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RESEARCH ARTICLE

ANTIMÜLLERIAN HORMONE AS AN OVARIAN RESERVE MARKER IN POSTPONING PREGNANCY IN WOMEN AFTER 37 YEARS OLD

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ABSTRACT

The modern woman tends to postpone her pregnancy after the age of 40 due to her professional life and achievements. However, this trend can lead to problems in fertility rates since the female ovarian reserve falls dramatically after the age of 37. Therefore, ovarian reserve markers such as antimüllerian hormfone (HAM) have been evaluated for being a potent clinical marker of ovarian reserve in female after 37 years old. The aim of this study was to present the antimüllerian hormone as the gold standard marker for ovarian reserve in women after 37 years old, indicating the importance of HAM in ovarian aging. It was done a review of the current literature regarding HAM and postponement of pregnancy through scientific articles in indexed databases during 2016 to March 2017. The study demonstrated that successful results for a pregnancy after 37 years of age are highly dependent on the ovarian reserve, and HAM has been shown to be the best marker for these results. The study also found that HAM could be a good predictor for menopause. We concluded that HAM should be included in the protocols of fertility hormones for women who want to be pregnant after 37 years of age, as well as could be a predict for menopause.

INTRODUCTION

The postponement of pregnancy in the modern woman after the age of 40 has an impact in low birth rates, especially in developed countries (WHO, 2016), and a high important emotional consequences in the life of women for those who do not get pregnant. This occur due to the fertility rate of women begin to fall after the age of 37 drastically, reaching 90% of infertility after 40 years old (Machado, 2011; Yunes, 2010).

The tendency to postpone the first gestation among couples in recent years may seem to be associated with the numerical increase of sub fertility cases and, consequently, the demand for assisted reproductive services (Taeuber, 2011), but still with lower success numbers (Navot *et al*., 2004, Menken *et al*., 2010). This low success rate after 37 years is basically due to the scarce ovarian reserve and the poor quality of the remaining oocytes, which carriers 70-80% of chromosomal or genetic damages. The evaluation of the ovarian reserve is important to advise the patient for a properly protocol to be used or if it is not necessary at all, reducing the costs, psychological issues and the demand for fertilization clinics (Nardo *et al*., 2008; Gravena *et al*. 2012; La Marca, 2009a,b,c,d). The present study is a mini review of the current literature regarding antimüllerian hormone. A research was conducted using scientific articles in indexed databases during 2016 to March 2017. A total of 63 articles were used, however 49 were selected as a reference for discussion. The aim of this study was to present the antimüllerian hormone as the gold standard marker for ovarian reserve in women after 37 years old, indicating the importance of HAM in ovarian aging.

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Antimüllerian Hormone (HAM)

The antimüllerian hormone (HAM) is a glycoprotein member of the TGF-beta superfamily (Transforming Growth Factor beta), which also includes inhibins, activins, proteins related to bone morphogenesis (BMPs) and growth differentiation factors (GDFs). It is mainly produced in the preantral and antral follicles by the granulosa cells with the function of inhibiting the activation of the primordial follicles and reducing the sensitivity of the developing antral follicles on the action of FSH (Fanchin *et al.*, 2003a,b). HAM is expressed in girls' ovaries since the 36th week of intrauterine life with a high concentration from puberty to 30 years of women age, when it starts to decline (Fanchin *et al*., 2003a,b).

HAM has been recently pointed out by several groups of researchers as the best ovarian reserve marker when compared with the other fertility markers such as follicle stimulating hormone (FSH), luteinizing hormone (LH), inhibin B and estradiol. In addition, the studies presented HAM as a good predictor to menopause (Seifer *et al*., 2002; Van Rooij *et al*.,

2002; Fanchin *et al*., 2003a,b; Penüarrubia *et al*., 2005; 2009b, 2010).

