Plzeň. lék. Sborn., 79, 2013: 19–24

OTHER CLINICAL APPLICATIONS OF AMH IN CONNECTION WITH THE OVARIAN RESERVE

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Anti-Müllerian hormone (AMH), also known as Müllerian Inhibiting Substance (MIS), is a glycoprotein dimer composed of two 72 kDa monomers (1). AMH is a member of the Transforming Growth Factor-β (TGF-β) superfamily. The AMH gene is located in the short arm of chromosome 19 (2). AMH uses two cell receptors: type I receptor (MISRI) and type II receptor (MISRII) which are present on the AMH target-tissues (gonads and Müllerian ducts) (3). The expression of AMH is restricted to the Sertoli cells of the fetal and postnatal testis in the male, and granulosa cells of the postnatal ovary in the female. AMH plays an important role in male sex differentiation as its production by the embryonic testes induces the regression of the Müllerian ducts (4). The measurement of AMH serum levels is currently a useful tool in the examination of the ovarian reserve. Many studies have been performed on the topic of ovarian reserve, ovarian aging and on the prediction of the ovarian response to the hormonal stimulation arising from in vitro fertilization (IVF). However, IVF is not the only reason for measuring AMH.

AMH during the life of a woman

There is a fall in serum AMH levels shortly after birth, with concentrations only increasing again after about two years of age. This age is called a mini-puberty in neonatal girls (5). An initial smaller peak of serum concentration of AMH is observed at eight years of age followed by a fall in AMH serum levels between the ages of eight and twelve. There then follows a rise that peaks between twenty five and twenty seven years of age. After the age of twenty seven AMH serum levels begin decreasing slowly until the menopause. AMH is produced by early growing follicles at all stages up to the early antral stage but it is unknown which follicle class contributes most to circulating concentrations. The rising granulosa cell mass (and thus AMH production per follicle) will be balanced by progressively declining numbers of follicles at each stage of growth (6).

AMH and polycystic ovary syndrome (PCOS)

The diagnostic criteria of the European Society for Human Reproduction (ESHRE) and the American Society of Reproductive Medicine (ASRM) were established for the diagnostics of this syndrome. PCOS is clinically diagnosed when at least two of the following three features are present: chronic oligo- or anovulation, biochemical

hyperandrogenemia or hyperandrogenism and polycystic ovarian morphology identified under ultrasound examination (PCO) (7). The common clinical manifestations of PCOS include menstruation disorders and androgen excess, hirsutism and male pattern alopecia (8). The syndrome is diagnosed in 5–10% of women of reproductive age. Polycystic ovary syndrome is also associated with metabolic disorders. The incidence of diabetes mellitus type 2 is ten times higher in women with PCOS than in healthy women and 30–50% of women with PCOS develop glucose intolerance or diabetes mellitus type 2 after the age of 30 (9).

Women with PCOS have a two to six times greater number of follicles in their ovaries. AMH production was increased by up to 75% in women with PCOS compared to controls (10). According some authors the high AMH levels in women with PCOS are attributed to the high number of small antral follicles with a diameter of 2–5 mm. AMH values correlate positively with the number of this type of follicles (11, 12).

In a recent in vitro study, it was found that AMH production per granulosa cell was increased by up to 75% in women with PCOS compared to controls. According to the authors, the higher levels should be attributed to the increased number of follicles as well as to the intrinsic aberrant follicular function. AMH excess, via endocrine or paracrine paths, plays an essential role in the braking of the process of follicular maturation (13).

It is known that AMH levels decrease with age in women with normal ovulatory cycles. A similar but slower decline is observed in women with PCOS (14). High AMH levels were observed in girls aged 12–18 years with PCOS compared to healthy controls (15). However, increased AMH levels have been found in girls born of mothers with PCOS (16).

AMH concentrations in women with PCOS were independently and positively correlated with testosterone, androstendione and free androgen index (FAI) values (17). A great number of women with PCOS have insulin resistance and compensatory hyperinsulinemia. It is not yet clear whether there is a correlation between AMH levels and HOMA-IR values in women with PCOS. There have been differing results from related studies (18). Metformin administration in anovulatory patients with PCOS exerts a differential influence on ovarian AMH levels on the basis of ovulatory response. Changes in AMH levels in antral follicular fluid during metformin treatment could play a role in the local mechanisms mediating ovulatory restoration (19).

AMH vs. antral follicle count (AFC)

The relationship between AMH and AFC has recently been the subject of some very intense discussion. Additional parameters of ovarian age have been tested and only AFC and AMH follow the observed pattern of oocyte loss histologically. Although AMH may be more cost-effective, some doctors prefer AFC as a slightly more accurate noninvasive measure for ovarian aging (20). AMH serum levels correlated very strongly with AFC but the quality of the information of both parameters differs to a small extent regarding ovarian reserve. However, with current information, it cannot be definitively stated that endocrine markers (especially AMH as a single indicator) are better than sonographic markers (21). The production of AMH starts in a very small type of follicle (less than 2 mm). Based on the measurement of AMH concentration in follicular fluid we can state

that AMH is produced in greater quantities in smaller follicles (than in larger follicles). Using sonography we can distinguish follicles larger than 2 mm. The two parameters thus provide us with slightly different information. Many IVF centers use both parameters in routine practice for the evaluation of the ovarian reserve.

