker can be used as a measure of the number and functionality of Sertoli cells.[44] However, to date, there is no evidence that serum AMH measurement can help predict a positive result for fertility assessment (by ejaculation or surgical exploration) in these conditions, except for AMH or AMH-R2 gene mutations.

Reproduction in Adult Men with a History of Isolated Hypospadias or a More Marked Variation in Genital Development

Hypospadias observed at birth may be an indicator of a gonadal dysfunction, especially if it is "severe" (i.e., middle or posterior) or if it is associated with other abnormalities of genital development (cryptorchidism, small penis size, anomaly of the internal genital organs.) Therefore, male reproductive abnormalities can be observed in adulthood, with gonadal dysfunction.

In the case of hypospadias, the findings in adulthood on reproductive parameters are the same if the hypospadias are isolated or associated with a more severe variation in genital development during childhood.[45,46]

Currently, none of the above studies have evaluated or used AMH levels as a male reproductive marker. We suppose that if these clinical situations are related to gonadal dysfunction, then serum AMH values in this population, such as serum FSH levels and sperm parameters, may be altered. However, this remains to be confirmed. Monitoring serum AMH levels in these boys during childhood and puberty makes it possible to inform and guide young people at the end of puberty on whether they wish to explore or even preserve fertility.

Discriminating Congenital Hypogonadotropic Hypogonadism from Pubertal Delays

Constitutional pubertal delay and congenital HH share similar clinical phenotypes of delayed sexual maturation in prepubertal boys. Gonadotropin and testosterone serum concentrations are very low in prepubertal childhood and hence have little clinical significance. However, AMH, which is a good marker of Sertoli cells, is of great importance in the differential diagnosis of congenital HH and constitutional pubertal delay.[34]

Congenital HH affects the development of Sertoli cells, as severe gonadotropin deficiency leads to a decreased number of Sertoli cells and, therefore, low serum AMH and inhibin B levels.[47–49]

The early pubertal increase in serum inhibin B concentration is tightly associated with a decrease in serum AMH levels and, therefore, may reflect the differentiation of Sertoli cells mediated by the increase in intratesticular androgen concentrations. Therefore, the assessment of AMH levels may predict the clinical onset of puberty.

Interestingly, low serum AMH levels and prepubertal testicular volume in patients may be of clinical value in the early diagnosis of congenital HH. Very low serum AMH levels in children with profound congenital HH are associated with impaired Sertoli cell population development.[47,48]

Childhood with constitutional delay of puberty had an eugonadal state of Sertoli cells, and serum AMH levels were within the normal range for prepubertal boys.[48]

In untreated patients with HH, recombinant FSH treatment induces a progressive increase in serum AMH levels, whereas the addition of hCG treatment induces a decrease in serum AMH concentrations owing to the hCG-induced increase in intratesticular testosterone levels, which induces the inhibition of AMH transcription. However, the administration of exogenous testosterone did not result in a decrease in serum AMH concentration, which may be related to the low intratesticular testosterone levels in patients with congenital HH.[26]

Secretory or Nonobstructive Azoospermia

Azoospermia is a major cause of male infertility with a prevalence of ~1% in the male population. It is defined as the complete absence of spermatozoa in the ejaculate.

Nonobstructive azoospermia (NOA) is defined as the absence of sperm in the ejaculate due to failure of spermatogenesis, and is the most severe form of male infertility. NOA is diagnosed in ~10% of infertile men. The etiology of NOA is

either intrinsic testicular impairment or inadequate gonadotropin production.

Klinefelter Syndrome (47,XXY)

Klinefelter syndrome is a primary hypogonadal disorder of genetic origin, and it is characterized by the presence of an X-chromosome polysomy in male patients. Klinefelter syndrome is characterized by accelerated germ cell depletion and occurs in ~10 to 12% of NOA men.[50] In boys with Klinefelter syndrome, circulating AMH concentrations are within the reference range until mid-puberty, when severe impairment is observed with a decrease in serum AMH concentrations much lower than that in healthy boys,[51,52] and serum AMH levels decline to subnormal concentrations in adults. Therefore, reduction in serum AMH levels appears to be a specific feature of testicular failure associated with Klinefelter syndrome.[51,53] Furthermore, we previously reported that the serum concentration of AMH could be predictive of sperm retrieval results in testicular sperm extraction in a small cohort of nonmosaic KS patients.[54]

