REVISTA BRASILEIRA DE REUMATOLOGIA

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Review article

Anti-Müllerian hormone levels as a predictor of ovarian reserve in systemic lupus erythematosus patients: a review☆

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ARTICLE INFO

Article history:
Received 29 January 2014
Accepted 2 May 2014
Available online 7 January 2015

Keywords:
Anti-Müllerian hormone
Ovarian reserve
Systemic lupus erythematosus

ABSTRACT

The anti-Müllerian hormone (AMH) is secreted from granulosa cells of growing ovarian follicles and appears to be the best endocrine marker capable of estimating ovarian reserve. Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women of reproductive age and may negatively affect their fertility due to disease activity and the treatments used. Recently, several studies assessed AMH levels to understand the real impact of SLE and its treatment on fertility.

Hormônio anti-Mülleriano como preditor de reserva ovariana em pacientes lúpicas: uma revisão

Palavras-chave:
Hormônio anti-Mülleriano
Reserva ovariana
Lúpus eritematoso sistêmico

RESUMO

O hormônio anti-Mülleriano (HAM) é secretado a partir das células da granulosa dos folículos ovarianos em crescimento e parece ser o melhor marcador endócrino capaz de estimar a reserva ovariana. O lúpus eritematoso sistêmico (LES) é uma doença autoimune que acomete predominantemente mulheres em idade reprodutiva e pode afetar negativamente sua fertilidade pela atividade da doença, bem como pelos tratamentos usados. Conhecer o real impacto do LES e de seu tratamento na fertilidade vem sendo o objetivo de estudos recentes, os quais têm usado o HAM para esse fim.

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http://dx.doi.org/10.1016/j.rbre.2014.05.008
2255-5021/

Introduction

Better treatment conditions and the management of infections have not only contributed to increase the survival of systemic lupus erythematosus (SLE) patients, but also provided better quality of life, so nowadays most of these patients are able to work normally. With the increasing participation of women in the labor market, the moment they decide to have their first child has been increasingly postponed. Female fertility starts to decline at the beginning of the third decade of life and could be hampered in SLE patients due to disease activity and its treatment. This makes fertility-related problems in such patients more and more important, hence the need to have effective markers to predict ovarian reserve.

Anti-Müllerian hormone as an ovarian reserve marker

Around the twentieth week of pregnancy, the number of oocytes reaches a maximum of six to seven million and, in a continuous process of atresia/apoptosis, only one to two million follicles reach the neonatal period.[1] Only oogonia that enter meiosis will survive atresia in the fetal ovary before birth. At menarche, around 300 thousand are viable. Women use around 500 primordial follicles during the reproductive years. At menopause, the ovary is formed by dense stroma and rare remaining scattered oocytes.[2]

Follicular growth starts in the fetus, in a continuous pattern, and is related to the total mass of follicles and with factors released by atretic ovarian follicles. Follicular growth cycles and subsequent atresia initiate before birth and continue through the reproductive years. The viability of the oocyte declines in older women in reproductive age before they present any measurable serum or intrafollicular hormone concentration decrease.[3] Menopause is associated with a marked decline in the number of oocytes, which is attributed to the progressive atresia of the original *pool* of oocytes. However, evidences of complete depletion of oocytes are currently limited.[3]

The anti-Müllerian hormone (AMH), also called Müllerian-inhibiting substance, is a polypeptide, member of the transforming growth factor-β (TGFβ) family. It is involved in the sexual differentiation of the male embryo, inducing regression of the Müllerian duct, embryological precursor of the female reproductive tract.[4] In female individuals, it starts expressing in the fetal ovary after the 36th week of pregnancy. It is expressed by the granulosa cells of growing ovarian follicles: primary, secondary, preantral and small antral, being produced at higher levels by the last two.[5] It has two main mechanisms of action in the ovary: inhibits the initial recruitment of primary follicles from primordial follicles, and inhibits the sensitivity of antral follicles to follicle-stimulating hormone (FSH) during cyclical recruitment (Fig. 1). The AMH prevents the premature depletion of follicles.[6] Despite the "anti" prefix, the AMH has no role in the production of antibodies.