AMH and granulosa cell tumors (GCTs)

AMH is expressed in ovarian granulosa cells from birth up to the menopause. It is possible to use AMH as a marker of granulosa cell tumours. It has been shown that AMH serum levels are increased in 76% to 93% of women affected by GCTs (22). The mean AMH level was more than ten times higher than in healthy women. AMH is an extremely sensitive and specific marker in the follow-up of patients ovariectomized for GCTs. The elevation of AMH serum levels precedes the detection of a recurrence by about 16 months (23). Early detection of recurrences is of great importance in a system of follow-up of patients with GCT because a high incidence of recurrences are even observed 10–20 years after the resection of the primary tumour (24, 25).

AMH, chemotherapy and radiation

All measurements of the ovarian reserve demonstrated statistically significant changes during chemotherapy and pelvic radiation. The AMH levels rise as the ovarian reserve increases. The impact on the ovarian reserve depends on the type of drugs and number of therapeutic cycles. Alkylating agents have the worst impact on the ovarian reserve. The degree of increase to the ovarian reserve depends on the dose and number of therapeutic cycles (26). Hovewer, a slow recovery of AMH levels was observed after chemotherapy. Alkylating agent exposure and baseline ovarian reserve were closely associated with the magnitude of impairment, while pretreatment AMH levels were linked to the rate of recovery of AMH after treatment. In adjusted models, participants with a pretreatment AMH level >2 ng/mL recovered at a rate of 11.9% per month after chemotherapy, whereas participants with pretreatment AMH levels ≤2 ng/mL recovered at a rate of 2.6% per month after therapy. Baseline ovarian reserve and alkylating agent exposure effect the magnitude of acute changes to the ovarian reserve brought about by chemotherapy. The rate of recovery of AMH is impacted by pretreatment levels (27).

AMH and endometriosis

Findings regarding the relationship of AMH serum levels and endometriosis suggest that endometriosis do not diminish the ovarian reserve. (28) AMH levels decreased significantly at the sixth month after surgery. (29) These findings should be taken into account in the decision of surgery in women with a desire for future pregnancy.

CONCLUSION

The topic of the clinical use of AMH extends further than most of us realize. From a historical point of view the first ELISA measurements of AMH were taken for the

diagnostics of sexual development disorders in children. The boom in the measurement of AMH started around the year 2000, as it became nown that AMH correlates very well with the ovarian reserve. The topic of AMH and IVF is now well known and widely discussed. We understand that not all questions on this topic have been answered. However, the aim of our present article was to draw the attention of the medical community to additonal indications that extend from AMH which are, in our opinion, also very interesting and which are now beginning to draw the attention of leading positions in professional medical circles.

SUMMARY

Many studies have been performed on the topics of ovarian reserve, ovarian aging and on the prediction of the ovarian response to the hormonal stimulation involved in in vitro fertilization (IVF). The measurement of AMH serum levels is currently a useful tool in the examination of the ovarian reserve. However, IVF is not the only reason for determination of AMH. The aim of this article is to present the topic of AMH from a different point of view. Polycystic ovary syndrome (PCOS) is a big challenge not only for AMH examination but for the whole of medicine today. The relationship between AMH serum levels and antral follicle count (AFC) has been a very hot topic for medical discussion over the last few years. AMH is a very sensitive tumor marker used in the diagnostics of ovarian granulosa cell tumors (GCTs). Cancer treatment places a burden on the entire organism, including healthy cells. Follicles are very sensitive to radiation and chemotherapeutic agents. The changes in the number of follicles are monitored very sensitively using AMH serum levels. Endometriosis has not the direct influence on the ovarian reserve and AMH serum levels.

Acknowledgements

This study was supported by the project of Ministry of Health of the Czech Republic for conceptual development of research organization 00669806 – Faculty Hospital in Pilsen.

Další klinické aplikace AMH ve spojitosti s ovariální rezervou

SOUHRN

Na téma ovariální rezervy byla v minulosti provedena řada studií. Velká většina těchto studií byla provedena v souvislosti s procesem in vitro fertilizace (IVF). Měření sérových hladin Anti-Mülleriánského hormonu (AMH) je v současné době užitečným nástrojem v rámci zjišťování ovariální rezervy. Nicméně, IVF není jediným důvodem pro stanovení AMH. Cílem tohoto článku je podívat se na téma stanovení AMH z jiného úhlu pohledu a upozornit na další klinické stavy, u kterých je užitečné provádět stanovení

AMH. Syndrom polycystických ovarií (PCOS) je v současné době velkou výzvou nejen pro vyšetření AMH ale i pro medicínu jako takovou. Vztah mezi sérovými hladinami AMH a počtem antrálních folikulů (AFC) určovaných ultrazvukem je velmi žhavé téma diskutované v lékařských kruzích v posledních několika letech. AMH je též velmi citlivý nádorový marker a používá se k diagnostice a sledování ovariálních nádorů granulózových buněk (GCTs). Chemoterapie klade zátěž na celý organismus, včetně zdravých buněk. Ovariální folikuly jsou velmi citlivé na chemoterapii a ozáření. Změny v počtu folikulů mohou být v průběhu terapie sledovány pomocí stanovení AMH v séru. Endometrióza nemá přímý vliv na ovariální rezervu a hladiny AMH v séru.

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