Varicocele

Varicocele is the abnormal dilation of the veins of the pampiniform plexus resulting from altered venous drainage. It is a common pathology in the general population (15–20% of men) and is considered one of the main causes of male infertility.[55] The impact of varicocele on spermatogenesis is progressive, and consequently decreases male fertility over time. Varicocele impairs testicular blood supply, resulting in a reduction in oxygenated blood and nutrient supply to the local testis, which causes a decline in the quality and quantity of spermatogenesis. In addition, expansion of the veins induces dysfunction of the testicular nervous plexus, which regulates testicular temperature. Higher temperatures can contribute to testicular atrophy and infertility.[56]

AMH serum levels were reported to be higher in prepubertal boys (Tanner 1 Stage) with varicocele than in controls. A similar profile was observed during puberty (Tanner stages III, IV, and V). Likewise, inhibin B serum concentrations were higher in pubertal boys with varicocele than in controls.[57] Alteration of gonadal hormonal serum profiles in boys with varicocele may reveal an early abnormality in the regulation of Sertoli cell function. AMH serum concentration levels in adult subfertile men with varicocele were reported to be lower, as were serum inhibin concentrations, compared with control individuals.[58,59] These data are consistent with other studies showing elevated serum FSH levels in adult men with varicocele.[42] These modifications are a reflection of Sertoli cell alteration and dysfunction, contributing to sperm alterations.

Iatrogenic Impact on Fertility after Cancer Treatment

Current data show that both radiotherapy and chemotherapy primarily affect germ cells of the testis, whereas Leydig cells are less affected.[60,61] We previously reported that serum levels of both the Sertoli cell markers AMH and inhibin B were lower in individuals with cytotoxic spermatogenic failure (related to radiotherapy or chemotherapy). Furthermore, we observed that these individuals had a low sperm retrieval rate during testicular sperm extraction.[54] A few clinical studies have explored the direct effects of cancer treatments on Sertoli cell function. Two studies, including a few patients treated with polychemotherapy or hematopoietic cell transplantation, showed that serum AMH levels were below normal with age.[62,63]

Obstructive Azoospermia

Obstructive azoospermia (OA) is associated with mechanical obstruction of the seminal tract, which may be congenital or may be caused by infection or trauma. Usually, spermatogenesis is largely preserved in OA patients. We previously reported that serum AMH concentrations in individuals with OA were similar to those in healthy men.[54] In addition, some previous studies have reported that no significant differences in serum AMH levels were found in cases of oligospermia and OA compared with infertile individuals with normal sperm concentrations.[64,65]

AMH and Sperm Parameters

The association between serum AMH concentrations and semen quality has been addressed previously in both preclinical studies and in humans, but the results are conflicting.

Interestingly, blood AMH concentrations were found to be positively correlated to sperm concentration, total sperm count, and progressive sperm motility.[1,44,66,67] Nevertheless, some authors do not find a significant correlation between blood AMH levels and semen characteristics.[68–71] A negative association between serum AMH levels and total sperm motility and progressive motility was observed in dogs.[72]

Previous studies evaluating seminal plasma AMH have described a significant positive relationship between seminal plasma AMH levels and sperm concentration, total sperm count, and progressive sperm motility.[67,71,73,74] However, no correlation was observed in other studies.[75,76]

The mechanisms underlying the role of AMH in the regulation of sperm motility are unknown. After puberty, AMH is secreted bidirectionally by Sertoli cells, apically into the lumen of the seminiferous tubules, and basally into blood circulation. The seminal fluid concentrations of AMH can be up to 10 times higher than the serum levels.[76,77]

Interestingly, two studies reported that AMH can improve human sperm motility.[78,79] The expression of AMH-R2 in human spermatozoa, which we recently documented, may support this hypothesis. AMH-R2 was found to be highly expressed in the middle piece of human ejaculated spermatozoa (►**Fig. 3**),[1] which is responsible for the initiation of sperm motility.