The term "ovarian reserve" describes the number and quality of the remaining oocytes in the ovaries. The amount of remaining primordial follicles appears to correlate with the number of growing follicles. As only growing follicles produce AMH, their plasma levels reflect the amount of remaining primordial follicles.[7] Studies in mice[8] and chimpanzees[9] have shown strong correlation between the levels of AMH and the number of primordial follicles.

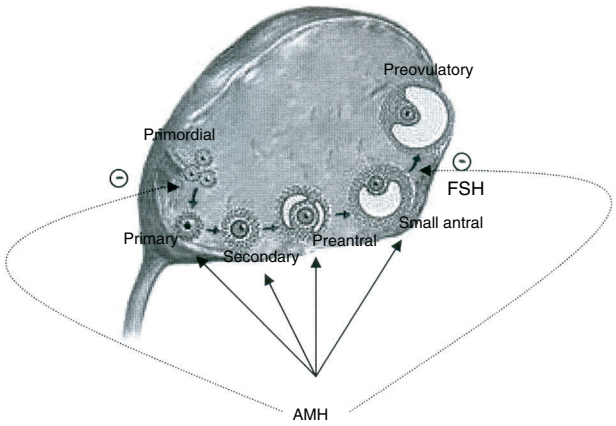

Fig. 1 – Anti-Müllerian hormone (AMH) and folliculogenesis. AMH is secreted by growing follicles and secretion increases over follicular development. Highest levels are secreted by preantral and small antral follicles. AMH inhibits the initial recruitment of primary follicles from the pool of primordial follicles and reduces the sensitivity of antral follicles to follicle-stimulating hormone (FSH) during recruitment.

Other current tests to estimate the ovarian reserve include hormone (FSH, estradiol, inhibin B) and sonographic markers (antral follicle count and measurement of ovarian volume). These tests direct or indirectly reflect the number of remaining antral follicles. Antral follicle count is a direct sonographic measurement. In the early follicular phase, the levels of inhibin B and estradiol are considered dependent on the number of antral follicles. FSH levels are regulated by negative feedback of these two granulosa cell products, so they indirectly reflect the *pool* of antral follicles. The age-related decline of oocytes leads to reduced levels of estradiol and inhibin B and, consequently, the increase of FSH.[10] Compared with these hormonal markers, AMH plasma levels appear to associate better with the longitudinal decline of oocytes/follicles over time, even before the occurrence of irregular cycles.[11] As opposed to the cyclic fluctuations of FSH, estradiol and inhibin B, the AMH has small or absent intracyclic fluctuation. Therefore, the AMH reflects the continued growth of small follicles. AMH levels are relatively unaffected by conditions that suppress late stages of FSH-dependent follicular development, like pregnancy,[12] the use of hormonal contraceptives[13] and the treatment with GnRH agonists. In addition to that, the AMH does not appear to be affected by the body mass index (BMI) or smoking.[14] The predictive value of the AMH to estimate ovarian reserve is still uncertain. Several longitudinal prospective studies following normo-ovulatory women for more than 11 years have shown that the AMH is the best endocrine marker to assess ovarian aging, and that AMH plasma levels, with reasonable accuracy, can predict the onset of menopause.[15]

Table 1 – Summary of published articles.

Study	Design	Follow-up	Main results
Lawrenz et al.[28]	Case–control (33 patients in each group)	February 2009 to May 2010, Germany	SLE patients have significantly lower AMH levels than healthy controls.
Mok et al.[29]	Cohort study, 216 SLE patients	June to October, 2009, China	The mean AMH level was significantly lower in patients who had been previously exposed to cyclophosphamide.
Morel et al.[30]	Case–control (56 patients in each group)	2012, France	Low AMH levels in SLE patients, with significant decrease associated with age and prior use of cyclophosphamide.
Malheiro et al.[31]	Case–control (27 patients in each group)	Brazil	The mean values of ovarian reserve were similar in both groups. SLE patients showed wider distribution of AMH values.