The studies showed that HAM acts as a modulator of follicular recruitment and in the regulation of steroidogenesis (Figure 1) (Fanchin *et al*., 2003a,b; Visser & Themen, 2005). They also presented HAM as the most reliable serum marker and the gold standard for predicting ovarian reserve through estimating the amount and activity of the recruitment units from an initial pool of follicles in early stages of maturation (Van Rooij *et al*., 2002; Fanchin *et al*., 2003a,b; Visser & Themen, 2005; Muttukrishna, 2005; Rocha, 2013).

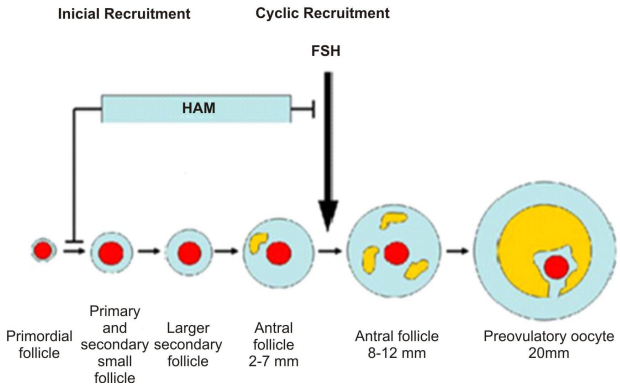

Figure 1 Function of HAM in follicular development. In red is the oocyte; In blue, the granulosa; In yellow, the follicular fluid (Broekmans *et al*., 2008 – adapted).

The ovarian reserve refers to the amount of ovules that the woman has in her ovaries. The woman has the highest number of ovules before birth – around 7,000 million in the 36th week of gestation – in primordial follicle stage. At birth, this number has already reduced to 2 million of primordial follicles and this process never ceases, regardless of being pregnant, using hormones or taking birth control pills (Arbo *et al*., 2007; Somukirana *et al*., 2007). Therefore, when the girl reaches the puberty (menarche), she has 500,000 of ovules approximately. These ovules will be consumed on average of 1,000 per cycle in order to only one becomes mature (dominant follicle); followed by atresia for the others. Therefore, the women at 37 years old have around 25,000 ovules and at 50, practically nothing (Rocha, 2013) (Figure 2).

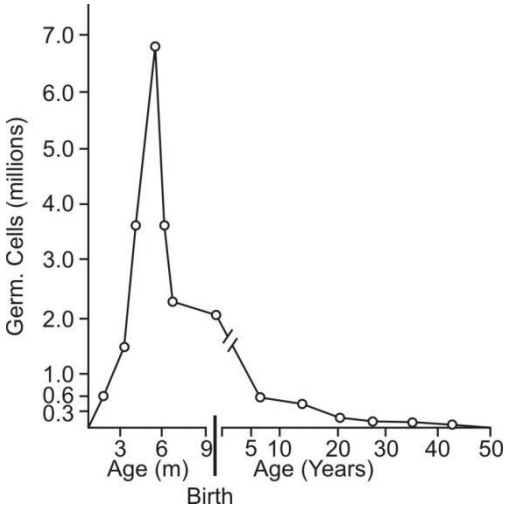

Figure 2 Reserve of germ cells throughout a woman's life (Saraiva, 2010 – adapted).

Figure 2 shows the high peak in the number of ovules produced before birth in the woman. As the age advances, the number of ovules decreases until arriving at the menopause almost without reserve.

In women, HAM levels do not appear to change under conditions in which endogenous gonadotrophin release is decreased, such as during pregnancy (La Marca, 2005b), in the treatment of the GnRH agonist (Mohamed *et al.*, 2006), and in the short-term administration of oral contraceptives, as it happens with FSH, inhibin B and estradiol, indicating that the ovarian activity non cyclic independent FSH persists even when FSH secretion is suppressed by the pituitary gland (Nero, 2008; La Marca, 2009b, 2010d). HAM becomes very low or undetectable in menopause (La Marca, 2006, 2007, 2009a, b). The correlation between the ovarian reserve pool and HAM is so narrow that it is now used as a good predictor for menopause (La Marca, 2009a,b, 2010; Robertson *et al*., 2008). Figure 3 shows the serum levels of HAM, in which the ovarian reserve decreases with the advancement of the woman's age, reducing the chances of fertilization (La Marca, 2006).