Two previous studies have reported interesting observations. In a previous study, the authors examined the effects of recombinant human AMH on fresh and cryopreserved spermatozoa and found significantly higher motility in both fresh and cryopreserved spermatozoa after 5 and 22 hours of incubation with AMH. However, the effects of AMH are suppressed by co-incubation with anti-AMH antibodies.[78] In another study, seminal plasma concentrations of AMH

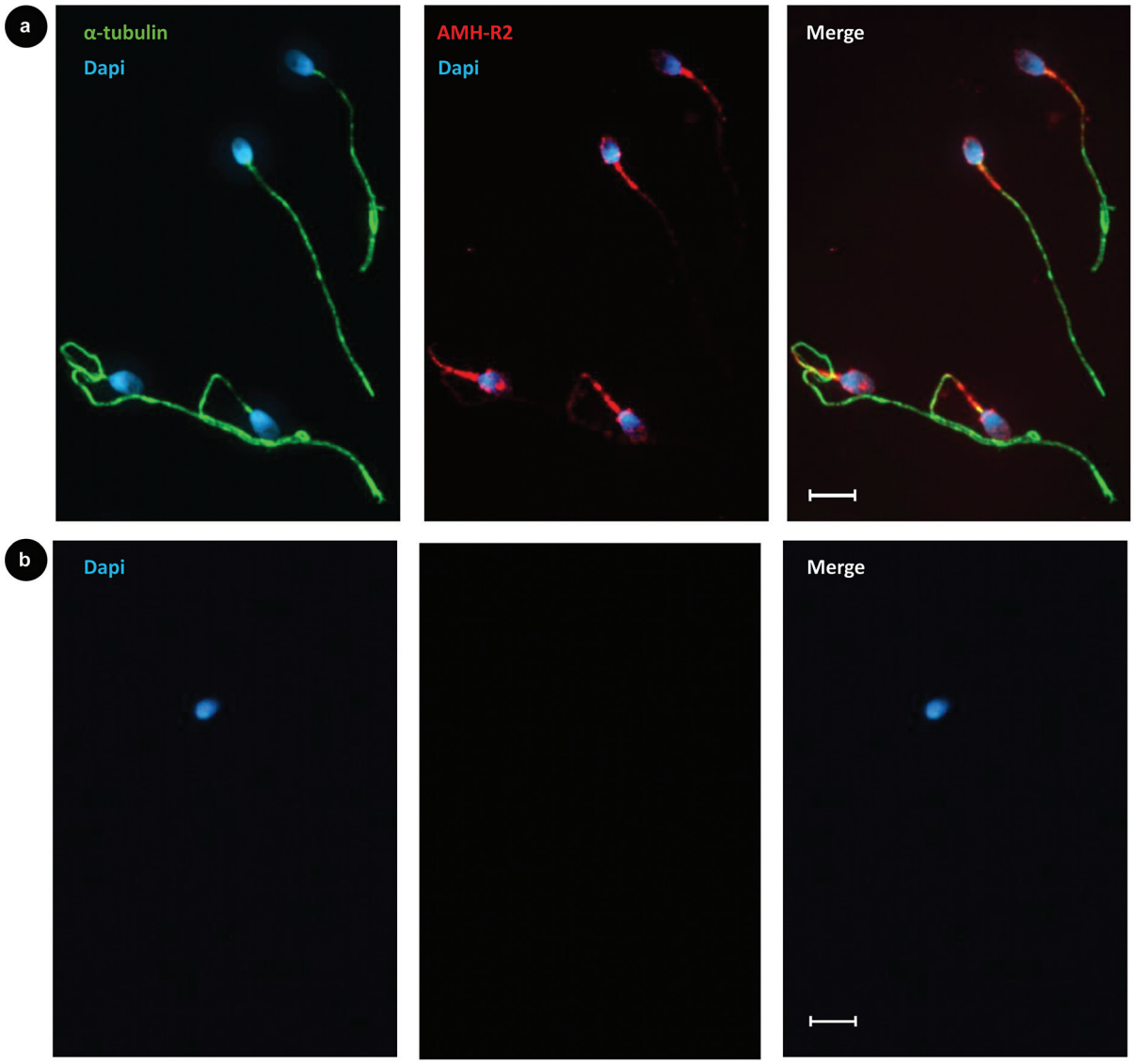

Fig. 3 Immunolocalization of anti-Müllerian hormone type II receptor (AMH-R2) with α-tubulin in human ejaculated spermatozoa. (**a**) In human ejaculated spermatozoa, AMH-R2 (red; anti-AMH-R2 antibody) is highly expressed in the middle α-tubulin (green) is expressed in the middle piece, and tail. (**b**) Absence of staining without primary antibodies. Only secondary antibodies and 4,6-diaminopyrimidine, 2-pyrolylindole nuclear counterstaining (blue) were used. Scale bars = 5 µm.

were suggested as predictive markers for sperm motility recovery after cryopreservation in asthenozoospermic men.[79] However, these two studies had some limitations, such as the low number of individuals included and the use of visual evaluation to study sperm motility.

Testicular Senescence

Testicular aging is associated with loss of germ cells and impaired spermatogenesis. Additionally, the spermatogenesis microenvironment, composed of Sertoli and Leydig cells, displays significant alterations with age, such as decreased number, morphological variations, organelle aging, abnormal hormone secretion, and blood–testicular barrier defects.[80] Serum AMH concentrations were reported to be reduced with increasing age[2,81,82] and were negatively correlated with serum FSH and LH levels, which suggests that decreased serum AMH levels represent an age-related reduction in Sertoli cell function.

Conclusions

AMH is a key factor indispensable for the normal development of male genitals. Serum AMH determination is used by pediatric endocrinologists as a specific marker of immature Sertoli cell number and function during childhood. A measurable value of AMH in a boy with bilateral cryptorchidism is predictive of undescended testes, whereas an undetectable value is highly suggestive of anorchia, testicular dysgenesis, or ovaries. In adult men, physicians specializing in male reproduction try to understand its potential use as a marker of male fertility.

Our recent research highlights a new potential physiological function of blood-circulating AMH in the negative

feedback regulation of FSH secretion, probably through the modulation of gonadotropic cell activity in the pituitary gland. In addition, the expression of AMH-R2 in human spermatozoa could be indicative of the potential role of seminal AMH in the regulation of sperm motility. However, further studies are required to confirm these hypotheses.

Unlike serum inhibin B, serum AMH measurement could be a good indicator of testicular failure for both exocrine and endocrine functions, which can help practitioners monitor testicular function and assist in decision-making regarding the time to explore fertility or perform testicular sperm extraction in young adult men with a medical or surgical history that can cause testicular damage and affect their function.

Authors' Contributions

I confirm that all authors participated in writing the manuscript and have seen and approved the submitted version.