The AMH appears to be an early, reliable and direct predictor of declining ovarian function. However, there is no consensus regarding appropriate threshold values. Literature data showed significant dispersion of serum AMH concentrations in comparable populations obtained from two different ultrasensitive immunoassays available in the market – *AMH Beckman Coulter ELISA* and *AMH Diagnostic System laboratories (DSL) ELISA*. A previous study found AMH levels around 4.6 times lower with the DSL kit, showing that the cut-off value varies according to the assay being used.[16] In studies that assessed the success rate of *in vitro* fertilization, serum AMH levels below 0.5 ng/mL strongly suggested follicular depletion, while serum levels $\geq$1.26 ng/mL were consistent with a good ovarian reserve.[15,17]

How can lupus systemic erythematosus impair fertility?

Infertility is defined as the failure to conceive after 12 months of regular unprotected intercourse. Autoimmunity can interfere with many aspects associated with fertility, causing, for example, tubal function changes, ovarian failure, embryo implantation failure and miscarriages.

A case–control study conducted in 2009 in Finland assessed the reproductive history of SLE women compared with healthy controls. The authors found no difference in the mean age at menarche and the frequency of infertility. However, menopause occurred earlier among SLE patients.[18]

Around 10–30% of women with premature ovarian failure (POF) have a concomitant autoimmune disease.[19] Autoimmune reactions against ovaries can be general or partial, leading to a fluctuating course of POF. The evidence of an autoimmune basis for POF is given by the presence of antibodies against steroid-producing cells in around 80% of patients and oophoritis with infiltration of CD4+ and CD8+ T lymphocytes.[20]

It is suggested that fertility in some patients could be reduced due to menstrual irregularities and anovulatory cycles during disease activity and the administration of high doses of corticosteroids.[21] At least 53% of SLE patients under the age of 40 present some degree of menstrual irregularity, while menstrual alterations are more frequent among patients with greater disease activity.[22] The ovarian function can be reduced by autoimmune oophoritis in SLE, leading to POF, while a reduced ovarian reserve is associated with reduced AMH levels.[23] Lupus nephritis can result in end stage renal disease and amenorrhea together with hyperprolactinemia.[24] Around one third of SLE women present antiphospholipid antibodies, which could explain the SLE/miscarriage association.[25]

Therapeutic agents prescribed to treat SLE may impair fertility, such as is the case of high doses of steroids, NSAIDs and cyclophosphamide, which, in particular, influence the ovarian function, especially at older ages. A study published in 2006 found 39% of prevalence of ovarian failure among patients treated with cyclophosphamide under the age of 30 and 59% of patients aged 30–40.[26] A cohort study performed from September 2010 to July 2011 in the United States, comparing the reproductive history of young women with rheumatic diseases, with or without prior exposure to cyclophosphamide, concluded that more women with prior exposure to cyclophosphamide had amenorrhea, infertility and nulliparity.[27]

Ovarian reserve assessment in premenopausal SLE patients through anti-Müllerian hormone – state-of-the-art

Few studies using AMH to assess ovarian reserve in SLE patients have been published to date. A case–control study conducted in Germany from February 2009 to May 2010 analyzed the influence of SLE in ovarian reserve considering disease activity and disease duration. The ovarian reserve was determined through serum AMH levels in 33 premenopausal SLE patients without prior exposure to cyclophosphamide and in 33 age-matched control patients. AMH levels in SLE patients were significantly lower than in healthy controls. No significant differences were found between the groups in relation to the number of children and abortions, and there was no correlation between the AMH level and the duration of the disease or SLEDAI as a disease activity index. Despite presenting mild disease activity, the ovarian reserve of SLE patients was significantly smaller than that of age-matched healthy controls.[28]