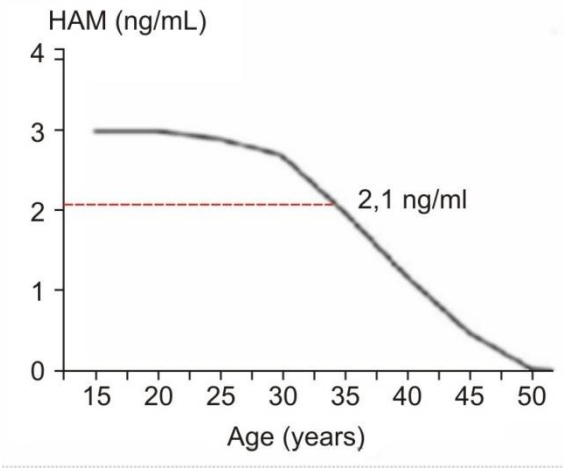

Figure 3 The value of HAM and the age of the woman (La Marca, 2010 -adapted).

HAM is secreted by the gonads, produced by granulosa cells from the preantral and antral follicles (cells that cover the follicle), restricting the expression of growing follicles, until they have reached the size 7mm and state of differentiation to be selected by dominance by the action of FSH (Weenen *et al*., 2004) (Figure 4).

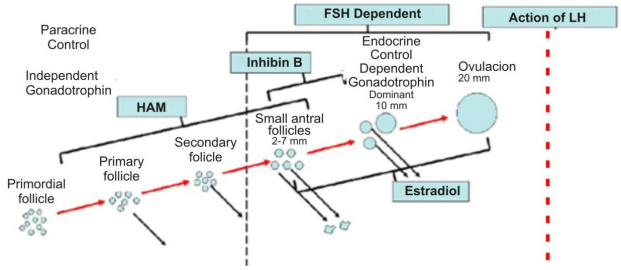

Figure 4 Expression of HAM throughout folliculogenesis and its relation with FSH, inhibin B and estradiol. Unlike other markers, HAM presents a direct reflection in the number of primordial follicles during follicular development. FSH, inhibin B and estradiol are connected by negative feedbacks with indirect reflexes in the number of antral follicles (La Marca, 2012 – adapted).

Therefore, the pituitary gland responds to the action of hypothalamic GnRH by first producing FSH and then LH in women with normal ovulation. FSH is crucial as a stimulator of folliculogenesis and its concentration is controlled by a negative feedback mechanism. This mechanism works by producing a peptidic hormone (inhibin B), which inhibit the

production of FSH in the pituitary gland. The inhibin B is produced by the granulosa cells of the developing follicle, altering their levels in the follicular phase of cycle (Kurobe, 2013; Reis, 2009).

In the follicular phase, FSH stimulates the ovary follicle, which causes the growth of the dominant ovules (7mm to 20mm), previously selected by HAM when it reaches 7mm, and also triggers the production of estrogen in the follicle by ovarian granulosa cells. The increase in estrogen levels informs the pituitary to stop producing FSH and begin to synthesize more LH, when the luteal phase of the cycle begins: LH stimulates the production of progesterone and estrogen from the corpus luteum. The progesterone prepares the uterus for implantation of the embryo and if fertilization occurs, the embryo produces chorionic gonadotrophin, which maintains the corpus luteum; or, if there is no fertilization, the ovule degenerates and menstruation occurs (Silva & Vilodre, 2009).