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Conflict of Interest

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References

1 Benderradji H, Barbotin AL, Leroy-Billiard M, et al. Defining reference ranges for serum anti-Müllerian hormone on a large cohort of normozoospermic adult men highlights new potential physiological functions of AMH on FSH secretion and sperm motility. J Clin Endocrinol Metab 2022;107(07):1878–1887
2 Aksglaede L, Sørensen K, Boas M, et al. Changes in anti-Müllerian hormone (AMH) throughout the life span: a population-based study of 1027 healthy males from birth (cord blood) to the age of 69 years. J Clin Endocrinol Metab 2010;95(12):5357–5364
3 di Clemente N, Wilson C, Faure E, et al. Cloning, expression, and alternative splicing of the receptor for anti-Müllerian hormone. Mol Endocrinol 1994;8(08):1006–1020
4 Cate RL, Mattaliano RJ, Hession C, et al. Isolation of the bovine and human genes for Müllerian inhibiting substance and expression of the human gene in animal cells. Cell 1986;45(05):685–698
5 Barbotin AL, Peigné M, Malone SA, Giacobini P. Emerging roles of anti-Müllerian hormone in hypothalamic-pituitary function. Neuroendocrinology 2019;109(03):218–229
6 Cohen-Haguenauer O, Picard JY, Mattéi MG, et al. Mapping of the gene for anti-Müllerian hormone to the short arm of human chromosome 19. Cytogenet Cell Genet 1987;44(01):2–6
7 Baarends WM, Uilenbroek JT, Kramer P, et al. Anti-Müllerian hormone and anti-Müllerian hormone type II receptor messenger ribonucleic acid expression in rat ovaries during postnatal development, the estrous cycle, and gonadotropin-induced follicle growth. Endocrinology 1995;136(11):4951–4962
8 Mishina Y, Rey R, Finegold MJ, et al. Genetic analysis of the Müllerian-inhibiting substance signal transduction pathway in mammalian sexual differentiation. Genes Dev 1996;10(20): 2577–2587
9 Shi Y, Massagué J Mechanisms of TGF-β signaling from cell membrane to the nucleus. Cell 2003;113(06):685–700
10 Josso N, Clemente Nd. Transduction pathway of anti-Müllerian hormone, a sex-specific member of the TGF-β family. Trends Endocrinol Metab 2003;14(02):91–97
11 Moses MM, Behringer RR. A gene regulatory network for Müllerian duct regression. Environ Epigenet 2019;5(03):dvz017
12 Rey R, Lukas-Croisier C, Lasala C, Bedecarrás P. AMH/MIS: what we know already about the gene, the protein and its regulation. Mol Cell Endocrinol 2003;211(1-2):21–31
13 Rey RA, Grinspon RP. Normal male sexual differentiation and aetiology of disorders of sex development. Best Pract Res Clin Endocrinol Metab 2011;25(02):221–238
14 Renault CH, Aksglaede L, Wøjdemann D, Hansen AB, Jensen RB, Juul A. Minipuberty of human infancy - a window of opportunity to evaluate hypogonadism and differences of sex development? Ann Pediatr Endocrinol Metab 2020;25(02):84–91
15 Bergadá I, Milani C, Bedecarrás P, et al. Time course of the serum gonadotropin surge, inhibins, and anti-Müllerian hormone in normal newborn males during the first month of life. J Clin Endocrinol Metab 2006;91(10):4092–4098
16 Lukas-Croisier C, Lasala C, Nicaud J, et al. Follicle-stimulating hormone increases testicular anti-Mullerian hormone (AMH) production through Sertoli cell proliferation and a nonclassical cyclic adenosine 5′-monophosphate-mediated activation of the AMH Gene. Mol Endocrinol 2003;17(04):550–561
17 Grumbach MM. A window of opportunity: the diagnosis of gonadotropin deficiency in the male infant. J Clin Endocrinol Metab 2005;90(05):3122–3127
18 Müller J, Skakkebaek NE. Quantification of germ cells and seminiferous tubules by stereological examination of testicles from 50 boys who suffered from sudden death. Int J Androl 1983;6(02): 143–156
19 Nistal M, Abaurrea MA, Paniagua R. Morphological and histometric study on the human Sertoli cell from birth to the onset of puberty. J Anat 1982;134(Pt 2):351–363
20 Lee MM, Donahoe PK, Silverman BL, et al. Measurements of serum Müllerian inhibiting substance in the evaluation of children with nonpalpable gonads. N Engl J Med 1997;336(21):1480–1486
21 Boukari K, Meduri G, Brailly-Tabard S, et al. Lack of androgen receptor expression in Sertoli cells accounts for the absence of anti-Mullerian hormone repression during early human testis development. J Clin Endocrinol Metab 2009;94(05):1818–1825
22 Rey R. Endocrine, paracrine and cellular regulation of postnatal anti-Müllerian hormone secretion by Sertoli cells. Trends Endocrinol Metab 1998;9(07):271–276
23 Rey R, al-Attar L, Louis F, et al. Testicular dysgenesis does not affect expression of anti-Müllerian hormone by Sertoli cells in premeiotic seminiferous tubules. Am J Pathol 1996;148(05):1689–1698
24 Al-Attar L, Noël K, Dutertre M, et al. Hormonal and cellular regulation of Sertoli cell anti-Müllerian hormone production in the postnatal mouse. J Clin Invest 1997;100(06):1335–1343
25 Rey R, Lordereau-Richard I, Carel JC, et al. Anti-Müllerian hormone and testosterone serum levels are inversely during normal and precocious pubertal development. J Clin Endocrinol Metab 1993;77(05):1220–1226
26 Young J, Chanson P, Salenave S, et al. Testicular anti-Mullerian hormone secretion is stimulated by recombinant human FSH in patients with congenital hypogonadotropic hypogonadism. J Clin Endocrinol Metab 2005;90(02):724–728
27 Teixeira J, Maheswaran S, Donahoe PK. Müllerian inhibiting substance: an instructive developmental hormone with diagnostic and possible therapeutic applications. Endocr Rev 2001;22 (05):657–674
28 Gustafson ML, Lee MM, Asmundson L, MacLaughlin DT, Donahoe PK. Müllerian inhibiting substance in the diagnosis and management of intersex and gonadal abnormalities. J Pediatr Surg 1993; 28(03):439–444
29 Long WQ, Ranchin V, Pautier P, et al. Detection of minimal levels of serum anti-Müllerian hormone during follow-up of patients with