AMH levels and its relationship with age and prior exposure to cyclophosphamide were investigated in a cohort of 216 Chinese SLE patients followed from July 2009 to October 2009. It was found that the mean level of AMH was significantly lower in patients who had prior exposure to cyclophosphamide, according to their ages. However, there was no significant differences when users or non-users of other immunosuppressive agents, such as mycophenolate mofetil, azathioprine and calcineurin inhibitors, were compared.[29]

A case–control study conducted in 2012 in France found low AMH levels in SLE patients with significant decrease associated with age and prior use of cyclophosphamide. Nevertheless, the risk of pregnancy failure was low (15.8%). The prior use of cyclophosphamide was a predictor while AMH levels were not.[30]

A case–control study with a small number of patients (27 in each group) conducted in Brazil found similar mean ovarian reserve values in both groups. However, SLE patients showed broader distribution of AMH levels. The ovarian function was more compromised in patients with higher cumulative dose of cyclophosphamide and higher disease damage score.[31] The summary of the main articles published to date can be seen in Table 1.

Conclusion

AMH has been increasingly reported as a reliable marker of ovarian reserve. The role of cyclophosphamide as the cause of infertility, evidenced by lower levels of AMH in age-matched and previously exposed patients, is well established. However, further studies, with larger number of patients, are necessary to assess differences in the ovarian reserve of SLE patients when compared with controls, and the implications of disease activity on the fertility of these patients. Agents with less ovarian toxicity could be offered to patients with reduced AMH levels and to those who wish to become pregnant.