Clinical hormone markers function are established for the investigation of the female cycle and ovarian function in which serum FSH, LH, estradiol and inhibin B levels are requested on the third day of the cycle (Verissimo & Silvestre, 2016). However, it is now known that their levels in the blood circulation do not reflect the follicular dynamics, since there is no strong correlation with the population of primordial follicles and these markers (Tremellen, 2005; Fanchin *et al.*, 2005a,b). The search for more representative results of the ovarian capacity to respond to the exogenous stimulus has directed the focus of science to two markers: the serum concentration of HAM and the antral follicles count (AFC) made by ultrasound (Linhares, 2014). So, HAM is considered the representative gold marker as representative of the ovarian function reserve in contrast to FSH, inhibin B and estradiol. HAM also has the advantage of reduced variability of serum concentrations throughout the female cycle (Fanchin *et al.*, 2005; La Marca, 2006), which gives it credibility and uniformity regarding the moment of dosage, i.e., its dosage is independent of the phase of the female cycle, and is now considered the gold standard for monitoring ovarian depletion (Scheffer *et al.*, 2007; Fanchin *et al.*, 2003a,b; Broekmans *et al.*, 2006).

Besides scientific studies have shown that HAM could measure women ovarian reserve capacity with high precision, it also could demonstrate the quality of ovules when associated with antral follicles count (AFC) made by ultrasound (Machado, 2011; La Marca, 2009b). HAM is the one that best reflects the continued decline of the follicle pool. The decrease in HAM with age appears before other variables, indicating that this is the best marker of ovarian age and transition to menopause (Saraiva, 2010).

The HAM concentration in the serum is a reflection of the follicular pool, so the reduction in the amount of small follicles is accompanied by reduction in circulating blood (Box 1).

Box 1 HAM reference values in the serum of women.

Result: ng/mL	
Low	< 0.14 ng/mL
Reduced	0.14 to 0.7 ng/mL
Normal	0.7 to 2.1 ng/mL
Method: Chemiluminescence	

Álvaro Laboratory (2017 – adapted).

Several authors have considered HAM as the most reliable serum marker for ovarian reserve prediction, estimating the quantity, quality, and activity of the recruitable units of an initial pool of follicles in early stages of maturation (Van Rooij *et al.*, 2002; Fanchin *et al.*, 2003 a,b; Muttukrishna, 2005; Romão, 2012; Tso, 2014).

Recent studies indicate that HAM is an important marker of ovarian reserve due to its serum levels show a decline throughout the reproductive life of the woman and are undetectable after menopause (Van Rooij *et al*., 2004, 2008; Shin, 2008; Van Disseldorp *et al.*, 2008). Similarly, early ovarian aging and premature ovarian failure have been associated with low or undetectable serum HAM levels (La Marca, 2006b, De Koning *et al.*, 2008, Kurobe, 2013; Knauff *et al*., 2008). In addition, HAM levels do not change significantly during the female cycle (Hehenkamp *et al.*, 2006; La Marca, 2006a; Streuli *et al.*, 2008), while all other hormones secreted by the ovary and released by the pituitary show significant variations throughout the cycle.

CONCLUSION

According to the studies, the relationship of HAM with the antral follicle count shows a clear relationship of this hormone with the ovarian reserve, making it the gold standard marker for this purpose. Likewise, HAM reference values for women with normal reproductive cycle indicate ovarian reserve fall through the woman's age, indicating this marker as a good predictor for menopause.

HAM also showed superiority regarding ovarian reserve over other fertility and ovulation markers because there is no variation during the cycle, whereas FSH, LH, inhibit B, estradiol and other hormones used as markers of ovulation and fertilization undergo large fluctuations during the female cycle. The stability of HAM can evaluate more precisely the ovarian pool of women in any day of the cycle, showing the ovarian reserve.

The addition of HAM to the routine of fertility exams to women after 37 years who would like to become pregnant or for those who has low ovarian reserve, ovarian pathologies, and early menopause or in the age of menopause would be of great benefit to women health. As our study focused in the postponed pregnancy, the insertion of HAM in routine exams for later pregnancy could lead to a better prognosis for a future gestation, either natural or *in vitro* fertilization, especially for those who may be fertilized by artificial insemination, as it would reduce costs and emotional impacts.

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