ovarian granulosa cell tumor by means of a highly sensitive enzyme-linked immunosorbent assay. J Clin Endocrinol Metab 2000;85(02):540–544
30 Wang PY, Protheroe A, Clarkson AN, Imhoff F, Koishi K, McLennan IS. Müllerian inhibiting substance contributes to sex-linked biases in the brain and behavior. Proc Natl Acad Sci U S A 2009;106(17): 7203–7208
31 Cimino I, Casoni F, Liu X, et al. Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion. Nat Commun 2016;7(01):10055
32 Josso N, Rey RA, Pask A. Editorial: fetal testicular hormones. Front Endocrinol (Lausanne) 2022;13:1090088
33 Picard JY, Cate RL, Racine C, Josso N. The persistent Müllerian duct syndrome: an update based upon a personal experience of 157 cases. Sex Dev 2017;11(03):109–125
34 Josso N, Rey RA. What does AMH tell us in pediatric disorders of sex development? Front Endocrinol (Lausanne) 2020;11:619
35 Virtanen HE, Bjerknes R, Cortes D, et al. Cryptorchidism: classification, prevalence and long-term consequences. Acta Paediatr 2007;96(05):611–616
36 Grinspon RP, Rey RA. Anti-Müllerian hormone and Sertoli cell function in paediatric male hypogonadism. Horm Res Paediatr 2010;73(02):81–92
37 Albescú JZ, Bergadá C, Cullen M. Male fertility in patients treated for cryptorchidism before puberty. Fertil Steril 1971;22(12): 829–833
38 Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med 2007;356(18):1835–1841
39 Engeler DS, Hösli PO, John H, et al. Early orchiopexy: prepubertal intratubular germ cell neoplasia and fertility outcome. Urology 2000;56(01):144–148
40 Thorup J, McLachlan R, Cortes D, et al. What is new in cryptorchidism and hypospadias–a critical review on the testicular dysgenesis hypothesis. J Pediatr Surg 2010;45(10):2074–2086
41 Matuszczak E, Hermanowicz A, Debek W, Oksiuta M, Dzienis-Koronkiewicz E, Zelazowska-Rutkowska B. Serum AMH concentration as a marker evaluating gonadal function in boys operated on for unilateral cryptorchidism between 1st and 4th year of life. Endocrine 2012;41(02):334–337
42 Demircan M, Akinci A, Mutus M. The effects of orchiopexy on serum anti-Müllerian hormone levels in unilateral cryptorchid infants. Pediatr Surg Int 2006;22(03):271–273
43 Guibourdenche J, Lucidarme N, Chevenne D, et al. Anti-Müllerian hormone levels in serum from human foetuses and children: pattern and clinical interest. Mol Cell Endocrinol 2003;211(1-2):55–63
44 Tüttelmann F, Dykstra N, Themmen APN, Visser JA, Nieschlag E, Simoni M. Anti-Müllerian hormone in men with normal and reduced sperm concentration and men with maldescended testes. Fertil Steril 2009;91(05):1812–1819
45 Kumar S, Tomar V, Yadav SS, Priyadarshi S, Vyas N, Agarwal N. Fertility potential in adult hypospadias. J Clin Diagn Res 2016;10 (08):PC01–PC05
46 Asklund C, Jensen TK, Main KM, Sobotka T, Skakkebaek NE, Jørgensen N. Semen quality, reproductive hormones and fertility of men operated for hypospadias. Int J Androl 2010;33(01):80–87
47 Hero M, Tommiska J, Vaaralahti K, et al. Circulating antimüllerian hormone levels in boys decline during early puberty and correlate with inhibin B. Fertil Steril 2012;97(05):1242–1247
48 Rey RA, Grinspon RP, Gottlieb S, et al. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology 2013;1(01):3–16
49 Coutant R, Biette-Demeneix E, Bouvattier C, et al. Baseline inhibin B and anti-Mullerian hormone measurements for diagnosis of hypogonadotropic hypogonadism (HH) in boys with delayed puberty. J Clin Endocrinol Metab 2010;95(12):5225–5232