Funding

Fundo de Incentivo à Pesquisa e Eventos (FIPE/HCPA), Brazil.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Peters H, Byskov AG, Grinsted J. Follicular growth in fetal and prepubertal ovaries in humans and other primates. J Clin Endocrinol Metab. 1978;7:469–85.
2. Freitas, Menke, Rivoir, Passos. Rotinas em ginecologia. 6th ed. Porto Alegre: Artmed; 2011.
3. Richardson SJ, Senikas V, Nelson JF. Follicular depletion during the menopausal transition: evidence for accelerated loss and ultimate exhaustion. J Clin Endocrinol Metab. 1987;65:1231–7.
4. Lee MM, Donahoe PK. Mullerian inhibiting substance: a gonadal hormone with multiple functions. Endocr Rev. 1993;14:152–64.
5. La Marca A, Stabile G, Artenisio AC, Volpe A. Serum anti-Müllerian hormone throughout the human menstrual cycle. Hum Reprod. 2006;21:3103–7.
6. Visser JA, De Jong FH, Laven JS, Themmen AP. Anti-Müllerian hormone: a new marker for ovarian function. Reproduction. 2006;131:1–9.
7. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod. 1992;7:1342–6.
8. Kevenaar ME, Meerasahib MF, Kramer P, Van de Lang-Born BM, De Jong FH, Groome NP, et al. Serum anti-Müllerian hormone levels reflect the size of the primordial follicle pool in mice. Endocrinology. 2006;147:3228–34.
9. Appt SE, Clarkson TB, Chen H, Adams MR, Christian PJ, Hoyer PB, et al. Serum anti-Müllerian hormone predicts ovarian reserve in a monkey model. Menopause. 2009;16:597–601.
10. Burger HG, Cahir N, Robertson DM. Serum inhibins A and B fall differentially as FSH rises in perimenopausal women. Clin Endocrinol (Oxf). 1998;48:809–13.
11. De Vet A, Laven JS, De Jong FH, Themmen AP, Fause BC. Anti-Müllerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril. 2002;77:357–62.
12. La Marca A, Giulini S, Orvieto R, De Leo V, Volpe A. Anti-Müllerian hormone concentrations in maternal serum during pregnancy. Hum Reprod. 2005;20:1569–72.
13. Li HW, Wong Cy, Yeung WS, Ho PC, Ng EH. Serum anti-Müllerian hormone level is not altered in women using hormonal contraceptives. Contraception. 2011;83:582–5.
14. Shaw CM, Stanczyk FZ, Egleston BL, Kahle LL, Spittle SC, Godwin AK, et al. Serum anti-Müllerian hormone in healthy premenopausal women. Fertil Steril. 2011;95:2718–21.
15. Broekmans FJ, Kwee J, Hendriks DJ. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod. 2006;12:685–718.
16. Fréour T, Mirallié S, Bach-Ngohou K, Denis M, Barrière P, Masson D. Measurement of serum anti-Müllerian hormone by Beckman Coulter Elisa and DSL Elisa: comparison and relevance in assisted reproduction technology (ART). Clin Chim Acta. 2007;375:162–4.
17. Gnoth C, Schuring AN, Friol K, Tigges J, Mallmann P, Godehardt E. Relevance of anti-Müllerian hormone measurement in a routine IVF program. Hum Reprod. 2008;23:1359–65.
18. Ekblom-Kullberg S, Kautiainen H, Alha P, Helve T, Leirisalo-Repo M, Julkunen H. Reproductive health in women with systemic lupus erythematosus compared to population controls. Scand J Rheumatol. 2009;38:375–80.
19. Nelson LM. Clinical practice, primary ovarian insufficiency. N Engl J Med. 2009;360:606–14.
20. Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Ver. 1997;18:107–34.
21. Gayed M, Gordon C. Pregnancy and rheumatic diseases. Rheumatology (Oxf). 2007;46:1634–40.
22. Shabanova SS, Ananieva LP, Alekberova ZS, Guzov II. Ovarian function and disease activity in patients with systemic lupus erythematosus. Clin Exp Rheumatol. 2008;26:436–41.
23. Carp HJA, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun. 2012;38:J266–74.
24. Gomez F, De la Cueva R, Wauters JP, Lemarchand-Beraud T. Endocrine abnormalities in patients undergoing long-term hemodialysis. The role of prolactin. Am J Med. 1980;68:522–30.
25. Bizarro N, Tonutti E, Villalta D, Tampoia M, Tozzoli R. Prevalence and clinical correlation of anti-phospholipid-binding protein antibodies in anticardiolipin-negative patients with systemic lupus erythematosus and women with unexplained recurrent miscarriages. Arch Pathol Lab Med. 2005;129:61–8.
26. Manger K, Wildt L, Kalden JR, Manger B. Prevention of gonadal toxicity and preservation of gonadal function and fertility in Young women with systemic lupus erythematosus treated by cyclophosphamide: the Prego study. Autoimmun Rev. 2006;5:269–72.
27. Harward LE, Mitchell K, Pieper C, Copland S, Criscione-Schreiber LG, Clowse MEB. The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease. Lupus. 2013;22:81–6.
28. Lawrenz JC, Henes M, Henes E, Neunhoeffer M, Schmalzing T, Fehm, et al. Impact of systemic lupus erythematosus on

ovarian reserve in premenopausal women: evaluation by using anti-Müllerian hormone. Lupus. 2011;20:1193–7.
29. Mok CC, Chan PT, To CH. Anti-Müllerian hormone and ovarian reserve in systemic lupus erythematosus. Arthritis Rheum. 2013;65:206–10.
30. Morel N, Bachelot A, Ghillani-Dalbin P, Amoura Z, Galicier L. Study of anti-Müllerian hormone and the relationship with subsequent probability of pregnancy in 112 systemic lupus erythematosus patients exposed or not to cyclophosphamide. The 10th International Congress on SLE. Lupus. 2013;22:16.
31. Malheiro OB, Rezende CP, Ferreira GA, Reis FM, Federal University of Minas Gerais, Brazil. Ovarian reserve markers in reproductive age women with systemic lupus erythematosus. The 10th International Congress on SLE. Lupus. 2013;22:162.