50 Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P, Skakkebæk A. Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. Endocr Rev 2018;39(04):389–423
51 Bastida MG, Rey RA, Bergadá I, et al. Establishment of testicular endocrine function impairment during childhood and puberty in boys with Klinefelter syndrome. Clin Endocrinol (Oxf) 2007;67 (06):863–870
52 Lahlou N, Fennoy I, Carel JC, Roger M. Inhibin B and anti-Müllerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. J Clin Endocrinol Metab 2004; 89(04):1864–1868
53 Renault L, Labrune E, Giscard d'Estaing S, et al. Delaying testicular sperm extraction in 47,XXY Klinefelter patients does not impair the sperm retrieval rate, and AMH levels are higher when TESE is positive. Hum Reprod 2022;37(11):2518–2531
54 Benderradji H, Prasivoravong J, Marcelli F, et al. Contribution of serum anti-Müllerian hormone in the management of azoospermia and the prediction of testicular sperm retrieval outcomes: a study of 155 adult men. Basic Clin Androl 2021;31(01):15
55 Romeo C, Santoro G. Varicocele and infertility: why a prevention? J Endocrinol Invest 2009;32(06):559–561
56 Bellastella G, Carotenuto R, Caiazzo F, et al. Varicocele: an endocrinological perspective. Front Reprod Health 2022;4:863695
57 Trigo RV, Bergadá I, Rey R, et al. Altered serum profile of inhibin B, pro-alphaC and anti-Müllerian hormone in prepubertal and pubertal boys with varicocele. Clin Endocrinol (Oxf) 2004;60 (06):758–764
58 Goulis DCh, Mintziori G, Koliakos N, et al. Inhibin B and anti-Müllerian hormone in spermatic vein of subfertile men with varicocele. Reprod Sci 2011;18(06):551–555
59 Goulis DG, Iliadou PK, Tsametis C, et al. Serum anti-Müllerian hormone levels differentiate control from subfertile men but not men with different causes of subfertility. Gynecol Endocrinol 2008;24(03):158–160
60 Schwartz CL, ed. Survivors of childhood and adolescent cancer: a multidisciplinary approach. In: Pediatric oncology. 2nd ed. Berlin: Springer; 2005:348
61 Leroy C, Cortet-Rudelli C, Desailloud R. [Endocrine consequences in young adult survivors of childhood cancer treatment]. Ann Endocrinol (Paris) 2015;76(6, Suppl 1):S29–S38
62 Cuny A, Trivin C, Brailly-Tabard S, et al. Inhibin B and anti-Müllerian hormone as markers of gonadal function after treatment for medulloblastoma or posterior fossa ependymoma during childhood. J Pediatr 2011;158(06):1016–1022.e1
63 Laporte S, Couto-Silva AC, Trabado S, et al. Inhibin B and anti-Müllerian hormone as markers of gonadal function after hematopoietic cell transplantation during childhood. BMC Pediatr 2011; 11(01):20
64 Muttukrishna S, Yussoff H, Naidu M, et al. Serum anti-Müllerian hormone and inhibin B in disorders of spermatogenesis. Fertil Steril 2007;88(02):516–518
65 Xiong Z, Ye Z, Tu J, Meng TQ, Ren N. [Serum anti-Müllerian hormone level for differential diagnosis of obstructive and non-obstructive azoospermia]. Zhonghua Nan Ke Xue 2019;25(09): 823–827
66 Shu J. Serum anti – Mullerian hormone in azoospermia approach. Farmacia 2023;71(02):280–287
67 Peng LP, Shao Y, Wang CC, et al. [Correlation of serum anti-Müllerian hormone with semen parameters]. Zhonghua Nan Ke Xue 2017;23(06):531–535
68 Aksglaede L, Olesen IA, Carlsen E, Petersen JH, Juul A, Jørgensen N. Serum concentration of anti-Müllerian hormone is not associated with semen quality. Andrology 2018;6(02):286–292
69 Kucera R, Ulcova-Gallova Z, Windrichova J, Losan P, Topolcan O. Anti-Müllerian hormone in serum and seminal plasma in comparison with other male fertility parameters. Syst Biol Reprod Med 2016;62(03):223–226

70 El-Halawaty S, Azab H, Said T, et al. Assessment of male serum anti-Mullerian hormone as a marker of spermatogenesis and ICSI outcome. Gynecol Endocrinol 2011;27(06):401–405
71 Rashad M, Azab M. Assessment of semen parameters and anti-Müllerian hormone level in patients with chronic kidney disease on hemodialysis: a case control study. JOMH 2021;17(04):72–77
72 Domain G, Buczkowska J, Kalak P, et al. Serum anti-Müllerian hormone: a potential semen quality biomarker in stud dogs? Animals (Basel) 2022;12(03):323
73 Andersen JM, Herning H, Witczak O, Haugen TB. Anti-Müllerian hormone in seminal plasma and serum: association with sperm count and sperm motility. Hum Reprod 2016;31(08):1662–1667
74 Mostafa T, Amer MK, Abdel-Malak G, et al. Seminal plasma anti-Müllerian hormone level correlates with semen parameters but does not predict success of testicular sperm extraction (TESE). Asian J Androl 2007;9(02):265–270
75 Turhan G, Çil N, Kabukçu C, Turan T, Fenkçi İV, Abban Mete G. Relationship of seminal plasma anti-Müllerian hormone concentration with sperm morphology and sperm DNA damage. J Urol Surg 2022;9(04):272–280
76 Holst BS, Panzani D, Camillo F, Svensson A, Rota A. Anti-Müllerian hormone (AMH) concentrations are maximal at puberty in male donkeys and secretion is redirected from the blood stream to seminal plasma. Anim Reprod Sci 2020;218:106484
77 Fénichel P, Rey R, Poggioli S, Donzeau M, Chevallier D, Pointis G. Anti-Müllerian hormone as a seminal marker for spermatogenesis in non-obstructive azoospermia. Hum Reprod 1999;14(08):2020–2024
78 Siow Y, Fallat ME, Amin FA, Belker AM. Müllerian inhibiting substance improves longevity of motility and viability of fresh and cryopreserved sperm. J Androl 1998;19(05):568–572
79 Nery SF, Vieira MAF, Dela Cruz C, et al. Seminal plasma concentrations of anti-Müllerian hormone and inhibin B predict motile sperm recovery from cryopreserved semen in asthenozoospermic men: a prospective cohort study. Andrology 2014;2(06):918–923
80 Dong S, Chen C, Zhang J, Gao Y, Zeng X, Zhang X. Testicular aging, male fertility and beyond. Front Endocrinol (Lausanne) 2022;13:1012119
81 Chong YH, Dennis NA, Connolly MJ, et al. Elderly men have low levels of anti-Müllerian hormone and inhibin B, but with high interpersonal variation: a cross-sectional study of the Sertoli cell hormones in 615 community-dwelling men. PLoS One 2013;8(08):e70967
82 Ramezani Tehrani F, Mansournia MA, Solaymani-Dodaran M, Minooee S, Azizi F. Serum variations of anti-Mullerian hormone and total testosterone with aging in healthy adult Iranian men: a population-based study. PLoS One 2017;12(07):e0179634